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.

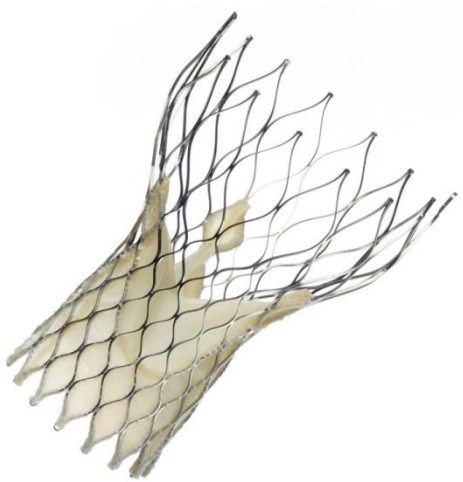

Figure 1: CoreValve Transcatheter Aortic Valve

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.

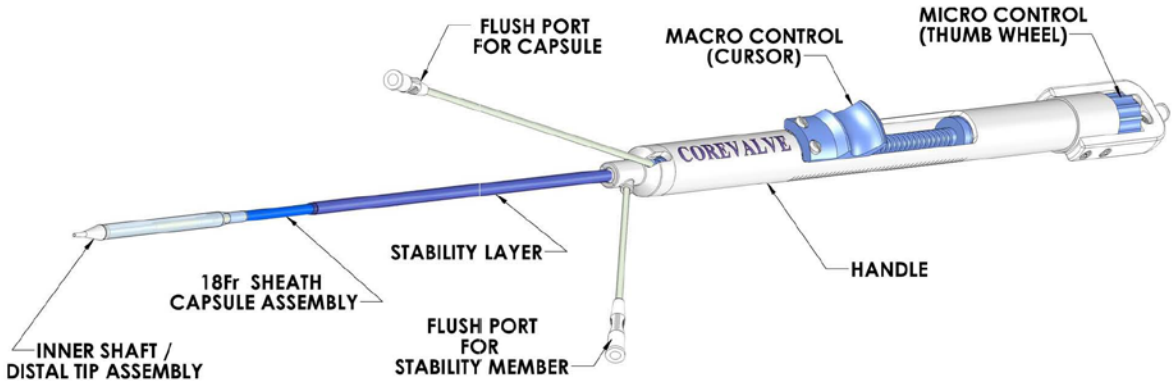

Figure 2: CoreValve Delivery Catheter System

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.

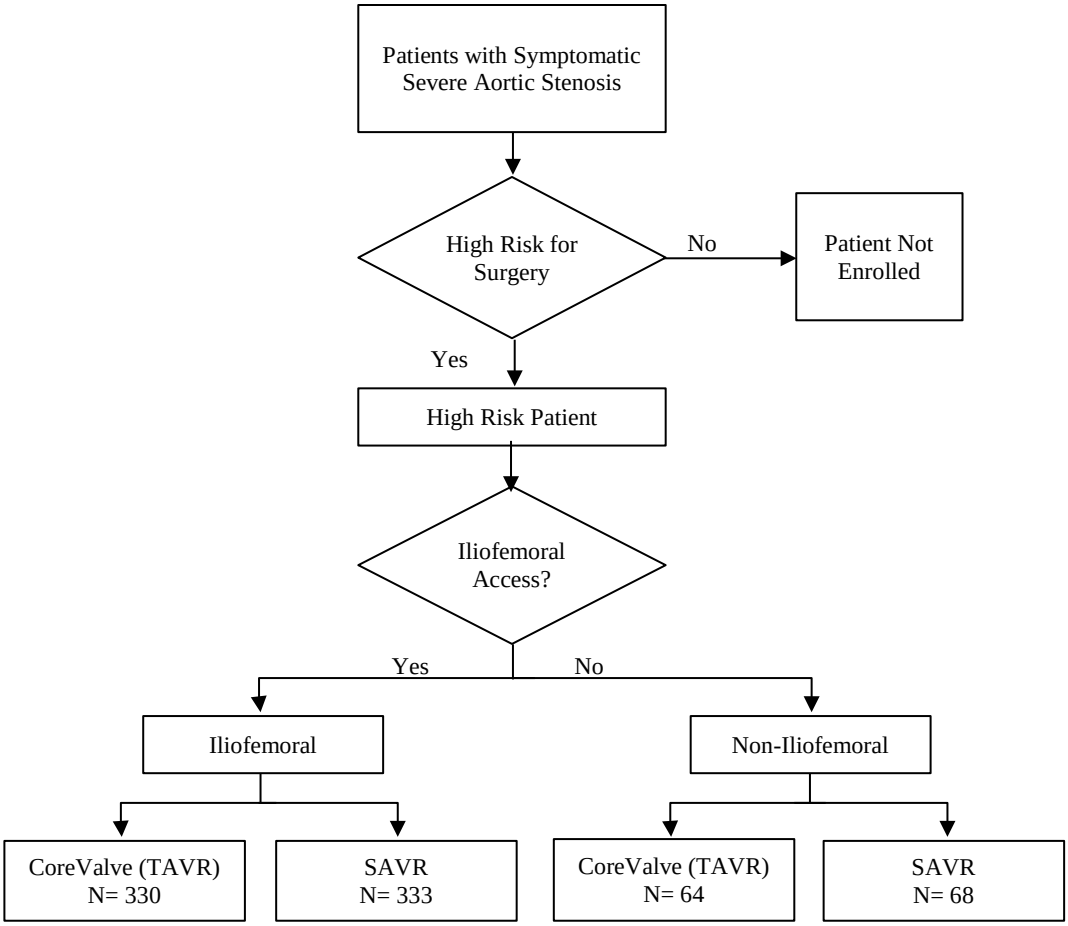

Figure 4: CoreValve High Risk Cohort Patient Flow-chart – ITT Population

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.

