SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name:	Replacement Heart Valve
Device Trade Name:	Medtronic CoreValve™ System (MCS): Transcatheter Aortic Valve (TAV), Models MCS-P4-23-AOA (23 mm; CoreValve™ Evolut™), MCS-P3-26-AOA (26 mm), MCS-P3-29-AOA (29 mm), and MCS-P3-31-AOA (31 mm); Delivery Catheter System (DCS), Models DCS-C4-18FR and DCS-C4-18FR-23; and Compression Loading System (CLS), Model CLS-3000-18FR
Device Procode:	NPT
Applicant Name and Address:	Medtronic CoreValve LLC 3576 Unocal Place Santa Rosa, CA 95403
Date of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P130021
Date of FDA Notice of Approval:	January 17, 2014

II. INDICATIONS FOR USE

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

III. CONTRAINDICATIONS

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

- known hypersensitivity or contraindication to aspirin, heparin (HIT/HITTS) and bivalirudin, ticlopidine, clopidogrel, Nitinol (Titanium or Nickel), or sensitivity to contrast media, which cannot be adequately premedicated

- ongoing sepsis, including active endocarditis
- preexisting mechanical heart valve in aortic position

IV. WARNINGS AND PRECAUTIONS

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

V. DEVICE DESCRIPTION

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

V.1. Transcatheter Aortic Valve (TAV)

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

Figure 1: CoreValve Transcatheter Aortic Valve

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

Table 1: Patient Anatomical Diameters

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

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

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

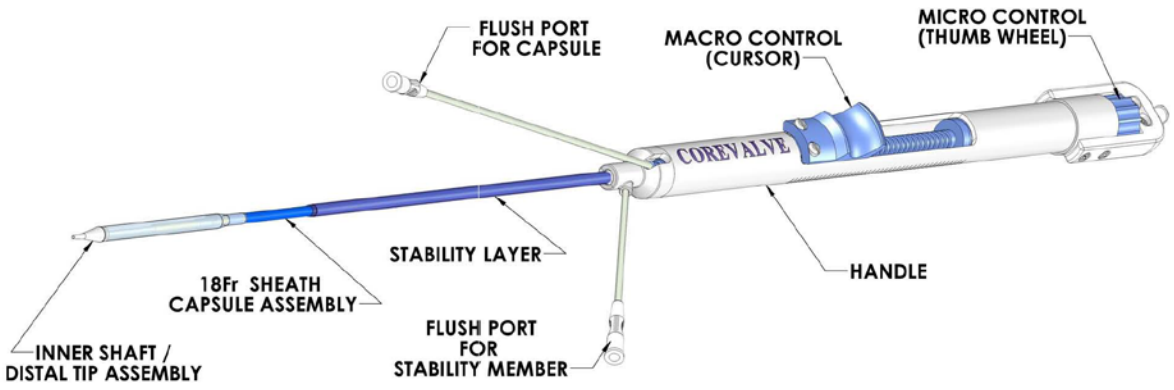

Figure 2: CoreValve Delivery Catheter System

V.3. Compression Loading System (CLS)

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

Figure 3: CoreValve Compression Loading System

The CLS comprises the following elements:

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

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Alternatives for patients deemed to be at extreme risk, or non-operable (non-surgical), for surgical aortic valve replacement include: treatment with other approved transcatheter aortic valve implantation therapy, temporary relief using a percutaneous technique called balloon aortic valvuloplasty (BAV), or medical therapy (no obstruction-relieving intervention). Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The current Medtronic CoreValve System is commercially available in over 50 countries, as listed in Table 2. It has not been withdrawn from marketing for any reason related to its safety or effectiveness.

Table 2: Countries where Medtronic CoreValve System is commercialized

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

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

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

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

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

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

For the specific adverse events that occurred in the clinical study, please see Section 10.

