SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Aortic valve, prosthesis, percutaneously delivered

Device Trade Name: LOTUS Edge™ Valve System

Device Procode: NPT

Applicant's Name and Address: Boston Scientific Corporation
300 Boston Scientific Way
Marlborough, MA 01752-1234

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P180029

Date of FDA Notice of Approval: April 23, 2019

II. INDICATIONS FOR USE

The LOTUS Edge™ Valve System is indicated for relief of aortic stenosis in patients with symptomatic heart disease due to severe native calcific aortic stenosis (aortic valve area [AVA] of ≤ 1.0 cm^2 or index of ≤ 0.6 cm^2/m^2) who are judged by a heart team, including a cardiac surgeon, to be at high or greater risk for open surgical therapy (i.e., predicted risk of surgical mortality $\geq 8\%$ at 30 days, based on the Society of Thoracic Surgeons (STS) risk score and other clinical comorbidities unmeasured by the STS risk calculator).

III. CONTRAINDICATIONS

The LOTUS Edge™ Valve System is contraindicated in patients who have: a non-calcified aortic annulus; an active systemic infection, sepsis, or endocarditis; known hypersensitivity to contrast agents that cannot be adequately pre-medicated, or known hypersensitivity or contraindication to aspirin, thienopyridines, heparin, nickel, titanium, tantalum, bovine-derived materials or polyurethanes; or severe arterial tortuosity or calcification that would prevent safe placement of the introducer sheath.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the LOTUS Edge™ Valve System labeling.

V. DEVICE DESCRIPTION

The LOTUS Edge™ Valve System consists of a pre-loaded, stent-mounted tissue valve prosthesis that is delivered to the native annulus by a catheter delivery system.

LOTUS Edge™ Valve Implant

The valve consists of three glutaraldehyde-fixed bovine pericardial tissue valve leaflets supported on a braided nitinol frame. The braided valve structure is designed to foreshorten and expand radially when delivered, and is then locked in position using a post-and-buckle locking mechanism. An outer seal around the lower inflow end of the device is designed to minimize paravalvular regurgitation. Radiopaque tantalum markers are present on the buckle and post components of the locking mechanism to aid in visualization of the locking procedure under fluoroscopy. The valve is available in 23 mm, 25 mm, and 27 mm diameters.

Figure 1. LOTUS Edge™ Valve Implant

LOTUS Edge™ Delivery System

The LOTUS Edge™ Valve System delivery catheter is used to deliver, deploy, and release the valve in the intended implant location. The delivery system is comprised of three main assemblies:

- An outer catheter assembly also referred to as the outer sheath
- An inner catheter assembly which consists of a Multi-Lumen Extrusion (MLE) and the delivery system locking assembly. The MLE houses delivery system components that interact with the valve implant including the push pull rods, release mandrel, the nosecone /nosecone extension and coupler finger, guide, collars and sheathing aids.
- A controller assembly (also referred to as delivery system handle), which is used to control placement and release of the valve.

The delivery system is compatible with a 0.035” guidewire. The LOTUS Edge Valve System may be introduced at the access site using either the Lotus Introducer set or the iSLEEVE Introducer set. Both the Lotus and iSLEEVE Introducer sets are cleared for market under 510(k).

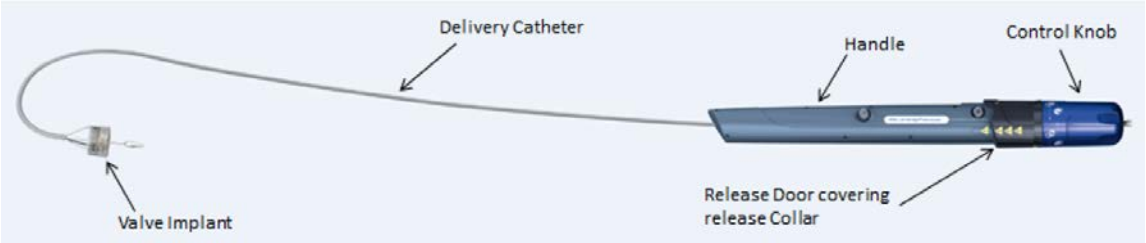


Figure 2. LOTUS Edge™ Valve System

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the correction of severe calcific aortic stenosis, including: treatment with other approved transcatheter aortic valve implantation devices, surgical aortic valve replacement, temporary relief using a percutaneous technique called balloon aortic valvuloplasty (BAV), or medical therapy. 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 LOTUS Edge™ Valve System is marketed in the following countries:

- Germany
- Great Britain
- Austria
- Finland
- Czech Republic
- Denmark
- Sweden
- Spain
- Italy
- Netherlands
- Portugal
- Switzerland
- France

The LOTUS Edge™ Valve System was voluntarily withdrawn from marketing on October 28, 2016 to implement design changes to improve device deliverability and deployment. The modified device was re-introduced to the market on March 20, 2019.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device.

- Abnormal lab values (including electrolyte imbalance)

- Access site complications (including arteriovenous (AV) fistula, hematoma or lymphatic problems)
- Allergic reaction (including to medications, anesthesia, contrast, or device materials, including nickel, titanium, tantalum, bovine-derived materials or polyurethanes)
- Anemia
- Angina
- Arrhythmia or new conduction system injury (including need for pacemaker insertion)
- Bleeding or hemorrhage (possibly requiring transfusion or additional procedure)
- Cardiac arrest
- Cardiac failure / low cardiac output
- Cerebrovascular accident, stroke, transient ischemic attack or cerebral infarction including asymptomatic neuroimaging findings
- Coronary obstruction
- Death
- Device misplacement, migration or embolization
- Emboli (including air, tissue, thrombus or device materials)
- Endocarditis
- Fever or inflammation
- Heart failure
- Hemodynamic instability or shock
- Hemolysis and/or hemolytic anemia
- Hypertension/hypotension
- Infection (local and/or systemic)
- Mitral valve insufficiency
- Myocardial infarction
- Myocardial or valvular injury (including perforation or rupture)
- Nerve injury or neurological deficits (including encephalopathy)
- Pain
- Pericardial effusion or tamponade
- Peripheral ischemia or infarction
- Permanent disability
- Pleural effusion
- Pulmonary edema
- Renal insufficiency or failure
- Respiratory insufficiency or failure
- Restenosis (including pannus formation)
- Valve dysfunction, deterioration or failure
- Valve or device thrombosis
- Valvular stenosis or regurgitation (central or paravalvular)
- Vessel injury (including spasm, trauma, dissection, perforation, rupture, pseudoaneurysm or arteriovenous fistula)

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

IX. SUMMARY OF NONCLINICAL STUDIES

In vitro studies on the LOTUS Edge™ Valve System were conducted in accordance with national and international standards and FDA guidance documents. Testing verified that all components of the LOTUS Edge™ Valve System met its product performance and design specifications and is summarized below.

A. Laboratory Studies

Biocompatibility

A series of biocompatibility tests were conducted to demonstrate that the materials and components of the LOTUS Edge™ Valve System are biocompatible. Testing was conducted on the both the valve implant and the delivery system in accordance with EN ISO 10993-1 *Biological Evaluation of Medical Devices - Part 1: Evaluation and Testing within a risk management process* and FDA Guidance *Use of International Standard ISO 10993-1 Biological Evaluation of Medical Devices - Part 1: Evaluation and Testing within a risk management process*. Test samples for the studies consisted of all patient-contacting portions of the devices (direct and indirect contact) exposed to all manufacturing processes, including sterilization. All results were acceptable.

Table 1. Summary of Biocompatibility Testing – LOTUS Edge™ Valve Implant

Test Name	Test Description	Test Article and Results
MEM Elution Cytotoxicity/ ISO 10993- 5	MEM Elution Cytotoxicity: ISO 10993- 5	Pass, non-cytotoxic
Guinea Pig Maximization Sensitization/	Guinea Pig Maximization Sensitization: ISO 10093 - 10	Pass, non-sensitizer
Intracutaneous Reactivity	Intracutaneous Reactivity: ISO 10993- 10	Pass, non-irritant
Acute Systemic Injection	Acute Systemic Injection: ISO 10993- 11	Pass, non-toxic
Materials Mediated Rabbit Pyrogen	Materials Mediated Rabbit Pyrogen: ISO 10993- 11	Pass, non-pyrogenic
Subacute Toxicity Intraperitoneal and Intravenous	Subacute Toxicity Intraperitoneal: ISO 10993- 11	Pass, non-toxic
Ames Mutagenicity	Ames Mutagenicity: ISO 10993- 3	Pass, non-mutagenic
Mouse Lymphoma	Mouse Lymphoma: ISO 10993- 3	Pass, non-mutagenic
Mouse Micronucleus	Mouse Micronucleus: ISO 10993- 3	Pass

Test Name	Test Description	Test Article and Results
Partial Thromboplastin Time	Partial Thromboplastin Time: ISO 10993- 4	Pass, non-activator
Complement Activation	Complement Activation: ISO 10993- 4	Pass comparable to control device
In Vitro Hemocompatibility	In Vitro Hemocompatibility: ISO 10993- 4	Pass
Hemolysis Indirect / Extract & Direct Contact	Indirect / Extract Hemolysis: ISO 10993- 4	Pass, non-hemolytic
Extractables & Leachables IR/GC-MS/UPLC-MS, ICP-MS	Extractables & Leachables: ISO 10993- 18	Acceptable based on toxicological risk assessment of identified residuals
Glutaraldehyde residual analysis / Formaldehyde residual analysis	Glutaraldehyde residual analysis / Formaldehyde residual analysis: ISO 10993- 4	Acceptable based on toxicological risk assessment of identified residuals

Table 2. Summary of Biocompatibility Testing – LOTUS Edge™ Delivery System

Test Name	Test Description	Test Article and Results
MEM Elution Cytotoxicity/ ISO 10993- 5	MEM Elution Cytotoxicity: ISO 10993- 5	Pass, non-cytotoxic
Guinea Pig Maximization Sensitization/	Guinea Pig Maximization Sensitization: ISO 10093 - 10	Pass, non-sensitizer
Intracutaneous Reactivity	Intracutaneous Reactivity: ISO 10993- 10	Pass, non-irritant
Acute Systemic Injection	Acute Systemic Injection: ISO 10993- 11	Pass, non-toxic
Materials Mediated Rabbit Pyrogen	Materials Mediated Rabbit Pyrogen: ISO 10993- 11	Pass, non-pyrogenic
Ames Mutagenicity	Ames Mutagenicity: ISO 10993- 3	Pass, non-mutagenic
Mouse Lymphoma	Mouse Lymphoma: ISO 10993- 3	Pass, non-mutagenic
Complement Activation	Complement Activation: ISO 10993- 4	Pass comparable to control device
In Vitro Hemocompatibility	In Vitro Hemocompatibility: ISO 10993- 4	Pass

Test Name	Test Description	Test Article and Results
Hemolysis Indirect / Extract & Direct Contact	Indirect / Extract Hemolysis: ISO 10993- 4	Pass, non-hemolytic
In vivo Thromboresistance study	In vivo Thromboresistance study (in sheep):ISO 10993- 4	Pass
USP Physicochemical <661>	USP Physicochemical <661>: ISO 10993- 18	Characterization of chemical residuals

Design Performance Testing

In vitro studies were conducted to evaluate the design and performance attributes of the LOTUS Edge™ Valve System. Testing included materials and mechanical property testing, corrosion assessment, hydrodynamic performance assessment, device durability and structural integrity assessment, device compatibility, delivery system performance, valve performance, and MRI compatibility testing. Where relevant, the studies were conducted in accordance with ISO 5840: Cardiovascular Implants-Cardiac Valve Prostheses. The matrix of the tests performed and the corresponding results are provided in Table 3 below. The results showed that LOTUS Edge™ Valve System meets its specified design performance requirements.