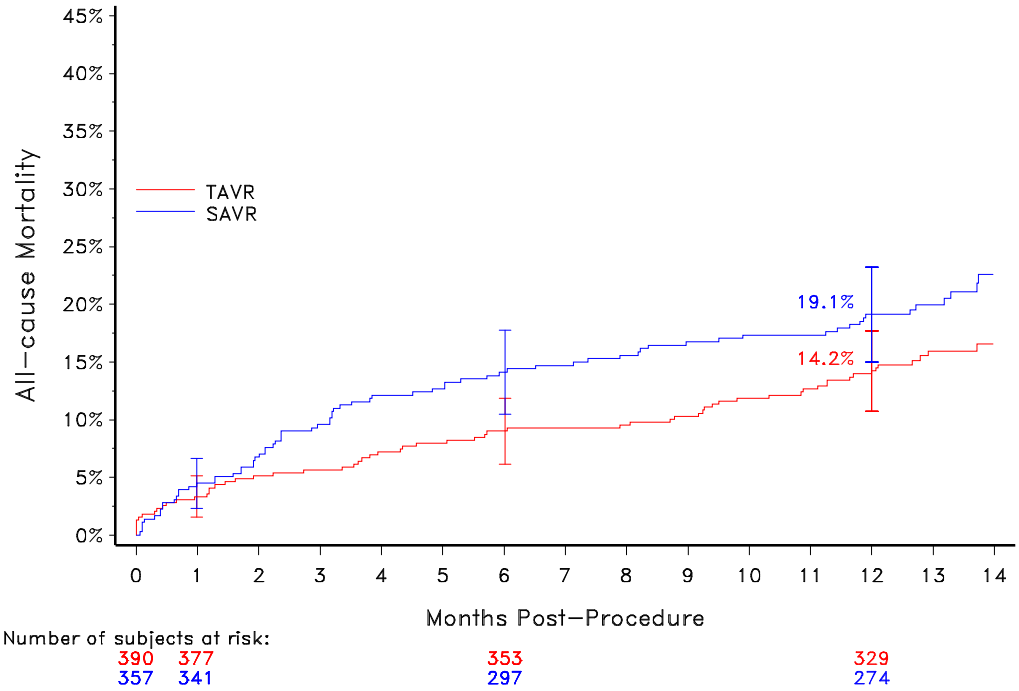

Figure 5: All-Cause Mortality Kaplan-Meier Event Rate – As Treated Population

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	

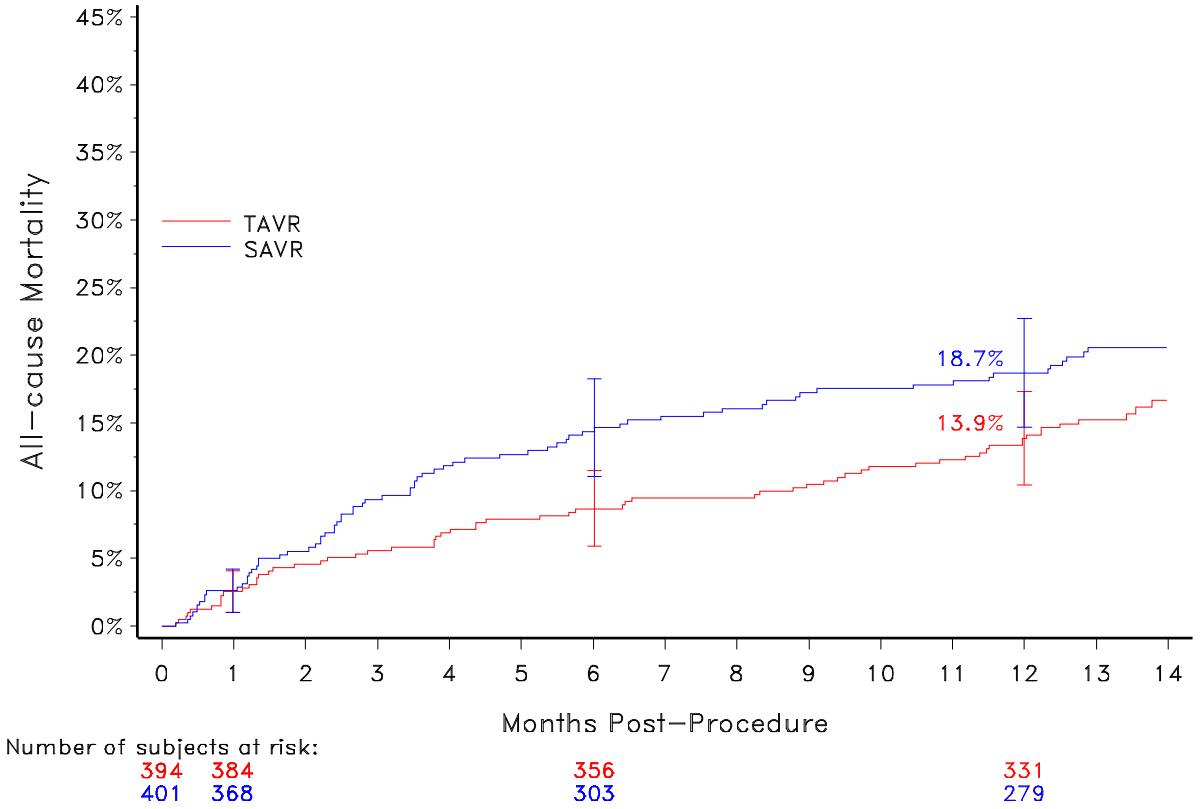

Figure 6: All-Cause Mortality Kaplan-Meier Event Rate – Intent-to-Treat Population