IX. SUMMARY OF PRECLINICAL STUDIES

A. Laboratory Testing

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

Biocompatibility

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

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

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

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

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

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

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

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

Bench Testing

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

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

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

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

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

B. Animal Studies

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

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

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

C. Sterilization

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

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

D. Packaging and Shelf Life

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

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

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

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

X. SUMMARY OF PRIMARY CLINICAL STUDY

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

A. Study Design

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

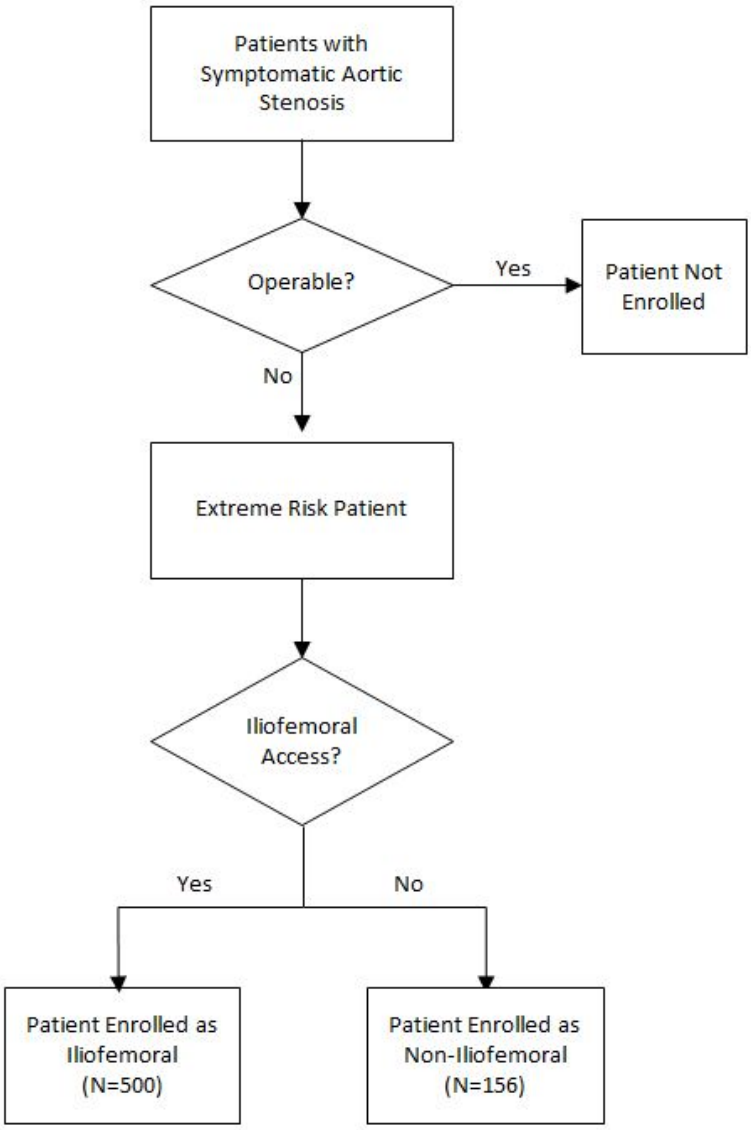

Figure 4: CoreValve Extreme Risk Cohort Trial Enrollment Diagram

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

1. Clinical Inclusion and Exclusion Criteria

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

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

Inclusion Criteria

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

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

Exclusion Criteria

- Evidence of an acute MI ≤ 30 days before the procedure
- Any percutaneous coronary or peripheral interventional procedure performed within 30 days prior to the procedure
- Blood dyscrasias as defined by: leukopenia (WBC < 1000 mm^3), thrombocytopenia (platelet count < 50,000 cells/mm^3), history of bleeding diathesis or coagulopathy
- Untreated clinically significant coronary artery disease (CAD) requiring revascularization
- Cardiogenic shock manifested by low cardiac output, vasopressor dependence, or mechanical hemodynamic support
- Need for emergency surgery for any reason
- Severe ventricular dysfunction with left ventricular ejection fraction (LVEF) < 20% as measured by resting echocardiogram
- Recent (within 6 months) cerebrovascular accident (CVA) or transient ischemic attack (TIA)
- End stage renal disease requiring chronic dialysis or creatinine clearance < 20 cc/min.
- Active Gastrointestinal (GI) bleeding within the past 3 months
- A known hypersensitivity or contraindication to any of the following which cannot be adequately pre-medicated:
  - Aspirin
  - Heparin (HIT/HITTS) and bivalirudin
  - Nitinol (titanium or nickel)
  - Ticlopidine and clopidogrel
