

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name: Aortic valve, prosthesis, percutaneously delivered

Device Trade Name: Medtronic CoreValve™ System (MCS): Transcatheter Aortic Valve (TAV), Models MCS-P4-23-AOA (23 mm; CoreValve™ Evolut™), MCS-P3-26-AOA (26 mm), MCS-P3-29-AOA (29 mm), and MCS-P3-31-AOA (31 mm); Delivery Catheter System (DCS), Models DCS-C4-18FR and DCS-C4-18FR-23; and Compression Loading System (CLS), Model CLS-3000-18FR

Device Procode: NPT

Applicant Name and Address: Medtronic CoreValve LLC
3576 Unocal Place
Santa Rosa, CA 95403

Date of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P130021/S010

Date of FDA Notice of Approval: March 30, 2015

The Medtronic CoreValve system was approved under PMA P130021 and PMA Supplement P130021/S002 with an indication for relief of aortic stenosis in patients with symptomatic heart disease due to severe native calcific aortic stenosis (aortic valve area $\leq 1.0 \text{ cm}^2$ or aortic valve area index $\leq 0.6 \text{ cm}^2/\text{m}^2$, a mean aortic valve gradient of $\geq 40 \text{ mm Hg}$, or a peak aortic-jet velocity of $\geq 4.0 \text{ m/s}$) 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 $\geq 8\%$ or at a $\geq 15\%$ risk of mortality at 30 days). The SSEDs to support this indication are available on the following FDA websites:

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

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

II. INDICATIONS FOR USE

The Medtronic CoreValve system is indicated for use in patients with symptomatic heart disease due to either severe native calcific aortic stenosis or failure (stenosed, insufficient, or combined) of a surgical bioprosthetic aortic valve who are judged by a heart team, including a cardiac surgeon, to be at high or greater risk for open surgical therapy (i.e., Society of Thoracic Surgeons operative risk score $\geq 8\%$ or at a $\geq 15\%$ risk of mortality at 30 days).

III. CONTRAINDICATIONS

The Medtronic CoreValve system is contraindicated for patients presenting with any of the following conditions:

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

IV. WARNINGS AND PRECAUTIONS

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

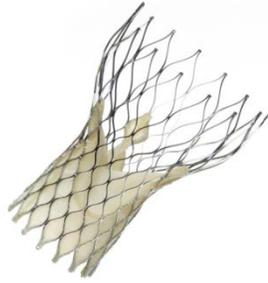
V. DEVICE DESCRIPTION

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

Transcatheter Aortic Valve (TAV)

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

Figure 1: CoreValve Transcatheter Aortic Valve



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

Table 1: Patient Anatomical Diameters

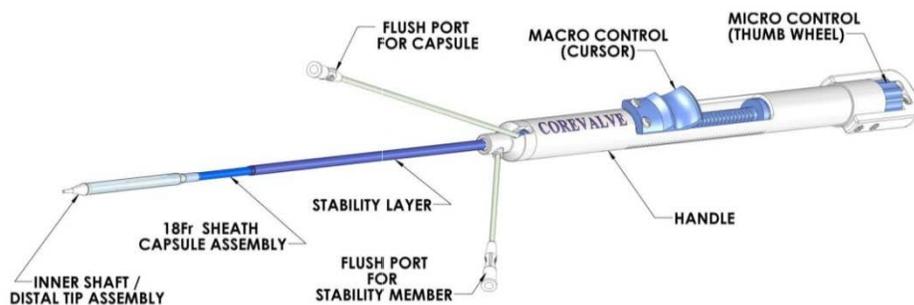
Bioprosthesis Model	Size	Aortic Annulus Diameter	Ascending Aorta Diameter
CoreValve™ Evolut™ Bioprosthesis			
MCS-P4-23-AOA	23 mm	17*/18mm–20 mm	≤34 mm
CoreValve™ Bioprosthesis			
MCS-P3-26-AOA	26 mm	20 mm–23 mm	≤40 mm
MCS-P3-29-AOA	29 mm	23 mm–26 mm	≤43 mm
MCS-P3-31-AOA	31 mm	26 mm–29 mm	≤43 mm

* 17mm for surgical bioprosthetic aortic annulus

Delivery Catheter System with AccuTrak Stability Layer (AccuTrak DCS)

The DCS (Figure 2) is used to deploy the TAV. The TAV is loaded within the capsule which features an atraumatic, radiopaque tip and protective sheath. The AccuTrak stability layer is fixed at the handle and extends down the outside of the catheter shaft to provide a barrier between the catheter and vessel walls. The handle features macro and micro adjustment control of the retractable capsule sheath. There are two models of the DCS: model DCS-C4-18FR-23 for the 23 mm TAV only and model DCS-C4-18FR for the 26, 29, and 31 mm TAVs.