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

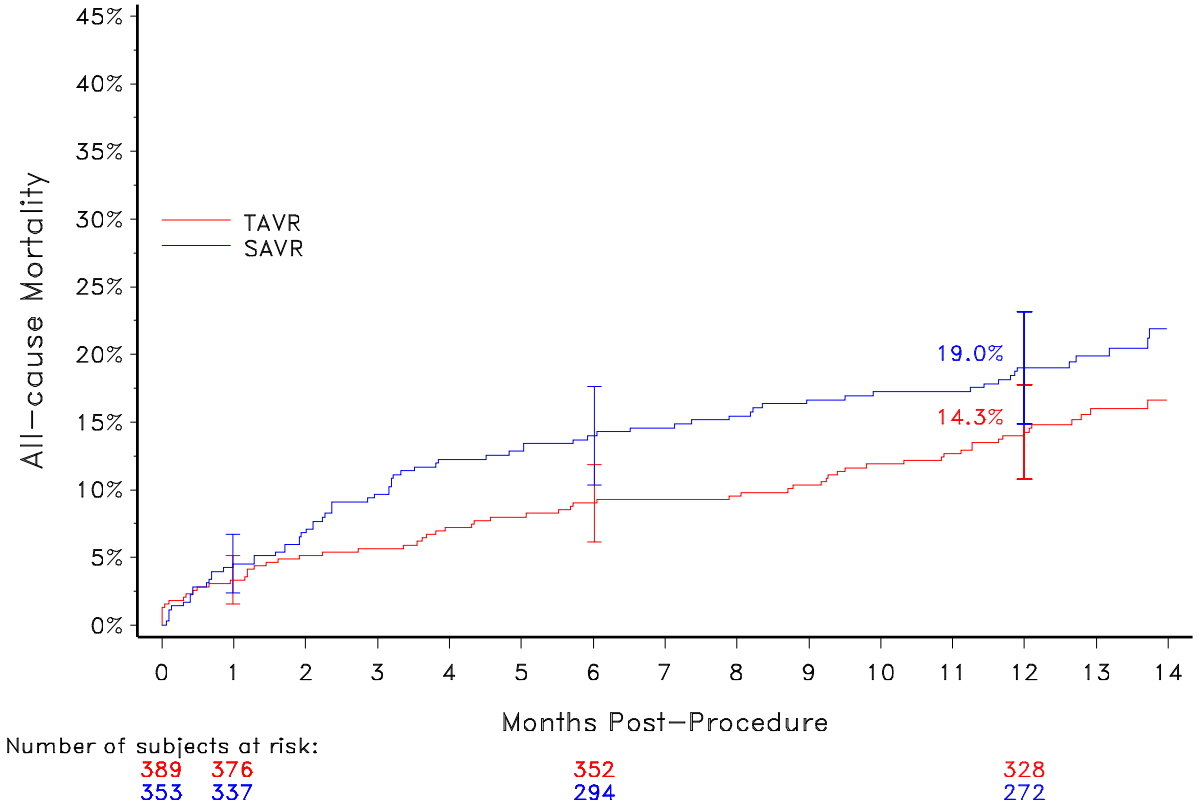

Figure 7: All-Cause Mortality Kaplan-Meier Event Rate – Implanted Population

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

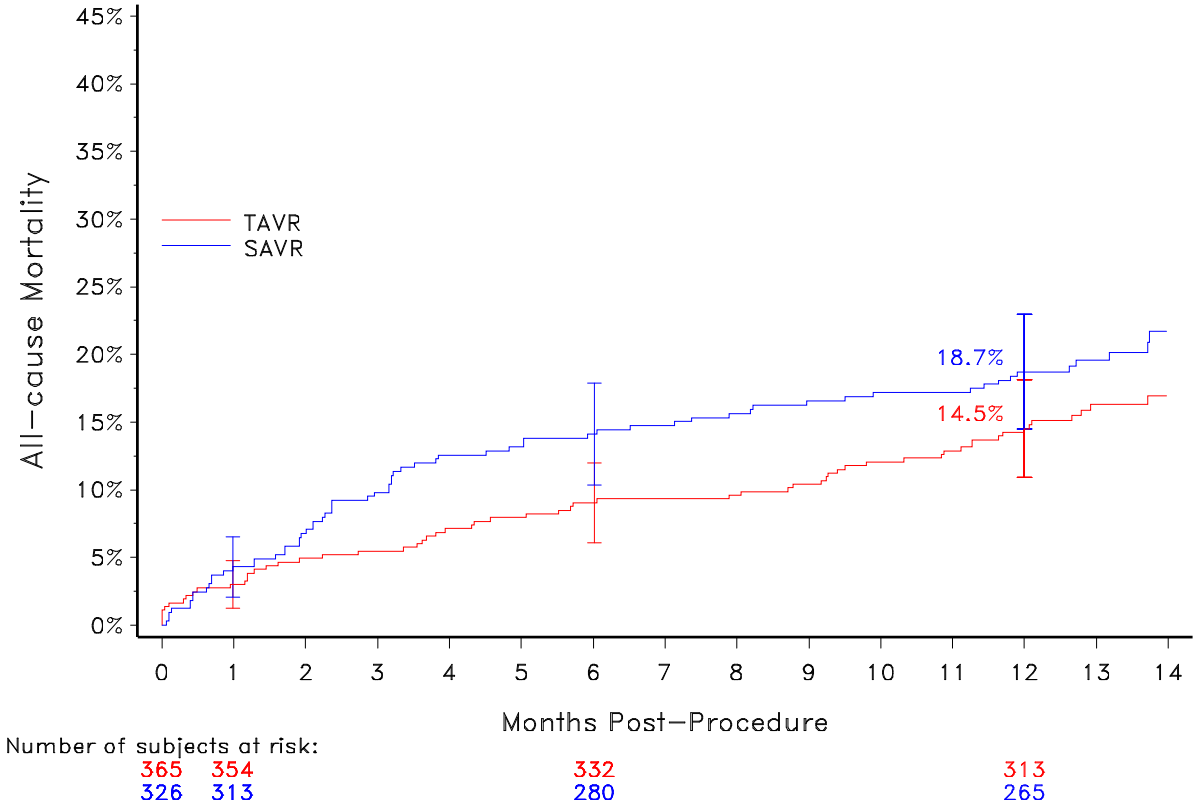