Table 3. Summary of LOTUS Edge™ Valve System Design Performance Testing

In Vitro Test Description	Purpose/Acceptance Criteria	Result (Pass/ Fail)
Materials and Mechanical Property Testing		
Raw Material Properties	Assess the properties of raw materials in accordance with ISO 5840-3, ASTM F2063-12, ASTM F560-13, ASTM F2516-07, and ASTM F2082-06.	N/A - Characterization
Post-Processing Properties	Assess the properties of raw materials in the post processed condition in accordance with ISO 5840-3, ASTM F2063-12, ASTM F560-13, ASTM F2516-07, and ASTM F2082-06.	N/A - Characterization
Corrosion Assessment		

In Vitro Test Description	Purpose/Acceptance Criteria	Result (Pass/ Fail)
Corrosion Resistance	Verify the corrosion resistance of the valve in accordance with ISO 5840-3, ISO 25539-1, ASTM F3044-14, and per ASTM F2129-08.	Pass
Nickel Leach	Determine the nickel ion release rate from the LOTUS Edge™ Valve through experimental and theoretical methods in accordance with FDA Guidance Document: Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems.	Pass
Surface Assessment	Assess the surface composition and visualize the surface finish of the LOTUS Edge™ Valve in accordance with FDA Guidance Document: Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems April 2010.	N/A - Characterization
Catheter Corrosion Assessment	Verify that the patient contacting and fluid contacting portions of the catheter are resistant to corrosion in accordance with ISO 10555-1.	Pass
Hydrodynamic Performance		
Steady Backflow Leakage (Nominal)	Measure the static leakage of the valve under a range of applied static back pressures in accordance with ISO 5840-3 including Annex N.	N/A - Characterization
Steady Backflow Leakage (Axisymmetric Deformation)		
Pulsatile Flow	Assess valve performance in clinically relevant shapes by simulating physiological pressure and flow waveforms in accordance with ISO 5840-3.	N/A - Characterization
Bernoulli Equation	Verify the Bernoulli relationship under in vitro physiological pulsatile flow conditions across all sizes valve.	N/A - Characterization
Flow Visualization	Assess valve performance under varying cardiac outputs in accordance with ISO 5840-3 including Annex N.	N/A - Characterization
Device Durability		

In Vitro Test Description	Purpose/Acceptance Criteria	Result (Pass/ Fail)
Accelerated Wear Testing	Assess the durability and continued function of the valve in clinically relevant shapes after 200 million cycles. Commercially available reference valves were also tested for comparative purposes and validation of the testing conditions in accordance with ISO 5840-3.	Pass
Dynamic Failure Mode Testing	Identify the failure modes associated with the LOTUS Edge™ Valve, under extended Accelerated Wear Testing in accordance with ISO 5840-3.	N/A – Characterization
Structural Reliability		
Material Fatigue Life Determination	Determine the fatigue limit of the Nitinol material used to make the structural components of the LOTUS Edge™ Valve in accordance with ISO 5840-3. Use finite element analysis (FEA) using relevant in vivo boundary conditions to build a computational model of the deformations (fatigue stresses and strains) that occur within the device during clinical loading in accordance with ISO 5840-3.	N/A – Inputs to the Factor of Safety (FOS)
In Vivo Boundary Conditions		
Finite Element Analysis		
Factor of Safety (FOS)	Use FEA computational model to determine appropriate Factor of Safety (FOS)	Pass
Fatigue Demonstration Test	Determination of frame fatigue resistance to 600 million cycles and evaluation of failure mode of the structural components of the LOTUS Edge™ Valve in accordance with ISO 5840-3.	Pass
Fatigue Testing to Failure		N/A - Characterization
Device Compatibility		
Compatibility: Introducer	Assess the compatibility of the LOTUS Edge™ Valve with the relevant introducer and guidewire.	Pass
Compatibility: Guidewire		Pass
Compatibility: Flush Ports	Assess compatibility of the flush ports in accordance with EN 1707 to demonstrate that the device flush ports conform to the requirements of EN 1707 and ISO 594-2.	Pass
Compatibility: Catheter Effective Length	Verify the effective length in accordance with ISO 10555-1 Single use intravascular catheters – Part 1: General Requirements.	Pass

In Vitro Test Description	Purpose/Acceptance Criteria	Result (Pass/ Fail)
Compatibility: Catheter OD	Verify the maximum catheter outer diameter inserted into the vessel in accordance with ISO 10555-1 Single use intravascular catheters – Part 1: General Requirements.	Pass
Delivery System Performance		
Device Deliverability		
Deliverability (Trackability, Pushability, Kink Resistance)	Assess the ability to deliver the device to the target treatment site in a clinically relevant manner and function correctly in accordance with FDA Guidance Document: Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems along with ISO 5840-3 and ISO 25539-1.	Pass
Torquability	Assess the functionality of the LOTUS Edge™ Valve System following clinically challenging torsional loading. This testing ensures compliance to ISO 25539-1, ISO 5840-3 and FDA Guidance Document: Non-Clinical Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems.	Pass
Torque Strength	Assess device torque to failure while secured in a model that mimics the vasculature of the aorta including the aortic arch. This is in accordance with FDA Guidance Document: Non-Clinical Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems.	Pass
Retraction	Assess the ability to retract the delivery system with and without a sheathed valve attached in a clinically relevant manner in accordance with FDA Guidance Document: Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems.	Pass

In Vitro Test Description	Purpose/Acceptance Criteria	Result (Pass/ Fail)
Delivery System/Valve Component Visibility - Fluoroscopy	Assess the delivery system and valve component visibility during the simulated use testing by fluoroscopy in accordance with ISO 5840-3, ISO 25539-1 and FDA Guidance Document: Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems.	Pass
Component and Bond assessment to enable sheathing and unsheathing	This testing of the relevant component and bonds to ensure compliance to ISO 10555-1 and FDA Guidance Document: Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems.	Pass
Unsheathing: System Performance	Measurement of the forces experienced by the catheter components to ensure they do not exceed the tensile and compressive strength of the delivery system and valve components.	Pass
Sheathing: System Performance	Measurement of the displacement experienced by the catheter components to ensure they do not exceed the compressive strength of the delivery system and valve components.	Pass
Freedom from Leakage	Pressurize the system and verify there are no unacceptable leaks.	Pass
Particulate	Characterize the particulate levels of the LOTUS Edge™ device to ensure compliance to ISO 5840-3 and FDA Guidance Document: Non-Clinical Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems.	N/A - Characterization
Catheter Coating Characterization	Characterize the catheter coating integrity to ensure compliance to ISO 5840-3 and FDA Guidance Document: Non-Clinical Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems.	N/A - Characterization
Catheter Coating Thickness	Characterize the catheter coating thickness of the LOTUS Edge™ system.	N/A - Characterization
Valve Deployment Requirements		

In Vitro Test Description	Purpose/Acceptance Criteria	Result (Pass/ Fail)
Component and Bond assessment to enable locking and unlocking	The ability to lock and unlock the device in accordance with ISO 5840-3 and FDA Guidance Document: Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems.	Pass
Component and Bond assessment to enable valve deployment/release	The ability to deploy/release the valve in accordance with ISO 5840-3 and FDA Guidance Document: Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems.	Pass
Valve Performance		
Radial Outward Force	Determine the radial outward force of the valve when it is in the fully locked configuration in accordance with ISO 5840-3.	Pass
Crush Resistance	Determine valve functionality after lateral compression testing when the valve is in the fully locked configuration in accordance with ISO 5840-3.	Pass
Device Migration Resistance	Assess the resistance to valve migration under clinically relevant conditions in accordance with ISO 5840-3.	Pass
Hydrodynamic Performance: Effective Orifice Area	Determine the effective orifice area under pulsatile flow in accordance with ISO 5840-3.	Pass
Transvalvular and Total Regurgitant Fraction	Determine the transvalvular and total regurgitant fractions under pulsatile flow in accordance with ISO 5840-3.	Pass
MRI Compatibility	Assess magnetically induced displacement force and torque, radio frequency (RF) heating, and image artifacts of the valve in accordance with ISO 5840-3, ASTM F2052-14, ASTM F2213-06, ASTM F2182-11a, and ASTM F2119-07.	Pass

Sterilization

The LOTUS Edge™ Valve 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 a Sterility Assurance Level (SAL) of 10^{-6}.

Following the chemical sterilization, the final packaged device is sent to the contract sterilizer for e-beam sterilization. The e-beam sterilization cycle has been validated in accordance with ISO 11137-1 *Sterilization of health care products - Radiation - Requirements for development, validation and routine control of a sterilization process for medical devices*. The delivery system goes through e-beam sterilization using a dosage determined per the requirements of this standard. A routine sterilization dose has been validated to provide a minimum sterility assurance level (SAL) of at least 10^{-6} with an overall average product bioburden of ≤1000 CFU/device using the VD_{max}^{25} method.

Packaging and Shelf Life

The packaging used for the LOTUS Edge™ Valve System is a single barrier package. Each individual LOTUS Edge device is placed in a thermoformed co-polyester tray/lid. A pouched Stylet (used during device preparation) is placed in the tray with the device. The closed tray is placed inside a sealed pouch comprised of an uncoated Tyvek® film layer on one side and clear poly Nylon on the opposite side. The sealed pouch assembly is inserted between two foam end caps and placed in a multi-layer corrugated carton. A patient guide booklet (including implant card), electronic directions for use card and a temperature logger (used to monitor temperature) are added within the carton.

The LOTUS Edge™ Valve System is labeled with a 9-month shelf life based on real-time aging of the LOTUS Edge™ Valve implant and real-time and accelerated aging of the LOTUS Edge™ Valve System. Packaging and product integrity studies were conducted to ensure that the device meets specifications throughout the stated shelf life.

B. Animal Studies

The LOTUS Edge™ Valve System was evaluated in four animal studies. Safety, acute and chronic device performance, and biological response of the LOTUS Edge™ Valve System are supported by ovine study 12-024G. Calcification potential for the LOTUS Edge™ Valve System tissue compared to a commercially available control surgically implanted pericardial valve tissue is supported by rat implant studies TR5212 and TR5211. Thromboresistance of the LOTUS Edge™ Valve System is supported by ovine study TR4704. These studies are summarized in Table 4.

Table 4. Summary of LOTUS Edge Valve System In Vivo Studies

Study	Device and Number (N)	Device Size, Implant Location and Method	Species, Number of Animals Enrolled (N) and Age Category	Eval-uation Time Points	Number of Animals Surviving to Evaluation Time Points (n/N)	Objectives	Testing Summary
Lotus Valve Ovine 90- and 140-Day Safety and Biological Response Study 12-024G							
GLP Safety Study 12-024G	Lotus Valve (17)	27 mm Aortic annulus TAVR, femoral access	Ovine (23) Adolescent	90 and 140 days	(12/17) 90 days: 2 140 days: 10	To assess safety and biological response of the Lotus valve over 20 weeks of percutaneous implantation in the orthotopic position in adolescent sheep.	Results: Of 23 animals prescreened for implantation, 6 were euthanized prior to valve introduction due to vascular dissection at the access site. Lotus valves were deployed in 17 animals, of which 12 survived to scheduled termination (2 at 90 days, 10 at 140 days) without major adverse clinical events, complications, or other evidence of functional impairment. There were 5 unscheduled deaths that were procedurally related: • Two procedural deaths due to complete AV block followed by ventricular fibrillation (VF). • One death from right coronary obstruction due to the short aortic root in the sheep. • One death occurred during recovery from VF of unknown cause. • One death from ventricular embolization of the device likely related to implantation in the elastic annulus of a non-diseased animal model. All animals surviving to termination demonstrated normal hemodynamic parameters that met all published clinical VARC-2 criteria for transvalvular gradients and EOA. Pathology showed findings representative of percutaneous bioprosthetic valves chronically implanted in sheep. Radiographic calcification analysis of Lotus valves compared with explanted human bioprosthetic valves demonstrated no significant difference in calcification scores.

Study	Device and Number (N)	Device Size, Implant Location and Method	Species, Number of Animals Enrolled (N) and Age Category	Eval-uation Time Points	Number of Animals Surviving to Evaluation Time Points (n/N)	Objectives	Testing Summary
							Conclusions: Percutaneous implantation of the 27 mm Lotus Valve can be performed in the native aortic annulus of healthy sheep with survival for duration of 140 days. Lotus valve calcification did not exceed that of comparative human explanted valves. Taken together, the hemodynamic performance and histologic analysis demonstrate the safety of the Lotus valve.
Rat Calcification Studies TR5212 and TR5211							
Study TR5212	Test: Lotus Valve bovine pericardial tissue (30) Control: Mitroflow bovine pericardial valve tissue (30)	8 mm Diameter Peri-cardial Tissue Disk Dorsal sub-cutaneous Surgical implant-ation	Rat (10) Young	30 and 90 days	10/10	To evaluate calcification potential of bovine pericardial tissue used in Lotus valve compared to tissue from Mitroflow pericardial valve.	Results: *Histology:* In the Lotus group no calcification was observed at 30 or 90 days. In the Mitroflow group calcification mild to moderate was observed at 30 days and moderate to severe at 90 days. *Calcium Analysis*: Calcification was substantially less in Lotus tissue than Mitroflow. Conclusions: Results demonstrate a substantially reduced tendency for calcification of Lotus valve tissue compared to Mitroflow valve tissue in the young rat subcutaneous model at 30 and 90 days.
Study TR5211	Test 1: Lotus Valve bovine pericardial tissue, one-year aged (16)	8 mm Diameter Peri-cardial Tissue Disk	Rat (8) Young	60 days	8/8	To evaluate the effects of tissue aging on calcification potential of one-year aged	Results: *Histology*: No calcification was observed in 1-year aged and non-aged Lotus tissue groups. Moderate calcification was observed in Mitroflow group in 2 of 3 samples.