  - Contrast media
- Ongoing sepsis, including active endocarditis
- Subject refuses a blood transfusion
- Life expectancy < 12 months due to associated non-cardiac co-morbid conditions.
- Other medical, social, or psychological conditions that in the opinion of an Investigator precludes the subject from appropriate consent
- Severe dementia (resulting in either inability to provide informed consent for the trial/procedure, prevents independent lifestyle outside of a chronic care facility, or

will fundamentally complicate rehabilitation from the procedure or compliance with follow-up visits)
- Concurrently participating in an investigational drug or another device study
- Symptomatic carotid or vertebral artery disease
- Native aortic annulus size < 18 mm or > 29 mm per the baseline diagnostic imaging.
- Pre-existing prosthetic heart valve in any position
- Mixed aortic valve disease [AS and aortic regurgitation (AR) with severity (3-4+)]
- Moderate to severe (3-4+) or severe (4+) mitral or severe (4+) tricuspid regurgitation
- Moderate to severe mitral stenosis
- Hypertrophic obstructive cardiomyopathy
- New or untreated echocardiographic evidence of intracardiac mass, thrombus or vegetation
- Severe basal septal hypertrophy with an outflow gradient
- Aortic root angulation (angle between plane of aortic valve annulus and horizontal plane/vertebrae) > 70° (for femoral and left subclavian/axillary access) and > 30° (for right subclavian/axillary access)
- Ascending aorta that exceeded the maximum diameter for any given native aortic annulus size
- Congenital bicuspid or unicuspid valve verified by echocardiography
- Sinus of valsalva anatomy that would prevent adequate coronary perfusion
- Transarterial access not able to accommodate an 18Fr sheath

2. Follow-Up Schedule

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

3. Clinical Endpoints

Primary Safety and Effectiveness Endpoints

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

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

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

Secondary Safety and Effectiveness Endpoints

This study included the following secondary safety and effectiveness endpoints:

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

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

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

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

B. Accountability of PMA Cohort

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

Table 8: Total Patient Accountability

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

C. Study Population Demographics and Baseline Parameters

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

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

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

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

D. Safety and Effectiveness Results

1. Analysis Population

The primary analysis was the "Attempted Implant" analysis. An attempted implant procedure was defined as when the patient was brought into the procedure room and any of the following had occurred: anesthesia administered, vascular line placed, TEE placed or any monitoring line placed.