Figure 8: All-Cause Mortality Kaplan-Meier Event Rate – Per Protocol Population

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.

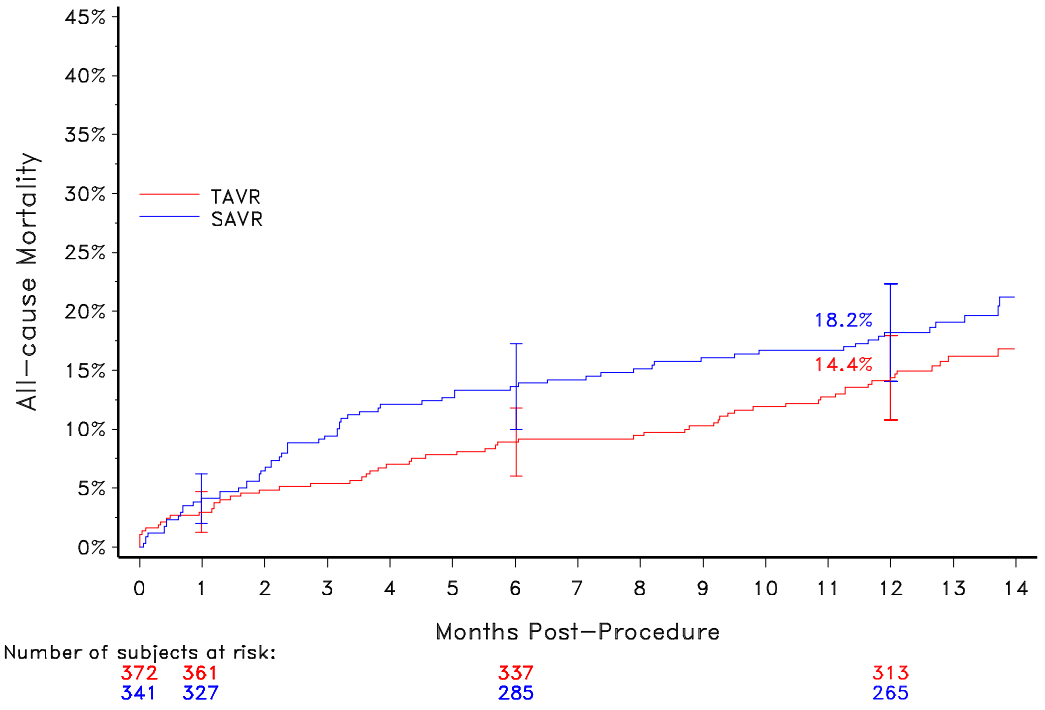

Figure 9: All-Cause Mortality Kaplan-Meier Event Rate – Modified Per Protocol Population

