LOTUS Edge™ Valve System
Transcatheater Aortic Valve Prosthesis
Premounted on Delivery System

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1.0 WARNING

Caution: Federal Law (USA) restricts this device to sale by or
on the order of a physician.

1.0 WARNING

Contents supplied STERILE using a Radiation process. The
valve portion of the device is sterilized using a chemical
solution. Do not use if USB Single Use Logger is not flashing
GREEN every 4 seconds in the ACTIVE display window. Do
not use if sterile barrier is damaged or the sterilization bottle
has been compromised. If damage is found, call your Boston
Scientific representative.

For single use only. Do not reuse, reprocess or resterilize.
Reuse, reprocessing or resterilization may compromise the
structural integrity of the device and/or lead to device
failure which, in turn, may result in patient injury, illness or
death. Reuse, reprocessing or resterilization may also create
a risk of contamination of the device and/or cause patient
infection or cross-infection, including, but not limited to,
the transmission of infectious disease(s) from one patient to
another. Contamination of the device may lead to injury, illness
or death of the patient.

After use, dispose of product and packaging in accordance
with hospital, administrative and/or local government policy.

2.0 DEVICE DESCRIPTION

The LOTUS Edge Valve System consists of a frame-mounted
bioprosthetic aortic valve, and a delivery system for introduction
and delivery of the valve implant.

The valve is intended as a permanently implanted device while
the delivery system is a single use device. The LOTUS Edge
Valve System is designed for retrograde delivery over a 0.035 in.
(0.89 mm) super/extra stiff guidewire.

The valve consists of glutaraldehyde-fixed (or cross linked)
non-viable bovine pericardial tissue valve leaflets, a polycarbonate-
based urethane outer seal designed to minimize paravalvular
regurgitation and a braided nitinol frame with locking mechanisms
for in-vivo stabilization of the valve. The braided structure is
designed to shorten axially and expand radially during delivery,
and is then locked in this position. The locking components have
tantalum (radiopaque) markers to aid in visualization of the locking
procedure under fluoroscopy.

The delivery system consists of the controller and the catheter.
The controller has two controls which are used to deploy the
valve: the control knob and the release ring. The control knob is
the sheathing/locking control at the proximal end of the controller
and is the principle control used to deploy the valve. The second
control, the release ring, detaches the deployed valve after the
operator is satisfied with the placement of the implant. The
controller also incorporates a safety cover which prevents
inadvertent operation of the release ring.

The valve is pre-mounted onto the delivery system. A
sterilization bottle filled with glutaraldehyde houses the valve
and the distal end of the delivery system.

A stylet is supplied with the LOTUS Edge Valve System for use
during device preparation. The LOTUS Edge Valve System is
available in sizes listed in Table I.

The LOTUS Edge Valve System can be used via a transfemoral
or transaortic access approach.

The valve is intended to be implanted in a native annulus size
range comparable to the diagnostic imaging measurements
outlined in Table I.
2. User Information

The LOTUS Edge Valve System should only be used by physicians who have undergone training on the implantation of this device. Patient treatment should be determined in consultation with the Heart Team.

3. INTENDED USE/INDICATIONS FOR USE

Non-viable bovine pericardial tissue valve leaflets

4. CONTRAINDICATIONS

Non-calcified aortic annulus.

5. WARNINGS

Valve implantation should only be performed in a facility where emergency aortic valve surgery is available.

6. PRECAUTIONS

Do not attempt to place the valve if patient’s annulus is outside of the dimensions specified in Table I. Patient prosthesis mismatch, valve migration or embolization may lead to severe patient compromise, additional procedures or death.

7. POTENTIAL ADVERSE EVENTS

Adverse events (in alphabetical order) potentially associated with transcatheter aortic valve implantation (including standard cardiac catheterization, BAV and the use of anesthesia) as well as additional risks related to the use of the LOTUS Edge Valve System are listed below.