Figure 2: CoreValve Delivery Catheter System



Compression Loading System (CLS)

The CLS (Figure 3) is a system of reduction cones and tubing designed to compress the TAV to an optimal diameter for manual loading into the DCS. Only one model of the CLS is available, i.e., model CLS-3000-18FR.

Figure 3: CoreValve Compression Loading System



The CLS comprises the following elements:

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

VI. ALTERNATIVE PRACTICES AND PROCEDURES

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

VII. MARKETING HISTORY

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

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

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

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

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

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

- death
- cardiac arrest
- coronary occlusion, obstruction, or vessel spasm (including acute coronary closure)
- emergent surgery (e.g., coronary artery bypass, heart valve replacement, valve explant)
- multi-organ failure
- heart failure
- myocardial infarction (MI)
- cardiogenic shock
- respiratory insufficiency or respiratory failure
- cardiovascular injury (including rupture, perforation, or dissection of vessels, ventricle, myocardium, or valvular structures that may require intervention)
- ascending aorta trauma
- cardiac tamponade
- cardiac failure or low cardiac output
- prosthetic valve dysfunction including, but not limited to, fracture; bending (out-of-round configuration) of the valve frame; under-expansion of the valve frame; calcification; pannus; leaflet wear, tear, prolapse, or retraction; poor valve coaptation; suture breaks or disruption; leaks; mal-sizing (prosthesis-patient mismatch); malposition (either too high or too low)/malplacement; regurgitation; stenosis
- thrombosis/embolus (including valve thrombosis)
- valve migration/valve embolization
- ancillary device embolization
- emergent percutaneous coronary intervention (PCI)
- emergent balloon valvuloplasty
- major or minor bleeding that may or may not require transfusion or intervention (including life-threatening or disabling bleeding)
- allergic reaction to antiplatelet agents, contrast medium, or anesthesia

- infection (including septicemia and endocarditis)
- stroke, transient ischemic attack (TIA), or other neurological deficits
- permanent disability
- renal insufficiency or renal failure (including acute kidney injury)
- mitral valve regurgitation or injury
- tissue erosion
- vascular access related complications (e.g., dissection, perforation, pain, bleeding, hematoma, pseudoaneurysm, irreversible nerve injury, compartment syndrome, arteriovenous fistula, stenosis)
- conduction system disturbances (e.g., atrioventricular node block, left-bundle branch block, asystole), which may require a permanent pacemaker
- cardiac arrhythmias
- encephalopathy
- pulmonary edema
- pericardial effusion
- pleural effusion
- myocardial ischemia
- peripheral ischemia
- bowel ischemia
- heart murmur
- hemolysis
- cerebral infarction-asymptomatic
- non-emergent reoperation
- inflammation
- fever
- hypotension or hypertension
- syncope
- dyspnea
- anemia
- angina
- abnormal lab values (including electrolyte imbalance)

For the specific adverse events that occurred in the clinical study, please see Section X.

IX. SUMMARY OF PRECLINICAL STUDIES

A summary of previously reported preclinical studies can be found in the SSED for the original PMA (http://www.accessdata.fda.gov/cdrh_docs/pdf13/P130021b.pdf).

