This supplement contains the following items:
1. Original protocol, final protocol, summary of changes.
2. Original statistical analysis plan, final statistical analysis plan, summary of changes

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REPRISE III: REpositionable Percutaneous Replacement of Stenotic Aortic Valve through Implantation of Lotus™ Valve System – Randomized Clinical Evaluation

CLINICAL PROTOCOL

Protocol Number: S2282

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2. Protocol Synopsis

REPRISE III: REpositionable Percutaneous Replacement of Stenotic Aortic Valve through Implantation of Lotus™ Valve System – Randomized Clinical Evaluation	
Objective(s)	To evaluate the safety and effectiveness of the Lotus™ Valve System for transcatheter aortic valve replacement (TAVR) in symptomatic subjects with calcific, severe native aortic stenosis who are considered at extreme or high risk for surgical valve replacement.
Intended Use	The Lotus Valve System is intended to improve aortic valve function for symptomatic subjects with calcific, severe native aortic stenosis who are at extreme or high risk for standard surgical valve replacement.
Test Device and Sizes	The Lotus Valve System consisting of two main components: - a bioprosthetic bovine pericardial aortic valve, and - a delivery system. Devices sizes include 23 mm, 25 mm, and 27 mm diameter.
Control Device and Sizes	Commercially available self-expanding CoreValve® Transcatheter Aortic Valve Replacement System (CoreValve) that is introduced percutaneously via the femoral artery using conventional catheterization techniques (Medtronic, Inc., Minneapolis, MN, USA). Devices sizes include 26 mm, 29 mm, and 31 mm diameter. ***Note 1:*** Every subject must be deemed treatable with an available size of both the test (Lotus) and the control (CoreValve) valve size approved for use and commercially available at the investigational center where the implant procedure is being performed. ***Note 2:*** A center may use the CoreValve® Evolut™ R Recapturable TAVR System with the aforementioned size matrix if it is approved and commercially available, but only if the center no longer has access to CoreValve.
Study Design	REPRISE III is a prospective, multicenter, 2:1 randomized (Lotus Valve System versus a commercially available CoreValve Transcatheter Aortic Valve Replacement System), controlled trial designed to evaluate the safety and effectiveness of the Lotus Valve System for TAVR in symptomatic subjects who have calcific, severe native aortic stenosis and who are at high or extreme risk for surgical aortic valve replacement (SAVR). There will be a non-randomized roll-in phase with only the test device for centers that do not have previous experience implanting the Lotus Valve;

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	each of these centers will perform at least 2 roll-in cases before commencing randomization. Data from roll-in subjects will be summarized separately from the randomized population. Roll-in subjects will not be included in the endpoint analyses. The REPRISE III study will be conducted in accordance with the relevant parts of the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practices (GCP) or the International Standard ISO 14155: 2011; ethical principles that have their origins in the Declaration of Helsinki; and pertinent individual country/state/local laws and regulations.
Planned Subjects/ Centers/ Countries	Subjects will be enrolled at up to 60 centers in the United States, Canada, Western Europe, and Australia. There will be up to 1032 subjects in REPRISE III. Up to 120 subjects will be enrolled and included in a roll-in phase (test device only) among centers that do not have previous experience implanting the Lotus Valve (a minimum of 2 roll-in subjects per center) before randomization begins. There will be 912 subjects enrolled and randomized.
Primary Endpoints	Primary Safety Endpoint: 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 Primary Effectiveness Endpoint: Composite of all-cause mortality, disabling stroke, or moderate or greater paravalvular aortic regurgitation (based on core lab assessment) at 1 year
Secondary Endpoint	Moderate or greater paravalvular aortic regurgitation (based on core lab assessment) at 1 year

Additional Measurements	Additional measurements based on the VARC[a,b] endpoints and definitions (see **Note 1** below) will be 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):
	  o Mortality: all-cause, cardiovascular, and non-cardiovascular
	  o Stroke: disabling and non-disabling
	  o Myocardial infarction (MI): periprocedural (≤72 hours post index procedure) and spontaneous (>72 hours post index procedure)
	  o Bleeding: life-threatening (or disabling) and major

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	○ Acute kidney injury (≤7 days post index procedure): based on the AKIN System 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 (NYHA class III or IV) ○ New permanent pacemaker 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 (see **Note** 2 below) ○ Grade of aortic valve regurgitation: paravalvular, central, and combined • 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, defined as absence of procedural mortality, correct positioning of a single transcatheter valve into the proper anatomical

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	location , intended performance of the study device (effective orifice area [EOA] >0.9 cm^2 for 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 mm Hg 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; see **Note 3** below) and assessed by an independent core laboratory, including effective orifice area, 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 mm Hg or a peak velocity <3m/sec with no moderate or severe prosthetic valve aortic regurgitation) • For subjects who received a permanent pacemaker related to the index procedure, results of pacemaker interrogation at 30 days and 1 year • Functional status as evaluated by the following: o 5-m gait speed test (at 1 year compared to baseline) o New York Heart Association (NYHA) classification • Neurological status (see **Note 4** below) as determined by the following: o Neurological physical exam at discharge and 1 year (conducted by a neurologist or neurology fellow) o National Institutes of Health Stroke Scale (NIHSS) at discharge and 1 year o Modified Rankin Scale (mRS) at all time points • Health status as evaluated by Kansas City Cardiomyopathy and SF-12 Quality of Life questionnaires at baseline; 1 and 6 months; and 1, 3, and 5 years ***Note 1:*** The most current VARC definitions and endpoints available at the beginning of the trial were used. ***Note 2:*** For the Lotus Valve (test), repositioning may be achieved with partial or full resheathing of the valve. ***Note 3:*** At least 1 echocardiogram must be obtained before discharge or 7 days (whichever comes first); if multiple echocardiographic studies are performed prior to discharge and within 7 days of the procedure, the latest

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	study performed will be used for analysis. ***Note 4:*** For subjects diagnosed with a neurological event (e.g., stroke, transient ischemic attack), a neurological physical exam (conducted by a neurologist or neurology fellow), NIHSS assessment, and mRS must be performed after the event; mRS must also be administered 90±14 days post-neurological event. a: Kappetein AP, *et al*. *J Am Coll Cardiol*. 2012;60:1438 b: Leon M, *et al. J Am Coll Cardiol.* 2011;57:253
Follow-up Schedule	All subjects implanted with a test or control device will be assessed at baseline, peri- and post-procedure, at discharge or 7 days post-procedure (whichever comes first), 30 days, 6 months, 1 year, and then annually for up to 5 years post-procedure. Subjects who are enrolled but not implanted with a test or control device at the time of the procedure will be followed for safety through 1 year.
Study Duration	Subjects implanted with a test or control device will be followed for 5 years after the procedure.
Adjunctive Pharmacologic Therapy	**Anticoagulant Therapy** Anticoagulant therapy (e.g., unfractionated heparin) per local standard of care must be administered during the implant procedure, with a recommended target activated clotting time of ≥250 seconds during the index procedure. **Anti-Platelet Therapy** Per society guidelines[c], antiplatelet therapy with aspirin and clopidogrel[d] is recommended after TAVR to decrease the risk of thrombotic or thromboembolic complications if there are no contraindications to these medications. Aspirin A loading dose of aspirin (recommended dose of 75–325 mg) is required for subjects who have not been taking aspirin for ≥72 hours at the time of the index procedure. The loading dose must be administered prior to the implant procedure. Subjects who have been taking aspirin daily for ≥72 hours at the time of the index procedure do not require a loading dose. After the valve implant procedure, aspirin (recommended dose of ≥75 mg daily) must be given for at least 1 month. It is recommended that daily aspirin be given indefinitely thereafter as per local standard of care. Clopidogrel

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	A loading dose of clopidogrel (recommended dose of ≥300 mg) is required for subjects who have not been taking clopidogrel for ≥72 hours at the time of the index procedure. The loading dose must be administered prior to the implant procedure. After the valve implant procedure, clopidogrel[d] (recommended dose of 75 mg daily) is required for at least 1 month. ***Note*:** If a subject requires chronic anticoagulation with warfarin (other anticoagulants are not permitted), either clopidogrel or aspirin is required prior to and after the implant procedure in addition to the anticoagulant therapy (but both aspirin and clopidogrel are not required). Subjects treated with warfarin should not be treated with a $P2Y_{12}$ inhibitor other than clopidogrel. c: Holmes, D. R., et al. *J Am Coll Cardiol*. 2012;59:1200-1254 Nishimura, R., et al. *J Am Coll Cardiol*. 2014;doi: 10.1016/j.jacc.2014.02.536 d: An alternative $P2Y_{12}$ inhibitor may be prescribed if subject is allergic to or intolerant of clopidogrel.
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 mm Hg or jet velocity >4.0 m/s, as measured by echocardiography 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 Case Review Committee [CRC]) and 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 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

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	○ Porcelain aorta ○ Severe pulmonary hypertension (>60 mmHg) ○ Prior chest radiation therapy ○ Coronary artery bypass graft(s) at risk with re-operation ○ Severe lung disease (need for supplemental oxygen, FEV_1 <50% of predicted, DLCO <60%, or other evidence of severe pulmonary dysfunction) ○ Neuromuscular disease that creates risk for mechanical ventilation or rehabilitation after surgical aortic valve replacement ○ Orthopedic disease that creates risk for rehabilitation after surgical aortic valve replacement ○ Childs Class A or B liver disease (subjects with Childs Class C disease are not eligible for inclusion in this trial) ○ 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 ○ 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:*** Extreme operative risk and high operative risk are defined as follows: **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. Risk of operative mortality and morbidity must be assessed via an in-person evaluation by a center cardiac surgeon and must be confirmed

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	by the CRC (which must include an experienced cardiac surgeon).
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 aortic or mitral valve. EC6. Subject has severe (≥3+) 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 mass, thrombus or vegetation or one requiring treatment. 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 is being treated with chronic anticoagulation therapy other than warfarin. ***Note:*** Subjects who require chronic anticoagulation with warfarin must be able to be treated additionally with either aspirin or clopidogrel. EC12. Subject has active peptic ulcer disease or gastrointestinal bleed requiring hospitalization or transfusion within the past 3 months, other clinically significant bleeding diathesis or coagulopathy 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

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	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 peripheral vascular disease including aneurysm defined as maximal luminal diameter ≥5 cm or with documented presence of thrombus, marked tortuosity, 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. 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.
Statistical Methods	
Analysis Sets	As-Treated: This population includes all subjects who sign an Informed Consent Form, are enrolled in the trial, are randomized, and received a study device, but is based on the treatment actually received. Intention-To-Treat (ITT): This population includes all subjects who sign an Informed Consent Form, are enrolled in the trial, and are randomized, whether or not an assigned study device is implanted.

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	Implanted: This population includes all subjects who sign an Informed Consent Form, are enrolled in the trial, and are implanted with the assigned, randomized study device. For all analysis sets, if a subject receives 2 valves, the subject is assigned to the group corresponding to the first valve received.
Primary Safety Endpoint Statistical Hypothesis	The primary safety endpoint (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) rate for the Lotus Valve is non-inferior to that for CoreValve.
Statistical Test Method for the Primary Safety Endpoint	A Farrington-Manning standardized test will be used to test the one-sided hypothesis of non-inferiority of the Lotus Valve versus CoreValve: H_0: P_{S_Lotus} minus $P_{S\_Control} \geq \Delta$ (Inferior) H_1: P_{S_Lotus} minus $P_{S\_Control} < \Delta$ (Non-inferior) where P_{S_Lotus} and $P_{S\_Control}$ are the rates of the primary safety endpoint for the Lotus Valve group (test) and the CoreValve group (control), respectively, and Δ (delta) is the non-inferiority margin. The primary analysis set for the primary safety endpoint is the implanted analysis set. This endpoint will also be analyzed for the ITT and as-treated analysis sets.
Sample Size Parameters for the Primary Safety Endpoint	• Expected Lotus Valve (test) rate = 40% • Expected CoreValve (control) rate = 40% • Non-inferiority margin (Δ) = 10.5% • Test significance level (α) = 0.025 (1-sided) • Test : Control ratio = 2:1 • Expected rate of attrition = 5% • Given enrollment of 912 subjects (608 Lotus Valve, 304 CoreValve) and 5% attrition, there is approximately 85% power to show non-inferiority with the given expected rates
Success Criteria for the Primary Safety Endpoint	If the *P* value from the Farrington-Manning standardized test is <0.025, the rate of the primary safety endpoint for the Lotus Valve will be concluded to be non-inferior to the CoreValve rate. This corresponds to the one-sided upper 97.5% confidence bound on the difference between treatment groups (Lotus Valve minus CoreValve) for the observed rate of the primary safety

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	endpoint being less than delta.
Primary Effectiveness Endpoint Statistical Hypothesis	The primary effectiveness endpoint (composite of all-cause mortality, disabling stroke, or moderate or greater paravalvular aortic regurgitation [based on core lab assessment] at 1 year) rate for the Lotus Valve group is noninferior to that for the CoreValve group. If non-inferiority is shown for the Lotus group for the primary safety and primary effectiveness endpoints, superiority is shown for the secondary endpoint, and the rate for the Lotus group is less than the rate for the CoreValve group for the primary effectiveness endpoint, then a test of superiority will be performed for the primary effectiveness endpoint.
Statistical Test Method for the Primary Effectiveness Endpoint – Non-Inferiority	A Farrington-Manning standardized test will be used to test the one-sided hypothesis of non-inferiority of the Lotus Valve versus CoreValve: H_0: P_{E_Lotus} minus $P_{E\_Control} \geq \Delta$ (Inferior) H_1: P_{E_Lotus} minus $P_{E\_Control} < \Delta$ (Non-inferior) where P_{E_Lotus} and $P_{E\_Control}$ correspond to the rates of the primary effectiveness endpoint for the Lotus Valve group (test) and the CoreValve group (control), respectively. The primary analysis set for the primary effectiveness endpoint is the implanted analysis set. This endpoint will also be analyzed for the ITT and as-treated analysis sets.
Sample Size Parameters for the Primary Effectiveness Endpoint – Non-Inferiority	• Expected Lotus Valve (test) rate $P_{E\_Lotus} = 32\%$ • Expected CoreValve (control) rate $P_{E\_Control} = 32\%$ • Non-inferiority margin (Δ) = 9.5% • Test significance level (α) = 0.025 (1-sided) • Test : Control ratio = 2:1 • Power ($1-\beta$) = 80% • Total number of evaluable subjects = 819 • Expected rate of attrition = 10% • N = 912 subjects (608 Lotus Valve, 304 CoreValve)
Success Criteria for the Primary Effectiveness Endpoint –	If the *P* value from the Farrington-Manning standardized test is <0.025, the rate of the primary effectiveness endpoint for the Lotus Valve will be concluded to be non-inferior to the CoreValve rate. This corresponds to the one-sided upper 97.5% confidence bound on the difference between treatment groups (Lotus Valve minus CoreValve) for the observed rate of

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Non-Inferiority	the primary effectiveness endpoint being less than delta.
Statistical Test Method for the Primary Effectiveness Endpoint – Superiority	A chi-square test will be used to test the two-sided hypothesis of superiority of the Lotus Valve versus CoreValve: H_0: $P_{E\_Lotus} = P_{E\_Control}$ H_1: $P_{E\_Lotus} \neq P_{E\_Control}$ where P_{E_Lotus} and $P_{E\_Control}$ correspond to the rates of the primary effectiveness endpoint for the Lotus Valve group (test) and the CoreValve group (control), respectively. The primary analysis set for superiority test of the primary effectiveness endpoint is the ITT analysis set. This endpoint will also be analyzed for the as-treated and implanted analysis sets.
Sample Size Parameters for the Primary Effectiveness Endpoint – Superiority	• Expected Lotus Valve (test) rate $P_{E\_Lotus} = 22\%$ • Expected CoreValve (control) rate $P_{E\_Control} = 32\%$ • Test significance level (α) = 0.05 (2-sided) • Test : Control ratio = 2:1 • Power ($1-\beta$) = 80% • Total number of evaluable subjects = 684 • Expected rate of attrition = 10% • Given enrollment of 912 subjects (608 Lotus Valve, 304 CoreValve) and 10% attrition, there is approximately 86% power to show superiority with the given expected rates
Success Criteria for the Primary Effectiveness Endpoint – Superiority	If the *P* value from the chi-square test is <0.05 and the rate of the Lotus Valve group is less than the rate of the CoreValve group, the rate of the primary effectiveness endpoint for the Lotus Valve will be concluded to be superior to the CoreValve rate. This corresponds to the two-sided upper 95% confidence bound on the difference between treatment groups (Lotus Valve minus CoreValve) for the observed rate of the primary effectiveness endpoint being less than zero.
Secondary Endpoint Statistical Hypothesis	The secondary endpoint of moderate or greater paravalvular aortic regurgitation rate at 1 year (based on core lab assessment) for the Lotus Valve group is superior to that for the CoreValve group.

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Statistical Test Method for the Secondary Endpoint	A chi-square test will be used to test the two-sided hypothesis of superiority: H_0: $P_{AR\_Lotus} = P_{AR\_Control}$ H_1: $P_{AR\_Lotus} \neq P_{AR\_Control}$ where P_{AR_Lotus} and $P_{AR\_Control}$ correspond to the moderate or greater paravalvular aortic regurgitation rates at 1 year for the Lotus Valve group (test) and the CoreValve group (control), respectively. The primary analysis set for the secondary endpoint is the ITT analysis set. This endpoint will also be analyzed for the as-treated and implanted analysis sets.
Sample Size Parameters for the Secondary Endpoint	• Expected Lotus Valve (test) rate P_{AR_Lotus} = 1.1% • Expected CoreValve (control) rate $P_{AR\_Control}$ = 5.3% • Test significance level (α) = 0.05 (2-sided) • Test : Control ratio = 2:1 • Expected rate of attrition = 25% • Given enrollment of 912 subjects (608 Lotus Valve, 304 CoreValve) and 25% attrition, there is approximately 86% power to show superiority with the given expected rates
Success Criteria for the Secondary Endpoint	If the *P* value from the chi square test is <0.05, and the rate of moderate or greater paravalvular aortic regurgitation at 1 year for the Lotus Valve group is less than the rate of the CoreValve group, the moderate or greater paravalvular aortic regurgitation rate at 1 year for the Lotus Valve group will be concluded to be superior to that of the CoreValve group. This corresponds to the two-sided upper 95% confidence bound on the difference between treatment groups (Lotus Valve minus CoreValve) for the observed rate of the secondary endpoint being less than zero.

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4. Introduction

This protocol specifies procedures and contains information relevant to the clinical evaluation of the Lotus™ Valve System, a transfemoral aortic valve replacement device designed and manufactured by Boston Scientific Structural Heart a Division of Boston Scientific Corporation (BSC). The Lotus Valve System consists of a pre-loaded, stent-mounted tissue valve prosthesis and catheter delivery system designed to enable predictable and precise placement of the valve during transcatheter aortic valve replacement (TAVR). Early leaflet function during valve deployment and the presence of a radiopaque tantalum marker on the braided frame facilitate optimal initial positioning of the valve. If needed, the valve may be partially or fully resheathed for repositioning prior to final release or can be fully retrieved if during the procedure the decision is made not to implant. The valve also has a polycarbonate-based urethane outer seal (Adaptive Seal™) designed to minimize paravalvular leakage. Additional device information can be found in Section 5.

4.1. *Justification for the Use of the Investigational Device in Human Subjects*

4.1.1. Treatments for Aortic Stenosis

The incidence of aortic stenosis (AS), which most commonly occurs in the very elderly, is increasing due to the aging of the world-wide population and the lack of drug therapies to prevent, halt, or effectively slow the stenotic process[1-3]. It is estimated that nearly 5% of elderly ≥75 years of age have AS and its prevalence is expected to increase as a result of an aging population[4-6]. Aortic stenosis is associated with high rates of death and complications after the appearance of symptoms[7,8].

The standard of care for AS in patients who do not have serious comorbidities is surgical aortic valve replacement (SAVR), which has been shown to reduce symptoms and improve survival[5,7,9-11]. Between 1999 and 2011, the rate of surgical AVR for elderly subjects in the United States has increased and outcomes have improved[11]. However, up to one-third of patients with severe AS are not treated with SAVR because of their comorbidities and consequent peri-operative risk (e.g., advanced age, left ventricular dysfunction, etc.)[5,12-14]. With standard medical therapy, mortality after 1 year among these patients may be as high as 50%[13-15]. Percutaneous transluminal aortic valvuloplasty, which was introduced as an alternative to SAVR in elderly and/or high-surgical-risk subjects, can provide symptomatic relief and/or temporary improvement but does not provide definitive treatment in subjects with severe calcific AS. It is also associated with relatively high mortality and complication rates[16].

