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

Digitally signed by Kojevnikov Dmitrii
Date: 2023.10.13 17:16:09 EEST
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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

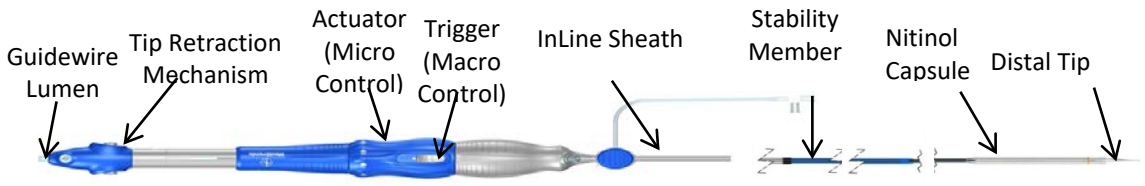
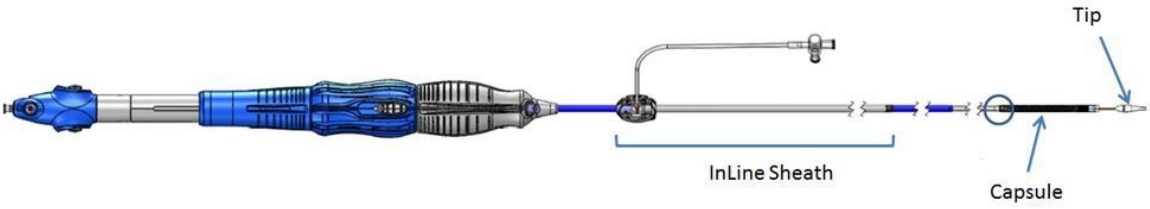


Figure 3: EnVeo PRO Delivery Catheter System



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

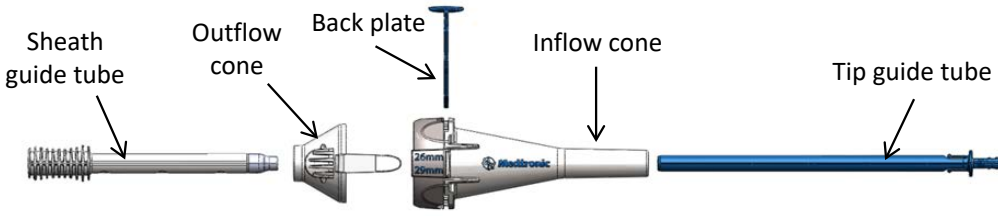


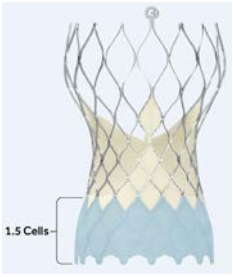
Figure 5: EnVeo PRO Loading System

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

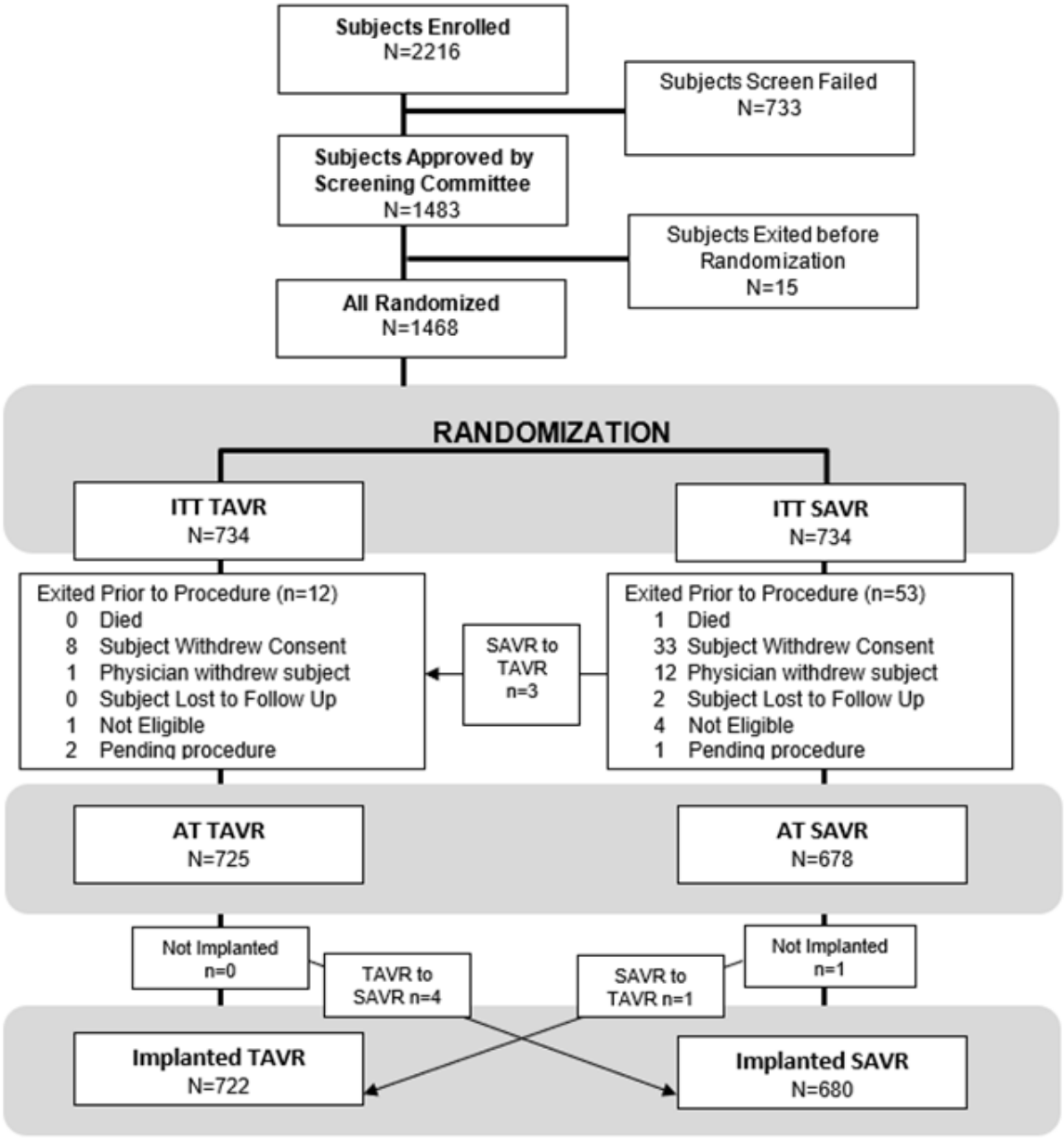
(PP), as summarized in Table 2 and Figure 7. The primary analysis was the AT analysis.

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

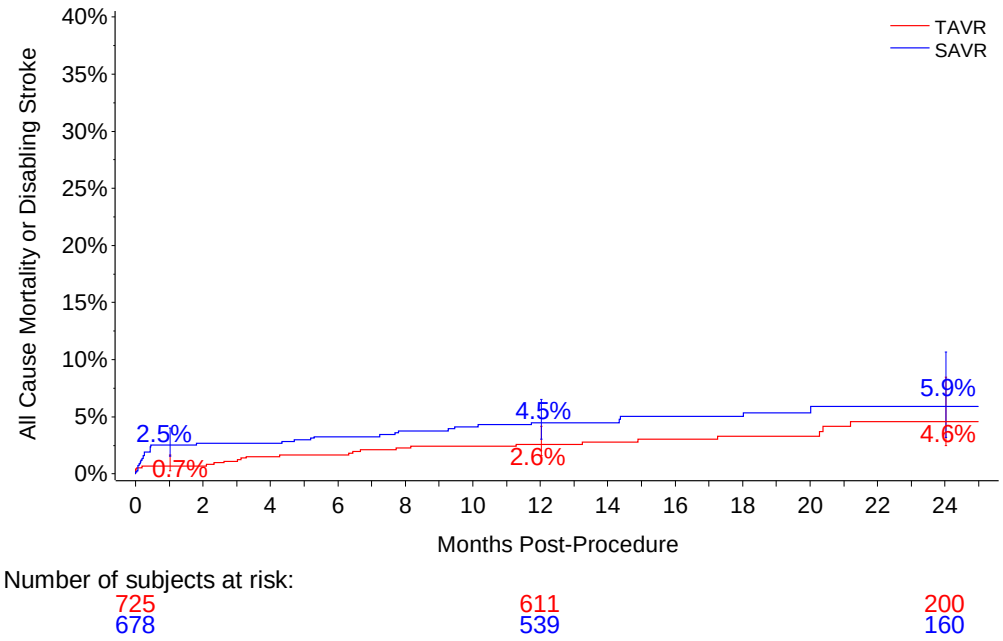
	"Early Win" Analysis*		**Supplemental Analysis†**	
	TAVR (N=725)	**SAVR (N=678)**	**TAVR (N=725)**	**SAVR (N=678)**
Posterior median (95% BCI)	5.3% (3.3%, 8.0%)	6.7% (4.4%, 9.6%)	4.4% (2.9%, 6.4%)	6.2% (4.3%, 8.6%)
Difference (TAVR-SAVR) posterior median (95% BCI)	-1.4% (-4.9%, 2.1%)		-1.8% (-4.6%, 1.0%)	
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

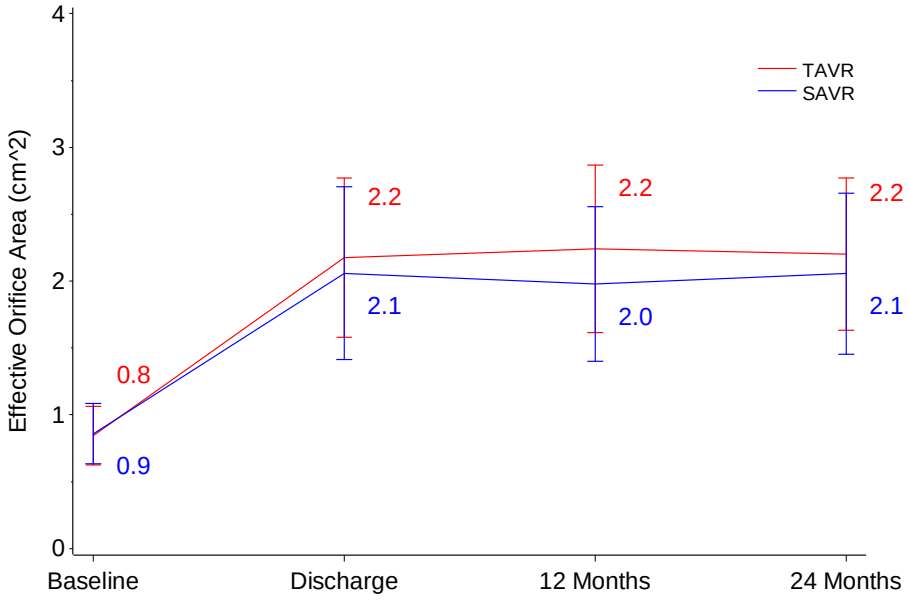
Secondary Endpoint	TAVR Mean±SD (N)	SAVR Mean±SD (N)	Difference (TAVR – SAVR) (90% BCI)	Posterior Probability Prob (H_A | data)	Threshold	Test Result
Non-inferiority testing						
#1 Mean gradient at 12 months	8.6 ± 3.7 (409)	11.2 ± 4.9 (339)	-2.6 (-3.1, -2.1)	>0.999	0.95	Passed
#2 EOA at 12 months	2.3 ± 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

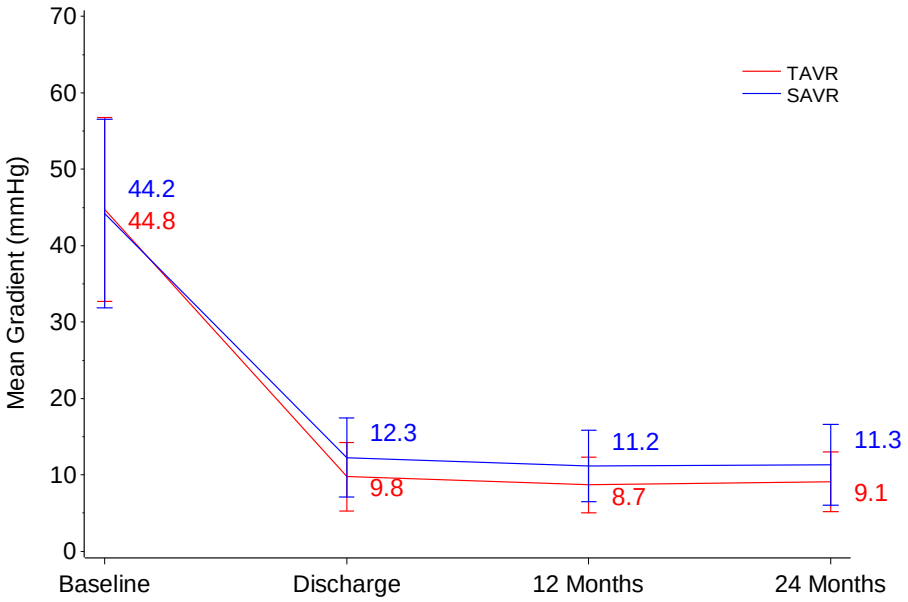
The EOA, mean aortic gradient, total aortic regurgitation (AR), and paravalvular regurgitation values obtained over time for the TAVR and SAVR patients are shown in Figure 9 through Figure 12, respectively. The increase in EOA and decrease in gradient were sustained through 24 months in both cohorts. 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)



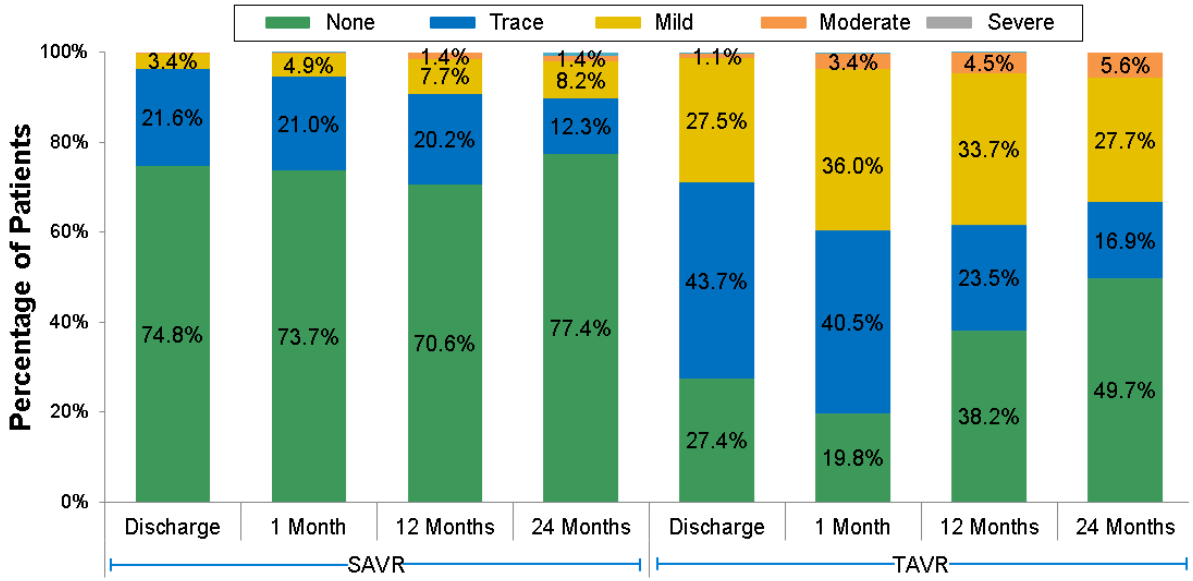
Note: Line plot with mean and standard deviation.

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



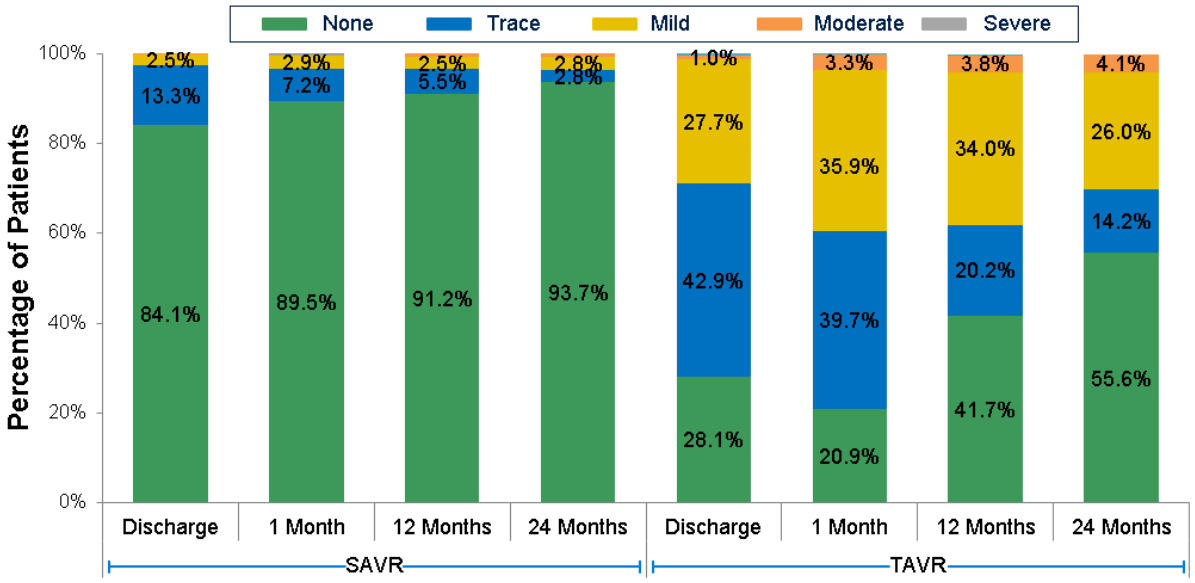
Note: Line plot with mean and standard deviation.

Figure 11: Total Aortic Regurgitation (Implanted Population)



Note: Values < 1.0% are not labeled.

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

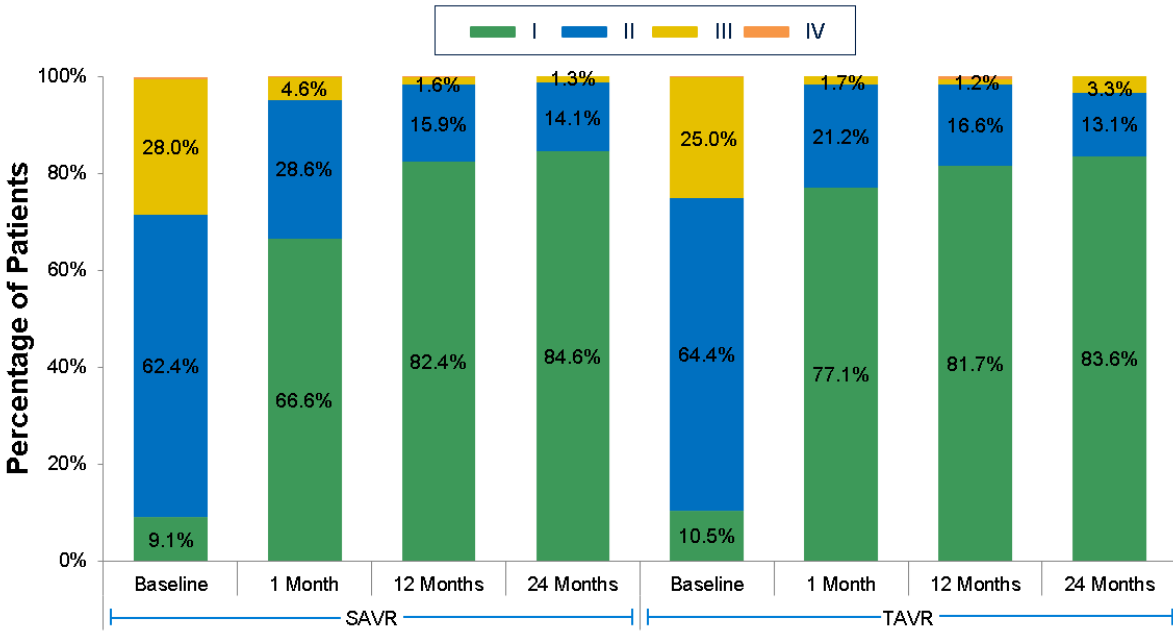


Note: Values < 1.0% are not labeled.

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)



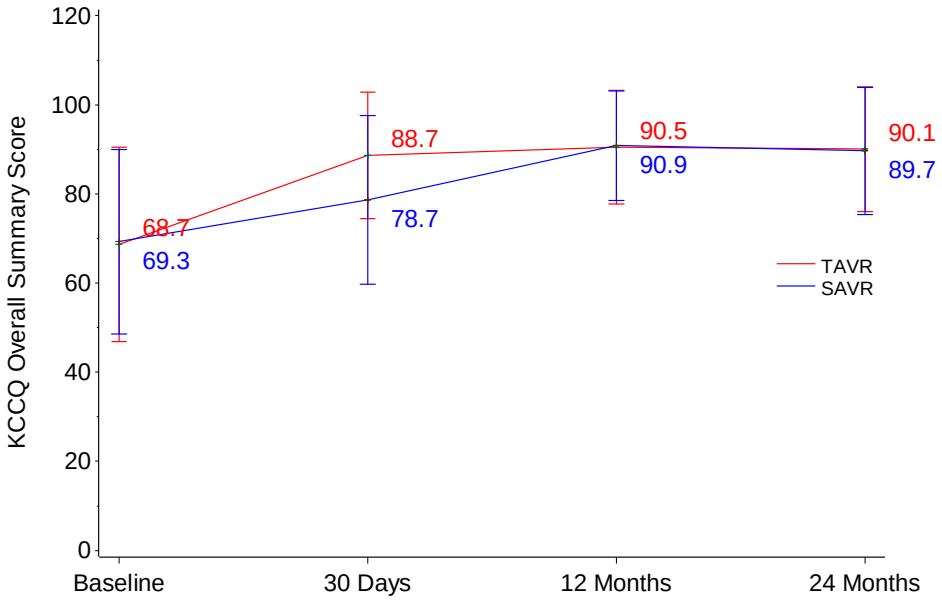
Note: Values < 1.0% are not labeled.

QoL

KCCQ

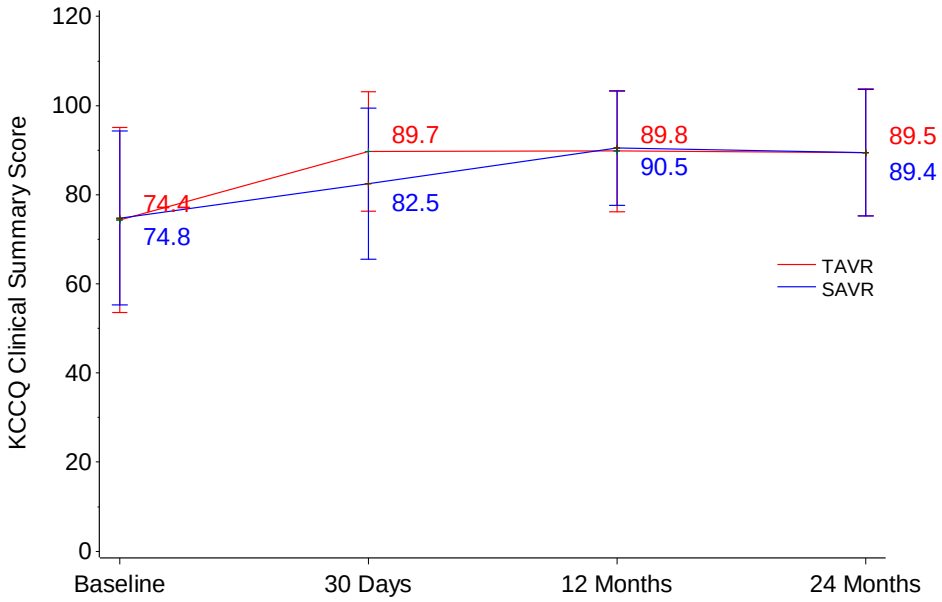
The KCCQ overall and clinical summary scores for the two treatment cohorts are shown in Figure 14 and Figure 15, respectively. In TAVR patients, the mean KCCQ overall summary score increased from 68.7 at baseline to 90.5 at 12 months and 90.1 at 24 months, and the mean KCCQ clinical summary score increased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

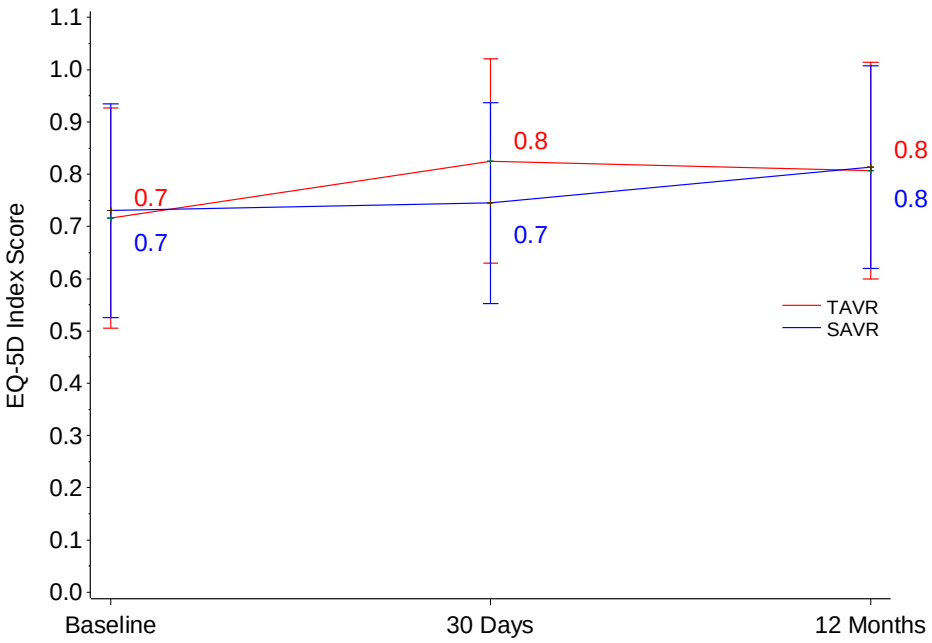


Note: Line plot with mean and standard deviation.

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)

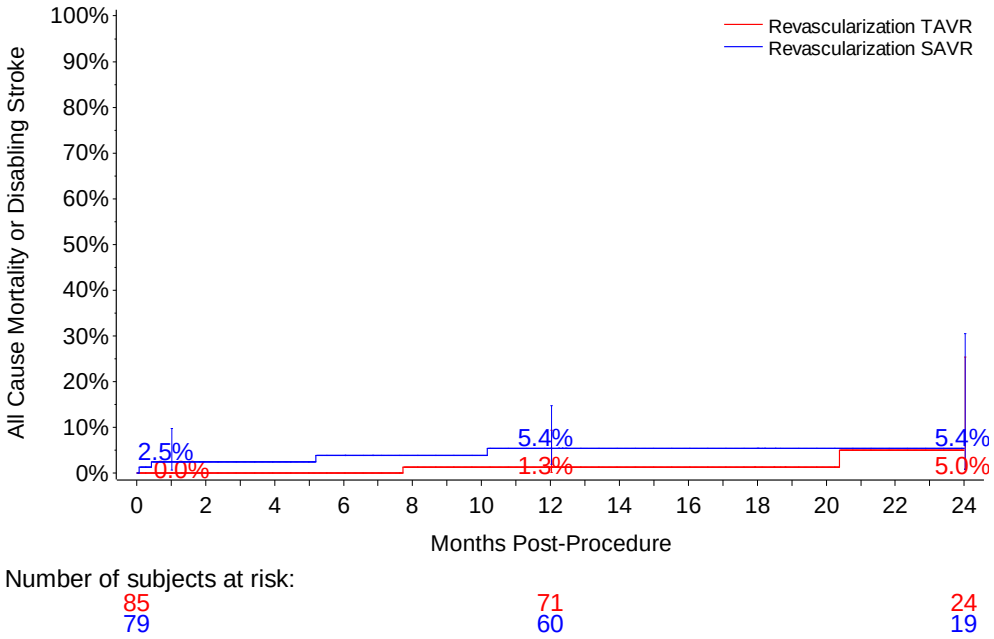
4. Subgroup Analyses

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:

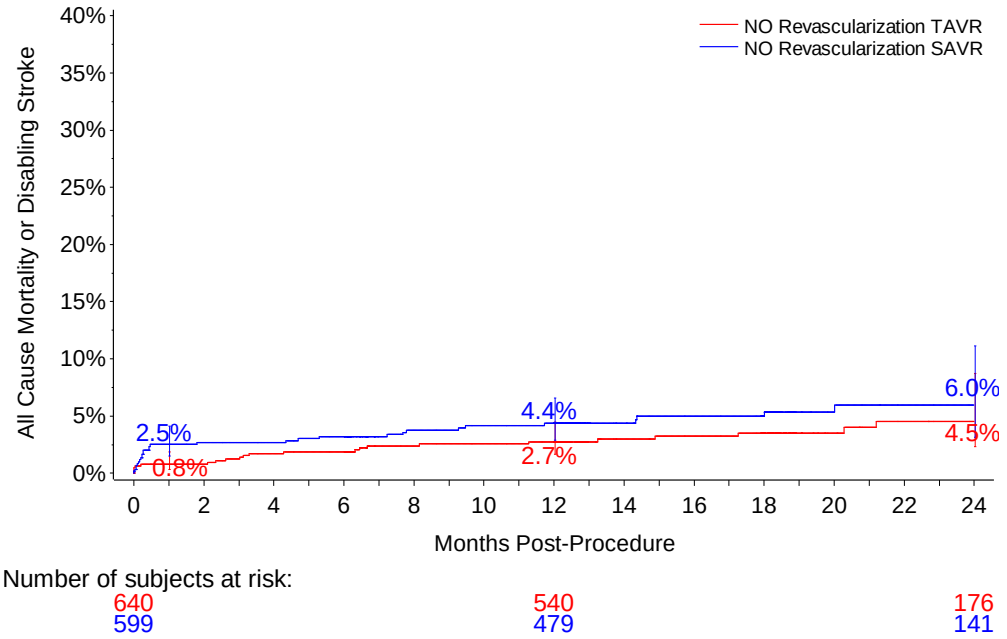
The K-M curves of all-cause mortality or disabling stroke are shown in Figures 17 and 18 for patients with and without the need for concomitant revascularization, respectively.

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

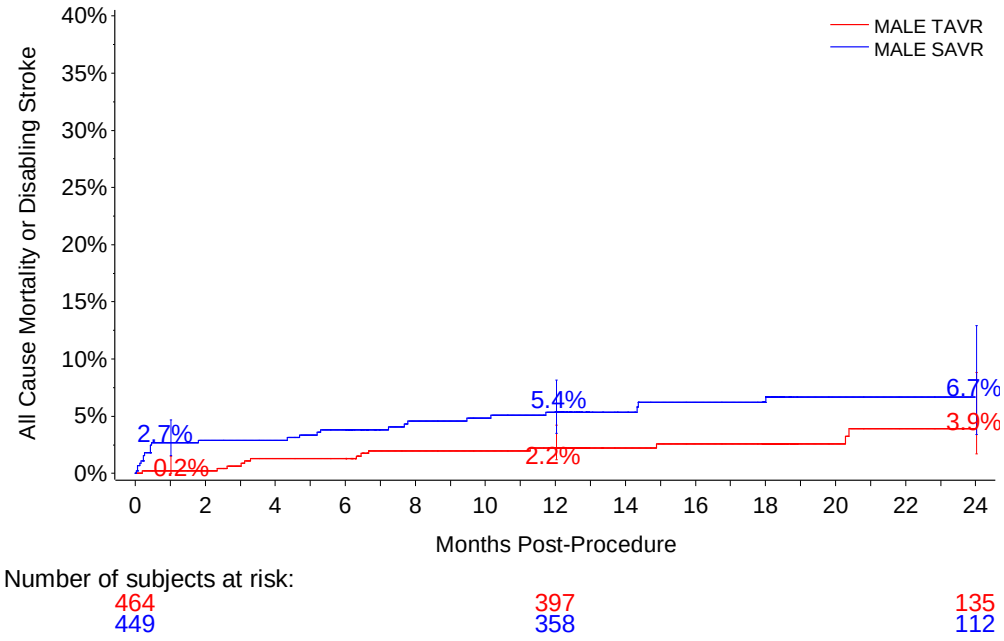


Note: The confidence intervals were calculated without multiplicity adjustment. The adjusted confidence intervals could be wider than presented here. As such, confidence intervals are provided to illustrate the variability only and should not be used to draw any statistical conclusion. The trial was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

All-Cause Mortality or Disabling Stroke Stratified by Gender:

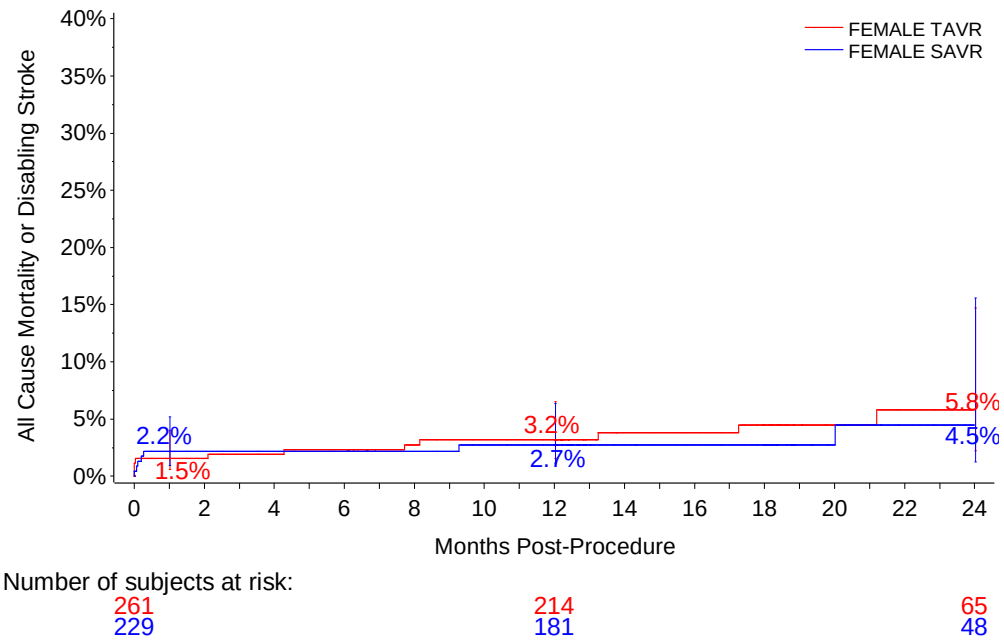
The K-M curves of all-cause mortality or disabling stroke are shown in Figures 19 and 20, for the male and female patients, respectively.

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.

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name:	Replacement Heart Valve
Device Trade Name:	Medtronic CoreValve™ System (MCS): Transcatheter Aortic Valve (TAV), Models MCS-P4-23-AOA (23 mm; CoreValve™ Evolut™), MCS-P3-26-AOA (26 mm), MCS-P3-29-AOA (29 mm), and MCS-P3-31-AOA (31 mm); Delivery Catheter System (DCS), Models DCS-C4-18FR and DCS-C4-18FR-23; and Compression Loading System (CLS), Model CLS-3000-18FR
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
Date of FDA Notice of Approval:	January 17, 2014

II. INDICATIONS FOR USE

The Medtronic CoreValve™ System is indicated for relief of aortic stenosis in patients with symptomatic heart disease due to severe native calcific aortic stenosis (aortic valve area ≤ 0.8 cm^2, a mean aortic valve gradient of > 40 mmHg, or a peak aortic-jet velocity of > 4.0 m/s) and with native aortic annulus diameters between 18 and 29 mm who are judged by a heart team, including a cardiac surgeon, to be at extreme risk or inoperable for open surgical therapy (predicted risk of operative mortality and/or serious irreversible morbidity ≥50% at 30 days).

III. CONTRAINDICATIONS

The Medtronic CoreValve System is 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
- preexisting mechanical heart valve in aortic position

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Medtronic CoreValve System labeling.

V. DEVICE DESCRIPTION

The Medtronic CoreValve System (MCS) is designed to replace the native aortic heart valve without open heart surgery and without concomitant surgical removal of the failed native valve. It consists of 3 components: the Transcatheter Aortic Valve (TAV), the Delivery Catheter System (DCS), and the Compression Loading System (CLS).

V.1. Transcatheter Aortic Valve (TAV)

The TAV (Figure 1) is manufactured by suturing three valve leaflets and skirt, made from a single layer of porcine pericardium, onto a self-expanding, multi-level, radiopaque frame made of Nitinol. The bioprosthesis is processed with alpha-amino oleic acid (AOA®), which is an antimineralization treatment derived from oleic acid, a naturally occurring long-chain fatty acid.

Figure 1: CoreValve Transcatheter Aortic Valve

The TAV is available for a range of aortic annulus and ascending aorta diameters as shown in Table 1. Note that the 23 mm TAV has its own device name, called CoreValve™ Evolut™.

Table 1: Patient Anatomical Diameters

Bioprosthesis Model	Size	Aortic Annulus Diameter	Ascending Aorta Diameter
CoreValve™ Evolut™ Bioprosthesis			
MCS-P4-23-AOA	23 mm	18 mm–20 mm	≤34 mm
CoreValve™ Bioprosthesis			
MCS-P3-26-AOA	26 mm	20 mm–23 mm	≤40 mm
MCS-P3-29-AOA	29 mm	23 mm–26 mm	≤43 mm
MCS-P3-31-AOA	31 mm	26 mm–29 mm	≤43 mm

V.2. Delivery Catheter System with AccuTrak Stability Layer (AccuTrak DCS)

The DCS (Figure 2) is used to deploy the TAV. The TAV is loaded within the capsule which features 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. There are two models of the DCS: model DCS-C4-18FR-23 for the 23 mm TAV only and model DCS-C4-18FR for the 26, 29, and 31 mm TAVs.

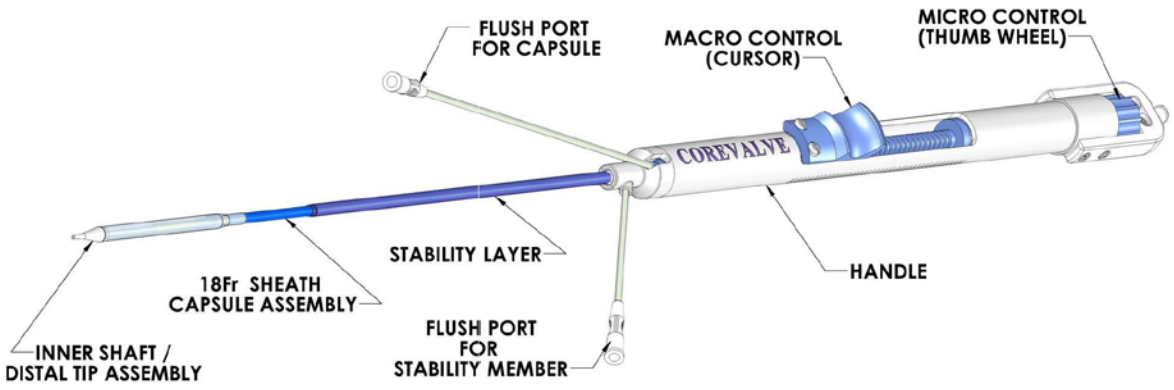


Figure 2: CoreValve Delivery Catheter System

V.3. Compression Loading System (CLS)

The CLS (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. Only one model of the CLS is available, i.e., model CLS-3000-18FR.

Figure 3: CoreValve Compression Loading System

The CLS 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

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Alternatives for patients deemed to be at extreme risk, or non-operable (non-surgical), for surgical aortic valve replacement include: treatment with other approved transcatheter aortic valve implantation therapy, temporary relief using a percutaneous technique called 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 current Medtronic CoreValve System is commercially available in over 50 countries, as listed in Table 2. It has not been withdrawn from marketing for any reason related to its safety or effectiveness.

Table 2: Countries where Medtronic CoreValve System is commercialized

Commercially Available			
Afghanistan	Finland	Moldova	Tajikistan
Albania	France	Netherlands	Thailand
Argentina	Georgia	New Zealand	Turkmenistan
Armenia	Germany	Panama	Turkey
Austria	Greece	Peru	United Kingdom
Azerbaijan	Guatemala	Philippines	Croatia
Belgium	Hong Kong	Poland	Israel
Belarus	Hungary	Portugal	Ukraine
Bosnia & Herzegovina	Ireland	Romania	Uruguay
Brazil	Israel	Russia	Uzbekistan
Canada	Italy	Saudi Arabia	Venezuela
Chile	Kazakhstan	Serbia	

Commercially Available			
Colombia	Kyrgyzstan	Slovakia	
Croatia	Latvia	Slovenia	
Cyprus	Lithuania	South Africa	
Czech Republic	Luxembourg	South Korea	
Denmark	Malaysia	Spain	
Dominican Republic	Malta	Sweden	
Ecuador	Mexico	Switzerland	
Estonia	Montenegro	Taiwan	

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Potential risks associated with the implantation of the Medtronic CoreValve System may include, but are not limited to, the following:

- 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)
- 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)
- perforation of the myocardium or a vessel
- 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 10.

IX. SUMMARY OF PRECLINICAL STUDIES

A. Laboratory Testing

A series of non-clinical laboratory studies were performed on the Medtronic CoreValve System as recommended per ISO 5840: 2005, Cardiovascular implants – Cardiac valve prostheses and relevant FDA Guidance Documents.

Biocompatibility

Biocompatibility evaluations were completed on the components (TAV, DCS, and CLS) of the Medtronic CoreValve System in accordance with ISO 10993-1:2009, Biological Evaluation of Medical Devices Part 1: Evaluation and Testing, and FDA's General Program Memorandum No. G95-1, Use of International Standard ISO-10993, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing." The required testing for each component was determined based on the nature and duration of body contact in accordance with ISO 10993-1:2009. Summaries of the test results for the TAV, DCS, and CLS are provided in Table 3-Table 5, respectively.

Table 3: Summary of Medtronic CoreValve Transcatheter Aortic Valve Biocompatibility Testing

Biological Effect per ISO 10993-1	Test Method	Test Result
Cytotoxicity	ISO MEM Elution	Pass
	ISO Agarose Overlay – Direct contact method	Pass
Sensitization	ISO Guinea Pig Maximization Sensitization Test	Pass
Irritation	Intracutaneous Irritation Study in Rabbits	Pass
(Acute) Systemic Toxicity	Systemic Toxicity in Mice	Pass
	USP Pyrogen Study, Material Mediated	Pass
Hemocompatibility	ASTM Hemolysis	Pass
	Partial Thromboplastin Time (PTT)	Pass
	Complement Activation (C3a, SC5b-9)	Pass
	In vivo Thrombogenicity in Porcine Model	Pass
Genotoxicity	Bacterial Reverse Mutation Study	Pass
	Chromosomal Aberration study in Mammalian Cells	Pass
	Mouse Peripheral Blood Micronucleus Study	Pass
Subacute/ Subchronic Toxicity	4-week Systemic Toxicity Study in Rats following Subcutaneous Implantation	Pass
	13-week Systemic Toxicity Study in Rats following Subcutaneous Implantation	Pass
Chronic Toxicity	Chronic toxicity was evaluated as part of the *in vivo* animal studies	Pass
Carcinogenicity	As the TAV is made of well-characterized materials and the results from the aforementioned genotoxicity studies demonstrated no mutagenic response, carcinogenicity testing was not conducted.	Not Required
Biodegradation	The materials used in MCS have no known absorption, distribution, biotransformation, or leachable elimination properties that make them a candidate for this test procedure. Therefore, biodegradation testing was not deemed necessary.	Not Required

Biological Effect per ISO 10993-1	Test Method	Test Result
Reproductive/ Developmental Toxicity	The MCS does not have any potential impact on the reproductive potential of the patient, hence this test was not deemed necessary.	Not Required

Table 4: Summary of Medtronic CoreValve Delivery Catheter System Biocompatibility Testing

Biological Effect per ISO 10993-1	Test Method	Test Result
Cytotoxicity	ISO MEM Elution	Pass
Sensitization	ISO Guinea Pig Maximization Sensitization Test	Pass
Irritation	Intracutaneous Irritation Study in Rabbits	Pass
(Acute) Systemic Toxicity	Systemic Toxicity in Mice	Pass
	USP Pyrogen Study, Material Mediated	Pass
Hemocompatibility	ASTM Hemolysis	Pass
	Partial Thromboplastin Time (PTT)	Pass
	Complement Activation (C3a, SC5b-9)	Pass
	In vivo Thrombogenicity in Porcine Model	Pass

Table 5: Summary of Medtronic CoreValve Compression Loading System Biocompatibility Testing

Biological Effect per ISO 10993-1	Test Method	Test Result
Cytotoxicity	ISO MEM Elution	Pass
Hemocompatibility	Modified ASTM Hemolysis (direct contact and extract method)	Pass
(Acute) Systemic Toxicity	USP Pyrogen Study, Material Mediated	Pass

Bench Testing

Medtronic conducted comprehensive preclinical bench testing and computational analysis on the Medtronic CoreValve System, including the TAV, the DCS, and the CLS. All testing was conducted in accordance with national and international standards and FDA guidance documents. Testing verified that all components of the Medtronic CoreValve System met its product performance and design specifications. The tests are summarized in Table 6.