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

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

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

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

2. Primary Safety and Effectiveness Endpoint

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

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

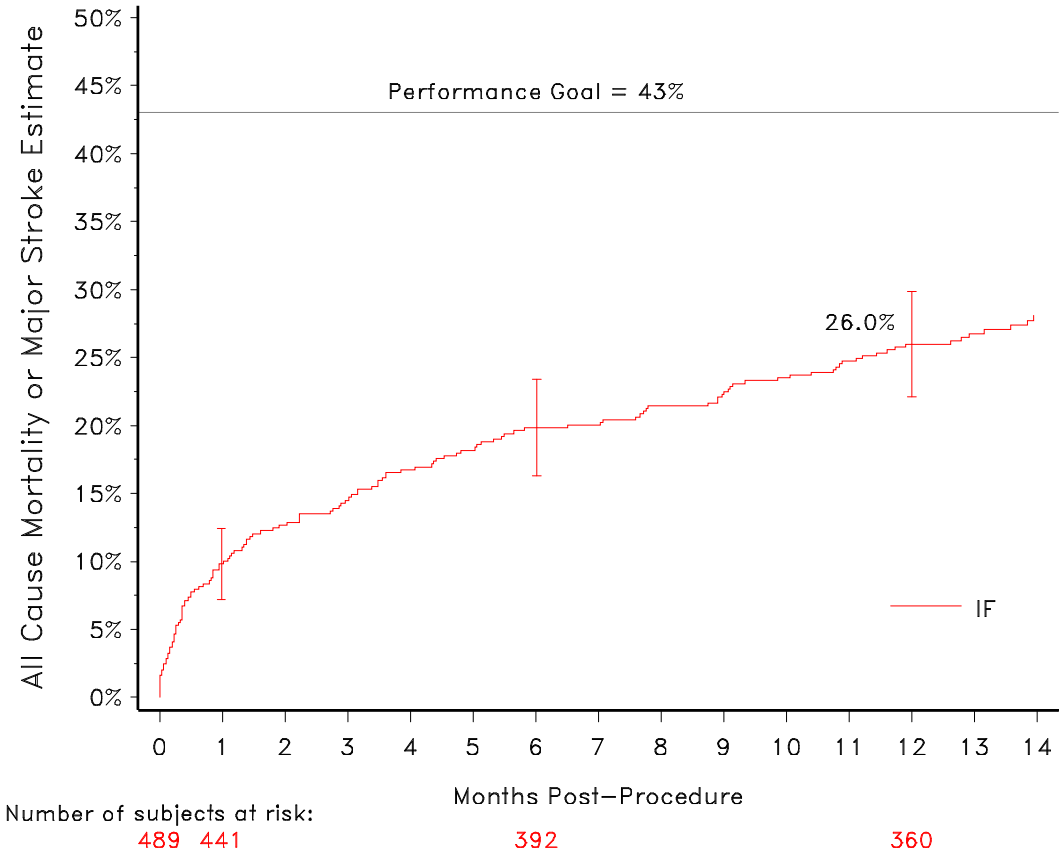

Figure 5: Primary Endpoint: All-Cause Mortality or Major Stroke Kaplan-Meier Event Rate — Iliofemoral Attempted Implant

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

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

3. Key Secondary Safety and Effectiveness Endpoints

Adverse Events that Occurred in the PMA Clinical Study

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

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

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

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

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

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

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

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

Neurological Events

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

Table 13: CEC Adjudicated Neurological Events – Iliofemoral Attempted Implant

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

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

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

Echocardiographic Assessment of Valve Performance (Total Aortic Regurgitation)

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

Table 15: Total Aortic Regurgitation by Visit – Implanted Population

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

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

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

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

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

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

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

Conduction Disturbance Requiring Permanent Pacemaker Implantation

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

Table 18: Conduction Disturbance Requiring Pacemaker – Attempted Implant

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

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

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

Ratio of Days Alive out of Hospital versus Total Days Alive

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

New York Heart Association (NYHA) Functional Class

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

Table 19: NYHA Classification By Visit – Attempted Implant

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

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

Quality of Life (QoL) Change

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

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

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

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

Table 20: Quality of Life – Iliofemoral Attempted Implant

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

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

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

Hierarchical Testing of Secondary Endpoints

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

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

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

4. Additional Study Observations

Procedure Data

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

Table 23: TAVR Procedure Data (Attempted Implant)

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

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

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

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

Plus-minus values present the mean ± standard deviation.