Transcatheter aortic valve replacement (TAVR) has recently emerged as a less invasive treatment strategy in subjects who are not suitable candidates for open-heart surgery[17-21] and more than 60,000 transcatheter aortic valve prostheses have been implanted worldwide[22]. Patients with severe aortic stenosis undergo a joint interdisciplinary screening process, including comprehensive multimodality imaging[23-26], prior to procedure recommendation. Because existing surgical risk scores imperfectly characterize risk[27-30], center Heart Teams also consider other co-morbidities and patient frailty. While not captured well by any of the

standard risk scores, these added measures help to more fully characterize a patient population that potentially benefits from TAVR[31].

Transcatheter aortic valve replacement was initially performed through a retrograde transfemoral approach and an antegrade transapical approach. Two additional retrograde approaches, transaortic through the ascending aorta and trans-subclavian, were subsequently described[20,32]. Evidence of the safety of the procedure using either a balloon expandable or a self-expanding bioprosthetic heart valve has rapidly accumulated through observational studies[33-39], device-specific registries[40-54], and national registries[55-62]. In the randomized Placement of Aortic Transcatheter Valves (PARTNER) trial, patients unsuitable for surgical valve replacement who underwent TAVR with a balloon-expandable device experienced significant reductions in mortality and repeat hospitalization compared to those receiving conventional medical therapy at 1 and 2 years[14,63] and high-surgical-risk patients receiving either TAVR or surgical replacement had a similar mortality risk[64,65]. In the randomized U.S. CoreValve High Risk Study, TAVR with a self-expanding transcatheter aortic-valve bioprosthesis was associated with a significantly higher rate of survival at 1 year compared to SAVR[66].

A recently published expert consensus document lists TAVR as a reasonable alternative to SAVR in AS patients with high surgical risk[8] and a subsequent consensus document outlines patient selection for TAVR.[67] The potential of TAVR to be a treatment option for a considerable number of patients with AS has resulted in significant advances in the technology aiming to simplify the procedure and minimize adverse events[68,69]. Standardized endpoint definitions were published by the Valve Academic Research Consortium (VARC) in 2011 (VARC-1[70]) and updated in 2012 (VARC-2[71]).

Table 4.1-1 summarizes the peri-operative event rates through 30 days post-procedure from several TAVR studies that enrolled subjects similar to those planned for this study, as well as results from inoperable and high risk subjects in PARTNER, the U.S. CoreValve Extreme Risk Pivotal Trial, and the U.S. CoreValve High Risk Study. A more detailed summary of the available literature is presented in the Investigator Brochure.

Table 4.1-1: Events from Peri-Operative to 30 Days (Transfemoral Approach)

Study	Device/N	Death (%)	Myocardial Infarction (%)	Major Stroke (%)	Bleeding (%)	Acute Kidney Injury (%)	Vascular Complications (%)
Webb, et al. 2009[33]	EW/113[a]	8	N/A	5.3	11.6	4.4	8
Rodés-Cabau, et al. 2010[41]	EW/168[a]	9.5	0.6	3.0	N/A	N/A	N/A
Thomas, et al. 2010[42]	EW/463[a]	6.3	N/A	2.4	9.9	1.3	22.9
Leon, et al. 2010[14]	EW/267[b]	5	0	5	16.8	1.1	16.2[c] 30.7
Smith, et al. 2011[64]	EW/244[a,d]	3.4	0	3.8	9.3	2.9	14[c] 22.7
Piazza, et al. 2008[40]	CV/646	8	0.6	1.9[e]	N/A	N/A	1.2
Munoz-Garcia, et al. 2012[72]	CV/133[f]	4.5	0.8	1.5	N/A	N/A	2.2[c]
Buchanan, et al. 2011[35]	CV, EW/305	4.7	1.3	1.0	33.1	10.2[g]	15.7[c]
Moat, et al. 2011[57]	CV, EW/599	5.5	1.0	4.0[h]	N/A	N/A	6.2
Zahn, et al. 2011[56]	CV, EW/697[i]	12.4	0.3	2.8[e]	N/A	N/A	17.1[j]
Bosmans, et al. 2011[58]	CV/133[a] EW/99[a]	8 CV; 6 EW	N/A	5[e,k]	N/A	6[k,l]	N/A
Tamburino, et al. 2012[36]	CV, EW/218[m]	6.9	0.0	2.3	5.5	N/A	N/A
Gilard, et al. 2012[59]	CV, EW/2361[a]	8.5	0.8	2.2	1.2[n]	N/A	5.5[c]
Spargias, et al. 2013[60]	CV/67, EW/59	1.0	N/A	0.0[e]	2.0[c]	N/A	9.0[o]
Mack, et al. 2013[62]	EW/3833[a,d,h] EW/1139[a,b,h] EW/1687[a,d] EW/489[a,b]	3.8[a,d,h] 5.4[a,b,h] 5.0[a,d] 6.7[a,b]	0.5[a,d,h] 0.8[a,b,h] N/A[a,b,d]	3.8[a,d,e,h] 5.4[a,b,e,h] 3.2[a,d,e] 1.6[a,b,e]	3.2[a,c,d,h] 3.6[a,b,c,h] N/A[a,b,d]	1.3[a,d,h,l] 1.7[a,b,h,l] 1.5[a,d,l] 1.6[a,b,l]	6.4[c,h,k]
Popma, et al. 2014[73]	CV/489[b]	8.4	1.2	2.3	12.7[n] 24.9[c]	11.8	8.2[c]
Adams, et al. 2014[66]	CV/390[a,d]	3.3	0.8	3.9	13.6[n] 28.1[c]	6.0	5.9[c]
Abdel-Wahab, et al. 2014[74]	CV/117; EW/121	5.1 CV; 4.1 EW	0 CV; 0.8 EW	2.6[e] CV; 5.8[e] EW	12.0[n] CV 8.3[n] EW 14.5[c] CV 19.0[c] EW	9.4 CV 4.1 EW	11.1[c] CV 9.9[c] EW

Table 4.1-1: Events from Peri-Operative to 30 Days (Transfemoral Approach)

Study	Device/N	Death (%)	Myocardial Infarction (%)	Major Stroke (%)	Bleeding (%)	Acute Kidney Injury (%)	Vascular Complications (%)

a: Transfemoral approach population only
b: Inoperable subjects
c: Major
d: High risk subjects
e: All stroke
f: Femoral access in 90.9% of cases
g: Stage 3
h: In hospital
i: 92.4% transfemoral and 3.2% subclavian; 84% of all procedures were CV
j: Groin problem with need of transfusion
k: All subjects
l: Dialysis
m: Femoral access in 97.2% of cases
n: Life-threatening bleeding
o: All vascular complications
Abbreviations: CV=CoreValve; EW=Edwards; N/A=not available

4.1.2. REPRISE I Study

The aforementioned results notwithstanding, TAVR with early generation devices has been associated with increased stroke risk and vascular complications when compared to surgical valve replacement[64-66]. Cerebrovascular accidents and vascular complications associated with TAVR have been significant predictors of mortality[75,76]. The paravalvular regurgitation more commonly seen with TAVR compared to surgery has also been accompanied by higher early and late mortality[45,65,77]. While careful patient selection may serve to mitigate these risks[78-80], device design improvements such as seen with the Lotus Valve System (Section 5.1) may enable more precise placement and minimize or eliminate paravalvular regurgitation.

The prospective, single arm, multicenter REPRISE I (REpositionable Percutaneous Replacement of Stenotic Aortic Valve through Implantation of Lotus™ Valve SystEm) feasibility study (N=11) assessed the acute safety and performance of the Lotus Valve System in symptomatic subjects with calcified stenotic aortic valves who were considered high risk for surgical valve replacement[81]. The primary endpoint was clinical procedural success, defined as successful implantation of a Lotus Valve (per the VARC-1 definitions[70]) without in-hospital major adverse cardiovascular and cerebrovascular events (MACCE, defined as all-cause mortality, periprocedural myocardial infarction ≤72 hours after the index procedure, major stroke, urgent/emergent conversion to surgery or repeat procedure for valve-related dysfunction) through discharge or 7 days post-procedure, whichever came first. Clinical follow-up will extend through 5 years. Safety endpoints are adjudicated by an independent Clinical Events Committee (CEC); prosthetic valve function and cardiac function endpoints are assessed by independent echocardiography and electrocardiography core labs. The study is registered at ClinicalTrials.gov, Identifier NCT01383720.

To ensure proper use of the Lotus Valve System and mitigate any procedural complication that could be secondary to misuse or misinterpretation of the Instructions For Use, a comprehensive training and proctorship program was implemented in this study supported by an experienced proctoring physician assigned by Boston Scientific. Given the importance of selecting appropriate subjects, a Case Review Committee (CRC) comprised of the Principal Investigators, other investigators experienced with TAVR, and the Sponsor was established. This committee was responsible for reviewing and confirming subject eligibility across study sites during the screening process.

The primary endpoint was achieved in 9/11 subjects[81]. The device was successfully implanted in all 11 subjects but there was a device failure in 1 subject based on not meeting one of four VARC-1 criteria[70] for device success (the mean gradient of 22 mmHg in this subject was greater than the VARC-1 cutoff of 20 mmHg). The Echocardiography Core Lab concluded that the device failure resulted from a hyperdynamic state in the subject and noted that the prosthetic valve appeared to be functioning well. Ten (10) of 11 subjects had no in-hospital MACCE; there were no deaths and 1 major stroke. Paravalvular regurgitation at discharge TTE was mild in 2 subjects, trivial in 1 subject, and absent in the other 8 subjects; these outcomes compare favorably with published data[14,40,56,64,82].

To date, data are available through 1 year[81]. There were no additional MACCE events beyond the primary endpoint. The 1-year VARC-1[70] combined safety endpoint, including

MACCE, life threatening/disabling bleeding, major vascular complications, and Stage 3 acute kidney injury, was 3/11; the aforementioned subject with the major stroke also had a small left femoral dissection treated with balloon inflation during the procedure and there were 2 life-threatening/disabling bleeds through 30 days that were unrelated to valve implantation and resolved. Conduction disturbances led to implantation of a permanent pacemaker (PPM) before discharge in 4 subjects; 2 of these 4 subjects had paced rhythms at 1 year. While all REPRISE I subjects were NYHA Class II (n=6) or III (n=5) at baseline, this distribution was significantly improved between baseline and 30 days (3 in Class I, 7 in Class II, 1 in Class III; P=0.02) and baseline and 1 year (5 in Class I, 6 in Class II; P=0.004). The mean aortic valve gradient was 11.7±3.0 mmHg for the cohort at 30 days and 15.4±4.6 mmHg at 1 year. Paravalvular aortic regurgitation was mild (2/11) or absent (9/11) at 30 days and mild (1/11) or absent/trivial (10/11) at 1 year; there was no moderate or severe paravalvular aortic regurgitation at any time post implantation of the Lotus Valve. The results of the REPRISE I feasibility study support the safety and performance of the Lotus Valve System.

4.1.3. REPRISE II Study

The REpositionable Percutaneous Replacement of Stenotic Aortic Valve through Implantation of Lotus™ Valve System – Evaluation of Safety and Performance (REPRISE II) clinical trial was designed to evaluate the safety and performance of the Lotus Valve System for TAVR in symptomatic subjects with calcific stenotic aortic valves who were considered high risk for surgical valve replacement. This prospective, single-arm, multicenter, CE-Mark study enrolled 120 subjects at 14 investigative centers in Australia, France, Germany and the United Kingdom. As noted above for REPRISE I (Section 4.1.2), a comprehensive training and proctorship program was implemented and a CRC was responsible for reviewing and confirming subject eligibility across study sites during the screening process. The study is registered at ClinicalTrials.gov, Identifier NCT01627691.

Safety endpoints in the ongoing REPRISE II study are adjudicated by an independent CEC; prosthetic valve function and cardiac function endpoints are assessed by independent echocardiography and electrocardiography core labs. The primary device performance endpoint was the mean aortic valve pressure gradient at 30 days post implant as measured by echocardiography. This endpoint was analyzed on an as-treated (subjects who received the Lotus Valve) basis. A one-sample *t*-test was used to test the one-sided hypothesis that the primary device performance endpoint is less than the prespecified performance goal (PG) of 18 mmHg. Two interim analyses were conducted on the first 40 and 60 subjects; the alpha-adjustment for multiple comparisons was 0.01123 and 0.00792, respectively. The alpha level adjustment for the final analysis conducted on the fully enrolled cohort of 120 subjects was 0.01305.The primary safety endpoint was all-cause mortality at 30 days after the implant procedure and was evaluated on an intent-to-treat basis.

The 30-day mean aortic valve pressure gradient was 11.45±5.20 mmHg with a one-sided 98.695% upper confidence bound of 12.64. The *P* value from the one-sample *t*-test was <0.0001 and so the Lotus Valve was concluded to have a 30-day mean aortic pressure gradient <18 mmHg and the primary device performance endpoint was met. Table 4.1-2

shows device performance endpoints, clinical outcomes, and echocardiographic outcomes through 30 days[83]. Successful vascular access, delivery and deployment of the Lotus Valve along with successful retrieval of the delivery system was achieved in all 120 subjects. Repositioning and/or retrieval was successful in all patients in whom it was attempted. Mortality was 4.2% and the disabling stroke rate was 1.7%. There were no repeat procedures for valve-related dysfunction. Core lab assessment of paravalvular aortic regurgitation at 30 days indicated no severe regurgitation and 1 case of moderate regurgitation; in 83.3% (80/96) of subjects there was trace/trivial or no paravalvular regurgitation. The observed clinical results are consistent with other TAVR studies (see Table 4.1-1) and the rates of paravalvular regurgitation are lower[14,64,66,73,74]. Table 4.1-3 shows 6-month clinical (time-to-event analysis) and echocardiographic outcomes. Mortality was 8.4% and the disabling stroke rate was 3.5%. Most subjects (81%) had none/trivial paravalvular aortic regurgitation at 6 months; there was no severe paravalvular regurgitation. The results of the REPRISE II study support the safety and performance of the Lotus Valve System.

Table 4.1-2: 30-Day Outcomes in REPRISE II

Outcomes	REPRISE II (N=120)
Clinical Outcomes at 30 Days (CEC Adjudicated)	
All-cause mortality	4.2% (5/119)
Cardiovascular	4.2% (5/119)
All stroke	6.1% (7/115)
Disabling stroke	1.7% (2/115)
Major vascular complications	2.6% (3/116)
Life-threatening or disabling bleeding	5.1% (6/117)
Major bleeding	17.9% (21/117)
Acute kidney injury – Stage 2 or 3	3.5% (4/115)
Coronary obstruction (periprocedural)	0.9% (1/115)
Valve-related dysfunction requiring repeat procedure (surgical/interventional)	0.0% (0/115)
New permanent pacemaker implantation resulting from new or worsened conduction disturbances	29.1% (34/117)
Periprocedural MI (≤72 hours after index procedure)	3.4% (4/117)
Hospitalization for valve-related symptoms or worsening congestive heart failure	4.3% (5/115)
Atrial fibrillation or atrial flutter (new onset)	5.2% (6/115)
Ventricular septal perforation (periprocedural)	0.0% (0/115)
Mitral apparatus damage (periprocedural)	2.6% (3/115)
Cardiac tamponade (periprocedural)	4.3% (5/117)
Prosthetic aortic valve malpositioning	0.0% (0/115)
Prosthetic aortic valve thrombosis	0.0% (0/115)
Prosthetic aortic valve endocarditis	0.0% (0/115)
Device Performance Endpoints	
Successful vascular access, delivery, and deployment of the Lotus Valve System, and successful retrieval of the delivery system	100.0% (120/120)
Successful repositioning (partial or complete resheathing of the Lotus Valve in the catheter and redeployment in a more accurate position within the aortic valve annulus) of the Lotus Valve System if repositioning is attempted for the last valve	100.0% (32/32)

Table 4.1-2: 30-Day Outcomes in REPRISE II

Outcomes	REPRISE II (N=120)
attempted	
Successful retrieval (complete resheathing of the Lotus Valve in the catheter and removal from the body) of the Lotus Valve System if retrieval is attempted	100.0% (6/6)
Valve Performance by Transthoracic Echocardiography (30 Days-Core Lab Assessment)	
Aortic valve area (effective orifice area) (cm^2)	1.67±0.43 (78)
Mean aortic valve gradient (mmHg)	11.45±5.20 (97)
Peak aortic gradient (mmHg)	21.30±9.26 (97)
Peak aortic velocity (cm/s)	2.25±0.48 (97)
Paravalvular Aortic Regurgitation	
None	78.1% (75/96)
Trace/trivial	5.2% (5/96)
Mild	15.6% (15/96)
Moderate	1.0% (1/96)
Severe	0.0% (0/96)

Values are % (count/sample size) or mean±SD (n)
Note: Denominators for clinical event rates are based on the number of subjects who have either had an event within 30 days post-procedure or who were event-free with last follow-up at least 23 days post-procedure.

Table 4.1-3: 6-Month Outcomes in REPRISE II

Outcomes	REPRISE II (N=120)
Clinical Outcomes at 6 Months (CEC Adjudicated)	
All-cause mortality	8.4% (10)
Cardiovascular	5.9% (7)
All stroke	9.5% (11)
Disabling stroke	3.5% (4)
Major vascular complications	2.5% (3)
Life-threatening or disabling bleeding	5.0% (6)
Major bleeding	19.5% (23)
Acute kidney injury – Stage 2 or 3	3.4% (4)
Valve-related dysfunction requiring repeat procedure (surgical/interventional)	0.0% (0)
New permanent pacemaker implantation resulting from new or worsened conduction disturbances	29.5% (35)
Spontaneous MI (> 72 hours after index procedure)	0.0% (0)
Hospitalization for valve-related symptoms or worsening congestive heart failure	5.2% (6)
Atrial fibrillation or atrial flutter (new onset)	6.0% (7)
Prosthetic aortic valve malpositioning	0.0% (0)
Prosthetic aortic valve thrombosis	0.0% (0)
Prosthetic aortic valve endocarditis	0.9% (1)
Valve Performance by Transthoracic Echocardiography (6 Months-Core Lab Assessment)	
Aortic valve area (effective orifice area) (cm^2)	1.71±0.44 (88)
Mean aortic valve gradient (mmHg)	11.39±4.57 (93)
Peak aortic gradient (mmHg)	20.95±8.10 (93)

Table 4.1-3: 6-Month Outcomes in REPRISE II

Outcomes	REPRISE II (N=120)
Peak aortic velocity (cm/s)	2.26±0.42 (94)
Paravalvular Aortic Regurgitation	
None	79.8% (71/89)
Trace/trivial	1.1% (1/89)
Mild	18.0% (16/89)
Moderate	1.1% (1/89)
Severe	0.0% (0/89)

Values are % (n); % (count/sample size), or mean±SD (n)
Clinical event rates are presented as Kaplan-Meier estimates.

4.2. *Justification for the Study*

As noted above, the Lotus Valve System potentially provides a number of performance and safety features beyond that of earlier TAVR devices. These include an enhanced ability to place the valve correctly at the first attempt, the capacity to reposition the device if the initial deployment is considered to be suboptimal, the ability to retrieve the device if during the procedure the decision is made to replace it with another valve to optimize implant or not to implant, and the aforementioned outer seal designed to minimize paravalvular leakage. The anticipated risks and benefits associated both with the Lotus Valve System and with participation in this clinical investigation are summarized in the Investigator Brochure and in Section 19 of this document. The conclusion of this risk-benefit analysis demonstrates that the known risks associated with the procedure, and specifically the use of the Lotus Valve System, have been mitigated to acceptable limits. It was also concluded that the aforementioned design features may improve procedural safety and longer term clinical outcomes. The available Sponsor-provided training program and proctorship for physicians further mitigates risk. The result is a procedure with residual subject risk comparable to that of currently available transcatheter aortic valves and potential benefit compared with other alternatives.

It is therefore determined that:

- All applicable risks have been addressed through appropriate testing and any residual risks are acceptable when weighed against the potential benefits to the subject.
- The potential benefits of the use of the device out-weigh the risks.

5. Device Description

The study devices are intended to improve aortic valve function for symptomatic subjects with calcific, severe native aortic stenosis who are at extreme or high risk for standard surgical valve replacement. Every subject must be deemed treatable with an available size of

both the test and the control device approved for use and commercially available at the investigational center where the implant procedure is being performed.

5.1. *Lotus Valve System Investigational Device (Test)*

The Lotus Valve System (Figure 5.1-1) has two main parts: a bioprosthetic aortic valve implant and a catheter-based delivery system for introduction and delivery of the valve implant. The device is introduced percutaneously via the femoral artery using conventional catheterization techniques. Femoral access using the surgical cut-down approach can also be performed to gain access into the aortic vessel. Device sizes include 23 mm, 25 mm, and 27 mm diameter. More detailed product information is contained in the Investigator Brochure and Instructions For Use (IFU).