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

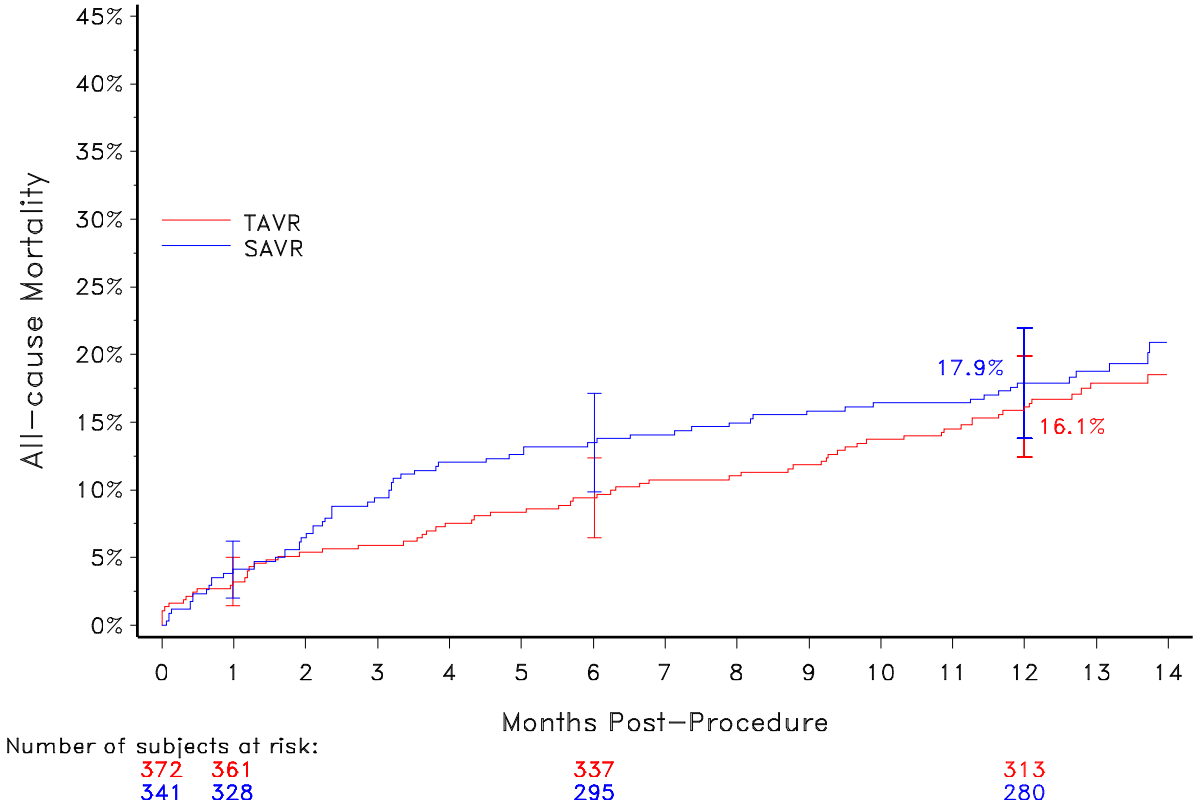

Figure 10: All-Cause Mortality Kaplan-Meier Event Rate – Modified Per Protocol Population – Worst Case Scenario

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

	0-30 Days				0-12 Months			
Event	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.