Table 6: Summary of *In Vitro* Studies for Medtronic CoreValve System (MCS)

Test	Applicable Standards	Test Description	Results
Transcatheter Aortic Valve (TAV)			
Frame Raw Material Analysis	ASTM F2063-05, ASTM F2633, ASTM F2516-07, ASTM E8	This test verified that the incoming raw materials conform to chemical and mechanical property requirements of the MCS TAV frame.	Pass
Frame Mechanical Property Characterization of Post-Processed Material	ASTM F2516-07, ASTM E8	This test characterized the mechanical properties of the Nitinol tubing of the MCS TAV frames.	NA – Characterization Testing
Corrosion Testing	ISO 5840: 2005, ASTM F2129-08	This test evaluated the corrosion resistance of the MCS TAV in accordance with ASTMF2129	Pass
Mechanical Characterization of Porcine Pericardium	ASTM 2063	This test characterized the mechanical properties of the MCS TAV porcine pericardium.	NA – Characterization Testing
Dimensional Verification	FDA Guidance Document for Intravascular Stents	This test verified that the dimensions of the MCS TAV frame are within specified requirements.	Pass
Transformation Temperature, A_f	ASTM 2082-02	This test verified that the MCS TAV frames conform to the required Af temperature specification.	Pass
Frame Radial Force Characterization	EN ISO 14299: 2004, ISO 5480: 2005, FDA Guidance Document for Intravascular Stents	This test characterized the frame radial force of the MCS TAV frame.	NA – Characterization Testing
Magnetic Resonance Imaging	ASTM F2052-06, ASTM F2503-08, ASTM F2213-06, ASTM F2119-07, ASTM F2182-11a	This test characterized the performance of the MCS TAV in an MR field and determined the compatibility. The following is in the IFU: Nonclinical testing and modeling has demonstrated that the Medtronic CoreValve bioprosthesis is MR Conditional. It can be scanned safely under the following conditions: Static magnetic field of 1.5 tesla and 3 tesla Spatial gradient field of 2500 gauss/cm Normal operating mode only with a maximum whole body SAR of 2.0 W/kg for 15 minutes as read from equipment monitor	Pass
Radiopacity	ISO 5840: 2005, ISO 25539-1: 2003, FDA Guidance Document for Intravascular Stents	This test evaluated the ability to visualize the MCS TAV and DCS under standard imaging.	Pass
Finite Element Analysis (FEA)	None	FEA was used to characterize the structural behavior of the MCS TAV frame under *in vivo* operational conditions.	NA – Characterization Testing

Test	Applicable Standards	Test Description	Results
Device Level Fatigue Testing of TAV Frames (600M)	ISO 5840: 2005, FDA Guidance Document for Heart Valves	This test evaluated the MCS TAV frame fatigue resistance to 600 Million cycles.	NA – Characterization Testing
Material Fatigue Testing (600M)	ISO 5840: 2005, FDA Guidance Document for Heart Valves	This test determined the Nitinol material fatigue limit using representative material test coupons.	NA – Characterization Testing
Hydrodynamic Testing	ISO 5840: 2005, FDA Guidance Document for Heart Valves	This test evaluated the hydrodynamic performance of the MCS TAV in round and out of round conditions compared against a commercially approved surgical valve. Pulsatile Flow Test Flow Visualization Test Verification of Bernoulli Relationship	Pass
Accelerated Wear Testing	ISO 5840: 2005, FDA Guidance Document for Heart Valves	This test evaluated the structural durability of the MCS TAV in round and out of round conditions compared against commercially approved surgical valve to 200 Million cycles.	Pass
Dynamic Failure Mode	ISO 5840: 2005, FDA Guidance Document for Heart Valves	This test induced valve failure to determine the primary mode and location of failure of the MCS TAV.	NA – Characterization Testing
Migration	ISO 5840: 2005, FDA Guidance Document for Heart Valves	This test evaluated the migration resistance of the MCS TAV.	Pass
Delivery Catheter System (DCS)			
Surface Finish Examination/ Dimensional Conformations	ISO 10555-1 (Amd 2, 2004), ISO 25539-1: 2009, FDA Guidance Document for Intravascular Stents	This test verified that the surfaces & dimensions of the MCS DCS meet specification.	Pass.
Bond/Tubing Tensile Strengths	ISO 10555-1 (Amd 2, 2004), ISO 25539-1: 2009, FDA Guidance Document for Intravascular Stents	This test verified that the bonds and tubing of the MCS DCS meet the strength specifications.	Pass
Catheter Compressive Strength	ISO 25539-1: 2003(E)	This test verified that the MCS DCS can withstand the forces necessary to deliver the TAV to the treatment site.	Pass
Kink Resistance	ISO 25539-1: 2003(E)	This test verified the ability of the MCS DCS to accommodate the curvature encountered during clinical use.	Pass
Flushability	ISO 25539-1: 2009	This test verified the ability of the MCS DCS to be purged.	Pass

Test	Applicable Standards	Test Description	Results
Corrosion Resistance	ISO 10555-1 (Amd 2, 2004)	This test verified the corrosion resistance of the metallic components of the MCS DCS.	Pass
Macro and Micro Controls	ISO 25539-1: 2009	This test verified the macro and micro controls of the MCS DCS handle function as intended.	Pass
Guidewire Verification / Introducer compatibility	ISO 25539-1: 2009	This test verified the compatibility with a 0.035" guidewire and 18Fr introducer sheath.	Pass
Hemostasis	ISO 25539-1: 2009, ISO 11070: 1998	This test determined the ability of the MCS DCS components to maintain hemostasis.	Pass
Cather Loading System (CLS)			
Dimensional Verification	None	This test verified that the components of the MCS CLS meet dimensional specifications.	Pass
MCS System Testing			
Deployment Accuracy	ISO 25539-1: 2009	This test verified the deployment accuracy of the MCS DCS when used with the TAV.	Pass
Systems Deployment Force Testing	ISO 25539-1: 2009	This test evaluated the system's ability to load and characterize the deployment force.	Pass
Torque Characterization	ISO 25539-1: 2009	This test characterized the maximum torque that may be applied to the MCS DCS.	NA – Characterization Testing
TAV Device Foreshortening	ASTM F2081-06, ISO 25539-1:2009, FDA Guidance Document for Intravascular Stents	This test determined the relationship between the MCS TAV frame length and diameter when crimped and deployed.	NA – Characterization Testing
Frame & Valve Integrity post-Tracking and Deployment	ISO 25539-1: 2009, FDA Guidance Document for Heart Valves, FDA Guidance Document for Intravascular Stents	This test evaluated the effects of crimping, tracking, and deployment on MCS TAV frame and valve integrity.	Pass
System Usability	ISO 25539-1:2003(E), ANSI/AAMI HE74:2001, BS EN 62366:2008	This test assessed the user's ability to use the MCS DCS with TAV and CLS.	Pass

B. Animal Studies

Four animal studies were performed in support of the safety and performance of the current Medtronic CoreValve System (MCS). Two of those four studies were conducted to evaluate the chronic *in vivo* safety and performance of the MCS TAV in an ovine and a porcine model, respectively. The other two studies were simulated use evaluation of the performance of models DCS-C4-18FR and DCS-C4-18FR-23 of the AccuTrak DCS using an *in vivo* porcine model. These studies are summarized in Table 7.

Table 7: Summary of *In Vivo* Studies for Medtronic CoreValve System

Study Information	Chronic Orthotopic Study	Chronic Descending Aorta Study	Simulated use study for AccuTrak DCS (DCS-C4-18FR)	Simulated use study for AccuTrak Short Capsule DCS (DCS-C4-18FR-23)
Device evaluated	26mm TAV	26mm TAV	AccuTrak DCS (DCS-C4-18FR)	AccuTrak Short Capsule DCS (DCS-C4-18FR-23)
Animal Model	Micro-Yucatan pig	Sheep	Yorkshire pigs	Yorkshire pigs
Methods	Percutaneous delivery of the MCS in the pig's native aortic valve.	Percutaneous delivery of the MCS in the proximal descending aorta (Hufnagel) after creation of sufficient aortic insufficiency of the native aortic valve.	Delivery performance of the AccuTrak delivery system was confirmed.	Delivery performance of the AccuTrak delivery system was confirmed.
Valve Implant Location	Orthotopic position	Descending aorta	Orthotopic position	Orthotopic position
Duration	45 and 90 days	150 ±10 days	Acute	Acute
Major Endpoints	• To evaluate the hemodynamic performance of the Medtronic CoreValve System • To assess the in vivo response to the Medtronic CoreValve System	• Evaluate the safety and performance of the device in a sheep's descending aorta after creating sufficient aortic insufficiency (AI) of the native aortic valve (Hufnagel Model) • Identifying unanticipated or potential complications and adverse events associated with the use of the device • Assess morbidity or mortality of the study animals • Gross and microscopic examinations	• Accessibility of the intended vascular location • Trackability of the system over the recommended guidewire along the path of the vessel(s) to the intended location • Deployment of the TAV • Withdrawal of the catheter • Visualization of the system under fluoroscopy during access, placement, deployment, withdrawal, and after withdrawal • Hemostasis, or how effectively blood loss is minimized when using the system	• Accessibility of the intended vascular location • Trackability of the system over the recommended guidewire along the path of the vessel(s) to the intended location • Deployment of the TAV • Withdrawal of the catheter • Visualization of the system under fluoroscopy during access, placement, deployment, withdrawal, and after withdrawal • Hemostasis, or how effectively blood loss is minimized when using the system
Results	Animals survived • Group 1: 45 days, 4 animals • Group 2: 90 days, 8 animals	Animals survived to 150 days: 7 • Test article (MCS): 6 animals • Control article: 1 animal	The AccuTrak DCS met all simulated use evaluation acceptance criteria.	The AccuTrak DCS and 23 mm CoreValve bioprosthesis met all simulated use evaluation acceptance criteria.
Conclusion	The device performed as intended; thereby, demonstrating safety of the device.	The safety of the device was shown by adequate hemodynamic performance and in vivo healing response.		

C. Sterilization

The Medtronic CoreValve System TAV undergoes liquid chemical sterilization in a glutaraldehyde solution. The terminal sterilization process involves incubation of the bioprosthesis in sterilant solution at elevated temperature for a defined period of time. The validated terminal liquid chemical sterilization process has demonstrated Sterility Assurance Levels (SAL) of 10^{-6}.

The AccuTrak DCS and the CLS are sterilized via Ethylene Oxide (EtO) in accordance with internal quality control procedures and ANSI/AAMI/ISO 11135:2007 Medical Device – Validation and Routine Control of Ethylene Oxide Sterilization. Residual testing was conducted per ISO 10993-7:2008 Biological Evaluation of Medical Devices – Part 7: Ethylene Oxide Sterilization Residuals. The validated EtO sterilization process has demonstrated Sterility Assurance Levels (SAL) of 10^{-6}.

D. Packaging and Shelf Life

The Medtronic CoreValve System components are all packaged separately. The TAV component is stored in glutaraldehyde in a glass jar and placed in a protective carton. Evaluations have demonstrated that packaging sterility and performance are maintained after sterilization and one year real time aging.

The AccuTrak DCS is placed on a tray and then pouched. The pouched DCSs are then placed in their respective cartons. Evaluations have demonstrated packaging sterility and integrity are maintained after sterilization and one year real time aging.

The CLS is also pouched and placed in a carton. Evaluations have demonstrated packaging sterility and performance are maintained after sterilization and one year real time aging.

The shelf life of all components of the Medtronic CoreValve System is 1 year. Dimensional, functional, and biochemical testing, where applicable, was performed on aged components and compared to baseline performance to ensure the components meet specifications throughout the stated shelf life.

X. SUMMARY OF PRIMARY CLINICAL STUDY

Medtronic performed a clinical study to establish a reasonable assurance of safety and effectiveness of transcatheter aortic replacement with the Medtronic CoreValve System for iliofemoral or non-iliofemoral (i.e., subclavian and direct aortic) delivery in patients with severe symptomatic native aortic valve stenosis who have been determined by two cardiac surgeons to be at extreme risk for open aortic valve replacement and in whom existing co-morbidities would not preclude the expected benefit from correction of the aortic stenosis. The study was conducted in the U.S. under IDE G100012. A summary of the clinical study is presented below.

A. Study Design

The CoreValve U.S. pivotal trial used to support this PMA was a prospective, non-randomized, unblinded, multi-center investigational study evaluating the safety and effectiveness of the Medtronic CoreValve System in a stratified population of patients unsuitable for cardiac surgery (referred to as the Extreme Risk study). Once the patient was determined as being at extreme risk for surgery, a determination of vascular access was made. All enrolled patients were assigned to transcatheter aortic valve replacement (TAVR) with the Medtronic CoreValve System (MCS). Patients received the CoreValve device through either an iliofemoral or a non-iliofemoral (subclavian or direct aortic) access route. The trial enrollment diagram is shown in Figure 4.

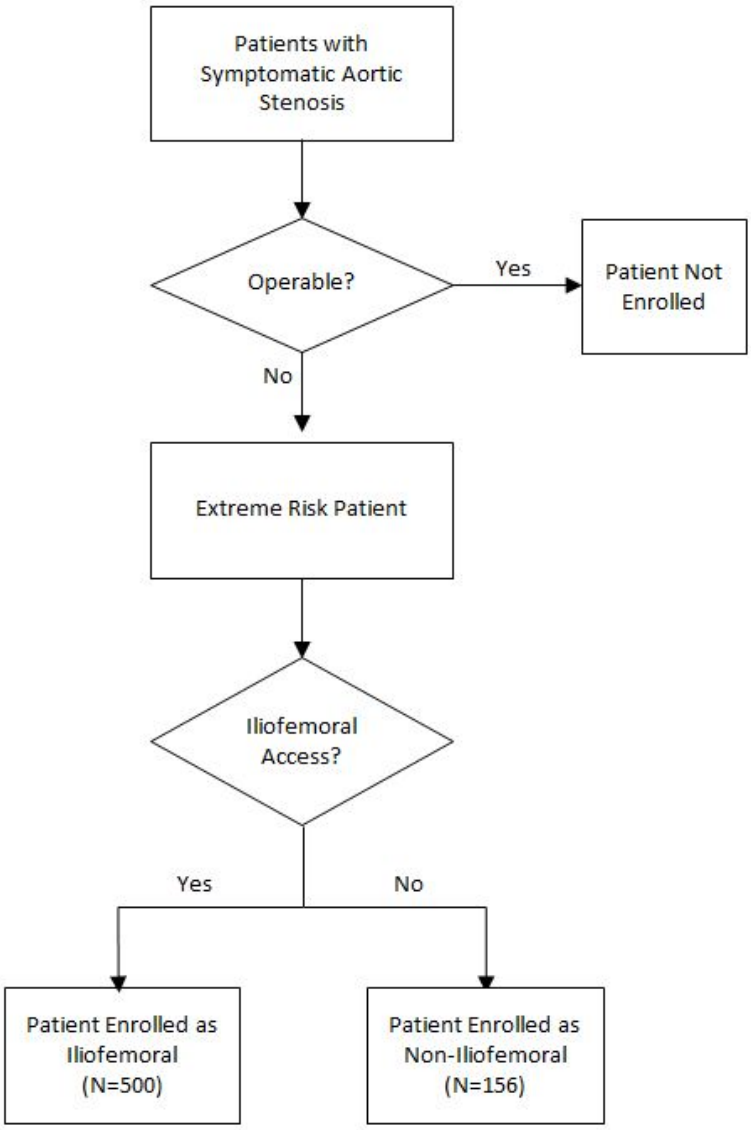


Figure 4: CoreValve Extreme Risk Cohort Trial Enrollment Diagram

The trial was conducted at 41 investigational sites in the U. S. and a total of 656 iliofemoral and non-iliofemoral patients were enrolled between February 17, 2011 and August 23, 2012 in the Extreme Risk cohort. Five hundred (500) iliofemoral patients were enrolled to receive a 23, 26, 29, or 31 mm TAV and are included in the primary analysis. One hundred fifty-six (156) non-iliofemoral patients were enrolled to receive a 23, 26, 29, or 31 mm TAV and are not included in the primary analysis in accordance with the protocol. The database for this PMA reflected data from events through September 30, 2013. Contractors were utilized for monitoring and analysis of data for several aspects of the study, including: an independent Data Safety Monitoring Board (DSMB) that could contract an independent statistician; a Clinical Events Committee (CEC) that was responsible for adjudicating adverse events, an echocardiography core laboratory, and an economics quality of life core laboratory.

1. Clinical Inclusion and Exclusion Criteria

Because tools such as the Society of Thoracic Surgeons (STS) risk calculator can only accommodate a limited number of risk factors and do not account for frailty, disabilities and anatomical characteristics which confer a prohibitive risk for surgical aortic valve replacement (e.g. porcelain aorta) these tools were not used as stand-alone mechanisms for identifying patients at extreme risk for cardiac surgery. Therefore, a team of two cardiac surgeons and one interventional cardiologist at each investigational site were required to assess patient suitability for inclusion in the study, taking into account risk factors not covered by the STS calculator. A central screening committee made a subsequent assessment of patient risk and agreed on patient eligibility or ineligibility.

The inclusion and exclusion criteria for the Extreme Risk study are summarized below:

Inclusion Criteria

- Subject must have had co-morbidities such that one cardiologist and two cardiac surgeons agreed that medical factors preclude operation, based on a conclusion that the probability of death or serious morbidity exceeds the probability of meaningful improvement. Specifically, the predicted operative risk of death or serious, irreversible morbidity is ≥ 50% at 30 days (Extreme Risk)
- Subject had senile degenerative aortic valve stenosis with:
  - Mean gradient > 40 mmHg or jet velocity greater than 4.0 m/sec by either resting or dobutamine stress echocardiogram, or simultaneous pressure recordings at cardiac catheterization (either resting or dobutamine stress), AND
  - An initial aortic valve area of ≤ 0.8 cm^2 (or aortic valve area index ≤ 0.5 cm^2/m^2) by resting echocardiogram or simultaneous pressure recordings at cardiac catheterization

- Subject was symptomatic from his/her aortic stenosis (AS), as demonstrated by New York Heart Association (NYHA) Functional Class II or greater
- The subject or the subject's legal representative had been informed of the nature of the study, agreed to its provisions and had provided written informed consent as approved by the Institutional Review Board (IRB) of the respective clinical site
- The subject and the treating physician agreed that the subject would return for all required post-procedure follow-up visits

Exclusion Criteria

- Evidence of an acute MI ≤ 30 days before the procedure
- Any percutaneous coronary or peripheral interventional procedure performed within 30 days prior to the procedure
- Blood dyscrasias as defined by: leukopenia (WBC < 1000 mm^3), thrombocytopenia (platelet count < 50,000 cells/mm^3), history of bleeding diathesis or coagulopathy
- Untreated clinically significant coronary artery disease (CAD) requiring revascularization
- Cardiogenic shock manifested by low cardiac output, vasopressor dependence, or mechanical hemodynamic support
- Need for emergency surgery for any reason
- Severe ventricular dysfunction with left ventricular ejection fraction (LVEF) < 20% as measured by resting echocardiogram
- Recent (within 6 months) cerebrovascular accident (CVA) or transient ischemic attack (TIA)
- End stage renal disease requiring chronic dialysis or creatinine clearance < 20 cc/min.
- Active Gastrointestinal (GI) bleeding within the past 3 months
- A known hypersensitivity or contraindication to any of the following which cannot be adequately pre-medicated:
  - Aspirin
  - Heparin (HIT/HITTS) and bivalirudin
  - Nitinol (titanium or nickel)
  - Ticlopidine and clopidogrel
  - Contrast media
- Ongoing sepsis, including active endocarditis
- Subject refuses a blood transfusion
- Life expectancy < 12 months due to associated non-cardiac co-morbid conditions.
- Other medical, social, or psychological conditions that in the opinion of an Investigator precludes the subject from appropriate consent
- 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)
- Concurrently participating in an investigational drug or another device study
- Symptomatic carotid or vertebral artery disease
- 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 [AS and aortic regurgitation (AR) with severity (3-4+)]
- Moderate to severe (3-4+) or severe (4+) mitral or severe (4+) tricuspid regurgitation
- Moderate to severe mitral stenosis
- Hypertrophic obstructive cardiomyopathy
- New or untreated echocardiographic evidence of intracardiac mass, thrombus or vegetation
- Severe basal septal hypertrophy with an outflow gradient
- Aortic root angulation (angle between plane of aortic valve annulus and horizontal plane/vertebrae) > 70° (for femoral and left subclavian/axillary access) and > 30° (for right subclavian/axillary access)
- Ascending aorta that exceeded the maximum diameter for any given native aortic annulus size
- 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

Follow-up periods were discharge or 7 days, whichever comes first, 30 days, 6 months, 12 months, and annually thereafter to a minimum of 5 years post procedure, and patients were followed for a minimum of 12 months prior to submission of the PMA.

3. Clinical Endpoints

Primary Safety and Effectiveness Endpoints

The primary endpoint of the study was to demonstrate the safety and effectiveness in transarterial delivery of the Medtronic CoreValve System (MCS), as measured by all-cause death or major stroke at 12 months, in the treatment of symptomatic severe aortic stenosis in patients necessitating aortic valve replacement, with predicted operative mortality or serious, irreversible morbidity risk ≥ 50% at 30 days (Extreme Risk). A performance goal of 43% was pre-specified for the 12-month rate of all-cause mortality or major stroke in TAVR patients with the Medtronic CoreValve System, which was based on review of literature for alternative treatments for extreme risk patients. The hypothesis for the primary endpoint was as follows:

$$H_0: \pi_{\text{MCS TAVR}} \geq 43.0\%$$
$$H_A: \pi_{\text{MCS TAVR}} < 43.0\%$$

It was also developed *a priori* that the primary endpoint would be examined for the null hypothesis for the iliofemoral study cohort only and the results of the non-iliofemoral study cohort would be reported separately using descriptive statistics. This distinction must be borne in mind when viewing the results of the non-iliofemoral study cohort presented, for convenience only, alongside those of the iliofemoral study cohort later in this summary.

Secondary Safety and Effectiveness Endpoints

This study included the following secondary safety and effectiveness endpoints:

1. Major adverse cardiovascular or cerebrovascular events (MACCE)-free survival at 30 days, 6 months, 12 months and annually thereafter up to 5 years
2. The occurrence of individual MACCE components at 30 days, 6 months, 12 months and annually thereafter up to 5 years
3. Major adverse events (MAE) at 30 days, 6 months,12 months and annually thereafter up to 5 years
4. Conduction disturbance requiring permanent pacemaker implantation (PPI) at 30 days, 6 months, 12 months and annually thereafter up to 5 years
5. Change in NYHA class from baseline at 30 days, 6 months, 12 months and annually thereafter up to 5 years.
6. Change in distance walked during 6-minute walk test (6MWT) from baseline to 30 days and baseline to 12 months
7. Ratio of days alive out of hospital versus total days alive assessed at 12 months follow-up
8. Quality of life (QoL) change from baseline at 30 days, 6 months, 12 months and annually thereafter up to 5 years
9. Echocardiographic assessment of valve performance at discharge, 30 days, 6 months, 12 months and annually thereafter up to 5 years using the following measures:
    - Transvalvular mean gradient
    - Effective orifice area (EOA)
    - Degree of aortic regurgitation (AR, transvalvular and paravalvular)
10. Aortic valve disease hospitalization
11. Cardiovascular deaths and valve-related deaths
12. Strokes
13. Index procedure related MAEs
14. Length of index procedure hospital stay
15. Device success defined as follows:
    - Successful vascular access, delivery and deployment of the device, and successful retrieval of the delivery system
    - Correct position of the device in the proper anatomical location (placement in the annulus with no impedance on device function)

- Intended performance of the prosthetic valve (aortic valve area > 1.2 cm^2 for 26, 29 and 31 mm valves, ≥ 0.9 cm^2 for 23 mm valve (by echocardiography using the continuity equation) and mean aortic valve gradient < 20 mmHg or peak velocity < 3 m/sec, without moderate or severe prosthetic valve AR)
    - assessed acutely in a resting state, either within 24-48 hours after the index procedure or before hospital discharge
- Only one valve implanted in the proper anatomical location

16. Procedural success, defined as device success and absence of in-hospital MACCE
17. Evidence of prosthetic valve dysfunction at 30 days, 6 months, 12 months and annually thereafter up to 5 years

Four (4) of the above secondary endpoints involve hierarchical hypothesis testing, which are changes from baseline to 12 months in transvalvular mean gradient, effective orifice area, NYHA classification, and KCCQ score.

B. Accountability of PMA Cohort

At the time of database lock, 458 of the 656 patients enrolled were available for the analysis at the 1 year time point. Table 8 depicts the accountability at each follow-up period for the "All Enrolled" population (see Analysis Population section for definition).

Table 8: Total Patient Accountability

Follow up Period	Variable	All Enrolled (N=656)
1 month	Expected	583
	Number withdrew	10
	Number died before visit	60
	Lost to follow up	0
	Other	3
	Visit compliance	572 (98.1%)
6 months	Expected	503
	Number withdrew	0
	Number died before visit	80
	Lost to follow up	0
	Other	0
	Visit compliance	485 (96.4%)
12 months	Expected	462
	Number withdrew	1
	Number died before visit	40
	Lost to follow up	0
	Other	0
	Visit compliance	458 (99.1%)

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for an aortic stenosis valve replacement study performed in the U.S., as shown in Table 9. A high proportion of the patients had significant co-morbidities, frailties, or disabilities. The mean age for patients participating in the trial was approximately 83 years old, and slightly less than 50% of patients were male. The mean STS score was approximately 10. Greater than 90% of all patients were in NYHA classes III or IV. Additionally, coronary artery disease was present in approximately 80% of patients, and greater than 30% of patients had previous MI. Peripheral vascular disease, chronic obstructive pulmonary disease (COPD), and home oxygen use were more prevalent in non-iliofemoral patients.

Table 9: Demographics of the Study Population (All Enrolled)

Demographic	Iliofemoral N=500	Non-Iliofemoral N=156
Age (yrs)	83.1 ± 8.6	81.6 ± 7.7
Gender (Male)	48.0% (240/500)	44.9% (70/156)
NYHA Classification		
II	8.6% (43/500)	8.3% (13/156)
III	63.6% (318/500)	66.0% (103/156)
IV	27.8% (139/500)	25.6% (40/156)
STS Score (Risk of Mortality, %)	10.3 ± 5.5	10.5 ± 5.7
Coronary Artery Disease	81.8% (409/500)	78.8% (123/156)
Previous MI	31.0% (155/500)	31.4% (49/156)
Previous Interventions		
Coronary Artery Bypass Surgery	39.0% (195/500)	41.0% (64/156)
Percutaneous Coronary Intervention	37.4% (187/500)	30.1% (47/156)
Balloon Valvuloplasty	20.4% (102/500)	22.4% (35/156)
Cerebral Vascular Disease	24.0% (119/496)	28.4% (44/155)
Prior Stroke	13.6% (68/499)	14.2% (22/155)
Peripheral Vascular Disease	36.0% (179/497)	59.0% (92/156)
Chronic Lung Disease/COPD	59.6% (298/500)	69.9% (109/156)
Home Oxygen	30.8% (154/500)	41.7% (65/156)
Creatinine Level >2 mg/dl	4.6% (23/500)	2.6% (4/156)
Atrial Fibrillation / Atrial Flutter	47.4% (236/498)	48.4% (75/155)
Pre-Existing Permanent Pacemaker Placement / ICD	25.8% (129/500)	24.4% (38/156)
Aorta Calcification[1]: Severe/Porcelain		
Severe	16.6% (83/499)	17.5% (27/154)
Porcelain	5.2% (26/499)	7.8% (12/154)
Chest Wall Deformity	5.6% (28/500)	1.9% (3/156)
Hostile Mediastinum	12.0% (60/499)	9.0% (14/156)
Cirrhosis of the Liver	3.0% (15/500)	1.3% (2/156)
Wheelchair Bound	16.6% (83/500)	12.2% (19/156)
Echocardiographic Findings		
Ejection Fraction (visual estimate, %)	53.2 ± 13.6 (498)	54.3 ± 15.3 (156)
Aortic Valve Area (cm^2)	0.67 ± 0.25 (485)	0.62 ± 0.23 (153)

Demographic	Iliofemoral N=500	Non-Iliofemoral N=156
Mean Gradient across Aortic Valve (MGV_2, mmHg)	47.72 ± 13.53 (498)	49.67 ± 16.85 (156)
Mitral Regurgitation: Moderate/Severe	24.2% (120/496)	23.2% (36/155)
[1]. Aorta Calcification is measured on screening CT Angiogram Plus-minus values present the mean ± standard deviation.		

D. Safety and Effectiveness Results

1. Analysis Population

The primary analysis was the "Attempted Implant" analysis. An attempted implant procedure was defined as when the patient 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.

The "Attempted Implant" iliofemoral population (n=489) included all patients who were implanted via iliofemoral, had an attempted implant via iliofemoral, or were enrolled iliofemoral and no access site was reported during the attempted procedure (i.e., the patient had an attempted implant, but the procedure was aborted prior to obtaining access site).

The "Attempted Implant" non-iliofemoral population (n=150) included all patients who were implanted via non-iliofemoral, had an attempted implant via non-iliofemoral, or were enrolled non-iliofemoral and no access site was reported during the attempted procedure.

The "Implanted" population consisted of all "Attempted Implant" patients who were actually implanted with the CoreValve device. To be considered implanted, the patient's device disposition form must have shown at least one device with a final disposition of "Implanted." There were a total of 486 and 148 "Implanted" patients in the iliofemoral and non-iliofemoral cohorts, respectively.

The "All Enrolled" population consisted of all patients who were enrolled, regardless of whether a CoreValve device was implanted. The number of "All Enrolled" iliofemoral and non-iliofemoral patients was 500 and 156, respectively.

2. Primary Safety and Effectiveness Endpoint

The primary endpoint of all-cause mortality or major stroke at 12 months includes all deaths (cardiovascular and non-cardiovascular) from any cause after a valve intervention. Major stroke is a stroke causing clinically important disability (defined as a Modified Rankin score ≥ 2 at 90 days). Figure 5 and Table 10 show K-M rates of all-cause mortality or major stroke in the attempted implant population for the iliofemoral patients up to 12 months follow-up, which were 9.8% at 1 month, 19.8%

at 6 months and 26.0% at 12 months (Primary Endpoint). The primary endpoint was therefore met and the null hypothesis for the Primary Endpoint (K-M Rate ≥ 43%) rejected.

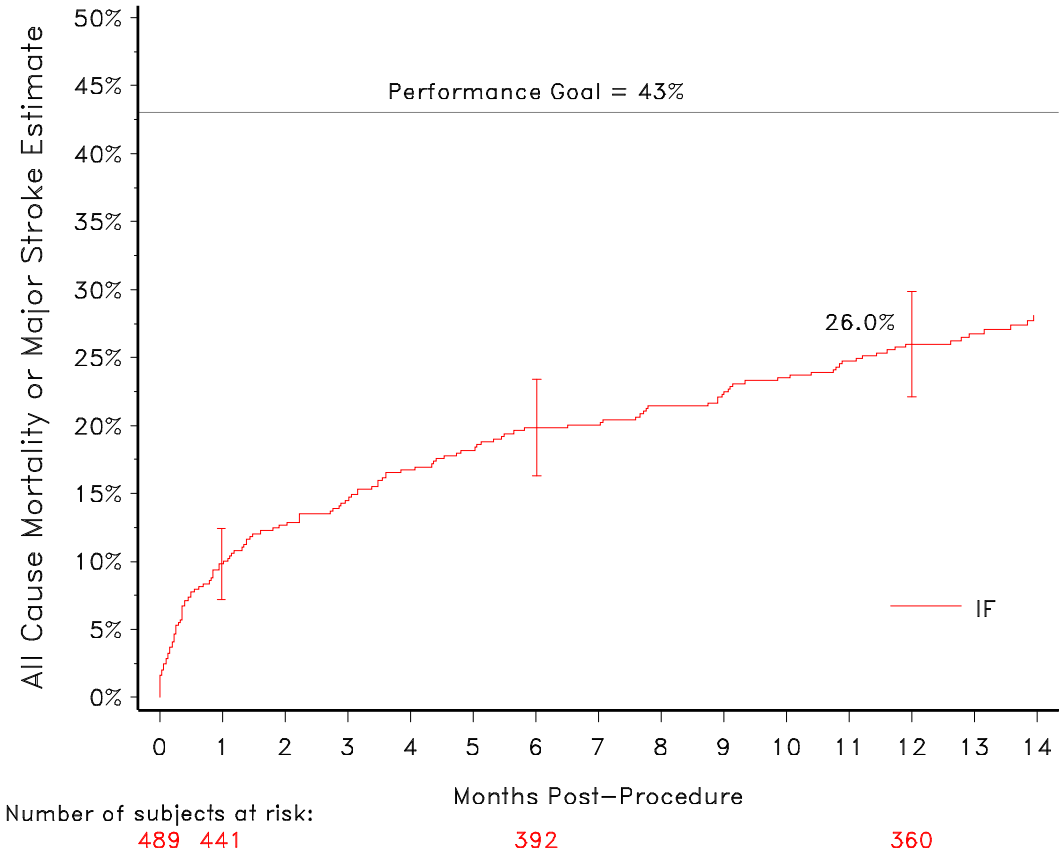


Figure 5: Primary Endpoint: All-Cause Mortality or Major Stroke Kaplan-Meier Event Rate — Iliofemoral Attempted Implant

Table 10: Primary Endpoint: All-Cause Mortality or Major Stroke – Iliofemoral Attempted Implant

Interval Post Procedure (months)*	Attempted Implant N=489			
	0	1	6	12
# at start of interval	489	441	392	360
# events in interval	48	49	30	47
# event cumulative	48	97	127	174
K-M Event Rate	1.6	9.8	19.8	26.0
Lower 95% CI	0.5	7.2	16.3	22.1
Upper 95% CI	2.8	12.5	23.4	29.9
*0 = 0-29 days, 1 = 30-182 days, 6 = 183-364 days, 12 = ≥365 days. Cumulative probability of event estimate is based on the Kaplan-Meier method.				

3. Key Secondary Safety and Effectiveness Endpoints

Adverse Events that Occurred in the PMA Clinical Study

Table 11 and Table 12 provide a summary of the adverse events (AEs) that occurred in this study for the iliofemoral and non-iliofemoral cohorts, respectively.

Table 11: CEC Adjudicated Adverse Event Summary – Iliofemoral Attempted Implant

	Iliofemoral N=489								
Event	0-30 Days			0-6 Months			0-12 Months		
	# Events	# Patients	K-M Rate (%)	# Events	# Patients	K-M Rate (%)	# Events	# Patients	K-M Rate (%)
All-Cause Mortality or Major Stroke	52	48	9.8%	106	97	19.8%	139	127	26.0%
All-Cause Mortality	41	41	8.4%	91	91	18.6%	119	119	24.3%
Cardiovascular	41	41	8.4%	73	73	15.0%	88	88	18.3%
Valve-Related[1]	12	12	2.5%	19	19	4.1%	23	23	5.1%
Neurological Events	80	74	15.5%	120	101	21.5%	141	117	25.3%
All Stroke	20	19	4.0%	26	24	5.2%	34	31	7.0%
Major Stroke	11	11	2.3%	15	15	3.2%	20	19	4.3%
Bleed	191	179	36.7%	225	200	41.4%	236	206	42.8%
Life Threatening or Disabling	63	62	12.7%	81	77	16.1%	88	83	17.6%
Major Bleed	128	121	24.9%	144	133	27.7%	148	136	28.5%
Major Vascular Complication	44	40	8.2%	45	41	8.4%	45	41	8.4%
Acute Kidney Injury	57	57	11.8%	57	57	11.8%	57	57	11.8%
MI	6	6	1.2%	7	7	1.5%	9	9	2.0%
MACCE[2]	72	60	12.3%	131	110	22.5%	171	143	29.2%
Cardiogenic Shock	13	13	2.7%	13	13	2.7%	13	13	2.7%
Cardiogenic Tamponade	9	9	1.9%	10	10	2.1%	10	10	2.1%
Reintervention	5	5	1.1%	7	7	1.5%	9	8	1.8%
Surgical	0	0	0.0%	0	0	0.0%	0	0	0.0%
Percutaneous	5	5	1.1%	7	7	1.5%	9	8	1.8%
Valve Endocarditis	0	0	0.0%	1	1	0.2%	5	5	1.3%
Valve Thrombosis	0	0	0.0%	0	0	0.0%	0	0	0.0%
Valve Embolism/ Device Migration	0	0	0.0%	1	1	0.2%	1	1	0.2%

[1] Valve-related death is any death caused by prosthetic valve dysfunction, valve thrombosis, embolism, bleeding event, or implanted valve endocarditis or related to reintervention on the operated valve.

[2] MACCE includes all-cause death, myocardial infarction (MI), all stroke, and reintervention.

Table 12: CEC Adjudicated Adverse Event Summary – Non-Iliofemoral Attempted Implant

	Non-Iliofemoral N=150								
Event	0-30 Days			0-6 Months			0-12 Months		
	# Events	# Patients	K-M Rate (%)	# Events	# Patients	K-M Rate (%)	# Events	# Patients	K-M Rate (%)
All-Cause Mortality or Major Stroke	28	23	15.3%	56	48	32.0%	67	59	39.4%
All-Cause Mortality	17	17	11.3%	43	43	28.7%	54	54	36.0%
Cardiovascular	17	17	11.3%	35	35	23.6%	42	42	28.8%
Valve-Related[1]	4	4	2.8%	6	6	4.5%	7	7	5.4%
Neurological Events	36	32	21.8%	43	38	26.6%	46	40	28.5%
All Stroke	14	13	8.8%	18	17	12.0%	19	18	13.0%
Major Stroke	11	11	7.5%	13	13	9.1%	13	13	9.1%
Bleed	92	87	58.3%	104	94	63.5%	106	96	65.1%
Life Threatening or Disabling	36	36	24.2%	42	42	28.5%	43	43	29.4%
Major Bleed	56	55	37.1%	62	59	40.8%	63	60	41.9%
Major Vascular Complication	13	13	8.7%	14	14	9.5%	14	14	9.5%
Acute Kidney Injury	21	21	14.2%	21	21	14.2%	21	21	14.2%
MI	3	3	2.1%	3	3	2.1%	3	3	2.1%
MACCE[2]	34	26	17.3%	64	52	34.7%	77	62	41.4%
Cardiogenic Shock	9	9	6.0%	9	9	6.0%	9	9	6.0%
Cardiogenic Tamponade	2	2	1.3%	2	2	1.3%	2	2	1.3%
Reintervention	0	0	0.0%	0	0	0.0%	1	1	1.0%
Surgical	0	0	0.0%	0	0	0.0%	0	0	0.0%
Percutaneous	0	0	0.0%	0	0	0.0%	1	1	1.0%
Valve Endocarditis	1	1	0.7%	1	1	0.7%	2	2	1.7%
Valve Thrombosis	0	0	0.0%	1	1	0.8%	2	1	0.8%
Valve Embolism/ Device Migration	0	0	0.0%	0	0	0.0%	0	0	0.0%

[1] Valve-related death is any death caused by prosthetic valve dysfunction, valve thrombosis, embolism, bleeding event, or implanted valve endocarditis or related to reintervention on the operated valve.
[2] MACCE includes all-cause death, myocardial infarction (MI), all stroke, and reintervention.

Neurological Events

Table 13 and Table 14 provide a summary of the neurological events that occurred in this study for the iliofemoral and non-iliofemoral cohorts. Stroke and TIA were defined according to the Valve Academic Research Consortium I (VARC-I) definitions [1].

Table 13: CEC Adjudicated Neurological Events – Iliofemoral Attempted Implant

	Attempted Implant N=489								
Event	0-30 Days			0-6 Months			0-12 Months		
	# Events	# Patients	K-M Rate (%)	# Events	# Patients	K-M Rate (%)	# Events	# Patients	K-M Rate (%)
All Stroke	20	19	4.0%	26	24	5.2%	34	31	7.0%
Major Stroke	11	11	2.3%	15	15	3.2%	20	19	4.3%
Ischemic	9	9	1.9%	13	13	2.8%	17	16	3.6%
Hemorrhagic	2	2	0.4%	2	2	0.4%	3	3	0.7%
Minor Stroke	9	9	1.9%	11	11	2.4%	14	14	3.2%
Ischemic	9	9	1.9%	11	11	2.4%	14	14	3.2%
Hemorrhagic	0	0	0.0%	0	0	0.0%	0	0	0.0%
TIA	3	3	0.6%	4	4	0.9%	5	5	1.1%
Intracranial Hemorrhage	1	1	0.2%	2	2	0.4%	2	2	0.4%

Table 14: CEC Adjudicated Neurological Events – Non-Iliofemoral Attempted Implant

	Attempted Implant N=150								
Event	0-30 Days			0-6 Months			0-12 Months		
	# Events	# Patients	K-M Rate (%)	# Events	# Patients	K-M Rate (%)	# Events	# Patients	K-M Rate (%)
All Stroke	14	13	8.8%	18	17	12.0%	19	18	13.0%
Major Stroke	11	11	7.5%	13	13	9.1%	13	13	9.1%
Ischemic	11	11	7.5%	12	12	8.3%	12	12	8.3%
Hemorrhagic	0	0	0.0%	1	1	0.9%	1	1	0.9%
Minor Stroke	3	3	2.1%	5	5	3.7%	6	6	4.7%
Ischemic	3	3	2.1%	4	4	2.9%	5	5	3.8%
Hemorrhagic	0	0	0.0%	1	1	0.8%	1	1	0.8%
TIA	2	2	1.4%	3	3	2.3%	3	3	2.3%
Intracranial Hemorrhage	0	0	0.0%	1	1	0.9%	1	1	0.9%

Echocardiographic Assessment of Valve Performance (Total Aortic Regurgitation)

Table 15 summarizes the total aortic regurgitation (AR) severity over time in the iliofemoral and non-iliofemoral cohorts.

Table 15: Total Aortic Regurgitation by Visit – Implanted Population

	Screening/ Baseline	1 month	6 months	12 months
Iliofemoral (N=486)				
None	11.7% (56/477)	9.1% (38/419)	19.9% (73/367)	21.3% (70/329)
Trivial	36.5% (174/477)	32.7% (137/419)	33.5% (123/367)	40.7% (134/329)
Mild	43.0% (205/477)	43.0% (180/419)	36.5% (134/367)	31.6% (104/329)
Moderate	8.6% (41/477)	14.1% (59/419)	9.8% (36/367)	6.4% (21/329)
Severe	0.2% (1/477)	1.2% (5/419)	0.3% (1/367)	0.0% (0/329)
Non-Iliofemoral (N=148)				
None	12.2% (18/147)	19.0% (23/121)	33.3% (32/96)	39.0% (32/82)
Trivial	28.6% (42/147)	33.9% (41/121)	27.1% (26/96)	36.6% (30/82)
Mild	48.3% (71/147)	34.7% (42/121)	35.4% (34/96)	20.7% (17/82)
Moderate	10.9% (16/147)	10.7% (13/121)	4.2% (4/96)	2.4% (2/82)
Severe	0.0% (0/147)	1.7% (2/121)	0.0% (0/96)	1.2% (1/82)

Echocardiographic Assessment of Valve Performance (Effective Orifice Area (EOA) and Mean Gradient)

The effective orifice area (EOA) and mean gradient values obtained over time for the iliofemoral and non-iliofemoral patients in the Implanted population are shown in Table 16 and Table 17, respectively.

Table 16: Effective Orifice Area (cm^2) By Visit (Core Lab) –Implanted Population

	Baseline	1 month	12 months
Iliofemoral	0.73 ± 0.23 (389)	1.86 ± 0.56 (386)	1.88 ± 0.54 (307)
Non-Iliofemoral	0.72 ± 0.27 (129)	1.82 ± 0.64 (114)	1.85 ± 0.51 (74)
Plus-minus values present the mean ± standard deviation.			

Table 17: Mean Gradient (mmHg) By Visit (Core Lab) –Implanted Population

	Baseline	1 month	12 months
Iliofemoral	47.3 ± 14.6 (481)	8.7 ± 4.2 (418)	8.9 ± 4.1 (330)
Non-Iliofemoral	49.5 ± 17.1 (143)	9.7 ± 5.8 (126)	9.5 ± 5.7 (83)
Plus-minus values present the mean ± standard deviation.			

Conduction Disturbance Requiring Permanent Pacemaker Implantation

Table 18 presents the pacemaker implantation rate for the iliofemoral and non-iliofemoral Attempted Implant cohorts.