Figure 5.1-1: Lotus™ Valve System

5.1.1. Lotus Valve

The Lotus Valve (Figure 5.1-2) consists of 3 bovine pericardial leaflets. The commissures of the leaflets are attached to the valve frame through portions of the locking components. The valve frame is made of a single nitinol wire strand woven into a braid. The wire ends of this frame are encapsulated by a tantalum crimp that is used as a radiopaque marker, and which is located in the center of the frame height. The braided structure is designed to foreshorten and expand radially when delivered, and is then locked in this position using a post and buckle locking mechanism.

The Adaptive Seal™ is made of a polycarbonate-based urethane and is located on the outside bottom half of the frame. This seal provides a barrier between the native annulus and the frame to help reduce paravalvular leakage.

The valve is deployed in a beating heart and rapid pacing is not required during valve deployment. The valve begins to function early in the deployment process, facilitating maintenance of cardiac output and hemodynamic stability during deployment.

The device is designed to produce a final diameter of 23 mm, 25 mm, or 27 mm (depending on valve size) when the valve is locked. The frame height of all valve sizes in the deployed state is approximately 19 mm.

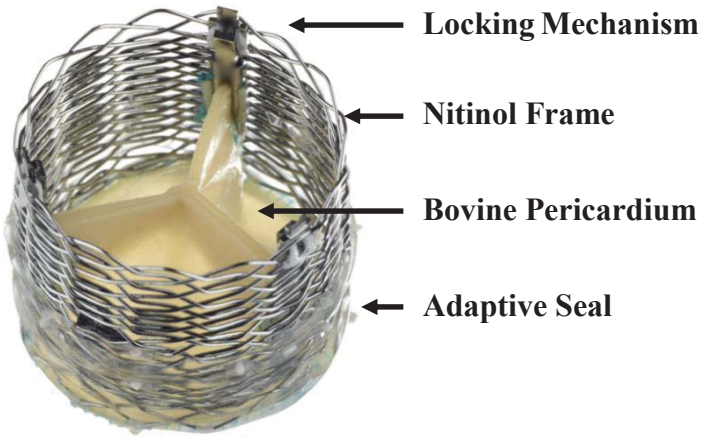

Figure 5.1-2: Lotus Valve Implant

5.1.2. Lotus Delivery System

The Lotus Delivery System is made of the catheter and the Lotus Controller.

- The catheter is a sheath in which mandrels allowing the shortening, locking, unlocking, and elongation of the valve, as well as its releasing, connect from the Lotus Controller to the valve. The catheter has a hydrophilic coating to facilitate the insertion. The tip of the catheter seats on the shoulder of a nosecone to provide a smooth transition.
- The Lotus Controller is shown in Figure 5.1-3.
  - The Lotus Controller has 3 ports; 2 of the ports are for flushing purposes and one is the Guidewire Port.
  - The Control Knob at the proximal end of the Lotus Controller is the primary control used to deploy the valve. It operates both the sheathing/unsheathing function as well as the locking/unlocking function.
    - The sheathing/unsheathing capability allows the implant to be pulled into or pushed out of the outer sheath.
    - The locking function shortens the valve implant into the locked configuration; the unlocking function elongates the valve.
  - The Release Ring is used when the operator is ready to release the valve. A Safety Cover covers the Release Ring to avoid inadvertent premature release.

Figure 5.1-3: Lotus Controller

5.1.3. Lotus Introducer Set

The Lotus Introducer Set will be used as an accessory to the Lotus Valve System during the procedure. It is composed of a dilator and an introducer sheath manufactured with materials commonly used in medical devices having contact with circulating blood. The Lotus Introducer is suitable for use in subjects requiring the 23 mm valve with femoral artery lumen diameter ≥6.0 mm or for use in subjects requiring the 25 mm or 27 mm valve with femoral artery lumen diameter ≥6.5 mm. In countries where the Lotus Introducer Set is approved, the commercial devices will be used. In countries where it is not approved, it will be considered an investigational device..

5.2. *CoreValve Transcatheter Aortic Valve Replacement System (Control)*

The control device is the commercially available self-expanding CoreValve® Transcatheter Aortic Valve Replacement System (CoreValve) that is introduced percutaneously via the femoral artery using conventional catheterization techniques (Medtronic, Inc., Minneapolis, MN, USA).

Devices sizes include 26 mm, 29 mm, and 31 mm diameter.

Note1: Every subject must be deemed treatable with an available size of both the test (Lotus) and the control (CoreValve) valve approved for use and commercially available at the investigational center where the implant procedure is being performed.

Note 2: A center may use the CoreValve® Evolut™ R Recapturable TAVR System with the aforementioned size matrix if it is approved and commercially available, but only if the center no longer has access to CoreValve.

5.3. *Device Labeling*

5.3.1. Test Device

The study Manual of Operations includes the IFU for the Lotus Valve System. Study devices are labeled on the top and one side (one label wraps around the top and side) of the outer carton and on the sterile pouch. Packaging will include peelable, self-adhesive labels for each unit shipped. The labeling will include the following information.

- Product Name
- Part/Reference number
- Lot number
- Expiration (use by) date (labeled as month/year, device not to be used after the last day of the indicated month)

The following statement appears on the label.

Caution: Investigational Device. Limited by Federal Law (USA) to Investigational Use.

In addition, the following statements appear on the product labeling.

CAUTION: Exclusively for Clinical Investigations.

Device labeling will be provided in local language(s) as per respective national regulations.

5.3.2. Control Device

Information is provided in the IFU supplied with the commercially available CoreValve or CoreValve® Evolut™ R System (if used because a center no longer has access to CoreValve).

6. Objectives

The objective of the REPRISE III trial is to evaluate the safety and effectiveness of the Lotus™ Valve System for transcatheter aortic valve replacement (TAVR) in symptomatic subjects with calcific, severe native aortic stenosis who are considered at extreme or high risk for surgical valve replacement.

7. Endpoints

Outcomes will be assessed on an intention-to-treat (ITT) basis, an implanted basis, and an as-treated basis. The ITT analysis population includes subjects who sign an Informed Consent Form (see Section 20), are enrolled in the trial (see Section 10.1 for point of enrollment), and are randomized, whether or not an assigned study device is implanted. The implanted analysis population includes ITT subjects who are implanted with an assigned, randomized

study device. The as-treated population includes subjects who sign an Informed Consent Form, are enrolled in the trial, are randomized, and received a study device, with the analysis based on the treatment actually received. For all analysis sets, if a subject receives 2 valves, the subject is assigned to the group corresponding to the first valve received. Endpoint definitions can be found in Table 26.2-1.

7.1. *Primary Endpoints*

7.1.1. Primary Safety Endpoint

The primary safety endpoint is 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 analysis set for the primary safety endpoint is the implanted analysis set.

7.1.2. Primary Effectiveness Endpoint

The primary effectiveness endpoint is a composite of all-cause mortality, disabling stroke, or moderate or greater paravalvular aortic regurgitation (based on core lab assessment) at 1 year. The primary analysis set for the primary effectiveness endpoint is the implanted analysis set.

7.1.3. Secondary Endpoint

The secondary endpoint is the rate of moderate or greater paravalvular aortic regurgitation based on core lab assessment at 1 year. The primary analysis set for the secondary endpoint is the ITT analysis set.

7.2. *Additional Measurements*

Additional measurements based on the VARC endpoints and definitions[70,71] (see **Note 1** below) will be 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 (see **Note 2** below) adjudicated by an independent Clinical Events Committee (CEC; Section 22.1.1):
  - 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 System[84,85] 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 CHF (NYHA class III or IV)
  - New permanent pacemaker implantation resulting from new or worsened conduction disturbances (definitions in Table 26.2-1; see **Note 3** below)
  - 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 (see **Note 4** below)
  - Grade of aortic valve regurgitation: paravalvular, central and combined; the overall distribution of paravalvular aortic regurgitation (none, trace/trivial, mild, moderate, severe) will be determined as well as the percentage of subjects who have moderate or severe paravalvular regurgitation and the percentage of subjects who have mild, moderate or severe paravalvular regurgitation
- 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 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 mm Hg 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; see **Note 5** below) and assessed by an independent core laboratory, including effective orifice area, mean and peak aortic gradients, peak aortic velocity, and grade of aortic regurgitation (see **Note 6** below).

- 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 mm Hg 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[86] (at 1 year compared to baseline)
  - New York Heart Association (NYHA) classification
- Neurological status (see **Note 7** below) as determined by the following:
  - Neurological physical exam by a neurologist or neurology fellow 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[87] and SF-12[88] Quality of Life (QOL) questionnaires at baseline; 1 and 6 months; and 1, 3, and 5 years
- Resource utilization associated with the procedure and/or follow-up.

Note 1: The most current VARC definitions and endpoints available at the beginning of the trial were used.

Note 2: The VARC-2[70,71] safety composite at 30 days includes all-cause mortality, all stroke (disabling and non-disabling), life-threatening bleeding, acute kidney injury (Stage 2 or 3), coronary artery obstruction requiring intervention, major vascular complication, and repeat procedure for valve-related dysfunction. The VARC-2 time-related valve safety composite includes structural valve deterioration (valve-related dysfunction requiring repeat procedure [TAVR or SAVR]), prosthetic valve endocarditis, prosthetic valve thrombosis, thromboembolic events (e.g., stroke), and VARC bleeding (unless clearly unrelated to valve therapy based on investigator assessment)

Note 3: Clinical indications for permanent pacemaker implantation are outlined in the ACCF/AHA/HRS Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities[89]. Permanent pacemaker implantation should generally be performed only for accepted Class I indications.

Note 4: For the Lotus Valve System, repositioning may be achieved with partial or full resheathing of the valve; the proportion of subjects with partial valve resheathing and full valve resheathing will be determined.

Note 5: At least 1 echocardiogram must be obtained before discharge or 7 days (whichever comes first); if multiple echocardiographic studies are performed prior to discharge and within 7 days of the procedure, the latest study performed will be used for analysis.

Note 6: The VARC-2[70,71] clinical efficacy composite (after 30 days) includes all-cause mortality, all stroke, required hospitalization for valve-related symptoms or worsening CHF

(NYHA class III or IV), and prosthetic heart valve dysfunction (mean aortic valve gradient ≥20 mmHg, effective orifice area ≤0.9-1.1 cm^2 and/or Doppler velocity index [DVI] <0.35, AND/OR moderate or severe prosthetic valve aortic regurgitation [per VARC definition]). The need for hospitalization associated with valve-related symptoms or worsening CHF serves as a basis for calculation of a "days alive outside the hospital" endpoint. This includes heart failure, angina, or syncope due to aortic valve disease requiring intervention or intensified medical management; clinical symptoms of CHF with objective signs including pulmonary edema, hypoperfusion, or documented volume overload AND administration of intravenous diuresis or inotropic therapy, performance of aortic valvuloplasty, institution of mechanical support (intra-aortic balloon pump or ventilation for pulmonary edema), or hemodialysis for volume overload; clear documentation of anginal symptoms AND no clinical evidence that angina was related to coronary artery disease or acute coronary syndrome; documented loss of consciousness not related to seizure or tachyarrhythmia.

Note 7: For subjects diagnosed with a neurological event (e.g., stroke, transient ischemic attack), a neurological physical exam (conducted by a neurologist or neurology fellow), NIHSS assessment, and mRS must be performed after the event. Additionally, mRS must be administered at 90±14 days post-neurological event (see Table 11.1-1). If a subject who has not received a study device (investigational or control) experiences a neurological event within the first 30 days after the index procedure, mRS must be performed on that subject after the event and at 90±14 days post-neurological event and the results must be reported to the Sponsor.

8. Design

8.1. *Scale and Duration*

The REPRISE III clinical study is a prospective, multicenter, randomized controlled trial designed to evaluate the safety and efficacy of the Lotus Valve System for TAVR in symptomatic subjects who have calcific, severe native aortic stenosis and who are at extreme or high risk for surgical valve replacement. There will be a non-randomized roll-in phase with only the test device for centers that do not have previous experience implanting the Lotus Valve.

All subjects implanted will be followed at baseline, peri- and post-procedure, at discharge or 7 days post-procedure (whichever comes first), 30 days, 6 months, and then annually for up to 5 years post-procedure. Enrolled subjects who do not have a study device implanted will be assessed through 1 year post procedure for safety/adverse events.

The REPRISE III study will be conducted in accordance with the relevant parts of the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practices (GCP) or the International Standard ISO 14155: 2011; ethical principles that have their origins in the Declaration of Helsinki; and pertinent individual country/state/local laws and regulations. See Section 11 below for additional information on study design and data collection.

The REPRISE III study will be registered at ClinicalTrials.gov prior to enrollment of the first subject.

8.2. *Treatment Assignment*

Screening materials from eligible subjects who are identified by the investigators as having met the inclusion and exclusion criteria (see below and Table 9.3-1, respectively) and who provide written informed consent, will be reviewed by a Case Review Committee (CRC; see Section 22.2) to assess and confirm suitability of subjects for enrollment.

Eligible subjects will be randomized in a 2:1 allocation to receive either the Lotus Valve System (test) or a commercially available self-expanding CoreValve® Transcatheter Aortic Valve Replacement System (control). The randomization schedules will be computer-generated, using a pseudo-random number generator. Randomization will be stratified by center and by high or extreme risk status (see Section 26.2 for definitions). All randomized subjects will have unique identification numbers. Random permuted blocks will be employed to ensure approximate balance of treatment allocation within each stratum. Instructions on randomization are provided in the Manual of Operations. Subject should be randomized within 7 calendar days of CRC approval. Subjects should be treated within 14 calendar days of randomization and no later than 30 calendar days after randomization.

Note: There will be a non-randomized roll-in phase with only the test device for centers that do not have previous experience implanting the Lotus Valve; each of these centers will perform at least 2 roll-in cases before commencing randomization. All roll-in subjects will have unique identification numbers.

8.2.1. Treatment

See Section 5 for a detailed description of the devices and information on device sizes.

The test device is the Lotus Valve System, which consists of a bioprosthetic bovine pericardial aortic valve and a delivery system. The Lotus Introducer Set is used as an accessory in the procedure.

The control device is the commercially available CoreValve Transcatheter Aortic Valve Replacement System.

8.3. *Study Design Justification*

There will be up to 1032 subjects in REPRISE III. In order to support the stated objectives of this study (see Section 6) while also limiting the potential exposure of study subjects to risk, up to 120 subjects will be enrolled in the roll-in phase of this study (at centers without previous Lotus Valve experience) and 912 subjects will be randomized and enrolled. Up to 60 centers in the United States, Canada, Western Europe, and Australia will participate in the study. Safety and effectiveness results will be reported on all enrolled subjects (see Section 21 for information on safety reporting). In addition to the risk-benefit analysis noted in Section 4.2 (see also Section 19), ongoing dynamic data safety monitoring will be performed throughout the trial to minimize risk to subjects (see Section 22.1). All implanted

subjects will be followed for up to 5 years post index procedure. Per society guidelines[8,90], antiplatelet therapy with aspirin and clopidogrel is recommended after TAVR to decrease the risk of thrombotic or thromboembolic complications if there are no contraindications to these medications.

9. Subject Selection

9.1. *Study Population and Eligibility*

The study will include subjects presenting with symptomatic calcific, severe native aortic stenosis who are considered at extreme or high risk for surgical valve replacement (see definitions of operative risk in Section 26.2). Traditionally underrepresented populations are expected to be included in the subject population. Because aortic stenosis most commonly occurs in the very elderly, women represent the majority of subjects enrolled in many TAVR trials. All efforts will be made to minimize attrition in REPRISE III. Since the very elderly will represent the majority of subjects enrolled in the trial, these efforts are by definition targeted to traditionally under-represented groups.

Prior to being eligible for the REPRISE III study, a subject must meet all of the inclusion criteria (Section 9.2) and none of the exclusion criteria (Section 9.3). The inclusion and exclusion criteria are not expected to have a negative effect on recruitment or retention of traditionally under-represented populations.

9.2. *Inclusion Criteria*

Subjects who meet all of the following criteria (Table 9.2-1) may be given consideration for inclusion in this clinical investigation, provided no exclusion criterion (Table 9.3-1) is met.

Table 9.2-1: 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 mm Hg or jet velocity >4.0 m/s, as measured by echocardiography
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 Case Review Committee [CRC]) and 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

	○ Porcelain aorta ○ Severe pulmonary hypertension (>60 mmHg) ○ Prior chest radiation therapy ○ Coronary artery bypass graft(s) at risk with re-operation ○ Severe lung disease (need for supplemental oxygen, FEV_1 <50% of predicted, DLCO <60%, other evidence of major pulmonary dysfunction) ○ Neuromuscular disease that creates risk for mechanical ventilation or rehabilitation after surgical aortic valve replacement ○ Orthopedic disease that creates risk for rehabilitation after surgical aortic valve replacement ○ Childs Class A or B liver disease (subjects with Childs Class C disease are not eligible for inclusion in this trial) ○ 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 ○ 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*:**	Extreme operative risk and high operative risk are defined as follows: **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. Risk of operative mortality and morbidity must be assessed via an in-person evaluation by a center cardiac surgeon and must be confirmed by the CRC (which must include an experienced cardiac surgeon).

Abbreviations: AVA=aortic valve area; CRC=Clinical Review Committee; NYHA=New York Heart Association; STS=Society of Thoracic Surgeons

9.3. *Exclusion Criteria*

Subjects who meet any one of the following criteria (Table 9.3-1) will be excluded from this clinical study.

Table 9.3-1: 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

Table 9.3-1: REPRISE III Exclusion Criteria

	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.
EC6.	Subject has severe (≥3+) 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 mass, thrombus or vegetation or one requiring treatment.
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 is being treated with chronic anticoagulation therapy other than warfarin. Subject requires chronic anticoagulation therapy (warfarin) and cannot tolerate concomitant therapy with either aspirin or clopidogrel. ***Note:*** Subjects who require chronic anticoagulation with warfarin must be able to be treated additionally with either aspirin or clopidogrel.
EC12.	Subject has active peptic ulcer disease or gastrointestinal bleed requiring hospitalization or transfusion within the past 3 months, other clinically significant bleeding diathesis or coagulopathy 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 peripheral vascular disease including aneurysm defined as maximal luminal diameter ≥5 cm or with documented presence of thrombus, marked tortuosity, 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.
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.

Table 9.3-1: REPRISE III Exclusion Criteria

EC26. Subject has severe incapacitating dementia.

* An alternative $P2Y_{12}$ inhibitor may be prescribed if subject is allergic to or intolerant of clopidogrel.
Abbreviations: AV= atrioventricular; CK=creatine kinase; MI=myocardial infarction; PCI=percutaneous coronary intervention

10. Subject Accountability

10.1. *Point of Enrollment*

10.1.1. Roll-in Subjects

There will be a non-randomized roll-in phase with only the test device for centers that do not have previous experience implanting the Lotus Valve. For this roll-in phase, subjects confirmed eligible for the study by the CRC (see Section 22.2) and who provided written informed consent are considered enrolled in the study as soon as an attempt is made to insert the Lotus Valve System into the subject's femoral artery.

10.1.2. Randomized Subjects

Subjects confirmed eligible for the study by the CRC (see Section 22.2) and who provided written informed consent are considered enrolled in the study upon randomization.

10.2. *Withdrawal*

All subjects enrolled in the clinical study (including those withdrawn from the clinical study or lost to follow-up) shall be accounted for and documented. If a subject withdraws from the clinical investigation, the reason(s) shall be reported. If such withdrawal is due to problems related to investigational device safety or performance, the investigator shall ask for the subject's permission to follow his/her status/condition outside of the clinical study.

11. Study Methods

11.1. *Data Collection*

The study event schedule is shown diagrammatically in Figure 11.1-1 and discussed in Table 11.1-1 and Sections 11.2 through 11.12. The methods are based on recommendations in the 2012 ACCF/AATS/SCAI/STS Expert Consensus Document on Transcatheter Aortic Valve Replacement[8] and the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease[90].