Table I: LOTUS Edge™ Valve System Dimensional Information

<table>
<thead>
<tr>
<th>Valve Size</th>
<th>Frame Height</th>
<th>Outer Diameter</th>
<th>Nominal Length</th>
<th>Diameter</th>
<th>With iSLEEVE™ Introducer Set</th>
<th>With Lotus™ Introducer Set</th>
<th>Access Site to Basal Plane Distance</th>
</tr>
</thead>
<tbody>
<tr>
<td>23 mm</td>
<td>19 mm</td>
<td>7.2 mm</td>
<td>114 cm</td>
<td>≥ 20 mm &amp; ≤ 23 mm</td>
<td>≥ 5.9 mm</td>
<td>≥ 6.5 mm</td>
<td>≥ 6.0 cm</td>
</tr>
<tr>
<td>25 mm</td>
<td></td>
<td>7.4 mm</td>
<td>115 cm</td>
<td>≥ 23 mm &amp; ≤ 25 mm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>27 mm</td>
<td></td>
<td></td>
<td></td>
<td>≥ 25 mm &amp; ≤ 27 mm</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Available imaging modalities provide important information on the anatomy of the aortic valve complex and should be used in a complementary fashion to select proper valve size. Valve sizing may vary slightly from the above chart based on such information.

6.2 Implantation Precautions

- Perform balloon aortic valvuloplasty (BAV) with an appropriately sized balloon prior to delivery of the valve to the aortic annulus at the discretion of the implanting physician.
- Partial resheathing (and subsequent unsheathing) can be performed an unlimited number of times during any phase of the procedure prior to valve release. Valve may be completely resheathed (past the post markers) once during the procedure at any phase prior to valve delivery system as it may adversely impact valve hemodynamic performance and/or result in vascular or myocardial trauma.

6.2.1 For Transaortic Access

- Throughout the procedure, ensure the introducer sheath remains 1 cm to 2 cm below the aortotomy site.
- If repositioning is required, ensure the catheter tip remains distal to the introducer sheath tip.

6.3 Post-Implantation Precautions

- Use caution when removing the delivery system. Seat the nosecone in the catheter tip prior to withdrawal through the introducer sheath.

7.0 Adverse Events

- 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)
- Angina
- Arrhythmia or new conduction system injury (including need for pacemaker insertion)
- Bleeding or hemmorhage (possibly requiring transfusion or additional procedure)
- 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 neurologic deficits (including encephalopathy)
- Pain
- Pericardial effusion or tamponade
- Peripheral ischemia or infarction
- Permanent disability
- Pleural effusion
- Pulmonary edema
- Renal insufficiency or failure
8.0 MAGNETIC RESONANCE IMAGING (MRI) SAFETY INFORMATION

Non-clinical testing has demonstrated that the LOTUS Edge™ Valve is MRI Conditional. A patient with this device can be safely scanned in an MRI system meeting the following conditions:

- Static magnetic field of 1.5 or 3.0 Tesla
- Maximum spatial field gradient of 9,900 gauss/cm (99 T/m) or less
- Maximum MR system reported, whole body averaged specific absorption rate (SAR) of 2 W/kg (Normal Operating Mode)

Under the scan conditions defined above, the LOTUS Edge Valve is expected to produce a maximum temperature rise of 1.5°C after 15 minutes of continuous scanning. In non-clinical testing, the image artifact caused by the device extends as far as 10.4 mm from the LOTUS Edge Valve frame when imaged with a gradient echo pulse sequence and a 3 Tesla MR System.

10.2 Package Removal

4. To remove the Tray Lid from the Tray base, hold the base at the locations marked “HOLD” and separate the Tray lid by lifting from the locations marked “LIFT”.

5. Remove the stilette and place it in the second rinse bowl.

10.3 Device Preparation

2. Drain glutaraldehyde from sterilization bottle into a waste container.

3. Remove all three luer caps (distal, proximal and guidewire).

5. Remove the stylet and place it in the second rinse bowl.

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11.0 CLINICAL STUDIES
11.1 REPRISE III Randomized Controlled Trial (RCT)
Primary Objective: The primary objective of the REPRISE III RCT was to evaluate the safety and effectiveness of the Lotus™ Valve System for transcatheter aortic valve replacement (TAVR) in symptomatic patients with calcific, severe native aortic stenosis who are considered at extreme or high risk for surgical valve replacement. The Lotus Valve System studied in the REPRISE III RCT is the early iteration of the Lotus Edge™ Valve System. The LOTUS Edge Valve System represents a modification to the Lotus Valve System to improve flexibility and deliverability, to reduce the profile of the delivery system. Additionally, Depth Guard™ Technology was incorporated to minimize the depth the frame travels into the left ventricular outflow tract. While the delivery system was modified to make LOTUS Edge more flexible than its predecessor, the valve component is essentially the same as that of the Lotus Valve System with additional radiopaque tantalum markers on the valve and post components of the locking mechanism to aid visualization of the locking procedure under fluoroscopy.