Study	Device and Number (N)	Device Size, Implant Location and Method	Species, Number of Animals Enrolled (N) and Age Category	Eval-uation Time Points	Number of Animals Surviving to Evaluation Time Points (n/N)	Objectives	Testing Summary
	Control 1: Lotus Valve bovine pericardial tissue, non-aged (16) Control 2: Mitroflow bovine pericardial valve tissue (16)	Dorsal sub-cutaneous Surgical implant-ation				and non-aged adult bovine pericardial tissue used in Lotus valve compared to tissue from Mitroflow pericardial valve in the young rat subcutaneous model at 60 days.	*Calcium Analysis:* Calcification was substantially less in Lotus aged and non-aged tissues compared to Mitroflow. Conclusions: Results demonstrate reduced tendency for calcification of Lotus valve tissue, both aged and non-aged, compared to Mitroflow valve tissue in the young rat subcutaneous model at 60 days, and no impact of aging on the calcification potential of Lotus valve tissue.
Lotus Valve Ovine 90-Day Study TR4704 (Leveraged Support for Thrombogenicity Assessment)							
Study TR4704	Lotus Valve (8)	27 mm Aortic annulus TAVR, femoral access	Ovine (8) Adolescent	90 days	3/8	To assess the healing characteristics and calcification of the 27 mm Lotus valve in the adolescent ovine model for 90 days of implantation.	Results: Eight animals were implanted. There were 5 unscheduled deaths: 4 due to valve embolization and 1 due to VF during implantation. Three animals survived to scheduled termination at 90 days with no thrombus, hemolysis, systemic toxicity, or changes in valve shape or hemodynamics observed. Conclusions: CT prescreening allowed selection animals for implantation. Fixation of the valve was challenging in non-calcified annular tissue. Repositioning of valve was successfully performed. Complete valve and delivery system retrieval and removal can be performed if necessary. Normal healing and no evidence of hemolysis was observed. No patient safety risks were identified.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

The applicant performed a clinical study, REPRISE III, to establish a reasonable assurance of safety and effectiveness of transcatheter aortic valve replacement with the first-generation LOTUS Valve System in patients with calcific, severe, symptomatic, native aortic stenosis who were at high or extreme risk for open surgery. The study was conducted in the US, Canada, Western Europe, and Australia under IDE #G140090. Data from this clinical study were the basis for the PMA approval decision.

The LOTUS Edge™ Valve System represents a modification to the first-generation LOTUS Valve System to improve flexibility and deliverability, and to reduce the profile of the delivery system. The device design modifications were primarily related to the delivery system. Compared to the LOTUS valve implant, the LOTUS Edge™ valve implant is similar with additional radiopaque tantalum markers on the buckle and post components of the locking mechanism to aid in visualization of the locking procedure under fluoroscopy. The safety and performance of the LOTUS Edge Valve System was supported by two prospective, single-arm studies conducted outside the US (OUS): the REPRISE NG DS (Cohort C) and REPRISE Edge studies.

Following a voluntary field safety corrective action in October 2016, additional design modifications were made to the LOTUS Edge delivery system to improve deliverability and deployment. The safety and performance of the modified LOTUS Edge design were evaluated in a prospective, single-arm nested registry study in the US and Australia.

A summary of the primary clinical study, REPRISE III, is presented below. A summary of the supplemental clinical studies to evaluate the safety and performance of the LOTUS Edge design modifications is presented in Section XI.

A. Study Design

Patients were treated between September 22, 2014 and December 24, 2015. The database for this PMA reflected data collected through March 8, 2017 and included 912 randomized patients enrolled at 55 investigational sites in the US, Germany, France, Australia, the Netherlands, and Canada.

The REPRISE III clinical study was a prospective, multicenter, randomized controlled trial designed to evaluate the safety and effectiveness of the Lotus Valve System for transcatheter aortic valve replacement in symptomatic subjects with calcific, severe native aortic stenosis who were at high or extreme risk for open surgery.

The control group was the CoreValve® Transcatheter Aortic Valve Replacement System. Subjects were randomized 2:1 to the Lotus Valve System (23 mm, 25 mm, and 27 mm valve sizes) or a commercially available CoreValve® (26 mm, 29 mm, and 31 mm valve sizes). A center was allowed to use CoreValve Evolut™ R Recapturable TAVR System with the aforementioned size matrix if the center no

longer had access to CoreValve®. A frequentist analysis plan was used to demonstrate non-inferiority of the Lotus Valve System compared to the CoreValve® TAVR System in both safety and effectiveness endpoints.

All potential eligible subjects were reviewed by a Case Review Committee to confirm suitability prior to enrollment. An independent Clinical Events Committee (CEC) adjudicated safety events. Independent core laboratories assessed echocardiography data; computed tomography (CT) and rotational X-ray angiography data; and electrocardiography data. Any explanted test devices were to be analyzed by an independent histopathology core laboratory. The primary and secondary endpoints and Valve Academic Research Consortium (VARC) clinical endpoints[1,2] were also validated by independent study statisticians.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the REPRISE III study was limited to patients who met the following inclusion criteria:

Table 5: REPRISE III Inclusion Criteria

IC1. Subject has documented calcific, severe native aortic stenosis with an initial AVA of ≤1.0 cm^2 (or AVA index of ≤0.6 cm^2/m^2) and a mean pressure gradient ≥40 mmHg or jet velocity ≥4.0 m/s, as measured by echocardiography and/or invasive hemodynamics.
IC2. Subject has a documented aortic annulus size of ≥20 mm and ≤27 mm based on the center's assessment of pre-procedure diagnostic imaging (and confirmed by the CRC) and, for the randomized cohort, is deemed treatable with an available size of both test and control device.
IC3. Subject has symptomatic aortic valve stenosis with NYHA Functional Class ≥ II.
IC4. There is agreement by the heart team (which must include a site investigator interventionalist and a site investigator cardiac surgeon) that subject is at high or extreme operative risk for surgical valve replacement (see **Note 1** below for definitions of extreme and high risk, the required level of surgical assessment, and CRC confirmation) and that TAVR is appropriate. Additionally, subject has at least one of the following. • Society of Thoracic Surgeons (STS) score ≥8% -OR- • If STS <8, subject has at least one of the following conditions: o Hostile chest o Porcelain aorta o Severe pulmonary hypertension (>60 mmHg) o Prior chest radiation therapy o Coronary artery bypass graft(s) at risk with re-operation o Severe lung disease (need for supplemental oxygen, FEV_1 <50% of predicted, DLCO <60%, other evidence of major pulmonary dysfunction) o Neuromuscular disease that creates risk for mechanical ventilation or rehabilitation

Table 5: REPRISE III Inclusion Criteria

after surgical aortic valve replacement o Orthopedic disease that creates risk for rehabilitation after surgical aortic valve replacement o Childs Class A or B liver disease (subjects with Childs Class C disease are not eligible for inclusion in this trial) o Frailty as indicated by at least one of the following: 5−meter walk >6 seconds, Katz ADL score of 3/6 or less, body mass index <21, wheelchair bound, unable to live independently o Age ≥90 years o Other evidence that subject is at high or extreme risk for surgical valve replacement (CRC must confirm agreement with site heart team that subject meets high or extreme risk definition) IC5. Heart team (which must include a cardiac interventionalist and an experienced cardiac surgeon) assessment that the subject is likely to benefit from valve replacement. IC6. Subject (or legal representative) understands the study requirements and the treatment procedures, and provides written informed consent. IC7. Subject, family member, and/or legal representative agree(s) and subject is capable of returning to the study hospital for all required scheduled follow up visits.
Note 1: Extreme operative risk and high operative risk were defined as shown below. The risk of operative mortality and morbidity was to be assessed via an in-person evaluation by a center cardiac surgeon and was confirmed by the CRC (which included an experienced cardiac surgeon). **Extreme Operative Risk:** Predicted operative mortality or serious, irreversible morbidity risk ≥50% at 30 days. **High Operative Risk:** Predicted operative mortality or serious, irreversible morbidity risk ≥15% at 30 days. Abbreviations: AVA=aortic valve area; CRC=Case Review Committee; NYHA=New York Heart Association; RCT=randomized controlled trial; STS=Society of Thoracic Surgeons; TAVR=transcatheter aortic valve replacement

Patients were <u>not</u> permitted to enroll in the REPRISE III study if they met any of the following exclusion criteria:

Table 6: REPRISE III Exclusion Criteria

EC1. Subject has a congenital unicuspid or bicuspid aortic valve. EC2. Subject has had an acute myocardial infarction within 30 days prior to the index procedure (defined as Q-wave MI or non–Q-wave MI with total CK elevation ≥ twice normal in the presence of CK-MB elevation and/or troponin elevation). EC3. Subject has had a cerebrovascular accident or transient ischemic attack within the past 6 months prior to study enrollment. EC4. Subject has end-stage renal disease or has GFR <20 (based on Cockcroft-Gault formula). EC5. Subject has a pre-existing prosthetic heart aortic or mitral valve.

Table 6: REPRISE III Exclusion Criteria

EC6. Subject has severe (4+) aortic, tricuspid, or mitral regurgitation.
EC7. Subject has a need for emergency surgery for any reason.
EC8. Subject has a history of endocarditis within 6 months of index procedure or evidence of an active systemic infection or sepsis.
EC9. Subject has echocardiographic evidence of new intra-cardiac vegetation or intraventricular or paravalvular thrombus requiring intervention.
EC10. Subject has Hgb <9 g/dL, platelet count <50,000 cells/mm^3 or >700,000 cells/mm^3, or white blood cell count <1,000 cells/mm^3.
EC11. Subject requires chronic anticoagulation therapy after the implant procedure and cannot be treated with warfarin (other anticoagulants are not permitted in the first month) for at least 1 month concomitant with either aspirin or clopidogrel[a].
EC12. Subject has had a gastrointestinal bleed requiring hospitalization or transfusion within the past 3 months, or has other clinically significant bleeding diathesis or coagulopathy that would preclude treatment with required antiplatelet regimen, or will refuse transfusions.
EC13. Subject has known hypersensitivity to contrast agents that cannot be adequately pre-medicated, or has known hypersensitivity to aspirin, all $P2Y_{12}$ inhibitors, heparin, nickel, tantalum, titanium, or polyurethanes.
EC14. Subject has a life expectancy of less than 12 months due to non-cardiac, comorbid conditions based on the assessment of the investigator at the time of enrollment.
EC15. Subject has hypertrophic obstructive cardiomyopathy.
EC16. Subject has any therapeutic invasive cardiac or vascular procedure within 30 days prior to the index procedure (except for balloon aortic valvuloplasty or pacemaker implantation, which are allowed).
EC17. Subject has untreated coronary artery disease, which in the opinion of the treating physician is clinically significant and requires revascularization.
EC18. Subject has severe left ventricular dysfunction with ejection fraction <20%.
EC19. Subject is in cardiogenic shock or has hemodynamic instability requiring inotropic support or mechanical support devices.
EC20. Subject has severe vascular disease that would preclude safe access (e.g., aneurysm with thrombus that cannot be crossed safely, marked tortuosity, significant narrowing of the abdominal aorta, severe unfolding of the thoracic aorta, or symptomatic carotid or vertebral disease).
EC21. Subject has thick (>5 mm) protruding or ulcerated atheroma in the aortic arch
EC22. Subject has arterial access that is not acceptable for the test and control device delivery systems as defined in the device Instructions For Use.
EC23. Subject has current problems with substance abuse (e.g., alcohol, etc.).
EC24. Subject is participating in another investigational drug or device study that has not reached its primary endpoint.

Table 6: REPRISE III Exclusion Criteria

EC25. Subject has untreated conduction system disorder (e.g., Type II second degree atrioventricular block) that in the opinion of the treating physician is clinically significant and requires a pacemaker implantation. Enrollment is permissible after permanent pacemaker implantation.
EC26. Subject has severe incapacitating dementia.
a: An alternative $P2Y_{12}$ inhibitor may be prescribed if subject is allergic to or intolerant of clopidogrel. Abbreviations: CK=creatine kinase; MI=myocardial infarction; PCI=percutaneous coronary intervention

2. Follow-up Schedule

All patients were scheduled to return for follow-up examinations at discharge or 7 days post-procedure (whichever comes first), 30 days, 6 months, 1 year, and then annually for 5 years post-procedure. Enrolled patients who did not receive a study valve (Lotus or CoreValve) were followed for 1 year.

Preoperatively, patients were screened to confirm they met the eligibility criteria, including imaging assessments of valve function and arterial structure/disease. In addition, baseline assessments included neurological assessment, laboratory tests, and quality of life surverys. Postoperatively, the objective parameters measured during the study included New York Heart Association (NYHA) Classification, neurological physical examination, antiplatelet and anticoagulation medications (if applicable), transthoracic echocardiogram (TTE) evaluation, quality of life surveys, adverse event collection, and 4D CT imaging of the prosthetic valve (at 30 days and 1 year). Adverse events and complications were recorded at all visits.

The key timepoints are shown below in the tables summarizing safety and effectiveness.