Table 18: Conduction Disturbance Requiring Pacemaker – Attempted Implant

	Iliofemoral N=489		Non-Iliofemoral N=150	
	# of Patients	K-M Event Rate (%)	# of Patients	K-M Event Rate (%)
New Permanent Pacemaker Implant[1]				
0-30 Days	104	21.6%	24	16.4%
0-12 Months	123	26.2%	30	21.5%
Permanent Pacemaker Implant[2]				
0-30 Days	104	29.4%	24	22.0%
0-12 Months	121	34.9%	30	28.8%

[1] Patients with pacemaker or ICD at baseline are included in the denominator.

[2] Patients with pacemaker or ICD at baseline are excluded from the numerator and denominator. Note 2 patients with baseline pacemaker/ICD, received new pacemaker/ICD between 31-365 days.

Ratio of Days Alive out of Hospital versus Total Days Alive

The total hospital days through 12 months (mean ± SD), including the days in hospital for the index procedure when the CoreValve was implanted or attempted, were 14.4 ± 15.1 days and 16.7 ± 13.0 days for the iliofemoral and non-iliofemoral cohorts, respectively. The ratio of days alive out of hospital versus total days alive assessed at 12 months was 0.86 ± 0.27 and 0.80 ± 0.31 for the iliofemoral and non-iliofemoral cohorts, respectively. The ratio of days alive is interpreted as on average subjects spent 86% of days alive after procedure out of the hospital.

New York Heart Association (NYHA) Functional Class

An evaluation of cardiac symptom severity based on NYHA classification was conducted at several evaluation time points through the first year of follow-up. Data at baseline and 1 year are presented in Table 19 for the iliofemoral and non-iliofemoral cohorts.

Table 19: NYHA Classification By Visit – Attempted Implant

NYHA Classification	Iliofemoral N=489	Non-Iliofemoral N=150
Baseline		
NYHA I	0.0% (0/485)	0.0% (0/148)
NYHA II	8.7% (42/485)	8.1% (12/148)
NYHA III	64.7% (314/485)	70.3% (104/148)
NYHA IV	26.6% (129/485)	21.6% (32/148)
Died prior to visit	0.0% (0/485)	0.0% (0/148)
Exit prior to visit	0	0
Visit occurred but NYHA not obtained	4	2

NYHA Classification	Iliofemoral N=489	Non-Iliofemoral N=150
Visit missed	0	0
12 Month		
NYHA I	43.3% (200/462)	28.4% (40/141)
NYHA II	24.0% (111/462)	24.1% (34/141)
NYHA III	5.4% (25/462)	8.5% (12/141)
NYHA IV	1.1% (5/462)	0.0% (0/141)
Died prior to visit	26.2% (121/462)	39.0% (55/141)
Exit prior to visit	1	0
Visit occurred but NYHA not obtained	21	8
Visit missed	5	1

Quality of Life (QoL) Change

The QoL changes from baseline at 30 days and 12 months were evaluated using the Kansas City Cardiomyopathy Questionnaire (KCCQ), the QualityMetric's SF-12v2® Health Survey (SF12), and the EuroQoL (EQ-5D), as shown in Table 20 and Table 21 for the iliofemoral and non-iliofemoral cohorts, respectively.

The KCCQ is a validated self-administered 23-item questionnaire that quantifies physical limitations, symptoms, self-effectiveness, social interference and quality of life. These individual scales are incorporated into an Overall Summary Score which combines the domains of physical limitation, symptoms, QoL, and social limitation with values ranging from 0-100; higher scores indicate lesser symptoms and better quality of life. Previous studies have suggested that KCCQ Overall Summary scores correlate roughly with New York Heart Association Functional Class as follows: Class I ≈ KCCQ Summary Score 75-100; Class II ≈ 60-74; Class III ≈ 45-59; and Class IV ≈ 0-44. In addition, there is a Clinical Summary Score that combines the domains of physical limitation and symptoms.

SF12 is a shorter version of the SF-36v2® Health Survey that uses 12 questions to measure functional health and well-being from the patient's point of view and is generally reported in two summary scores which evaluate physical (the SF-12 Physical Summary Score) and mental (the SF-12 Mental Summary Score) health. Values range from 0-100; higher scores indicate better functional health and well-being.

The EQ-5D is a measure of self-reported health outcomes that is applicable to a wide range of health conditions and treatments. It consists of 2 parts: a descriptive system (Part I) and a visual analogue scale (Part II). Part I of the scale consists of 5 single-item dimensions including: mobility, self care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has a 3 point response scale designed to indicate the level of the problem. The overall EQ-5D score from Part is evaluated on a scale where 0.0 = death and 1.0 = perfect health. Part II uses a vertical graduated visual analogue scale (thermometer) to measure health status, ranging from worst imaginable health state to best imaginable health state.

Table 20: Quality of Life – Iliofemoral Attempted Implant

	Baseline	1 month	12 months
KCCQ			
Overall Summary Score	37.9 ± 22.1 (454)	62.3 ± 25.5 (266)	68.8 ± 23.6 (287)
Change from Baseline	--	24.2 ± 28.9 (260)	27.9 ± 27.1 (265)
Clinical Summary Score	42.0 ± 22.4 (454)	62.3 ± 24.9 (266)	66.3 ± 23.4 (287)
Change from Baseline	--	20.2 ± 28.0 (260)	20.8 ± 26.8 (265)
SF12			
Physical Component	28.5 ± 8.3 (422)	34.9 ± 10.1 (245)	34.3 ± 10.5 (259)
Change from Baseline	--	5.9 ± 10.4 (223)	5.5 ± 10.8 (229)
Mental Component	45.8 ± 12.3 (422)	49.8 ± 12.0 (245)	51.9 ± 11.8 (259)
Change from Baseline	--	3.7 ± 14.2 (223)	5.2 ± 13.7 (229)
EQ-5D	0.65 ± 0.23 (445)	0.73 ± 0.24 (261)	0.73 ± 0.21 (275)
Change from Baseline	--	0.09 ± 0.29 (252)	0.06 ± 0.25 (250)
Plus-minus values present the mean ± standard deviation.			

Table 21: Quality of Life – Non-Iliofemoral Attempted Implant

	Baseline	1 month	12 months
KCCQ			
Overall Summary Score	42.5 ± 22.3 (141)	51.0 ± 25.5 (74)	65.1 ± 22.4 (81)
Change from Baseline	--	7.9 ± 33.5 (71)	21.9 ± 26.8 (76)
Clinical Summary Score	46.7 ± 23.0 (141)	53.7 ± 24.6 (74)	65.2 ± 21.3 (81)
Change from Baseline	--	6.8 ± 32.0 (71)	18.1 ± 24.9 (76)
SF12			
Physical Component	27.9 ± 8.0 (130)	32.0 ± 9.2 (66)	34.0 ± 9.4 (80)
Change from Baseline	--	1.9 ± 10.4 (57)	4.6 ± 10.0 (72)
Mental Component	47.6 ± 12.0 (130)	45.1 ± 14.7 (66)	49.0 ± 13.3 (80)
Change from Baseline	--	-1.7 ± 16.2 (57)	2.4 ± 14.3 (72)
EQ5D	0.67 ± 0.23 (138)	0.66 ± 0.25 (72)	0.73 ± 0.20 (80)
Change from Baseline	--	-0.00 ± 0.30 (69)	0.05 ± 0.25 (74)
Plus-minus values present the mean ± standard deviation.			

Hierarchical Testing of Secondary Endpoints

Four pre-specified secondary endpoints were explored for iliofemoral patients using a hierarchical test procedure, as shown in Table 24. Change from baseline to 12 months was evaluated for measures of forward flow hemodynamic performance (EOA and mean gradient) and the improvement in these parameters was found to be statistically significant ($p<0.0001$). Similarly, improvement in NYHA functional classification was evaluated and found to be statistically significant ($p<0.0001$). The Kansas City Cardiomyopathy Questionnaire (KCCQ) was used to evaluate changes from baseline in physical limitations, symptoms, self-effectiveness, social interference and quality of life and a statistically significant improvement was identified in the overall summary score ($p<0.0001$).

Table 22: Secondary Endpoints: Hierarchical Testing – Iliofemoral Attempted Implant

Secondary Endpoint	Paired Evaluations	Average Paired Difference (12 Month – Baseline)	Hypothesis Test $H_0: \mu_{change} = 0$ $H_A: \mu_{change} \neq 0$	
			P-value	Success
#9 / Mean Gradient	326	-39.82 ± 14.83	<0.0001	PASS
#9 / EOA	245	1.16 ± 0.57	<0.0001	PASS
#5 / NYHA	338	-1.6 ± 0.9	<0.0001	PASS
#8 / KCCQ – Overall Summary Score	265	27.9 ± 27.1	<0.0001	PASS
Plus-minus values present the mean ± standard deviation.				

4. Additional Study Observations

Procedure Data

Table 25 provides a summary of the transcatheter valve implantation procedure for the iliofemoral and non-iliofemoral cohorts, respectively. Mean total time in the Catheterization Laboratory or Operating Room for patients in the iliofemoral cohort was approximately 3.5 hours while mean total procedure time (skin-to-skin) was on average slightly greater than 1 hour. Mean total time in the Catheterization Laboratory or Operating Room for the non-iliofemoral cohort was approximately 4 hours while mean total procedure time was slightly greater than 1 hour.

Table 23: TAVR Procedure Data (Attempted Implant)

	Iliofemoral N=489	Non-Iliofemoral N=150
Time to Procedure (days)	8.9 ± 12.3 (489)	10.2 ± 15.5 (150)
Total Time in Cath Lab or OR (min)	214.8 ± 64.9 (486)	258.7 ± 72.5 (148)
Total procedure time (min) (skin to skin)	66.1 ± 39.0 (484)	60.5 ± 46.5 (145)
General Anesthesia	94.4% (459/486)	99.3% (147/148)
Valve-in-Valve Procedure	2.5% (12/486)	0.7% (1/148)
Emergent Operation Due to Device or Procedure	0.0% (0/486)	0.0% (0/148)
Number of Devices Used		
0	0.6% (3/489)	1.3% (2/150)
1	93.3% (456/489)	94.7% (142/150)
2	6.1% (30/489)	4.0% (6/150)
Valve Size Implanted		
23mm	2.5% (12/486)	6.1% (9/148)
26mm	35.0% (170/486)	41.2% (61/148)
29mm	58.4% (284/486)	49.3% (73/148)
31mm	4.1% (20/486)	3.4% (5/148)
Device Success[1]	84.6% (397/469)	88.7% (125/141)

	Iliofemoral N=489	Non-Iliofemoral N=150
Procedure Success[2]	77.6% (370/477)	77.5% (110/142)

[1] Device success is defined as deployment, only 1 valve implanted, only 1 valve in correct anatomic location, EOA >1.2cm^2 for 26, 29 and 31mm and ≥ 0.9 cm^2 for 23mm, mean gradient < 20mmHg, and aortic regurgitation < moderate.

[2] Procedure success is defined as device success and absence of in-hospital MACCE.

Plus-minus values present the mean ± standard deviation.

Valve-in-Valve Experience

In the "All Enrolled" population, a total of 17 patients had more than one CoreValve device implanted. Fourteen (14) patients had a CoreValve-in-CoreValve procedure (CViCV). All of the CViCV procedures were due to device malpositioning and/or aortic insufficiency; one of these patients received valve-in-valve due to native calcification causing under-expansion. Additionally, 3 patients had a non valve-in-valve implant of a second valve.

Comparison between the Iliofemoral (IF) and Non-Iliofemoral (NIF) Cohorts

Due to heterogeneity in the MCS procedure, patient characteristics (such as anatomy access, distinguishing differences not allowing for an iliofemoral approach) and potential clinical variability and outcome, the non-iliofemoral cohort is not included in the primary analysis. To provide contextual reference for the non-iliofemoral cohort, results of the subgroup analyses by iliofemoral and non-iliofemoral access sites for the primary endpoint and the key secondary endpoints #1-3 are presented in Figure 6, Table 26, and Table 27.

The 12-month rate of all-cause mortality or major stroke for the "Attempted Implant" population of the non-iliofemoral cohort was 39.4% with an upper 95% CI of 47.2%, which was higher than that for the iliofemoral cohort. The non-iliofemoral cohort also had higher rates of MACCE, all-cause death, all-stroke, and MAE.

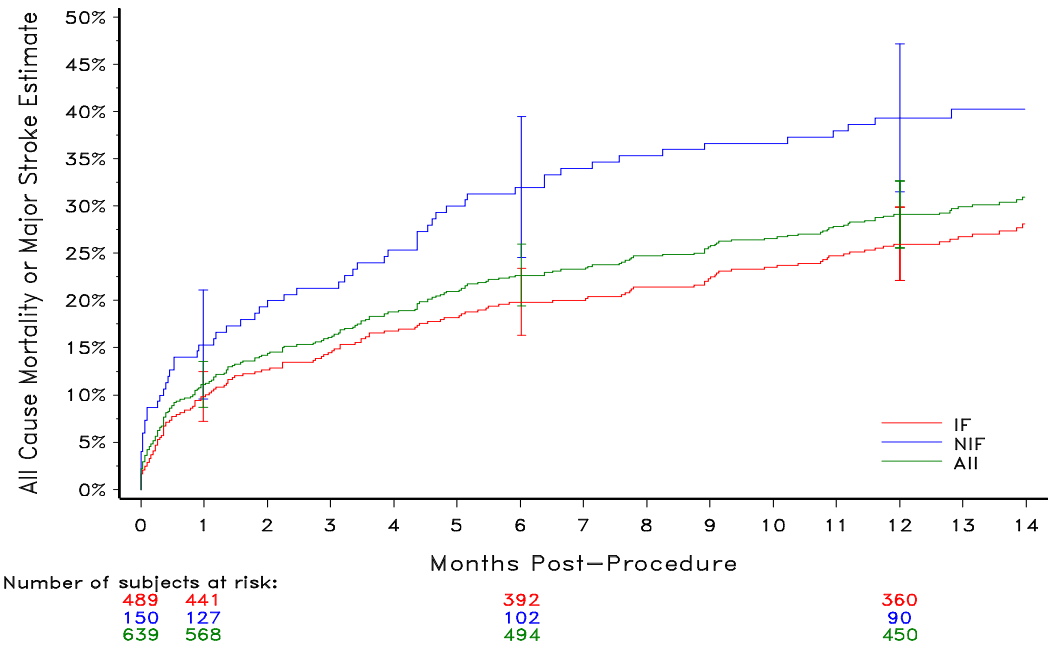


Figure 6: All-Cause Mortality or Major Stroke Kaplan-Meier Event Rate – Attempted Implant

Table 24: All-Cause Mortality or Major Stroke – Attempted Implant

Interval Post Procedure (months)*	Iliofemoral (IF) N=489				Non-Iliofemoral (NIF) N=150				All N=639			
	0	1	6	12	0	1	6	12	0	1	6	12
# at start of interval	489	441	392	360	150	127	102	90	639	568	494	450
# events in interval	48	49	30	47	23	25	11	8	71	74	41	55
# event cumulative	48	97	127	174	23	48	59	67	71	145	186	241
K-M Event Rate	1.6	9.8	19.8	26.0	4.0	15.3	32.0	39.4	2.2	11.1	22.7	29.1
Lower 95% CI	0.5	7.2	16.3	22.1	0.9	9.6	24.5	31.5	1.1	8.7	19.4	25.6
Upper 95% CI	2.8	12.5	23.4	29.9	7.1	21.1	39.5	47.2	3.3	13.5	25.9	32.6

*0 = 0-29 days, 1 = 30-182 days, 6 = 183-364 days, 12 ≥ 365.
Cumulative probability of event estimate is based on the Kaplan-Meier method.

Table 25: Kaplan-Meier Estimate of Event-Free Rates: Results by IF (N=489) and NIF (N=150) Cohorts

Secondary Objective	Event	Access Site	Days post Attempted Implant			*p*-value*
			30 days	6 months (183 days)	12 months (365 days)	
#1	MACCE	IF	87.7%	77.5%	70.8%	0.004
		NIF	82.7%	65.3%	58.6%	
#2	All-Cause Death	IF	91.6%	81.4%	75.7%	0.004
		NIF	88.7%	71.3%	64.0%	

Secondary Objective	Event	Access Site	Days post Attempted Implant			*p*-value*
			30 days	6 months (183 days)	12 months (365 days)	
	Myocardial Infarction	IF	98.8%	98.5%	98.0%	0.861
		NIF	97.9%	97.9%	97.9%	
	All Stroke	IF	96.0%	94.8%	93.0%	0.015
		NIF	91.2%	88.0%	87.0%	
	Reintervention	IF	98.9%	98.5%	98.2%	0.408
		NIF	100.0%	100.0%	99.0%	
#3	MAE	IF	46.2%	40.1%	37.2%	<0.001
		NIF	30.7%	24.0%	20.0%	
*p-value from Log-Rank test comparing freedom from curves through 365 days						

Gender Analysis

The primary endpoint and secondary endpoints #1-3 (MACCE, individual MACCE components, and MAE) were examined for differences in outcome between genders. The 1-year all-cause mortality or major stroke K-M rate was 23.1% in the female group and 29.1% in the male group, as shown in Figure 7 and Table 28. No effect of gender on the primary endpoint was found. Additionally, no effect of gender on secondary endpoints #1-3 was found, as shown in Table 29.

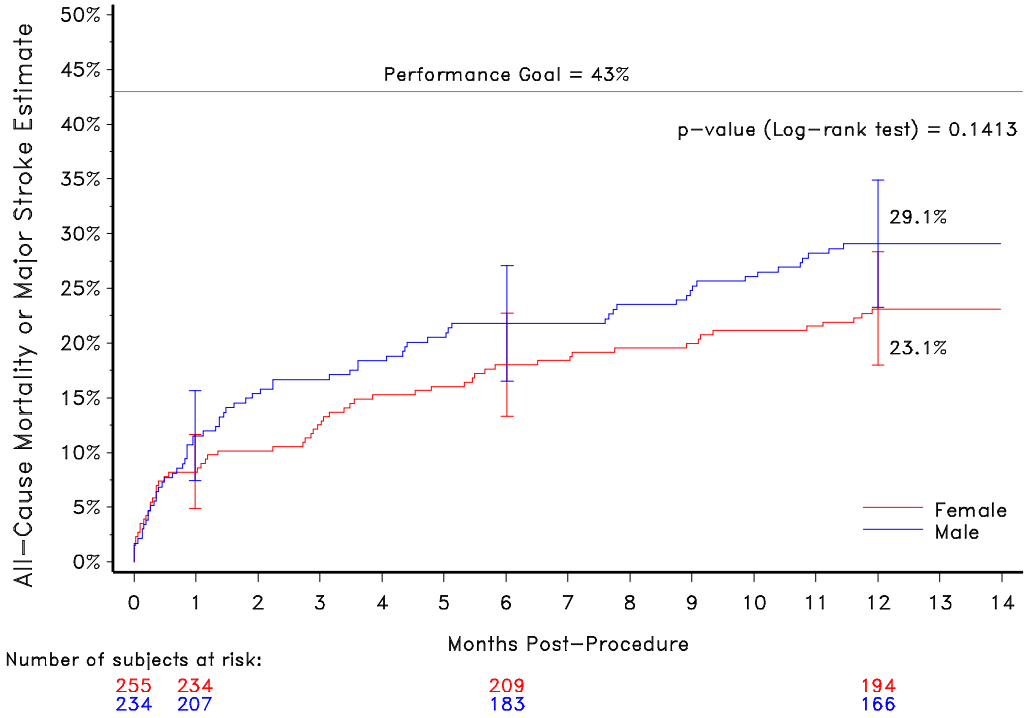


Figure 7: Primary Endpoint: All-Cause Mortality or Major Stroke by Gender – Iliofemoral Attempted Implant

Table 26: Primary Endpoint: All-Cause Mortality or Major Stroke by Gender – Iliofemoral Attempted Implant

Interval Post Procedure (months)*	Female N=255				Male N=234			
	0	1	6	12	0	1	6	12
# at start of interval	255	234	209	194	234	207	183	166
# events in interval	21	25	13	23	27	24	17	24
# event cumulative	21	46	59	82	27	51	68	92
K-M Free From Event	1.6	8.2	18.0	23.1	1.7	11.5	21.8	29.1
Lower 95% CI	0.0	4.9	13.3	18.0	0.0	7.4	16.5	23.2
Upper 95% CI	3.1	11.6	22.8	28.3	3.4	15.6	27.1	34.9

*0 = 0-29 days, 1 = 30-182 days, 6 = 183-364 days, 12 = ≥365 days.
Cumulative probability of event estimate is based on the Kaplan-Meier method.

Table 27: Kaplan-Meier Estimate of Event-Free Rates: Results by Female (N=255) and Male (N=234) Cohorts

Secondary Endpoint	Event	Access Site	Days post Attempted Implant			*p*-value*
			30 days	6 months (183 days)	12 months (365 days)	
#1	MACCE	Female	90.2%	80.4%	74.5%	0.0521
		Male	85.0%	74.4%	66.7%	
#2	All-Cause Death	Female	93.7%	83.5%	78.8%	0.0855
		Male	89.3%	79.1%	72.2%	
	Myocardial Infarction	Female	99.6%	99.6%	98.7%	0.2460
		Male	97.9%	97.4%	97.4%	
	All Stroke	Female	95.2%	94.3%	92.4%	0.5562
		Male	97.0%	95.4%	93.8%	
	Reintervention	Female	100%	100%	99.5%	0.0219
		Male	97.8%	96.8%	96.8%	
#3	MAE	Female	43.1%	38.4%	35.3%	0.1830
		Male	49.6%	41.9%	39.3%	

**p*-value from Log-Rank test comparing freedom from curves through 365 days

Mortality or Major Stroke Stratified by STS Score

A *post hoc* analysis was conducted to compare the Kaplan-Meier (K-M) event rates for all-cause mortality or major stroke between Attempted Implant iliofemoral patients in different STS score categories (<5%, 5-15%, >15%), as shown in Figure 8 and Table 30. The majority of patients (n=341) had an STS score between 5-15 and the K-M rate of all-cause mortality or major stroke for these patients was similar to that for patients with an STS score of <5 (23.5% and 25.0%, respectively, at 12 months). Patients with an STS score of >15 had numerically higher event rates for all-cause mortality or major stroke at both 1 month (15.5%) and 12 months (36.9%) follow-up, indicating that very high STS scores did show predictive value in this patient population. The Log-rank p-value for the K-M analysis was 0.042, indicating a statistically significant difference in the event rate between the STS cohorts.

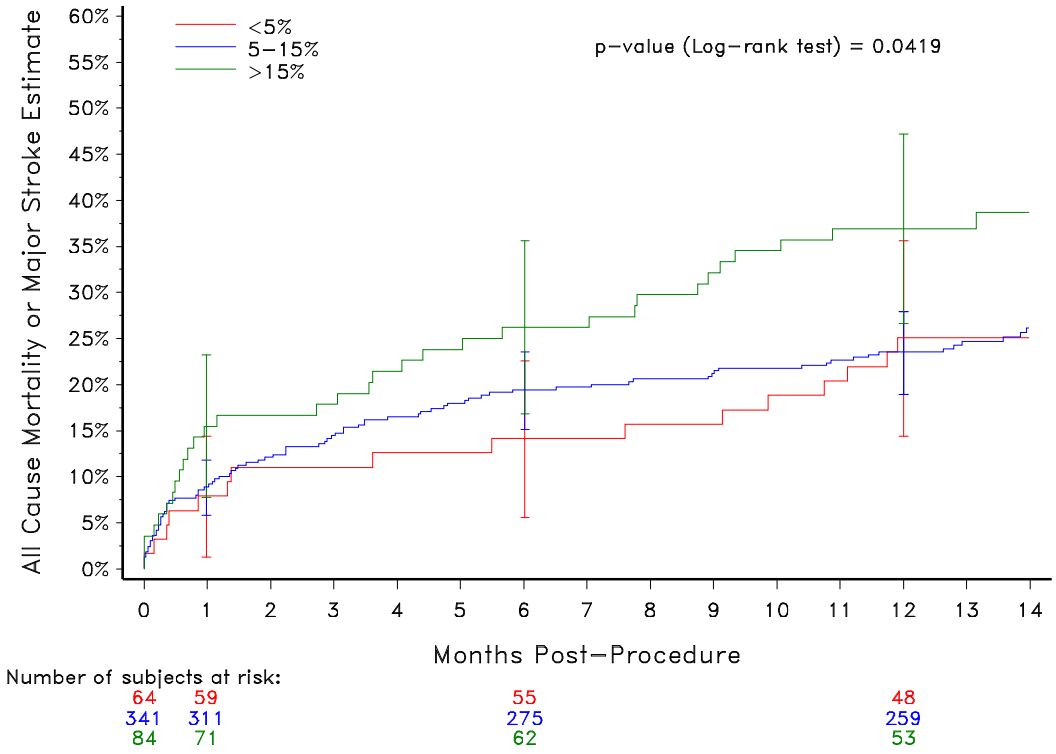


Figure 8: Primary Endpoint: All-Cause Mortality or Major Stroke Stratified by STS Score – Attempted Implant Iliofemoral

Table 28: Primary Endpoint: All-Cause Mortality or Major Stroke Stratified by STS Score – Iliofemoral Attempted Implant

Interval Post Procedure	STS < 5% N=64				STS 5 - 15% N=341				STS > 15% N=84			
(months)*	0	1	6	12	0	1	6	12	0	1	6	12
# at start of interval	64	59	55	48	341	311	275	259	84	71	62	53
# events in interval	5	4	7	5	30	36	14	34	13	9	9	8
# event cumulative	5	9	16	21	30	66	80	114	13	22	31	39
Event Rate Estimate	1.6	7.8	14.1	25.0	1.2	8.8	19.4	23.5	3.6	15.5	26.2	36.9
Lower 95% CI	0.0	1.2	5.5	14.4	0.0	5.8	15.2	19.0	0.0	7.7	16.8	26.6
Upper 95% CI	4.6	14.4	22.6	35.6	2.3	11.8	23.5	28.0	7.5	23.2	35.6	47.2

*0 = 0-29 days, 1 = 30-182 days, 6 = 183-364 days, 12 = ≥365 days.
Cumulative probability of event estimate at the end of the interval (Pc) based on the Kaplan-Meier method.

Post-Implant Aortic Regurgitation and All-Cause Mortality

A *post hoc* sub-group analysis was performed for iliofemoral patients of the Implanted population to investigate the relationship between all-cause mortality and severity of aortic regurgitation at discharge (7 days post procedure or discharge, whichever is first). Four sub-groups of iliofemoral patients with none/trace, mild, moderate and severe total aortic regurgitation as assessed at discharge were analyzed. The results from the analysis are shown in Figure 9 and Table 31.

All-cause mortality at 12 months was highest in the patients with severe aortic regurgitation (87.5%, note that only 8 patients were included in this subgroup) and was lowest in the patients with none/trace aortic regurgitation (17.8 %). All-cause mortality in patients with mild aortic regurgitation (23.9 %) was similar to freedom from mortality in patients with moderate aortic regurgitation (22.2%). These data indicate that aortic regurgitation up to mild in severity was not a strong driver of mortality in this study.

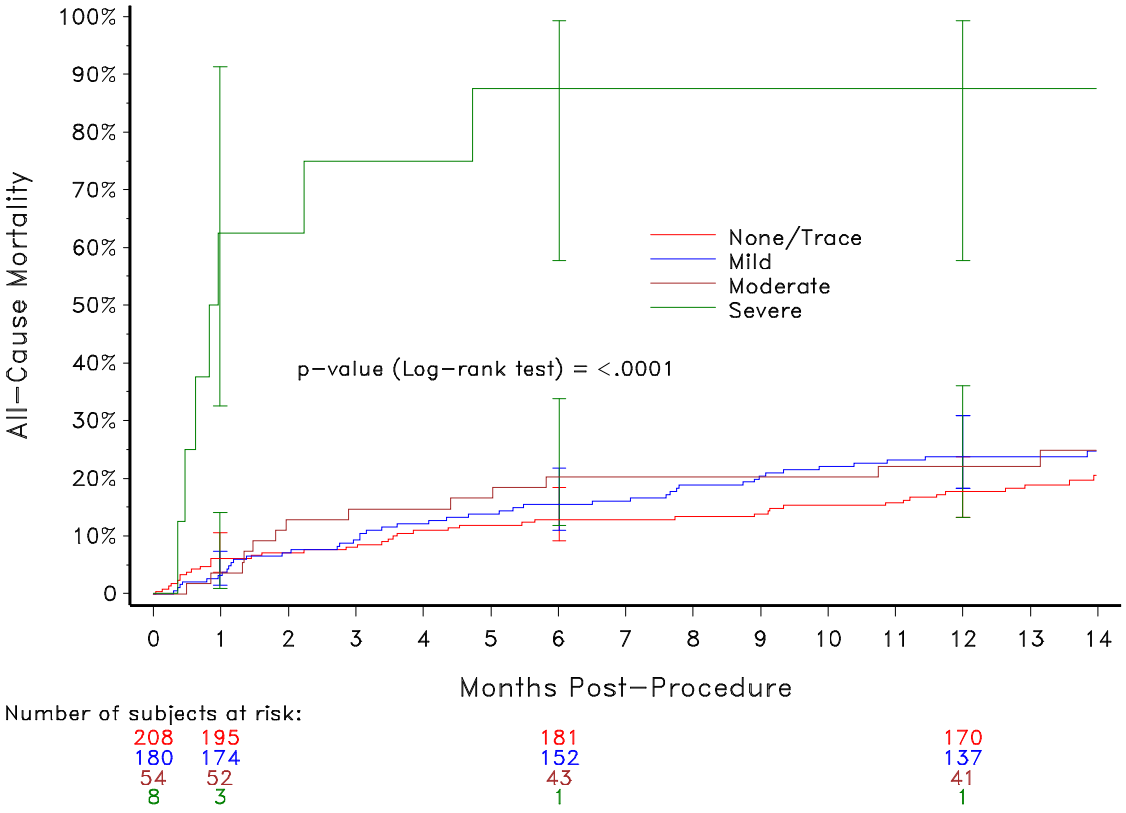


Figure 9: All Cause Mortality Rate by Total Aortic Regurgitation at Discharge – Iliofemoral Implanted

Table 29: All Cause Mortality by Total Aortic Regurgitation at Discharge – Iliofemoral Implanted

Interval Post Procedure (months)*	None/Trace N=208				Mild N=180				Moderate N=54				Severe N=8			
	0	1	6	12	0	1	6	12	0	1	6	12	0	1	6	12
# at start of interval	208	195	181	170	180	174	152	137	54	52	43	41	8	3	1	1
# events in interval	13	14	10	19	6	22	15	21	2	9	1	6	5	2	0	0
# event cumulative	13	27	37	56	6	28	43	64	2	11	12	18	5	7	7	7
Event Rate Estimate	0.0	6.2	13.0	17.8	0.0	3.3	15.6	23.9	0.0	3.7	20.4	22.2	0.0	62.5	87.5	87.5
Lower 95% CI	NA	3.7	9.1	13.2	NA	1.5	11.0	18.3	NA	0.9	11.8	13.2	NA	32.6	57.7	57.7
Upper 95% CI	NA	10.5	18.4	23.7	NA	7.3	21.7	30.8	NA	14.0	33.8	36.0	NA	91.3	99.3	99.3

*0 = 0-29 days, 1 = 30-182 days, 6 = 183-364 days, 12 = ≥365 days.
Cumulative probability of event estimate at the end of the interval (Pc) based on the Kaplan-Meier method.

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 329 investigators, of which none were full-time or part-time employees of the sponsor and 18 had disclosable financial interests/arrangements 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: 9
- Significant payment of other sorts: 7
- 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 Systems Device panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XII. CONCLUSIONS DRAWN FROM THE PRECLINICAL AND CLINICAL STUDIES

A. Safety Conclusions

The results from the pre-clinical laboratory studies performed on the Medtronic CoreValve System for biocompatibility, hydrodynamic performance, and structural integrity demonstrate that this device is suitable for long-term implant. The clinical study met the pre-specified performance goal for all-cause mortality or major stroke at 12 months. There was a mortality benefit in the patient population studied, but a relatively higher risk of conduction disturbance requiring permanent pacemaker implantation. In addition, the clinical data suggest that there appears to be a higher health risk in these extreme risk patients who present with more significant additional comorbidities that are indicated by an STS risk score > 15% and those patients whose vasculature is not able to accommodate iliofemoral access.

B. Effectiveness Conclusions

The preclinical data demonstrate that the valve performs acceptably. In the clinical study, there was an improvement in the hemodynamic parameters (EOA and mean gradient), as well as subjective parameters such as the NYHA class and Quality of Life parameters evaluated. The valve performs as intended regardless of the arterial route of delivery.

C. Benefit-Risk Conclusions

The probable benefits of the device are based on data collected in a clinical study conducted to support PMA approval as described above. The benefits of the Medtronic CoreValve System include improved valve hemodynamic performance, improved functional status as measured by the NYHA classification, improved QoL, and reduced mortality.

The probable risks of the Medtronic CoreValve System include procedure related complications such as death, stroke, major vascular complications, bleeding, conduction disturbance, and acute kidney injury, as summarized in Table 11 and Table 12.

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

D. Overall Conclusions

The preclinical and clinical studies submitted in the PMA application provide reasonable assurance that the Medtronic CoreValve System, available in valve sizes 23, 26, 29 and 31 mm, are safe and effective for the replacement of native aortic valves in symptomatic severe aortic stenosis patients who are deemed to be at extreme surgical risk, defined as 50% or greater 30-day risk of operative mortality or serious, irreversible comorbidity.

XIII. CDRH DECISION

CDRH issued an approval order on January 17, 2014. The final conditions of approval cited in the approval order are described below.

The applicant must conduct three post-approval studies (PAS):

1. *PAS 1 Continued follow-up of the IDE pivotal cohort (extreme risk patients):* This study should be conducted per protocol in PAS 1 Addendum (Version 1) to Medtronic CoreValve U.S. Pivotal Trial (Extreme Risk Patients) Clinical Investigational Plan (Version 12) as submitted to FDA by email on December 13, 2013. The study will consist of all IDE patients currently enrolled and alive who received the Medtronic CoreValve® System (MCS).

   The objective of this PAS is to characterize the clinical outcomes at year 2 and annually through 5 years post-procedure. The safety and effectiveness endpoints listed in the protocol include major adverse cardiovascular and cerebrovascular events (MACCE), change in functional status and quality of life, conduction disturbance requiring permanent pacemaker implantation, echocardiographic assessment, and valve dysfunction. All available patients in the IDE study (656 iliofemoral and non-iliofemoral and 63 roll-in patients) in all sites (41) will be followed annually through 5 years.

2. *PAS 2 Continued follow-up of continued access protocol (CAP) cohort (extreme risk patients):* This study should be conducted per PAS 2 Addendum (Version 1) to Medtronic CoreValve Continued Access Study Clinical Investigational Plan (Version 5) as submitted to FDA by email on December 13, 2013. The study will consist of all CAP patients currently enrolled and alive who received the Medtronic CoreValve® System (MCS).

   The objective of this PAS is to characterize the clinical outcomes at year 2 and annually through 5 years post-procedure. The safety and effectiveness endpoints as listed in the protocol include major adverse cardiovascular and cerebrovascular

events (MACCE), change in functional status and quality of life, conduction disturbance requiring permanent pacemaker implantation, echocardiographic assessment, and valve dysfunction. All available patients in the CoreValve® Continued Access Study (approximately 1640 extreme risk patients, including both iliofemoral and non-iliofemoral implant access) in all sites (45) will be followed-up at 1 month, 6 months, annually to 5 years post implant.

3. *PAS 3 New enrollment (extreme risk patients):* This study should be conducted per study protocol dated January 4, 2014, Version 0.4 as submitted to the FDA by email. This study will be a prospective non-randomized registry study using STS/ACC TVT Registry (TVT-R) housed jointly by the American College of Cardiology and Society for Thoracic Surgeons.

   The primary safety objective is to characterize the composite safety endpoint at 30 days and 12 months, as per TVT-R definition: all-cause mortality, all stroke, life-threatening (or disabling) bleeding, acute kidney injury-stage 3 (including renal replacement therapy), peri-procedural myocardial infarction, and repeat procedure for valve-related dysfunction (surgical or interventional therapy). The secondary safety endpoints will be the individual components of the composite safety endpoint listed above per the TVT-R definition at 30 days and 12 months.

   Device success (intra-procedure) is measured per TVT-R definition.

   Additional safety/effectiveness objectives are to evaluate: (1) the neurological, vascular and quality of life outcomes at 30 days and 12 months, (2) the learning curves at 30 days, and (3) long term survival and safety annually through 5 years post-implant.

   The analyses will be descriptive and no statistical hypothesis testing will be performed. Comparisons of PAS3 to the Pivotal (PAS1) and CAP (PAS2) continued follow-up patients will be made in learning curves at 30 days and the survival rate annually out to 5 years as well as other components of the TVT-R safety composite adverse events.

   A total of 5000 consecutive patients in TVT-R from all participating US sites will be enrolled. The data collection for this study (i.e. pre-procedure, peri-procedure, post-procedure, discharge, 30-day, and one-year follow-up) must be nested within TVT-R. The long-term follow-up (annually through 5 years post-implant) will be conducted through linkage of the TVT-R data to Centers for Medicare and Medicaid Services (CMS) claims data.

   Within 30 days of receipt of this letter, the applicant must submit a PMA supplement that includes a complete protocol for PAS3.

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

XIV. APPROVAL SPECIFICATIONS

Directions for use: See final approved labeling (Instructions for Use).

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the final labeling (Instructions for Use).

Post-approval Requirements and Restrictions: See Approval Order.

XV. REFERENCES

[1] Leon MB, Piazza N, Nikolsky E, et al. Standardized endpoint definitions for transcatheter aortic valve implantation clinical trials: a consensus report from the Valve Academic Research Consortium. European Heart Journal 2011; 32:205–217.

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name:	Aortic valve, prosthesis, percutaneously delivered
Device Trade Name:	Medtronic CoreValve™ system (MCS): transcatheter aortic valve (TAV), models MCS-P4-23-AOA-US (23 mm; CoreValve™ Evolut™), MCS-P3-26-AOA-US (26 mm), MCS-P3-29-AOA-US (29 mm), and MCS-P3-31-AOA-US (31 mm); delivery catheter system (DCS), models DCS-C4-18F-US and DCS-C4-18F-23US; and compression loading system (CLS), model CLS-3000-18F-US
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/S002
Date of FDA Notice of Approval:	June 12, 2014

Priority Review: Granted priority review status on March 14, 2014 because the device offers significant advantages over existing approved alternatives.

The original PMA P130021 was approved on January 17, 2014 and is indicated for relief of aortic stenosis in patients with symptomatic heart disease due to severe native calcific aortic stenosis (aortic valve area ≤ 0.8 cm2, a mean aortic valve gradient of > 40 mmHg, or a peak aortic-jet velocity of > 4.0 m/s) and with native aortic annulus diameters between 18 and 29 mm who are judged by a heart team, including a cardiac surgeon, to be at extreme risk or inoperable for open surgical therapy (predicted risk of operative mortality and/or serious irreversible morbidity ≥50% at 30 days). The SSED to support the indication is available on the CDRH website (http://www.accessdata.fda.gov/cdrh_docs/pdf13/P130021b.pdf) and is incorporated by reference here. The current supplement was submitted to expand the indication for the Medtronic CoreValve system.

II. INDICATIONS FOR USE

The Medtronic CoreValve™ system is indicated for relief of aortic stenosis in patients with symptomatic heart disease due to severe native calcific aortic stenosis (aortic valve area ≤1.0 cm^2 or aortic valve area index ≤0.6 cm^2/m^2, a mean aortic valve gradient of ≥40 mm Hg, or a peak aortic-jet velocity of ≥4.0 m/s) and with native anatomy appropriate for the 23, 26, 29, or 31 mm valve system who are judged by a heart team, including a cardiac surgeon, to be at high or greater risk for open surgical therapy (i.e., Society of Thoracic Surgeons operative risk score ≥8% or at a ≥15% risk of mortality at 30 days).

III. CONTRAINDICATIONS

The Medtronic CoreValve system is 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 system labeling.

V. DEVICE DESCRIPTION

The Medtronic CoreValve system (MCS) is designed to replace the native aortic heart valve without open heart surgery and without concomitant surgical removal of the failed native valve. It consists of 3 components: the transcatheter aortic valve (TAV), the delivery catheter system (DCS), and the compression loading system (CLS).

V.1. Transcatheter Aortic Valve (TAV)

The TAV (Figure 1) is manufactured by suturing three valve leaflets and skirt, made from a single layer of porcine pericardium, onto a self-expanding, multi-level, radiopaque frame made of Nitinol. The bioprosthesis is processed with alpha-amino oleic acid (AOA®), which is an antimineralization treatment derived from oleic acid, a naturally occurring long-chain fatty acid.

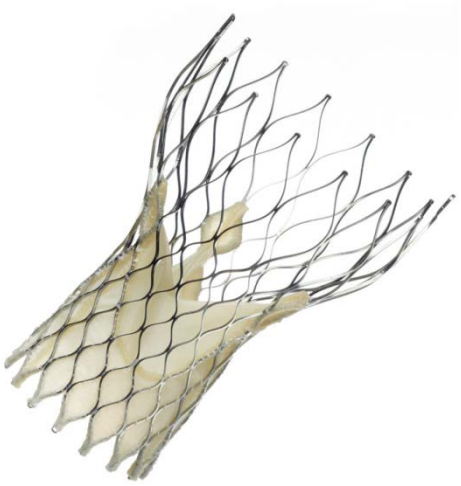


Figure 1: CoreValve Transcatheter Aortic Valve

The TAV is available for a range of aortic annulus and ascending aorta diameters as shown in Table 1. Note that the 23 mm TAV has its own device name, called CoreValve™ Evolut™.

Table 1: Patient Anatomical Diameters

Bioprosthesis Model	Size	Aortic Annulus Diameter	Ascending Aorta Diameter
CoreValve™ Evolut™ Bioprosthesis			
MCS-P4-23-AOA-US	23 mm	18 mm–20 mm	≤34 mm
CoreValve™ Bioprosthesis			
MCS-P3-26-AOA-US	26 mm	20 mm–23 mm	≤40 mm
MCS-P3-29-AOA-US	29 mm	23 mm–26 mm	≤43 mm
MCS-P3-31-AOA-US	31 mm	26 mm–29 mm	≤43 mm

V.2. Delivery Catheter System with AccuTrak Stability Layer (AccuTrak DCS)

The DCS (Figure 2) is used to deploy the TAV. The TAV is loaded within the capsule which features 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. There are two models of the DCS: model DCS-C4-18F-23US for the 23 mm TAV only and model DCS-C4-18F-US for the 26, 29, and 31 mm TAVs.

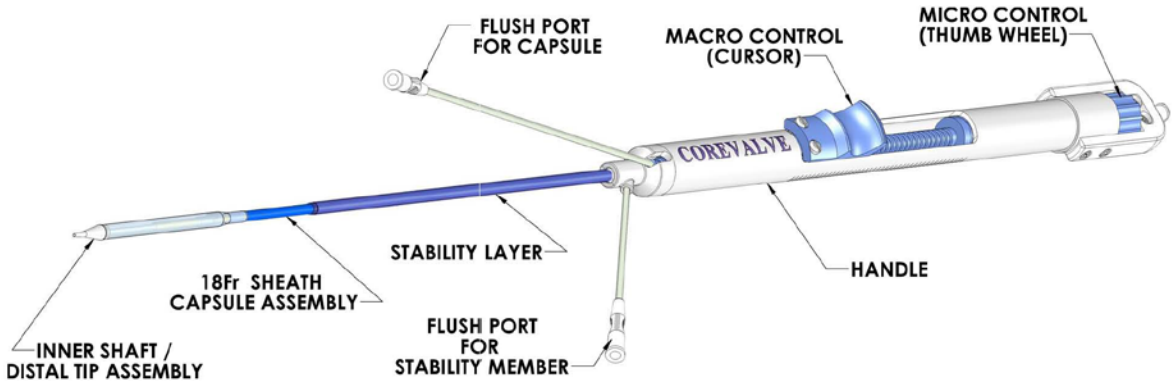


Figure 2: CoreValve Delivery Catheter System

V.3. Compression Loading System (CLS)

The CLS (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. Only one model of the CLS is available, i.e., model CLS-3000-18F-US.

Figure 3: CoreValve Compression Loading System

The CLS 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

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Alternatives for patients deemed to be at high risk for surgical aortic valve replacement include: surgical aortic valve replacement (SAVR), treatment with other approved transcatheter aortic valve implantation therapy, temporary relief using a percutaneous technique called 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 treatment option that best meets their needs.

VII. MARKETING HISTORY

The current Medtronic CoreValve system is commercially available in over 70 countries, as listed in Table 2. It has not been withdrawn from marketing for any reason related to its safety or effectiveness.