Design: The REPRISE III clinical study is a prospective, multicenter, randomized (2:1), controlled trial designed to evaluate the safety and effectiveness of the Lotus Valve System for transcatheter aortic valve replacement in symptomatic patients with calcific, severe native aortic stenosis.

Patients had documented calcified severe native aortic stenosis with an initial aortic valve area (AVA) of ≤ 1.0 cm² [or AVA index of ≤ 0.6 cm²/m²] and a mean pressure gradient ≥ 40 mmHg or a jet velocity ≥ 4 m/s, were NYHA Functional Class ≥ II, and were determined by a heart team to be at high or extreme risk for surgery (predicted operability mortality or serious, irreversible morbidity risk ≥ 10% or ≥ 50%, respectively). Based on pre-procedure diagnostic imaging, patients had a documented aortic annulus size of ≤ 20 mm and ≤ 27 mm.

Patients were randomized 2:1 to the Lotus Valve System (23 mm, 25 mm, and 27 mm valve sizes) or a commercially available CoreValve® Valve (28 mm, 29 mm, and 31 mm valve sizes). A center was allowed to use CoreValve® Evolut® R Valve System with the aforementioned size matrix if the center no longer had access to CoreValve Valve.

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 effectiveness endpoint was the composite of all-cause mortality, disabling stroke, and moderate or greater paravalvular regurgitation (PVR, based on independent core lab assessment) at 1 year. The secondary endpoint was the core-lab determined rate of moderate or greater PVR at 1 year.

A total of 912 patients (607 Lotus, 305 CoreValve) were randomized and enrolled at 55 sites in Australia, Canada, Europe and the United States. Follow-up includes clinical assessments 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. The study is now considered complete with regard to the primary endpoint.

The following data summarize the results from the REPRISE III RCT.

11.1.1 Demographics
Table III presents demographics and baseline clinical characteristics for the Intention-to-Treat (ITT) analysis set. The two cohorts were well-balanced. Overall, mean age was around 80 years and about half of the patients were female. The proportion of patients considered at extreme surgical risk was similar between the 2 groups.