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

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

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

X. SUMMARY OF PRIMARY CLINICAL STUDY

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

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

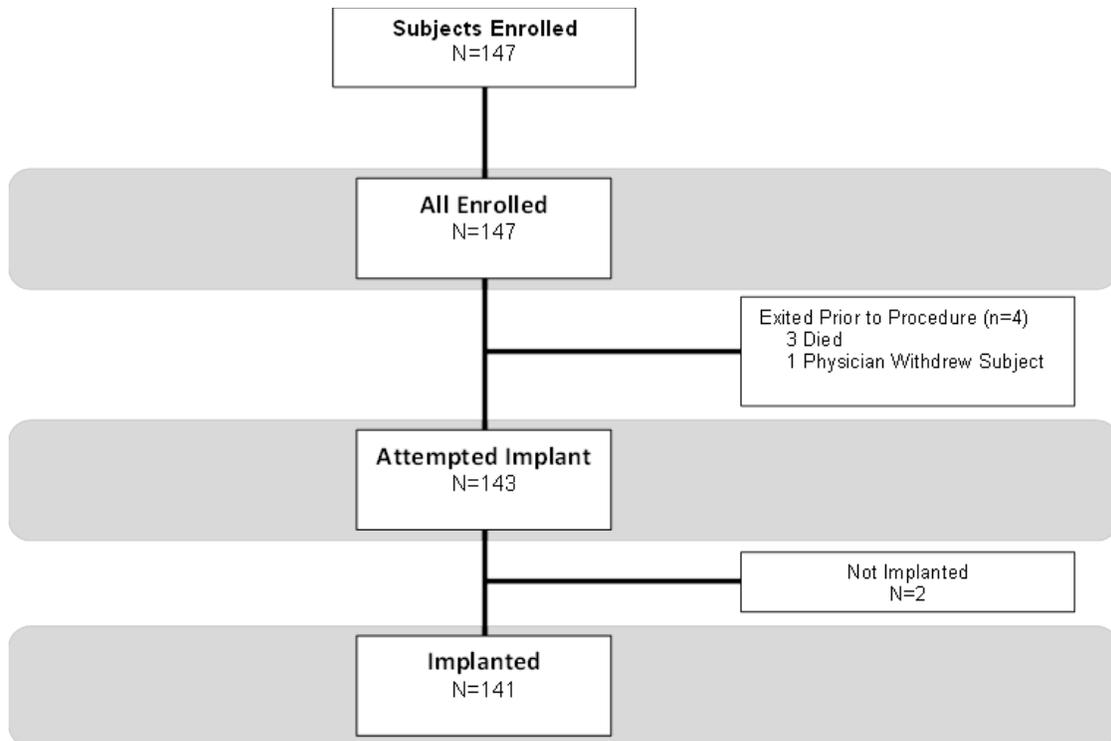
The clinical data presented herein came from Registry 6, the “TAV-in-SAV” observational study.

A. Study Design

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

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

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



1. Clinical Inclusion and Exclusion Criteria

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

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

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

Inclusion Criteria

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

Exclusion Criteria

Clinical

- Evidence of an acute myocardial infarction ≤ 30 days before the MCS TAVR procedure
- Any percutaneous coronary or peripheral interventional procedure performed within 30 days prior to the MCS TAVI procedure
- Blood dyscrasias as defined: leukopenia (WBC $< 1000\text{mm}^3$), 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 TIA
- Active gastrointestinal (GI) bleeding that would preclude anticoagulation

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

Anatomical

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

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

* 17mm for surgical bioprosthetic aortic annulus

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

Vascular

- Transarterial access not able to accommodate an 18Fr sheath.

2. Follow-Up Schedule

All patients were scheduled for follow-up examinations at discharge or 7 days, whichever comes first, 30 days, 6 months, 12 months, and annually thereafter to a minimum of 5 years post procedure. Patients reported herein were followed for a minimum of 30 days.

3. Clinical Endpoints

Primary Safety and Effectiveness Endpoints

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

Secondary Safety and Effectiveness Endpoints

The secondary endpoints are as follows:

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

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

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

B. Accountability of Study Cohort

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

Table 4: Total Patient Accountability

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

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

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

C. Study Population Demographics and Baseline Parameters

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

Table 5: Subject Demographics and Baseline Characteristics – Attempted Implant

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

¹Plus-minus values present the mean ± standard deviation.

²Aorta calcification is measured on screening CT Angiogram.

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

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

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

D. Safety and Effectiveness Results

1. Analysis Populations

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

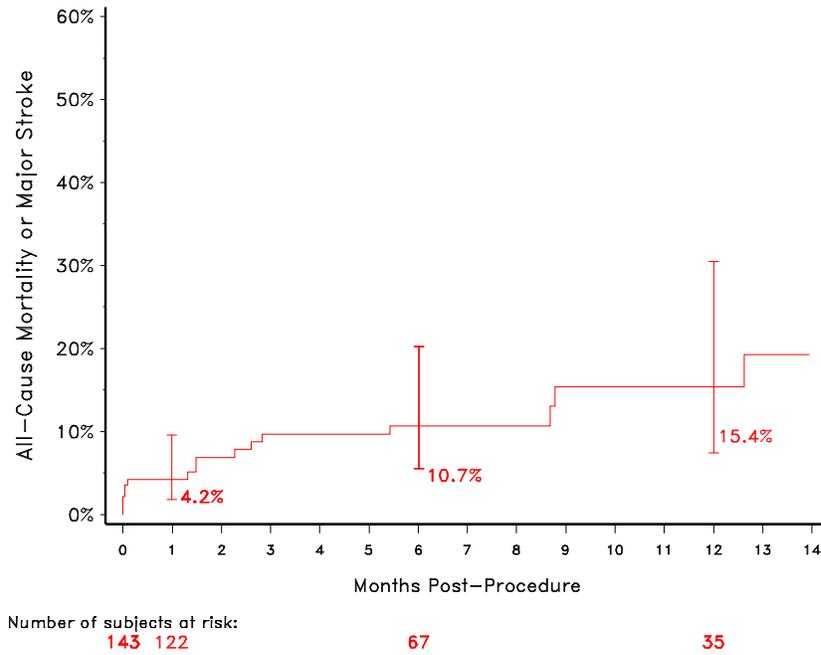
The “Attempted Implant” population consisted of “All Enrolled” subjects with an attempted implant procedure, defined as when the subject was brought into the procedure room and any of the following had occurred: anesthesia administered, vascular line placed, TEE placed or any monitoring line placed.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