Table 2: Countries where Medtronic CoreValve system is commercialized

Commercially Available			
Afghanistan	Finland	Moldova	Tajikistan
Albania	France	Netherlands	Thailand
Argentina	Georgia	New Zealand	Turkmenistan
Armenia	Germany	Panama	Turkey
Austria	Greece	Peru	United Kingdom
Azerbaijan	Guatemala	Philippines	Croatia
Belgium	Hong Kong	Poland	Israel
Belarus	Hungary	Portugal	Ukraine
Bosnia & Herzegovina	Ireland	Romania	Uruguay
Brazil	Israel	Russia	United States
Canada	Italy	Saudi Arabia	Uzbekistan
Chile	Kazakhstan	Serbia	Venezuela
Colombia	Kyrgyzstan	Slovakia	
Croatia	Latvia	Slovenia	
Cyprus	Lithuania	South Africa	
Czech Republic	Luxembourg	South Korea	
Denmark	Malaysia	Spain	
Dominican Republic	Malta	Sweden	
Ecuador	Mexico	Switzerland	
Estonia	Montenegro	Taiwan	

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Potential risks associated with the implantation of the Medtronic CoreValve system may include, but are not limited to, the following:

- 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)
- 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

No additional preclinical testing was necessary for the current supplement. A summary of previously reported preclinical studies can be found in the SSED for the original PMA (http://www.accessdata.fda.gov/cdrh_docs/pdf13/P130021b.pdf).

X. SUMMARY OF PRIMARY CLINICAL STUDY

A clinical study was conducted to establish a reasonable assurance of safety and effectiveness of transcatheter aortic valve replacement (TAVR) therapy with the Medtronic CoreValve system as compared with surgical aortic valve replacement (SAVR) in patients with severe symptomatic native aortic valve stenosis who were deemed to be at high risk for open surgical therapy. The study was conducted in the U.S. under IDE G100012. A summary of the clinical study is presented below.

A. Study Design

The CoreValve U.S. pivotal trial consisted of two patient cohorts, i.e., the Extreme Risk Cohort, which was presented in the original PMA (P130021), and the High Risk Cohort. The High Risk Cohort presented herein was a prospective, randomized, unblinded, multi-center investigational study. Patients who were determined to be at high risk for SAVR were randomized to treatment with either TAVR or SAVR. Randomization was stratified by suitability for potential iliofemoral delivery (as assessed prior to randomization) of the CoreValve system. Of the 795 patients enrolled into the trial, 394 were randomized to TAVR (330 for iliofemoral and 64 for non-iliofemoral) and 401 to SAVR (333 iliofemoral eligible patients and 68 non-iliofemoral eligible patients). Non-iliofemoral access included subclavian and direct aortic routes. The trial patient flowchart is shown in Figure 4.

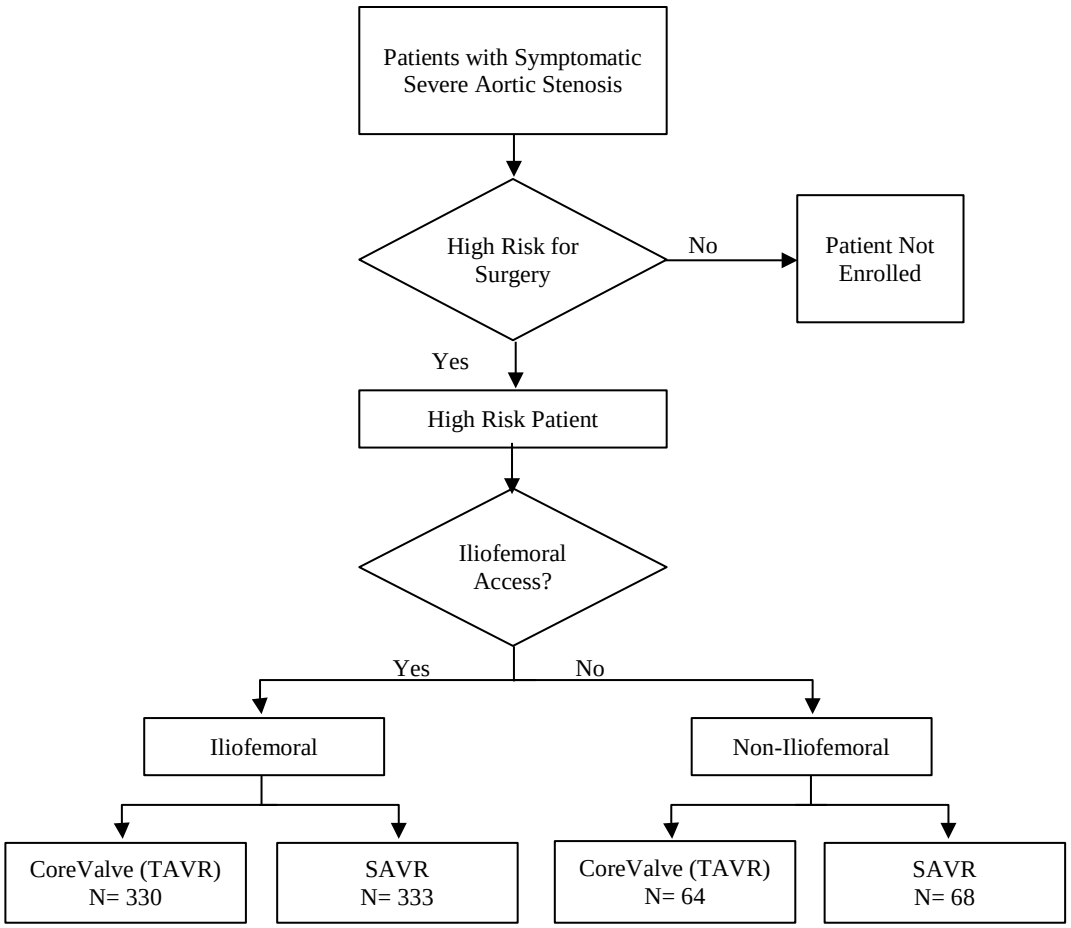


Figure 4: CoreValve High Risk Cohort Patient Flow-chart – ITT Population

The trial was conducted at 45 investigational sites. A total of 795 patients were enrolled between February 02, 2011 and July 23, 2013. The database for this PMA supplement reflected data from events through November 8, 2013. Contractors were utilized for interpretation and analysis of data for several aspects of the study, including an independent Data Safety Monitoring Board (DSMB) that could contract an independent statistician, a Clinical Events Committee (CEC) that was responsible for adjudicating adverse events, an echocardiography core laboratory, and a quality of life (QoL) core laboratory.

1. Clinical Inclusion and Exclusion Criteria

Because tools such as the Society of Thoracic Surgeons (STS) risk calculator can only accommodate a limited number of risk factors and do not account for frailty, disabilities and anatomical characteristics that confer a prohibitive risk for SAVR (e.g., porcelain aorta), these tools were not used as stand-alone mechanisms for identifying patients at high risk for cardiac surgery. Therefore, a team of two cardiac surgeons and one interventional cardiologist at each investigational site were required to assess patient suitability for inclusion in the study, taking into account risk factors

not covered by the STS risk calculator. A central screening committee made a subsequent assessment of patient risk and agreed on patient eligibility or ineligibility.

The inclusion and exclusion criteria for the study are summarized below:

Inclusion Criteria

- Subject must have co-morbidities such that one cardiologist and two cardiac surgeons agree predicted risk of operative mortality is ≥15% (and predicted operative mortality or serious, irreversible morbidity risk of < 50%) at 30 days
- Subject has senile degenerative aortic valve stenosis with:
  - mean gradient > 40 mmHg or jet velocity greater than 4.0 m/sec by either resting or dobutamine stress echocardiogram, or simultaneous pressure recordings at cardiac catheterization (either resting or dobutamine stress), AND
  - an initial aortic valve area of ≤ 0.8 cm^2 (or aortic valve area index ≤ 0.5 cm^2/m^2) by resting echocardiogram or simultaneous pressure recordings at cardiac catheterization
- Subject is symptomatic from his/her aortic valve stenosis, as demonstrated by New York Heart Association (NYHA) Functional Class II or greater
- The subject or the subject's legal representative has been informed of the nature of the trial, agrees to its provisions and has provided written informed consent as approved by the IRB of the respective clinical site
- The subject and the treating physician agree that the subject will return for all required post-procedure follow-up visits

Exclusion Criteria

Clinical

- Evidence of an acute myocardial infarction ≤ 30 days before the intended treatment
- Any percutaneous coronary or peripheral interventional procedure performed within 30 days prior to the index procedure including bare metal stents. Additionally, any drug eluting stents placed within 6 months prior to the index procedure
- Blood dyscrasias as defined: leukopenia (WBC < 1000mm^3), thrombocytopenia (platelet count <50,000 cells/mm^3), history of bleeding diathesis or coagulopathy
- Untreated clinically significant coronary artery disease requiring revascularization
- Cardiogenic shock manifested by low cardiac output, vasopressor dependence, or mechanical hemodynamic support
- Need for emergency surgery for any reason
- Severe ventricular dysfunction with left ventricular ejection fraction (LVEF) < 20% as measured by resting echocardiogram
- Recent (within 6 months) cerebrovascular accident (CVA) or transient ischemic attack (TIA)

- End stage renal disease requiring chronic dialysis or creatinine clearance < 20 cc/min
- Active Gastrointestinal (GI) bleeding within the past 3 months
- A known hypersensitivity or contraindication to any of the following which cannot be adequately pre-medicated:
    - aspirin
    - heparin (HIT/HITTS)
    - nitinol (titanium or nickel)
    - ticlopidine and clopidogrel
    - contrast media
- Ongoing sepsis, including active endocarditis
- Subject refuses a blood transfusion
- Life expectancy < 12 months due to associated non-cardiac co-morbid conditions.
- Other medical, social, or psychological conditions that in the opinion of an Investigator precludes the subject from appropriate consent
- 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)
- Currently participating in an investigational drug or another device trial
- Symptomatic carotid or vertebral artery disease
- Subject has been offered surgical aortic valve replacement but declined

Anatomical

- 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+))
- Moderate to severe (3-4+) or severe (4+) mitral or severe (4+) tricuspid regurgitation
- Moderate to severe mitral stenosis
- Hypertrophic obstructive cardiomyopathy
- New or untreated echocardiographic evidence of intracardiac mass, thrombus or vegetation
- Severe basal septal hypertrophy with an outflow gradient
- Aortic root angulation (angle between plane of aortic valve annulus and horizontal plane/vertebrae) > 70° (for femoral and left subclavian/axillary access) and > 30° (for right subclavian/axillary access)
- Ascending aorta that exceeded the maximum diameter for any given native aortic annulus size
- Congenital bicuspid or unicuspid valve verified by echocardiography
- Sinus of valsalva anatomy that would prevent adequate coronary perfusion
- Vascular Transarterial access not able to accommodate an 18Fr sheath

2. Follow-Up Schedule

Follow-up periods were discharge or 7 days, whichever comes first, 30 days, 6 months, 12 months, and annually thereafter to a minimum of 5 years post procedure. Patients were followed for a minimum of 12 months prior to submission of this PMA application.

3. Clinical Endpoints

Primary Safety and Effectiveness Endpoints

The primary endpoint was all-cause mortality rate at 12 months. The primary hypothesis was that TAVR with the Medtronic CoreValve system was non-inferior to SAVR for the primary endpoint, as expressed as follows:

H_0: $\pi_{MCS\ TAVR} \geq \pi_{SAVR} + 7.5\%$

H_A: $\pi_{MCS\ TAVR} < \pi_{SAVR} + 7.5\%$

where $\pi_{MCS\ TAVR}$ and π_{SAVR} represent the event rate for the primary endpoint for the CoreValve arm and the SAVR arm, respectively. Assuming that non-inferiority was proven at the one-sided 0.05 level, a subsequent pre-specified test for superiority would be performed at the one-sided 0.05 level. Because this was a closed test procedure, no adjustment for multiplicity was needed.

Secondary Safety and Effectiveness Endpoints

The study included the following secondary endpoints:

1. Major adverse cardiovascular or cerebrovascular event (MACCE; defined as a composite of all-cause mortality, MI, all stroke, and aortic valve reintervention) at 30 days, 6 months, 12 months and annually thereafter up to 5 years
2. The occurrence of individual MACCE components at 30 days, 6 months, 12 months and annually thereafter up to 5 years
3. Major adverse events (MAE) at 30 days, 6 months,12 months and annually thereafter up to 5 years
4. Conduction disturbance requiring permanent pacemaker implantation (PPI) at 30 days, 6 months, 12 months and annually thereafter up to 5 years
5. Change in NYHA class from baseline at 30 days, 6 months, 12 months and annually thereafter up to 5 years
6. Change in distance walked during 6-minute walk test (6MWT) from baseline to 30 days and baseline to 12 months
7. Ratio of days alive out of hospital versus total days alive assessed at 12 months follow-up
8. QoL change from baseline at 30 days, 6 months, 12 months and annually thereafter up to 5 years
9. Echocardiographic assessment of valve performance at discharge, 30 days, 6 months, 12 months and annually thereafter up to 5 years using the following measures:

- Transvalvular mean gradient
- Effective orifice area (EOA)
- Degree of aortic regurgitation (transvalvular and paravalvular)

10. Aortic valve disease hospitalization at 30 days, 6 months, 12 months and annually thereafter up to 5 years
11. Cardiovascular deaths and valve-related deaths at 30 days, 6 months, 12 months and annually thereafter up to 5 years
12. Strokes and transient ischemic attacks (TIAs) at 30 days, 6 months, 12 months and annually thereafter up to 5 years
13. Index procedure related MAEs
14. Length of index procedure hospital stay
15. Device success defined as follows:
    - Successful vascular access, delivery and deployment of the device, and successful retrieval of the delivery system
    - Correct position of the device in the proper anatomical location (placement in the annulus with no impedance on device function)
    - Intended performance of the prosthetic valve (aortic valve area > 1.2 cm^2 for 26, 29, and 31 mm valves, ≥ 0.9 cm^2 for 23 mm valve (by echocardiography using the continuity equation) and mean aortic valve gradient < 20 mmHg or peak velocity < 3 m/sec, without moderate or severe prosthetic valve AR). Performance is assessed acutely in a resting state, either within 24-48 hours after the index procedure or before hospital discharge
    - Only one valve implanted in the proper anatomical location
16. Procedural success, defined as device success and absence of in-hospital MACCE
17. Evidence of prosthetic valve dysfunction at 30 days, 6 months, 12 months and annually thereafter up to 5 years

Note: Secondary endpoints #15-17 were only for the TAVR cohort.

Six (6) of the above secondary endpoints were included in a hierarchical testing protocol, namely, changes from baseline to 12 months in transvalvular mean gradient, effective orifice area, NYHA classification, and KCCQ score, MACCE rate at 30 days or hospital discharge, whichever was later, and change from baseline to 1 month in SF-12.

The MACCE rate was also a powered secondary endpoint, with the following superiority hypothesis that TAVR with CoreValve was superior to SAVR in the binary rate of MACCE at 30 days or hospital discharge, whichever was longer:

H_0: $\pi_{MCS\ TAVR} = \pi_{SAVR}$

H_A: $\pi_{MCS\ TAVR} < \pi_{SAVR}$

where $\pi_{MCS\ TAVR}$ and π_{SAVR} represent the MACCE rate for the CoreValve arm and the SAVR arm, respectively.

B. Accountability of PMA Cohort

At the time of database lock, 734 of the 795 patients enrolled were available for assessment of the primary endpoint. Table 3 depicts the disposition of patients at each follow-up period for the Intent-to-Treat population (see Analysis Population section for definition).

Table 3: Overall Study Compliance

Follow up Period	Variable	TAVR N=394	SAVR N=401
1 month	Expected	375	344
	Number withdrew	2	37
	Number died before visit	17	18
	Lost to follow up	0	0
	Other	0	1
	Visit Pending	0	1
	Visit compliance	98.1% (368)	95.6% (329)
6 months	Expected	353	304
	Number withdrew	0	3
	Number died before visit	21	37
	Lost to follow up	0	0
	Other	0	0
	Visit Pending	1	0
	Visit compliance	95.2% (336)	91.8% (279)
12 months	Expected	325	282
	Number withdrew	2	3
	Number died before visit	24	18
	Lost to follow up	0	0
	Other	0	1
	Visit Pending	2	0
	Visit compliance	98.5% (320)	93.6% (264)

* Visit Pending: Since 23mm candidates continued to be enrolled through July 2013, these subjects have 1 month, 6 month, or 12 month visits pending.

C. Study Population Demographics and Baseline Parameters

The demographics of the study population were typical for an aortic stenosis valve replacement study performed in the U.S., as shown in Table 4. A high proportion of the patients had significant co-morbidities, frailties, or disabilities, and these risk factors were generally well balanced between the study arms. The mean age for patients participating in the trial was approximately 83 years old, and slightly greater than 50% of patients were male. The mean STS score was approximately 7. In addition, approximately 85% of all patients were in NYHA classes III or IV.

Table 4: Demographics of the Study Population (ITT)

	Iliofemoral		Non-Iliofemoral		Pooled		
Demographic	TAVR N=330	SAVR N=333	TAVR N=64	SAVR N=68	TAVR N=394	SAVR N=401	P-Values
Age (yrs)	83.4 ± 6.8	83.6 ± 6.3	81.8 ± 8.0	82.9 ± 6.5	83.2 ± 7.1	83.5 ± 6.3	0.5102
Gender (Male)	53.9% (178/330)	53.8% (179/333)	51.6% (33/64)	48.5% (33/68)	53.6% (211/394)	52.9% (212/401)	0.8464
NYHA Classification							
II	13.0% (43/330)	12.0% (40/333)	20.3% (13/64)	19.1% (13/68)	14.2% (56/394)	13.2% (53/401)	0.6723
III	65.2% (215/330)	69.7% (232/333)	67.2% (43/64)	66.2% (45/68)	65.5% (258/394)	69.1% (277/401)	
IV	21.8% (72/330)	18.3% (61/333)	12.5% (8/64)	14.7% (10/68)	20.3% (80/394)	17.7% (71/401)	
STS Score (Risk of Mortality, %)	7.3 ± 3.1	7.5 ± 3.1	7.2 ± 2.6	7.6 ± 3.9	7.3 ± 3.0	7.5 ± 3.2	0.2680
Coronary Artery Disease	75.5% (249/330)	74.2% (247/333)	75.0% (48/64)	86.8% (59/68)	75.4% (297/394)	76.3% (306/401)	0.7597
Previous MI	23.3% (77/330)	23.4% (78/333)	37.5% (24/64)	29.4% (20/68)	25.6% (101/394)	24.4% (98/401)	0.6972
Previous Interventions							
Coronary Artery Bypass Surgery	31.2% (103/330)	29.1% (97/333)	21.9% (14/64)	35.3% (24/68)	29.7% (117/394)	30.2% (121/401)	0.8828
Percutaneous Coronary Intervention	32.1% (106/330)	37.8% (126/333)	42.2% (27/64)	38.2% (26/68)	33.8% (133/394)	37.9% (152/401)	0.2226
Balloon Valvuloplasty	4.5% (15/330)	6.3% (21/333)	12.5% (8/64)	7.4% (5/68)	5.8% (23/394)	6.5% (26/401)	0.7048
Cerebral Vascular Disease	24.7% (81/328)	23.2% (77/332)	29.0% (18/62)	35.9% (23/64)	25.4% (99/390)	25.3% (100/396)	0.9660
Prior Stroke	13.6% (45/330)	12.6% (42/333)	9.4% (6/64)	16.4% (11/67)	12.9% (51/394)	13.3% (53/400)	0.8984
Peripheral Vascular Disease	37.6% (123/327)	37.2% (123/331)	62.5% (40/64)	68.7% (46/67)	41.7% (163/391)	42.5% (169/398)	0.8257
Chronic Lung Disease/COPD	44.5% (147/330)	46.2% (154/333)	45.3% (29/64)	38.2% (26/68)	44.7% (176/394)	44.9% (180/401)	0.9508
Home Oxygen	13.4% (44/329)	12.3% (41/333)	9.4% (6/64)	10.3% (7/68)	12.7% (50/393)	12.0% (48/401)	0.7472
Creatinine Level >2 mg/dl	3.3% (11/330)	4.5% (15/333)	3.1% (2/64)	5.9% (4/68)	3.3% (13/394)	4.7% (19/401)	0.3021
Atrial Fibrillation / Atrial Flutter	40.6% (134/330)	48.8% (162/332)	42.9% (27/63)	41.2% (28/68)	41.0% (161/393)	47.5% (190/400)	0.0640
Pre-Existing Permanent Pacemaker Placement / ICD	24.8% (82/330)	21.6% (72/333)	15.6% (10/64)	16.2% (11/68)	23.4% (92/394)	20.7% (83/401)	0.3669
Aorta Calcification[1]							
Severe	10.6% (35/330)	10.5% (35/333)	19.0% (12/63)	16.2% (11/68)	12.0% (47/393)	11.5% (46/401)	0.8307
Porcelain	0.0% (0/330)	0.0% (0/333)	1.6% (1/63)	0.0% (0/68)	0.3% (1/393)	0.0% (0/401)	0.4950
Chest Wall Deformity	1.8% (6/330)	0.3% (1/333)	4.7% (3/64)	0.0% (0/68)	2.3% (9/394)	0.2% (1/401)	0.0106

	Iliofemoral		Non-Iliofemoral		Pooled		
Demographic	TAVR N=330	SAVR N=333	TAVR N=64	SAVR N=68	TAVR N=394	SAVR N=401	P-Values
Hostile Mediastinum	3.9% (13/330)	0.9% (3/331)	3.1% (2/64)	2.9% (2/68)	3.8% (15/394)	1.3% (5/399)	0.0218
Cirrhosis of the Liver	2.4% (8/330)	1.8% (6/333)	3.1% (2/64)	1.5% (1/68)	2.5% (10/394)	1.7% (7/401)	0.4400
Wheelchair Bound	4.8% (16/330)	7.5% (25/333)	0.0% (0/64)	7.4% (5/68)	4.1% (16/394)	7.5% (30/401)	0.0389
Echocardiographic Findings							
Ejection Fraction (visual estimate, %)	58.1 ± 10.9	57.5 ± 11.8	57.4 ± 13.4	58.3 ± 12.4	58.0 ± 11.3	57.7 ± 11.9	0.7110
Aortic Valve Area (cm^2)	0.72 ± 0.23	0.73 ± 0.24	0.70 ± 0.18	0.71 ± 0.22	0.72 ± 0.23	0.73 ± 0.23	0. 5801
Mean Gradient across Aortic Valve (MGV_2, mmHg)	48.36 ± 15.09	47.69 ± 14.39	47.38 ± 16.74	48.08 ± 12.51	48.20 ± 15.35	47.75 ± 14.07	0. 6725
Mitral Regurgitation: Moderate/Severe	10.2% (33/325)	10.5% (34/324)	8.1% (5/62)	9.0% (6/67)	9.8% (38/387)	10.2% (40/391)	0. 8486
[1]. Aorta Calcification is measured on screening CT Angiogram Plus-minus values present the mean ± standard deviation.							

The STS score predicted a 30-day mortality of 7.5% for the average surgeon at the average hospital. The Kaplan-Meier (K-M) 30-day mortality for the As Treated SAVR arm was 4.5%. Therefore, the observed/expected ratio was 0.60 in this trial, indicating better than average care in the SAVR arm.

D. Safety and Effectiveness Results

1. Analysis Populations

The "Intent-to-Treat" (ITT) population consisted of all randomized patients. Patients were analyzed according to the randomization assignment and the access site eligibility stratification (iliofemoral or non-iliofemoral), regardless of whether a procedure was actually attempted, which device the patient actually received, and which access site was actually used.

The "As Treated" (AT) population consisted of all ITT patients with an attempted implant procedure, defined as when the patient 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. The AT population was the primary analysis population.

The "Implanted" population consisted of all AT patients who were actually implanted with either CoreValve or a surgical valve. To be considered implanted, a TAVR patient's device disposition form must show at least one CoreValve device with a

final disposition of “Implanted,” while an SAVR patient’s procedure form must indicate the valve manufacturer and model as well as the suture method.

The “Per Protocol” population consisted of all implanted subjects who: (1) were implanted according to their randomization and access site stratification; (2) had at least 12 months (365 days) of follow-up or had experienced the primary endpoint (death) prior to 12 months; (3) did not cross to a different type of procedure from their first attempted procedure types (TAVR or SAVR) before their 12 month visit; and (4) had satisfied all inclusion/exclusion criteria.

The “Modified Per Protocol” population consisted of all implanted subjects who: (1) were implanted according to their randomization and access site stratification; (2) did not cross to a different type of procedure from their first attempted procedure types (TAVR or SAVR) before their 12 month visit; and (3) had satisfied all inclusion/exclusion criteria.

For subgroup analyses on the AT and Implanted populations, TAVR patients were analyzed according to the access site (iliofemoral or non-iliofemoral) on the first attempted procedure form, while SAVR patients were analyzed according to the stratified access designation (iliofemoral or non-iliofemoral).

2. Primary Safety and Effectiveness Endpoint

The K-M rate of all-cause mortality at 12 months was 14.22% for TAVR and 19.12% for SAVR (Table 5). The difference between the two rates was -4.89% with an upper 1-sided 95% CI of -0.37%, which was statistically less than the pre-specified non-inferiority margin of 7.5% ($p<0.0001$). Therefore, the null hypothesis that TAVR was inferior to SAVR for the primary endpoint of all-cause mortality at 12 months was rejected and the alternative hypothesis that TAVR was non-inferior to SAVR within a non-inferiority margin of 7.5% was accepted. Subsequently, a pre-specified test for superiority of TAVR over SAVR was also conducted, which demonstrated that the rate of all-cause mortality at 12 months for TAVR was significantly less than that for SAVR at the one-sided 0.05 level ($p=0.0377$).

Table 5: Primary Endpoint: All-Cause Mortality at 12 Months – As Treated Population

	TAVR N=390	SAVR N=357
Total # of Patients	390	357
# of Patients Died within 1 Year	55	67
# of Patients Censored prior to 1 Year	7	16
# of Patients Alive at 1 Year	328	274
Mortality Rate at 1 Year (K-M)	14.22%	19.12%
Standard Error at 1 Year	1.78%	2.10%
Mortality Difference (TAVR-SAVR)	-4.89%	
Standard Error of Difference	2.75%	
95% 1-sided UCB for Difference	-0.37%	
Primary Objective – Non-Inferiority		
Non-inferiority Margin	7.50%	
Z-Score	-4.5019	
P-Value	<0.0001	
Non-Inferiority Test	Passed	
Primary Objective – Superiority		
Z-Score	-1.7776	
P-Value	0.0377	
Superiority Test	Passed	

The primary endpoint of all-cause mortality at 12 months included all deaths (cardiovascular and non-cardiovascular) from any cause after a valve intervention. Figure 5 and Table 6 show the K-M rates of all-cause mortality in the AT population for both study arms up to 12-month follow-up.

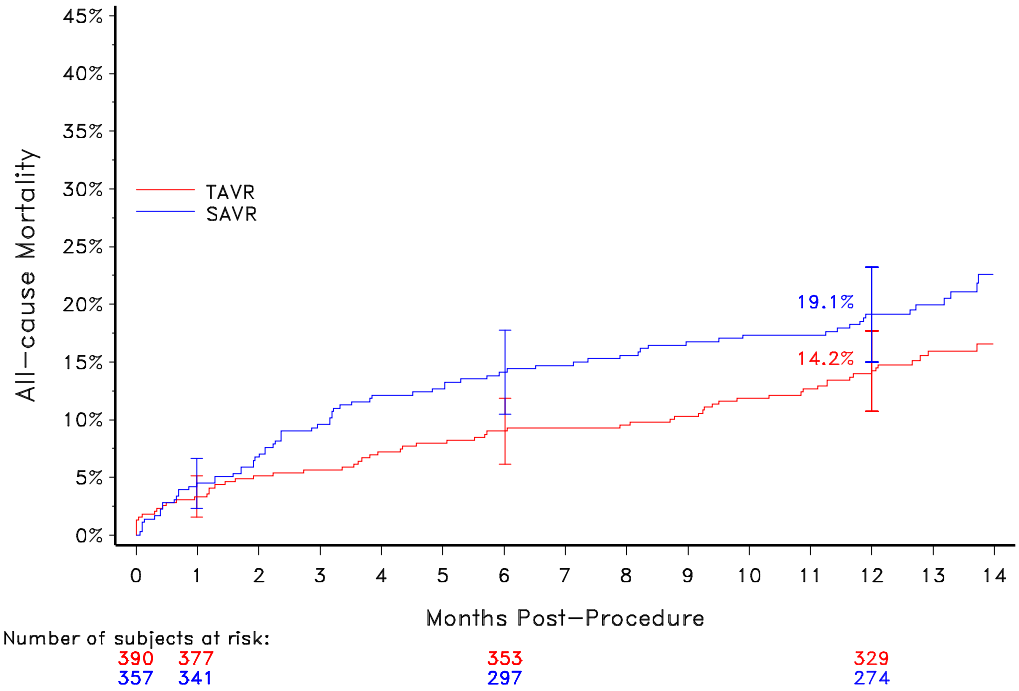


Figure 5: All-Cause Mortality Kaplan-Meier Event Rate – As Treated Population

Table 6: Primary Endpoint: All-Cause Mortality – As Treated Population

Interval Post Procedure (months)*	TAVR N=390				SAVR N=357			
	0	1	6	12	0	1	6	12
# at start of interval	390	377	353	329	357	341	297	274
# events in interval	13	22	19	20	15	35	17	17
# event cumulative	13	35	54	74	15	50	67	84
K-M Event Rate	1.3	3.3	9.0	14.2	0.0	4.5	14.1	19.1
Lower 95% CI	0.2	1.6	6.2	10.7	NA	2.3	10.5	15.0
Upper 95% CI	2.4	5.1	11.8	17.7	NA	6.6	17.7	23.2
*0 = 0-29 days, 1 = 30-182 days, 6 = 183-364 days, 12 ≥ 365 days. Cumulative probability of event estimate is based on the Kaplan-Meier method								

The primary endpoint hypothesis testing was also pre-specified for the ITT, Implanted, and Per Protocol populations, as presented in Tables 7 - 10 and Figures 6 - 8. Non-inferiority of TAVR compared to SAVR was concluded for all analysis populations ($p<0.0001$ for all). Subsequent superiority null hypothesis was rejected at one-sided 0.05 level for the ITT ($p=0.0365$) and Implanted ($p=0.042$) populations, but not for the Per Protocol population ($p=0.07$).

Table 7: Primary Endpoint: All-Cause Mortality at 12 Months – Pre-specified Additional Populations

	Intent-to-Treat		Implanted		Per Protocol	
	TAVR N=394	SAVR N=401	TAVR N=389	SAVR N=353	TAVR N=365	SAVR N=326
Total # of Patients	394	401	389	353	365	326
# of Patients Died within 1 Year	54	68	55	66	53	61
# of Patients Censored prior to 1 Year	9	54	7	15	0	0
# of Patients Alive at 1 Year	331	279	327	272	312	265
Mortality Rate at 1 Year (K-M)	13.87%	18.70%	14.26%	19.03%	14.52%	18.71%
Standard Error at 1 Year	1.75%	2.05%	1.78%	2.11%	1.84%	2.16%
Mortality Difference (TAVR-SAVR)	-4.83%		-4.77%		-4.19%	
Standard Error of Difference	2.70%		2.76%		2.84%	
95% 1-sided UCB for Difference	-0.40%		-0.23%		0.48%	
Primary Objective – Non-Inferiority						
Non-inferiority Margin	7.50%		7.50%		7.50%	
Z-Score	-4.5734		-4.4443		-4.1164	
P-Value	<0.0001		<0.0001		<0.0001	
Non-Inferiority Test	Passed		Passed		Passed	
Primary Objective – Superiority						
Z-Score	-1.7926		-1.7283		-1.4757	
P-Value	0.0365		0.0420		0.0700	
Superiority Test	Passed		Passed		Failed	

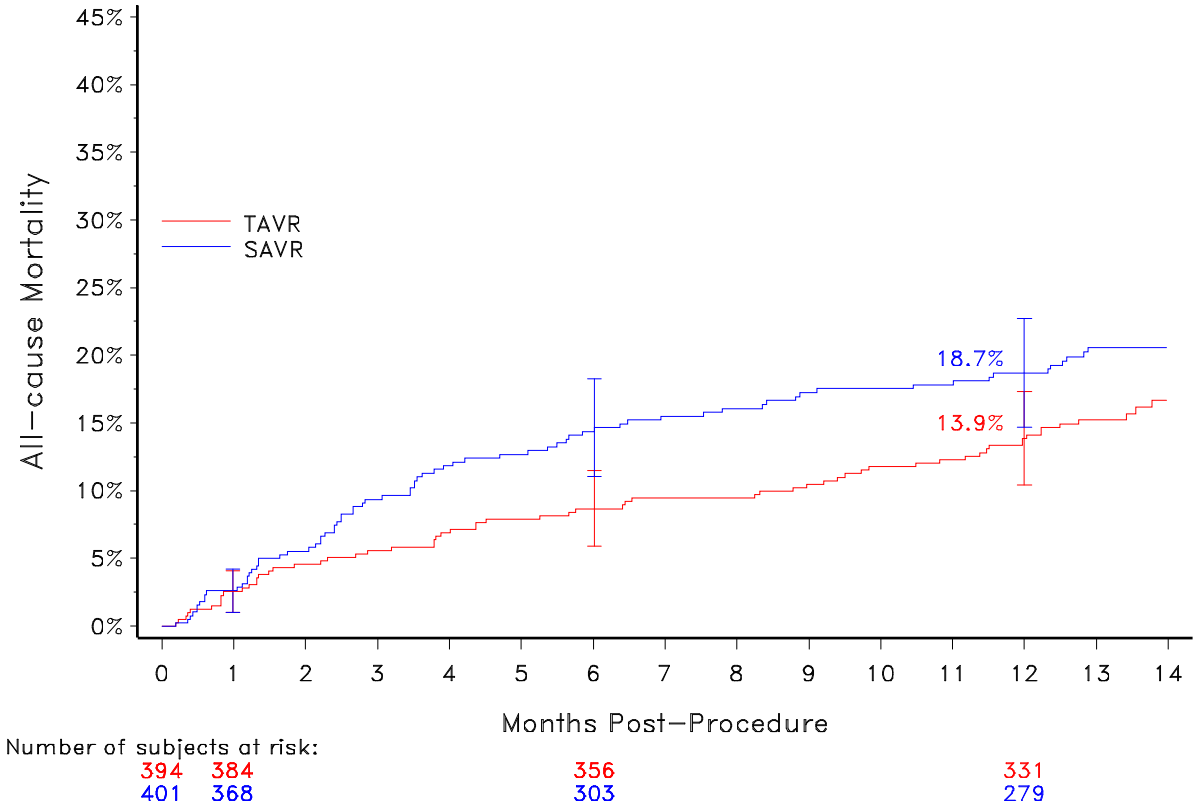


Figure 6: All-Cause Mortality Kaplan-Meier Event Rate – Intent-to-Treat Population

Table 8: Primary Endpoint: All-Cause Mortality – Intent-to-Treat Population

Interval Post Procedure (months)*	TAVR N=394				SAVR N=401			
	0	1	6	12	0	1	6	12
# at start of interval	394	384	356	331	401	368	303	279
# events in interval	10	24	20	22	10	43	15	21
# event cumulative	10	34	54	76	10	53	68	89
K-M Event Rate	0.0	2.5	8.7	13.9	0.0	2.6	14.7	18.7
Lower 95% CI	NA	1.0	5.9	10.4	NA	1.0	11.0	14.7
Upper 95% CI	NA	4.1	11.5	17.3	NA	4.2	18.3	22.7
*0 = 0-29 days, 1 = 30-182 days, 6 = 183-364 days, 12 ≥ 365 days. Cumulative probability of event estimate is based on the Kaplan-Meier method								

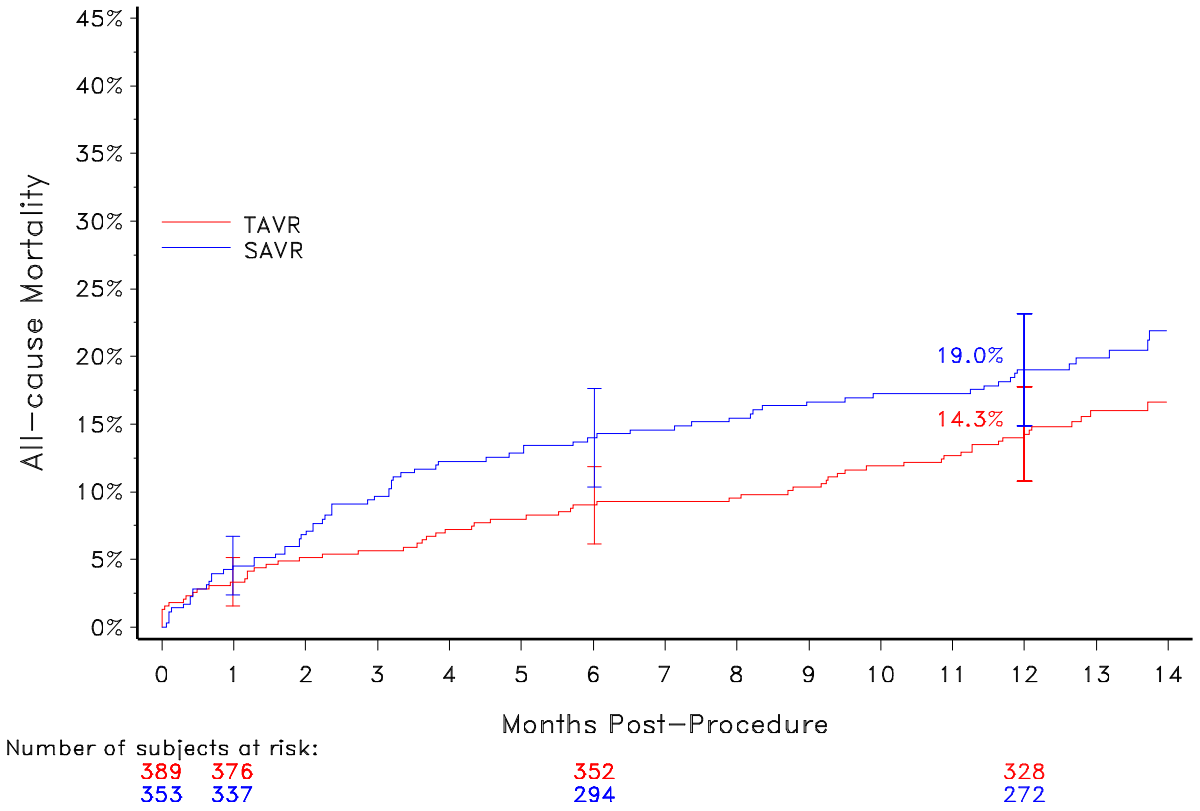


Figure 7: All-Cause Mortality Kaplan-Meier Event Rate – Implanted Population

Table 9: Primary Endpoint: All-Cause Mortality – Implanted Population

Interval Post Procedure (months)*	TAVR N=389				SAVR N=353			
	0	1	6	12	0	1	6	12
# at start of interval	389	376	352	328	353	337	294	272
# events in interval	13	22	19	20	15	34	17	16
# event cumulative	13	35	54	74	15	49	66	82
K-M Event Rate	1.3	3.3	9.0	14.3	0.0	4.5	14.0	19.0
Lower 95% CI	0.2	1.6	6.2	10.8	NA	2.4	10.4	14.9
Upper 95% CI	2.4	5.1	11.9	17.7	NA	6.7	17.6	23.2
*0 = 0-29 days, 1 = 30-182 days, 6 = 183-364 days, 12 ≥ 365 days. Cumulative probability of event estimate is based on the Kaplan-Meier method								

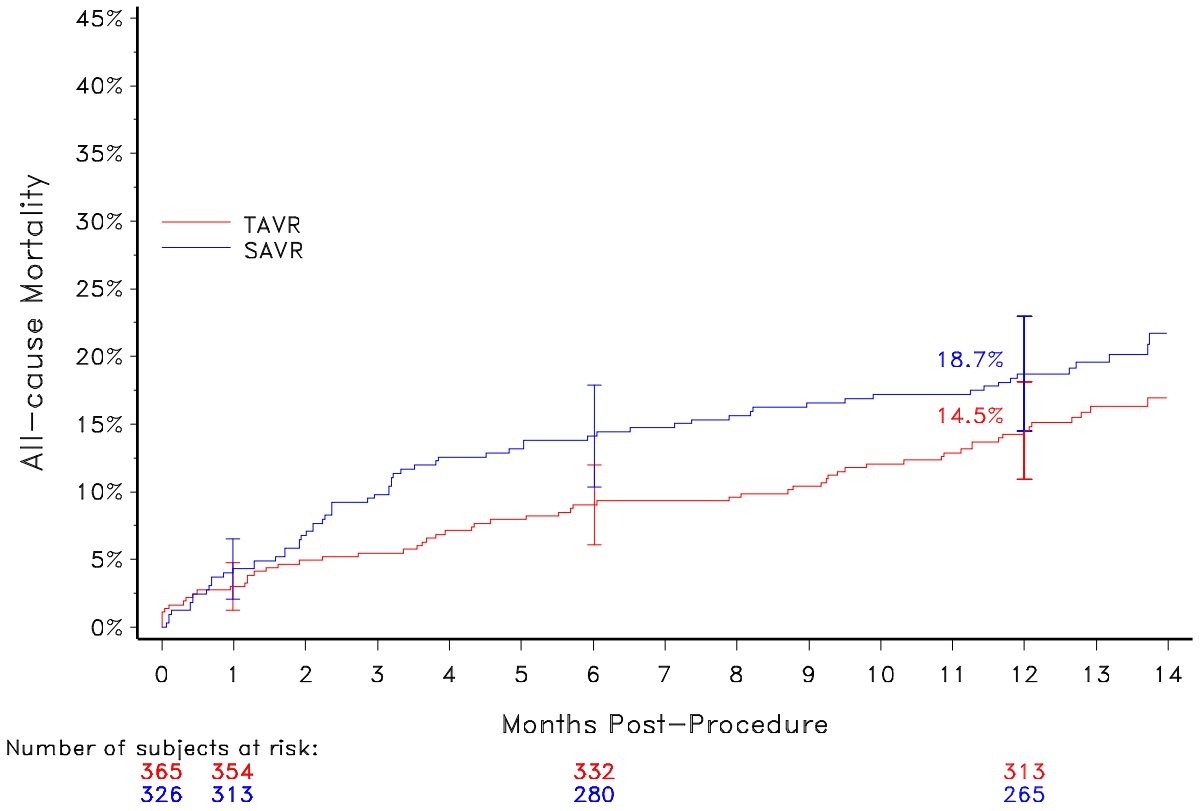


Figure 8: All-Cause Mortality Kaplan-Meier Event Rate – Per Protocol Population

Table 10: Primary Endpoint: All-Cause Mortality – Per Protocol Population

Interval Post Procedure (months)*	TAVR N=365				SAVR N=326			
	0	1	6	12	0	1	6	12
# at start of interval	365	354	332	313	326	313	280	265
# events in interval	11	22	19	20	13	33	15	15
# event cumulative	11	33	52	72	13	46	61	76
K-M Event Rate	1.1	3.0	9.0	14.5	0.0	4.3	14.1	18.7
Lower 95% CI	0.0	1.3	6.1	10.9	NA	2.1	10.3	14.5
Upper 95% CI	2.2	4.8	12.0	18.1	NA	6.5	17.9	22.9
*0 = 0-29 days, 1 = 30-182 days, 6 = 183-364 days, 12 ≥ 365 days. Cumulative probability of event estimate is based on the Kaplan-Meier method								

A *post hoc* analysis was also performed on the primary endpoint hypothesis testing for the Modified Per Protocol population. The Modified Per Protocol population included 22 additional subjects (7 TAVR, 15 SAVR) who were censored prior to 1 year as compared with the Per Protocol population. In addition, a *post hoc* analysis was conducted on the worst-case Modified Per Protocol population, which assumed all 7 censored TAVR subjects had died at the censoring time and all 15 censored SAVR subjects were alive at 1 year). In both analyses, non-inferiority was demonstrated. The results are presented in Tables 11 - 13 and Figures 9 and 10.

Table 11: Primary Endpoint: All-Cause Mortality at 12 Months – *post hoc* Additional Populations

	Modified Per Protocol		Modified Per Protocol Worst Case Scenario	
	TAVR N=372	SAVR N=341	TAVR N=372	SAVR N=341
Total # of Patients	372	341	372	341
# of Patients Died within 1 Year	53	61	60	61
# of Patients Censored prior to 1 Year	7	15	0	0
# of Patients Alive at 1 Year	312	265	312	280
Mortality Rate at 1 Year (K-M)	14.38%	18.21%	16.13%	17.89%
Standard Error at 1 Year	1.83%	2.11%	1.91%	2.08%
Mortality Difference (TAVR-SAVR)	-3.83%		-1.76%	
Standard Error of Difference	2.79%		2.82%	
95% 1-sided UCB for Difference	0.76%		2.88%	
Primary Objective – Non-Inferiority				
Non-inferiority Margin	7.50%		7.50%	
Z-Score	-4.0572		-3.2853	
P-Value	< 0.0001		0.0005	
Non-Inferiority Test	Passed		Passed	

Subjects (7 TAVR, 15 SAVR) censored before 1 year were included in the modified per protocol.
For worst case scenario the following assumptions were made for the censored subjects: the 7 TAVR subjects were assumed to have died on date of censoring and the 15 SAVR subjects were assumed to be alive at 1 year.