Table III: Demographics and Baseline Clinical Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Lotus™ (N=607)</th>
<th>CoreValve™ (N=305)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at time of consent (years)</td>
<td>82.8 ± 7.1 (607)</td>
<td>82.9 ± 7.6 (305)</td>
</tr>
<tr>
<td>Female</td>
<td>50.0% (304/607)</td>
<td>52.1% (159/305)</td>
</tr>
<tr>
<td>Overall Risk Assessments</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extreme risk</td>
<td>23.1% (140/607)</td>
<td>21.6% (66/305)</td>
</tr>
<tr>
<td>High risk</td>
<td>76.9% (467/607)</td>
<td>78.4% (228/305)</td>
</tr>
<tr>
<td>EuroSCORE II 2011%</td>
<td>6.4 ± 5.5 (605)</td>
<td>6.4 ± 5.5 (304)</td>
</tr>
<tr>
<td>STS Score (%)</td>
<td>6.7 ± 4.0 (607)</td>
<td>6.9 ± 4.1 (305)</td>
</tr>
<tr>
<td>STS Score &gt; 8</td>
<td>31.0% (188/607)</td>
<td>29.5% (90/305)</td>
</tr>
<tr>
<td>STS Score &lt; 8</td>
<td>69.0% (419/607)</td>
<td>70.5% (215/305)</td>
</tr>
<tr>
<td>Porcelain aorta</td>
<td>4.5% (19/419)</td>
<td>3.3% (7/215)</td>
</tr>
<tr>
<td>Severe pulmonary hypertension</td>
<td>8.1% (34/419)</td>
<td>8.4% (18/215)</td>
</tr>
<tr>
<td>Orthopedic disease</td>
<td>18.6% (78/419)</td>
<td>12.6% (27/215)</td>
</tr>
<tr>
<td>Neuromuscular disease</td>
<td>1.4% (6/419)</td>
<td>2.3% (5/215)</td>
</tr>
<tr>
<td>Prior chest radiation therapy</td>
<td>4.1% (17/419)</td>
<td>3.7% (6/215)</td>
</tr>
<tr>
<td>Hostile chest</td>
<td>4.1% (17/419)</td>
<td>4.7% (10/215)</td>
</tr>
<tr>
<td>Severe lung disease</td>
<td>15.3% (64/419)</td>
<td>14.0% (30/215)</td>
</tr>
<tr>
<td>CAGB at risk with re-operation</td>
<td>16.0% (67/419)</td>
<td>20.0% (43/215)</td>
</tr>
<tr>
<td>Childs Class A or B liver disease</td>
<td>1.7% (7/419)</td>
<td>1.9% (4/215)</td>
</tr>
<tr>
<td>Frailty</td>
<td>72.6% (304/419)</td>
<td>70.7% (152/215)</td>
</tr>
<tr>
<td>Age &gt; 90 years</td>
<td>10.0% (42/419)</td>
<td>12.6% (27/215)</td>
</tr>
<tr>
<td>Other</td>
<td>4.1% (17/419)</td>
<td>7.0% (15/215)</td>
</tr>
<tr>
<td>General Medical History</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus (medically treated)</td>
<td>30.3% (187/607)</td>
<td>32.6% (99/304)</td>
</tr>
<tr>
<td>History of hyperlipidemia (medically treated)</td>
<td>74.6% (452/607)</td>
<td>75.7% (238/304)</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>91.8% (557/607)</td>
<td>93.6% (286/305)</td>
</tr>
<tr>
<td>History of peripheral vascular disease</td>
<td>31.1% (187/607)</td>
<td>25.7% (78/304)</td>
</tr>
<tr>
<td>History of dialysis dependent renal failure</td>
<td>0.2% (1/607)</td>
<td>1.3% (4/305)</td>
</tr>
<tr>
<td>COPD - Supplemental oxygen dependent</td>
<td>6.5% (39/599)</td>
<td>6.3% (19/303)</td>
</tr>
<tr>
<td>Cardiac History</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of coronary artery disease</td>
<td>71.5% (433/606)</td>
<td>73.4% (224/305)</td>
</tr>
<tr>
<td>History of myocardial infarction</td>
<td>18.3% (109/597)</td>
<td>19.0% (58/305)</td>
</tr>
<tr>
<td>History of congestive heart failure</td>
<td>77.0% (463/601)</td>
<td>79.8% (241/302)</td>
</tr>
<tr>
<td>History of percutaneous coronary intervention</td>
<td>33.1% (201/607)</td>
<td>32.5% (99/305)</td>
</tr>
<tr>
<td>History of coronary artery bypass graft surgery</td>
<td>23.6% (142/608)</td>
<td>23.3% (71/305)</td>
</tr>
</tbody>
</table>
Results were similar for the ITT analysis set. The difference between treatment groups was less than the non-inferiority margin of 10.5% with a one-sided upper 97.5% confidence bound on the rate for the Lotus group (25.5%). Non-inferiority was concluded because the one-sided upper 97.5% confidence bound on the difference between treatment groups was not different between the 2 treatment groups to 1 year.

### 11.1.2 Procedural Characteristics

Procedural characteristics are shown in Table IV.

### 11.1.3 Study Results

#### 11.1.3.1 (i) Primary Safety and Effectiveness Endpoints

**Primary Safety Endpoint**

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, and major vascular complications was not different between the 2 treatment groups to 1 year.

### Table III: Demographics and Baseline Clinical Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Lotus™ (N=607)</th>
<th>CoreValve® (N=305)</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of atrial fibrillation</td>
<td>35.1% (213/606)</td>
<td>31.6% (190/604)</td>
</tr>
<tr>
<td>History of atrial flutter</td>
<td>4.9% (26/594)</td>
<td>6.7% (20/300)</td>
</tr>
<tr>
<td>Prior pacemaker implant</td>
<td>17.8% (108/607)</td>
<td>19.0% (59/305)</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class I</td>
<td>0.0% (0/607)</td>
<td>0.0% (0/305)</td>
</tr>
<tr>
<td>Class II</td>
<td>28.7% (174/607)</td>
<td>32.1% (98/305)</td>
</tr>
<tr>
<td>Class III</td>
<td>63.6% (386/607)</td>
<td>61.0% (186/305)</td>
</tr>
<tr>
<td>Class IV</td>
<td>7.7% (47/607)</td>
<td>6.9% (21/305)</td>
</tr>
</tbody>
</table>

**Neurological History**

- History of transient ischemic attack: 8.3% (50/601) vs. 7.9% (24/303)

**Cognitive and Daily Living Assessments**

- Mini-cognitive assessment for dementia score: 3.6 ± 1.4 (599) vs. 3.7 ± 1.4 (304)
- Katz Index Activities of Daily Living score: 5.6 ± 0.9 (605) vs. 5.6 ± 1.0 (305)