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

2. Primary Safety and Effectiveness Endpoint

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

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



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

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

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

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

²The confidence intervals are calculated without multiplicity adjustment. The adjusted confidence intervals could be wider than presented here. As such, confidence intervals are provided to illustrate the variability only and should not be used to draw any statistical conclusion.

3. Key Secondary Safety and Effectiveness Endpoints

Adverse Events

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

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

Table 8: Adverse Event Summary - Attempted Implant

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

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

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

³ Patients with pacemaker or ICD at baseline are not included in the denominator.

⁴ Patients with pacemaker or ICD at baseline are included in the denominator.

Echocardiographic Assessment of Total Aortic Regurgitation

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

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

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

Echocardiographic Assessment of EOA and Mean Gradient

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

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

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

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

NYHA Functional Class

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

Table 11: NYHA Classification By Visit – Attempted Implant

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

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

²One death was device related at 12 months.

QoL Measures

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

Table 12: Quality of Life – Attempted Implant

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

Plus-minus values are mean ± standard deviation.

4. Additional Study Observations

Procedure Data

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

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

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

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

¹Plus-minus values are mean \pm standard deviation.

²Device success is defined as: (1) successful vascular access, delivery and deployment of the device, and successful retrieval of the delivery system; (2) correct position of the device in the proper anatomical location (placement in the annulus with no impedance on device function), and (3) only one valve implanted in the proper anatomical location.

³Procedure success is defined as device success and absence of in-hospital MACCE.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 417 investigators, of which none were full-time or part-time employees of the sponsor and 10 had disclosable financial interests/arrangements related to the “TAV-in-SAV” study as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0
- Significant payment of other sorts: 9
- Proprietary interest in the product tested held by the investigator: 0
- Significant equity interest held by investigator in sponsor of covered study: 1

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. The information provided does not raise any questions about the reliability of the data.

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

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

XII. CONCLUSIONS DRAWN FROM THE PRECLINICAL AND CLINICAL STUDIES

A. Safety Conclusions

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

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

B. Effectiveness Conclusions

In the clinical study, the “TAV-in-SAV” subjects experienced an improvement of approximately 20 mmHg in mean pressure gradient and approximately 0.3 cm² in EOA from baseline to 30 days, which remained stable through the subsequent follow-up visits. However, it is of note that these subjects had a pressure gradient of 17.38 ± 8.71 mmHg at 30 days, which was much higher than that observed in the Extreme Risk Cohort (8.7 ± 4.2 mmHg). It is not clear whether this elevated pressure gradient will have any long-term impact on the patient outcome.

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

C. Benefit-Risk Conclusions

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

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

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

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

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

D. Overall Conclusions

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

XIII. CDRH DECISION

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

1. ***ODE Lead Post-Approval Study: Continued follow-up of the premarket cohort:***
The study will consist of all living subjects who were enrolled under the IDE in Registry 6: TAV- in-SAV. The objective of this study is to characterize the clinical outcomes annually through 5 years post-procedure. The safety and effectiveness endpoints include all-cause mortality, MACCE, change in functional status and quality of life, conduction disturbance requiring permanent pacemaker implantation, echocardiographic assessment, and valve dysfunction.
2. ***OSB Lead Surveillance:*** The applicant is required to actively participate as a stakeholder and support the operations of the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry (TVTR) to ensure that FDA surveillance occurs for the MCS for 5 years. This surveillance should monitor the following: (1) device success (intra-procedure); (2) all-cause mortality, all stroke, life-threatening (or disabling) bleeding, acute kidney injury-stage 3 (including renal replacement therapy), peri-procedural myocardial infarction, and repeat procedure for valve-related dysfunction (surgical or interventional therapy) at 30 days and 12 months; (3) neurological, vascular and quality of life outcomes at 30 days and 12 months; and (4) all-cause

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

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

XIV. APPROVAL SPECIFICATIONS

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

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

Post-approval Requirements and Restrictions: See Approval Order.

XV. REFERENCES

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