Valve-in-Valve Experience

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

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

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

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

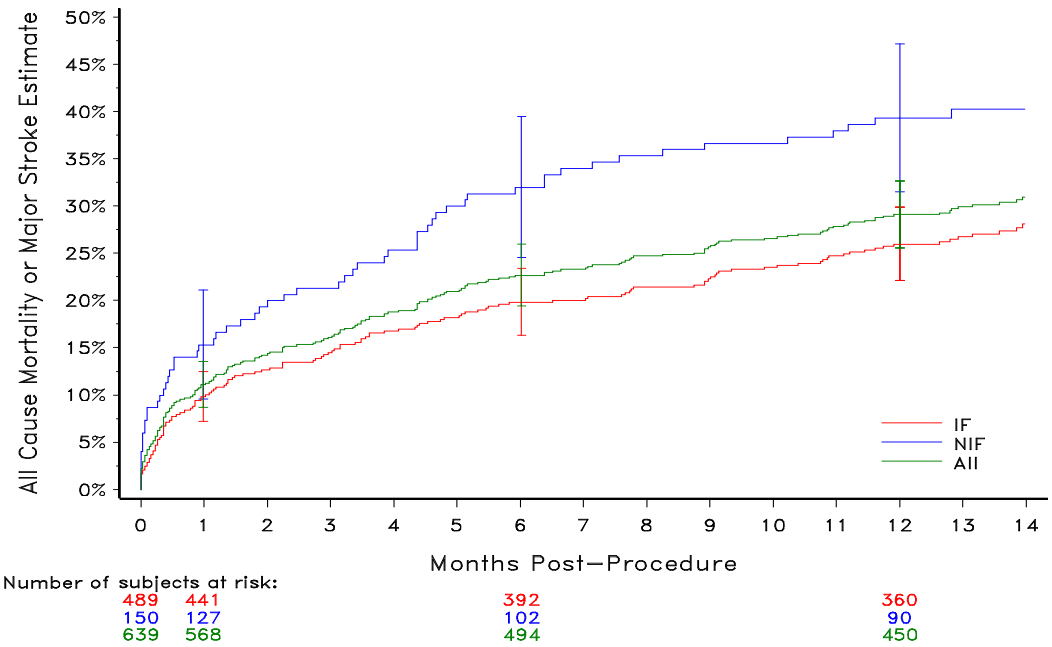

Figure 6: All-Cause Mortality or Major Stroke Kaplan-Meier Event Rate – Attempted Implant