**Strength and Balance Assessments**

- Use of wheelchair: 5.8% (35/606) vs. 4.9% (15/305)
- Gait speed average to walk 5 meters (seconds): 8.7 ± 5.2 (565) vs. 8.7 ± 4.2 (285)
- Falls in the past 6 months: 0.4 ± 1.1 (604) vs. 0.5 ± 1.8 (304)
- Maximal grip strength average (kg): 21.1 ± 10.1 (605) vs. 20.4 ± 9.7 (305)

**Echocardiographic Findings**

- Aortic valve area (cm²): 0.69 ± 0.19 (541) vs. 0.70 ± 0.19 (280)
- Mean aortic valve gradient (mmHg): 44.6 ± 13.35 (575) vs. 43.8 ± 12.31 (294)
- Doppler velocity index: 0.22 ± 0.05 (553) vs. 0.23 ± 0.05 (292)

Values are presented as mean ± standard deviation (n) or % (count/sample size).

**Table IV: Procedural Characteristics**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Lotus (N=607)</th>
<th>CoreValve (N=305)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time from randomization to procedure (days)</td>
<td>13.0 ± 12.6 (596)</td>
<td>13.0 ± 12.6 (301)</td>
</tr>
<tr>
<td>Total procedure time (min)</td>
<td>86.8 ± 40.0 (596)</td>
<td>86.8 ± 40.0 (299)</td>
</tr>
<tr>
<td>Total time with study introducer (min)</td>
<td>50.4 ± 24.1 (596)</td>
<td>49.3 ± 24.1 (297)</td>
</tr>
<tr>
<td>Total time with study valve delivery system (min)</td>
<td>23.8 ± 17.6 (596)</td>
<td>15.0 ± 17.6 (298)</td>
</tr>
<tr>
<td>Total fluoroscopy time (min)</td>
<td>27.1 ± 12.2 (596)</td>
<td>21.0 ± 12.2 (299)</td>
</tr>
<tr>
<td>Total contrast used for procedure (cc)</td>
<td>110.6 ± 64.6 (593)</td>
<td>120.9 ± 64.6 (299)</td>
</tr>
<tr>
<td>Post-dilatation</td>
<td>1.5% (9/596)</td>
<td>31.2% (94/301)</td>
</tr>
<tr>
<td>TEE used during implant procedure</td>
<td>93.8% (535/596)</td>
<td>55.7% (167/300)</td>
</tr>
<tr>
<td>Successful vascular access, delivery and deployment of the study valve system, and successful retrieval of the delivery system</td>
<td>97.8% (563/596)</td>
<td>99.0% (297/300)</td>
</tr>
<tr>
<td>Conversion to open heart surgery</td>
<td>0.7% (4/596)</td>
<td>0.7% (2/300)</td>
</tr>
<tr>
<td>Unplanned use of cardiopulmonary bypass</td>
<td>0.7% (4/596)</td>
<td>1.0% (3/300)</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation (n) or % (count/sample size).

**Table V: Non-Inferiority Testing for the Primary Safety Endpoint**

<table>
<thead>
<tr>
<th>Analysis Set</th>
<th>Outcome</th>
<th>One-sided 97.5% UCB</th>
<th>Non-inferiority Margin</th>
<th>One-sided P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implanted</td>
<td>All-cause mortality</td>
<td>2.3% (7/303)</td>
<td>2.5% (15/601)</td>
<td>0.0015</td>
</tr>
<tr>
<td></td>
<td>Stroke</td>
<td>4.3% (13/303)</td>
<td>4.8% (29/601)</td>
<td>0.0003</td>
</tr>
<tr>
<td></td>
<td>Disabling</td>
<td>3.3% (10/303)</td>
<td>2.0% (12/601)</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td>Life-threatening or disabling bleeding</td>
<td>9.0% (5/50)</td>
<td>8.0% (4/49)</td>
<td>0.013</td>
</tr>
<tr>
<td></td>
<td>Major bleeding</td>
<td>5.9% (18/303)</td>
<td>4.8% (26/50)</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td>Major vascular complications</td>
<td>5.3% (16/303)</td>
<td>7.0% (4/62)</td>
<td>0.0003</td>
</tr>
<tr>
<td></td>
<td>Acute kidney injury</td>
<td>3.6% (11/303)</td>
<td>2.5% (5/15)</td>
<td>0.0004</td>
</tr>
</tbody>
</table>

Values are presented as % (count/sample size).