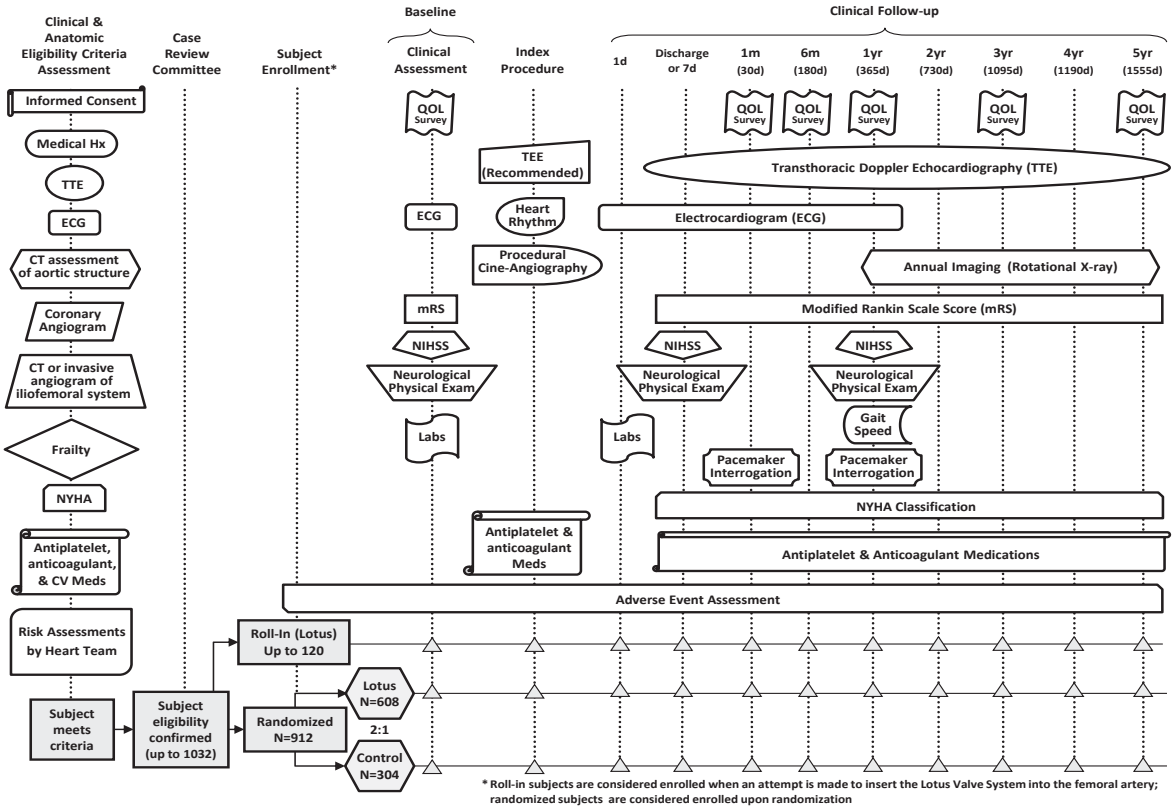

Figure 11.1-1: REPRISE III Study Design

Table 11.1-1: Study Event Schedule

Assessment	Screening[a]	Baseline	Procedure	Within 1 Day Post-procedure	Prior to Discharge or 7 Days Post-Procedure	30 Days[b] (±7 Days) Office Visit	6 Months[b] (±30 Days) Office Visit	12 Months[b] (±30 Days) Office Visit	24–60 Months[b] [Annual] (±45 Days) Office Visit
Signed Informed Consent Form[c]	X								
Demographics and medical history, including cardiac, neurological, renal (e.g., creatinine) and peripheral disease	X								
NYHA Classification	X				X	X	X	X	X
Neurological physical exam[d]		X			X			X	
NIHSS[d]		X			X			X	
Modified Rankin Scale[d]		X			X	X	X	X	X
12-lead ECG[e]	X	X	X[e]	X	X	X	X	X	
Laboratory tests[f]		X		X					
Risk assessments[g]	X								
Frailty, disability and comorbidity[h]	X							X	
Antiplatelet and anticoagulant (if applicable) medications	X		X		X	X	X	X	X
Other CV medications	X								
TTE[i]	X				X	X	X	X	X
TEE[j]			X						
Coronary angiogram[k]	X								
CT angiogram of aortic structure[l]	X								

Table 11.1-1: Study Event Schedule

Assessment	Screening[a]	Baseline	Procedure	Within 1 Day Post-procedure	Prior to Discharge or 7 Days Post-Procedure	30 Days[b] (±7 Days) Office Visit	6 Months[b] (±30 Days) Office Visit	12 Months[b] (±30 Days) Office Visit	24–60 Months[b] [Annual] (±45 Days) Office Visit
CT angiogram of iliofemoral system[m]	X								
Annual imaging (rotational X-ray)[n]								X	X
QOL surveys[o]		X				X	X	X	X[p]
Procedural cine-angiography (including post-deployment aortogram)[q]			X						
Pacemaker interrogation[r]						X		X	
AE and ADE assessments[s]			X	X	X	X	X	X	
Device deficiencies, SAE, SADE, USADE, UADE and CEC event assessments[t]			X	X	X	X	X	X	X

a: It is recommended that screening materials for CRC review be submitted electronically within 5 days of a scheduled CRC call in order to be considered for review (unless otherwise specified).

b: All follow-up dates will be calculated from the date of the index procedure. Visits must be an office/clinical visit, but may be done in-hospital should the subject be admitted at the time. Subjects who are enrolled but do not receive a study device (test or control) will be followed for 1 year to assess for safety but do not need to have protocol required TTE or ECG.

c: Study-specific consent includes screening consent to perform required assessments that will be evaluated by the CRC to confirm subject eligibility. If the study Informed Consent Form is modified during the course of the study, study subjects will be re-consented as necessary.

d: Neurological physical examination must be performed by a neurologist or neurology fellow. NIHSS and mRS must be performed by certified personnel (external certification for NIHSS; internal or external certification for mRS). The assessors should be independent (not involved with the care of study subjects). For subjects diagnosed with a neurological event (e.g., stroke, transient ischemic attack), a neurological physical exam, mRS, and NIHSS must be performed after the event; mRS must also be administered at 90±14 days post-neurological event. If a subject who has not received a study device (investigational or control) experiences a neurological event within the first 30 days after the index procedure, mRS must be performed on that subject after the event and at 90±14 days post-neurological event and the results must be reported to the Sponsor.

Table 11.1-1: Study Event Schedule

Assessment	Screening[a]	Baseline	Procedure	Within 1 Day Post-procedure	Prior to Discharge or 7 Days Post-Procedure	30 Days[b] (±7 Days) Office Visit	6 Months[b] (±30 Days) Office Visit	12 Months[b] (±30 Days) Office Visit	24–60 Months[b] [Annual] (±45 Days) Office Visit

e: All baseline and post-procedure 12-lead ECGs must be performed according to the ECG Core Laboratory guidelines (see study Manual of Operations). Heart rhythm strip should be obtained after BAV and before Lotus Valve insertion.

f: Laboratory tests at baseline include CBC with platelets, albumin, serum creatinine, and cardiac enzymes. Cardiac enzymes (CK is required, CK-MB or troponin if CK is elevated) must be collected twice at intervals per standard of care within 6-24 hours post-procedure. Acute kidney injury (AKI) should be assessed through discharge/7 days based on the AKIN system.

g: Consists of STS score (v 2.73), euroSCORE II (2011), and heart team assessment including an in-person evaluation by a center cardiac surgeon that must be confirmed by the CRC (which must include an experienced cardiac surgeon). In the United States, the Centers for Medicare and Medicaid Services require independent evaluations by 2 cardiac surgeons for reimbursement.

h: Frailty, disability, and comorbidity risk assessments must be captured at screening: height, weight, cognitive function (Mini-Cognitive Assessment for Dementia), strength and balance (use of wheelchair, gait speed to walk 5 meters, number of falls in the past 6 months, maximal grip strength), and activities of daily living (Katz Index); at 1 year, gait speed to walk 5 meters must be assessed again.

i: Transthoracic echocardiogram (TTE) is required for all subjects who have a valve implanted in the aortic position. This includes assessment of EOA, peak and mean aortic valve pressure gradients, aortic regurgitation assessment, and LVEF. Screening TTE must be performed within 60 days prior to CRC review. At least 1 echocardiogram must be obtained before discharge or 7 days (whichever comes first); if multiple echocardiographic studies are performed prior to discharge and within 7 days of the procedure, the latest study performed will be used for analysis. All TTEs must be performed according to the Echocardiography Core Laboratory procedure guidelines (see study Manual of Operations). If a subject does not receive an implanted valve, then no follow-up TTE is required.
Note: In cases of low flow low gradient aortic stenosis, dobutamine can be used to assess the grade of aortic stenosis; the subject may be enrolled if echocardiographic criteria are met with this augmentation. In cases where a subject who has met the echocardiographic criteria for enrollment receives BAV prior to the index procedure and subsequently no longer meets the REPRISE III aortic valve pressure gradient or EOA criteria, the subject may still be enrolled based on the pre-BAV echocardiographic data.

j: TEE is recommended but not required during the implant procedure.

k: A coronary angiogram must be performed within 365 days prior to CRC review. If there is concern regarding the current extent of coronary artery disease or aortic stenosis, the CRC may recommend a repeat study closer to the time of enrollment.

l: A CT angiogram of the aortic complex must be performed within 180 days prior to CRC review (and should be performed within 90 days if possible) to evaluate the aortic valve anatomy and aortic root dimensions for device sizing. CT angiogram must be performed according to the CT/X-ray Core Laboratory procedure guidelines (see study Manual of Operations). It must be sent to the Core Laboratory for detailed measurements and analyses in advance of the CRC meeting where results will be reviewed to confirm subject's eligibility.

m: An assessment of the iliofemoral system must be performed within 180 days prior to CRC review (and should be performed within 90 days if possible). A CT angiogram of the iliofemoral system should be performed for complete visualization of the iliac and femoral arteries to assess for dimensions, tortuosity, and calcification. The CT angiogram should be performed per the procedure guidelines (see study Manual of Operations) and sent to the CT Core Laboratory with the screening CT angiogram of the aortic structure. An iliofemoral invasive angiogram may be substituted for the iliofemoral CT angiogram.

Table 11.1-1: Study Event Schedule

Assessment	Screening[a]	Baseline	Procedure	Within 1 Day Post-procedure	Prior to Discharge or 7 Days Post-Procedure	30 Days[b] (±7 Days) Office Visit	6 Months[b] (±30 Days) Office Visit	12 Months[b] (±30 Days) Office Visit	24–60 Months[b] [Annual] (±45 Days) Office Visit

n: Annual imaging using rotational x-ray to assess for structural valve frame integrity must be performed on subjects who receive the Lotus Valve. Please refer to the Imaging Core Laboratory procedure guidelines (see study Manual of Operations). Results must be forwarded to the CT/X-Ray Core Laboratory for analysis. If additional imaging is performed (e.g., cardiac CT or MRI scan), data may be provided for analysis.

o: Includes the Kansas City Cardiomyopathy and SF-12 QOL questionnaires. Baseline QOLs should be performed within 30 days prior to the index procedure.

p: QOL survey at 36 and 60 months.

q: Procedural cine-angiogram including the final post-deployment aortogram of the ascending aorta must be performed and sent to the CT/X-Ray Core Laboratory for analysis.

r: For subjects who received a permanent pacemaker related to the index procedure, pacemaker dependence must be captured at the 30-day and 1-year visits via pacemaker interrogation. Pacemaker interrogation should also include assessment of the percentage of beats where the ventricles are paced..

s: AEs and ADEs will be monitored and collected from the time of enrollment through 12-month follow-up. For subjects who do not receive the study device, AEs will be monitored through 1-year follow-up.

t: Information on device deficiencies for the test and the control devices, as well as all SAEs, SADEs, UADEs, USADEs, and CEC events will be monitored and reported to Boston Scientific for all enrolled subjects from the time of enrollment through termination of the study. For subjects who do not receive a study device (test or control), the mentioned events will be monitored through 1 year post-index procedure. Please refer to Section 7.2 for a list of CEC events and Table 26.2-1 for definitions of these events, which specify data required for CEC adjudication. Complaint reporting of any device deficiencies for any commercially available products used should also be carried out using the manufacturer's processes.

Abbreviations: AE=adverse event; ADE=adverse device effect; AKI=acute kidney injury; BAV=balloon aortic valvuloplasty; CBC=complete blood count; CEC=Clinical Events Committee; CK-MB=creatine kinase-myoglobin band; CRC=Case Review Committee; CT=computed tomography; CV=cardiovascular; ECG=electrocardiogram; EOA= effective orifice area; LDH=lactate dehydrogenase; LV=left ventricle; MRI=magnetic resonance imaging; mRS=modified Rankin Scale; NIHSS=National Institutes of Health Stroke Scale; NYHA=New York Heart Association; QOL=Quality of Life; SAE=serious adverse event; SADE=serious adverse device effect; STS=Society of Thoracic Surgery; TEE=transesophageal Doppler echocardiography; TTE=transthoracic Doppler echocardiography; UADE=unanticipated adverse device effect; USADE=unanticipated serious adverse device effect

11.2. *Study Candidate Screening*

Subjects will be evaluated for eligibility by the center heart team (which must include a cardiac interventionalist and an experienced cardiac surgeon). Assessment will be based on results from the Society of Thoracic Surgeons (STS) score (≥8%) and/or agreement by the heart team that the subject is at extreme or high operative risk of serious morbidity or mortality with surgical valve replacement (see Table 9.2-1 for inclusion criteria and operative risk definitions). Risk of operative mortality and morbidity is to be assessed via an in-person evaluation by a center cardiac surgeon and must be confirmed by the CRC (which must include an experienced cardiac surgeon). In the United States, the Centers for Medicare and Medicaid Services (CMS) require independent evaluations by 2 cardiac surgeons for reimbursement. The heart team must also agree that the subject is likely to benefit from valve replacement.

Clinical assessment and evaluation as well as all collected tests and images (e.g., echocardiography, computerized tomography [CT], angiography) performed in preparation for TAVR will be reviewed by the CRC (see Section 8.2 and Section 22.2). The CRC will be comprised of experienced cardiac surgeons, interventional cardiologists, and Sponsor staff proficient with the Lotus Valve System and will confirm subject eligibility for enrollment.

11.3. *Subject Informed Consent*

Informed consent (see Section 20) must be obtained from a potential subject prior to conducting any preoperative assessments that are not part of the local routine preparation and evaluation of a subject for TAVR, even if the subject's eligibility has not yet been completely determined.

The Investigator/designee, who has been trained on the protocol, will explain the nature and scope of the study, potential risks and benefits of participation, and answer questions for the subject. If the subject agrees to participate, the Informed Consent form (ICF) must be signed and personally dated by the subject or his/her legally authorized representative. The Investigator/designee must also sign the ICF prior to subject enrollment. Any additional persons required by the center's Institutional Review Board (IRB)/Independent Ethics Committee (IEC) to sign the ICF must also comply. Study personnel should explain to the subject that even if the subject agrees to participate in the study and signs the ICF, the heart team and/or the CRC may determine that the subject is not a suitable candidate for the study and/or TAVR procedure.

If during the course of the preoperative evaluations, the subject is found not to be eligible for inclusion in the study, the subject should be notified. Reason for ineligibility will be accounted for as "screening failure" and will be documented as such in the screening module. If the subject has signed the ICF, but is found not eligible for inclusion in the study prior to or during the procedure, the subject should receive the appropriate treatment as identified by the clinical investigator. Information regarding the screening failure will be captured on the screening module and subject will be included in the "screening cohort" accountability.

11.4. *Screening Assessments*

The following screening tests and procedures must be performed and submitted to the CRC (Section 22.2) for evaluation to confirm a subject's eligibility for the study. Screening assessment documentation should be provided at least 5 days in advance of a scheduled CRC meeting via electronic upload. It is planned that CRC meetings will take place at least weekly or as needed to ensure timely review and confirmation of subject eligibility. Only after CRC approval of a subject's suitability for enrollment should the subject be randomized (within 7 calendar days).

Sites will be trained on the screening process as detailed in the REPRISE III Training Plan (see Section 17.4.1). Specific data points will be collected in the REPRISE III electronic Case Report Forms (eCRFs) as shown below.

- Clinical assessments
  - Demographics including age and gender
  - Medical history (general medical; cardiac [including previous cardiac surgery]; neurological, renal [including creatinine] and peripheral disease; and other medical conditions)
  - Physical examination including weight and height
  - NYHA classification
  - Current antiplatelet and other cardiovascular medications
  - 12-lead electrocardiogram (ECG) at screening and/or baseline must be performed according to the ECG Core Laboratory guidelines (see study Manual of Operations) and forwarded to Core Laboratory for analysis
  - Risk assessments: STS Score (2.73), euroSCORE II (2011), heart team assessment including an in-person evaluation by a center cardiac surgeon and any frailty assessments (detailed in next bullet). In the United States, CMS requires independent evaluations by 2 cardiac surgeons for reimbursement.
- Frailty, disability, and comorbidity assessments (collected prospectively)
  - Nutritional assessment
    - Albumin
    - Body Mass Index from the physical exam
  - Cognitive function: Mini-Cognitive Assessment for Dementia[91,92] (see study Manual of Operations).
  - Strength and balance
    - Use of wheelchair
    - Gait speed as measured by a stopwatch for a subject to walk 5 meters (3 measures averaged)[93-95]
    - Number of falls in the past 6 months
    - Maximal grip strength (kg) in the dominant hand (3 measures averaged), using a Jamar hand-held dynamometer[96]

  - Activities of daily living: Katz Index[92,97] is based on an evaluation of the functional independence or dependence of a subject in bathing, dressing, going to toilet, transferring, continence, and feeding. A point is assigned for independence in each of the 6 functions, and 0 points if there is any dependence in these 6 categories.

- Imaging assessments
  - Within 60 days prior to CRC review, TTE (2-D, M-Mode, and color) must be carried out. The evaluation should include assessment of effective orifice area (EOA), peak systolic and mean aortic valve gradient pressure, aortic regurgitation assessment, mitral regurgitation, LVEF, left ventricular end-diastolic and end-systolic diameter, tricuspid regurgitation (TR) jet velocity, and left atrial (LA) volume. The TTEs must be performed according to the Echocardiography Core Laboratory procedure guidelines (see study Manual of Operations). All TTEs for enrolled subjects must be sent to the Echocardiography Core Laboratory for independent analyses. In cases of low flow, low gradient aortic stenosis dobutamine can be used to assess the grade of aortic stenosis (maximum dobutamine dose of 20 mcg/kg/min recommended)[8]; the subject may be enrolled if echocardiographic criteria are met with this augmentation. In cases where a subject who has met the echocardiographic criteria for enrollment receives balloon aortic valvuloplasty (BAV) prior to the index procedure and subsequently no longer meets the REPRISE III aortic valve pressure gradient or EOA criteria, the subject may still be enrolled based on the pre-BAV echocardiographic data.
  - A coronary angiogram must be performed within 365 days prior to CRC review. If there is concern regarding the current extent of coronary artery disease or aortic stenosis, the CRC may recommend a repeat study closer to the time of enrollment. An aortogram and hemodynamics including simultaneous ascending aorta and left ventricle pressure measurements should be performed.
  - A CT angiogram of the aortic complex must be performed 180 days prior to the CRC review and should be performed within 90 days, if possible, to evaluate the aortic valve anatomy and aortic root dimensions to determine eligibility and device sizing. It must meet the CT Core Laboratory procedure guidelines (see study Manual of Operations) and forwarded in advance to the Core Laboratory for detailed measurements and independent analyses, which will be reviewed by the CRC to confirm subject's eligibility.
  - An assessment of the iliofemoral system must be performed within 180 days prior to the CRC review (and should be performed within 90 days if possible). A CT angiogram of the iliofemoral system should be performed for complete visualization of the iliac and femoral arteries to assess for dimensions, tortuosity, and calcification. The CT angiogram of the iliofemoral system should be performed per the procedure guidelines (see study Manual of Operations) and sent to the CT Core Laboratory with the screening CT angiogram of the aortic structure for independent measurements and review by the CRC to confirm subject's eligibility. An iliofemoral invasive angiogram may be substituted for the iliofemoral CT angiogram.

11.5. *Baseline Assessments*

The following assessments must be completed within 30 days prior to the index procedure, unless otherwise specified below. The REPRISE III electronic eCRFs identify the specific data points to be collected.

- Confirmation of eligibility criteria
- Neurological physical examination, which must be performed by a neurologist or neurology fellow (see Table 11.1-1); assessors should be independent (not involved with the care of study subjects).
- NIH Stroke Scale (NIHSS), which must be performed by certified personnel (external certification); assessors should be independent (not involved with the care of study subjects)
- Modified Rankin Scale score, which must be performed by certified personnel (external or internal certification); assessors should be independent (not involved with the care of study subjects)
- Laboratory tests
  - Complete blood count (CBC) with platelets
  - Serum creatinine
  - Cardiac enzymes (CK is required, CKMB or troponin if CK is elevated)
- 12-lead electrocardiogram (ECG) at screening and/or baseline must be performed according to the ECG Core Laboratory guidelines (see study Manual of Operations) and forwarded to Core Laboratory for analysis.
- Quality Of Life (QOL) Surveys: Kansas City Cardiomyopathy[87] and SF-12[88] QOL Questionnaires must be administered to the subject within 30 days prior to the procedure.

11.6. *Preprocedure Medications*

- Antiplatelet Therapy:

  Subjects must be treated with aspirin and a thienopyridine prior to valve implantation.