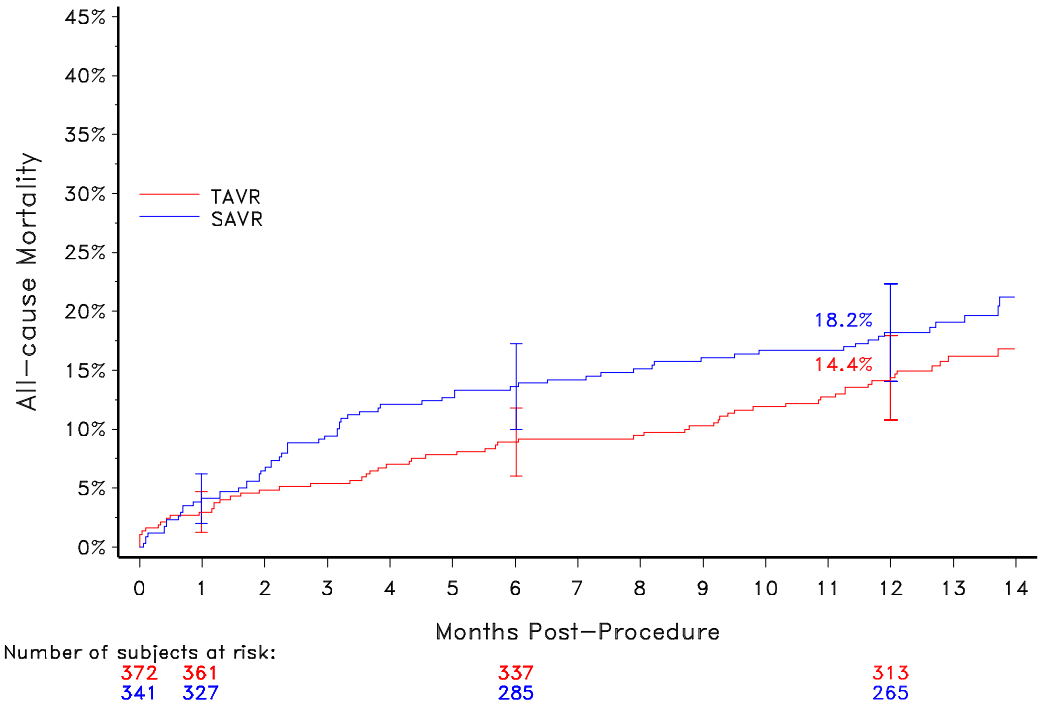


Figure 9: All-Cause Mortality Kaplan-Meier Event Rate – Modified Per Protocol Population

Table 12: Primary Endpoint: All-Cause Mortality – Modified Per Protocol Population

Interval Post Procedure (months)*	TAVR N=372				SAVR N=341			
	0	1	6	12	0	1	6	12
# at start of interval	372	361	337	313	341	327	285	265
# events in interval	11	22	19	20	13	33	15	15
# event cumulative	11	33	52	72	13	46	61	76
K-M Event Rate	1.1	3.0	8.9	14.4	0.0	4.1	13.6	18.2
Lower 95% CI	0.0	1.2	6.0	10.8	NA	2.0	9.9	14.1
Upper 95% CI	2.1	4.7	11.8	18.0	NA	6.2	17.3	22.3
*0 = 0-29 days, 1 = 30-182 days, 6 = 183-364 days, 12 ≥ 365 days. Cumulative probability of event estimate is based on the Kaplan-Meier method								

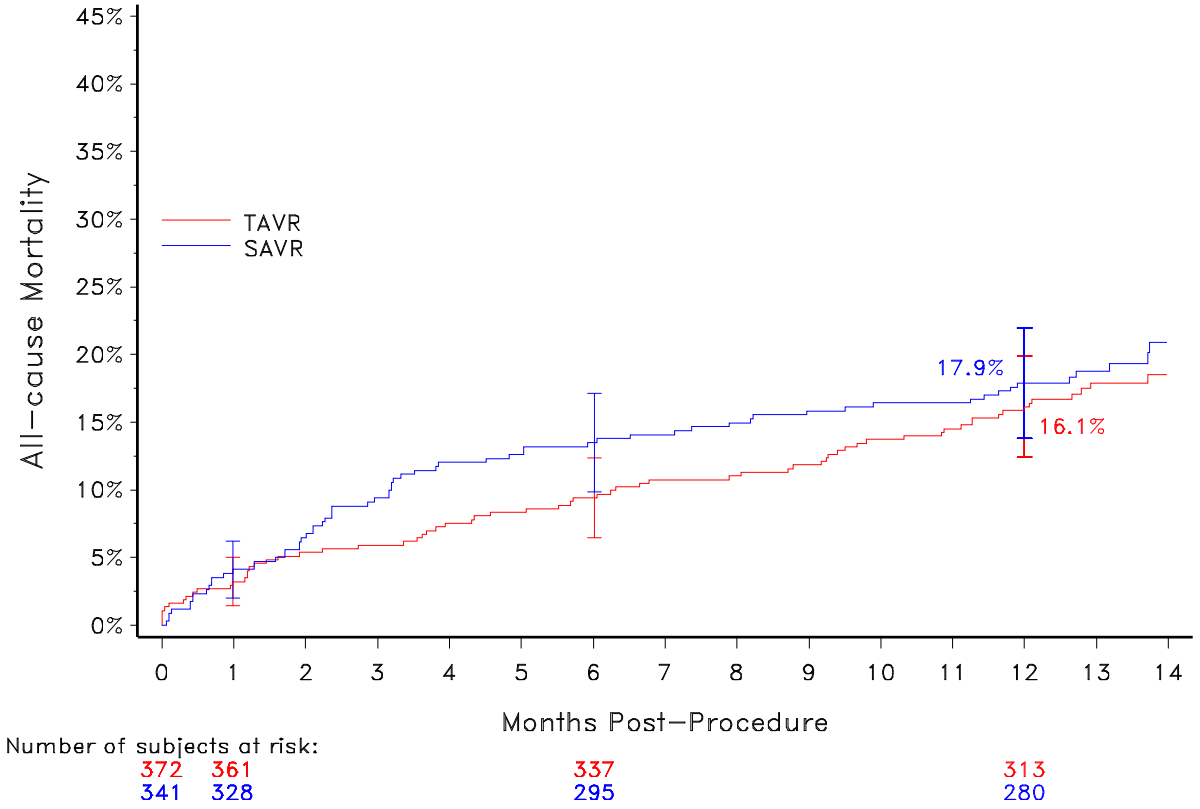


Figure 10: All-Cause Mortality Kaplan-Meier Event Rate – Modified Per Protocol Population – Worst Case Scenario

Table 13: Primary Endpoint: All-Cause Mortality – Modified Per Protocol Population – Worst Case Scenario

Interval Post Procedure (months)*	TAVR N=390				SAVR N=357			
	0	1	6	12	0	1	6	12
# at start of interval	372	361	337	313	341	328	295	280
# events in interval	11	24	24	20	13	33	15	15
# event cumulative	11	35	59	79	13	46	61	76
K-M Event Rate	1.1	3.2	9.4	16.1	0.0	4.1	13.5	17.9
Lower 95% CI	0.0	1.4	6.4	12.4	NA	2.0	9.9	13.8
Upper 95% CI	2.1	5.0	12.4	19.9	NA	6.2	17.1	22.0

*0 = 0-29 days, 1 = 30-182 days, 6 = 183-364 days, 12 ≥ 365 days.
Cumulative probability of event estimate is based on the Kaplan-Meier method
For worst case scenario the following assumptions were made for the censored subjects: the 7 TAVR subjects were assumed to have died on date of censoring and the 15 SAVR subjects were assumed to be alive at 1 year.

3. Key Secondary Safety and Effectiveness Endpoints

Hierarchical Testing of Secondary Endpoints

Hypothesis testing was performed on six pre-specified secondary endpoints using a hierarchical test procedure, as shown in Table 14. TAVR was found to be statistically non-inferior to SAVR within the pre-specified non-inferiority margins in terms of changes in mean gradient and EOA as well as in NYHA functional classification and KCCQ from baseline to 12 months. However, TAVR was not found to be statistically superior to SAVR with respect to the MACCE rate (p=0.1033), which was a powered secondary endpoint, as discussed in more detail later. In other words, the powered secondary endpoint of MACCE rate was not met. As a result, no hypothesis testing was conducted on SF-12 per the pre-specified hierarchical testing protocol.

Table 14: Secondary Endpoints: Hierarchical Testing

Secondary Objective	TAVR	SAVR	Difference (TAVR-SAVR)	Confidence Limit of the Difference	p-value	Test Result
Implanted Population						
#9 / Mean gradient change (12 Month – Baseline; mmHg) Ha: TAVR > SAVR-15 95% Lower CI	39.04 ± 13.63 (n=290)	35.42 ± 15.42 (n=222)	3.62	1.49	<0.0001	Passed
#9 / EOA change (12 Month – Baseline; cm^2) Ha: TAVR > SAVR-0.375 95% Lower CI	1.20 ± 0.53 (n=253)	0.81 ± 0.50 (n=182)	0.39	0.31	<0.0001	Passed
AT Population						
#5 / NYHA change (12 Month – Baseline) Ha: TAVR > SAVR-0.375 95% Lower CI	1.46 ± 0.76 (n=305)	1.46 ± 0.81 (n=232)	-0.001	-0.11	<0.0001	Passed

Secondary Objective	TAVR	SAVR	Difference (TAVR-SAVR)	Confidence Limit of the Difference	p-value	Test Result
#8 / KCCQ change (12 Month – Baseline) Ha: TAVR > SAVR-5 95% Lower CI	23.20 ± 25.56 (n=243)	21.88 ± 26.57 (n=189)	1.32	-2.84	0.0063	Passed
Powered Secondary #1 / MACCE event rate at 1 Month (K-M) Ha: TAVR < SAVR 97.5% Upper CI	8.21% (n=390)	10.93% (n=357)	-2.73%	1.51%	0.1033	Failed
#8 / SF-12 change (1 Month – Baseline) Ha: TAVR ≠ SAVR 95% two-sided CI	4.91 ± 10.26 (n=215)	-0.12 ± 10.04 (n=158)	5.03	(2.94, 7.13)	NA	Not Tested
Plus-minus values present the mean ± standard deviation.						

Powered Secondary Hypothesis

For the AT population, the MACCE rate was 8.21% for TAVR and 10.93% for SAVR (p = 0.1033). The null hypothesis that TAVR was equal to SAVR in the MACCE rate could not be rejected. Of note is that the MACCE rate observed in the trial for SAVR was considerably lower than that assumed in the power calculation (20% vs. 12.1%), which resulted in the pre-specified sample size being too small to detect a difference between the two study arms even if a difference exists. Therefore, this particular secondary endpoint was underpowered for the specified hypothesis testing.

Adverse Events that Occurred in the PMA Clinical Study

Table 15 provides a summary of the adverse events (AEs) that occurred in this study for the TAVR and SAVR treatment arms.

Table 15: Adverse Event Summary – As Treated Population

Event	0-30 Days				0-12 Months			
	TAVR N=390		SAVR N=357		TAVR N=390		SAVR N=357	
	# Pts (#Event)	K-M Rate (%)	# Pts (#Event)	K-M Rate (%)	# Pts (#Event)	K-M Rate (%)	# Pts (#Event)	K-M Rate (%)
All-Cause Mortality	13 (13)	3.3%	16 (16)	4.5%	55 (55)	14.2%	67 (67)	19.1%
Cardiovascular	12 (12)	3.1%	16 (16)	4.5%	40 (40)	10.4%	44 (44)	12.8%
Valve-Related[1]	9 (9)	2.3%	2 (2)	0.6%	21 (21)	5.6%	7 (7)	2.2%
Non-Cardiovascular	1 (1)	0.3%	0 (0)	0.0%	15 (15)	4.2%	23 (23)	7.3%
Reintervention	3 (3)	0.8%	0 (0)	0.0%	7 (7)	1.9%	0 (0)	0.0%
Surgical	2 (2)	0.5%	0 (0)	0.0%	3 (3)	0.8%	0 (0)	0.0%
Percutaneous	1 (1)	0.3%	0 (0)	0.0%	4 (4)	1.1%	0 (0)	0.0%

Event	0-30 Days				0-12 Months			
	TAVR N=390		SAVR N=357		TAVR N=390		SAVR N=357	
	# Pts (#Event)	K-M Rate (%)	# Pts (#Event)	K-M Rate (%)	# Pts (#Event)	K-M Rate (%)	# Pts (#Event)	K-M Rate (%)
All Stroke	19 (20)	4.9%	22 (23)	6.2%	33 (34)	8.8%	42 (45)	12.6%
Major Stroke	15 (16)	3.9%	11 (11)	3.1%	22 (23)	5.8%	23 (23)	7.0%
Minor Stroke	4 (4)	1.0%	12 (12)	3.4%	11 (11)	3.0%	20 (22)	6.0%
All-Cause Mortality or Major Stroke	23 (29)	5.9%	24 (27)	6.7%	63 (78)	16.3%	79 (90)	22.5%
CEC Adjudicated Bleed[2, 6]	150 (161)	38.5%	NA	NA	160 (186)	41.2%	NA	NA
Life Threatening or Disabling	48 (53)	12.3%	NA	NA	59 (65)	15.3%	NA	NA
Major Bleed	106 (108)	27.3%	NA	NA	110 (121)	28.4%	NA	NA
Re-Classified Bleed[3]	157 (170)	40.3%	243 (258)	68.1%	167 (195)	43.0%	252 (290)	70.8%
"Life Threatening or Disabling"	53 (58)	13.6%	125 (130)	35.0%	64 (70)	16.6%	136 (150)	38.4%
"Major Bleed"	109 (112)	28.1%	123 (128)	34.5%	114 (125)	29.5%	130 (140)	36.7%
Major Vascular Complication	23 (23)	5.9%	6 (6)	1.7%	24 (24)	6.2%	7 (7)	2.0%
Acute Kidney Injury	23 (23)	6.0%	54 (54)	15.1%	23 (23)	6.0%	54 (54)	15.1%
MI	3 (3)	0.8%	3 (3)	0.8%	7 (7)	1.9%	5 (5)	1.5%
Peri-Procedural	3 (3)	0.8%	2 (2)	0.6%	3 (3)	0.8%	2 (2)	0.6%
Spontaneous	0 (0)	0.0%	1 (1)	0.3%	4 (4)	1.1%	3 (3)	0.9%
Cardiac Perforation	5 (5)	1.3%	0 (0)	0.0%	5 (5)	1.3%	0 (0)	0.0%
Cardiogenic Shock	9 (9)	2.3%	11 (11)	3.1%	9 (9)	2.3%	11 (11)	3.1%
Cardiac Tamponade	6 (6)	1.5%	4 (4)	1.1%	7 (7)	1.8%	5 (5)	1.4%
Valve Endocarditis	0 (0)	0.0%	0 (0)	0.0%	2 (2)	0.6%	4 (4)	1.4%
Valve Thrombosis	0 (0)	0.0%	0 (0)	0.0%	0 (0)	0.0%	0 (0)	0.0%
Valve Embolism/Device Migration	0 (0)	0.0%	0 (0)	0.0%	0 (0)	0.0%	0 (0)	0.0%
MACCE[4]	30 (39)	7.7%	37 (42)	10.4%	79 (103)	20.4%	96 (117)	27.3%
MAE[5, 6]	200 (311)	51.3%	NA	NA	229 (417)	58.8%	NA	NA
Aortic Valve Hospitalization	15 (15)	3.9%	18 (19)	5.2%	59 (85)	16.1%	43 (59)	13.5%

[1] Valve-related death is any death caused by prosthetic valve dysfunction, valve thrombosis, embolism, bleeding event, or implanted valve endocarditis or related to reintervention on the operated valve.

[2]For TAVR, periprocedural transfusions meeting VARC I major and life-threatening bleeding criteria were adjudicated as events by the CEC irrespective of whether an overt bleeding complication had occurred. Since peri-procedural transfusions meeting VARC I criteria may be considered standard of care for SAVR procedures depending on the clinical circumstances, the same criteria were not applied and evidence of an overt bleeding complication (in addition to units transfused) were required to adjudicate an event for SAVR only. This makes a direct comparison of the CEC adjudicated bleeding rates in the trial inappropriate. For this reason, CEC adjudicated bleeding complications are shown for TAVR only.

[3] For the transfusion-based reclassification of bleeding events, units transfused were summed during the procedure, on the day of the procedure and the day following the procedure. Patients who received 2-3 units of packed red blood cells or homologous whole blood were considered to have had a "major bleeding complication" and patients receiving ≥4 units were considered to have had a "life-threatening or disabling bleeding complication" for both TAVR and SAVR. The nomenclature of the original adjudication was applied for consistency with this transfusion based re-classification.

[4]MACCE includes all-cause death, myocardial infarction (MI), all stroke, and reintervention.

[5] MAE includes all death, MI, all stroke, reintervention, cardiac perforation, cardiac tamponade, cardiogenic shock, valve embolism/device migration, prosthetic valve dysfunction, acute kidney injury, major vascular complication, life threatening of disabling bleed, major bleed, valve endocarditis VARC I Definitions.

[6] Bleeding complications and MAE rate cells have been intentionally left blank for SAVR in this table because of differing definitions employed for bleeding complications have made comparison of the rates to TAVR inappropriate.

Neurological Events

Table 16 provides a summary of the neurological events that occurred in this study for the TAVR and SAVR treatment arms. Stroke and TIA were defined according to the Valve Academic Research Consortium I (VARC-I) definitions.[1]

Table 16: CEC Adjudicated Neurological Events – As Treated Population

Event	0-30 Days				0-12 Months			
	TAVR N=390		SAVR N=357		TAVR N=390		SAVR N=357	
	# Pts (#Event)	K-M Rate (%)	# Pts (#Event)	K-M Rate (%)	# Pts (#Event)	K-M Rate (%)	# Pts (#Event)	K-M Rate (%)
Neurological Events	56 (61)	14.5%	79 (90)	22.2%	79 (101)	20.8%	110 (133)	31.9%
All Stroke	19 (20)	4.9%	22 (23)	6.2%	33 (34)	8.8%	42 (45)	12.6%
Major Stroke	15 (16)	3.9%	11 (11)	3.1%	22 (23)	5.8%	23 (23)	7.0%
Ischemic	14 (14)	3.6%	9 (9)	2.5%	19 (19)	5.0%	18 (18)	5.5%
Hemorrhagic	1 (2)	0.3%	0 (0)	0.0%	3 (4)	0.8%	3 (3)	0.9%
Undetermined	0 (0)	0.0%	2 (2)	0.6%	0 (0)	0.0%	2 (2)	0.6%
Minor Stroke	4 (4)	1.0%	12 (12)	3.4%	11 (11)	3.0%	20 (22)	6.0%
Ischemic	3 (3)	0.8%	11 (11)	3.1%	10 (10)	2.7%	18 (20)	5.4%
Hemorrhagic	0 (0)	0.0%	1 (1)	0.3%	0 (0)	0.0%	2 (2)	0.6%
Undetermined	1 (1)	0.3%	0 (0)	0.0%	1 (1)	0.3%	0 (0)	0.0%
TIA	3 (3)	0.8%	1 (1)	0.3%	6 (7)	1.6%	5 (5)	1.6%
Encephalopathy	36 (38)	9.4%	61 (66)	17.2%	49 (57)	13.0%	69 (81)	19.7%
Cerebral Infarction-Asymptomatic	0 (0)	0.0%	0 (0)	0.0%	0 (0)	0.0%	0 (0)	0.0%
Intracranial Hemorrhage	0 (0)	0.0%	0 (0)	0.0%	3 (3)	0.9%	2 (2)	0.7%

Echocardiographic Assessment of Total Aortic Regurgitation

Table 17 summarizes the total aortic regurgitation (AR) severity over time in the TAVR and SAVR treatment arms.

Table 17: Total Aortic Regurgitation by Visit (Core Lab) – Implanted Population

Interval / Valve Size	All TAVR N=389	All SAVR N=353
Screening/ Baseline		
None	15.1% (58/385)	14.7% (51/346)
Trace	37.9% (146/385)	33.2% (115/346)
Mild	41.8% (161/385)	46.0% (159/346)
Moderate	5.2% (20/385)	5.5% (19/346)
Severe	0.0% (0/385)	0.6% (2/346)
1 Month		
None	12.3% (44/359)	65.3% (201/308)
Trace	41.2% (148/359)	22.7% (70/308)
Mild	36.5% (131/359)	10.7% (33/308)
Moderate	8.1% (29/359)	1.3% (4/308)
Severe	1.9% (7/359)	0.0% (0/308)

Interval / Valve Size	All TAVR N=389	All SAVR N=353
6 Month		
None	21.4% (68/318)	60.3% (152/252)
Trace	37.4% (119/318)	28.2% (71/252)
Mild	29.9% (95/318)	9.9% (25/252)
Moderate	9.7% (31/318)	1.6% (4/252)
Severe	1.6% (5/318)	0.0% (0/252)
12 Month		
None	28.6% (85/297)	68.2% (152/223)
Trace	35.4% (105/297)	21.5% (48/223)
Mild	29.0% (86/297)	9.0% (20/223)
Moderate	6.7% (20/297)	0.9% (2/223)
Severe	0.3% (1/297)	0.4% (1/223)

Echocardiographic Assessment of EOA and Mean Gradient

The EOA and the mean gradient values obtained over time for the TAVR and SAVR patients in the Implanted population are shown in Table 18.

Table 18: Effective Orifice Area (cm^2) & Mean Gradient (mmHg) By Visit (Core Lab) – Implanted Population

	EOA (cm^2)		Mean Gradient (mmHg)	
	TAVR N=389	SAVR N=353	TAVR N=389	SAVR N=353
Screening/Baseline	0.72 ± 0.23 (349)	0.73 ± 0.24 (306)	48.27 ± 15.31 (387)	47.65 ± 13.85 (350)
1 Month	1.95 ± 0.56 (344)	1.60 ± 0.51 (280)	8.88 ± 3.87 (356)	11.71 ± 5.71 (311)
6 Month	1.91 ± 0.53 (293)	1.57 ± 0.49 (226)	9.05 ± 4.07 (318)	12.11 ± 6.32 (253)
12 Month	1.91 ± 0.51 (274)	1.57 ± 0.49 (206)	9.07 ± 3.49 (291)	12.40 ± 7.38 (224)
Plus-minus values present the mean ± standard deviation.				

Conduction Disturbance Requiring Permanent Pacemaker Implantation

Table 19 presents the pacemaker implantation rate for the TAVR and SAVR patients in the AT population. Table 20 summarizes subjects with key measurements on the screening electrocardiogram and subsequent rate of new permanent pacemaker implantation (PPI) at 30 days in these subjects. Subjects with pre-existing right bundle branch block (RBBB) and atrioventricular block (AVB) experienced higher PPI post CoreValve implant; however due to the limited sample size, limited conclusions can be developed. Additionally, no conclusions can be developed for subjects with pre-existing right bundle branch block (LBBB) due to the limited sample size. These variables are consistent with results from literature. De Carlo et al. evaluated 275 consecutive patients with no prior history of PPI and underwent a CoreValve implantation.[2] Using univariate analyses, patients with longer PR interval, longer QRS duration or RBBB at baseline were identified as having significantly higher PPI rate than those without. Furthermore, using multivariate analyses, baseline RBBB and longer PR interval were identified as independent predictors of PPI.

Table 19: Conduction Disturbance Requiring Pacemaker – As Treated Population

	TAVR N=390		SAVR N=357	
	# of Patients	K-M Event Rate (%)	# of Patients	K-M Event Rate (%)
New Permanent Pacemaker Implant[1]				
0-30 Days	76	19.8%	25	7.1%
0-12 Months	85	22.3%	38	11.3%
Permanent Pacemaker Implant[2]				
0-30 Days	76	25.7%	24	8.6%
0-12 Months	84	28.6%	36	13.5%

[1] Patients with pacemaker or ICD at baseline are included in the denominator.

[2] Patients with pacemaker or ICD at baseline are excluded from the numerator and denominator. Note one (1) TAVR patient and two (2) SAVR patients with baseline pacemaker/ICD, received new pacemaker/ICD between 30-365 days.

Table 20: Site Reported Screening Electrocardiogram and Rate of New Permanent Pacemaker Implantation (PPI) at 30 Days (High Risk TAVR AT subjects without Pre-Existing IPG/ICD)

	PPI (%)	
Measurement	Present at Screening	Not Present at Screening
PR Interval (ms)		
PR <200	21.97% (38/173)	
PR >=200	30.77% (24/78)	
Ventricular Conduction Delays		
LBBB	16.00% (4/ 25)	26.39% (71/269)
RBBB	63.64% (28/ 44)	18.80% (47/250)
AtrioVentricular Block		
AVB	32.84% (22/ 67)	23.28% (54/232)
1st Degree	30.36% (17/ 56)	
2nd Degree		
MOBITZ I		
MOBITZ II		
3rd Degree		
Other	45.45% (5/ 11)	

Ratio of Days Alive out of Hospital versus Total Days Alive

The ratio of days alive out of hospital to total days alive was compared at 12 months between TAVR and SAVR patients (Table 21). All hospitalizations, including the hospital stays for device implantations, were analyzed. The ratio was 0.92 ± 0.20 for TAVR and 0.88 ± 0.23 for SAVR, which can be interpreted as follows: on average TAVR patients spent 92% and SAVR patients spent 88% of days alive after procedure out of the hospital.

Table 21: Ratio of Days Alive Out of Hospital – As Treated Population

	TAVR N=390	SAVR N=357
Total Number of Days Followed (Alive)	331.1 ± 91.8	310.1 ± 111.7
Number of Days in Hospital	12.7 ± 14.5	16.3 ± 14.0
Ratio Days Alive and Out of Hospital	0.92 ± 0.20	0.88 ± 0.23
Plus-minus values present the mean ± standard deviation.		

NYHA Functional Class

The NYHA classification was evaluated at several time points through the first year of follow-up, as shown in Table 22.

Table 22: NYHA Classification By Visit – As Treated Population

NYHA Classification	TAVR N=390	SAVR N=357
Baseline		
NYHA I	0.0% (0/390)	0.0% (0/350)
NYHA II	16.9% (66/390)	18.3% (64/350)
NYHA III	69.7% (272/390)	66.3% (232/350)
NYHA IV	13.3% (52/390)	15.4% (54/350)
Died prior to visit	0.0% (0/390)	0.0% (0/350)
Exit prior to visit	0	0
Visit occurred but NYHA not obtained	0	7
Visit missed	0	0
1 Month		
NYHA I	43.4% (163/376)	32.6% (108/331)
NYHA II	39.4% (148/376)	40.8% (135/331)
NYHA III	13.0% (49/376)	18.4% (61/331)
NYHA IV	0.3% (1/376)	4.2% (14/331)
Died prior to visit	4.0% (15/376)	3.9% (13/331)
Exit prior to visit	0	1
Visit occurred but NYHA not obtained	7	10
Visit missed	7	15

NYHA Classification	TAVR N=390	SAVR N=357
12 Month		
NYHA I	48.2% (176/365)	44.1% (134/304)
NYHA II	30.7% (112/365)	28.3% (86/304)
NYHA III	4.7% (17/365)	4.6% (14/304)
NYHA IV	0.0% (0/365)	0.7% (2/304)
Died prior to visit	16.4% (60/365)	22.4% (68/304)
Exit prior to visit	2	8
Visit occurred but NYHA not obtained	15	27
Visit missed	5	18

QoL Change

The QoL changes from baseline at 30 days and 12 months were evaluated using the Kansas City Cardiomyopathy Questionnaire (KCCQ), the QualityMetric's SF-12v2® Health Survey (SF12), and the EuroQoL (EQ-5D), as shown in Tables 23 - 25 for the TAVR and SAVR cohorts.

The KCCQ is a validated self-administered 23-item questionnaire that quantifies physical limitations, symptoms, self-effectiveness, social interference and quality of life. These individual scales are incorporated into an Overall Summary Score which combines the domains of physical limitation, symptoms, QoL, and social limitation with values ranging from 0-100; higher scores indicate lesser symptoms and better quality of life. Previous studies have suggested that KCCQ Overall Summary scores correlate roughly with New York Heart Association Functional Class as follows: Class I ≈ KCCQ Summary Score 75-100; Class II ≈ 60-74; Class III ≈ 45-59; and Class IV ≈ 0-44. In addition, there is a Clinical Summary Score that combines the domains of physical limitation and symptoms.

SF12 is a shorter version of the SF-36v2® Health Survey that uses 12 questions to measure functional health and well-being from the patient's point of view and is generally reported in two summary scores which evaluate physical (the SF-12 Physical Summary Score) and mental (the SF-12 Mental Summary Score) health. Values range from 0-100; higher scores indicate better functional health and well-being.

The EQ-5D is a measure of self-reported health outcomes that is applicable to a wide range of health conditions and treatments. It consists of 2 parts: a descriptive system (Part I) and a visual analogue scale (Part II). Part I of the scale consists of 5 single-item dimensions including: mobility, self care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has a 3 point response scale designed to indicate the level of the problem. The overall EQ-5D score from Part I is evaluated on a scale where 0.0 = death and 1.0 = perfect health. Part II uses a vertical graduated visual analogue scale (thermometer) to measure health status, ranging from worst imaginable health state to best imaginable health state.

FDA cautions interpretation of these results in the setting of an unblinded trial, particularly in a comparison of patients undergoing open heart surgery versus patients receiving less invasive TAVR.

Table 23: KCCQ By Visit – As Treated Population

KCCQ	TAVR N=390	SAVR N=357
Baseline		
Overall Summary Score	46.9 ± 23.4	46.6 ± 22.3
Clinical Summary Score	51.4 ± 23.3	50.8 ± 22.3
1 Month		
Overall Summary Score	66.2 ± 24.1	51.6 ± 25.4
Change from Baseline	19.0 ± 29.4	3.7 ± 27.6
Clinical Summary Score	66.8 ± 23.5	54.8 ± 24.5
Change from Baseline	14.8 ± 28.6	2.2 ± 26.6
12 Months		
Overall Summary Score	72.1 ± 21.8	70.5 ± 22.1
Change from Baseline	23.2 ± 25.6	21.9 ± 26.6
Clinical Summary Score	69.9 ± 22.1	68.3 ± 22.2
Change from Baseline	16.7 ± 25.7	15.3 ± 26.1
Plus-minus values present the mean ± standard deviation.		

Table 24: SF12 By Visit – As Treated Population

SF-12	TAVR N=390	SAVR N=357
Baseline		
Physical Component	30.8 ± 9.2	31.0 ± 8.6
Mental Component	47.5 ± 12.1	48.4 ± 11.7
1 Month		
Physical Component	35.9 ± 9.5	31.7 ± 8.5
Change from Baseline	4.9 ± 10.3	-0.1 ± 10.0
Mental Component	51.1 ± 11.1	45.0 ± 13.1
Change from Baseline	2.6 ± 13.1	-2.5 ± 13.4
12 Months		
Physical Component	37.0 ± 11.2	36.9 ± 9.7
Change from Baseline	6.0 ± 11.6	5.2 ± 10.3
Mental Component	52.8 ± 10.8	52.5 ± 10.5
Change from Baseline	4.5 ± 11.9	3.2 ± 12.1
Plus-minus values present the mean ± standard deviation.		

Table 25: EQ-5D By Visit – As Treated Population

EQ-5D	TAVR N=390	SAVR N=357
Baseline		
Index Score	0.73 ± 0.20	0.73 ± 0.18
1 Month		
Index Score	0.78 ± 0.19	0.67 ± 0.25
Change from Baseline	0.04 ± 0.24	-0.07 ± 0.26
12 Months		
Index Score	0.78 ± 0.18	0.78 ± 0.18
Change from Baseline	0.04 ± 0.20	0.01 ± 0.19
Plus-minus values present the mean ± standard deviation.		

4. Additional Study Observations

Procedure Data

As recommended in the protocol, the procedure was to occur within 30 days of randomization. As such, time to procedure was calculated between the randomization date and the date for the first attempted procedure. It was 13.1 ± 10.9 days for TAVR patients and 18.1 ± 14.3 days for SAVR patients.

Table 26 provides a summary of the procedure data for the TAVR cohort. The mean total time in the catheterization laboratory or operating room was approximately 3.5 hours for patients in the iliofemoral cohort, while the mean total procedure time (skin-to-skin) was on average slightly greater than 1 hour. In comparison, the mean total time in the catheterization laboratory or operating room was approximately 4 hours for the non-iliofemoral cohort, while the mean total procedure time was slightly less than 1 hour.

Table 26: TAVR Procedure Data - As Treated Population

	TAVR IF N=323	TAVR NIF N=67	TAVR N=390
Number of Index Procedures[1]	323	66	389
Total Time in Cath Lab or OR (min)	209.6 ± 58.6	249.1 ± 63.4	216.3 ± 61.2
Total Procedure Time (min)	61.4 ± 33.9	55.6 ± 41.7	60.4 ± 35.3
Total CoreValve Delivery Time (min)	13.5 ± 11.3	15.4 ± 13.4	13.8 ± 11.7
Number of Valves Used			
0[2]	0.0% (0/323)	1.5% (1/67)	0.3% (1/390)
1	91.3% (295/323)	92.5% (62/67)	91.5% (357/390)
2	8.4% (27/323)	6.0% (4/67)	7.9% (31/390)
3	0.3% (1/323)	0.0% (0/67)	0.3% (1/390)
Number of Valves Implanted			
0	0.0% (0/323)	1.5% (1/67)	0.3% (1/390)
1	95.0% (307/323)	98.5% (66/67)	95.6% (373/390)
2	5.0% (16/323)	0.0% (0/67)	4.1% (16/390)
3	0.0% (0/323)	0.0% (0/67)	0.0% (0/390)

	TAVR IF N=323	TAVR NIF N=67	TAVR N=390
Valve Size Implanted			
23 mm	1.5% (5/323)	1.5% (1/66)	1.5% (6/389)
26 mm	29.4% (95/323)	40.9% (27/66)	31.4% (122/389)
29 mm	49.5% (160/323)	48.5% (32/66)	49.4% (192/389)
31 mm	19.5% (63/323)	9.1% (6/66)	17.7% (69/389)
Device Success[3]	86.9% (273/314)	87.3% (55/63)	87.0% (328/377)
Procedure Success[4]	81.5% (260/319)	82.8% (53/64)	81.7% (313/383)

[1] The table includes patients with the index procedure. Index procedure (TAVR): the first procedure that the Medtronic CoreValve system delivery catheter is introduced.

[2] A single patient had no valves used or implanted during the procedure as the patient became hypotensive after the TEE probe was placed and the patient was converted to SAVR.

[3] Device success is defined as deployment, only 1 valve implanted, only 1 valve in correct anatomic location, EOA >1.2cm^2 for 26, 29 and 31mm and ≥ 0.9 cm^2 for 23mm, mean gradient < 20mmHg or peak velocity < 3 m/sec, and aortic regurgitation < moderate.

[4] Procedure success is defined as device success and absence of in-hospital MACCE.

Valve-in-Valve Experience

In the "As Treated" population, a total of 16 patients had more than one CoreValve devices implanted. Fourteen (14) patients had a CoreValve-in-CoreValve procedure, all of which were due to device malpositioning and/or residual aortic regurgitation. Two (2) patients had a non valve-in-valve implant of a second valve (i.e., the first CoreValve was placed in the aorta).

Results by Access Routes - Iliofemoral (IF) and Non-Iliofemoral (NIF) Cohorts

Primary Endpoint Stratified by Access Route

The study was powered to demonstrate non-inferiority of TAVR compared to SAVR for the primary endpoint for all patients (iliofemoral and non-iliofemoral) pooled. It was pre-specified that the primary endpoint would be assessed for different access route subgroups independently, but this assessment was not powered and would not be the basis for assessing success or failure of the primary endpoint. The all-cause mortality rates are shown in Figure 11 and Table 27 for the iliofemoral subgroup and Figure 12 and Table 28 for the non-iliofemoral subgroup.

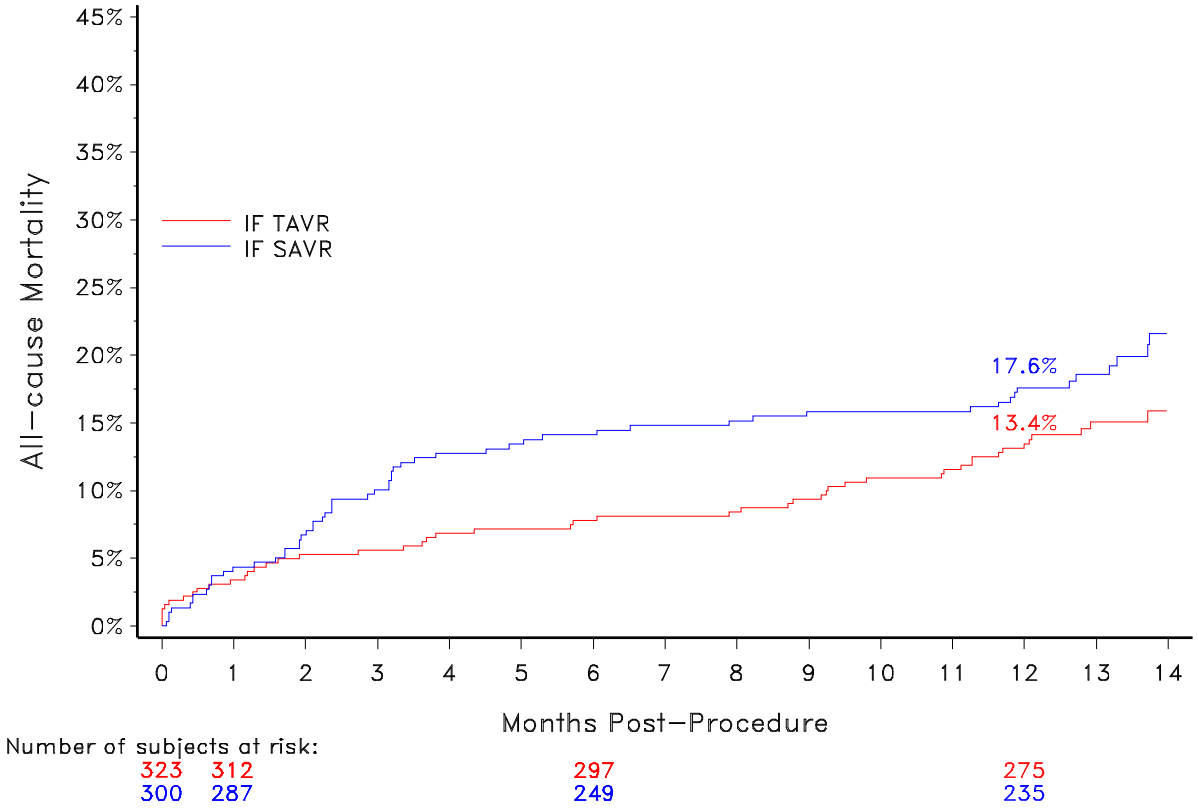


Figure 11: All-Cause Mortality – Iliofemoral As Treated Population

Table 27: All-Cause Mortality – Iliofemoral As Treated Population

Interval Post Procedure (months)*	TAVR N=390				SAVR N=357			
	0	1	6	12	0	1	6	12
# at start of interval	323	312	297	275	300	287	249	235
# events in interval	11	14	17	19	12	30	10	16
# event cumulative	11	25	42	61	12	42	52	68
K-M Event Rate	1.2	3.4	7.8	13.4	0.0	4.3	14.1	17.6
*0 = 0-29 days, 1 = 30-182 days, 6 = 183-364 days, 12 ≥ 365 days. Cumulative probability of event estimate is based on the Kaplan-Meier method								

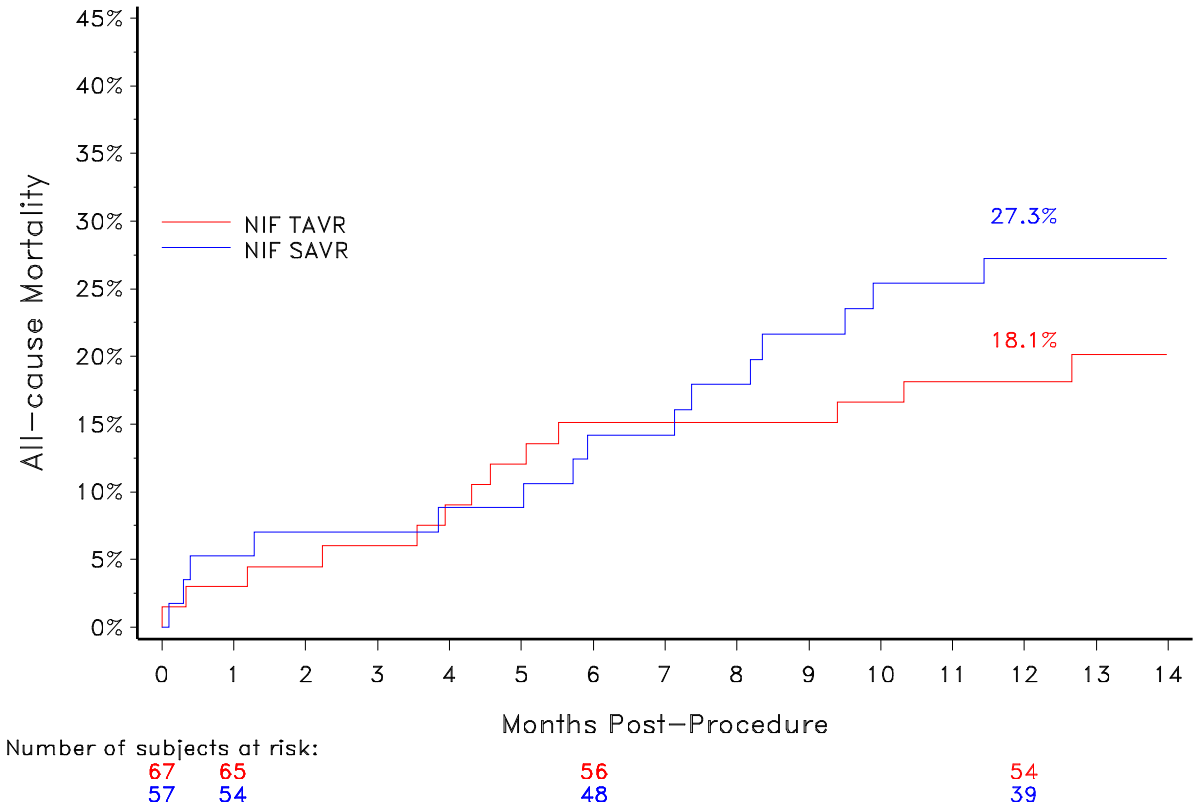


Figure 12: All-Cause Mortality – Non-Iliofemoral As Treated Population

Table 28: All-Cause Mortality – Non-Iliofemoral As Treated Population

Interval Post Procedure (months)*	TAVR N=390				SAVR N=357			
	0	1	6	12	0	1	6	12
# at start of interval	67	65	56	54	57	54	48	39
# events in interval	2	8	2	1	3	5	7	1
# event cumulative	2	10	12	13	3	8	15	16
K-M Event Rate	1.5	3.0	15.1	18.1	0.0	5.3	14.2	27.3
*0 = 0-29 days, 1 = 30-182 days, 6 = 183-364 days, 12 ≥ 365 days. Cumulative probability of event estimate is based on the Kaplan-Meier method								

AEs Stratified by Access Route

The AEs for the iliofemoral patients and non-iliofemoral patients in both study arms are shown in Tables 29 and 30, respectively.