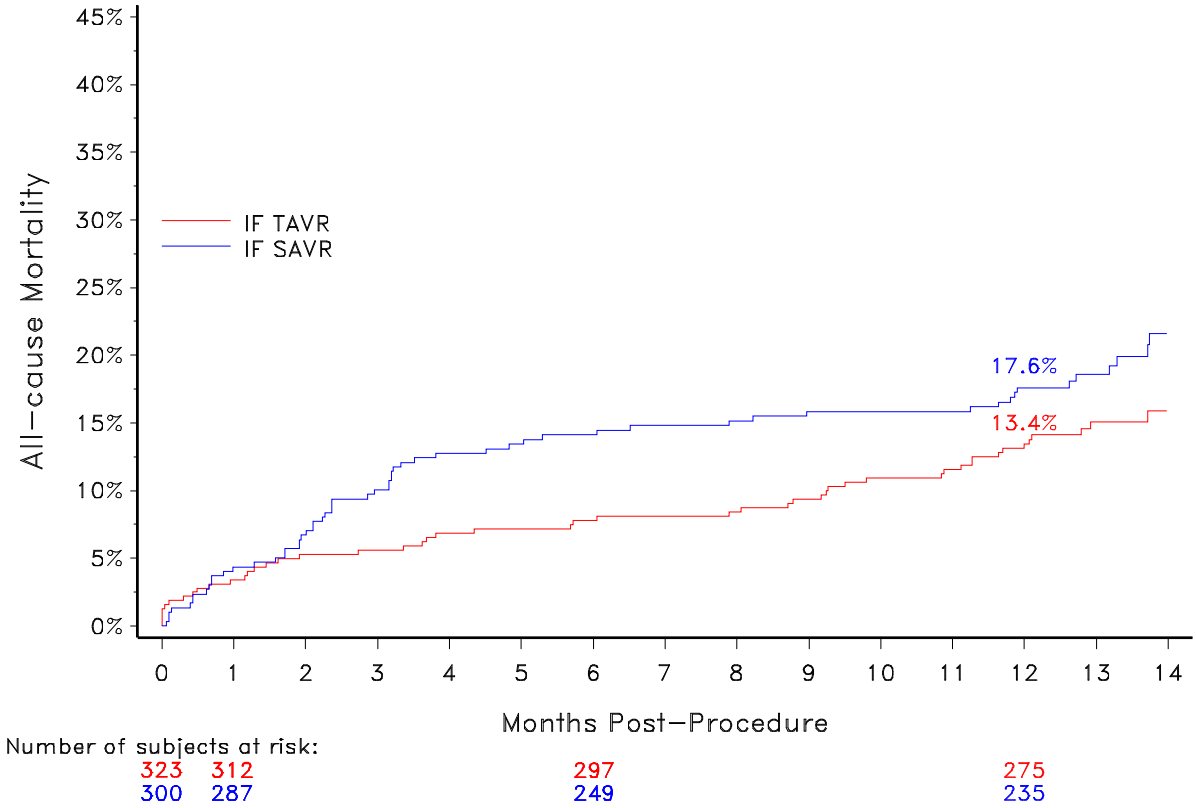

Figure 11: All-Cause Mortality – Iliofemoral As Treated Population

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

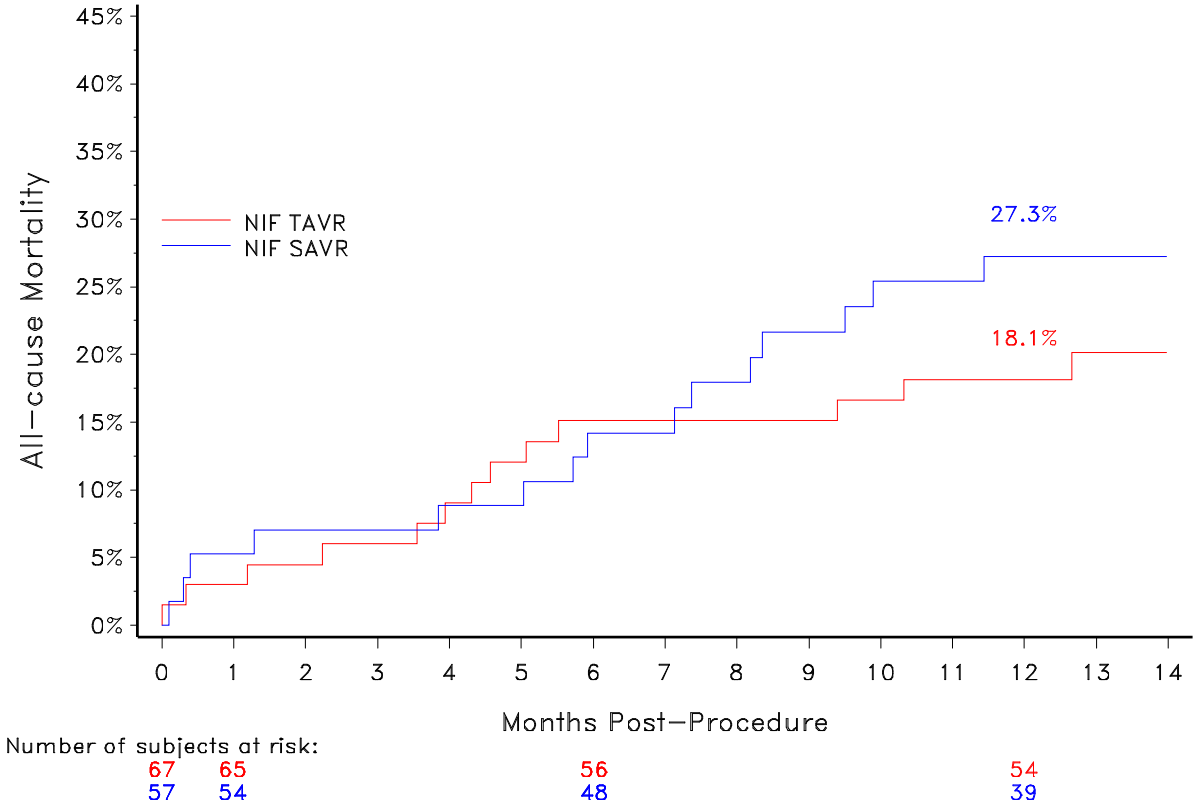

Figure 12: All-Cause Mortality – Non-Iliofemoral As Treated Population

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.