  Aspirin

  A loading dose of aspirin (recommended dose of 75–325 mg) is required for subjects who have not been taking aspirin for ≥72 hours at the time of the index procedure. The loading dose must be administered prior to the implant procedure. Subjects who have been taking aspirin daily for ≥72 hours at the time of the index procedure do not require a loading dose.

  Clopidogrel

  A loading dose of clopidogrel (recommended dose of ≥300 mg) is required for subjects who have not been taking clopidogrel for ≥72 hours at the time of the index procedure. The loading dose must be administered prior to the implant procedure.

Note 1: An alternative $P2Y_{12}$ inhibitor (e.g., ticlopidine) may be prescribed if subject is allergic to or intolerant of clopidogrel.

Note 2: If the study-specific dosages and durations for antiplatelet medications conflict with country-specific labeling for the medications, the country-specific labeling should take precedence.

Note 3: If a subject requires chronic anticoagulation with warfarin (other anticoagulants are not permitted), either clopidogrel or aspirin is required prior to the implant procedure in addition to the anticoagulant therapy (but both aspirin and clopidogrel are not required). Subjects treated with warfarin should not be treated with a $P2Y_{12}$ inhibitor other than clopidogrel.

- Anticoagulant therapy (e.g., unfractionated heparin) must be administered per local standard of care during the implant procedure, with a recommended target activated clotting time of ≥250 seconds during the implantation procedure.
- Additionally, the subject should be given prophylactic antibiotic therapy according to the local practice. The choice of antibiotic drug is left to the investigator's discretion.

11.7. *Index Procedure*

For sites in the US, CMS coverage criteria require that both the cardiac surgeon and interventional cardiologist members of the heart team participate in the technical aspects of the index procedure.

The preparation of the subject for the percutaneous procedure will be performed following standard techniques.

11.7.1. Medtronic CoreValve (Control) Cohort

The IFU associated with the control device (CoreValve) should be followed. A final post-deployment aortogram of the ascending aorta and rotational angiography of the valve frame must be performed and forwarded to the Core Laboratory with the procedural cine-angiogram for analysis.

Labels from devices used during the procedure (e.g., CoreValve, Introducer, etc.) should be retained so that they can be included in the appropriate source documents and reported in the eCRFs. During the procedure, designated center study personnel must capture necessary information on acute device/delivery system performance and procedure. The following information will be collected during the procedure.

- Date of procedure
- Specifics of device type (such as size and model)
- Time of first vascular puncture (femoral) and time of vascular closure (skin-to-skin time)
- Introducer insertion and removal time

- Descriptive information on balloon valve annuloplasty (e.g., size of balloon, number of balloon inflations)
- Any devices used and adjunctive procedures performed during implant procedure
- Heart rhythm after balloon valvuloplasty with rhythm strip should be recorded
- Valve catheter insertion and removal time
- Descriptive information on valve implantation procedure
- Adverse event (AE) assessment and associated treatment (including AE, serious adverse event [SAE], serious adverse device effect [SADE], unanticipated adverse device effect [UADE]/unanticipated serious adverse device effect [USADE], adverse device effect [ADE] and Clinical Events Committee [CEC] events; see Section 21).
- Device deficiencies assessment

11.7.2. Lotus Valve (Test) Cohort

The Lotus Introducer is prepared and introduced in the patient's femoral artery, as described in the Lotus Introducer IFU.

11.7.2.1. Valvuloplasty

A balloon valvuloplasty on the native valve following standard techniques must be performed with an appropriately sized valvuloplasty balloon (avoid oversizing). Careful attention should be paid to the position of the guidewire throughout the procedure. Prior to introduction of the Lotus Valve System, the subject's hemodynamic status and heart rhythm must be assessed, and a heart rhythm strip should be obtained.

Information on the balloon valvuloplasty, including number of inflations, should be documented in the source data and will be captured in the eCRFs.

Note: If the subject becomes hemodynamically unstable after the valvuloplasty for reasons unrelated to the aortic valve annulus and/or leaflets, the Lotus Valve implantation should be interrupted until the subject is stable.

11.7.2.2. Preparing and Using the Lotus Valve System

The Lotus Valve implantation procedure requires two operators: First and Second Operators. Both operators must comply with the IFU and must be adequately trained and certified by BSC personnel in accordance with the training plan before performing the procedure (see Section 17.4.1 for additional information on training). Guidelines provided by the Sponsor for valve size selection should be followed.

The Lotus Valve System must be prepared in accordance with the IFU. Device preparation should only be performed by persons who have completed appropriate training with the Lotus Valve.

Prior to insertion of the Lotus Valve catheter into the Lotus Introducer, the recommended target ACT of ≥250 seconds should be confirmed, with additional boluses of heparin administered if needed.

The Lotus Valve IFU should be followed. The following summarizes the Lotus Valve System procedure.

1) The Lotus delivery catheter is back-loaded onto a 0.035 in (0.89 mm) Super/Extra Stiff guidewire, maintaining proper guidewire positioning across the native valve and into the ventricle.
2) The Lotus catheter is inserted in the Lotus Introducer and carefully advanced through the aorta and the aortic arch under fluoroscopy.
3) The catheter is then advanced slowly through the aortic annulus. The valve is then mechanically expanded into the desired position.
4) Prior to the release of the Lotus Valve, assessment of its position and function is performed using contrast injection and/or TEE.
5) If the position of the valve is deemed too aortic or too ventricular, the valve is then partially or completely resheathed inside the catheter, with a repositioning made by either pulling or pushing the catheter carefully, using the radiopaque marker as a guide. The valve can then be re-expanded.
6) Once the Lotus Valve position is deemed satisfactory and the valve is fully locked, the release process is then initiated and the Lotus Valve is detached from the catheter.
7) The nosecone is recaptured and the system pulled out of the body.
8) A final post-deployment aortogram of the ascending aorta (including recommended rotational angiography of the valve frame) must be performed and forwarded to the Core Laboratory with the procedural cine-angiogram for analysis.
9) The Lotus Introducer is then removed.
10) The femoral access is then closed according to standard practice.

Labels from the devices used during the procedure (e.g., the Lotus Valve System, Lotus Introducer) should be retained so that they can be included in the appropriate source documents and reported in the eCRFs.

During the procedure, designated center study personnel must capture necessary information on acute device/delivery system performance and procedure. The following information will be collected during the procedure.

- Date of procedure
- Device size (23 mm, 25 mm, or 27 mm) and model
- Time of first vascular puncture (femoral) and time of vascular closure (skin-to-skin time)
- Lotus Introducer insertion and removal time

- Descriptive information on balloon valve annuloplasty (e.g., size of balloon, number of balloon inflations)
- Any devices used and adjunctive procedures performed during implant procedure
- Heart rhythm after balloon valvuloplasty with rhythm strip should be recorded
- Lotus Valve catheter insertion and removal time
- Descriptive information on Lotus Valve implantation procedure and information on valve repositioning or retrieval (if performed)
- Adverse event (AE) assessment and associated treatment (including AE, serious adverse event [SAE], serious adverse device effect [SADE], unanticipated adverse device effect [UADE]/unanticipated serious adverse device effect [USADE], adverse device effect [ADE] and Clinical Events Committee [CEC] events; see Section 21).
- Device deficiencies assessment (for the Lotus Valve System)

Note: All Lotus Valve implantation procedures will be performed with the support/presence of trained BSC personnel.

11.8. *Post-Procedure*

The following are to be performed post-procedure.

- Per society guidelines, antiplatelet therapy with aspirin and a thienopyridine is recommended to reduce the risk of thrombotic or thromboembolic complications if there are no contraindications to these medications[8,90]. Subjects must be treated with aspirin and clopidogrel for at least 1 month following valve implantation. Extended dual antiplatelet therapy may be administered per physician choice.
    - After the valve implant procedure, aspirin (recommended dose of ≥75 mg daily) must be given for at least 1 month. It is recommended that daily aspirin be given indefinitely thereafter as per local standard of care. Aspirin dose may be adjusted to the closest approximation based on local tablet formulation availability.
    - After the valve implant procedure, clopidogrel (recommended dose of 75 mg daily) is required for at least 1 month.
      Note: An alternative $P2Y_{12}$ inhibitor (e.g., ticlopidine) may be prescribed if subject is allergic to or intolerant of clopidogrel.
    - If a subject requires chronic anticoagulation with warfarin (other anticoagulants are not permitted), either clopidogrel or aspirin is required after the implant procedure in addition to the anticoagulant therapy (but both aspirin and clopidogrel are not required). Subjects treated with warfarin should not be treated with a $P2Y_{12}$ inhibitor other than clopidogrel.
- Prophylactic antibiotic regimen should be completed as per local practice.
- Additional medications may be used at the investigator's discretion.

- It is recommended that the subject's heart rhythm be monitored using telemetry for at least 48 hours after the index procedure.
- 12-lead ECG must be completed within 24 hours post-procedure per the ECG Core Laboratory guidelines (see study Manual of Operations) and must be forwarded to the Core Laboratory for analysis.
- Cardiac enzymes (CK is required, CK-MB or troponin if CK is elevated) must be collected twice at intervals per standard of care within 6-24 hours post-procedure.

11.9. *Prior to Discharge or 7 Days Post-Procedure (Whichever Comes First)*

Subjects must be evaluated prior to discharge or 7 days post-procedure (whichever comes first) based on the assessments below. The REPRISE III eCRFs identify the specific data points to be collected.

- Weight and height
- NYHA classification
- Neurological physical examination, which must be performed by a neurologist or neurology fellow; assessors should be independent (not involved with the care of study subjects)
- NIHSS, which must be performed by certified personnel (external certification); assessors should be independent (not involved with the care of study subjects)
- Modified Rankin Scale score, which must be performed by certified personnel (external or internal certification); assessors should be independent (not involved with the care of study subjects)
- 12-lead ECG per the Core Laboratory guidelines (see study Manual of Operations) and must be forwarded for analysis.
- TTE, including assessment of effective orifice area, peak systolic and mean aortic valve gradient pressure, aortic regurgitation assessment, mitral regurgitation, LVEF, left ventricular end-diastolic and end-systolic diameter, TR jet velocity and LA volume, per the Echocardiography Core Laboratory procedure guidelines (see study Manual of Operations). All TTEs for enrolled subjects must be sent to the Echocardiography Core Laboratory for independent analyses.

  Note: For all subjects who have a valve implanted in the aortic position during the index procedure at least 1 echocardiogram must be obtained before discharge or 7 days (whichever comes first); if multiple echocardiographic studies are performed prior to discharge and within 7 days of the procedure, the latest study performed will be used for analysis. Subjects who do not receive a transcatheter valve during the index procedure are not required to have follow-up TTE.
- Current antiplatelet and anticoagulant (if applicable) medications

- Complete adverse event (AE, SAE, SADE, UADE/USADE, ADE, and CEC events) and device deficiencies assessment (with associated treatment)

11.10. *Follow-up*

All implanted subjects will be evaluated at 30 days, 6 months, 12 months, 24 months, 36 months, 48 months, and 60 months post index procedure. Subjects who do not have a study device implanted will be assessed through 1 year post procedure for safety/adverse events. Physical clinic visits or follow-up visits are scheduled for appointed times after the date of the procedure. It is important that this schedule be maintained as closely as possible for all subjects. Boston Scientific Corporation recognizes that subjects may not be able to return for all scheduled visits at precisely the date required, and therefore, a period of time in which each visit is allowed is indicated in Table 11.1-1. Visits not completed will be considered missed and recorded as protocol deviations. Visits completed outside these windows will be recorded as protocol deviations. After 6 months, visits will be scheduled on an annual basis from 1 through 5 years. Each follow-up visit must be performed by study personnel; data from the required tests and images as well as medical assessments will be recorded in source documentation and captured in the eCRFs. The determination of specified study endpoints and measurements such as valve function and CEC events will require data from images and tests as outlined in the event definitions (Table 26.2-1).

In the event that study personnel learn of a subject's hospitalization outside the study center, the center should make every effort to obtain copies of reports or results based on tests (e.g., echocardiogram) and/or procedures performed on the study subject.

Note: A subject who has received a study valve should not be enrolled in a clinical trial of an investigational drug/device/treatment until the subject has reached the REPRISE III primary effectiveness endpoint (1 year).

11.10.1.30-Day Follow-up (30±7 Days)

All enrolled subjects must be evaluated 30 days after the index procedure. During the 30-day follow-up, the following assessments must be completed. The REPRISE III eCRFs identify the specific data points to be collected.

- Weight and height
- NYHA classification
- Modified Rankin Scale score, which must be performed by certified personnel (external or internal certification); assessors should be independent (not involved with the care of study subjects)
- 12-lead ECG per the Core Laboratory guidelines (see study Manual of Operations) and must be forwarded to the Core Laboratory for analysis.
- Current antiplatelet, anticoagulant (if applicable) medications

- TTE including assessment of effective orifice area, peak systolic and mean aortic valve gradient pressure, aortic regurgitation assessment, mitral regurgitation, LVEF, left ventricular end-diastolic and end-systolic diameter, TR jet velocity and LA volume. TTE must be performed per the Echocardiography Core Laboratory procedure guidelines (see study Manual of Operations). All TTEs for enrolled subjects must be sent to the Echocardiography Core Laboratory for independent analyses.
  Note: TTE must be done for all subjects who have a valve implanted in the aortic position during the index procedure. Subjects who do not receive a transcatheter valve during the index procedure are not required to have follow-up TTE.
- Quality of Life Surveys: Kansas City Cardiomyopathy and SF-12 Quality of Life Questionnaires
- Complete adverse event (AE, SAE, SADE, UADE/USADE, ADE and CEC events) and device deficiencies assessment (with associated treatment)
- For subjects who received a permanent pacemaker related to the index procedure, pacemaker dependence and percentage of beats where the ventricles are paced via pacemaker interrogation; please see the study Manual of Operations for determining pacemaker dependency.

11.10.2. 6-Month (180±30 Days) Follow-up

All implanted subjects must be evaluated at 6 months after the index procedure. During the 6-month follow-up, the following assessments must be completed. The REPRISE III eCRFs identify the specific data points to be collected.

- Weight and height
- NYHA classification
- Modified Rankin Scale score, which must be performed by certified personnel (external or internal certification); assessors should be independent (not involved with the care of study subjects)
- 12-lead ECG per the Core Laboratory guidelines (see study Manual of Operations) and must be forwarded for analysis
- Current antiplatelet, anticoagulant (if applicable) medications
- TTE, including assessment of effective orifice area, peak systolic and mean aortic valve gradient pressure, aortic regurgitation assessment, mitral regurgitation, LVEF, left ventricular end-diastolic and end-systolic diameter, TR jet velocity and LA volume, per the Echocardiography Core Laboratory procedure guidelines (see study Manual of Operations). It must be sent to the Core Laboratory for independent analysis.
  Note: TTE must be done for all subjects who have a valve implanted in the aortic position during the index procedure. Subjects who do not receive a transcatheter valve during the index procedure are not required to have follow-up TTE.

- Complete adverse event (AE, SAE, SADE, UADE/USADE, ADE and CEC events) and device deficiencies assessment (with associated treatment)
- Quality of Life Surveys: Kansas City Cardiomyopathy and SF-12 Quality of Life Questionnaires

11.10.3.12-Month (365±30 Days) Follow-up

All implanted subjects must be evaluated at 12 months after the index procedure. During the 12-month follow-up, the following assessments must be completed. The REPRISE III eCRFs identify the specific data points to be collected.

- Physical examination including weight and height
- NYHA classification
- Modified Rankin Scale score, which must be performed by certified personnel (external or internal certification); assessors should be independent (not involved with the care of study subjects
- Neurological physical examination, which must be performed by a neurologist or neurology fellow (see Table 11.1-1); assessors should be independent (not involved with the care of study subjects
- NIHSS, which must be performed by certified personnel (external certification); assessors should be independent (not involved with the care of study subjects
- Gait speed to walk 5 meters
- Rotational x-ray angiography performed on subjects who received the Lotus Valve to assess for structural valve frame integrity per the Imaging Core Laboratory procedure guidelines (see study Manual of Operations). It must be forwarded to the Core Laboratory for analysis.
- 12-lead ECG per the Core Laboratory Guidelines (see study Manual of Operations) and must be forwarded for analysis
- Current antiplatelet and anticoagulant (if applicable) medications
- TTE, including assessment of effective orifice area, peak systolic and mean aortic valve gradient pressure, aortic regurgitation assessment, mitral regurgitation, LVEF, left ventricular end-diastolic and end-systolic diameter, TR jet velocity and LA volume, per the Echocardiography Core Laboratory procedure guidelines (see study Manual of Operations). It must be forwarded to the Core Laboratory for independent analysis. **Note**: TTE must be done for all subjects who have a valve implanted in the aortic position during the index procedure. Subjects who do not receive a transcatheter valve during the index procedure are not required to have follow-up TTE.
- Complete adverse event (AE, SAE, SADE, UADE/USADE, ADE and CEC events) and device deficiencies assessment (with associated treatment)

- Quality of Life Surveys: Kansas City Cardiomyopathy and SF-12 Quality of Life Questionnaires
- For subjects who received a permanent pacemaker related to the index procedure, pacemaker dependence and percentage of beats where the ventricles are paced via pacemaker interrogation; please see the study Manual of Operations for determining pacemaker dependency.

11.10.4. Annual Follow-up (±45 Days)

All enrolled subjects implanted with a Lotus Valve must be evaluated at 24, 36, 48, and 60 months after the index procedure. During the annual follow-up, the following assessments must be completed. The REPRISE III eCRFs identify the specific data points to be collected.

- Physical examination including weight and height
- NYHA classification
- Modified Rankin Scale score, which must be performed by certified personnel (external or internal certification); assessors should be independent (not involved with the care of study subjects
- Current antiplatelet, anticoagulant (if applicable)
- TTE, including assessment of effective orifice area, peak systolic and mean aortic valve gradient pressure, aortic regurgitation assessment, mitral regurgitation, LVEF, left ventricular end-diastolic and end-systolic diameter, TR jet velocity, and LA volume, per the Echocardiography Core Laboratory procedure guidelines. All TTEs must be forwarded to the Core Laboratory for independent analyses.
  Note: TTE must be done for all subjects who have a valve implanted in the aortic position during the index procedure.
- Rotational x-ray angiography performed on subjects who received the Lotus Valve to assess for structural valve frame integrity per the Imaging Core Laboratory procedure guidelines (see study Manual of Operations). It must be forwarded to the Core Laboratory for analysis. If additional imaging is performed (e.g., cardiac CT or MRI scan), data may also be provided for analysis.
- Complete serious adverse event (SAE, SADE, USADE, and CEC events) and device deficiencies assessment (with associated treatment).
- Quality of Life Surveys: Kansas City Cardiomyopathy and SF-12 Quality of Life Questionnaires at 3 years and 5 years

11.10.5. Management of Missed or Late Visits

Missed or late visits will be recorded as protocol deviations and will be reviewed as such by the Sponsor or designee on a regular basis in accordance with applicable standard operating procedures.

Note: An in-person visit is required. If an in-person assessment cannot be performed, follow-up by telephone should be attempted. Subject or subject's physician should provide rationale for why the subject cannot come in for the follow-up visit.

11.10.6. Procedure for Determining when a Subject is Lost to Follow-up

A subject will be considered "lost to follow-up" and terminated from the study when all of the following criteria have been met.

- Failure to complete 2 consecutive visits without due cause (beginning with the 6-month and 1-year visits, i.e., subjects should not be considered lost to follow-up prior to the 1-year follow-up visit)
- Documentation of 3 unsuccessful attempts, one of which must be in written communication, by the Investigator or his/her designee to contact the subject or next of kin
- Notification from the Investigator to Sponsor reporting subject as lost to follow up

11.10.7. Withdrawal and Replacement of Subjects

While all efforts will be made to minimize attrition, subjects may withdraw from the study at any time, with or without reason and without prejudice to further treatment. Withdrawn subjects will not undergo any additional study follow-up, nor will they be replaced. The reason for withdrawal will be recorded (if given) in all cases of withdrawal. The investigator may discontinue a subject from participation in the study if the investigator feels that the subject can no longer fully comply with the requirements of the study or if any of the study procedures are deemed potentially harmful to the subject. Data that have already been collected on withdrawn subjects will be retained and used for analysis but no new data will be collected after withdrawal.

11.10.8. Explant Procedure

If a Lotus Valve test device is explanted during conventional scheduled or emergent surgical valve replacement or during an autopsy, if possible, the explanted valve should be sent to an independent histopathology core laboratory for macroscopic and microscopic analyses. Please refer to the study Manual of Operations for recommendations on the explant procedure and shipment of the explanted valve.

If a control device is explanted during conventional scheduled or emergent surgical valve replacement or during an autopsy, please follow the directions in the associated IFU.