Table 29: Adverse Event Summary – Iliofemoral As Treated Population

Event	0-30 Days				0-12 Months			
	TAVR N=323		SAVR N=300		TAVR N=323		SAVR N=300	
	# Pts (#Event)	K-M Rate (%)	# Pts (#Event)	K-M Rate (%)	# Pts (#Event)	K-M Rate (%)	# Pts (#Event)	K-M Rate (%)
All-Cause Mortality	11 (11)	3.4%	13 (13)	4.3%	43 (43)	13.4%	52 (52)	17.6%
Cardiovascular	10 (10)	3.1%	13 (13)	4.3%	32 (32)	10.1%	35 (35)	12.0%
Valve-Related[1]	8 (8)	2.5%	1 (1)	0.3%	18 (18)	5.7%	4 (4)	1.5%
Non-Cardiovascular	1 (1)	0.3%	0 (0)	0.0%	11 (11)	3.7%	17 (17)	6.3%
Reintervention	2 (2)	0.6%	0 (0)	0.0%	6 (6)	2.0%	0 (0)	0.0%
Surgical	1 (1)	0.3%	0 (0)	0.0%	2 (2)	0.7%	0 (0)	0.0%
Percutaneous	1 (1)	0.3%	0 (0)	0.0%	4 (4)	1.3%	0 (0)	0.0%
All Stroke	16 (17)	5.0%	15 (15)	5.0%	28 (29)	9.0%	30 (32)	10.8%
Major Stroke	12 (13)	3.7%	6 (6)	2.0%	18 (19)	5.8%	13 (13)	4.7%
Minor Stroke	4 (4)	1.3%	9 (9)	3.0%	10 (10)	3.3%	17 (19)	6.2%
CEC Adjudicated Bleed[2, 6]	107 (112)	33.1%	NA	NA	117 (136)	36.4%	NA	NA
Life Threatening or Disabling	32 (34)	9.9%	NA	NA	42 (45)	13.2%	NA	NA
Major Bleed	76 (78)	23.6%	NA	NA	80 (91)	25.0%	NA	NA
Re-Classified Bleed[3]	113 (119)	35.0%	204 (218)	68.0%	123 (143)	38.3%	210 (238)	70.2%
"Life Threatening or Disabling"	35 (37)	10.8%	105 (110)	35.0%	45 (48)	14.1%	113 (121)	38.0%
"Major Bleed"	80 (82)	24.9%	103 (108)	34.4%	85 (95)	26.6%	108 (117)	36.2%
Major Vascular Complication	21 (21)	6.5%	5 (5)	1.7%	22 (22)	6.8%	6 (6)	2.0%
Acute Kidney Injury	16 (16)	5.0%	43 (43)	14.3%	16 (16)	5.0%	43 (43)	14.3%
MI	3 (3)	0.9%	2 (2)	0.7%	7 (7)	2.3%	4 (4)	1.4%
Peri-Procedural	3 (3)	0.9%	2 (2)	0.7%	3 (3)	0.9%	2 (2)	0.7%
Spontaneous	0 (0)	0.0%	0 (0)	0.0%	4 (4)	1.4%	2 (2)	0.8%
Cardiac Perforation	4 (4)	1.2%	0 (0)	0.0%	4 (4)	1.2%	0 (0)	0.0%
Cardiogenic Shock	6 (6)	1.9%	8 (8)	2.7%	6 (6)	1.9%	8 (8)	2.7%
Cardiac Tamponade	5 (5)	1.5%	3 (3)	1.0%	6(6)	1.9%	4 (4)	1.3%
Valve Endocarditis	0 (0)	0.0%	0 (0)	0.0%	2 (2)	0.7%	3 (3)	1.2%
Valve Thrombosis	0 (0)	0.0%	0 (0)	0.0%	0 (0)	0.0%	0 (0)	0.0%
Valve Embolism/Device Migration	0 (0)	0.0%	0 (0)	0.0%	0 (0)	0.0%	0 (0)	0.0%
MACCE[4]	26 (33)	8.0%	29 (30)	9.7%	65 (85)	20.2%	76 (88)	25.6%
MAE[5, 6]	151 (239)	46.7%	NA	NA	177 (331)	54.8%	NA	NA
Aortic Valve Hospitalization	8 (8)	2.5%	11 (12)	3.8%	44 (68)	14.5%	30 (43)	11.3%
New Permanent Pacemaker Implant[7]	64 (65)	26.5%	21 (21)	9.0%	70 (72)	29.1%	33 (33)	14.9%

Event	0-30 Days				0-12 Months			
	TAVR N=323		SAVR N=300		TAVR N=323		SAVR N=300	
	# Pts (#Event)	K-M Rate (%)	# Pts (#Event)	K-M Rate (%)	# Pts (#Event)	K-M Rate (%)	# Pts (#Event)	K-M Rate (%)
Permanent Pacemaker Implant[8]	64 (65)	20.1%	21 (21)	7.1%	71 (73)	22.4%	34 (24)	12.1%

[1] Valve-related death is any death caused by prosthetic valve dysfunction, valve thrombosis, embolism, bleeding event, or implanted valve endocarditis or related to reintervention on the operated valve.

[2]For TAVR, periprocedural transfusions meeting VARC I major and life-threatening bleeding criteria were adjudicated as events by the CEC irrespective of whether an overt bleeding complication had occurred. Since peri-procedural transfusions meeting VARC I criteria may be considered standard of care for SAVR procedures depending on the clinical circumstances, the same criteria were not applied and evidence of an overt bleeding complication (in addition to units transfused) were required to adjudicate an event for SAVR only. This makes a direct comparison of the CEC adjudicated bleeding rates in the trial inappropriate. For this reason, CEC adjudicated bleeding complications are shown for TAVR only.

[3] For the transfusion-based reclassification of bleeding events, units transfused were summed during the procedure, on the day of the procedure and the day following the procedure. Patients who received 2-3 units of packed red blood cells or homologous whole blood were considered to have had a "major bleeding complication" and patients receiving ≥4 units were considered to have had a "life-threatening or disabling bleeding complication" for both TAVR and SAVR. The nomenclature of the original adjudication was applied for consistency with this transfusion based re-classification.

[4] MACCE includes all-cause death, myocardial infarction (MI), all stroke, and reintervention.

[5] MAE includes all death, MI, all stroke, reintervention, cardiac perforation, cardiac tamponade, cardiogenic shock, valve embolism/device migration, prosthetic valve dysfunction, acute kidney injury, major vascular complication, life threatening of disabling bleed, major bleed, valve endocarditis VARC I Definitions.

[6] Bleeding complications and MAE rate cells have been intentionally left blank for SAVR in this table due to differing definitions employed for bleeding complications have made comparison of the rates to TAVR inappropriate.

[7] Patients with pacemaker or ICD at baseline are not included.

[8] Patients with pacemaker or ICD at baseline are included.

Table 30: Adverse Event Summary – Non-Iliofemoral As Treated Population

Event	0-30 Days				0-12 Months			
	TAVR N=67		SAVR N=57		TAVR N=67		SAVR N=57	
	# Pts (#Event)	K-M Rate (%)	# Pts (#Event)	K-M Rate (%)	# Pts (#Event)	K-M Rate (%)	# Pts (#Event)	K-M Rate (%)
All-Cause Mortality	2 (2)	3.0%	3 (3)	5.3%	12 (12)	18.1%	15 (15)	27.3%
Cardiovascular	2 (2)	3.0%	3 (3)	5.3%	8 (8)	12.4%	9 (9)	16.8%
Valve-Related[1]	1 (1)	1.5%	1 (1)	1.8%	3 (3)	4.8%	3 (3)	6.0%
Non-Cardiovascular	0 (0)	0.0%	0 (0)	0.0%	4 (4)	6.6%	6 (6)	12.6%
Reintervention	1 (1)	1.5%	0 (0)	0.0%	1 (1)	1.5%	0 (0)	0.0%
Surgical	1 (1)	1.5%	0 (0)	0.0%	1 (1)	1.5%	0 (0)	0.0%
Percutaneous	0 (0)	0.0%	0 (0)	0.0%	0 (0)	0.0%	0 (0)	0.0%
All Stroke	3 (3)	4.5%	7 (8)	12.3%	5 (5)	7.7%	12 (13)	22.3%
Major Stroke	3 (3)	4.5%	5 (5)	8.8%	4 (4)	6.1%	10 (10)	18.7%
Minor Stroke	0 (0)	0.0%	3 (3)	5.3%	1 (1)	1.6%	3 (3)	5.3%
CEC Adjudicated Bleed[2, 6]	43 (49)	64.2%	NA	NA	43 (50)	64.2%	NA	NA
Life Threatening or Disabling	16 (19)	23.9%	NA	NA	17 (20)	25.5%	NA	NA
Major Bleed	30 (30)	45.1%	NA	NA	30 (30)	45.1%	NA	NA
Re-Classified Bleed[3]	44 (51)	65.7%	39 (40)	68.4%	44 (52)	65.7%	42 (52)	74.3%
"Life Threatening or Disabling"	18 (21)	26.9%	20 (20)	35.1%	19 (22)	28.5%	23 (29)	40.5%
"Major Bleed"	29 (30)	43.6%	20 (20)	35.1%	29 (30)	43.6%	22 (23)	39.8%
Major Vascular Complication	2 (2)	3.0%	1 (1)	1.8%	2 (2)	3.0%	1 (1)	1.8%
Acute Kidney Injury	7 (7)	10.6%	11 (11)	19.3%	7 (7)	10.6%	11 (11)	19.3%

Event	0-30 Days				0-12 Months			
	TAVR N=67		SAVR N=57		TAVR N=67		SAVR N=57	
	# Pts (#Event)	K-M Rate (%)	# Pts (#Event)	K-M Rate (%)	# Pts (#Event)	K-M Rate (%)	# Pts (#Event)	K-M Rate (%)
MI	0 (0)	0.0%	1 (1)	1.8%	0 (0)	0.0%	1 (1)	1.8%
Peri-Procedural	0 (0)	0.0%	0 (0)	0.0%	0 (0)	0.0%	0 (0)	0.0%
Spontaneous	0 (0)	0.0%	1 (1)	1.8%	0 (0)	0.0%	1 (1)	1.8%
Cardiac Perforation	1 (1)	1.5%	0 (0)	0.0%	1 (1)	1.5%	0 (0)	0.0%
Cardiogenic Shock	3 (3)	4.5%	3 (3)	5.3%	3 (3)	4.5%	3 (3)	5.3%
Cardiac Tamponade	1 (1)	1.5%	1 (1)	1.9%	1 (1)	1.5%	1 (1)	1.9%
Valve Endocarditis	0 (0)	0.0%	0 (0)	0.0%	0 (0)	0.0%	1 (1)	2.3%
Valve Thrombosis	0 (0)	0.0%	0 (0)	0.0%	0 (0)	0.0%	0 (0)	0.0%
Valve Embolism/Device Migration	0 (0)	0.0%	0 (0)	0.0%	0 (0)	0.0%	0 (0)	0.0%
MACCE[4]	4 (6)	6.1%	8 (12)	14.0%	14 (18)	21.4%	20 (29)	36.1%
MAE[5, 6]	49 (72)	73.1%	NA	NA	52 (86)	77.6%	NA	NA
Aortic Valve Hospitalization	7 (7)	10.7%	7 (7)	12.9%	15 (17)	23.8%	13 (16)	25.2%
New Permanent Pacemaker Implant[7]	12 (12)	22.2%	3 (3)	6.3%	14 (14)	26.3%	3 (3)	6.3%
Permanent Pacemaker Implant[8]	12 (12)	18.2%	4 (4)	7.1%	14 (14)	21.7%	4 (4)	7.1%

[1] Valve-related death is any death caused by prosthetic valve dysfunction, valve thrombosis, embolism, bleeding event, or implanted valve endocarditis or related to reintervention on the operated valve.

[2]For TAVR, periprocedural transfusions meeting VARC I major and life-threatening bleeding criteria were adjudicated as events by the CEC irrespective of whether an overt bleeding complication had occurred. Since peri-procedural transfusions meeting VARC I criteria may be considered standard of care for SAVR procedures depending on the clinical circumstances, the same criteria werewas not applied and evidence of an overt bleeding complication (in addition to units transfused) were required to adjudicate an event for SAVR only. This makes a direct comparison of the CEC adjudicated bleeding rates in the trial inappropriate. For this reason, CEC adjudicated bleeding complications are shown for TAVR only.

[3] For the transfusion-based reclassification of bleeding events, units transfused were summed during the procedure, on the day of the procedure and the day following the procedure. Patients who received 2-3 units of packed red blood cells or homologous whole blood were considered to have had a "major bleeding complication" and patients receiving ≥4 units were considered to have had a "life-threatening or disabling bleeding complication" for both TAVR and SAVR. The nomenclature of the original adjudication was applied for consistency with this transfusion based re-classification.

[4] MACCE includes all-cause death, myocardial infarction (MI), all stroke, and reintervention.

[5] MAE includes all death, MI, all stroke, reintervention, cardiac perforation, cardiac tamponade, cardiogenic shock, valve embolism/device migration, prosthetic valve dysfunction, acute kidney injury, major vascular complication, life threatening of disabling bleed, major bleed, valve endocarditis VARC I Definitions.

[6] Bleeding complications and MAE rate cells have been intentionally left blank for SAVR in this table due to differing definitions employed for bleeding complications have made comparison of the rates to TAVR inappropriate.

[7] Patients with pacemaker or ICD at baseline are not included.

[8] Patients with pacemaker or ICD at baseline are included.

Gender Analysis

The primary endpoint and the powered secondary endpoint of MACCE rate were examined for gender differences, as shown in Figures 13 and 14 and Tables 31 and 32.

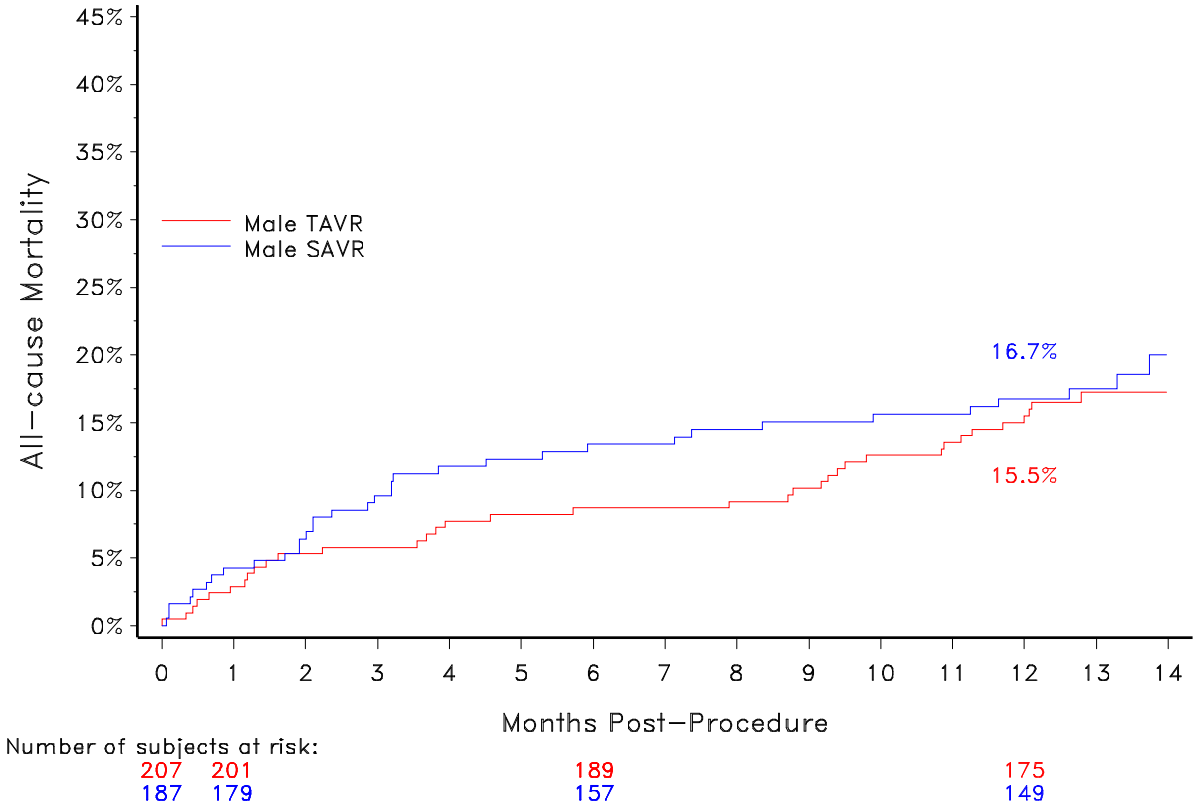


Figure 13: All-Cause Mortality at 12 Months for Male Patients – As Treated Population

Table 31: All-Cause Mortality for Male Patients – As Treated Population

Interval Post Procedure (months)*	TAVR N=207				SAVR N=187			
	0	1	6	12	0	1	6	12
# at start of interval	207	201	189	175	187	179	157	149
# events in interval	6	12	13	12	8	17	6	10
# event cumulative	6	18	31	43	8	25	31	41
K-M Event Rate	0.5	2.9	8.7	15.5	0.0	4.3	13.4	16.7
*0 = 0-29 days, 1 = 30-182 days, 6 = 183-364 days, 12 ≥ 365 days. Cumulative probability of event estimate is based on the Kaplan-Meier method								

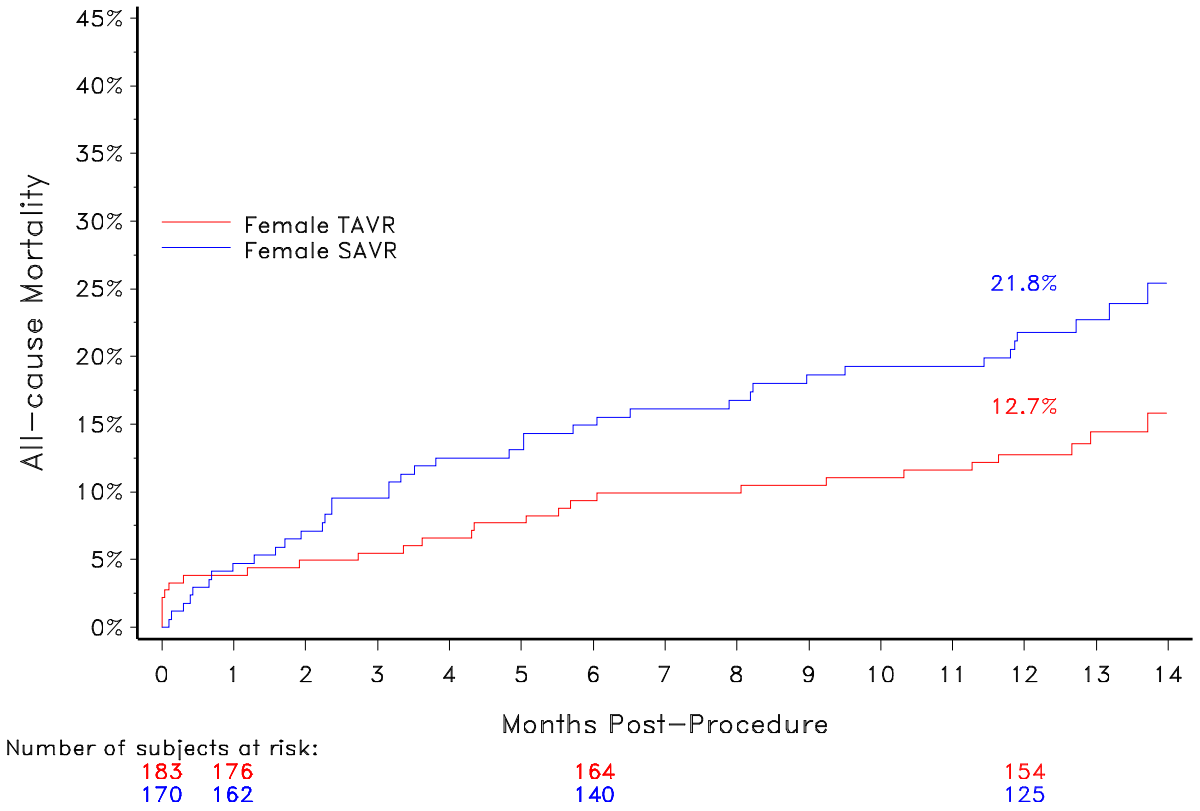


Figure 14: All-Cause Mortality at 12 Months for Female Patients – As Treated Population

Table 32: All-Cause Mortality for Female Patients – As Treated Population

Interval Post Procedure (months)*	TAVR N=183				SAVR N=170			
	0	1	6	12	0	1	6	12
# at start of interval	183	176	164	154	170	162	140	125
# events in interval	7	10	6	8	7	18	11	7
# event cumulative	7	17	23	31	7	25	36	43
K-M Event Rate	2.2	3.8	9.3	12.7	0.0	4.7	14.9	21.8
*0 = 0-29 days, 1 = 30-182 days, 6 = 183-364 days, 12 ≥ 365 days. Cumulative probability of event estimate is based on the Kaplan-Meier method								

Mortality Stratified by STS Score

An analysis was performed for TAVR patients to examine the relationship between all-cause mortality and STS predicted risk of mortality at baseline. Patients were stratified by STS score with the subgroups being STS < 4, STS 4-7, STS >7-15 and STS >15. The result is shown in Figure 15 and Table 33.

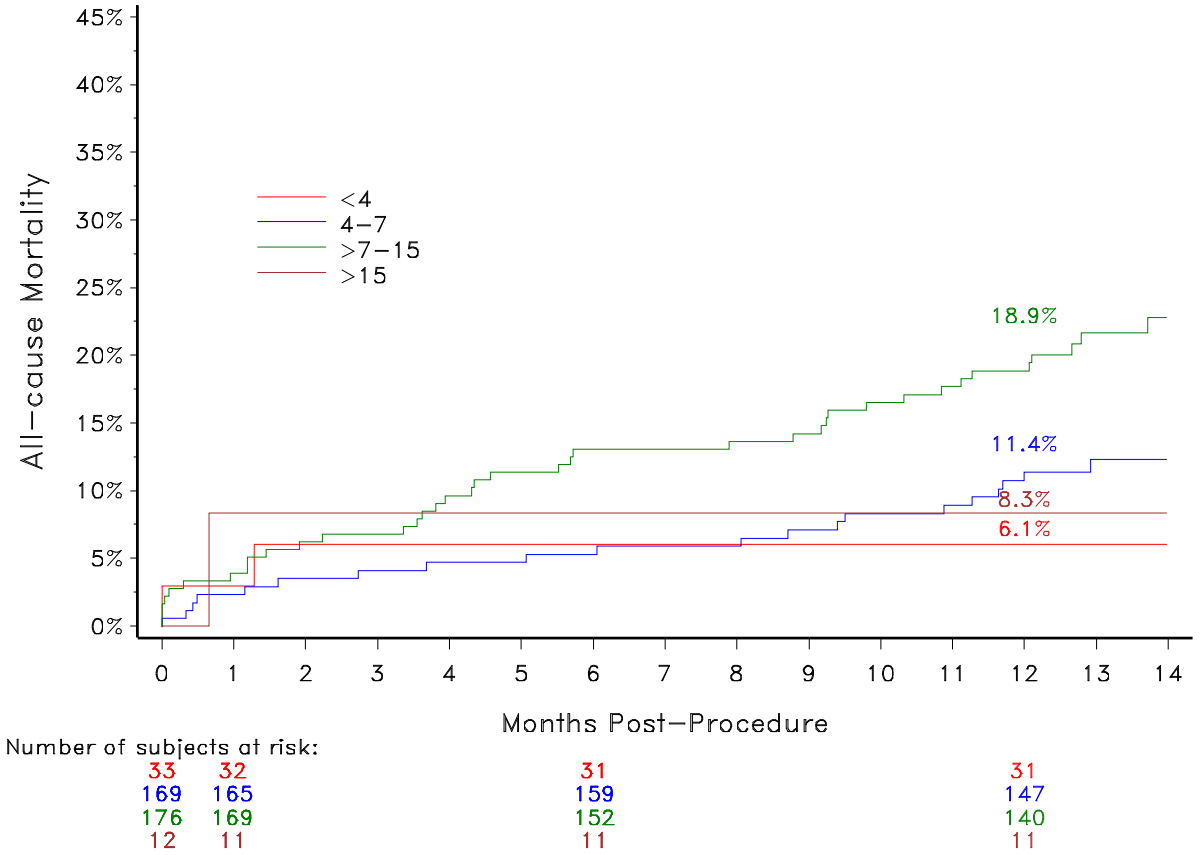


Figure 15: All-Cause Mortality by STS – TAVR As Treated Population

Table 33: All-Cause Mortality by STS – TAVR As Treated Population

Interval Post Procedure (months)	STS <4 N=33				STS 4 - 7 N=169			
	0	1	6	12	0	1	6	12
# at start of interval	33	32	31	31	169	165	159	147
# events in interval	1	1	0	0	4	5	9	6
# event cumulative	1	2	2	2	4	9	18	24
KM event Rate	3.0	3.0	6.1	6.1	0.6	2.4	5.3	11.4
	STS >7 - 15 N=176				STS >15 N=12			
Interval Post Procedure (months)	0	1	6	12	0	1	6	12
# at start of interval	176	169	152	140	12	11	11	11
# events in interval	7	16	10	14	1	0	0	0
# event cumulative	7	23	33	47	1	1	1	1
KM event Rate	1.7	4.0	13.1	18.9	0.0	8.3	8.3	8.3

*0 = 0-29 days, 1 = 30-182 days, 6 = 183-364 days, 12 ≥ 365 days.
Cumulative probability of event estimate is based on the Kaplan-Meier method.

Post-Implant Aortic Regurgitation and All-Cause Mortality

A *post hoc* subgroup analysis was performed for all TAVR patients (iliofemoral and non-iliofemoral) of the Implanted population to investigate the relationship between all-cause mortality and severity of aortic regurgitation at discharge (7 days post procedure or discharge, whichever is first). Two subgroups of iliofemoral patients with none/trace and greater than or equal to mild total aortic regurgitation at discharge were analyzed. The results from the analysis are shown in Figure 16 and Table 34, which show that residual aortic regurgitation at discharge appeared to be associated with long-term mortality in the TAVR patients. However, it was also noted that there were some differences in important baseline clinical characteristics of the patients between the two subgroups, as summarized in Table 35. As a result, it is not clear whether there was a causal relationship between residual aortic regurgitation and mortality. Nevertheless, the incidence of residual aortic regurgitation and its apparent association with late-term mortality will need to be carefully monitored in post-approval follow-up.

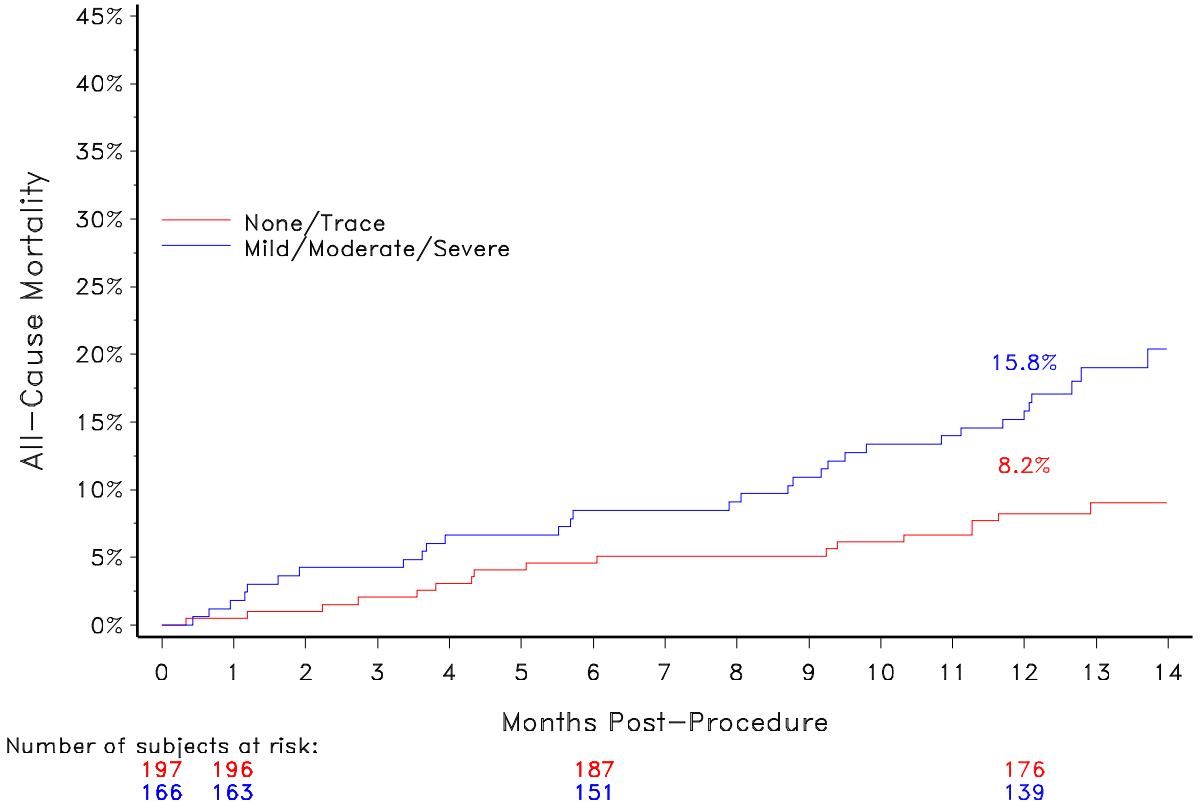


Figure 16 : All-Cause Mortality by Severity of Aortic Regurgitation (None/Trace vs Mild/Moderate/Severe) – TAVR Implanted Population

Table 34: All-Cause Mortality by Severity of Aortic Regurgitation (None/Trace vs Mild/Moderate/Severe) – TAVR Implanted Population

Interval Post Procedure (months)*	None/Trace N=197				Mild/Moderate/Severe N=166			
	0	1	6	12	0	1	6	12
# at start of interval	197	196	187	176	166	163	151	139
# events in interval	1	8	7	5	3	11	11	14
# event cumulative	1	9	16	21	3	14	25	39
K-M Event Rate	0.0	0.5	4.6	8.2	0.0	1.8	8.5	15.8
*0 = 0-29 days, 1 = 30-182 days, 6 = 183-364 days, 12 ≥ 365 days. Cumulative probability of event estimate is based on the Kaplan-Meier method								

Table 35: Patient Demographics and Clinical Characteristics Stratified by AR – TAVR Implanted Population

	None/Trace AR N=197	Mild/Moderate/Severe AR N=166
DEMOGRAPHICS		
Age (yrs)	82.7 ± 7.4	83.8 ± 6.4
Male	46.7% (92/197)	60.8% (101/166)
NYHA Class		
II	16.2% (32/197)	12.7% (21/166)
III	65.0% (128/197)	66.9% (111/166)
IV	18.8% (37/197)	20.5% (34/166)
STS Score (Risk of Mortality, %)	7.3 ± 3.1	7.2 ± 2.8
Coronary Artery Disease	73.1% (144/197)	77.7% (129/166)
Previous MI	25.4% (50/197)	22.9% (38/166)
Previous Interventions		
Coronary Artery Bypass Surgery	30.5% (60/197)	28.9% (48/166)
Percutaneous Coronary Intervention	35.5% (70/197)	31.9% (53/166)
Balloon Valvuloplasty	5.6% (11/197)	5.4% (9/166)
Cerebrovascular Disease	22.4% (44/196)	25.8% (42/163)
Prior Stroke	10.2% (20/197)	15.1% (25/166)
Peripheral Vascular Disease	44.7% (88/197)	34.1% (56/164)
Chronic Lung Disease/COPD	39.6% (78/197)	50.0% (83/166)
Home Oxygen	10.7% (21/196)	13.9% (23/166)
Creatinine Level >2 mg/dl	2.0% (4/197)	4.8% (8/166)
Atrial Fibrillation/Atrial Flutter	38.1% (75/197)	45.5% (75/165)
Pre-Existing Permanent Pacemaker Placement / ICD	19.3% (38/197)	26.5% (44/166)
Aorta Calcification[1]		
Severe	14.2% (28/197)	9.7% (16/165)
Porcelain	0.5% (1/197)	0.0% (0/165)
Chest Wall Deformity	2.5% (5/197)	2.4% (4/166)
Hostile Mediastinum	4.6% (9/197)	3.6% (6/166)
Wheelchair Bound	3.6% (7/197)	3.6% (6/166)
Plus-minus values present the mean ± standard deviation.		

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 329 investigators, of which none were full-time or part-time employees of the sponsor and 18 had disclosable financial interests/arrangements 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: 9
- Significant payment of other sorts: 7
- 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 Systems Device panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XII. CONCLUSIONS DRAWN FROM THE PRECLINICAL AND CLINICAL STUDIES

A. Safety Conclusions

The results from the pre-clinical and laboratory studies performed on the Medtronic CoreValve system for biocompatibility, hydrodynamic performance, and structural integrity demonstrate that this device is suitable for long-term implant.

The rates for all strokes (major and minor) and transient ischemic attacks (TIAs) were generally comparable between the CoreValve and the SAVR arms (K-M rate at one year: all stroke – 8.8% vs. 12.6%; TIAs – 1.6% vs. 1.6%).

The clinical study did not demonstrate superiority of CoreValve over SAVR for the pre-specified powered secondary endpoint of MACCE rate at one month or discharge, whichever was longer (K-M rate: 8.2% vs. 10.9%; p=0.10). Of note is that the

MACCE rate observed in the trial for SAVR was considerably lower than that assumed in the power calculation (12.1% vs. 20.0% at 30 days), which made this particular secondary hypothesis testing underpowered.

There was a relatively higher risk of greater than or equal to moderate residual aortic regurgitation (observed rate: 36.0% vs. 10.3% at one year), major vascular complications (K-M rate: 6.2% vs. 2.0% at one year), and conduction disturbance requiring permanent pacemaker implantation (K-M rate: 28.6% vs. 13.8 at one year) in the CoreValve arm than in the SAVR arm. The permanent pacemaker rate in the CoreValve arm was similar to what has been reported in previous studies. Studies suggest that the depth of the CoreValve implantation may correlate with occurrence of atrioventricular AV block. However, the current study was not powered to examine this association.[2]

No statistical differences were observed between genders for the primary endpoint of all-cause mortality and the secondary endpoint of MACCE rate. In addition, iliofemoral access had a numerically better outcome than non-iliofemoral access in terms of the primary endpoint.

B. Effectiveness Conclusions

For the pre-specified primary endpoint of all-cause mortality at one year among all subjects with an attempted implant procedure (AT population; inclusive of treatment via iliofemoral and non-iliofemoral access), the clinical data demonstrated that CoreValve was statistically non-inferior to SAVR in treating high risk, symptomatic severe aortic stenosis subjects (K-M rate: 14.2% vs. 19.1%; $p<0.0001$). Furthermore, a pre-specified superiority analysis demonstrated that CoreValve was statistically superior to SAVR for the primary endpoint at a one-sided significance level of 0.05 ($p=0.0377$).

CoreValve was also shown to be statistically non-inferior to SAVR within the pre-specified non-inferiority margins with respect to improvement in forward flow hemodynamics as evaluated echocardiographically by the mean gradient (39.04 ± 13.63 mmHg vs. 35.42 ± 15.42 mmHg) and the EOA (1.20 ± 0.53 cm^2 vs. 0.81 ± 0.50 cm^2), in functional classification as evaluated by the NYHA classification (1.46 ± 0.76 vs. 1.46 ± 0.81), and in cardiac symptoms as evaluated by the KCCQ score (23.20 ± 25.56 vs. 21.88 ± 26.57). However, residual regurgitation was more prevalent in the CoreValve arm.

C. Benefit-Risk Conclusions

The K-M estimate of the primary endpoint of all-cause mortality at one year was lower in the CoreValve arm as compared to that in the SAVR arm. It is worth noting that although the study primary endpoint passed the pre-specified superiority test after it passed the non-inferiority test, the statistical robustness of the superiority test should be interpreted based on the specific statistical parameters used. Additional

probable benefits of the TAVR therapy using CoreValve in the high operative risk patient population include relief of symptoms associated with aortic stenosis as well as improvements in the functional status and the QoL. It is also important to note that these probable benefits are achieved through a less invasive procedure as compared with open surgery. In addition, it should be noted that the longer term outcomes of the TAVR therapy using CoreValve have yet to be evaluated.

The probable risks of the TAVR therapy using CoreValve in the high operative risk patient population include procedure-related complications such as death, stroke, major vascular complications, and conduction disturbance requiring permanent pacemaker implant.

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

D. Overall Conclusions

The available preclinical and clinical data provide reasonable assurance that the Medtronic CoreValve system, available in valve sizes 23, 26, 29 and 31 mm, is safe and effective for the replacement of native aortic valves in symptomatic severe aortic stenosis patients who are deemed to be at high surgical risk, defined as Society of Thoracic Surgeons operative risk score of 8% or greater or as determined by a heart team to have a 15% or greater risk of operative mortality at 30 days.

XIII. CDRH DECISION

CDRH issued an approval order on June 12, 2014. The final conditions of approval cited in the approval order are described below.

1. ***PAS****: Continued follow-up of the premarket cohorts (high risk patients):* This study should be conducted in accordance with the two protocols submitted on June 6, 2014 via email (Clinical Investigational Plan (CIP) Addendum for high risk patients (Version 1) dated June 5, 2014, and CIP Addendum for high risk and extreme risk continued access patients (Version 2) dated June 5, 2014). The study will consist of all pivotal and continued access protocol (CAP) high risk patients currently enrolled and alive who received the Medtronic CoreValve™ system (MCS) or underwent surgical aortic valve replacement (SAVR).

   The objective of this PAS is to characterize the clinical outcomes annually through 5 years post-procedure. The safety and effectiveness endpoints as listed in the protocol include all-cause mortality, major adverse cardiovascular and cerebrovascular events (MACCE), change in functional status and quality of life, conduction disturbance requiring permanent pacemaker implantation, echocardiographic assessment, and valve dysfunction.

All available subjects in the pivotal study and CAP investigation at all investigational sites (45) will be followed annually to 5 years post implant.

2. ***Surveillance***: The applicant is required to actively participate as a stakeholder and support the operations of the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry (TVTR) to ensure that FDA surveillance occurs for the MCS for 5 years. This surveillance should monitor the following: (1) device success (intra-procedure); (2) all-cause mortality, all stroke, life-threatening (or disabling) bleeding, acute kidney injury-stage 3 (including renal replacement therapy), peri-procedural myocardial infarction, and repeat procedure for valve-related dysfunction (surgical or interventional therapy) at 30 days and 12 months; (3) neurological, vascular and quality of life outcomes at 30 days and 12 months; and (4) all-cause mortality, neurological and vascular outcomes annually through 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.

XV. REFERENCES

[1] Leon MB, Piazza N, Nikolsky E, et al. Standardized endpoint definitions for transcatheter aortic valve implantation clinical trials: a consensus report from the Valve Academic Research Consortium. European Heart Journal 2011; 32:205–217.

[2] De Carlo M, Giannini C, Bedogni F, et al. Safety of a conservative strategy of permanent pacemaker implantation after transcatheter aortic CoreValve implantation. American Heart Journal 2012;163:492-499.

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name:	Aortic valve, prosthesis, percutaneously delivered
Device Trade Name:	Medtronic CoreValve™ System (MCS): Transcatheter Aortic Valve (TAV), Models MCS-P4-23-AOA (23 mm; CoreValve™ Evolut™), MCS-P3-26-AOA (26 mm), MCS-P3-29-AOA (29 mm), and MCS-P3-31-AOA (31 mm); Delivery Catheter System (DCS), Models DCS-C4-18FR and DCS-C4-18FR-23; and Compression Loading System (CLS), Model CLS-3000-18FR
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/S010
Date of FDA Notice of Approval:	March 30, 2015

The Medtronic CoreValve system was approved under PMA P130021 and PMA Supplement P130021/S002 with an indication for relief of aortic stenosis in patients with symptomatic heart disease due to severe native calcific aortic stenosis (aortic valve area ≤1.0 cm^2 or aortic valve area index ≤0.6 cm^2/m^2, a mean aortic valve gradient of ≥40 mm Hg, or a peak aortic-jet velocity of ≥4.0 m/s) and with native anatomy appropriate for the 23, 26, 29, or 31 mm valve system who are judged by a heart team, including a cardiac surgeon, to be at high or greater risk for open surgical therapy (i.e., Society of Thoracic Surgeons operative risk score ≥8% or at a ≥15% risk of mortality at 30 days). The SSEDs to support this indication are available on the following FDA websites:

- P130021: http://www.accessdata.fda.gov/cdrh_docs/pdf13/P130021b.pdf
- P130021/S002: http://www.accessdata.fda.gov/cdrh_docs/pdf13/P130021S002b.pdf

These two SSEDs are incorporated by reference herein. The current supplement was submitted to expand the indication to include the treatment of a failed surgical bioprosthesis (TAV-in-SAV).

II. INDICATIONS FOR USE

The Medtronic CoreValve system is indicated 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 ≥8% or at a ≥15% risk of mortality at 30 days).

III. CONTRAINDICATIONS

The Medtronic CoreValve system is 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 system labeling.

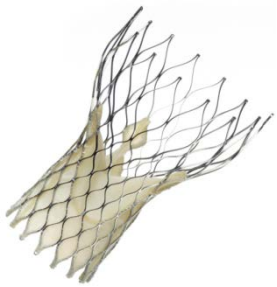
V. DEVICE DESCRIPTION

The Medtronic CoreValve system (MCS) is designed to replace a native aortic heart valve or a failed surgical bioprosthetic aortic valve without open heart surgery and without concomitant surgical removal of the failed native or bioprosthetic valve. It consists of 3 components: the Transcatheter Aortic Valve (TAV), the Delivery Catheter System (DCS), and the Compression Loading System (CLS).

Transcatheter Aortic Valve (TAV)

The TAV (Figure 1) is manufactured by suturing three valve leaflets and skirt, made from a single layer of porcine pericardium, onto a self-expanding, multi-level, radiopaque frame made of Nitinol. The bioprosthesis is processed with alpha-amino oleic acid (AOA®), which is an antimineralization treatment derived from oleic acid, a naturally occurring long-chain fatty acid.

Figure 1: CoreValve Transcatheter Aortic Valve



The TAV is available for a range of aortic annulus and ascending aorta diameters as shown in Table 1. Note that the 23 mm TAV has its own device name, called CoreValve™ Evolut™.

Table 1: Patient Anatomical Diameters

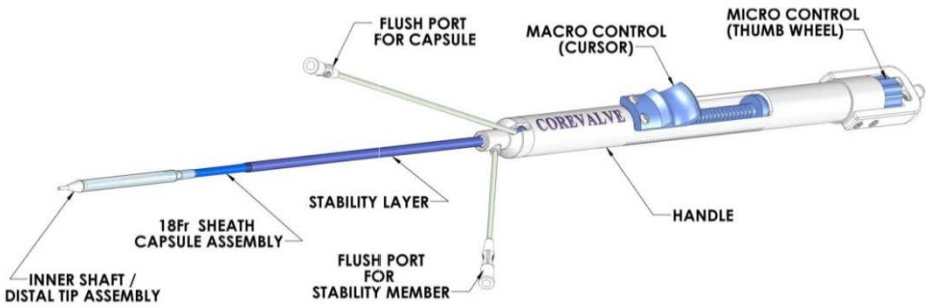
Bioprosthesis Model	Size	Aortic Annulus Diameter	Ascending Aorta Diameter
CoreValve™ Evolut™ Bioprosthesis			
MCS-P4-23-AOA	23 mm	17*/18mm–20 mm	≤34 mm
CoreValve™ Bioprosthesis			
MCS-P3-26-AOA	26 mm	20 mm–23 mm	≤40 mm
MCS-P3-29-AOA	29 mm	23 mm–26 mm	≤43 mm
MCS-P3-31-AOA	31 mm	26 mm–29 mm	≤43 mm

* 17mm for surgical bioprosthetic aortic annulus

Delivery Catheter System with AccuTrak Stability Layer (AccuTrak DCS)

The DCS (Figure 2) is used to deploy the TAV. The TAV is loaded within the capsule which features 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. There are two models of the DCS: model DCS-C4-18FR-23 for the 23 mm TAV only and model DCS-C4-18FR for the 26, 29, and 31 mm TAVs.

Figure 2: CoreValve Delivery Catheter System



Compression Loading System (CLS)

The CLS (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. Only one model of the CLS is available, i.e., model CLS-3000-18FR.

Figure 3: CoreValve Compression Loading System

The CLS 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

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Alternatives for patients with surgical bioprosthetic aortic valve failure (stenosed, insufficient, or combined) include: temporary relief using a percutaneous technique called balloon aortic valvuloplasty (BAV), or medical therapy (no obstruction-relieving intervention). For patients who are operable, redo surgical aortic valve replacement (SAVR) is an established safe and effective treatment option. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the treatment that best meets his/her expectations and lifestyle.

VII. MARKETING HISTORY

The current Medtronic CoreValve system is commercially available for the "TAV-in-SAV" procedure in over 60 countries, as listed in Table 2. It has not been withdrawn from marketing for any reason related to its safety or effectiveness.

Table 2: Countries where Medtronic CoreValve System is Approved for "TAV-in-SAV"

Afghanistan	Ecuador	Luxembourg	Slovenia
Albania	Estonia	Malaysia	South Africa
Argentina	Finland	Malta	Spain
Armenia	France	Mexico	Sweden
Austria	Georgia	Montenegro	Switzerland
Azerbaijan	Germany	Moldova	Tajikistan
Belgium	Greece	Netherlands	Thailand

Belarus	Guatemala	New Zealand	Turkmenistan
Bosnia & Herzegovina	Hungary	Panama	Turkey
Chile	Ireland	Peru	United Kingdom
Colombia	Israel	Poland	Croatia
Croatia	Italy	Portugal	Israel
Cyprus	Kazakhstan	Romania	Ukraine
Czech Republic	Kyrgyzstan	Russia	Uzbekistan
Denmark	Latvia	Serbia	Venezuela
Dominican Republic	Lithuania	Slovakia	

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Potential risks associated with the "TAV-in-SAV" implantation of the Medtronic CoreValve system may include, but are not limited to, the following:

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

Additional preclinical bench testing and computational analysis were performed on the Medtronic CoreValve system in the "TAV-in-SAV" configuration, as summarized in Table 3.