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

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

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

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

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

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

Gender Analysis

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

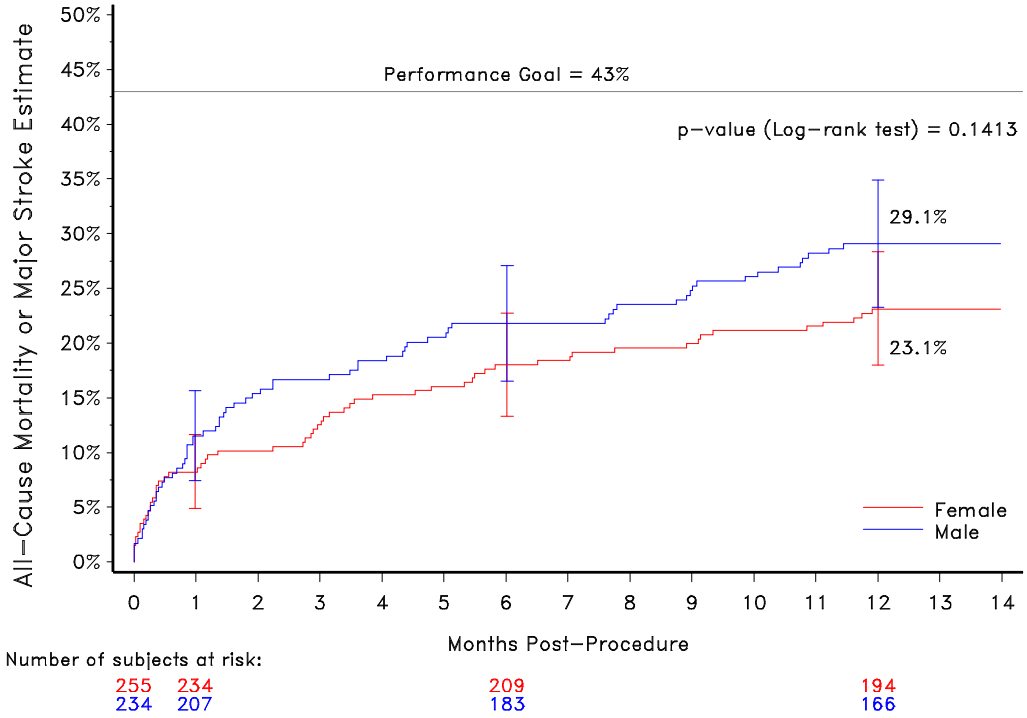

Figure 7: Primary Endpoint: All-Cause Mortality or Major Stroke by Gender – Iliofemoral Attempted Implant

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

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

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

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

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

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

Mortality or Major Stroke Stratified by STS Score

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

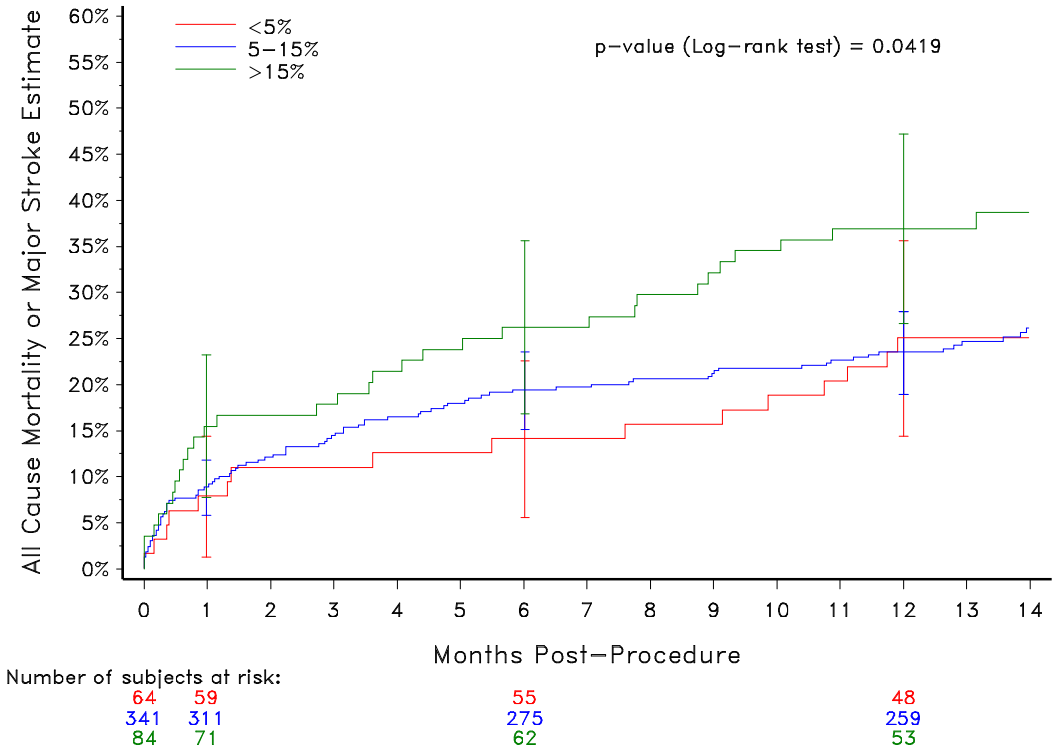

Figure 8: Primary Endpoint: All-Cause Mortality or Major Stroke Stratified by STS Score – Attempted Implant Iliofemoral