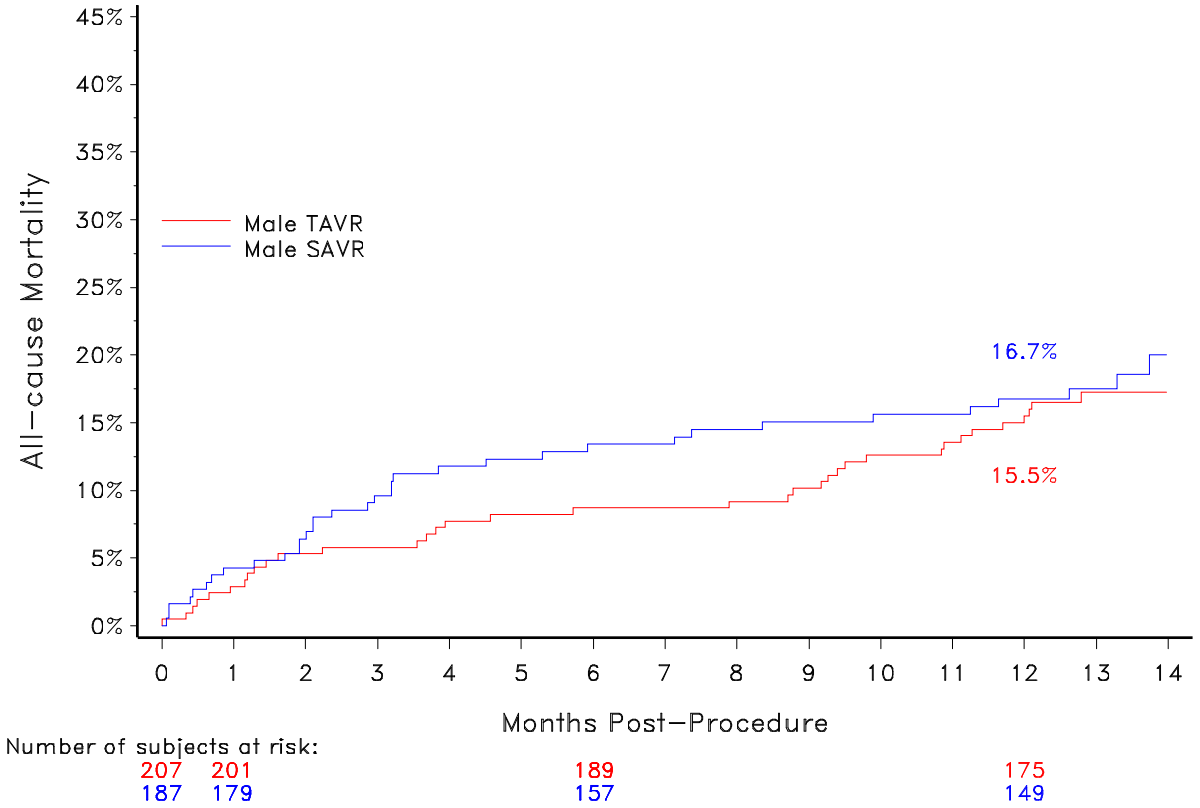

Figure 13: All-Cause Mortality at 12 Months for Male Patients – As Treated Population

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

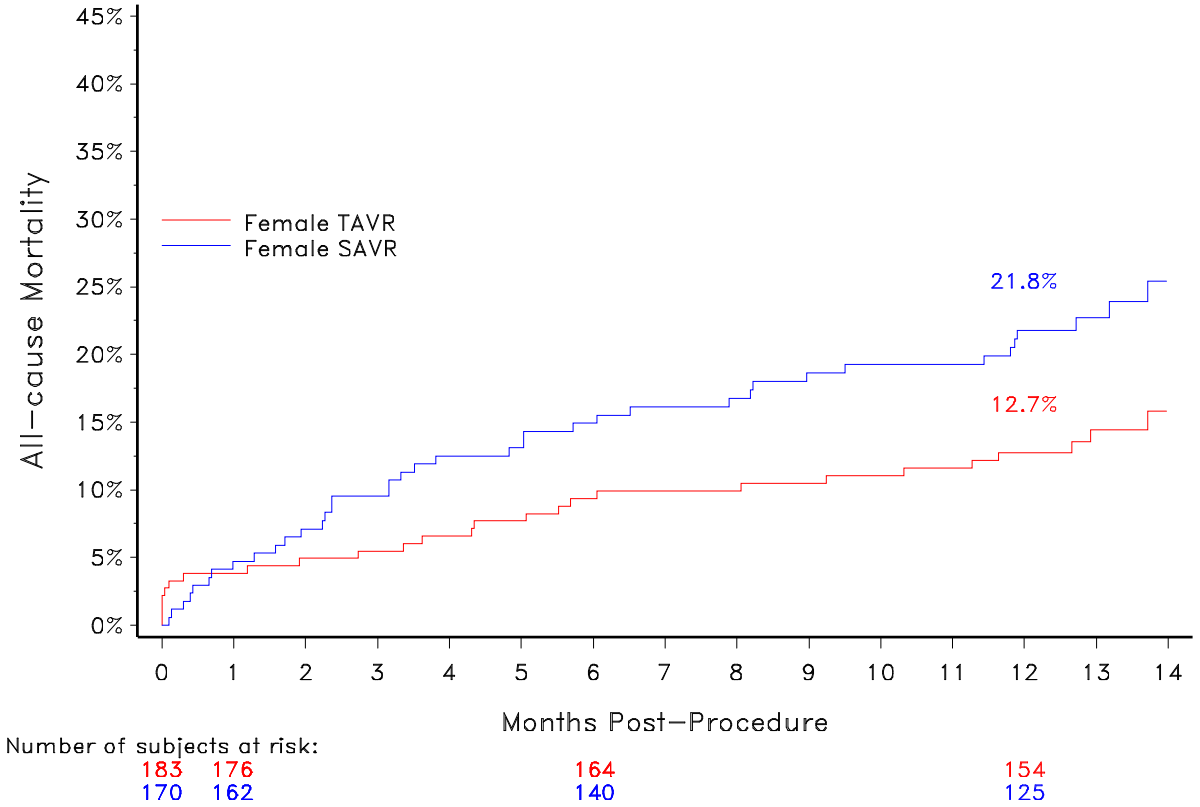

Figure 14: All-Cause Mortality at 12 Months for Female Patients – As Treated Population

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.