Information on the explant procedure must be documented in source notes and captured in the Explant Form of the eCRFs.

11.11. *Study Completion*

All subjects who receive a test or control device will be evaluated at 30 days, 6 months, 12 months, 24 months, 36 months, 48 months, and 60 months post index procedure. All visits

are office visits. A subject's participation in the study will be considered complete after the 60-month visit. For subjects who do not receive a test or control device, participation in the study will be considered complete after the 1-year visit.

11.12. *Source Documents*

It is preferable that original source documents (see Table 26.2-1 for definition) are maintained, when available. Where copies of the original source document as well as printouts of original electronic source documents are retained, it is recommended that these be signed and dated by a member of the investigation center team with a statement that it is a true reproduction of the original source document.

12. Statistical Considerations

12.1. *Endpoints*

Data from roll-in subjects (up to 120 subjects) will be summarized separately from the randomized population. Roll-in subjects will not be included in the endpoint analyses.

Testing of endpoints will be carried out in a hierarchal manner in order to ensure the experiment-wise type I error rate is controlled. Testing will be done in 3 steps with each step needing to reject the null hypothesis in order to proceed to the next step:

1. Test the primary safety endpoint (Section 12.1.1) and the primary hypothesis of the primary effectiveness endpoint (Section 12.1.2.1.1). If the null hypothesis for both endpoints is rejected to show non-inferiority of the Lotus group to the CoreValve group, then proceed to step 2.
2. Test the secondary endpoint (Section 12.1.3); if the null hypothesis is rejected to show superiority of the Lotus group over the CoreValve group, then proceed to step 3.
3. Test the secondary hypothesis of the primary effectiveness endpoint (Section 12.1.2.1.2).

12.1.1. Primary Safety Endpoint

The primary safety endpoint is the composite of all-cause mortality, stroke, life-threatening and major bleeding events, stage 2 or 3 acute kidney injury, or major vascular complications evaluated at 30 days after the implant procedure.

12.1.1.1. Statistical Hypothesis for the Primary Safety Endpoint

The statistical hypothesis is that the rate of the primary safety endpoint (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) for the Lotus Valve is non-inferior to that for CoreValve.

The primary safety endpoint is expressed as the proportion of subjects who experience mortality, stroke, life-threatening and major bleeding events, stage 2 or 3 acute kidney injury,

or major vascular complications within 30 days after the index procedure among all subjects who either experience mortality/stroke/life-threatening or major bleeding events/stage 2 or 3 acute kidney injury/major vascular complications within 30 days after the index procedure or are followed for at least 23 days after the index procedure.

The null and alternative hypotheses for the primary safety endpoint are as follows:

H_0: P_{S_Lotus} minus $P_{S\_Control} \geq \Delta$ (Inferior)

H_1: P_{S_Lotus} minus $P_{S\_Control} < \Delta$ (Non-inferior)

where P_{S_Lotus} and $P_{S\_Control}$ are the rates of the primary safety endpoint at 30 days for the Lotus Valve (test) group and the CoreValve group (control), respectively, and Δ (delta) is the non-inferiority margin.

A Farrington-Manning standardized test will be used to test the one-sided hypothesis of noninferiority in the difference between the rates of the two treatment groups, as described in the Statistical Analysis Plan. If the *P* value from the Farrington-Manning standardized test is <0.025, the rate of the primary safety endpoint for the Lotus Valve will be concluded to be non-inferior to the CoreValve rate. This corresponds to the one-sided upper 97.5% confidence bound on the difference between treatment groups (Lotus Valve minus CoreValve) for the observed rate of the primary safety endpoint at 1 year being less than the non-inferiority margin.

12.1.1.2. Sample Size Parameters for the Primary Safety Endpoint

The sample size calculation for the primary safety endpoint is based on the following assumptions.

- Expected Lotus Valve (test) rate = 40%
- Expected CoreValve (control) rate = 40%
- Non-inferiority margin (Δ) = 10.5%
- Test significance level (α) = 0.025 (1-sided)
- Test : Control ratio = 2:1
- Expected rate of attrition = 5%

Given enrollment of 912 subjects (608 Lotus Valve, 304 CoreValve) and 5% attrition, there is approximately 85% power to show non-inferiority with the given expected rates.

12.1.1.3. Statistical Methods – Primary Safety Endpoint

All subjects who are enrolled and randomized will be eligible for evaluation. Any events or hospitalizations occurring after enrollment but prior to the index procedure should be entered in the electronic data capture system; events with onset date starting from the time of the index procedure will be included in the primary endpoint analysis.

Handling of dropouts and missing data will depend on their frequency and the nature of the outcome measure. Sensitivity analyses (e.g., tipping-point analysis) will be performed to assess the impact of subjects with inadequate follow-up (i.e., missing data) on the primary

endpoint and to assess the robustness of the conclusion of the primary analysis. The sensitivity analysis of the primary endpoint, including events occurring after enrollment but prior to the index procedure, will be performed. Statistical models that account for censored data will be employed in appropriate circumstances (e.g., for time-to-event outcomes). Suspected invalid data will be queried and corrected in the database prior to statistical analysis. Additional information may be found in the Statistical Analysis Plan.

12.1.2. Primary Effectiveness Endpoint

The primary effectiveness endpoint is the composite of all-cause mortality, disabling stroke, or moderate or severe paravalvular aortic regurgitation (based on independent core lab assessment) at 1 year.

12.1.2.1. Statistical Hypothesis for the Primary Effectiveness Endpoint

12.1.2.1.1 Primary Hypothesis

The primary statistical hypothesis is that the rate of the primary effectiveness endpoint (composite of all-cause mortality, disabling stroke, or moderate or severe paravalvular aortic regurgitation [based on independent core lab assessment] at 1 year) for the Lotus Valve group is non-inferior to that for the CoreValve group.

The null and alternative hypotheses for the primary hypothesis of the primary effectiveness endpoint are as follows:

H_0: P_{E_Lotus} minus $P_{E\_Control} \geq \Delta$ (Inferior)

H_1: P_{E_Lotus} minus $P_{E\_Control} < \Delta$ (Non-inferior)

where P_{E_Lotus} and $P_{E\_Control}$ correspond to the rates of the primary effectiveness endpoint for the Lotus Valve group (test) and the CoreValve group (control), respectively, and Δ (delta) is the non-inferiority margin.

A Farrington-Manning test will be used to test the one-sided hypothesis of non-inferiority in the difference between the rates of the two treatment groups, as described in the Statistical Analysis Plan. If the *P* value from the Farrington-Manning standardized test is <0.025, the rate of the primary effectiveness endpoint for the Lotus Valve will be concluded to be non-inferior to the CoreValve rate. This corresponds to the one-sided upper 97.5% confidence bound on the difference between treatment groups (Lotus Valve minus CoreValve) for the observed rate of the primary effectiveness endpoint being less than the noninferiority margin.

12.1.2.1.2 Secondary Hypothesis

The secondary statistical hypothesis is that the rate of the primary effectiveness endpoint (composite of all-cause mortality, disabling stroke, or moderate or severe paravalvular aortic regurgitation [based on independent core lab assessment] at 1 year) for the Lotus Valve group is superior to that for the CoreValve group. This test will be carried out only if the null hypothesis from the statistical hypothesis is rejected for the primary safety endpoint (Section 12.1.1), the primary hypothesis of the primary effectiveness endpoint

(Section 12.1.2), and the secondary endpoint (Section 12.1.3), and the rate for the primary effectiveness endpoint for the Lotus group is less than that of the CoreValve group.

The null and alternative hypotheses for the secondary hypothesis of the primary effectiveness endpoint are as follows:

H_0: $P_{E\_Lotus} = P_{E\_Control}$

H_1: $P_{E\_Lotus} \neq P_{E\_Control}$

where P_{E_Lotus} and $P_{E\_Control}$ correspond to the rates of the primary effectiveness endpoint for the Lotus Valve group (test) and the CoreValve group (control), respectively.

A chi-square test will be used to test the two-sided hypothesis of superiority between the rates of the two treatment groups, as described in the Statistical Analysis Plan. If the *P* value from the chi-square test is <0.05 and the rate of the Lotus Valve group is less than the rate of the CoreValve group, the rate of the primary effectiveness endpoint for the Lotus Valve will be concluded to be superior to the CoreValve rate. This corresponds to the two-sided upper 95% confidence bound on the difference between treatment groups (Lotus Valve minus CoreValve) for the observed rate of the primary effectiveness endpoint being less than zero.

12.1.2.2. Sample Size Parameters for the Primary Effectiveness Endpoint

12.1.2.2.1 Primary Hypothesis

The sample size calculation for the primary hypothesis of the primary effectiveness endpoint at 1 year is based on the following assumptions.

- Expected Lotus Valve (test) rate = 32%
- Expected CoreValve (control) rate = 32%
- Non-inferiority margin (Δ) = 9.5%
- Test significance level (α) = 0.025 (1-sided)
- Test : Control ratio = 2:1
- Power ($1-\beta$) = 80%
- Total number of evaluable subjects = 819
- Expected rate of attrition = 10%

Given the above assumptions, at least 912 randomized subjects (608 Lotus Valve, 304 CoreValve) are needed to account for attrition.

12.1.2.2.2 Secondary Hypothesis

The sample size calculation for the secondary hypothesis of the primary effectiveness endpoint at 1 year is based on the following assumptions.

- Expected Lotus Valve (test) rate = 22%
- Expected CoreValve (control) rate = 32%

- Test significance level (α) = 0.05 (2-sided)
- Test : Control ratio = 2:1
- Expected rate of attrition = 10%

Given enrollment of 912 subjects (608 Lotus Valve, 304 CoreValve) and 10% attrition, there is approximately 86% power to show superiority with the given expected rates.

12.1.2.3. Statistical Methods – Primary Effectiveness Endpoint

Procedures similar to that described in Section 12.1.1.3 and discussed in the Statistical Analysis Plan will be applied to analysis of the primary effectiveness endpoint.

12.1.3. Secondary Endpoint

The secondary endpoint is the rate of moderate or greater paravalvular aortic regurgitation (based on review by an independent core lab) at 1 year. To control for experiment-wise type I error, testing for the secondary endpoint will be conducted only if the null hypotheses for the primary safety and the primary analysis of the primary effectiveness endpoints are rejected. That is, non-inferiority must be shown for the primary safety endpoint and the primary effectiveness endpoint for testing to be conducted for the secondary endpoint.

12.1.3.1. Statistical Hypothesis for the Secondary Endpoint

The statistical hypothesis is that the secondary endpoint of moderate or greater paravalvular aortic regurgitation rate at 1 year (based on review by an independent core lab) for the Lotus Valve is superior to that for the CoreValve group.

The null and alternative hypotheses for the secondary endpoint are as follows:

H_0: $P_{AR\_Lotus} = P_{AR\_Control}$

H_1: $P_{AR\_Lotus} \neq P_{AR\_Control}$

where P_{AR_Lotus} and $P_{AR\_Control}$ correspond to the rates of moderate or greater paravalvular aortic regurgitation at 1 year for the Lotus Valve group (test) and the CoreValve group (control), respectively.

A chi-square test will be used to test the two-sided hypothesis of superiority between the rates of the two treatment groups, as described in the Statistical Analysis Plan. If the *P* value from the chi-square test is <0.05 and the rate of the Lotus Valve group is less than the rate of the CoreValve group, the rate of moderate or greater paravalvular aortic regurgitation for the Lotus Valve group will be concluded to be superior to that of the CoreValve group.

12.1.3.2. Sample Size Parameters for the Secondary Endpoint

The sample size calculation for the secondary endpoint (moderate/severe paravalvular aortic regurgitation rate at 1 year) is based on the following assumptions.

- Expected Lotus Valve (test) rate P_{AR_Lotus} = 1.1%
- Expected CoreValve (control) rate $P_{AR\_Control}$ = 5.3%

- Test significance level (α) = 0.05 (2-sided)
- Test : Control ratio = 2:1
- Expected rate of attrition = 25%

Given enrollment of 912 subjects (608 Lotus Valve, 304 CoreValve) and 25% attrition, there is approximately 86% power to show superiority with the given expected rates.

12.1.3.3. Statistical Methods – Secondary Endpoint

Procedures similar to that described in Section 12.1.1.3 and discussed in the Statistical Analysis Plan will be applied to analysis of the secondary endpoint.

12.1.4. Baseline Comparability

Baseline data will be summarized by treatment group for the randomized subjects and separately for the roll-in subjects. Subject demographics, clinical and neurological history, risk factors, and preprocedure characteristics will be summarized using descriptive statistics (e.g., mean, standard deviation, n, minimum, maximum) for continuous variables and frequency tables or proportions for discrete variables. Treatments for the randomized subjects will be compared with a chi-square or Fisher exact test for discrete variables and a Student *t*-test for continuous variables. Treatment differences for the randomized subjects and their 95% confidence intervals will be presented. Procedural characteristics will be summarized similarly. No formal statistical testing will be done for the roll-in subjects.

12.1.5. Post-procedure Measurements

Post-procedure information will be collected at regularly scheduled follow-up examinations as detailed in the clinical study schedule (Table 11.1-1) and will be summarized using descriptive statistics for continuous variables (e.g., mean, standard deviation, n, minimum, maximum) and frequency tables or proportions for discrete variables. Estimates will be reported by treatment group and, for randomized subjects, differences between treatment groups and their 95% confidence intervals will be presented. Treatments for the randomized subjects will be compared with the chi-square or Fisher exact test for discrete variables and the Student t-test for continuous variables. No inferences are planned on the additional measurements and, therefore, alpha-adjustments for multiple comparisons will not be used. The Kaplan-Meier product-limit method will be used to estimate rates for time-to-event endpoints and treatment groups will be compared using the Log-rank and Wilcoxon tests. Adverse event and SAE rates will be reported. No formal statistical testing will be done for the roll-in subjects.

12.1.6. Subgroup Analyses for Randomized Subjects

Primary and pre-specified additional endpoints will be summarized and treatment groups will be compared for the following subgroups of randomized subjects.

- Gender (male and female)

- Extreme risk and high risk (see Table 26.2-1 for definitions of extreme and high operative risk)
- Region (North America, outside North America)

No adjustments for multiple comparisons will be made. Additional analyses may be performed as appropriate.

12.2. *General Statistical Methods*

All statistical analyses will be performed using the SAS System software, version 9.2 or later (Copyright© 2000 SAS Institute Inc., SAS Campus Drive, Cary, North Carolina 27513, USA. All rights reserved).

All statistical analyses will be conducted according to applicable Standard Operating Procedures, Work Instructions, and the study-specific Statistical Analysis Plan.

12.2.1. Analysis Sets

The primary endpoints and additional measurements will be analyzed on an ITT, an as-treated, and an implanted basis. For ITT analyses, all subjects who sign the IRB/IEC-approved study ICF (see Section 11.3), are enrolled in the trial, are randomized, and received a study device, will be included in the analysis, whether or not an assigned study valve (Lotus Valve or CoreValve) was implanted. The as-treated population includes all subjects who sign the IRB/IEC-approved study ICF, are enrolled in the trial, and are randomized, with the analysis based on the treatment actually received (for example, if a subject is assigned to receive a test device but instead receives a control device, that subject will be considered a control subject for the as-treated analyses). For implanted analyses, ITT subjects who had the assigned, randomized study valve (Lotus Valve or CoreValve) implanted will be included in the analysis. For all analysis sets, if a subject receives 2 valves, the subject is assigned to the group corresponding to the first valve received.

The primary safety endpoint, primary effectiveness endpoint (both hypotheses), and the secondary endpoint will all be analyzed for the ITT, as-treated, and implanted analysis sets. The primary analysis for the primary hypothesis of the primary effectiveness endpoint and the primary safety endpoint will be based on the implanted analysis set. The primary analysis set for the secondary hypothesis of the primary effectiveness endpoint and the secondary endpoint will be based on the ITT analysis set.

After 1 year, all analyses will be based on the safety analysis set. All subjects who sign the written ICF, are enrolled in the study, and have a study device implanted regardless of the device and treatment assignment will be included in the safety analysis set.

12.2.2. Control of Systematic Error/Bias

All subjects who have met the inclusion/exclusion criteria, received a positive recommendation from the CRC, and signed the Informed Consent Form will be eligible for

enrollment in the study. The center heart team's assessment of TTE measurements before device placement will contribute to the determination of subject eligibility for the study.

To control for inter-observer variability, data from independent core laboratories (see Section 13.3) will be used for analysis. These include an echocardiography core lab, a CT and rotational X-ray angiography core laboratory to assess all CT and rotational X-ray data using standard techniques, and an electrocardiography core laboratory to independently analyze protocol-required 12-lead ECGs performed for each subject.

12.2.3. Randomization Scheme

A computer generated list of random treatment allocations (i.e., a randomization schedule) will be used to assign subjects to treatment in a 2:1 ratio of Lotus Valve to CoreValve. Randomization will be stratified by center and risk factor (extreme and high operative risk with a targeted enrollment of at least 30% of subjects in each group; see Table 26.2-1 for operative risk definitions). Additional information is provided in the study Manual of Operations.

12.2.4. Reporting Events

For subjects who have a procedure or an attempted procedure, all events that occur from the date of the (attempted) procedure onward will be reported. For subjects who do not have a (attempted) procedure, events from the date of randomization to 30 days post-randomization will be reported. For time based clinical events, the cut-off for events for 30-day endpoints will be 30 days, for 6-month endpoints will be 180 days, for 1-year endpoints will be 365 days, and for 2-5 year endpoints will be 365 days times the number of years. For events at discharge or 7 days post-procedure, the cut-off for events will be the earlier of the date of discharge or 7 days post-procedure for each subject.

12.3. *Data Analyses*

Baseline and outcome variables will be summarized using descriptive statistics for continuous variables (mean, standard deviation, number of observations, minimum and maximum) and discrete variables (percentage and count/sample). See Section 12.1 for a discussion on analysis of the primary safety endpoint, primary effectiveness endpoint, secondary endpoint, and additional measurements.

12.3.1. Other Measurements

Other measurements not driven by statistical hypotheses are listed in Section 7.2.

12.3.2. Interim Analyses

No formal interim analyses are planned for the purpose of stopping this trial early for effectiveness or futility. An administrative analysis of 30-day data for the first 300 randomized patients will be performed by a statistician independent of BSC for European

regulatory agency review after these 300 patients have completed their 30-day follow-up visits.

12.3.3. Justification of Pooling

Analyses for the primary safety and effectiveness endpoints and the secondary endpoint will be presented using data pooled across institutions and surgical (high or extreme) risk groups. An assessment of the poolability of subjects across centers and surgical risk groups will be made using logistic regression. Main effects for the center (risk group) and treatment and the interaction of the center (risk group) by treatment will be included in separate logistic regression models with the primary safety endpoint, the primary effectiveness endpoint, and the secondary endpoint as the outcome. If the *P* value for center (risk group) by treatment interaction is ≥0.15, it can be concluded that the treatment effect is not different across the centers (risk groups) and the data can be pooled. In the analysis to justify pooling across centers, the centers with fewer than 6 subjects enrolled in the study will be combined into "virtual centers" based on geographic region so that "virtual centers" have ≥6 subjects but no more than the largest enrolling center.

12.3.4. Multivariable Analyses

Univariate and multivariate analyses will be performed to assess the effect of potential predictors on the primary safety and effectiveness endpoints and the secondary endpoint as described in the Statistical Analysis Plan.

12.3.5. Changes to Planned Analyses

Any changes to the planned statistical analyses made prior to performing the analyses will be documented in an amended Statistical Analysis Plan approved before performing the analyses. Changes from the planned statistical methods after performing the analyses will be documented in the clinical study report along with a reason for the deviation.

13. Data Management

13.1. *Data Collection, Processing, and Review*

Subject data will be recorded in a limited access secure electronic data capture (EDC) system. Only personnel trained and authorized will have access to the system.

The clinical database will reside on a production server hosted by Medidata. All changes made to the clinical data will be captured in an electronic audit trail and available for review by BSC or its representative. The associated RAVE software and database have been designed to meet regulatory compliance for deployment as part of a validated system compliant with laws and regulations applicable to the conduct of clinical studies pertaining to the use of electronic records and signatures. Database backups are performed regularly.

The Investigator provides his/her electronic signature on the appropriate eCRFs in compliance with local regulations. A written signature on printouts of the eCRFs must also be provided if required by local regulation. Changes to data previously submitted to the Sponsor require a new electronic signature by the Investigator acknowledging and approving the changes.

Visual and/or electronic data review will be performed to identify possible data discrepancies. Manual and/or automatic queries will be created in the EDC system and will be issued to the center for appropriate response. Center staff will be responsible for resolving all queries in the database.