3. Clinical Endpoints

Primary Safety Endpoint

The primary safety endpoint was a composite of all-cause mortality, stroke, life-threatening and major bleeding events, stage 2 or 3 acute kidney injury, or major vascular complications at 30 days. The primary hypothesis was as follows:

$$H_0: P_{S\_Lotus} - P_{S\_Control} \geq 10.5\%$$
$$H_A: P_{S\_Lotus} - P_{S\_Control} < 10.5\%$$

where P_{S_Lotus} denotes the event proportion in the test arm, and $P_{S\_Control}$ denotes the event proportion in the control arm. The test was performed as a one-sided test at $\alpha =$

0.025. The primary analysis was a non-inferiority analysis in the implanted analysis set. The endpoint was also analyzed for the intent-to-treat (ITT) and as-treated analysis sets.

Primary Effectiveness Endpoint

The primary effectiveness endpoint was a composite of all-cause mortality, disabling stroke, or moderate or greater paravalvular aortic regurgitation (PVR; based on core lab assessment) at 1 year. The primary hypothesis was as follows:

$$H_0: P_{S\_Lotus} - P_{S\_Control} \geq 9.5\%$$
$$H_A: P_{S\_Lotus} - P_{S\_Control} < 9.5\%$$

where P_{S_Lotus} denotes the event proportion in the test arm, and $P_{S\_Control}$ denotes the event proportion in the control arm. The test was performed as a one-sided test at $\alpha = 0.025$. The primary analysis was a non-inferiority analysis in the implanted analysis set. The endpoint was also analyzed for the intent-to-treat (ITT) and as-treated analysis sets.

Secondary Endpoint

The secondary endpoint was the rate of moderate or greater PVR based on core lab assessment at 1 year. A chi-square test was used to test the two-sided ($\alpha = 0.05$) hypothesis of superiority:

$$H_0: P_{AR\text{-}Lotus} = P_{AR\text{-}Control}$$
$$H_A: P_{AR\text{-}Lotus} \neq P_{AR\text{-}Control}$$

Where $P_{AR\text{-}Lotus}$ and $P_{AR\text{-}Control}$ correspond to the moderate or greater PVR rates at 1 year for the Lotus Valve group (test) and the CoreValve group (control), respectively. The primary analysis set was the ITT analysis set.

Additional Measurements

Additional measurements based on the VARC endpoints and definitions were collected peri- and post-procedure, at discharge or 7 days post-procedure (whichever comes first), 30 days, 6 months, and 1, 2, 3, 4, and 5 years post index procedure, unless otherwise specified below.

- Safety endpoints adjudicated by an independent Clinical Events Committee (CEC):
  - Mortality: all-cause, cardiovascular, and non-cardiovascular
  - Stroke: disabling and non-disabling
  - Myocardial infarction (MI): periprocedural (≤72 hours post index procedure) and spontaneous (>72 hours post index procedure)
  - Bleeding: life-threatening (or disabling) and major
  - Acute kidney injury (≤7 days post index procedure): based on the AKIN Stage 3 (including renal replacement therapy) or Stage 2

    - Major vascular complication
    - Repeat procedure for valve-related dysfunction (surgical or interventional therapy)
    - Hospitalization for valve-related symptoms or worsening congestive heart failure (CHF; New York Heart Association [NYHA] class III or IV)
    - New permanent pacemaker (PPM) implantation resulting from new or worsened conduction disturbances
    - New onset of atrial fibrillation or atrial flutter
    - Coronary obstruction: periprocedural (≤72 hours post index procedure)
    - Ventricular septal perforation: periprocedural (≤72 hours post index procedure)
    - Mitral apparatus damage: periprocedural (≤72 hours post index procedure)
    - Cardiac tamponade: periprocedural (≤72 hours post index procedure)
    - Prosthetic aortic valve malpositioning, including valve migration, valve embolization, or ectopic valve deployment
    - Transcatheter aortic valve (TAV)-in-TAV deployment
    - Prosthetic aortic valve thrombosis
    - Prosthetic aortic valve endocarditis
- Device performance endpoints peri- and post-procedure:
    - Successful vascular access, delivery and deployment of the study valve and successful retrieval of the delivery system
    - Successful retrieval of the study valve if retrieval is attempted
    - Successful repositioning of the study valve if repositioning is attempted
    - Grade of aortic valve regurgitation: paravalvular, central and combined; overall distribution of PVR (none, trace/trivial, mild, moderate, severe), the percentage of subjects with moderate or severe PVR, and the percentage of subjects with mild, moderate or severe PVR
- Clinical procedural success (30 days), defined as implantation of the study device in the absence of death, disabling stroke, major vascular complications, and life-threatening or major bleeding
- Procedural success (30 days), defined as absence of procedural mortality, correct positioning of a single transcatheter valve into the proper anatomical location, intended performance of the study device (effective orifice area [EOA] >0.9 cm^2 for body surface area [BSA] <1.6 m^2 and EOA >1.1 cm^2 for BSA ≥1.6 m^2 plus either a mean aortic valve gradient <20 mmHg or a peak velocity <3m/sec, and no moderate or severe prosthetic valve aortic regurgitation) plus no serious adverse events at 30 days
- Additional indications of prosthetic aortic valve performance as measured by transthoracic echocardiography (TTE) and assessed by an independent core laboratory, including EOA, mean and peak aortic gradients, peak aortic velocity, and grade of aortic regurgitation
- Modified device success (30 days), reported for subjects randomized and implanted with an assigned study device and defined as follows: absence of mortality with the originally implanted transcatheter valve in the proper anatomical location, no additional aortic valve procedures, and with the intended performance of the prosthetic valve (either a mean aortic valve gradient

<20 mmHg or a peak velocity <3m/sec with no moderate or severe prosthetic valve aortic regurgitation)

- Functional status as evaluated by the following:
  - 5-m gait speed test (at 1 year compared to baseline)
  - NYHA classification
- Neurological status as determined by the following:
  - Neurological physical exam by a neurologist, neurology fellow, neurology physician assistant, or neurology nurse practitioner at discharge and 1 year
  - National Institutes of Health Stroke Scale (NIHSS) at discharge and 1 year
  - Modified Rankin Scale (mRS) at all time points
- Health status as evaluated by Kansas City Cardiomyopathy and SF-12 Quality of Life (QOL) questionnaires at baseline; 1 and 6 months; and 1, 3, and 5 years

B. Accountability of PMA Cohort

At the time of database lock, of 912 patients enrolled in the PMA study (607 Lotus, 305 CoreValve), 97.4% (N=297) of CoreValve patients and 96.7% (N=587) of Lotus patients are available for analysis at the completion of the study, the 1-year post-operative visit.

Table 7: REPRISE III Subject Disposition

Measure	Lotus	Core Valve[a]
Intent-to-treat analysis set	607	305
Not treated with a study valve system (Lotus or CoreValve)	20	8
Treated with a study valve system but not the assigned randomized study valve system (crossover)	10	0
Implanted analysis set	577	297[b]
As-treated analysis set (includes crossovers)	577	307
Death before 365 days, no 12-month clinical follow-up performed	70	39
Eligible for 12-month clinical follow-up[c]	537	266
12-month clinical follow-up completed[d]	92.7% (498/537)	88.7% (236/266)
12-month follow-up completed <335 days[e]	2	0
No 12-month clinical follow-up performed	39	30
Premature discontinuation	18	18
Withdrew consent	13	14
Lost to follow-up	1	1
Investigator discretion	2	3
Completed study	1	0
Other	1	0
Missed 12-month follow-up visit	21	12
With later follow-up visit performed	0	0
No later follow-up visit performed	21	12
12-Month clinical follow-up or death[f]	93.6% (568/607)	90.2% (275/305)

Table 7: REPRISE III Subject Disposition

Measure	Lotus	Core Valve[a]
Subjects with a VARC event	364	164
Subjects with sufficient 12-month follow-up or had a VARC event[g]	96.7% (587/607)	97.4% (297/305)
12-Month transthoracic echocardiography assessment	482	228

Data are presented as n or % (count/sample size).

Note: In one subject (randomized to the Lotus group) the index procedure was stopped prior to insertion of the delivery system. This subject subsequently underwent the valve implant procedure 361 days after randomization and was implanted with CoreValve Evolut R after an unsuccessful attempt with Lotus. This report does not include outcomes data at 1 year for this subject because the data snapshot was taken before the 1-year follow-up visit had occurred.

a: The CoreValve group includes CoreValve and CoreValve Evolut R.

b: Includes 153 subjects with CoreValve and 144 subjects with CoreValve Evolut R.

c: Subjects who died prior to completion of follow-up window and prior to completing a 12-month clinical follow-up visit are considered ineligible and are excluded from calculation of proportion of subjects who completed the clinical follow-up visit.

d: Based on subjects eligible for 12-month clinical follow-up (excludes deaths before 365 days post-procedure).

e: Based on subjects without any event.

f: Includes subjects who have died in both the numerator and the denominator; based on the intent-to-treat analysis set.

g: Sufficient 12-month follow-up is defined as at least 335 days follow-up post randomization; a subject could have more than 1 VARC event.

Abbreviation: VARC=Valve Academic Research Consortium

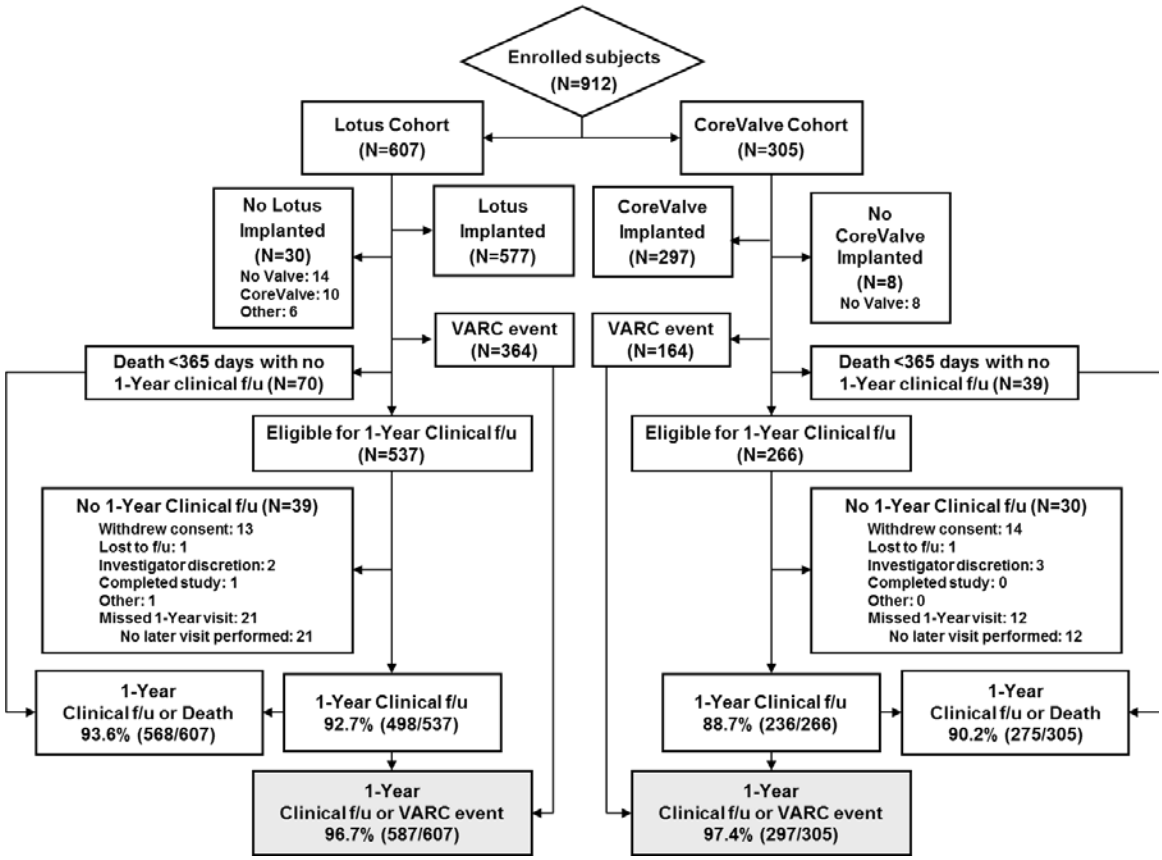


Figure 3. REPRISE III Randomized Subject Disposition (Intent-to-Treat)

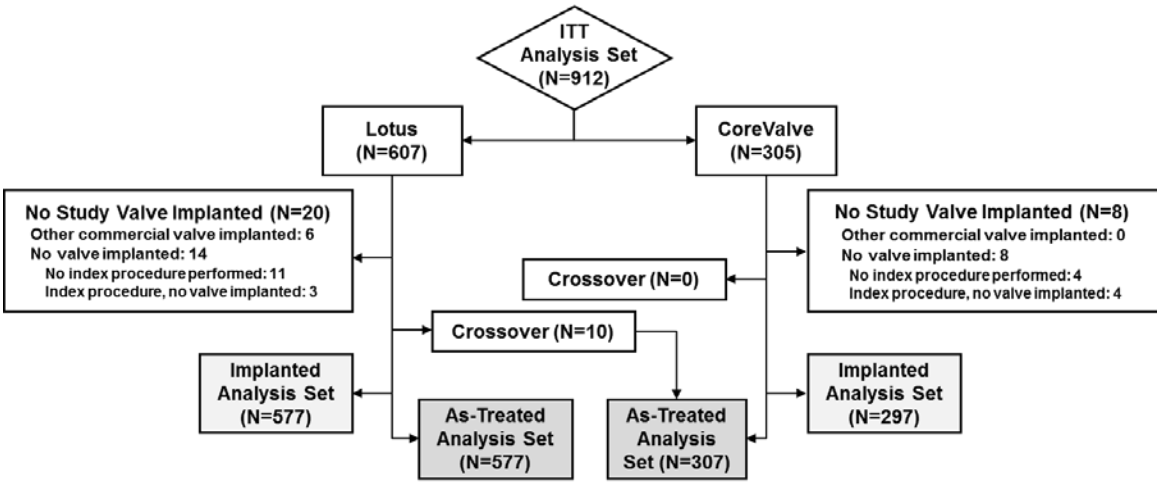


Figure 4. REPRISE III Randomized Subject Analysis Sets

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are summarized in Table 8, and are typical for a TAVR study performed in the US.