**Table VI: Components of the 30-Day Primary Safety Endpoint**

**Outcome**

- All-cause mortality: 2.5% (15/601) vs. 2.3% (7/303)
- Stroke: 4.3% (13/303) vs. 4.8% (29/601)
- Disabling: 3.3% (10/303) vs. 2.0% (12/601)
- Life-threatening or disabling bleeding: 9.0% (5/50) vs. 8.0% (4/49)
- Major bleeding: 5.9% (18/303) vs. 4.8% (26/50)
- Major vascular complications: 5.3% (16/303) vs. 7.0% (4/62)
- Acute kidney injury: 3.6% (11/303) vs. 2.5% (5/15)

**Primary Effectiveness Endpoint**

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 hypothesis of the primary effectiveness endpoint was that Lotus Valve is non-inferior to CoreValve Valve when tested using the implanted analysis set. The non-inferiority hypothesis for the primary effectiveness endpoint was met because in the implanted analysis set, the rate for the Lotus group (15.4%) was non-inferior to the rate for the CoreValve group (25.5%). Non-inferiority was concluded because the one-sided upper 97.5% confidence bound on the difference between treatment groups (Lotus minus CoreValve: -4.4%) was less than the non-inferiority margin of 9.5% with a P value < 0.0001. According to the pre-specified statistical analysis plan, a test for superiority of Lotus compared to CoreValve for the primary effectiveness endpoint was to be performed if the Lotus rate was below the CoreValve rate, non-inferiority was shown for the primary safety and primary effectiveness endpoints, and superiority was shown for the secondary endpoint. The primary analysis set for superiority testing of the primary effectiveness endpoint was the ITT analysis set. Lotus was found to be non-inferior and also superior to CoreValve for the primary effectiveness endpoint.

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

**Figure III:** Primary Safety Composite to 1 Year, Intent-To-Treat Analysis Set

Cumulative event rate ± 1.5 standard error

**Figure IV:** shows that the components of the 30-day primary safety endpoint were similar between the two treatment groups.

**Table VII:** shows the results of the non-inferiority and superiority testing for the primary effectiveness endpoint. Lotus was found to be non-inferior to CoreValve for the primary effectiveness endpoint.

**Table VIII:** shows that the components of the 30-day primary safety endpoint were similar between the two treatment groups.
Table VII: Non-Inferiority Testing and Superiority Testing for the Primary Effectiveness Endpoint

<table>
<thead>
<tr>
<th>Analysis Set</th>
<th>Lotus (N=607)</th>
<th>CoreValve (N=305)</th>
<th>Difference (95% CI)</th>
<th>P value *</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT (N=912)</td>
<td>(N=607)</td>
<td>(N=305)</td>
<td>-10.2% (-16.3%, -4.1%)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Implanted (N=874)</td>
<td>15.4% (130/856)</td>
<td>25.5% (66/259)</td>
<td>-10.1% (-12.6%, -3.9%)</td>
<td>0.0007</td>
</tr>
</tbody>
</table>

Rates are presented as % (count/sample size).

11.1.3 (iii) Additional Safety Data

Table VIII: Superiority Testing for the Secondary Endpoint

<table>
<thead>
<tr>
<th>Analysis Set</th>
<th>Lotus (N=607)</th>
<th>CoreValve (N=305)</th>
<th>Difference (95% CI)</th>
<th>P value *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intent-to-Treat (N=912)</td>
<td>6.9% (4/56)</td>
<td>6.9% (1/151)</td>
<td>-0.6% (-9.5%, -2.5%)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Implanted (N=874)</td>
<td>0.9% (7/661)</td>
<td>6.9% (15/226)</td>
<td>-6.0% (-9.6%, -2.6%)</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

Rates are presented as % (count/sample size).