Table 3: Summary of *In Vitro* Studies for Medtronic CoreValve System "TAV-in-SAV"

Test	Applicable Standards	Test Description	Results
Finite Element Analysis (FEA) -TAV-in-SAV	None	FEA was used to characterize the structural behavior of the MCS TAV frame deployed into an aortic surgical valve subjected to *in vivo* operational conditions.	NA – Characterization Testing
Finite Element Analysis (FEA) -17mm Annulus	None	FEA was used to characterize the structural behavior of the 23mm MCS TAV frame in a 17mm aortic annulus under in vivo operational conditions.	NA – Characterization Testing
Device Level Fatigue Testing of TAV Frames (600M)	ISO 5840: 2005, FDA Guidance Document for Heart Valves	This test evaluated the 23mm MCS TAV frame fatigue resistance to 600 Million cycles when deployed in a 17mm aortic annulus.	NA – Characterization Testing
Hydrodynamic Testing	ISO 5840: 2005, FDA Guidance Document for Heart Valves	This test evaluated the hydrodynamic performance of the MCS TAV in appropriately sized surgical valves.	Pass

X. SUMMARY OF PRIMARY CLINICAL STUDY

The Medtronic CoreValve system U.S. pivotal trial (IDE G100012) consists of two main cohorts (Extreme Risk Cohort and High Risk Cohort) and the following six Expanded Use Observational Cohorts:

- Registry 1: Severe (≥3-4+) mitral valve regurgitation
- Registry 2: Severe (≥3-4+) tricuspid valve regurgitation
- Registry 3: End stage renal disease requiring renal replacement therapy or creatinine clearance <20cc/min, but not requiring renal replacement therapy
- Registry 4: Low gradient, low output aortic stenosis
- Registry 5: 2 or more conditions listed above
- Registry 6: TAV-in-SAV

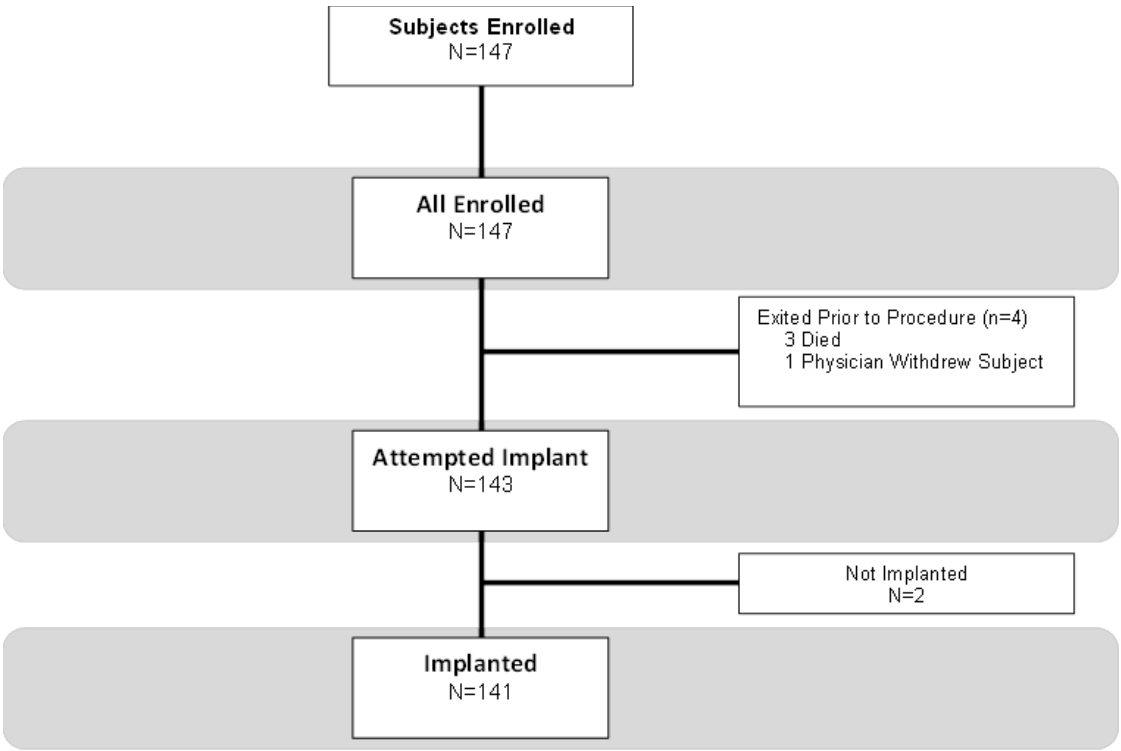
The clinical data presented herein came from Registry 6, the "TAV-in-SAV" observational study.

A. Study Design

The "TAV-in-SAV" registry was a prospective, non-randomized, observational, multi-center investigational study. The purpose of the study was to evaluate the safety and effectiveness of the Medtronic CoreValve system for the treatment of surgical bioprosthetic aortic valve failure (stenosed, insufficient, or combined) in subjects with significant co-morbidities who has a predicted operative mortality or serious, irreversible morbidity risk of ≥50% at 30 days for redo surgical aortic valve replacement.

The study was conducted at 37 investigational sites in the U.S. A total of 147 patients were enrolled between 24 March 2013 and 15 September 2014, as shown in the enrollment chart in Figure 4. The data set for this application reflected clinical events through 31 October 2014. Contractors were utilized for interpretation and analysis of data for several aspects of the study, including an independent Data Safety Monitoring Board (DSMB) that could contract an independent statistician, a Clinical Events Committee (CEC), and an echocardiography core laboratory.

Figure 4: CoreValve TAV-in-SAV Registry Patient Flowchart



1. Clinical Inclusion and Exclusion Criteria

Because tools such as the Society of Thoracic Surgeons (STS) risk calculator can only accommodate a limited number of risk factors and do not account for frailty,

disabilities and anatomical characteristics (e.g., porcelain aorta) that confer a prohibitive risk for surgical aortic valve replacement, these tools were not used as stand-alone mechanisms for identifying patients at extreme risk for cardiac surgery. Therefore, a team of two cardiac surgeons and one interventional cardiologist at each investigational site were required to assess patient suitability for inclusion in the study, taking into account risk factors not covered by the STS calculator. A central screening committee made a subsequent assessment of patient risk and agreed on patient eligibility or ineligibility.

The inclusion and exclusion criteria for the "TAV-in-SAV" registry study are summarized below:

Inclusion Criteria

- Subject must have co-morbidities such that one cardiologist and two cardiac surgeons agree that medical factors preclude operation, based on the conclusion that the probability of death or serious morbidity exceeds the probability of meaningful improvement. Specifically, the predicted operative risk of death or serious, irreversible morbidity is ≥50% at 30 days
- Stenosed, insufficient or combined bioprosthetic surgical aortic valve failure
- Subject is symptomatic from his/her aortic valve stenosis, as demonstrated by New York Heart Association (NYHA) Functional Class II or greater
- The subject or the subject's legal representative has been informed of the nature of the trial, agrees to its provisions and has provided written informed consent as approved by the IRB of the respective clinical site
- The subject and the treating physician agree that the subject will return for all required post-procedure follow-up visits

Exclusion Criteria

Clinical

- Evidence of an acute myocardial infarction ≤ 30 days before the MCS TAVR procedure
- Any percutaneous coronary or peripheral interventional procedure performed within 30 days prior to the MCS TAVI procedure
- Blood dyscrasias as defined: leukopenia (WBC < 1000mm3), thrombocytopenia (platelet count <50,000 cells/mm3), history of bleeding diathesis or coagulopathy
- Untreated clinically significant coronary artery disease requiring revascularization
- Cardiogenic shock manifested by low cardiac output, vasopressor dependence, or mechanical hemodynamic support
- Need for emergency surgery for any reason
- Severe ventricular dysfunction with left ventricular ejection fraction (LVEF) < 20% as measured by resting echocardiogram
- Recent (within 6 months) cerebrovascular accident (CVA) or TIA
- Active gastrointestinal (GI) bleeding that would preclude anticoagulation

- A known hypersensitivity or contraindication to all anticoagulation/antiplatelet regimens (including inability to be anticoagulated for the index procedure), nitinol, or allergic sensitivity to contrast media which cannot be adequately pre-medicated
- Ongoing sepsis, including active endocarditis
- Subject refuses a blood transfusion
- Life expectancy < 12 months due to associated non-cardiac co-morbid conditions
- Other medical, social, or psychological conditions that in the opinion of an Investigator precludes the subject from appropriate consent
- Severe dementia (resulting in either inability to provide informed consent for the study/procedure, prevents independent lifestyle outside of a chronic care facility, or will fundamentally complicate rehabilitation from the procedure or compliance with follow-up visits)
- Currently participating in an investigational drug or another device study
- Symptomatic carotid or vertebral artery disease.

Anatomical

- Subject has a surgical bioprosthetic annulus <17 mm or >29 mm
  - Stented SAV per the manufactured labeled inner diameter OR
  - Stentless SAV per the baseline diagnostic imaging.
- Pre-existing prosthetic heart valve with a rigid support structure in either the mitral or pulmonic position:
  - That could affect the implantation or function of the study valve OR
  - The implantation of the study valve could affect the function of the pre-existing prosthetic heart valve
- Moderate to severe mitral stenosis
- Hypertrophic obstructive cardiomyopathy
- Echocardiographic evidence of new or untreated intracardiac mass, thrombus or vegetation
- Severe basal septal hypertrophy with an outflow gradient
- Aortic root angulation (angle between plane of aortic valve annulus and horizontal plane/vertebrae) > 70° (for femoral and left subclavian/axillary access) and > 30° (for right subclavian/axillary access)
- Ascending aorta that exceeds the maximum diameter for any given bioprosthetic surgical* aortic annulus size (see table below)

Aortic Annulus Diameter	Ascending Aorta Diameter
17*/18 mm – 20 mm	>34 mm
20 mm – 23 mm	>40 mm
23 mm – 27 mm	>43 mm
27 mm – 29 mm	>43 mm

* 17mm for surgical bioprosthetic aortic annulus

- Sinus of valsalva anatomy that would prevent adequate coronary perfusion
- Degenerated surgical bioprosthesis presents with a significant concomitant perivalvular leak (between prosthesis and native annulus), is not securely fixed in the native annulus, or is not structurally intact (e.g., wireform frame fracture)
- Degenerated surgical bioprosthesis presents with a partially detached leaflet that in the aortic position may obstruct a coronary ostium

Vascular
- 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 comes first, 30 days, 6 months, 12 months, and annually thereafter to a minimum of 5 years post procedure. Patients reported herein were followed for a minimum of 30 days.

3. Clinical Endpoints

Primary Safety and Effectiveness Endpoints

The primary endpoint is all-cause mortality or major stroke, which was assessed at 30 days and 6 months in this application. The analyses were not hypothesis driven. The data at 12 months are also provided, but are largely incomplete at this time and the data collection is ongoing.

Secondary Safety and Effectiveness Endpoints

The secondary endpoints are as follows:
1. Major adverse cardiovascular or cerebrovascular events (MACCE) event rate at 30 days, 6 months, 12 months and annually thereafter up to 5 years
2. The occurrence of individual MACCE components at 30 days, 6 months, 12 months and annually thereafter up to 5 years
3. Major adverse events (MAE) at 30 days, 6 months,12 months and annually thereafter up to 5 years
4. Conduction disturbance requiring permanent pacemaker implantation (PPI) at 30 days, 6 months, 12 months and annually thereafter up to 5 years
5. Change in NYHA class from baseline at 30 days, 6 months, 12 months and annually thereafter up to 5 years
6. Change in distance walked during 6-minute walk test (6MWT) from baseline to 30 days and baseline to 12 months
7. Ratio of days alive out of hospital versus total days alive assessed at 12 months follow-up
8. Quality of life (QoL) change from baseline at 30 days, 6 months, 12 months and annually thereafter up to 5 years

9. Echocardiographic assessment of valve performance at discharge, 30 days, 6 months, 12 months and annually thereafter up to 5 years using the following measures:
    a. Transvalvular mean gradient
    b. Effective orifice area (EOA)
    c. Degree of aortic valve regurgitation (transvalvular and paravalvular)
10. Aortic valve disease hospitalizations at 30 days, 6 months, 12 months and annually thereafter up to 5 years
11. Cardiovascular deaths and valve-related deaths at 30 days, 6 months, 12 months and annually thereafter up to 5 years
12. Strokes (of any severity) and TIAs at 30 days, 6 months, 12 months and annually thereafter up to 5 years
13. Index procedure related MAEs
14. Length of index procedure hospital stay
15. Device success defined as follows:
    - Successful vascular access, delivery and deployment of the device, and successful retrieval of the delivery system,
    - Correct position of the device in the proper anatomical location (placement in the annulus with no impedance on device function),
    - Only one valve implanted in the proper anatomical location
16. Procedural success, defined as device success and absence of in-hospital MACCE
17. Evidence of prosthetic valve dysfunction at 30 days, 6 months, 12 months and annually thereafter up to 5 years

The secondary endpoints, where applicable, were assessed at 30 days and 6 months, and 12 months in this application.

B. Accountability of Study Cohort

At the time of database lock, 135 of the 143 patients (attempted implants) were available for assessment of the primary endpoint at 30 days. Table 4 depicts the disposition of patients at each follow-up period for the All Enrolled population (see Analysis Population section for definition).

Table 4: Total Patient Accountability

Follow up Period	Variable	Number of Patients (All Enrolled N=147)
1 month	Expected[1]	136
	Completed	135
	Number withdrew before visit	1
	Number died before visit	8
	Lost to follow up before visit	0
	Other exits before visit	1
	Visit pending[2]	1
	Visit compliance	99.3%
6 months	Expected	94
	Completed	89
	Number withdrew before visit	1
	Number died before visit	14
	Lost to follow up before visit	0
	Other exits before visit	3
	Visit pending	35
	Visit compliance	94.7%
12 months	Expected	34
	Completed	34
	Number withdrew before visit	1
	Number died before visit	17
	Lost to follow up before visit	0
	Other exits before visit	3
	Visit pending	92
	Visit compliance	100.0%

[1]Expected includes the subjects who had the specified visit completed, or for whom the visit window closed prior to the visit cutoff date, making the visit overdue, or who did not complete the visit with the last known status being alive and not withdrawn from the study.

[2]Visit pending is defined as the subjects whose last known status was alive and not withdrawn from the study and for whom the protocol visit window has not opened or the window has not closed and the follow-up visit has not yet occurred.

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are shown in Table 5. A high proportion of the patients had significant co-morbidities, frailties, or disabilities. The mean age was 76.7 years old, and 65.7% of patients were male. The mean STS score was 9.4%. In addition, 86.7% of all patients were in NYHA classes III or IV.

Table 5: Subject Demographics and Baseline Characteristics – Attempted Implant

Demographic	TAV-in-SAV N= 143
Age (years)	76.7 ± 10.8[1]
Gender (Male)	65.7% (94/143)
NYHA Classification	
I	0% (0/143)
II	13.3% (19/143)
III	63.6% (91/143)
IV	23.1% (33/143)
STS Score (Risk of Mortality, %)	9.4 ± 5.7
Coronary Artery Disease	76.9% (110/143)
Previous MI	23.8% (34/143)
Previous Interventions	
Coronary Artery Bypass Surgery	53.8% (77/143)
Percutaneous Coronary Intervention	32.2% (46/143)
Balloon Valvuloplasty	1.4% (2/143)
Cerebral Vascular Disease	23.9% (34/142)
Prior Stroke	14.7% (21/143)
Peripheral Vascular Disease	39.2% (56/143)
Chronic Lung Disease/COPD	64.8% (92/142)
Home Oxygen	18.9% (27/143)
Creatinine Level >2 mg/dl	7.0% (10/143)
Chronic Kidney Disease (Stage 4/5)	12.6% (18/143)
Chronic Renal Replacement Therapy	3.5% (5/143)
Atrial Fibrillation/Atrial Flutter	41.5% (59/142)
Preexisting Permanent Pacemaker Placement/ICD	21.0% (30/143)
Aorta Calcification[2]: Severe/Porcelain	
Severe	13.3% (19/143)
Porcelain	1.4% (2/143)
Chest Wall Deformity	2.8% (4/143)
Hostile Mediastinum	16.4% (23/140)
Cirrhosis of the Liver	1.4% (2/143)
Wheelchair Bound	3.5% (5/143)
Echocardiographic Findings	
Ejection Fraction (Visual Estimate, %)	53.6 ± 14.0
Aortic Valve Area (cm^2)	1.0 ± 0.6
Mean Gradient across Aortic Valve (MGV_2, mm Hg)	39.2 ± 18.2
Mitral Regurgitation: Moderate/Severe	21.8% (31/142)

[1]Plus-minus values present the mean ± standard deviation.
[2]Aorta calcification is measured on screening CT Angiogram.

Table 6 provides a summary of the failed surgical valves treated, which consisted of 83.2% stented valves, 6.3% homografts, and 10.5% stentless valves. Aortic stenosis was the predominant cause of prosthetic failure (59.4%), followed by aortic regurgitation (23.8%) and combined etiology (16.8%).

Table 6: Summary of Failed Bioprosthetic Surgical Valves - Attempted Implant

	TAV-in-SAV N=143
Type of bioprosthetic surgical valve	
Homograft	6.3% (9/143)
Stented	83.2% (119/143)
Stentless	10.5% (15/143)
Failure mode of surgical aortic bioprosthesis	
Combined	16.8% (24/143)
Regurgitation	23.8% (34/143)
Stenosis	59.4% (85/143)

D. Safety and Effectiveness Results

1. Analysis Populations

The "All Enrolled" population consisted of all subjects enrolled in the study, regardless of whether the implantation took place.

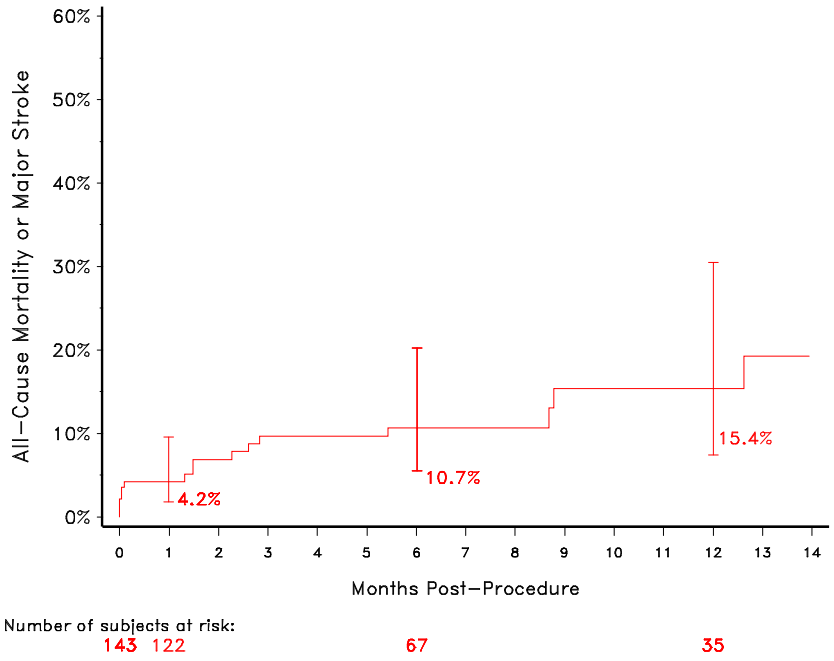
The "Attempted Implant" population consisted of "All Enrolled" subjects with an attempted implant procedure, defined as when the subject was brought into the procedure room and any of the following had occurred: anesthesia administered, vascular line placed, TEE placed or any monitoring line placed. The "Attempted Implant" population was the primary analysis population.

The "Implanted" population consisted of all "Attempted Implant" subjects who were actually implanted with a CoreValve device. To be considered implanted, a subject's device disposition form must show at least one CoreValve device with a final disposition of "Implanted."

2. Primary Safety and Effectiveness Endpoint

The estimated Kaplan-Meier (K-M) rate for all-cause mortality or major stroke was 4.2% at 30 days, 10.7% at 6 months, and 15.4% at 12 months for the Attempted Implant population, as shown in Figure 4 and Table 7.

Figure 4: All-Cause Mortality or Major Stroke - Attempted Implant



Note: The confidence intervals are 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.

Table 7: All-Cause Mortality or Major Stroke - Attempted Implant

	Follow-up Intervals (months)			
	0 (0-29 days)	**1 (30-182 days)**	**6 (183-364 days)**	**12 (365-729 days)**
# at start of interval	143	122	67	35
# events in interval	6	7	2	1
# event cumulative	6	13	15	16
K-M Event Rate[1]	2.1	4.2	10.7	15.4
Lower 95% CI[2]	0.7	1.8	5.5	7.4
Upper 95% CI	6.3	9.5	20.2	30.5

[1]Cumulative probability of event estimate at the beginning of the interval (Pc) based on the Kaplan-Meier method.

[2]The confidence intervals are 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.

3. Key Secondary Safety and Effectiveness Endpoints

Adverse Events

Table 8 provides a summary of the adverse events that occurred in this study. Note that stroke and TIA were defined according to the Valve Academic Research Consortium I (VARC-I) definitions.[1] Among the adverse events observed in the

study, bleeding complications (19.1%; K-M rate) and major vascular complications (11.9%; K-M rate) were the most frequently observed early adverse events.

Table 8: Adverse Event Summary - Attempted Implant

Event	0-30 Days		0-6 Months		0-12 Months	
	# Subjects (# Events)	K-M Event Rate (%)	# Subjects (# Events)	K-M Event Rate (%)	# Subjects (# Events)	K-M Event Rate (%)
All-Cause Mortality	5 (5)	3.5%	11 (11)	9.0%	13 (13)	13.8%
Cardiovascular	4 (4)	2.8%	6 (6)	4.7%	7 (7)	7.2%
Valve-Related[1]	0 (0)	0.0%	0 (0)	0.0%	1 (1)	2.7%
Reintervention	1 (1)	0.8%	2 (2)	1.7%	4 (4)	6.7%
Surgical	1 (1)	0.8%	2 (2)	1.7%	3 (3)	4.0%
Percutaneous	0 (0)	0.0%	0 (0)	0.0%	1 (1)	2.7%
Neurological Events	2 (2)	1.4%	5 (6)	4.5%	5 (6)	4.5%
All Stroke	1 (1)	0.7%	3 (4)	2.8%	3 (4)	2.8%
Major Stroke	1 (1)	0.7%	2 (3)	1.8%	2 (3)	1.8%
Ischemic	1 (1)	0.7%	1 (2)	0.7%	1 (2)	0.7%
Hemorrhagic	0 (0)	0.0%	1 (1)	1.1%	1 (1)	1.1%
Minor Stroke	0 (0)	0.0%	1 (1)	1.0%	1 (1)	1.0%
Ischemic	0 (0)	0.0%	1 (1)	1.0%	1 (1)	1.0%
Hemorrhagic	0 (0)	0.0%	0 (0)	0.0%	0 (0)	0.0%
TIA	0 (0)	0.0%	0 (0)	0.0%	0 (0)	0.0%
Intracranial Hemorrhage	0 (0)	0.0%	1 (1)	1.0%	1 (1)	1.0%
Bleed	27 (29)	19.1%	29 (33)	21.2%	30 (34)	23.9%
Life Threatening or Disabling	8 (8)	5.7%	11 (11)	8.8%	12 (12)	11.3%
Major Bleed	19 (21)	13.5%	19 (22)	13.5%	19 (22)	13.5%
Major Vascular Complication	17 (18)	11.9%	17 (18)	11.9%	17 (18)	11.9%
Acute Kidney Injury	3 (3)	2.2%	3 (3)	2.2%	3 (3)	2.2%
MI	1 (1)	0.7%	1 (1)	0.7%	1 (1)	0.7%
Cardiogenic Shock	4 (4)	2.8%	4 (4)	2.8%	4 (4)	2.8%
Cardiac Tamponade	1 (1)	0.7%	1 (1)	0.7%	2 (2)	3.4%
Valve Endocarditis	0 (0)	0.0%	0 (0)	0.0%	0 (0)	0.0%
Valve Thrombosis	0 (0)	0.0%	0 (0)	0.0%	0 (0)	0.0%
Valve Embolism/Device Migration	0 (0)	0.0%	0 (0)	0.0%	0 (0)	0.0%
MACCE[2]	7 (8)	5.0%	16 (18)	13.2%	19 (22)	19.9%
New Permanent Pacemaker Implant (method 1[3])	10 (10)	9.2%	11 (11)	10.5%	14 (14)	18.2%
New Permanent Pacemaker Implant (method 2[4])	10 (10)	7.3%	11 (11)	8.3%	14 (14)	15.0%

[1] Valve-related death is any death caused by prosthetic valve dysfunction, valve thrombosis, embolism, bleeding event, or implanted valve endocarditis or related to reintervention on the operated valve.
[2] MACCE includes all-cause death, myocardial infarction (MI), all stroke, and reintervention.
[3] Patients with pacemaker or ICD at baseline are not included in the denominator.
[4] Patients with pacemaker or ICD at baseline are included in the denominator.

Echocardiographic Assessment of Total Aortic Regurgitation

Table 9 summarizes the total aortic regurgitation (AR) severity by visit. Considering all valve sizes, the majority of patients had less than or equal to mild residual AR.

Table 9: Total Aortic Regurgitation by Visit and Valve Size – Implanted Population

	Site Data	Core Lab Data		
	Baseline	**1 month**	**6 months**	**12 months**
All Valve Sizes				
None	18.8% (26/138)	43.3% (55/127)	45.3% (39/86)	45.5% (15/33)
Trace	0.0% (0/138)	29.1% (37/127)	24.4% (21/86)	30.3% (10/33)
Mild	39.9% (55/138)	24.4% (31/127)	27.9% (24/86)	18.2% (6/33)
Moderate	21.0% (29/138)	3.1% (4/127)	2.3% (2/86)	6.1% (2/33)
Severe	20.3% (28/138)	0.0% (0/127)	0.0% (0/86)	0.0% (0/33)
23 mm				
None	24.7% (19/77)	55.7% (39/70)	56.5% (26/46)	58.3% (14/24)
Trace	0.0% (0/77)	24.3% (17/70)	21.7% (10/46)	29.2% (7/24)
Mild	48.1% (37/77)	20.0% (14/70)	19.6% (9/46)	12.5% (3/24)
Moderate	18.2% (14/77)	0.0% (0/70)	2.2% (1/46)	0.0% (0/24)
Severe	9.1% (7/77)	0.0% (0/70)	0.0% (0/46)	0.0% (0/24)
26 mm				
None	12.8% (5/39)	23.7% (9/38)	33.3% (8/24)	14.3% (1/7)
Trace	0.0% (0/39)	34.2% (13/38)	16.7% (4/24)	28.6% (2/7)
Mild	35.9% (14/39)	34.2% (13/38)	45.8% (11/24)	42.9% (3/7)
Moderate	25.6% (10/39)	7.9% (3/38)	4.2% (1/24)	14.3% (1/7)
Severe	25.6% (10/39)	0.0% (0/38)	0.0% (0/24)	0.0% (0/7)
29 mm				
None	12.5% (2/16)	46.7% (7/15)	41.7% (5/12)	0.0% (0/1)
Trace	0.0% (0/16)	40.0% (6/15)	41.7% (5/12)	100.0% (1/1)
Mild	25.0% (4/16)	13.3% (2/15)	16.7% (2/12)	0.0% (0/1)
Moderate	25.0% (4/16)	0.0% (0/15)	0.0% (0/12)	0.0% (0/1)
Severe	37.5% (6/16)	0.0% (0/15)	0.0% (0/12)	0.0% (0/1)
31 mm				
None	0.0% (0/6)	0.0% (0/4)	0.0% (0/4)	0.0% (0/1)
Trace	0.0% (0/6)	25.0% (1/4)	50.0% (2/4)	0.0% (0/1)
Mild	0.0% (0/6)	50.0% (2/4)	50.0% (2/4)	0.0% (0/1)
Moderate	16.7% (1/6)	25.0% (1/4)	0.0% (0/4)	100.0% (1/1)
Severe	83.3% (5/6)	0.0% (0/4)	0.0% (0/4)	0.0% (0/1)

Echocardiographic Assessment of EOA and Mean Gradient

The EOA and mean gradient by visit for the Implanted Population are shown in Table 10.

Table 10: EOA and Mean Gradient by Visit and Valve Size – Implanted Population

	Site Data	Core Lab Data			
	Baseline	**Discharge**	**1 month**	**6 months**	**12 months**
EOA (cm^2)					
All Valve Sizes	1.01 ± 0.61 (137)	1.31 ± 0.55 (101)	1.34 ± 0.58 (111)	1.34 ± 0.59 (73)	1.35 ± 0.43 (24)
23 mm	0.77 ± 0.32 (76)	1.05 ± 0.44 (53)	1.11 ± 0.45 (57)	1.11 ± 0.39 (40)	1.24 ± 0.35 (18)
26 mm	1.08 ± 0.52 (39)	1.42 ± 0.41 (29)	1.45 ± 0.59 (35)	1.57 ± 0.49 (21)	1.62 ± 0.61 (4)
29 mm	1.61 ± 0.93 (16)	1.90 ± 0.59 (15)	1.86 ± 0.61 (14)	1.84 ± 0.95 (9)	1.43 (1)
31 mm	1.96 ± 0.97 (6)	1.60 ± 0.56 (4)	1.71 ± 0.36 (5)	1.19 ± 0.85 (3)	2.11 (1)
Mean Gradient (mmHg)					
All Valve Sizes	39.12 ± 18.31 (141)	20.10 ± 11.00 (128)	17.69 ± 9.38 (127)	16.03 ± 6.96 (85)	18.01 ± 9.57 (32)
23 mm	45.52 ± 17.45 (78)	24.63 ± 12.16 (69)	21.02 ± 9.88 (69)	18.21 ± 6.74 (47)	19.71 ± 10.42 (23)
26 mm	33.33 ± 17.04 (40)	15.91 ± 6.35 (37)	14.36 ± 7.85 (37)	13.15 ± 6.94 (24)	14.17 ± 3.41 (7)
29 mm	26.77 ± 13.48 (17)	12.38 ± 5.83 (17)	11.92 ± 5.18 (16)	13.05 ± 5.41 (11)	20.20 (1)
31 mm	29.65 ± 17.86 (6)	14.90 ± 5.00 (5)	14.90 ± 4.32 (5)	15.73 ± 5.23 (3)	3.60 (1)

Plus-minus values are mean ± standard deviation. Numbers in the parentheses are the number of subjects.

NYHA Functional Class

The NYHA classification was evaluated at baseline, 1 month, 6 months, and 12 months, as shown in Table 11.

Table 11: NYHA Classification By Visit – Attempted Implant

	Baseline	**1 month**	**6 months**	**12 months**
NYHA Classification (including Died as a category)				
I	0.0% (0/143)	55.9% (76/136)	59.2% (58/98)	51.1% (24/47)
II	11.9% (17/143)	32.4% (44/136)	26.5% (26/98)	12.8% (6/47)
III	66.4% (95/143)	8.1% (11/136)	3.1% (3/98)	6.4% (3/47)
IV	21.7% (31/143)	0.0% (0/136)	0.0% (0/98)	0.0% (0/47)
Died prior to visit[1]	0.0% (0/143)	3.7% (5/136)	11.2% (11/98)	29.8% (14/47)[2]
NYHA Classification (survivors only)				
I	0.0% (0/143)	58.0% (76/131)	66.7% (58/87)	72.7% (24/33)
II	11.9% (17/143)	33.6% (44/131)	29.9% (26/87)	18.2% (6/33)
III	66.4% (95/143)	8.4% (11/131)	3.4% (3/87)	9.1% (3/33)
IV	21.7% (31/143)	0.0% (0/131)	0.0% (0/87)	0.0% (0/33)

[1]Died prior to visit includes all deaths even if the subject's procedure was not at least 6 month (n=6) or not at least 12 month (n=9) prior to the visit cutoff date.

[2]One death was device related at 12 months.

QoL Measures

The QoL was evaluated using the Kansas City Cardiomyopathy Questionnaire (KCCQ), the QualityMetric's SF-12v2® Health Survey (SF12), and the EuroQoL (EQ-5D), as shown in Table 12.

Table 12: Quality of Life – Attempted Implant

	Baseline	1 month	6 months	12 months
KCCQ (n)				
Overall Summary Score	46.2 ± 23.0 (140)	75.0 ± 22.3 (132)	77.2 ± 21.6 (87)	82.5 ± 16.9 (32)
Clinical Summary Score	51.5 ± 22.6 (140)	75.7 ± 22.2 (132)	76.5 ± 22.0 (87)	80.5 ± 19.9 (32)
SF12 (n)				
Physical Component	30.9 ± 9.8 (138)	38.8 ± 11.4 (130)	39.9 ± 12.0 (84)	35.3 ± 11.9 (32)
Mental Component	47.0 ± 12.4 (138)	53.6 ± 9.8 (130)	52.9 ± 11.4 (84)	58.4 ± 7.8 (32)
EQ-5D (n)	0.77 ± 0.17 (139)	0.85 ± 0.14 (133)	0.81 ± 0.16 (87)	0.83 ± 0.17 (32)

Plus-minus values are mean ± standard deviation.

4. Additional Study Observations

Procedure Data

Table 13 provides a summary of the transcatheter valve implantation procedures. The overall device success and procedure success rates were 92.2% and 88.7%, respectively.

Table 13: TAV-in-SAV Procedure Data (Attempted Implant)

	TAV-in-SAV N= 143
Time to Procedure (days)	4.2 ± 11.9[1]
Total Time in Cath Lab or OR (min)	216.7 ± 65.1
Total Procedure Time (min) (skin to skin)	52.1 ± 32.2
General Anesthesia	87.9% (124/141)
Valve-in-Valve Procedure	5.8% (8/138)
Emergent Operation Due to Device or Procedure	0.0% (0/141)
Number of Devices Used	
0	1.4% (2/143)
1	86.0% (123/143)
2	9.8% (14/143)
3	2.8% (4/143)
Number of Devices Implanted	
0	1.4% (2/143)
1	93.0% (133/143)
2	5.6% (8/143)
3	0.0% (0/143)
Valve Size Implanted	
23 mm	55.3% (78/141)
26 mm	28.4% (40/141)
29 mm	12.1% (17/141)

	TAV-in-SAV N= 143
31 mm	4.3% (6/141)
Device Success[2]	92.2% (130/141)
Procedure Success[3]	88.7% (125/141)

[1]Plus-minus values are mean ± standard deviation.
[2]Device success is defined as: (1) successful vascular access, delivery and deployment of the device, and successful retrieval of the delivery system; (2) correct position of the device in the proper anatomical location (placement in the annulus with no impedance on device function), and (3) only one valve implanted in the proper anatomical location.
[3]Procedure success is defined as device success and absence of in-hospital MACCE.

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 417 investigators, of which none were full-time or part-time employees of the sponsor and 10 had disclosable financial interests/arrangements related to the "TAV-in-SAV" 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: 0
- Significant payment of other sorts: 9
- 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. The information provided does not raise any questions about the reliability of the data.

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

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

XII. CONCLUSIONS DRAWN FROM THE PRECLINICAL AND CLINICAL STUDIES

A. Safety Conclusions

The results from the preclinical studies performed on the Medtronic CoreValve system as well as data collected in the clinical study demonstrate that the device is suitable for long-term implantation in a "TAV-in-SAV" configuration.

In the clinical study the K-M rate of all-cause mortality or major stroke was 4.2% at 30 days and 10.7% at 6 months for the Attempted Implant population. The device success and procedural success rates were high, which were 92.2% and 88.7%, respectively. The K-M rates of all stroke, MACCE, acute kidney injury, myocardial infarction, and permanent pacemaker implantation were 0.7%, 5.0%, 2.2%, 0.7%, and 7.3%, respectively, at 30 days. For all valve sizes, 96.8% of the implanted patients had less than or equal to mild total aortic regurgitation at 30 days. These results compared favorably with those of the Extreme Risk Cohort.

B. Effectiveness Conclusions

In the clinical study, the "TAV-in-SAV" subjects experienced an improvement of approximately 20 mmHg in mean pressure gradient and approximately 0.3 cm^2 in EOA from baseline to 30 days, which remained stable through the subsequent follow-up visits. However, it is of note that these subjects had a pressure gradient of 17.38 ± 8.71 mmHg at 30 days, which was much higher than that observed in the Extreme Risk Cohort (8.7 ± 4.2 mmHg). It is not clear whether this elevated pressure gradient will have any long-term impact on the patient outcome.

The improvement in hemodynamics is further demonstrated through functional classification as evaluated by NYHA classification and in cardiac symptoms as evaluated by KCCQ scores. Over 85% of subjects were in NYHA I/II at 30 days and 6 months as compared to 11.9% at baseline. The KCCQ score was approximately 75 points at 30 days and 6 months, with an improvement of nearly 30 points from baseline.

C. Benefit-Risk Conclusions

The benefits of the Medtronic CoreValve system for patients with a failed surgical bioprosthetic aortic valve included improved valve hemodynamic performance, improved functional status as measured by the NYHA classification, improved QoL, and reduced mortality.

The probable risks of the Medtronic CoreValve system included procedure related complications such as death, stroke, major vascular complications, bleeding, conduction disturbance, and acute kidney injury. However, most of these risks were

lower in the "TAV-in-SAV" subjects as compared with those observed in the Extreme Risk Cohort.

In conclusion, given the available information above, the data support that for patients with a failed (stenosed, regurgitant, or combined) surgical bioprosthetic aortic valve who are at extreme risk for redo surgical aortic valve replacement, the probable benefits of implanting a Medtronic CoreValve outweigh the probable risks.

Note that although the "TAV-in-SAV" observational study only enrolled subjects who were deemed to be at extreme risk for open surgical therapy, FDA believes the same benefit/risk profile can be reasonably expected in patients who are at high risk for open surgical therapy. As such, the expanded indication will include patients both at high and at extreme risk for redo aortic valve surgery.

D. Overall Conclusions

The preclinical and clinical studies submitted in the PMA supplement provide reasonable assurance that the Medtronic CoreValve system is safe and effective for the replacement of failed surgical bioprosthetic aortic valves in symptomatic severe aortic stenosis, aortic insufficiency, or combined patients who are deemed to be at high or greater risk for open surgical therapy (i.e., Society of Thoracic Surgeons operative risk score ≥8% or at a ≥15% risk of mortality at 30 days).

XIII. CDRH DECISION

CDRH issued an approval order on March 30, 2015. The final conditions of approval cited in the approval order are described below.

1. ***ODE Lead Post-Approval Study****: Continued follow-up of the premarket cohort:* The study will consist of all living subjects who were enrolled under the IDE in Registry 6: TAV- in-SAV. The objective of this study is to characterize the clinical outcomes annually through 5 years post-procedure. The safety and effectiveness endpoints include all-cause mortality, MACCE, change in functional status and quality of life, conduction disturbance requiring permanent pacemaker implantation, echocardiographic assessment, and valve dysfunction.

2. ***OSB Lead Surveillance***: The applicant is required to actively participate as a stakeholder and support the operations of the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry (TVTR) to ensure that FDA surveillance occurs for the MCS for 5 years. This surveillance should monitor the following: (1) device success (intra-procedure); (2) all-cause mortality, all stroke, life-threatening (or disabling) bleeding, acute kidney injury-stage 3 (including renal replacement therapy), peri-procedural myocardial infarction, and repeat procedure for valve-related dysfunction (surgical or interventional therapy) at 30 days and 12 months; (3) neurological, vascular and quality of life outcomes at 30 days and 12 months; and (4) all-cause

mortality, neurological and vascular outcomes annually through 5 years post implantation.

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

XIV. APPROVAL SPECIFICATIONS

Directions for use: See final approved labeling (Instructions for Use).

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the final labeling (Instructions for Use).

Post-approval Requirements and Restrictions: See Approval Order.

XV. REFERENCES

[1] Leon MB, Piazza N, Nikolsky E, et al. Standardized endpoint definitions for transcatheter aortic valve implantation clinical trials: a consensus report from the Valve Academic Research Consortium. European Heart Journal 2011; 32:205–217.

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 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/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 ≥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

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 ≥ 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).

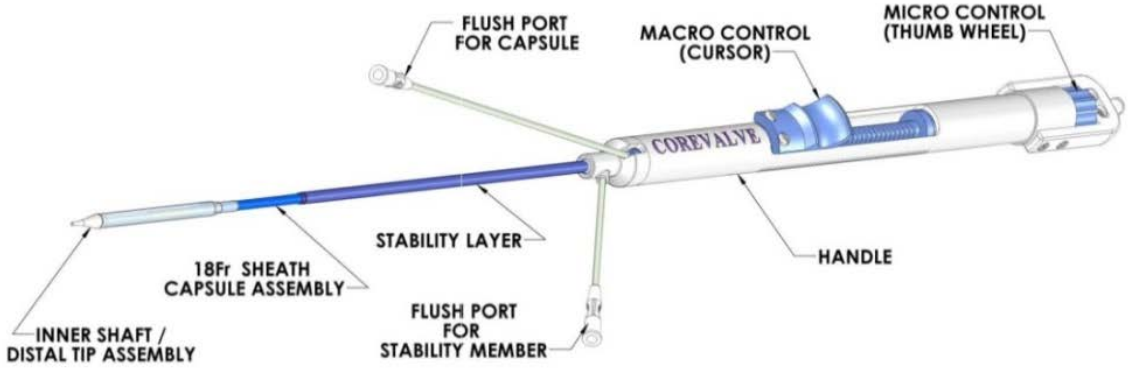
- **Medtronic CoreValve System**

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®), 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

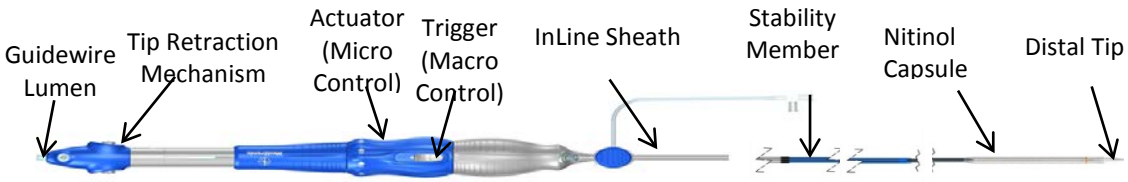
- **Medtronic CoreValve Evolut R System**

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

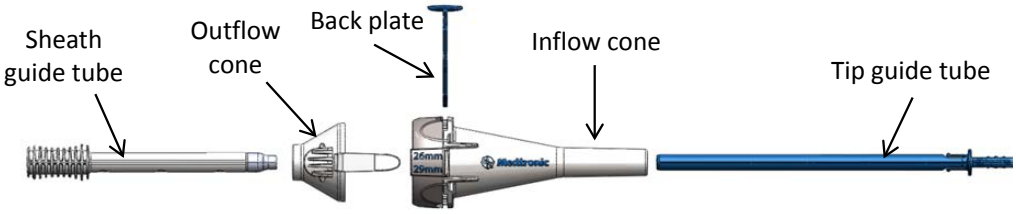
The EnVeo R DCS used with the Evolut R TAV is a single use, intravascular, over-the-wire delivery catheter, as shown in Figure 5. It is designed to be compatible with commercially available 0.035″ intravascular wires. The DCS incorporates a protective deployment sheath that houses and deploys the prosthesis.

Figure 5: EnVeo R Delivery Catheter System



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

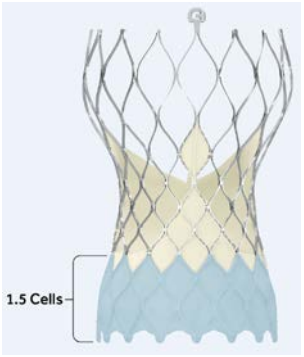
Figure 6: EnVeo R Loading System)



- **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)

*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, δ, 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 ≥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 ≤1.0 cm^2 or aortic valve area index < 0.6 cm^2/m^2, AND
     - Mean gradient > 40 mmHg or Vmax > 4 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 <u>not</u> 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^3), thrombocytopenia (platelet count <50,000 cells/mm^3), 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^2
    - 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 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) 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)	$H_A: \mu_{TAVR} < \mu_{SAVR}$

Order	Secondary Endpoint	Alternative Hypothesis
#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.