Table 8: Demographics and Baseline Clinical Characteristics

Variable	Lotus (N=607)	CoreValve (N=305)
Age at time of consent (years)	82.8±7.1 (607)	82.9±7.6 (305)
Female	50.1% (304/607)	52.1% (159/305)
Overall Risk Assessments		
Extreme risk	23.1% (140/607)	21.6% (66/305)
High risk	76.9% (467/607)	78.4% (239/305)
EuroSCORE 2011 (%)	6.4±5.5 (605)	6.4±5.5 (304)
STS Score (%)	6.7±4.0 (607)	6.9±4.1 (305)
STS Score ≥ 8	31.0% (188/607)	29.5% (90/305)
STS Score < 8	69.0% (419/607)	70.5% (215/305)
Porcelain aorta	4.5% (19/419)	3.3% (7/215)
Severe pulmonary hypertension	8.1% (34/419)	8.4% (18/215)
Orthopedic disease	18.6% (78/419)	12.6% (27/215)
Neuromuscular disease	1.4% (6/419)	2.3% (5/215)
Prior chest radiation therapy	4.1% (17/419)	3.7% (8/215)
Hostile chest	4.1% (17/419)	4.7% (10/215)
Severe lung disease	15.3% (64/419)	14.0% (30/215)
CABG at risk with re-operation	16.0% (67/419)	20.0% (43/215)
Childs Class A or B liver disease	1.7% (7/419)	1.9% (4/215)

Table 8: Demographics and Baseline Clinical Characteristics

Variable	Lotus (N=607)	CoreValve (N=305)
Frailty	72.6% (304/419)	70.7% (152/215)
Age ≥ 90 years	10.0% (42/419)	12.6% (27/215)
Other	4.1% (17/419)	7.0% (15/215)
General Medical History		
Diabetes mellitus (medically treated)	30.9% (187/606)	32.6% (99/304)
History of hyperlipidemia (medically treated)	74.6% (453/607)	75.7% (230/304)
History of hypertension	91.8% (557/607)	93.8% (286/305)
History of peripheral vascular disease	31.1% (187/602)	25.7% (78/304)
History of dialysis dependent renal failure	0.2% (1/603)	1.3% (4/305)
COPD - Supplemental oxygen dependent	6.5% (39/599)	6.3% (19/303)
Cardiac History		
History of coronary artery disease	71.5% (433/606)	73.4% (224/305)
History of myocardial infarction	18.3% (109/597)	19.0% (58/305)
History of congestive heart failure	77.0% (463/601)	79.8% (241/302)
History of percutaneous coronary intervention	33.1% (201/607)	32.5% (99/305)
History of CABG	23.6% (143/606)	23.3% (71/305)
History of atrial fibrillation	35.1% (213/606)	31.6% (96/304)
History of atrial flutter	4.9% (29/594)	6.7% (20/300)
Prior pacemaker implant	17.8% (108/607)	19.0% (58/305)
NYHA functional class		
Class I	0.0% (0/607)	0.0% (0/305)
Class II	28.7% (174/607)	32.1% (98/305)
Class III	63.6% (386/607)	61.0% (186/305)
Class IV	7.7% (47/607)	6.9% (21/305)
Neurological History		
History of transient ischemic attack	8.3% (50/601)	7.9% (24/303)
History of cerebrovascular accident	11.3% (68/603)	14.5% (44/304)
Cognitive and Daily Living Assessments		
Mini-cognitive assessment for dementia score	3.6±1.4 (599)	3.7±1.4 (304)
Katz Index Activities of Daily Living score	5.6±0.9 (605)	5.6±1.0 (305)
Strength and Balance Assessments		
Use of wheelchair	5.8% (35/606)	4.9% (15/305)
Gait speed average to walk 5 meters (seconds)	8.7±5.2 (565)	8.7±4.2 (285)
Falls in the past 6 months	0.4±1.1 (604)	0.5±1.8 (304)
Maximal grip strength average (kg)	21.1±10.1 (605)	20.4±9.7 (303)

Table 8: Demographics and Baseline Clinical Characteristics

Variable	Lotus (N=607)	CoreValve (N=305)
Echocardiographic Findings		
Aortic valve area (cm^2)	0.69±0.19 (541)	0.70±0.19 (280)
Mean aortic valve gradient (mmHg)	44.64±13.35 (575)	43.85±12.31 (294)
Doppler velocity index	0.22±0.05 (553)	0.23±0.05 (292)

Values are presented as mean±standard deviation (n) or % (count/sample size)
Abbreviations: CABG=coronary artery bypass graft; COPD=chronic obstructive pulmonary disease; NYHA=New York Heart Association; STS=Society of Thoracic Surgeons

D. Safety and Effectiveness Results

1. Safety Results

The primary safety endpoint was the composite of all-cause mortality, stroke, life-threatening and major bleeding events, stage 2 or 3 acute kidney injury, or major vascular complications at 30 days. The primary analysis set for the primary safety endpoint was the implanted analysis set, which includes all patients who signed an informed consent form, were enrolled in the trial, and were implanted with the assigned, randomized study device. The key safety outcomes for this study are presented below in Tables 9-10. Adverse effects are reported in Table 11.

Table 9: Non-Inferiority Testing for the Primary Safety Endpoint

Analysis Set	Lotus	CoreValve	Difference [95%CI]	One-sided 97.5% UCB [a]	Non-Inferiority Margin	One-sided *P* value [b]
Implanted (N=874)	(N=577)	(N=297)	3.1% [-2.3%, 8.5%]	8.32%	10.5%	0.0027
	20.3% (117/576)	17.2% (51/297)				
Intent-to-Treat (N=912)	(N=607)	(N=305)	2.8% [-2.4%, 8.0%]	7.75%	10.5%	0.0011
	19.0% (114/601)	16.2% (49/303)				

Rates are presented as % (count/sample size)
a: Farrington-Manning upper confidence bound
b: *P* value is from the Farrington-Manning test and based on the standard normal distribution
Abbreviations: CI=confidence interval; UCB=upper confidence bound

Figure 5 shows that the safety composite of all-cause mortality, stroke, life-threatening and major bleeding events, stage 2 or 3 acute kidney injury, and major vascular complications was not different between the treatment and control groups to 1 year.

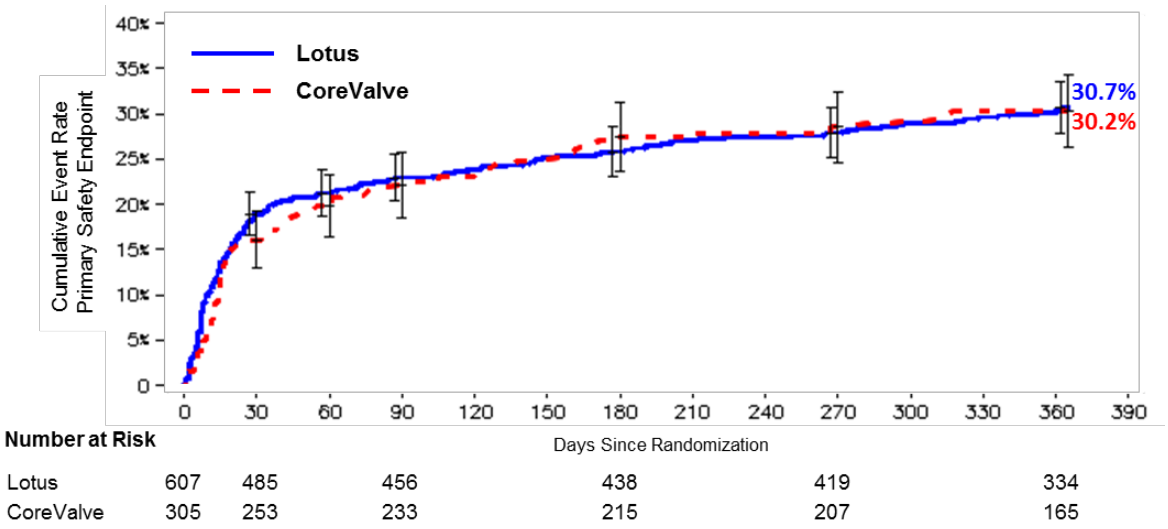


Figure 5. Primary Safety Composite to 1-year, Intent-to-Treat Analysis Set
Values are presented as cumulative event rate ± 1.5 standard error

Table 10 shows that the components of the 30-day primary safety endpoint were similar between the two groups.

Table 10: Components of the 30-Day Primary Safety Endpoint, ITT Analysis Set

Outcome	Lotus (N=607)	CoreValve (N=305)
All-cause mortality	2.5% (15/601)	2.3% (7/303)
Stroke	4.8% (29/601)	4.3% (13/303)
Disabling	2.0% (12/601)	3.3% (10/303)
Life-threatening or disabling bleeding	8.0% (48/601)	5.0% (15/303)
Major bleeding	4.8% (29/601)	5.9% (18/303)
Major vascular complications	7.0% (42/601)	5.3% (16/303)
Acute kidney injury	2.5% (15/601)	3.6% (11/303)
Values are presented as % (count/sample size)		

Time-to-event event curves (Kaplan-Meier analysis) to 1 year for all-cause death, all-cause death or disabling stroke, and disabling stroke are shown below for the ITT analysis set. The estimated event rate for all-cause death to 1 year was similar for the 2 cohorts (11.9% for Lotus and 13.7% for CoreValve; Figure 6). The combined outcome of all-cause death or disabling stroke to 1 year was 13.2% for Lotus compared to 17.9% for CoreValve (Figure 7). The estimated rate for disabling stroke to 1 year was 3.6% for Lotus compared to 7.3% for CoreValve (Figure 8).

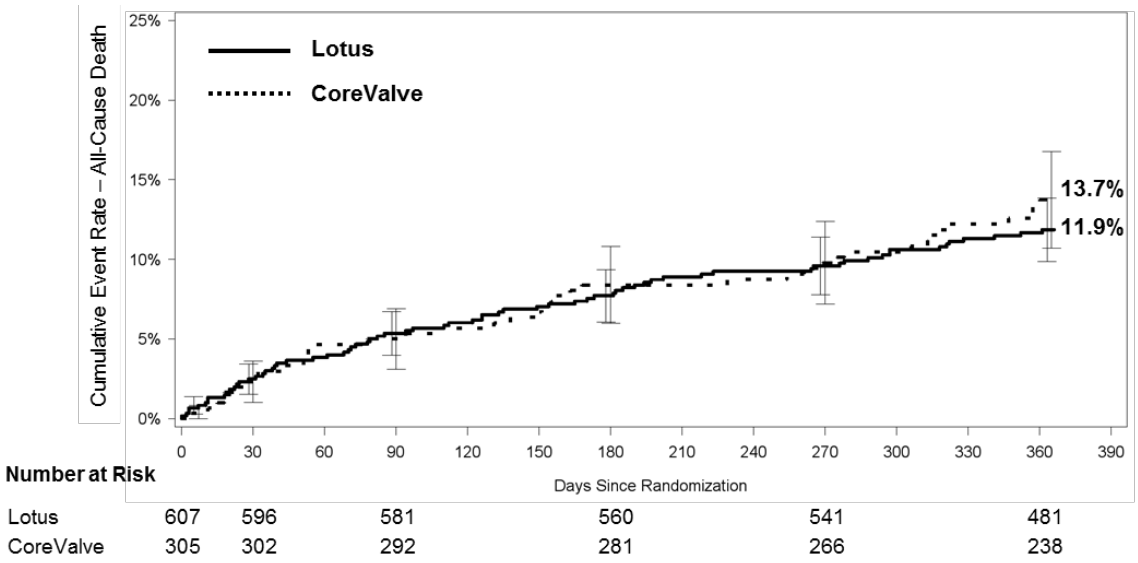


Figure 6: Kaplan-Meier Event Curve for All-Cause Death to 1 Year Post-Randomization, ITT Analysis Set