11.1.3 (iii) Additional Safety Data

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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>莲花(N=607)</th>
<th>莲花(N=305)</th>
<th>莲花(N=607)</th>
<th>莲花(N=305)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>2.5% (15/601)</td>
<td>3.3% (7/303)</td>
<td>11.9% (70/587)</td>
<td>13.5% (40/297)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>2.3% (14/601)</td>
<td>3.3% (7/303)</td>
<td>7.7% (45/587)</td>
<td>9.8% (29/297)</td>
</tr>
<tr>
<td>Non-cardiovascular</td>
<td>0.2% (1/601)</td>
<td>0.0% (0/303)</td>
<td>4.3% (25/587)</td>
<td>3.7% (11/297)</td>
</tr>
<tr>
<td>Stroke</td>
<td>4.8% (29/601)</td>
<td>4.2% (13/303)</td>
<td>7.0% (41/587)</td>
<td>9.4% (26/297)</td>
</tr>
<tr>
<td>Disabling</td>
<td>2.0% (12/601)</td>
<td>3.2% (10/303)</td>
<td>3.6% (21/587)</td>
<td>7.1% (21/297)</td>
</tr>
<tr>
<td>Ischemic</td>
<td>1.8% (1/601)</td>
<td>3.2% (10/303)</td>
<td>2.8% (17/587)</td>
<td>6.4% (19/297)</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>0.2% (1/601)</td>
<td>0.0% (0/303)</td>
<td>0.7% (4/587)</td>
<td>0.3% (1/297)</td>
</tr>
<tr>
<td>Undetermined</td>
<td>0.0% (0/601)</td>
<td>0.0% (0/303)</td>
<td>0.2% (1/587)</td>
<td>0.3% (1/297)</td>
</tr>
<tr>
<td>Non-disabling</td>
<td>2.8% (17/601)</td>
<td>1.0% (3/303)</td>
<td>3.6% (21/587)</td>
<td>2.4% (7/297)</td>
</tr>
<tr>
<td>Ischemic</td>
<td>2.3% (14/601)</td>
<td>1.0% (3/303)</td>
<td>3.1% (18/587)</td>
<td>2.4% (7/297)</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>0.2% (1/601)</td>
<td>0.0% (0/303)</td>
<td>0.2% (1/587)</td>
<td>0.0% (0/297)</td>
</tr>
<tr>
<td>Undetermined</td>
<td>0.3% (3/601)</td>
<td>0.0% (0/303)</td>
<td>0.3% (2/587)</td>
<td>0.0% (0/297)</td>
</tr>
<tr>
<td>All-cause mortality or disabling</td>
<td>4.0% (14/601)</td>
<td>5.3% (16/303)</td>
<td>13.3% (78/587)</td>
<td>17.8% (10/297)</td>
</tr>
<tr>
<td>Cardiac death or disabling stroke</td>
<td>3.4% (23/601)</td>
<td>5.2% (16/303)</td>
<td>9.5% (86/587)</td>
<td>14.8% (44/297)</td>
</tr>
<tr>
<td>Major vascular complications</td>
<td>7.0% (42/601)</td>
<td>5.3% (16/303)</td>
<td>7.7% (45/587)</td>
<td>6.1% (18/297)</td>
</tr>
<tr>
<td>Access site-related</td>
<td>4.7% (28/601)</td>
<td>3.3% (10/303)</td>
<td>5.1% (30/587)</td>
<td>3.7% (11/297)</td>
</tr>
<tr>
<td>Not access site-related</td>
<td>2.5% (15/601)</td>
<td>2.6% (9/303)</td>
<td>2.7% (16/587)</td>
<td>2.4% (7/297)</td>
</tr>
<tr>
<td>New PPM-implanted</td>
<td>29.1% (175/601)</td>
<td>15.8% (48/303)</td>
<td>34.2% (210/587)</td>
<td>18.5% (10/297)</td>
</tr>
<tr>
<td>No prior PPM</td>
<td>25.5% (175/601)</td>
<td>19.8% (48/303)</td>
<td>41.4% (210/587)</td>
<td>23.0% (10/297)</td>
</tr>
<tr>
<td>Bleeding</td>
<td>12.8% (77/601)</td>
<td>10.9% (33/303)</td>
<td>18.1% (106/587)</td>
<td>17.8% (103/297)</td>
</tr>
<tr>
<td>Life-threatening or disabling</td>
<td>8.0% (48/601)</td>
<td>5.0% (15/303)</td>
<td>9.5% (58/587)</td>
<td>9.8% (23/297)</td>
</tr>
<tr>
<td>Major</td>
<td>4.8% (25/601)</td>
<td>5.9% (14/303)</td>
<td>8.3% (49/587)</td>
<td>8.4% (25/297)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.7% (4/601)</td>
<td>1.3% (4/303)</td>
<td>3.2% (19/587)</td>
<td>4.4% (13/297)</td>
</tr>
<tr>
<td>Pari-procedural MI</td>
<td>0.5% (3/601)</td>
<td>1.0% (3/303)</td>
<td>0.5% (2/587)</td>
<td>1.3% (4/297)</td>
</tr>
<tr>
<td>Spontaneous MI</td>
<td>0.2% (1/601)</td>
<td>0.3% (1/303)</td>
<td>2.7% (16/587)</td>
<td>3.4% (10/297)</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>2.5% (15/601)</td>
<td>3.6% (11/303)</td>
<td>2.6% (15/587)</td>
<td>3.7% (11/297)</td>
</tr>
</tbody>
</table>

Values are presented as % (count/sample size).