13.2. *Data Retention*

The Investigator will maintain at the investigative center all essential study documents and source documentation that support the data collected on the study subjects in compliance with ICH/GCP guidelines. Documents must be retained for at least 2 years after the last approval of a marketing application or until at least 2 years have elapsed since the formal discontinuation of the clinical investigation of the product. These documents will be retained for a longer period of time by agreement with BSC or in compliance with other local regulations. It is BSC's responsibility to inform the Investigator when these documents no longer need to be maintained. The Investigator will take measures to ensure that these essential documents are not accidentally damaged or destroyed. If for any reason the Investigator withdraws responsibility for maintaining these essential documents, custody must be transferred to an individual who will assume responsibility and BSC must receive written notification of this custodial change.

13.3. *Core Laboratories*

13.3.1. Transthoracic Echocardiography (TTE) Core Laboratory

An independent Core Laboratory will review echocardiography images from all centers and every subject enrolled in this study for qualitative and quantitative analysis. These analyses will minimize bias and inconsistencies by providing an independent interpretation of all measurements using standard techniques. The TTE procedure guideline is provided by the core laboratory in the study Manual of Operations.

13.3.2. CT and Rotational X-Ray Angiography Core Laboratory

An independent Core Laboratory will centrally assess all of the CT and rotational X-ray angiography data in this study to reduce variability. These analyses will minimize bias and inconsistencies by providing an independent interpretation of all measurements using standard techniques. The screening CT Angiogram procedure guidelines and annual imaging acquisition protocol are provided by the core laboratory in the study Manual of Operations.

13.3.3. Electrocardiography (ECG) Core Laboratory

All 12-lead ECGs performed at each of the required protocol visits will be sent to an ECG core laboratory (see study Manual of Operations) for independent analyses. These analyses will minimize bias and will provide consistent interpretation of the ECGs.

13.3.4. Histopathology Core Laboratory

If a Lotus Valve (test device) is explanted during conventional scheduled or emergent surgical valve replacement or during an autopsy, please refer to the study Manual of Operations for recommendations on the explant procedure and shipment of the explanted valve to an independent histopathology laboratory for analyses.

14. Amendments

If a protocol revision is necessary which affects the rights, safety or welfare of the subjects or scientific integrity of the data, an amendment is required. Appropriate approvals (e.g., IRB/EC/FDA/CA) of the revised protocol must be obtained prior to implementation.

15. Deviations

An Investigator must not make any changes or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency. An investigator shall notify the Sponsor and the reviewing IRB/EC of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency, and those deviations which affect the scientific integrity of the clinical investigation. Such notice shall be given as soon as possible, but no later than 5 working days after the emergency occurred, or per prevailing local requirements, if sooner than 5 working days.

All deviations from the investigational plan, with the reason for the deviation and the date of occurrence, must be documented and reported to the Sponsor using the EDC CRF. Centers may also be required to report deviations to the IRB/EC, per local guidelines and government regulations.

Deviations will be reviewed and evaluated on an ongoing basis and, as necessary, appropriate corrective and preventive actions (including notification, center re-training, or discontinuation) will be put into place by the Sponsor.

16. Device Accountability

16.1. *Investigational Device*

The Lotus Valve System (investigational device) will be released by the Sponsor to the clinical center only after the center has been initiated and all regulatory approvals as well as required documentation have been collected from the center.

The Lotus Valve System shall be securely maintained, controlled, and used only in this clinical study. Additionally, the study personnel must follow the instructions related to the storage of the test and control devices as noted in the corresponding IFUs. Device Accountability Logs for the Lotus Valve System will be provided to the centers and will be used to track subjects and device allocations during the study.

The Sponsor shall keep records to document the physical location of all investigational devices from shipment of investigational devices to the investigation centers until return or disposal.

Centers must not dispose of any investigational devices for any reason at the center unless instructed to do so by BSC. Any investigational device that is disposed of at the center must be recorded in the Device Accountability Log. The PI must document the reasons for any discrepancy noted in device accountability.

The principal investigator or an authorized designee shall keep records documenting the receipt, use, return and disposal of the investigational devices, which shall include the following; this will be verified by personnel from BSC or its designee.

- Date of receipt
- Identification of each investigational device (Part/Reference, Lot numbers, valve size)
- Expiry date, as applicable
- Date of use
- Subject identification
- Date on which the investigational device was returned/explanted from subject, if applicable
- Date of return of unused, expired, or malfunctioning investigational devices, if applicable

Written procedures may be required by national regulations.

Once the Investigator and Center are notified in writing by BSC that subject enrollment is complete, all unused investigational devices must be returned to BSC or its designee. A copy of the Device Accountability Logs must also be provided to BSC.

16.2. *Control Device*

Appropriate information on control device size and model will be collected.

17. Compliance

17.1. *Statement of Compliance*

The REPRISE III study will be conducted in accordance with the relevant parts of the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practices (GCP) or the International Standard ISO 14155: 2011; ethical principles that have their origins in the Declaration of Helsinki; and pertinent individual country/state/local laws and regulations.

17.2. *Investigator Responsibilities*

The Principal Investigator of an investigational center is responsible for ensuring that the study is conducted in accordance with the Clinical Study Agreement, the investigational plan/protocol, ISO 14155 or ICH/GCP, ethical principles that have their origins in the Declaration of Helsinki, any conditions of approval imposed by the reviewing IRB/EC, and prevailing local and/or country laws and/or regulations, whichever affords the greater protection to the subject.

The Principal Investigator's responsibilities include, but are not limited to, the following.

- Prior to beginning the study, sign the Investigator Agreement and Protocol Signature page documenting his/her agreement to conduct the study in accordance with the protocol.
- Provide his/her qualifications and experience to assume responsibility for the proper conduct of the study and that of key members of the center team through up-to-date curriculum vitae or other relevant documentation and disclose potential conflicts of interest, including financial, that may interfere with the conduct of the clinical study or interpretation of results.
- Complete training requirements associated with the CoreValve device.
- Complete all Lotus Valve (investigational device) training requirements as detailed in the REPRISE III Training Plan (see Section 17.4.1).
- Make no changes in or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency; document and explain any deviation from the approved protocol that occurred during the course of the clinical investigation.
- Create and maintain source documents throughout the clinical study and ensure their availability with direct access during monitoring visits or audits; ensure that all clinical-investigation-related records are retained per requirements.
- Ensure the accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor in the CRFs and in all required reports.
- Record, report, and assess (seriousness and relationship to the device/procedure) every adverse event and observed device deficiency.

- Report to BSC, per the protocol requirements, all SAEs and device deficiencies that could have led to a SADE.
- Report to the IRB/EC and regulatory authorities any SAEs and device deficiencies that could have led to a SADE, if required by the national regulations or this protocol or by the IRB/EC, and supply BSC with any additional requested information related to the safety reporting of a particular event.
- Maintain the device accountability records and control of the investigational device, ensuring that the investigational device is used only by authorized/designated users and in accordance with this protocol and instructions/directions for use.
- Allow the Sponsor and Sponsor representatives to perform monitoring and auditing activities, and be accessible to the monitor and respond to questions during monitoring visits.
- Allow and support regulatory authorities and the IRB/EC when performing auditing activities.
- Ensure that informed consent is obtained in accordance with this protocol and local IRB/EC requirements.
- Provide adequate medical care to a subject during and after a subject's participation in a clinical study in the case of adverse events, as described in the ICF.
- Inform the subject of the nature and possible cause of any adverse events experienced.
- Inform the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required.
- Provide the subject with well-defined procedures for possible emergency situations related to the clinical study, and make the necessary arrangements for emergency treatment as needed.
- Ensure that clinical medical records are clearly marked to indicate that the subject is enrolled in this clinical study.
- Ensure that, if appropriate, subjects enrolled in the clinical investigation are provided with some means of showing their participation in the clinical investigation, together with identification and compliance information for concomitant treatment measures (contact address and telephone numbers shall be provided).
- Inform, with the subject's approval or when required by national regulations, the subject's personal physician about the subject's participation in the clinical investigation.
- Make all reasonable efforts to ascertain the reason(s) for a subject's premature withdrawal from clinical investigation while fully respecting the subject's rights.
- Ensure that an adequate investigation center team and facilities exist and are maintained and documented during the clinical investigation.

- Ensure that maintenance and calibration of the equipment relevant for the assessment of the clinical investigation is appropriately performed and documented, where applicable.

17.2.1. Delegation of Responsibility

When specific tasks are delegated by an investigator, included but not limited to conducting the informed consent process, the investigator is responsible for providing appropriate training and adequate supervision of those to whom tasks are delegated. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

17.3. *Institutional Review Board/ Ethics Committee*

Prior to gaining Approval-to-Enroll status, the investigational center will provide to the Sponsor documentation verifying that their IRB/EC is registered or that registration has been submitted to the appropriate agency, as applicable according to national/regulatory requirements.

A copy of the written IRB/EC and/or competent authority approval of the protocol (or permission to conduct the study) and Informed Consent Form, must be received by the Sponsor before recruitment of subjects into the study and shipment of investigational product/equipment. Prior approval must also be obtained for other materials related to subject recruitment or which will be provided to the subject.

Annual IRB/EC approval and renewals will be obtained throughout the duration of the study as required by local/country or IRB/EC requirements. Copies of the Investigator's reports and the IRB/EC continuance of approval must be provided to the Sponsor.

17.4. *Sponsor Responsibilities*

All information and data sent to BSC and its authorized designee concerning subjects or their participation in this study will be considered confidential by BSC. Only authorized BSC personnel, representatives, or designees will have access to these confidential records. Authorized regulatory personnel have the right to inspect and copy all records pertinent to this study. Study data collected during this study may be used by BSC for the purposes of this study, publication, and to support future research and/or other business purposes. Data used in the analysis and reporting of this study will not be identified by specific subject name.

Note: Boston Scientific may utilize a contract research organization (CRO) or other contractors to act as its representative for carrying out designated tasks.

Boston Scientific Corporation will keep subjects' health information confidential in accordance with all applicable laws and regulations. Boston Scientific Corporation may use subjects' health information to conduct this research, as well as for additional purposes, such as overseeing and improving the performance of its device, new medical research and proposals for developing new medical products or procedures, and other business purposes.

Information received during the study will not be used to market to subjects; subject names will not be placed on any mailing lists or sold to anyone for marketing purposes.

17.4.1. Training with the Lotus Valve System

The Sponsor is responsible for providing Investigators with the information and training on the Lotus Valve System they need to conduct the study properly. The Sponsor is responsible for maintaining documentation of attendance at each of the training sessions provided.

A Lotus Training Plan has been developed for this study that meets the requirements of ISO 5840-3:2013 and includes the following elements.

- Device Description: A detailed description of all components of the device including a summary of the basic principle of operation.
- CT and Procedural Angiography: A detailed review of pre-procedural and procedural imaging techniques to aid in sizing decisions and implantation of the Lotus valve.
- Step by Step Procedure: A detailed description of each step of the procedure. The training describes any warnings associated with any steps, and tips and tricks for a Lotus valve implantation.
- Implantation Techniques and Sizing: A detailed review of specific implantation techniques and valve sizing based on clinical cases.
- Directions for Use: An overview of the current Instructions for Use (IFU) manual.
- Device Demonstration: A hands-on training using standard Lotus valve components to practice the implantation procedure in a bench model or a robotic simulation system.
- Proctoring: The investigator and co-investigators as well as the scrub team will be proctored by an experienced TAVR physician on a minimum of 6 Lotus Valve implantation procedures. These are to be performed in the investigator's institution with his/her staff. If the proctor or investigators (First Operator and Second Operator) are not satisfied that these initial proctored procedures are sufficient preparation, then subsequent proctoring sessions may be added as needed.

Note: The training requirements listed above apply to centers that do not have previous experience implanting the Lotus Valve. For these centers there will be a roll-in phase with at least 2 roll-in subjects per center treated under the supervision of a proctor. The roll-in subjects will count towards the 6 required proctored cases.

17.4.2. Role of Boston Scientific Corporation Representatives

Boston Scientific Corporation personnel (including field clinical engineers) will provide training and technical support to the investigator and other health care personnel (collectively HCP) as needed during Lotus Valve implant and testing required by the protocol. Support may include addressing HCP questions or providing clarifications to HCPs concerning the operation of BSC equipment/devices. In addition, BSC personnel may perform certain activities to ensure study quality. These activities may include the following.

- Observing testing or medical procedures to provide information relevant to protocol compliance
- Reviewing collected data and study documentation for completeness and accuracy.

17.5. *Insurance*

Where required by local/country regulation, proof and type of insurance coverage by BSC for subjects in the study will be obtained.

18. Monitoring

Monitoring will be performed during the study according to the monitoring plan to assess continued compliance with the protocol and applicable regulations. In addition, the monitor verifies that study records are adequately maintained, that data are reported in a satisfactory manner with respect to timeliness, adequacy, and accuracy, and that the Investigator continues to have sufficient staff and facilities to conduct the study safely and effectively. The Investigator/institution guarantees direct access to original source documents by BSC personnel, their designees, and appropriate regulatory authorities.

The study may also be subject to a quality assurance audit by BSC or its designees, as well as inspection by appropriate regulatory authorities. It is important that the Investigator and relevant study personnel are available during on-site monitoring visits or audits and that sufficient time is devoted to the process.

19. Potential Risks and Benefits

Risks to clinical subjects associated with their participation in this clinical investigation, arising from the clinical procedures set out in the study protocol, have been identified from prior studies conducted by Boston Scientific Corporation and review of relevant literature, most recently from the Edwards Lifesciences' Placement of Aortic Transcatheter Valves (PARTNER) Trial[14,63-65], the PARTNER II trial[98], the CoreValve Extreme Risk Study[73] and the CoreValve High Risk Study[66].

Benefits to subjects anticipated to arise from the use of the investigational device have also been identified. These clinical risks and benefits are summarized below, with an assessment of the balance of risks and benefits to subjects.

Potential risks and benefits have been included in the study-specific template of the ICF provided to the study centers (see Section 20).

19.1. *Risks Associated with Transcatheter Aortic Valve Implantation Procedure*

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 Valve System and/or CoreValve include but may not be limited to the following.

- Abnormal lab values (including anemia and electrolytes)
- Allergic reaction (including to medications, anesthesia, contrast, or device materials)
- Angina
- Arrhythmia or new conduction system injury (including need for pacemaker insertion)
- Bleeding or hemorrhage (possibly requiring transfusion or intervention)
- Cardiac arrest
- Cardiac failure/low cardiac output
- Cerebrovascular accident, stroke or transient ischemic attack
- Coronary obstruction
- Death
- Device misplacement or migration
- Endocarditis
- Emboli (including air, calcium, tissue, thrombus or device materials)
- Fever
- Heart failure
- Hemolysis and/or hemolytic anemia
- Hematoma or lymphatic problems at the access sites
- Hemodynamic instability or shock
- Hypertension/hypotension
- Infection (local and/or systemic, including septicemia)
- Inflammation
- Mitral valve insufficiency
- Myocardial infarction
- Myocardial or valvular injury (including perforation or rupture)
- Nerve injury
- Pain

- Pericardial effusion or cardiac tamponade
- Peripheral ischemia or infarction
- Permanent disability
- Pleural effusion
- Pulmonary edema
- Renal insufficiency or failure
- Respiratory insufficiency or failure
- Valve dysfunction, deterioration or failure
- Valvular stenosis or regurgitation (central or paravalvular)
- Valve or device thrombosis
- Vessel injury (including spasm, trauma, dissection, perforation, rupture, arteriovenous fistula, or pseudoaneurysm)

As a result of these complications, the subject may require medical, percutaneous or surgical intervention, including re-operation and replacement of the implanted valve. Such complications can be fatal.

As the Lotus Valve is an investigational device, uncertainty remains over risks of experiencing some or all of the complications listed above. There may be risks that are unknown at this time.

19.2. *Risk Minimization Actions*

Additional risks may exist. Risks can be minimized through compliance with this protocol, performing procedures in the appropriate hospital environment, adherence to subject selection criteria, close monitoring of the subject's physiologic status during research procedures and/or follow-ups and by promptly supplying BSC with all pertinent information required by this protocol.

- Boston Scientific Corporation will employ measures throughout the course of this investigation consistent with the best practices and lessons learned from other ongoing TAVR trials and commercial use to minimize risk for subjects choosing to participate. All efforts will be made to minimize risks by selecting centers that are experienced and skilled in TAVR procedures.
- Risk mitigation will be accomplished through the following actions.
    - Clearly defining the inclusion/exclusion criteria to ensure only appropriate subjects are enrolled
    - Confirmation of eligible subjects by a Case Review Committee, including experienced investigators in TAVR

- Ensuring that treatment and follow-up of the subject are consistent with current medical practices
- Selection of investigators who are experienced and skilled in TAVR procedures
- Completion of training and proctorship provided by the Sponsor
- Performing all procedures in accordance with the IFU, including the preparation of the valve and delivery system
- Dynamic safety review processes, including assessment by the Data Monitoring Committee (DMC, Section 22.1) and CEC (Section 22.1) adjudication of specified events as recommended by VARC[70,71].

In addition to its repositioning and self-centering features designed to facilitate optimal positioning, the Lotus Valve System provides physicians with control throughout the procedure by allowing them to pause, assess, lock, un-lock, incrementally reverse, resheath and, if needed, retrieve the valve prior to final release. These features help the physician to do the following: place the valve correctly with the first attempt, reposition the device if the initial deployment is considered to be suboptimal, and retrieve the device if during the procedure the decision is made not to implant. The valve's outer seal is also designed to minimize paravalvular leakage.

Anticoagulation medication (e.g., heparin) will be administered during the procedure to reduce the risk of embolism and stroke. Additionally, post-procedure anti-platelet therapy is recommended to minimize any risk of thrombus formation, stroke, or transient ischemic attack. Neurological assessments will be performed at each required follow-up visit to identify any change in the neurological status of the subjects as recommended by VARC[70,71].

Cardiac enzyme measurements as well as ECGs post-procedure will be performed to detect periprocedural MI.

Subjects will be carefully monitored during the procedure, hospitalization, and throughout the follow-up period. Serial echocardiograms and electrocardiograms will be used to evaluate valve and general cardiac function. Any abnormal rhythm will be assessed and, if needed, the implantation of a permanent pacemaker will be performed. Annual imaging will also be performed to assess for structural valve frame integrity.

Subjects who are converted to standard surgical aortic valve replacement will be carefully monitored in a method appropriate for their surgical procedure.

Data will be monitored as they are submitted to BSC. Qualified employees of BSC, or a designee under contract, will conduct monitoring visits at the initiation of the study and at interim intervals described in the monitoring plan throughout the course of the study to evaluate protocol compliance and determine if there are any issues that could affect the safety or welfare of any subject in the study.

19.3. *Anticipated Benefits*

19.3.1. Potential Benefits to the TAVR Procedure

Transcatheter aortic valve replacement (TAVR) may offer certain advantages when compared to surgical replacement of the stenotic native aortic valve, particularly in high risk subjects. Known benefits associated with TAVR, as described in the scientific literature (see summary in Section 4.1 of this document and details in Sections 2 and 3 of the investigator brochure), potentially include the following.

- Minimally invasive procedure and reduced risks related to open heart surgery
- Shorter stay in the intensive care unit and overall hospital stay
- Reduced blood loss
- More rapid recovery
- Reduced need for general anesthesia and associated risks
- Opportunity to receive a new aortic prosthesis in spite of having been refused surgery or being of high surgical risk profile

19.3.2. Potential Benefit Using the Lotus Valve System

Potential benefits that may be associated specifically with use of the Lotus™ Valve System compared to other TAVR systems include the following.

- Pre-loaded delivery system minimizing time required and potential issues with preparing the device
- Accurate valve placement due to the ability to reposition the valve during deployment
- Device is minimally obstructive to the blood flow and maintains hemodynamic stability through the annulus during delivery because there is no balloon or other obstructive device required for deployment and due to early valve leaflet function
- Reduced need for post-dilation
- Reduced or obviated need for valve-in-valve repeat intervention
- Lower risk of ectopic valve placement and valve migration
- Reduced incidence of paravalvular aortic regurgitation due to the Adaptive Seal

19.4. *Risk to Benefit Rationale*

Review of the aforementioned clinical benefits versus risks takes into account the known risks/benefits that have been identified in the published literature on other TAVR devices. The estimation of risk also includes prior limited clinical experience with the Lotus Valve System including earlier generations of the device design. When used according to the IFU, all known risks associated with the TAVR procedure and the specific use of the Lotus Valve

System are mitigated to acceptable limits comparable to existing TAVR devices. The design features of full repositioning and retrievability may improve TAVR procedural safety. The Adaptive Seal may provide long term benefit as it is designed to minimize paravalvular regurgitation, which has been associated with long term mortality in TAVR.

20. Informed Consent

Subject participation in this clinical study is voluntary. Informed Consent is required from all subjects or their legally authorized representative. The Investigator is responsible for ensuring that Informed Consent is obtained prior to the use of any investigational devices, study-required procedures and/or testing, or data collection.