Values are presented as cumulative event rate ± 1.5 standard error

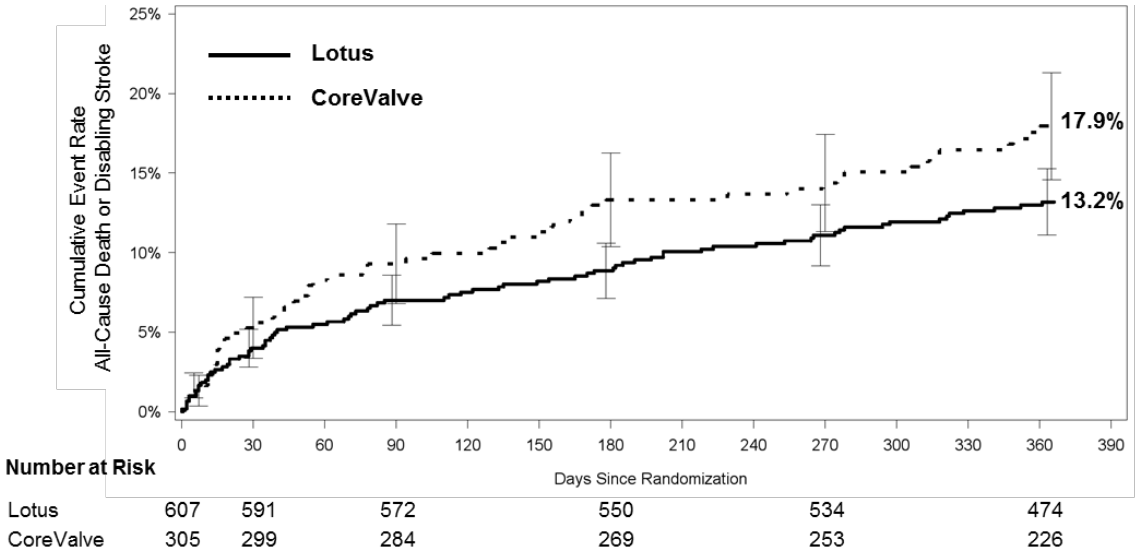


Figure 7: Kaplan-Meier Event Curve for All-Cause Death or Disabling Stroke to 1 Year Post-Randomization, ITT Analysis Set

Values are presented as cumulative event rate ± 1.5 standard error

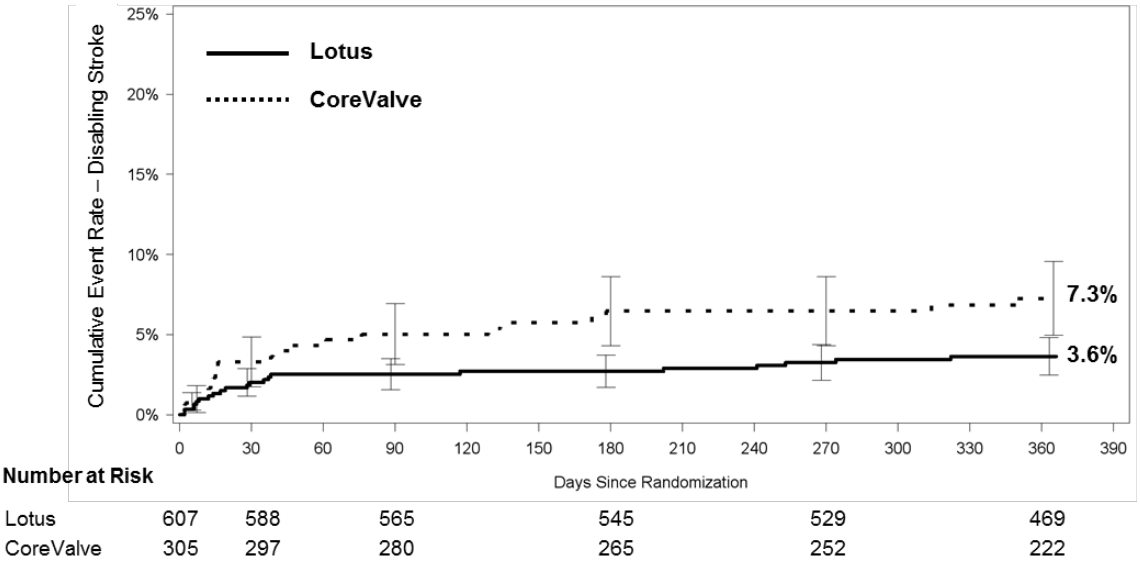


Figure 8: Kaplan-Meier Event Curve for Disabling Stroke to 1 Year Post-Randomization, ITT Analysis Set

Values are presented as cumulative event rate ± 1.5 standard error

Adverse effects that occurred in the PMA clinical study:

Table 11 shows binary rates of CEC-adjudicated, VARC-defined events occurring from randomization to 30 days and 1 year in the ITT analysis set.

Table 11: VARC Events Through 30 Days and 1 Year; ITT Analysis Set, Binary Rates

Outcome	30 Days		1 Year	
	Lotus (N=607)	CoreValve (N=305)	Lotus (N=607)	CoreValve (N=305)
All-cause mortality	2.5% (15/601)	2.3% (7/303)	11.9% (70/587)	13.5% (40/297)
Cardiovascular	2.3% (14/601)	2.3% (7/303)	7.7% (45/587)	9.8% (29/297)
Non-cardiovascular	0.2% (1/601)	0.0% (0/303)	4.3% (25/587)	3.7% (11/297)
Stroke	4.8% (29/601)	4.3% (13/303)	7.0% (41/587)	9.4% (28/297)
Disabling	2.0% (12/601)	3.3% (10/303)	3.6% (21/587)	7.1% (21/297)
Ischemic	1.8% (11/601)	3.3% (10/303)	2.9% (17/587)	6.4% (19/297)
Hemorrhagic	0.2% (1/601)	0.0% (0/303)	0.7% (4/587)	0.3% (1/297)
Undetermined	0.0% (0/601)	0.0% (0/303)	0.2% (1/587)	0.3% (1/297)
Non-disabling	2.8% (17/601)	1.0% (3/303)	3.6% (21/587)	2.4% (7/297)
Ischemic	2.3% (14/601)	1.0% (3/303)	3.1% (18/587)	2.4% (7/297)
Hemorrhagic	0.2% (1/601)	0.0% (0/303)	0.2% (1/587)	0.0% (0/297)
Undetermined	0.3% (2/601)	0.0% (0/303)	0.3% (2/587)	0.0% (0/297)
All-cause mortality or disabling stroke	4.0% (24/601)	5.3% (16/303)	13.3% (78/587)	17.8% (53/297)
Cardiac death or disabling stroke	3.8% (23/601)	5.3% (16/303)	9.5% (56/587)	14.8% (44/297)
Major vascular complications	7.0% (42/601)	5.3% (16/303)	7.7% (45/587)	6.1% (18/297)

Table 11: VARC Events Through 30 Days and 1 Year; ITT Analysis Set, Binary Rates

Outcome	30 Days		1 Year	
	Lotus (N=607)	CoreValve (N=305)	Lotus (N=607)	CoreValve (N=305)
Access site related	4.7% (28/601)	3.3% (10/303)	5.1% (30/587)	3.7% (11/297)
Not access site related	2.5% (15/601)	2.0% (6/303)	2.7% (16/587)	2.4% (7/297)
New PPM implanted[a]	29.1% (175/601)	15.8% (48/303)	34.2% (201/587)	18.5% (55/297)
No prior PPM[a]	35.5% (175/493)	19.6% (48/245)	41.4% (201/485)	23.0% (55/239)
Bleeding	12.8% (77/601)	10.9% (33/303)	18.1% (106/587)	17.8% (53/297)
Life-threatening or disabling	8.0% (48/601)	5.0% (15/303)	9.9% (58/587)	9.8% (29/297)
Major	4.8% (29/601)	5.9% (18/303)	8.3% (49/587)	8.4% (25/297)
Myocardial infarction	0.7% (4/601)	1.3% (4/303)	3.2% (19/587)	4.4% (13/297)
Peri-procedural MI	0.5% (3/601)	1.0% (3/303)	0.5% (3/587)	1.3% (4/297)
Spontaneous MI	0.2% (1/601)	0.3% (1/303)	2.7% (16/587)	3.4% (10/297)
Acute kidney injury	2.5% (15/601)	3.6% (11/303)	2.6% (15/587)	3.7% (11/297)
Stage 2	1.0% (6/601)	1.3% (4/303)	1.0% (6/587)	1.3% (4/297)
Stage 3	1.5% (9/601)	2.3% (7/303)	1.5% (9/587)	2.4% (7/297)
Repeat procedure for valve-related dysfunction	0.0% (0/601)	1.0% (3/303)	0.2% (1/587)	2.0% (6/297)
TAVR	0.0% (0/601)	0.7% (2/303)	0.0% (0/587)	1.7% (5/297)
Valvuloplasty	0.0% (0/601)	0.0% (0/303)	0.0% (0/587)	0.0% (0/297)
SAVR	0.0% (0/601)	0.0% (0/303)	0.2% (1/587)	0.0% (0/297)
Other	0.0% (0/601)	0.3% (1/303)	0.0% (0/587)	0.3% (1/297)
Hospitalization	1.7% (10/601)	3.0% (9/303)	11.2% (66/587)	13.8% (41/297)
New onset atrial fibrillation/flutter	5.8% (35/601)	4.3% (13/303)	6.6% (39/587)	4.7% (14/297)
Atrial fibrillation	5.8% (35/601)	4.3% (13/303)	6.6% (39/587)	4.7% (14/297)
Atrial flutter	0.0% (0/601)	0.0% (0/303)	0.0% (0/587)	0.0% (0/297)
Coronary obstruction	0.2% (1/601)	0.3% (1/303)	0.2% (1/587)	0.7% (2/297)
Cardiac tamponade	2.5% (15/601)	1.0% (3/303)	2.6% (15/587)	1.3% (4/297)
Prosthetic aortic valve malpositioning	0.0% (0/601)	2.6% (8/303)	0.0% (0/587)	2.7% (8/297)
Valve migration	0.0% (0/601)	0.7% (2/303)	0.0% (0/587)	0.7% (2/297)
Valve embolization	0.0% (0/601)	2.0% (6/303)	0.0% (0/587)	2.0% (6/297)
Ectopic valve deployment	0.0% (0/601)	0.3% (1/303)	0.0% (0/587)	0.3% (1/297)
TAV-in-TAV deployment	0.0% (0/601)	3.0% (9/303)	0.0% (0/587)	3.7% (11/297)
Prosthetic aortic valve thrombosis	0.0% (0/601)	0.0% (0/303)	1.5% (9/587)	0.0% (0/297)
Prosthetic aortic valve endocarditis	0.2% (1/601)	0.0% (0/303)	0.7% (4/587)	0.0% (0/297)

Values are presented as % (count/sample size).
a: Resulting from new or worsened conduction disturbances; "no prior PPM" indicates subjects without a PPM before the index procedure
Abbreviations: CEC=Clinical Events Committee; VARC=Valve Academic Research Consortium; MI=myocardial infarction; PPM=permanent pacemaker; SAVR=surgical aortic valve replacement; TAV=transcatheter aortic valve; TAVR=transcatheter aortic valve replacement

2. Effectiveness Results

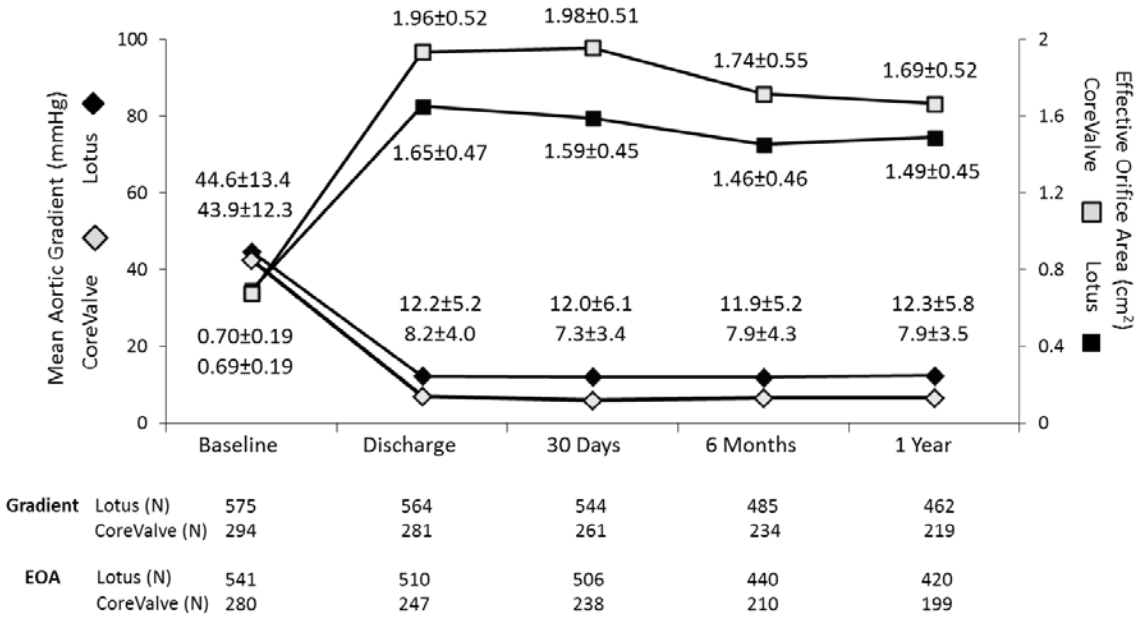
The primary effectiveness endpoint is the composite of all-cause mortality, disabling stroke, and moderate or greater PVR (based on independent core lab assessment) at 1 year. The primary analysis of effectiveness was based on the 874 evaluable patients at the 1-year time point in the implanted analysis set. Key effectiveness outcomes are presented in Table 12 and Figures 9-11.