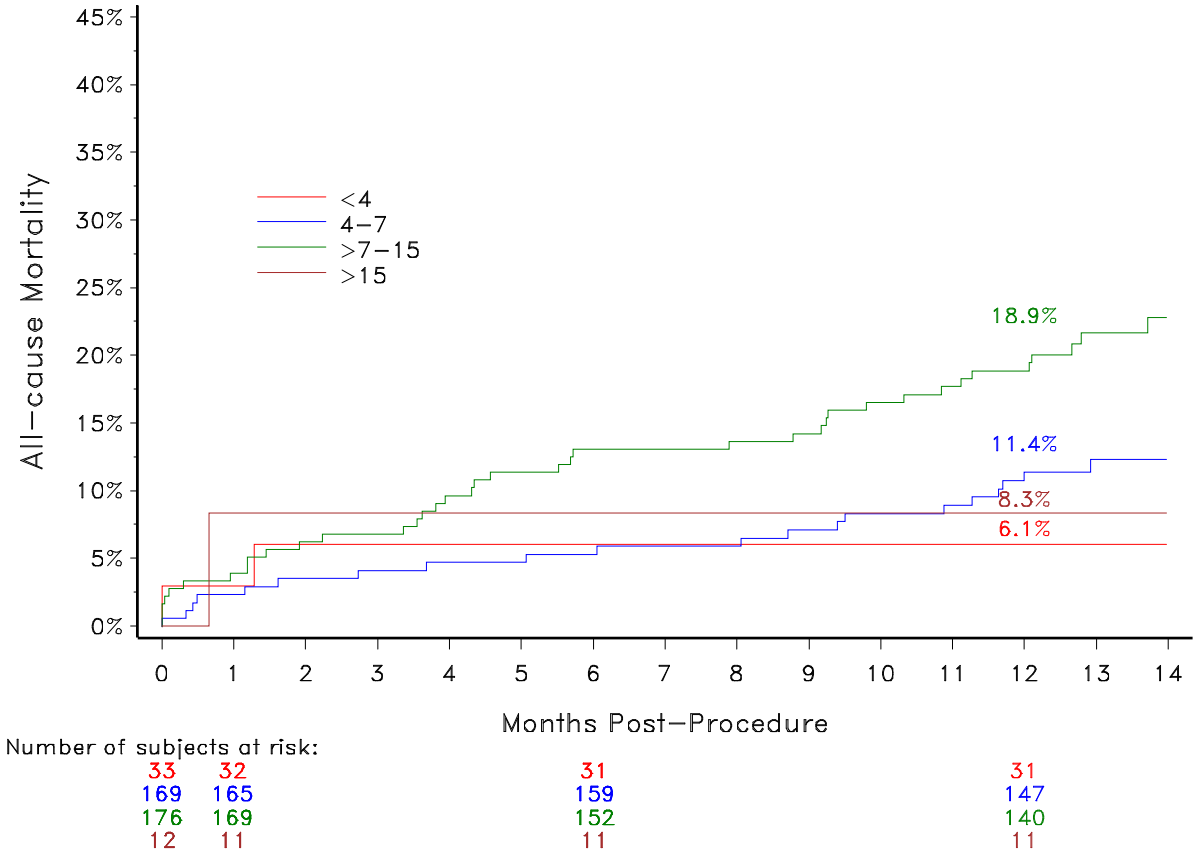

Figure 15: All-Cause Mortality by STS – TAVR As Treated Population

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.

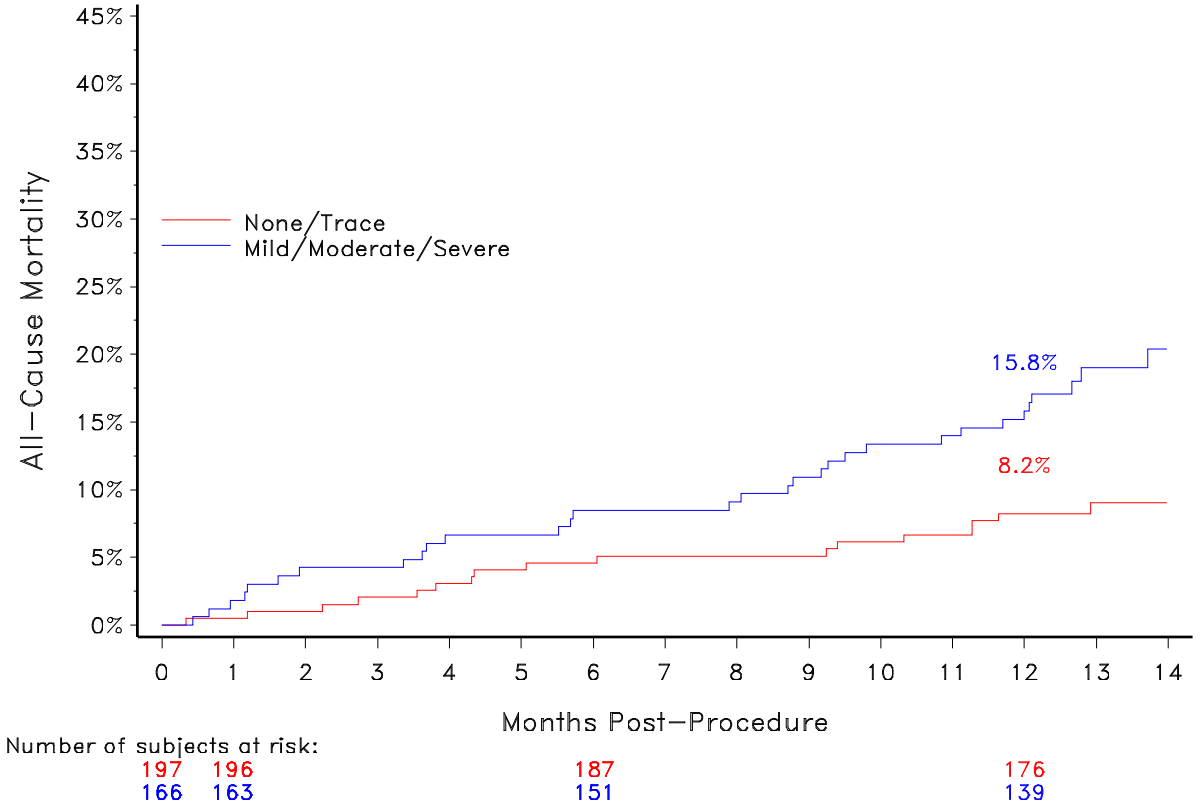

Figure 16 : All-Cause Mortality by Severity of Aortic Regurgitation (None/Trace vs Mild/Moderate/Severe) – TAVR Implanted Population

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.