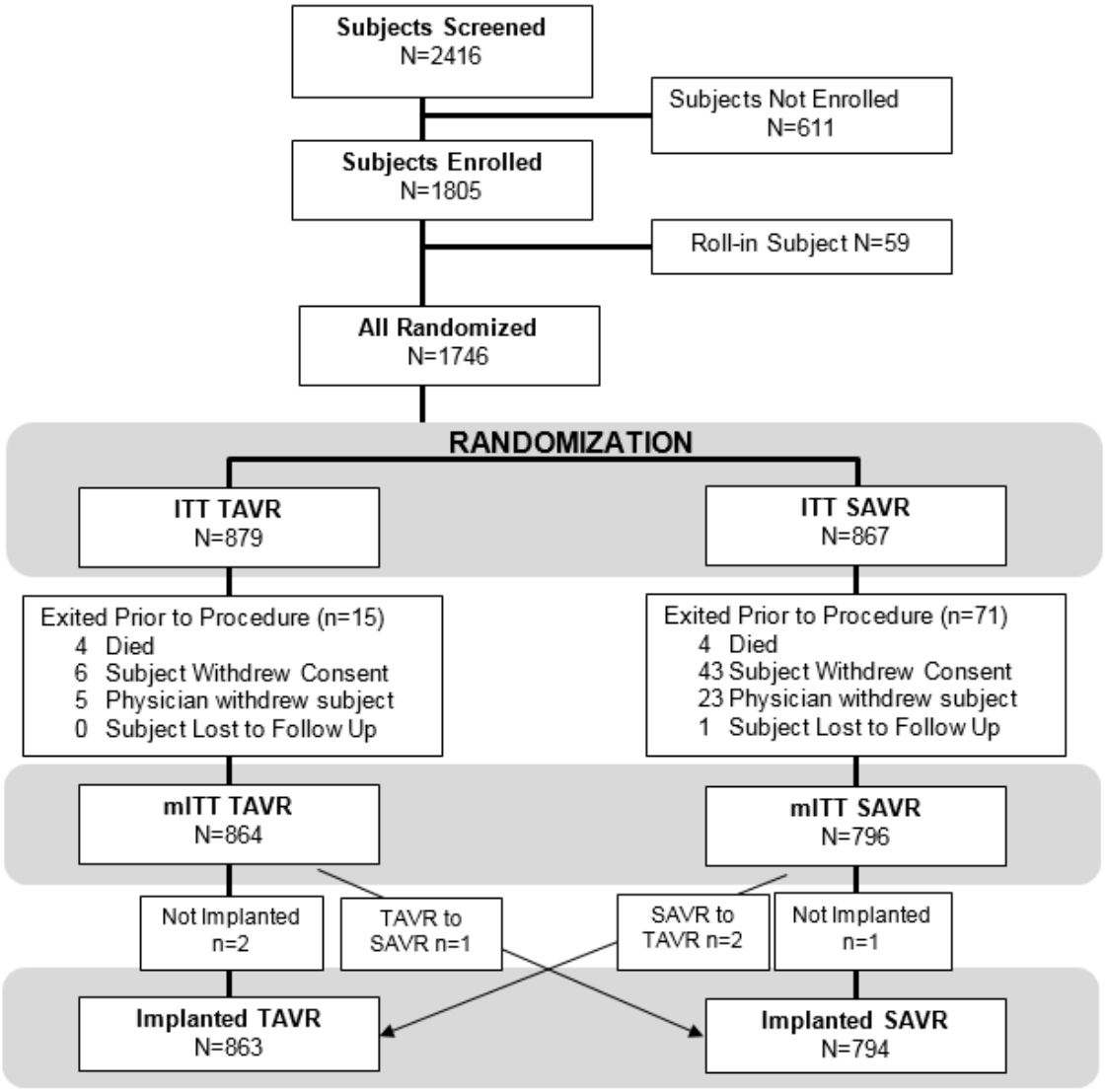
There were three different analysis populations defined in the protocol: intention-to-treat (ITT), modified intention-to-treat (mITT), and implanted (IMP), as summarized in Table 2 and Figure 8. The primary analysis was the mITT analysis.

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†	Lost to Follow-up	Pending Next Visit
SAVR						
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
TAVR						
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)†
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^2)	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.)
†BCI: Bayesian credible interval

D. Safety and Effectiveness Results

1. Primary Endpoint:

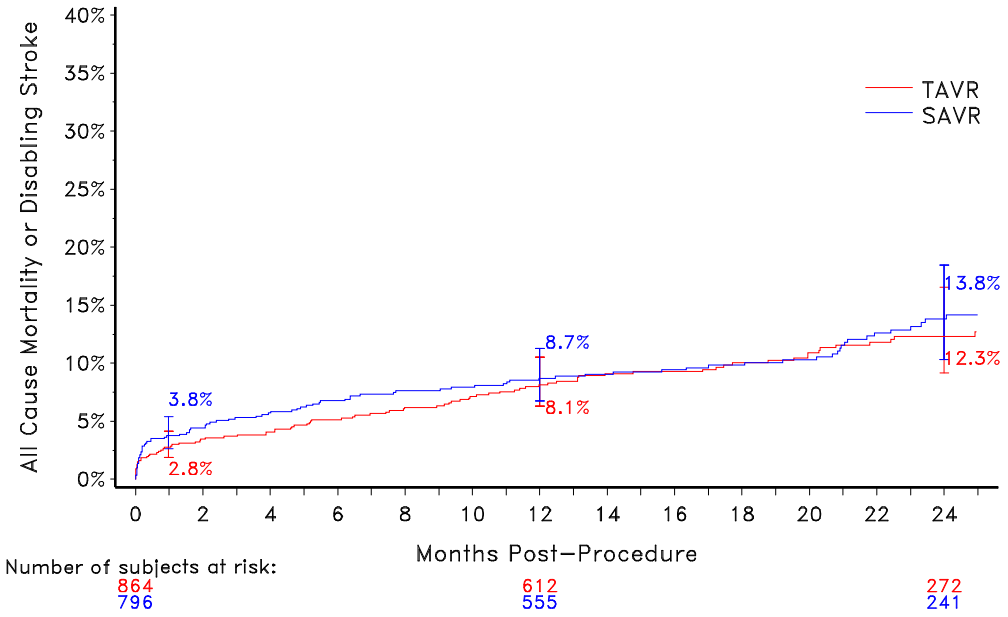
The "early win" assessment of the primary endpoint included all subjects in the mITT population (N = 1660). The median of the posterior distribution for the primary endpoint event rate was 12.6% for the TAVR arm and 14.0% for the SAVR arm, with a median of the posterior distribution of the difference 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

	SAVR (N=796)	**TAVR (N=864)**
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%)	
Non-inferiority testing				
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

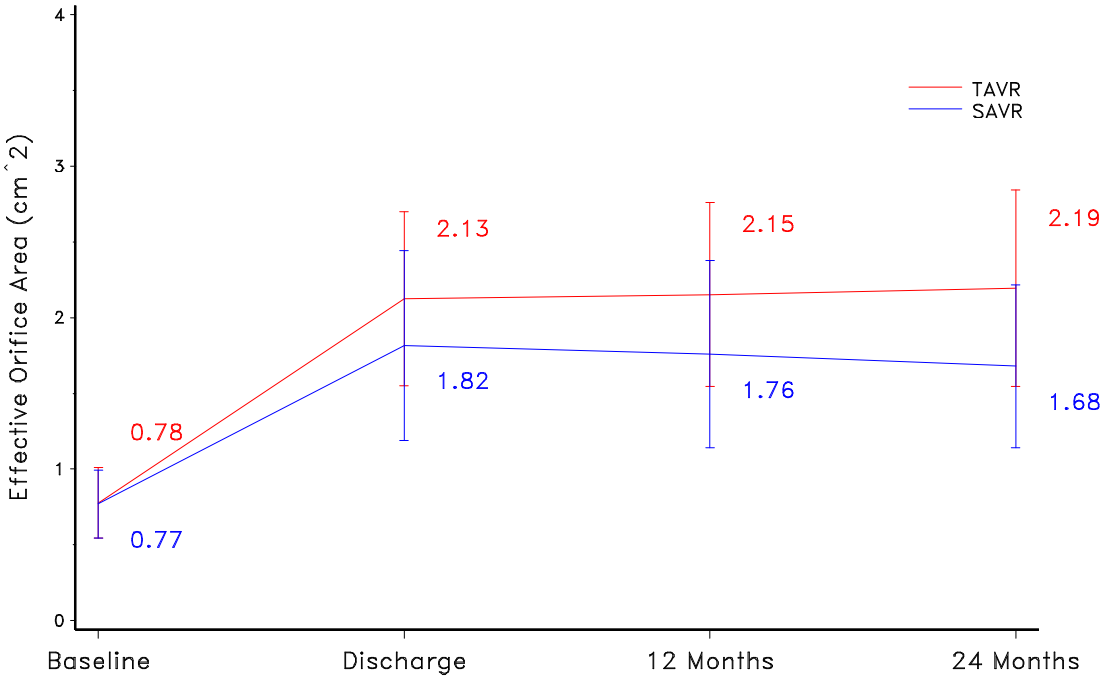
Secondary Endpoint	SAVR Mean ± SD (N)	TAVR Mean ± SD (N)	Difference (TAVR-SAVR) (95% BCI)	Posterior Probability $Pr(H_A \mid data)$	Threshold	Test Result
Non-inferiority testing						
#1 Mean gradient at 12 months	11.7 ± 5.6 (500)	8.3 ± 4.0 (590)	(-4.0, -2.8)	1.00	0.95	Passed
#2 EOA at 12 months	1.8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

Secondary Endpoint	SAVR Mean ± SD (N)	TAVR Mean ± SD (N)	Difference (TAVR-SAVR) (95% BCI)	Posterior Probability $Pr(H_A \mid data)$	Threshold	Test Result
#8 KCCQ summary score change (30 day – baseline)	5.9 ± 27.0 (700)	18.4 ± 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:

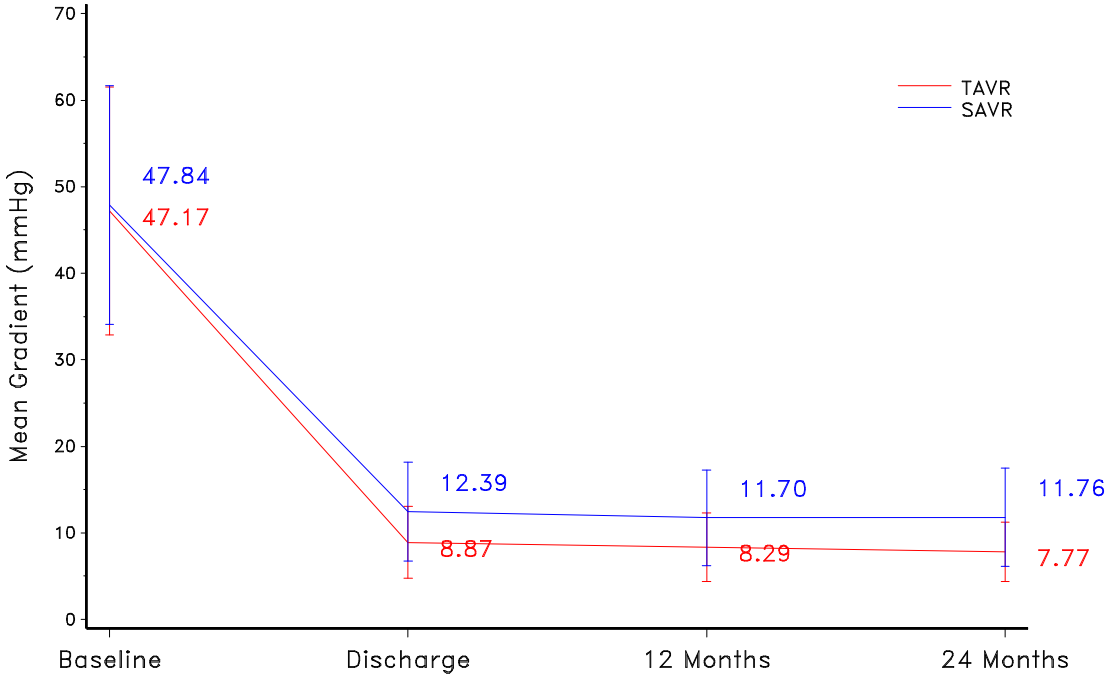
The effective orifice area (EOA), mean aortic gradient, total aortic regurgitation, and paravalvular regurgitation values obtained over time for the TAVR and SAVR subjects in the Implanted population are shown in Figures 10-13. In the TAVR subjects, the mean EOA increased from 0.78 cm^2 at baseline to 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)



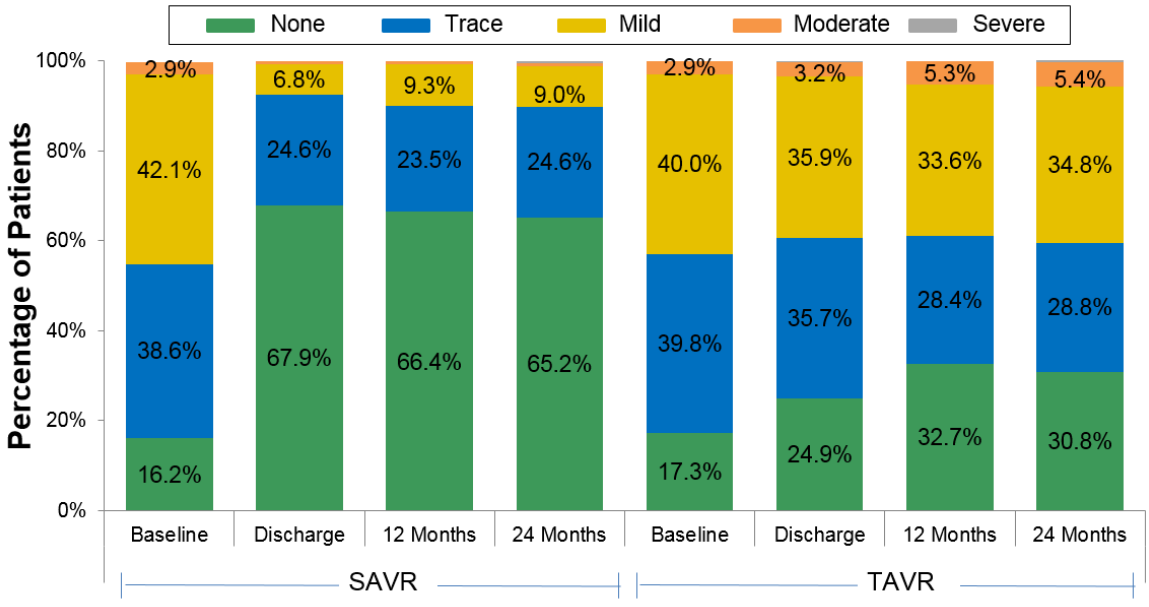
Note: Line plot with mean and standard deviation.

Figure 11: Mean Aortic Gradient (Implanted Population)



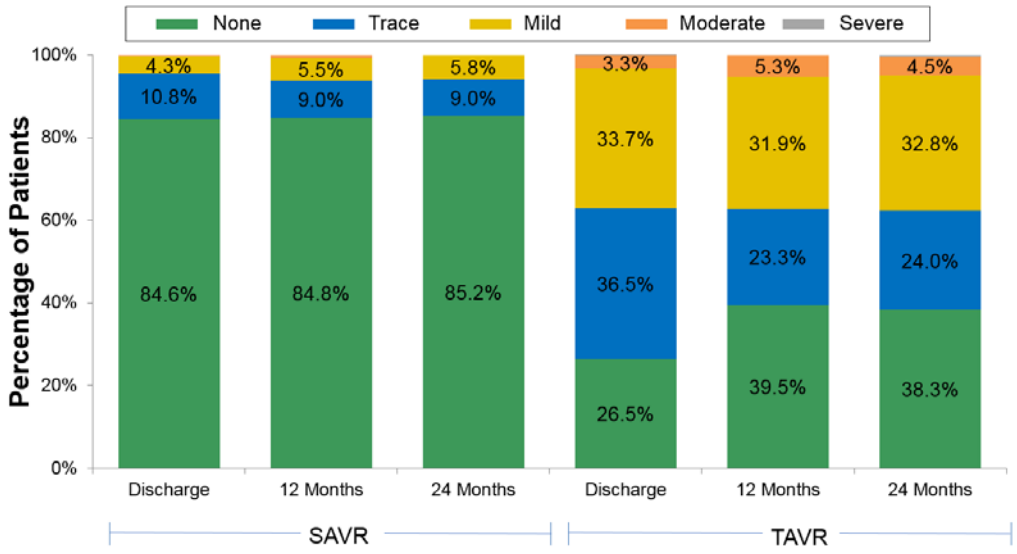
Note: Line plot with mean and standard deviation.

Figure 12: Total Aortic Regurgitation (Implanted Population)



Note: Values < 1.0% are not labeled.

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

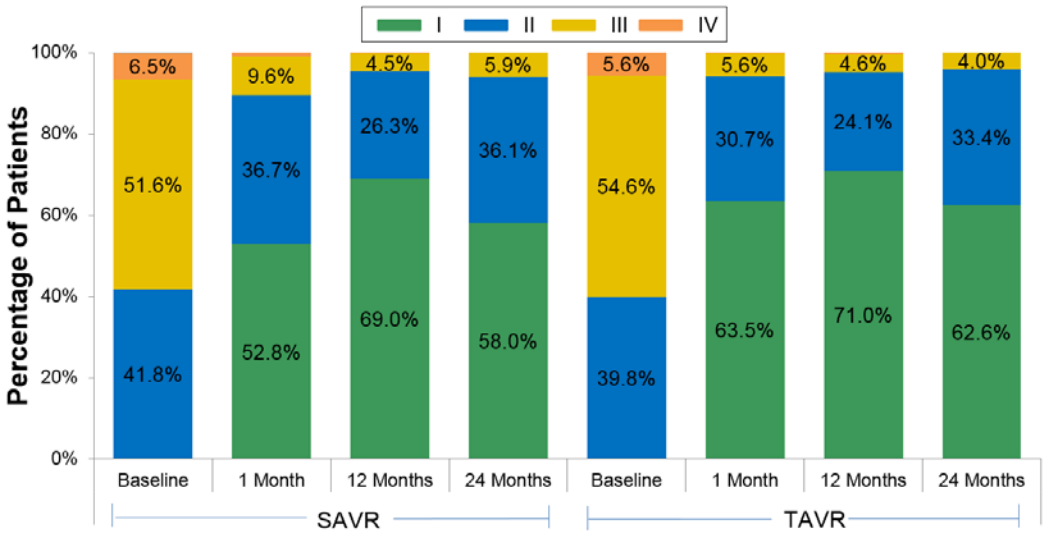


Note: Values < 1.0% are not labeled.

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)



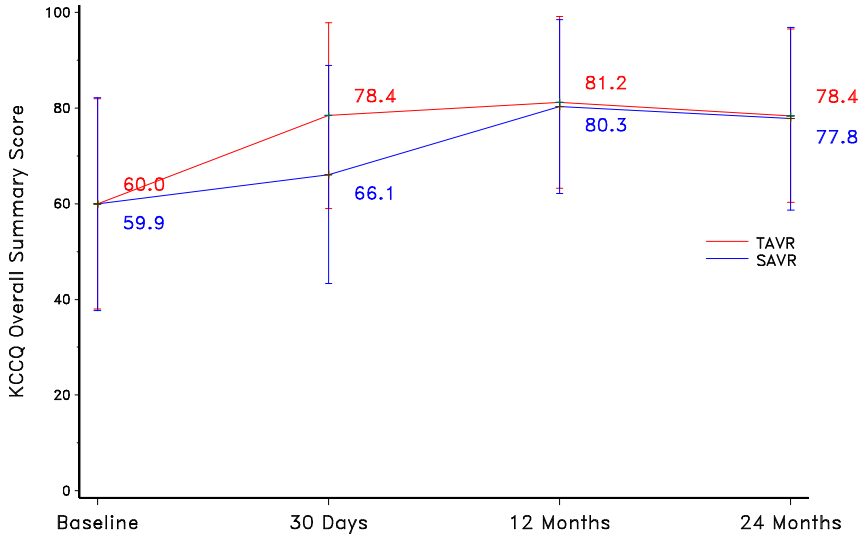
Note: Values < 1.0% are not labeled.

Health Status/QoL Change:

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

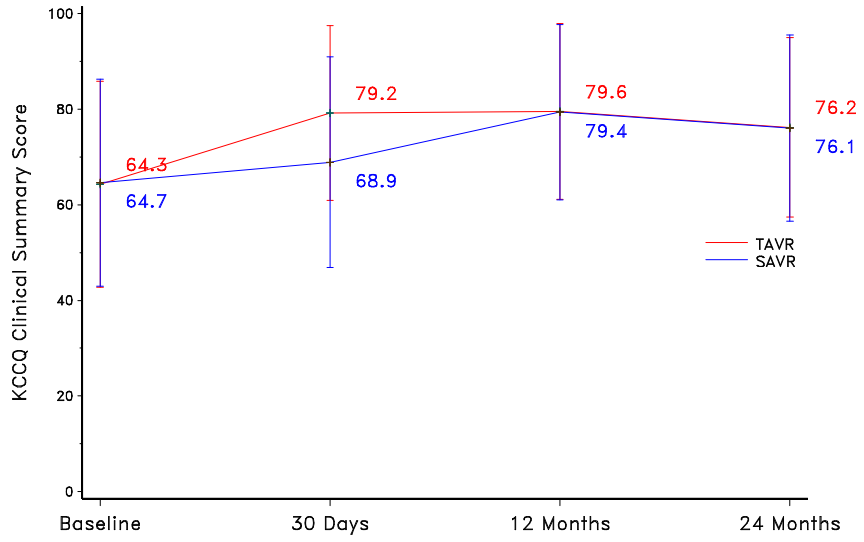
The KCCQ overall and clinical summary scores for the two treatment arms are shown in Figures 15 and 16, respectively.

Figure 15: KCCQ Overall Summary Score



Note: Line plot with mean and standard deviation.

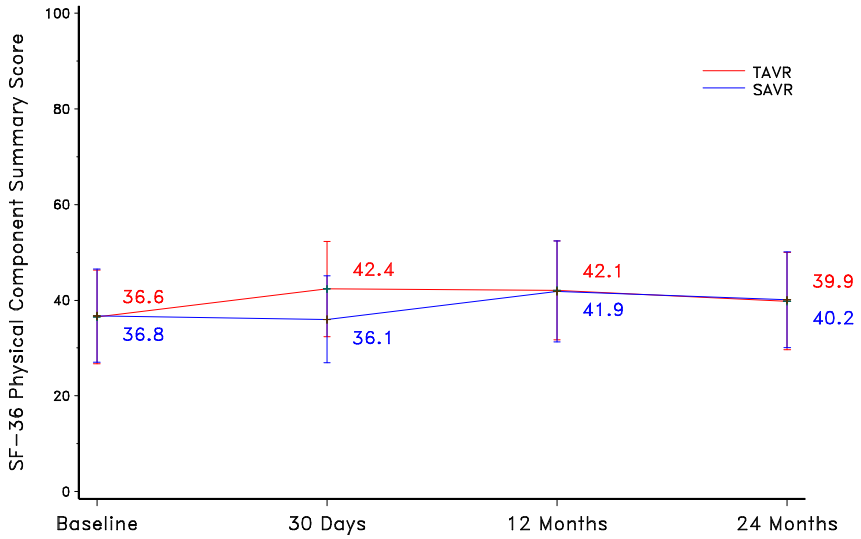
Figure 16: KCCQ Clinical Summary Score



Note: Line plot with mean and standard deviation.

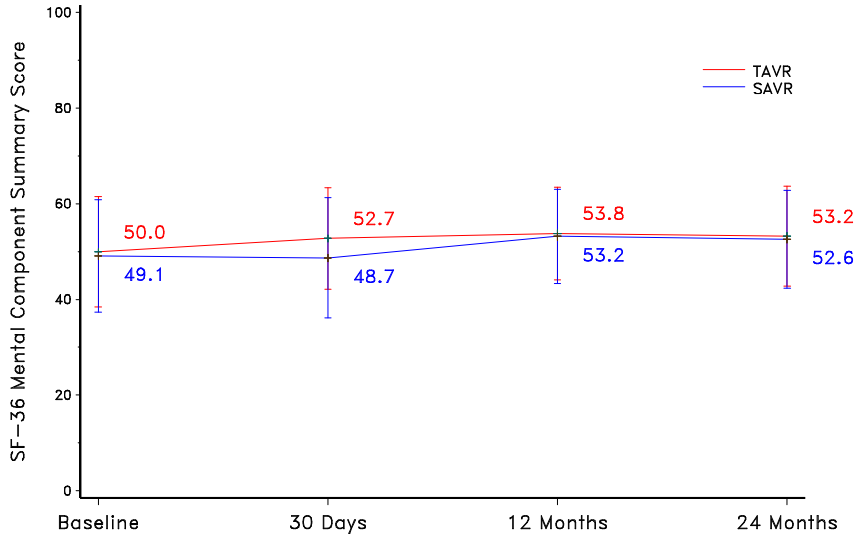
The SF-36 physical and mental component summary scores for the two treatment arms are shown in Figures 17 and 18, respectively.

Figure 17: SF-36 Physical Component Summary Score



Note: Line plot with mean and standard deviation.

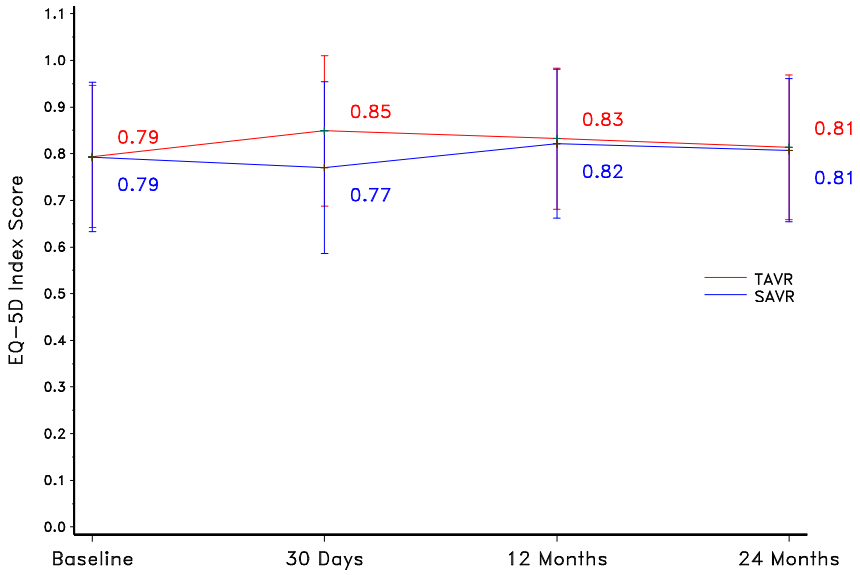
Figure 18: SF-36 Mental Component Summary Score



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‡	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§	6.5% (51, 51)	25.6% (220, 220)	8.6% (66, 68)	28.5% (242, 244)	9.8% (71, 74)	31.5% (256, 260)

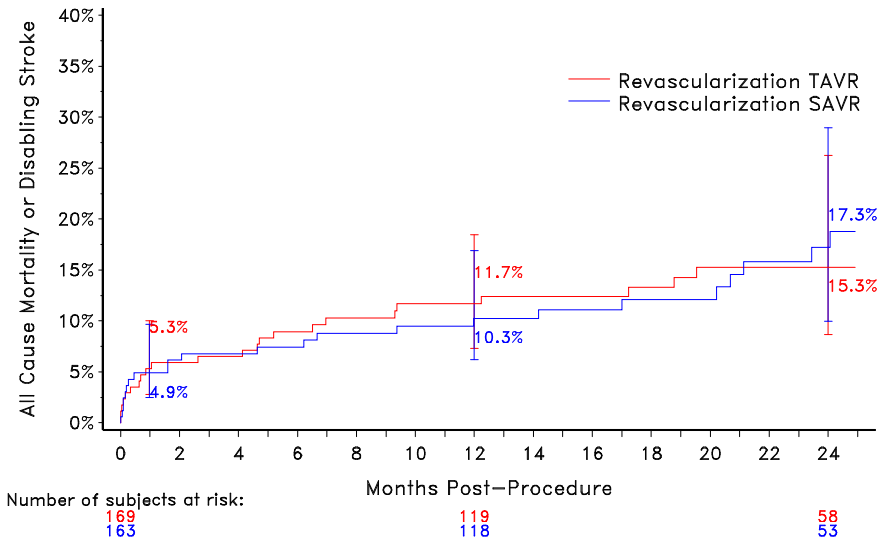
*Kaplan-Meier rate (# patients, # events).
†Valve-related death is any death caused by structural or non- structural valve dysfunction or aortic valve re-intervention.
‡Subjects with pacemaker or ICD at baseline are not included. Not adjudicated by CEC.
§Subjects with pacemaker or ICD at baseline are included. Not adjudicated by CEC.

4. Subgroup analyses

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

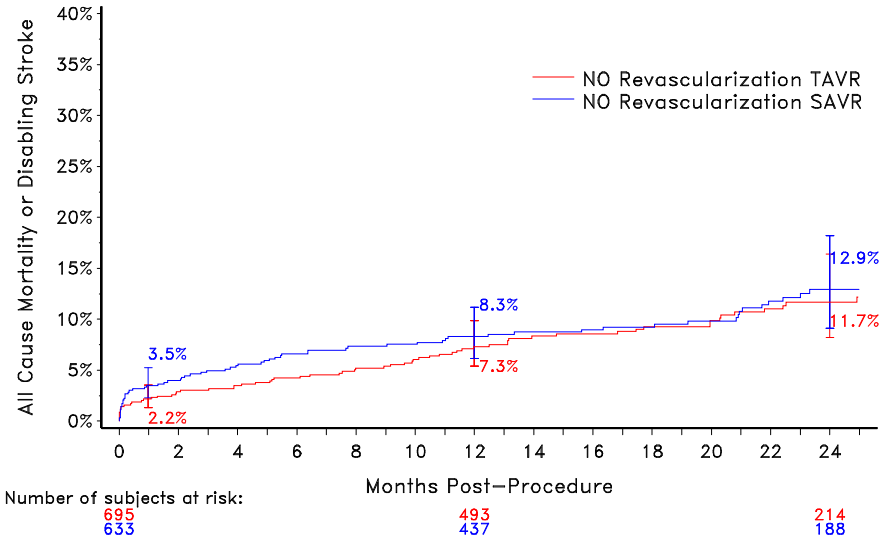
The K-M curves of all-cause mortality or disabling stroke are shown in Figures 20 and 21 for subjects with and without the need for concomitant revascularization, respectively.

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

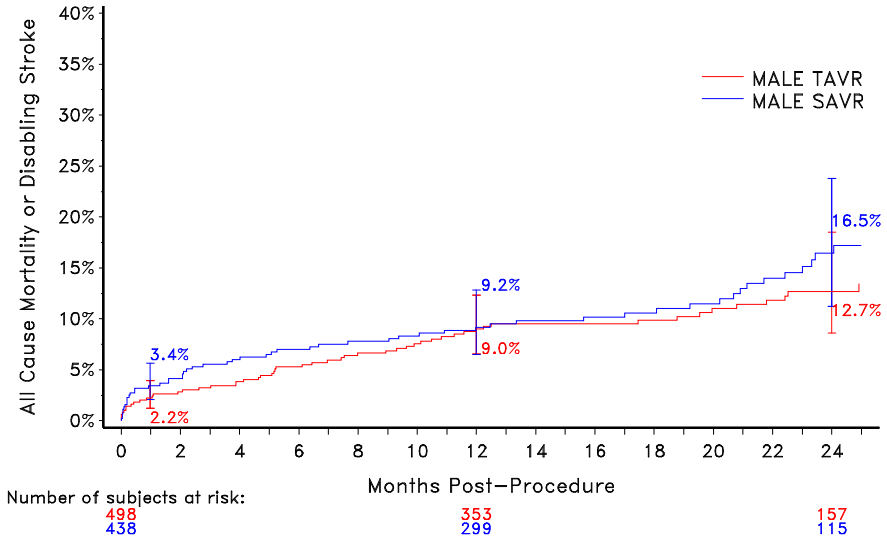


Note: The confidence intervals were calculated without multiplicity adjustment. The adjusted confidence intervals could be wider than presented here. As such, confidence intervals are provided to illustrate the variability only and should not be used to draw any statistical conclusion. The trial was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

All-Cause Mortality or Disabling Stroke Stratified by Gender:

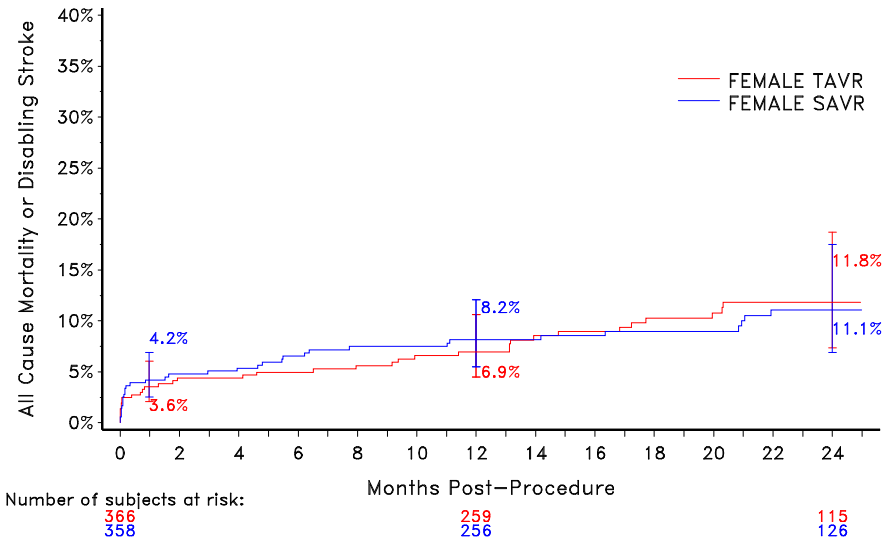
The K-M curves of all-cause mortality or disabling stroke are shown in Figures 21 and 22, for the male and female subjects, respectively.

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

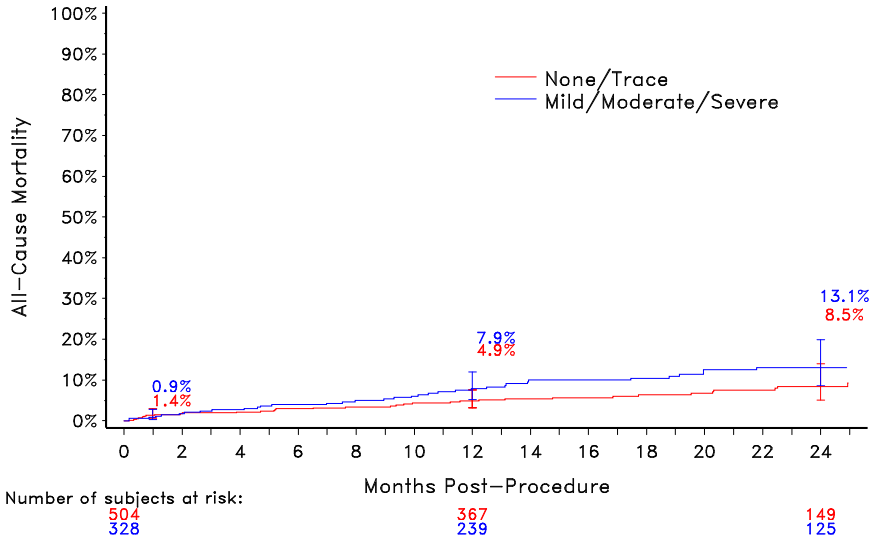


Note: The confidence intervals were calculated without multiplicity adjustment. The adjusted confidence intervals could be wider than presented here. As such, confidence intervals are provided to illustrate the variability only and should not be used to draw any statistical conclusion. The trial was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

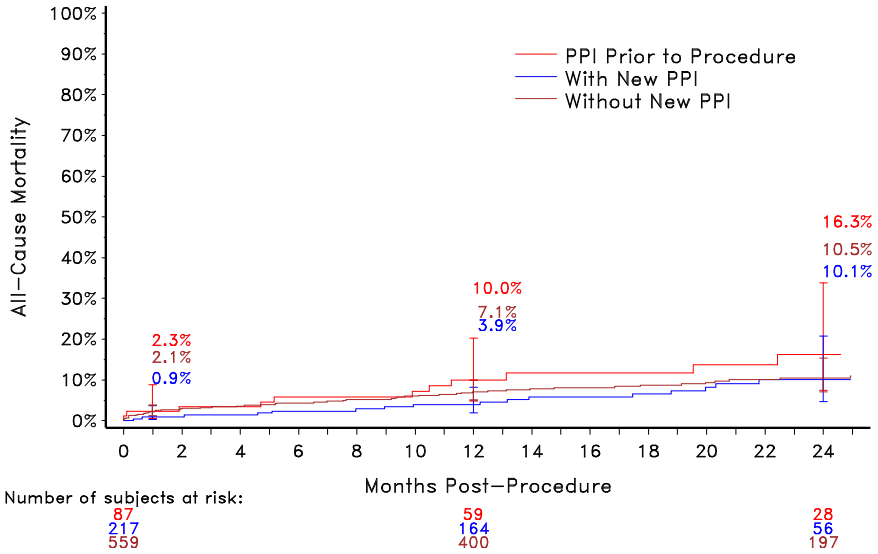


Note: The confidence intervals were calculated without multiplicity adjustment. The adjusted confidence intervals could be wider than presented here. As such, confidence intervals are provided to illustrate the variability only and should not be used to draw any statistical conclusion. The trial was 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 ± 7.2 mm vs. SAVR: 78.4 ± 7.1 mm). Patient prosthesis mismatch (PPM) is defined as an indexed EOA of 0.85-0.65 cm^2/m^2 (moderate) and < 0.65 cm^2/m^2 (severe) for subjects with a BMI <30 kg/cm^2, or 0.70-0.60 cm^2/m^2 (moderate) and < 0.60 cm^2/m^2 (severe) for subjects with a BMI ≥30 kg/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 ≤ 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

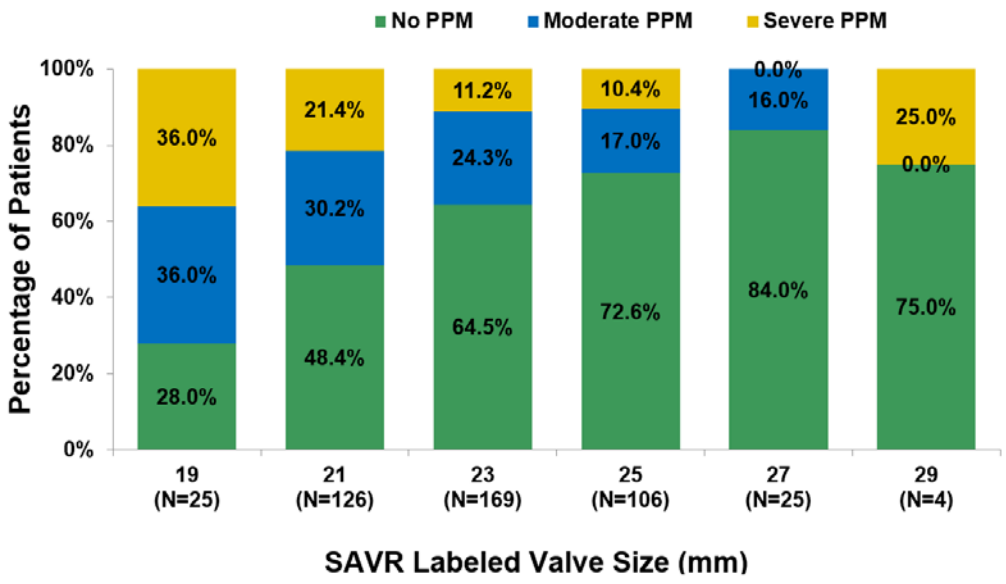


Figure 26: Prevalence of PPM at 12 Months in the TAVR Arm by Valve Size

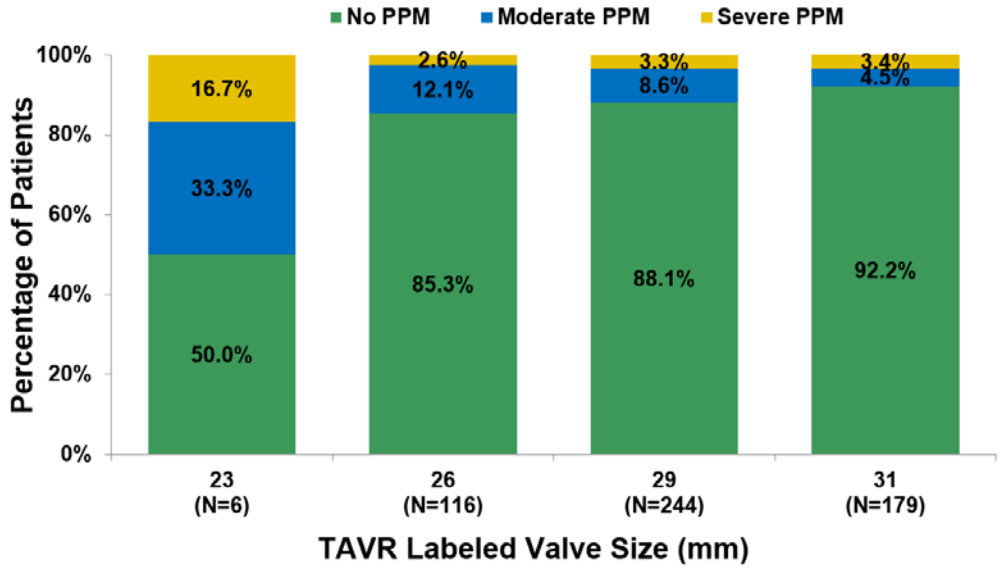
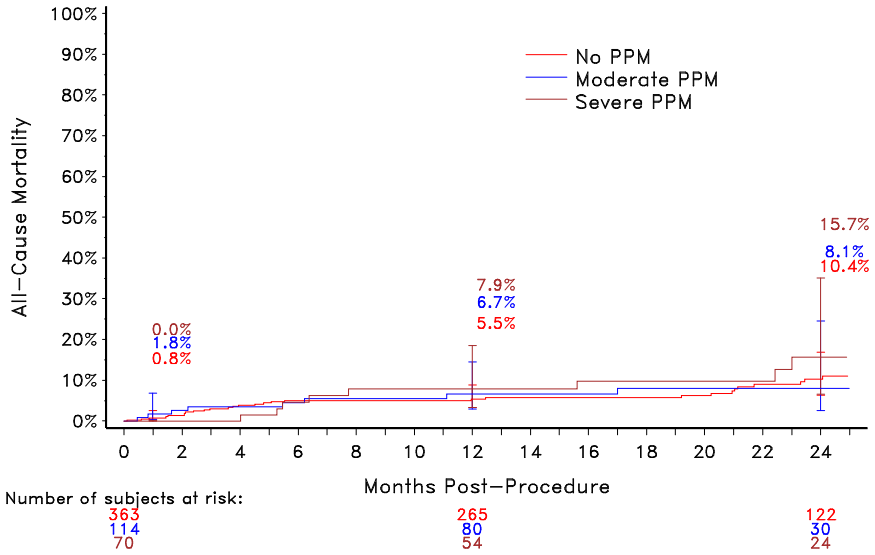
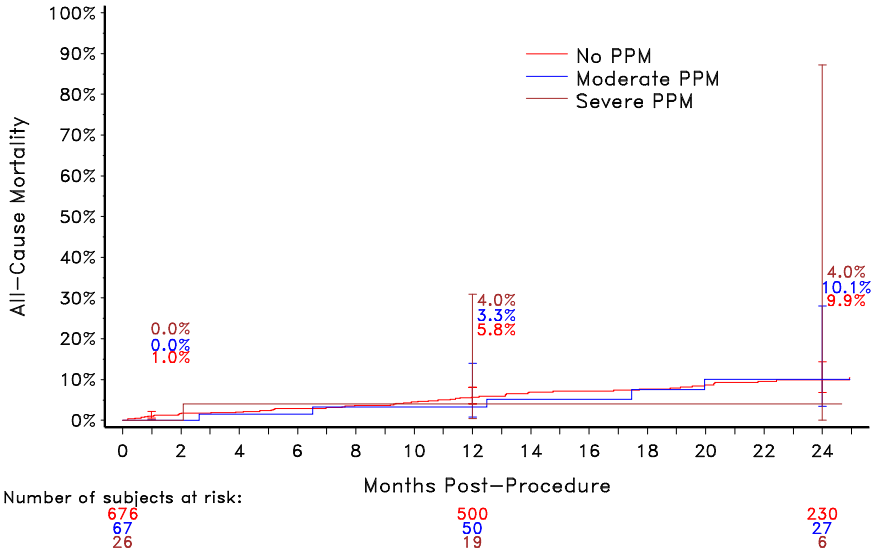


Figure 27: All-Cause Mortality by PPM - SAVR Implanted Population



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

Procedure Data	Summary Statistics* (N=864)
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)

*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^2 to 2.15 cm^2, 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 ± 4.9 days vs. 9.8 ± 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 ≥ 3% at 30 days, based on the STS risk score and other clinical co-morbidities 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.