Table 12: Non-Inferiority Testing and Superiority Testing for the Primary Effectiveness Endpoint

Analysis Set	Lotus	CoreValve	Difference [95%CI]	One-sided 97.5% UCB[a]	Non-Inferiority Margin	*P* value[b]	
						Non-Inferiority	Superiority
ITT (N=912)	(N=607)	(N=305)	-10.2% [-16.3%, -4.0%]	-4.54%	9.5%	<0.0001	0.0006
	15.8% (82/520)	26.0% (68/262)					
Implanted (N=874)	(N=577)	(N=297)	-10.1% [-16.2%, -3.9%]	-4.41%	9.5%	<0.0001	0.0007
	15.4% (78/506)	25.5% (66/259)					

Rates are presented as % (count/sample size).
a: Farrington-Manning upper confidence bound
b: *P* value is from the Farrington-Manning test and is based on the standard normal distribution for the non-inferiority testing and from the Chi-square test for the superiority testing.
Abbreviations: CI=confidence interval; ITT=intent-to-treat; UCB=upper confidence bound

As shown in Table 12, the Lotus Valve System demonstrated non-inferiority to the control (P<0.0001) and further met superiority in a subsequent analysis in both the ITT and Implanted analysis cohorts. Figure 9 shows that mean aortic gradient improved in both cohorts from baseline to discharge and remained generally constant out to 1 year. Mean effective orifice area (EOA) improved in both cohorts from baseline to discharge and remained above baseline with a slight reduction at 1 year. The Lotus Valve System appears to demonstrate a slightly lower EOA and higher mean gradient compared to CoreValve at each time point. However, this result is anticipated due to the larger size range of CoreValve implants used in the study compared to Lotus implants (23-, 25-, and 27-mm Lotus valves vs. 26-, 29-, and 31-mm CoreValve). Despite these differences, the clinical effectiveness outcomes (as demonstrated in Table 12 and Figures 10-11) are comparable between the Lotus Valve and CoreValve systems. Furthermore, left ventricle mass was the same in both cohorts at 1 year.



Gradient	Lotus (N)	575	564	544	485	462
	CoreValve (N)	294	281	261	234	219
EOA	Lotus (N)	541	510	506	440	420
	CoreValve (N)	280	247	238	210	199

Figure 9: Mean Aortic Gradient and Effective Orifice Area to 1 Year, ITT Analysis Set

Values are presented as mean ± standard deviation

PVR over time is illustrated in Figure 10. At discharge, 87.4% of evaluable patients in the Lotus cohort had no or trace PVR compared to 47.4% in the CoreValve cohort. At 30 days, 88.1% of evaluable patients in the Lotus group had no or trace PVR compared to 41.3% in the CoreValve group. At 1 year, 87.6% of evaluable patients in the Lotus cohort had no or trace PVR compared to 51.0% in the CoreValve cohort. There was no severe PVR in either cohort at any time.

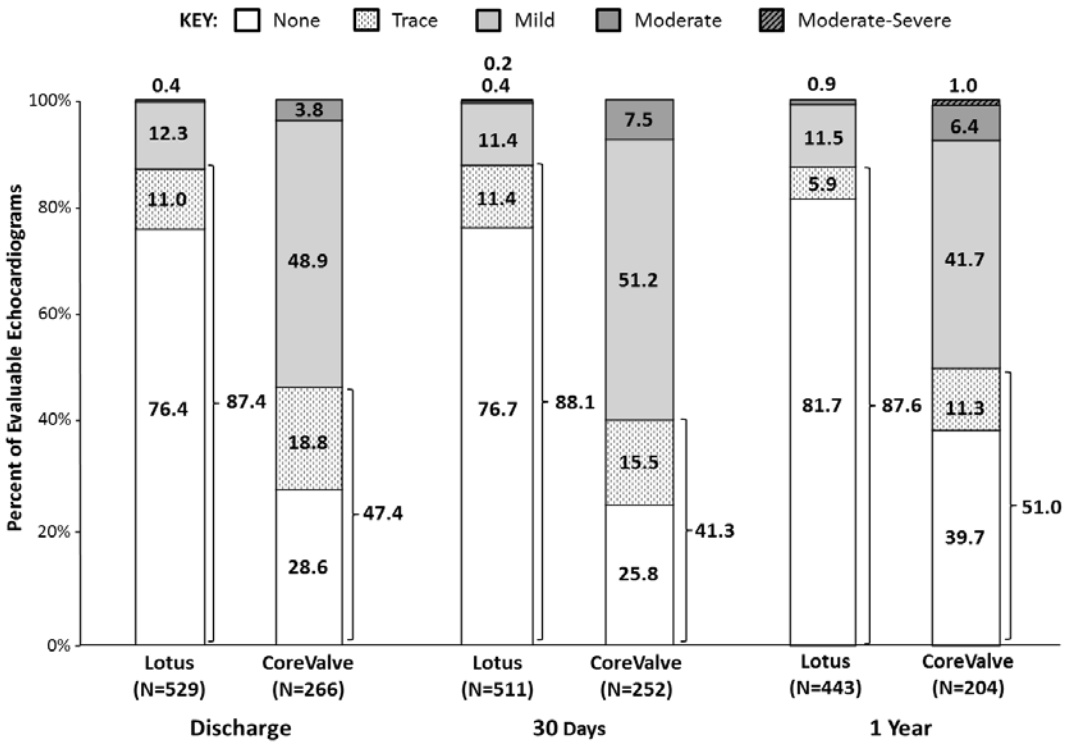


Figure 10: PVR over Time, ITT Analysis Set

(Figure shows results from evaluable echocardiograms that were gradable.)

NYHA functional status of patients from baseline to 1 year is shown in Figure 11. While all patients were classified as NYHA Class II, III, or IV at baseline, the majority in both cohorts were Class I or II at 30 days and 1 year.

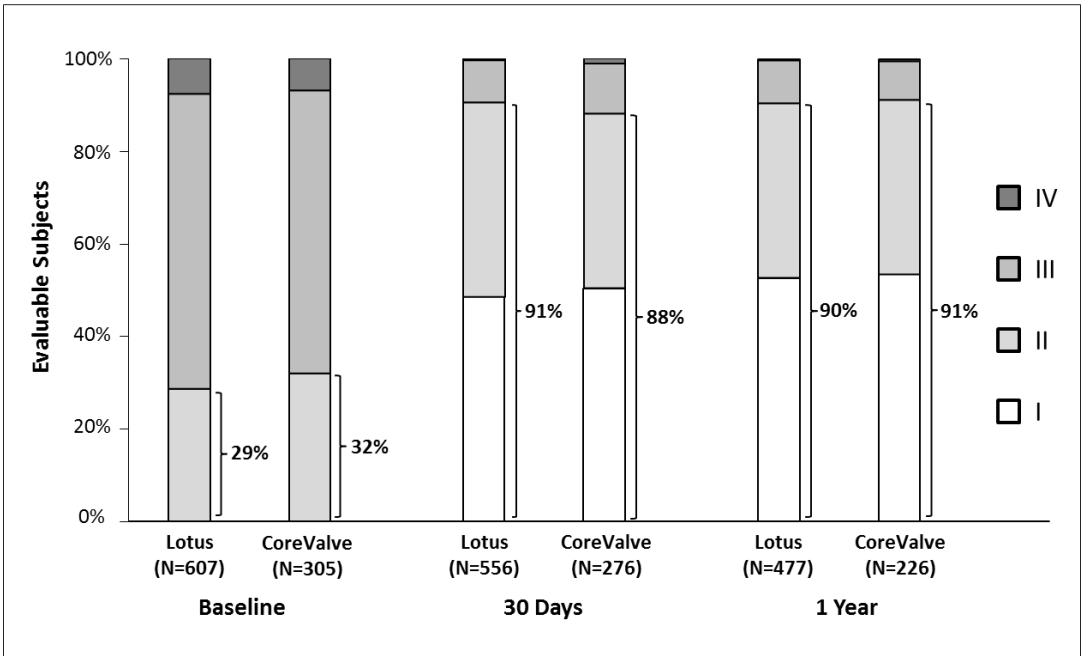


Figure 11: NYHA Functional Status over Time, ITT Analysis Set

Health status was evaluated using the SF-12 Quality of Life questionnaire and Kansas City Cardiomyopathy Questionnaire (KCCQ).

SF-12

Among assessed patients in the Lotus cohort, the mean SF-12 physical summary score improved from 31.9±9.0 at baseline to 37.0±9.8 at 30 days and remained high at 1 year (36.9±10.6). The mental health summary scores were 49.6±11.6, 52.9±10.9, and 53.6±9.7 at baseline, 30 days, and 1 year, respectively. Similar results were seen in the CoreValve cohort.

KCCQ

Among assessed patients in the Lotus cohort, the overall summary score improved from 51.9±23.5 at baseline to 73.0±21.3 at 30 days and remained high at 1 year (74.9±21.0). The clinical summary score improved from 55.2±23.3 to 73.1±21.4 at 30 days and was 73.1±21.3 at 1 year. Similar results were seen in the CoreValve cohort.

3. Secondary Endpoint Results

The secondary endpoint was the core-lab determined rate of moderate or greater PVR at 1 year. The primary analysis set for superiority testing of the secondary endpoint was the ITT analysis set. The secondary endpoint was met because in the ITT analysis set the rate of core-lab determined moderate or greater PVR for the Lotus group (0.9%) was superior to the rate for the CoreValve group (6.9%, *P* <0.0001).

Table 13: Superiority Testing for the Secondary Endpoint

Analysis Set	Lotus	CoreValve	Difference [95%CI]	*P* value [a]
Intent-to-Treat (N=912)	(N=607)	(N=305)	-6.1% [-9.6%, -2.6%]	<0.0001
	0.9% (4/452)	6.9% (15/216)		
Implanted (N=874)	(N=577)	(N=297)	-6.0% [-9.5%, -2.5%]	<0.0001
	0.9% (4/443)	6.9% (15/216)		
Rates are presented as % (count/sample size). a: *P* value is from the Chi-square test for the superiority testing.				

4. Other Results

Table 14 below shows the procedural characteristics for Lotus implant procedures compared to CoreValve procedures.

Measure	Lotus (N=607)	CoreValve (N=305)
Time from randomization to procedure (days)	13.0 ± 17.7 (596)	13.0 ± 12.6 (301)

Total procedure time (min)	86.8 ± 41.8 (596)	76.7 ± 40.6 (299)
Total time with study introducer (min)	50.4 ± 24.1 (595)	44.9 ± 36.9 (297)
Total time with study valve delivery system (min)	23.8 ± 17.6 (595)	15.0 ± 17.0 (298)
Total fluoroscopy time (min)	27.1 ± 10.8 (595)	22.2 ± 12.2 (299)
Total contrast used for procedure (cc)	110.6 ± 62.3 (593)	120.9 ± 64.6 (299)
Post-dilatation	1.5% (9/596)	31.2% (94/301)
TEE used during implant procedure	59.2% (353/596)	55.7% (167/300)
Successful vascular access, delivery and deployment of the study valve system, and successful retrieval of the delivery system	97.8% (583/596)	99.0% (297/300)
Conversion to open heart surgery	0.7% (4/596)	0.7% (2/300)
Unplanned use of cardiopulmonary bypass	0.7% (4/596)	1.0% (3/300)
Values are presented as mean ± standard deviation (n) or % (count/sample size) Abbreviation: TEE = Transesophageal Echocardiography		

5. Subgroup Analyses

Mortality and stroke rates were also evaluated based on gender. A total of 449 male patients (49.2%) were enrolled in the ITT analysis set; 303 were randomized to Lotus and 146 were randomized to CoreValve. There were 463 female patients (50.8%) in the ITT analysis set; 304 were in the Lotus arm and 159 were in the CoreValve arm. Table 15 shows mortality and stroke rates in male and female patients at 1 year. The outcomes suggest that the rates of mortality and stroke are similar between male and female patients; however, the study is not powered to drawn conclusions from this analysis.