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

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

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

Post-Implant Aortic Regurgitation and All-Cause Mortality

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

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

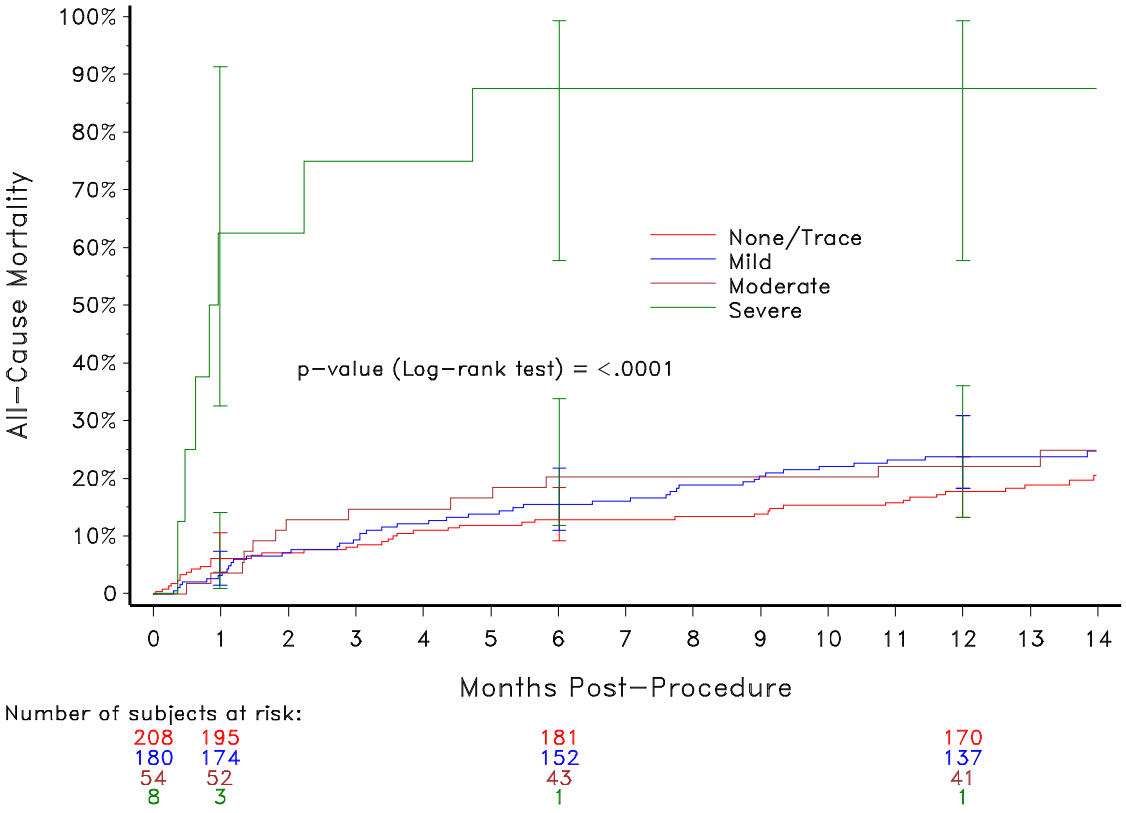

Figure 9: All Cause Mortality Rate by Total Aortic Regurgitation at Discharge – Iliofemoral Implanted

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

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

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

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 329 investigators, of which none were full-time or part-time employees of the sponsor and 18 had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 9
- Significant payment of other sorts: 7
- Proprietary interest in the product tested held by the investigator: 0
- Significant equity interest held by investigator in sponsor of covered study: 2

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

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

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

XII. CONCLUSIONS DRAWN FROM THE PRECLINICAL AND CLINICAL STUDIES

A. Safety Conclusions

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

B. Effectiveness Conclusions

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

C. Benefit-Risk Conclusions

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

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

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

D. Overall Conclusions

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

XIII. CDRH DECISION

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

XIV. APPROVAL SPECIFICATIONS

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

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

Post-approval Requirements and Restrictions: See Approval Order.

XV. REFERENCES

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