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

Time-to-event curves (Kaplan-Meier analysis) for year 1 to assess cause-specific 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). The combined outcome of all-cause death or disabling stroke to 1 year was 12.2% for Lotus compared to 17.9% for CoreValve. The estimated rate for disabling stroke to 1 year was 3.6% for Lotus compared to 7.3% for CoreValve.

Figure III: Kaplan-Meier Event Curve for 1 Year Post-Randomization, ITT Analysis Set

Cumulative event rate ± 1 standard error

[Image of Kaplan-Meier curve with error bars]

Boston Scientific, Master Brand DFU Template 8.2677in x 1.6929in A4, 92238519A) eDFU, MB, LOTUS Edge Valve System, EN, 50473081-01E

Black (K) AE v.0.0
At discharge, 87.4% 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 30 days, 88.1% of evaluable patients in the Lotus group had no or trace PVR compared to 51.0% in the CoreValve cohort. There was no severe PVR in either cohort.

Figure VII: Paravalvular Regurgitation over Time, ITT Analysis Set

NYHA functional status of patients from baseline to 1 year is shown in Figure VIII. 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 VIII: NYHA Functional Status over Time, ITT Analysis Set

11.1.3 (iv) Quality of Life

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 (38.9 ± 10.4). The mental health 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.

KCCQ

Among assessed patients in the Lotus cohort, the overall summary score improved from 51.9 ± 23.5 at baseline to 73.1 ± 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.

11.1.3 (vi) Gender Analysis

A total of 449 male patients (49.2%) were enrolled in the ITT analysis set; 304 were in the Lotus arm 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 146 were randomized to CoreValve. There were 463 female patients (50.8%) in the ITT analysis set; 304 were in the Lotus arm and 146 were randomized to CoreValve. Table X shows mortality and stroke rates in male and female patients at 1 year.

Table X: Mortality and Stroke at 1 Year by Gender, ITT Analysis Set

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Male Patients</th>
<th>Female Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lotus (N=303)</td>
<td>CoreValve (N=166)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>11.5% (34/295)</td>
<td>14.8% (21/142)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>8.1% (24/295)</td>
<td>12.0% (17/142)</td>
</tr>
<tr>
<td>Non-cardiovascular</td>
<td>3.4% (10/295)</td>
<td>2.8% (4/142)</td>
</tr>
<tr>
<td>Stroke</td>
<td>6.1% (18/295)</td>
<td>9.2% (13/142)</td>
</tr>
<tr>
<td>Disabling</td>
<td>2.7% (8/295)</td>
<td>7.7% (11/142)</td>
</tr>
<tr>
<td>Non-disabling</td>
<td>3.4% (10/295)</td>
<td>1.4% (2/142)</td>
</tr>
<tr>
<td>All-cause mortality or disabling stroke</td>
<td>12.9% (38/295)</td>
<td>18.3% (26/142)</td>
</tr>
</tbody>
</table>

Values are % (count/sample size)
11.2 Clinical Studies with the LOTUS Edge™ Valve System

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 essentially the same but with additional radiopaque tantalum markers to aid in visualization of the lacking procedure under fluoroscopy. The REPRISE III LOTUS Edge Nested Registry and REPRISE Edge studies evaluated the LOTUS Edge Valve System to confirm its acute performance and safety when used with the Lotus™ or iSLEEVE™ Introducer Set 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 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 XI and Table XII 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 XI. Pooled 30-Day Primary Safety Results from REPRISE NG DS (Cohort C) and REPRISE Edge, ITT Analysis Set

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

11.3 REPRISE III LOTUS Edge Nested Registry

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.

Primary Objective: The objective of the REPRISE III LOTUS Edge Nested Registry is to confirm performance of the LOTUS Edge Valve implantation procedure with the LOTUS Edge delivery system.

Design: The REPRISE III LOTUS Edge Nested Registry is a prospective, single-arm, multicenter study designed to evaluate the safety and performance of the LOTUS Edge Valve System for TAVR. Inclusion criteria and patient eligibility requirements are the same as for the RCT. A total of 50 subjects were enrolled at 4 centers in the US and Australia.

Study Results: Table XIII shows LOTUS Edge Nested Registry clinical outcomes at 30 days for the components of the RCT primary composite safety endpoint.

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

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

12.0 WARRANTY

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