Table 15: Mortality and Stroke to 1 Year by Gender; ITT Analysis Set

Outcome	Male Patients		Female Patients	
	Lotus (N=303)	CoreValve (N=146)	Lotus (N=304)	CoreValve (N=159)
All-cause mortality	11.5% (34/295)	14.8% (21/142)	12.3% (36/292)	12.3% (19/155)
Cardiovascular	8.1% (24/295)	12.0% (17/142)	7.2% (21/292)	7.7% (12/155)
Non-cardiovascular	3.4% (10/295)	2.8% (4/142)	5.1% (15/292)	4.5% (7/155)
Stroke	6.1% (18/295)	9.2% (13/142)	7.9% (23/292)	9.7% (15/155)
Disabling	2.7% (8/295)	7.7% (11/142)	4.5% (13/292)	6.5% (10/155)
Non-disabling	3.4% (10/295)	1.4% (2/142)	3.8% (11/292)	3.2% (5/155)
All-cause mortality or disabling stroke	12.9% (38/295)	18.3% (26/142)	13.7% (40/292)	17.4% (27/155)
Values are % (count/sample size)				

6. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 550 investigators of which none were full-time or part-time employees of the sponsor and 5 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: 0
- Significant payment of other sorts: 4
- 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. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

REPRISE NG DS (Cohort C) and REPRISE Edge Studies

The LOTUS Edge Valve System is a design iteration of the Lotus™ Valve System which was modified to improve flexibility and deliverability, to reduce the profile of the delivery system, and to minimize how deep the valve frame travels into the left ventricular outflow tract with the Depth Guard™ technology. The valve component is largely unmodified with the exception of additional radiopaque tantalum markers to aid in visualization of the locking procedure under fluoroscopy. The REPRISE NG DS (Cohort C) and REPRISE Edge studies evaluated the LOTUS Edge Valve System to confirm its acute performance and safety for TAVR in symptomatic subjects with severe calcific aortic valve stenosis who were at high risk for surgical aortic valve replacement (SAVR). Both studies have the same overall study design (prospective, single-arm, observational study), inclusion and exclusion criteria and assessments, and both studies use the same CEC and core laboratories (echocardiography, angiography and computed tomography/X-ray).

There were 21 subjects enrolled in REPRISE NG DS Cohort C at 2 centers in Australia and 15 subjects enrolled in REPRISE EDGE at 3 European centers to evaluate the same LOTUS Edge design. Table 16 and Table 17 show the pooled primary safety and effectiveness composite results and their components (defined similarly as in REPRISE III RCT) from both studies (N=36).

Table 16. Pooled 30-Day Primary Safety Results from REPRISE NG DS (Cohort C) and REPRISE Edge, ITT Analysis Set

Outcome	30 Days
	REPRISE NGDS (Cohort C) and REPRISE Edge (N=36)
Primary Safety Composite	22.2% (8/36)
All-cause mortality	0.0% (0/36)
All Stroke	5.6% (2/36)
Disabling	5.6% (2/36)
Life-threatening or Disabling bleeding	5.6% (2/36)
Major bleeding	13.9% (5/36)
Major vascular Complications	13.9% (5/36)
Acute kidney injury	0.0% (0/36)

Table 17. Pooled 1-Year Primary Effectiveness Results from REPRISE NG DS (Cohort C) and REPRISE Edge, ITT Analysis Set

Outcome	1 Year
	REPRISE NGDS (Cohort C) and REPRISE Edge (N=36)
Primary Effectiveness Composite	5.7% (2/35)
All-cause mortality	0.0% (0/36)
Disabling stroke	5.6% (2/36)
Moderate or greater PVR	0.0% (0/34)

REPRISE III LOTUS Edge Nested-Registry Study

Following a voluntary field corrective safety action, additional design modifications were made to the LOTUS Edge Valve System to improve deliverability and deployment. This modified version of the device was studied in the REPRISE III LOTUS Edge Nested Registry. The REPRISE III LOTUS Edge Nested Registry is a prospective, single-arm, multicenter, observational study designed to evaluate the safety and early performance of the LOTUS Edge Valve System with the modified LOTUS Edge delivery system. Inclusion criteria and patient eligibility requirements were the same as for the Lotus randomized controlled trial (RCT). A total of 50 subjects were enrolled at 4 centers in the US and Australia. Table 18 shows LOTUS Edge Nested Registry clinical outcomes at 30 days for the components of the RCT primary composite safety endpoint.

Table 18. 30-Day Primary Safety Composite and Components of REPRISE III LOTUS Edge Nested Registry, ITT Analysis Set

Outcome	30 Days
	REPRISE III LOTUS Edge Nested Registry (N=50)
Primary Safety Composite	14.3% (7/49)
All-cause mortality	0.0% (0/49)
Stroke	4.1% (2/49)
Disabling	2.0% (1/49)
Life-threatening or disabling bleeding	4.1% (2/49)
Major bleeding	6.1% (3/49)
Major vascular complications	6.1% (3/49)
Acute kidney injury	4.1% (2/49)

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

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory Systems Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The observed composite event rate of all-cause mortality, disabling stroke, and moderate or greater PVR at 1 year (i.e. the primary effectiveness endpoint) was 15.4% in the Lotus arm and 25.5% in the control arm. The one-sided upper 97.5% confidence bound on the difference between treatment groups (Lotus minus CoreValve; -4.41%) was less than the non-inferiority margin of 9.5% (P<0.0001). Thus, the clinical study met the primary effectiveness endpoint.

In addition, subjects receiving either the Lotus or control valve overall demonstrated clinically significant improvement in valve hemodynamics from baseline to 1 year. On average, the EOA increased from 0.7 cm^2 to 1.49 cm^2 and the mean pressure gradient decreased from 44.6 mmHg to 12.3 mmHg in patients who received the Lotus Valve. The Lotus Valve System demonstrated clinically significant reduction in PVR compared to the control. At 1 year, 87.6% of evaluable patients in the Lotus cohort had none or trace PVR compared to 51.0% in the CoreValve cohort. Furthermore, the core-lab determined rate of moderate or greater PVR at 1 year was 0.9% in the Lotus group compared to 6.9% in the CoreValve group. Statistical analysis of this endpoint demonstrated that Lotus is superior to CoreValve with respect to PVR reduction.

The improvement in hemodynamics was further demonstrated through improvements in NYHA Classification and quality of life evaluations. About 9% and 10% of patients were in NYHA Class III or IV at 30 days and 1 year, respectively, as compared to 71% at baseline. The mean Kansas City Cardiomyopathy Questionnaire (KCCQ) Clinical Summary Score increased from 51.9 at baseline to 74.9 at 1 year. The mean SF-12 physical summary score improved from 31.9 at baseline to 36.9 at 1 year.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and animal studies as well as data collected in clinical studies conducted to support PMA approval as described above. The results from the nonclinical laboratory (e.g., biocompatibility, hydrodynamic performance, durability, and structural integrity) and animal studies demonstrated that this device is suitable for long-term implant.

The observed composite event rate of all-cause mortality, stroke, life-threatening and major bleeding events, stage 2 or 3 acute kidney injury, or major vascular complications at 30 days (i.e. the primary safety endpoint) was 20.3% in the Lotus arm and 17.2% in the control arm. The one-sided upper 97.5% confidence bound on the difference between treatment groups was less than the non-inferiority margin of 10.5% with a *P* value <0.025 (*P*=0.0027). Thus, the clinical study met the primary safety endpoint. The differences in the observed rate of individual components of the composite at 30 days for the Lotus arm compared to the control were as follows: all-cause mortality (0.2%), stroke (0.5%), disabling stroke (-1.3%), life-threatening and major bleeding events (3.0%) , stage 2 or 3 acute kidney injury (-1.1%), or major vascular complications (1.7%).

Notably, the rate of new pacemaker implantation at 30-days and 1-year was clinically higher (approximately double) for the Lotus device (29.1% at 30-days, 34.2% at 1-year) compared to the control (15.8% at 30-days, 18.5% at 1-year).

The confirmatory studies to evaluate design modifications to the LOTUS Edge device demonstrated similar observed composite event rates to the Lotus arm of the RCT, suggesting that the design modifications did not adversely impact device safety or early performance. The observed composite rate and rates of individual components of the composite at 30 days for the LOTUS Edge nested registry study, which represents the final device design, were as follows: composite (14.3%), all-cause mortality (0.0%), stroke (4.1%), disabling stroke (2.0%), life-threatening and major bleeding events (4.1%) , stage 2 or 3 acute kidney injury (4.1%), or major vascular complications (6.1%).

C. Benefit-Risk Determination

The probable benefits of the device are also based on data collected in clinical studies conducted to support PMA approval as described above. The probable benefits

include improved valve hemodynamic performance with little to no PVR, improved functional status as measured by NYHA classification, and improved quality of life at 1 year as measured by the KCCQ and SF-12 clinical surveys, as compared to baseline.

The probable risks of the device are also based on data collected in clinical studies conducted to support PMA approval as described above. The probable risks include device and procedure-related complications such as death, stroke, myocardial infarction, life-threatening and major bleeding events, stage 2 or 3 acute kidney injury, major vascular complications, and need for a new permanent pacemaker implant.

Considering the overall benefit/risk profile of TAVR with the LOTUS Edge Valve System versus CoreValve in patients with high operative risk and above, the meaningful differences included clinically and statistically lower rates of the composite of all-cause death, disabling stroke, and moderate or greater PVR after 1 year, but a clinically higher rate of conduction disturbance requiring permanent pacemaker implantation in the Lotus patients than in the CoreValve patients. The potential risk of higher rate of pacemaker implantation is offset by the potential benefits of lower rate of PVR as well as lower rate of valve-related reintervention demonstrated for the Lotus device.

1. Patient Perspectives

   This submission did not include specific information on patient perspectives for this device.

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

D. Overall Conclusions

The preclinical and clinical studies submitted in this application provide reasonable assurance that the LOTUS Edge Valve System is safe and effective for the replacement of native aortic valves in patients with symptomatic severe aortic stenosis who are deemed to be at high or extreme surgical risk, defined as predicted risk of surgical mortality ≥ 8% at 30 days based on the Society of Thoracic Surgeons (STS) risk score and other clinical comorbidities unmeasured by the STS risk calculator.

XIV. CDRH DECISION

CDRH issued an approval order on April 23, 2019. The final conditions of approval cited in the approval order are described below.

The applicant must conduct one post-approval study (PAS) and participate in and support one surveillance study as follows:

1. ***Continued Follow-Up of the* REPRISE III Trial *Premarket Cohorts***: This study should be conducted in accordance with protocol version AK dated October 6, 2017. The study will consist of all living subjects who were enrolled in the REPRISE III randomized, roll-in, continued access, and nested registry cohorts under the IDE. Subject follow-up will continue for all cohorts based on the timelines and assessments stipulated in the IDE protocol.

   The objective of this PAS is to characterize the clinical outcomes annually through 5 years post-procedure. Data will be collected per the study protocol, including, but not limited to, the following key safety and effectiveness endpoints: all-cause mortality, all-cause and disabling stroke, life-threatening and major bleeding events, stage 2 or 3 acute kidney injury, major vascular complications, paravalvular aortic regurgitation, valve performance and durability, myocardial infarction, re-operation for valve-related dysfunction, rehospitalization for valve-related symptoms or worsening congestive heart failure, new permanent pacemaker implantation, new-onset atrial fibrillation, functional status as evaluated by New York Heart Association (NYHA) Class 5-meter gait speed test at 1 year, and health status as evaluated by Kansas City Cardiomyopathy Questionnaire (KCCQ) and SF-12 Quality of Life questionnaire at 1, 3, and 5 years.

2. ***Registry-Based Real-World Use Surveillance of the LOTUS Edge Valve System for the "High Risk and above" Indication***: The applicant has agreed to work with the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy (TVT) Registry to ensure that FDA surveillance occurs for the LOTUS Edge Valve System used for the "high risk and above" indication over the next 2 years (enrollment period). The applicant has also agreed to link the data to Centers for Medicare and Medicaid Services (CMS) database for long-term surveillance of these patients through 5 years post implantation (follow-up period). This surveillance will monitor the following: (1) device success (intra-procedure); (2) all-cause mortality, all stroke, life-threatening/major bleeding, new requirement for dialysis, peri-procedural myocardial infarction, and repeat procedure for valve-related dysfunction (surgical or interventional therapy) at 30 days and 12 months; (3) neurological (non-stroke), vascular complications, and quality of life (KCCQ) outcomes at 30 days and 12 months; and (4) all-cause mortality, all stroke, and repeat procedure for valve-related dysfunction (surgical or interventional therapy) at 2-5 year post implantation.

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

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

XVI. REFERENCES

[1] Kappetein AP, Head SJ, Genereux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. J Am Coll Cardiol 2012;60:1438-54.

[2] 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. J Am Coll Cardiol 2011;57:253-69.