The obtaining and documentation of Informed Consent must be in accordance with the principles of the Declaration of Helsinki; the relevant parts of ISO 14155: 2011 and the ICH guidelines for GCP; any applicable national regulations; and local Ethics Committee and/or Regulatory authority body, as applicable. The ICF must be approved by the center's IRB/EC, or central IRB, if applicable.

Boston Scientific Corporation will provide a study-specific template of the ICF to investigators participating in this study. The ICF template may be modified to meet the requirements of the investigative center's IRB/EC. Any modification requires approval from BSC or authorized representative prior to use of the form. The ICF must be in a language understandable to the subject and if needed, BSC will assist the center in obtaining a written consent translation. Translated consent forms must also have IRB/EC approval prior to their use. Privacy language shall be included in the body of the form or as a separate form as applicable.

The process of obtaining Informed Consent shall:

- be conducted by the Principal Investigator or designee authorized to conduct the process,
- include a description of all aspects of the clinical study that are relevant to the subject's decision to participate throughout the clinical study,
- avoid any coercion of or undue influence of subjects to participate,
- not waive or appear to waive subject's legal rights,
- use native language that is non-technical and understandable to the subject or his/her legal representative,
- provide ample time for the subject to consider participation and ask questions if necessary,
- ensure important new information is provided to new and existing subjects throughout the clinical study.

The ICF shall always be signed and personally dated by the subject or legal representative and by the investigator or an authorized designee responsible for conducting the informed

consent process. If a legal representative signs, the subject shall be asked to provide informed consent for continued participation as soon as his/her medical condition allows. The original signed ICF will be retained by the center and a copy of the signed and dated document and any other written information must be given to the person signing the form.

Failure to obtain subject consent will be reported by BSC to the applicable regulatory body according to their requirements. Any violations of the informed consent process must be reported as deviations to the Sponsor and local regulatory authorities (e.g. IRB/EC), as appropriate.

If new information becomes available that can significantly affect a subject's future health and medical care, that information shall be provided to the affected subject(s) in written form via a revised ICF or, in some situations, enrolled subjects may be requested to sign and date an addendum to the ICF. In addition to new significant information during the course of a study, other situations may necessitate revision of the ICF, such as if there are amendments to the protocol, a change in Principal Investigator, administrative changes, or following annual review by the IRB/EC. The new version of the ICF must be approved by the IRB/EC. Boston Scientific Corporation approval is required if changes to the revised ICF are requested by the center's IRB/EC. The IRB/EC will determine the subject population to be re-consented.

21. Safety Reporting

21.1. *Definitions and Classification*

Adverse event definitions are provided in Table 21.1-1.

Table 21.1-1: Adverse Event Definitions

Term	Definition[a]
Adverse Event (AE) *Ref: ISO 14155:2011*	Any untoward medical occurrence, unintended disease or injury or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device **Note 1**: This definition includes events related to the investigational medical device or the comparator. **Note 2**: This definition includes events related to the procedures involved. **Note 3**: For users or other persons, this definition is restricted to events related to investigational medical devices.
Adverse Device Effect (ADE) *Ref: ISO 14155:2011*	Adverse event related to the use of an investigational medical device **Note 1**: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. **Note 2**: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

Table 21.1-1: Adverse Event Definitions

Term	Definition[a]
Serious Adverse Event (SAE) *Ref: ISO 14155:2011*	Adverse event that: • Led to a death • Led to serious deterioration in the health of the subject, that either resulted in: o a life-threatening illness or injury, or o a permanent impairment of a body structure or a body function, or o in-patient or prolonged hospitalization, or o medical or surgical intervention to prevent life- threatening illness or injury or permanent impairment to a body structure or a body function, • Led to fetal distress, fetal death or a congenital abnormality or birth defect **Note**: Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered a serious adverse event.
Serious Adverse Device Effect (SADE) *Ref: ISO 14155:2011*	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated Adverse Device Effect (UADE) *Ref: 21 CFR Part 812*	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.
Unanticipated Serious Adverse Device Effect (USADE) *Ref: ISO 14155:2011*	Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report **Note**: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.
Device Deficiency *Ref: ISO 14155:2011* *Ref: MEDDEV 2.7/3 12/2010*	A device deficiency is any inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. **Note 1**: Device deficiencies include malfunctions, use errors, and inadequate labeling. **Note 2**: All device deficiencies that could have led to a SADE if a) suitable action had not been taken or b) if intervention had not been made or c) if circumstances had been less fortunate shall be reported as required by the local IRB/EC, national regulations, or the protocol.

a: Other definitions may apply per local reporting requirements.

Underlying diseases are not reported as AEs unless there is an increase in severity or frequency during the course of the investigation. Death should not be recorded as an AE, but should only be reflected as an outcome of a specific SAE (see Table 21.1-1 for AE definitions).

In-patient hospitalization is defined as the subject being admitted to the hospital, with the following exceptions.

- A hospitalization that is uncomplicated and elective/planned (i.e., planned prior to enrollment) does not have to be reported as an SAE.
- If complications or AEs occur during an elective/planned (i.e., planned prior to enrollment) hospitalization after enrollment, the complications and AEs must be reported as AEs or SAEs if they meet the protocol-specified definitions.

Any AE experienced by the study subject beginning from the time of randomization must be recorded in the eCRF.

Refer to Section 19 for the known risks associated with the study devices (test and control).

Based on the VARC[70,71] recommendations and definitions, the adverse events and/or safety endpoints requiring adjudication by the CEC include the following.

- 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 events: life-threatening (or disabling) and major
- Acute kidney injury (≤7 days post index procedure): based on the AKIN System[84,85] Stage 3 (including renal replacement therapy) or Stage 2
- Vascular complications: major
- Repeat procedure for valve-related dysfunction (surgical or interventional therapy)
- Hospitalization for valve-related symptoms or worsening congestive heart failure (NYHA class III or IV)
- New permanent pacemaker 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
- TAV-in-TAV deployment
- Prosthetic aortic valve thrombosis

- Prosthetic aortic valve endocarditis

Details on the CEC events and procedures are outlined in the CEC charter. Tests and images required to adjudicate these events are specified in the event definitions (see Table 26.2-1).

21.2. *Relationship to Study Device(s)*

The Investigator must assess the relationship of the AE to the study device as related or unrelated. See criteria in Table 21.2-1.

Table 21.2-1: Criteria for Assessing Relationship of Study Device to Adverse Event

Classification	Description
Unrelated	The adverse event is determined to be due to a concurrent illness or effect of another device/drug and is not related to the investigational product.
Related	• The adverse event is determined to be potentially related to the investigational product, and an alternative etiology is equally or less likely compared to the potential relationship to investigational product. • There is a strong relationship to investigational product, or recurs on re-challenge, and another etiology is unlikely. • There is no other reasonable medical explanation for the event.

21.3. *Investigator Reporting Requirements*

The communication requirements for reporting to BSC are as shown in Table 21.3-1.

Note: The "become aware date" for an event that requires reporting per the protocol is the date that study personnel listed on the Delegation of Authority Log identify or are notified of the event.

Centers should report control device-related deficiencies as per requirements in the control-device Instructions For Use.

Table 21.3-1: Investigator Reporting Requirements

Event Classification	Communication Method	Communication Timeline
Unanticipated Adverse Device Effect / Unanticipated Serious Adverse Device Effect (UADE/USADE)	Complete adverse event (AE) electronic case report form (eCRF) page with all available new and updated information	• Within 1 business day of first becoming aware of the event • Beginning from time of enrollment for all subjects • Terminating at the end of the study
	Provide copies of all relevant source documents requested by BSC	• As soon as possible after reporting the event
Serious Adverse Event (SAE) including Serious Adverse Device Effects (SADE)	Complete AE eCRF page with all available new and updated information	• Within 2 business days of first becoming aware of the event or as per local/regional regulations. • Beginning from time of enrollment

Table 21.3-1: Investigator Reporting Requirements

Event Classification	Communication Method	Communication Timeline
		for all subjects • Reporting required through the end of the study
	Provide all relevant source documentation (unidentified) for reported event	• When documentation is available
Adverse Event (AE)	Complete AE eCRF page	• As soon as possible before the next planned monitoring visit • Beginning from time of enrollment for all subjects • Reporting required through 12 months
Device Deficiencies, Failures, Malfunctions, and Product Nonconformities	Complete applicable eCRF fields/pages with all available new and updated information.	Investigational Device: • Within 1 business day of first becoming aware of the event and as per local/regional regulations • Beginning from time of Lotus Introducer sheath insertion for all subjects • Reporting required through the end of the study Control Device: • As required per IFU and as per local/regional regulations

Note: The AE eCRF page contains information such as date of AE, treatment of AE resolution, assessment of seriousness, and relationship to the device.

Abbreviations: AE=adverse event; BSC=Boston Scientific Corporation; eCRF=electronic case report form; IFU=Instructions for Use

21.4. *Device Deficiencies*

21.4.1. Boston Scientific Device Deficiencies

All Lotus Valve System device deficiencies (including but not limited to failures, malfunctions, use errors, product nonconformities, and labeling errors) must be documented on the appropriate eCRF and, if possible, the device should be returned to BSC for analysis. Instructions for returning the investigational device will be provided in the study Manual of Operations. If it is not possible to return the device, the investigator should document why the device was not returned and the final disposition of the device. Device deficiencies should also be documented in the subject's medical record.

Device deficiencies and other device issues should not be reported as AEs. Instead, they should be reported on the appropriate eCRF. If an AE results from a device deficiency or other device issue, the AE must be reported on the appropriate eCRF.

Device deficiencies that did not lead to an AE but could have led to a SAE if a) suitable action had not been taken, or b) intervention had not been made, or c) circumstances had been less fortunate must be reported as described in Table 21.3-1.

21.4.2. Control Device Deficiencies

Device deficiencies related to use of the control device (CoreValve) should be reported per the IFU and per applicable local/regional requirements. If an AE results from a device deficiency or other device issue, the AE must be reported on the appropriate eCRF.

21.5. *Reporting to Regulatory Authorities / IRBs / ECs / Investigators*

Boston Scientific Corporation will notify all participating study centers if UADEs, USADEs, SAEs, SADEs, or investigational device deficiencies occur which imply a possible increase in the anticipated risk of the procedure or use of the device or if the occurrence of certain SAEs/SADEs requires changes to the protocol or the conduct of the study in order to further minimize the unanticipated risks.

Boston Scientific Corporation is responsible for reporting AE information to all participating investigators and regulatory authorities as applicable according to local reporting requirements.

The PI is responsible for informing the IRB/EC, and regulatory authorities of UADEs, USADEs, SADEs, SAEs, Device Deficiencies and/or other CEC events as applicable according to local reporting requirements. A copy of the Investigator's reports and other relevant reports (if applicable) to the IRB/IEC must be provided to BSC in accordance with local requirements.

22. Committees

22.1. *Safety Monitoring Process*

To promote early detection of safety issues, the Clinical Events Committee (CEC) and Data Monitoring Committee (DMC; see below) will provide evaluations of safety events. Success of this program requires dynamic collection of unmonitored data as soon as the event is reported. This is expedited through the Sponsor or designee, which is responsible for coordinating the collection of information for the subject dossier from the centers and core laboratories. During regularly scheduled monitoring visits, clinical research monitors will support the dynamic reporting process through their review of source document information.

22.1.1. Clinical Events Committee

A CEC will be used in this study. A CEC is an independent group of individuals with pertinent expertise, including cardiovascular interventional therapy, cardiovascular surgery, and neurology, which reviews and adjudicates important endpoints and relevant adverse events reported by study investigators. The CEC will review a safety event dossier, which may include copies of subject source documents provided by study sites, and adjudicate study endpoint related clinical events. The responsibilities, qualifications, membership, and committee procedures of the CEC are outlined in the CEC charter.

22.1.2. Data Monitoring Committee

The DMC is responsible for the oversight review of all AEs. The DMC will include leading experts in cardiovascular interventional therapy, cardiovascular surgery, and biostatistics who are not participating in the study and who have no affiliation with BSC. During the course of the study, the DMC will review accumulating safety data to monitor the incidence of CEC events and other trends that would warrant modification or termination of the study. Responsibilities, qualifications, membership, and committee procedures are outlined in the DMC Charter.

22.2. *Case Review Committee*

A Case Review Committee (CRC) will be comprised of experienced cardiac surgeons and interventional cardiologists, including the Study Coordinating PIs, Center PIs, other Investigators, Proctors and Medical Consultants experienced in TAVR for their clinical/medical expertise, and the Sponsor for technical expertise on the Lotus Valve System requirements. This committee will be responsible for the review of subject screening data to confirm eligibility given the increased surgical risk of the subject population being studied and to ensure consistency of subjects enrolled across study centers. Responsibilities, qualifications, membership, and committee procedures are outlined in the CRC Charter.

22.3. *Steering Committee*

A Steering Committee consisting of Sponsor Clinical Management, the Study Coordinating PIs, cardiac surgeons, and other investigators experienced in TAVR will be convened. Responsibilities may include oversight of the overall conduct of the study with regard to protocol development, study progress, subject safety, overall data quality and integrity, as well as disseminating any study results through appropriate scientific sessions and publications. Steering Committee members may participate in the review and approval of all requests for data analysis, abstract and manuscript preparation and submission.

23. Suspension or Termination

23.1 Premature Termination of the Study

Boston Scientific Corporation reserves the right to terminate the study at any stage but intends to exercise this right only for valid scientific or administrative reasons and reasons related to protection of subjects. Investigators, associated IRBs/ECs, and regulatory authorities, as applicable, will be notified in writing in the event of study termination.

23.1.1 Criteria for Premature Termination of the Study

Possible reasons for premature study termination include, but are not limited to, the following.

- The occurrence of unanticipated adverse device effects that present a significant or unreasonable risk to subjects enrolled in the study.
- An enrollment rate far below expectation that prejudices the conclusion of the study.
- A decision on the part of BSC to suspend or discontinue development of the device.

23.2 Termination of Study Participation by the Investigator or Withdrawal of IRB/EC Approval

Any investigator or IRB/EC in the REPRISE III study may discontinue participation in the study or withdrawal approval of the study, respectively, with suitable written notice to BSC. Investigators, associated IRBs/ECs, and regulatory authorities, as applicable, will be notified in writing in the event of these occurrences.

23.3 Requirements for Documentation and Subject Follow-up

In the event of premature study termination a written statement as to why the premature termination has occurred will be provided to all participating centers by BSC. The IRB/EC and regulatory authorities, as applicable, will be notified. Detailed information on how enrolled subjects will be managed thereafter will be provided.

In the event an IRB/EC terminates participation in the study, participating investigators, associated IRBs/ECs, and regulatory authorities, as applicable, will be notified in writing. Detailed information on how enrolled subjects will be managed thereafter will be provided by BSC.

In the event an investigator terminates participation in the study, study responsibility will be transferred to a co-investigator, if possible. In the event there are no opportunities to transfer investigator responsibility; detailed information on how enrolled subjects will be managed thereafter will be provided by BSC. The investigator must return all documents and investigational product to BSC, unless this action would jeopardize the rights, safety, or welfare of the subjects.

23.4 Criteria for Suspending/Terminating a Study Center

Boston Scientific Corporation reserves the right to stop the inclusion of subjects at a study center at any time after the study initiation visit if no subjects have been enrolled or if the center has multiple or severe protocol violations/noncompliance without justification and/or fails to follow remedial actions.

In the event of termination of investigator participation, all study devices and testing equipment, as applicable, will be returned to BSC unless this action would jeopardize the rights, safety or well-being of the subjects. The IRB/EC and regulatory authorities, as applicable, should be notified. All subjects enrolled in the study at the center will continue to be followed per this protocol. The Principal Investigator at the center must make provision for these follow-up visits unless BSC notifies the investigational center otherwise.

24. Publication Policy

In accordance with the Corporate Policy on the Conduct of Human Subject Research, BSC requires disclosure of its involvement as a sponsor or financial supporter in any publication or presentation relating to a BSC study or its results. In accordance with the Corporate Policy for the Conduct of Human Subject Research, BSC will submit study results for publication (regardless of study outcome) in a timely manner. Boston Scientific Corporation follows authorship principals as set forth in the Uniform Requirements of the International Committee of Medical Journal Editors (ICMJE; http://www.icmje.org). In order to ensure the public disclosure of study results in a timely manner, while maintaining an unbiased presentation of study outcomes, BSC personnel may assist authors and investigators in publication preparation provided the following guidelines are followed.

- All authorship and contributorship requirements as described above must be followed.
- BSC involvement in the publication preparation and the BSC Publication Policy should be discussed with the Coordinating Principal Investigator(s) and/or Steering Committee at the onset of the project.
- The First and Senior authors are the primary drivers of decisions regarding publication content, review, approval, and submission.

25. Bibliography

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26. Abbreviations and Definitions

26.1. *Abbreviations*

Abbreviations are shown in Table 26.1-1.

Table 26.1-1: Abbreviations and Acronyms

Abbreviation/Acronym	Definition
ADE	adverse device effect
AE	adverse event
AKIN	Acute Kidney Injury Network
AR	aortic regurgitation
AS	aortic stenosis
AV	atrioventricular
AVA	aortic valve area

Table 26.1-1: Abbreviations and Acronyms

Abbreviation/Acronym	Definition
AVR	aortic valve replacement
BARC	Bleeding Academic Research Consortium
BMI	body mass index
BSA	body surface area
BSC	Boston Scientific Corporation
CBC	complete blood count
CEC	Clinical Events Committee
CK	creatine kinase
CK-MB	creatine kinase-myoglobin band, a fraction of creatine kinase
CRC	Case Review Committee
CT	computed tomography
CVA	cerebrovascular accident
DVI	Doppler velocity index
ECG	Electrocardiogram
eCRF	electronic case report form
EOA	effective orifice area
GCP	Good Clinical Practices
ICF	Informed Consent form
ICH	International Conference on Harmonisation
IEC/IRB	Independent Ethics Committee/Institutional Review Board
IFU	Instructions for Use
ISO	International Organization For Standardization
ITT	intention to treat
LBBB	left bundle branch block
LDH	lactate dehydrogenase
LV	left ventricle
LVEF	left ventricular ejection fraction
MACCE	major adverse cardiovascular and cerebrovascular events
MI	myocardial infarction
MRI	magnetic resonance imaging
mRS	Modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
NYHA	New York Heart Association classification
PPM	permanent pacemaker
QOL	quality of life
SADE	serious adverse device effect
SAE	serious adverse event
SAVR	surgical aortic valve replacement
TAVR	transcatheter aortic valve replacement
TEE	transesophageal Doppler echocardiography
TIA	transient ischemic attack
TTE	transthoracic Doppler echocardiography

Table 26.1-1: Abbreviations and Acronyms

Abbreviation/Acronym	Definition
UADE	unanticipated adverse device effect
USADE	unanticipated serious adverse device effect
URL	upper reference limit (defined as 99th percentile of normal reference range)
VARC	Valve Academic Research Consortium

26.2. *Definitions*

Terms are defined in Table 26.2-1. See Table 26.1-1 for abbreviations.

Table 26.2-1: Definitions

Term	Definition
ACUTE KIDNEY INJURY (AKI) (AKIN System[84,85])	Change in serum creatinine (up to 7 days) compared to baseline: • Stage 1: Increase in serum creatinine to 150–199% (1.5–1.99 × increase compared with baseline) OR increase of ≥0.3 mg/dl (≥26.4 mmol/L) • Stage 2: Increase in serum creatinine to 200–299% (2.0–2.99 × increase compared with baseline) • Stage 3: Increase in serum creatinine to ≥300% (>3 × increase compared with baseline) OR serum creatinine of ≥4.0 mg/dL (≥354 mmol/L) with an acute increase of at least 0.5 mg/dL (44 mmol/L) -OR- Based on urine output (up to 7 days): • Stage 1: <0.5 ml/kg per hour for >6 but <12 hours • Stage 2: <0.5 ml/kg per hour for >12 but <24 hours • Stage 3: <0.3 ml/kg per hour for ≥24 hours or anuria for ≥12 hours Note 1: Subjects receiving renal replacement therapy are considered to meet Stage 3 criteria irrespective of other criteria.
ACUTE VESSEL OCCLUSION	The state of complete luminal obstruction with no antegrade blood flow
ADVERSE EVENT *Ref: ISO 14155:2011* (AE)	Any untoward medical occurrence, unintended disease or injury or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device. Note 1: This definition includes events related to the investigational medical device or the comparator. Note 2: This definition includes events related to the procedures involved. Note 3: For users or other persons, this definition is restricted to events related to investigational medical devices.
ADVERSE EVENT BECOME AWARE DATE	The become aware date for an adverse event that requires reporting per the protocol is the date that study personnel listed on the Delegation of Authority Log identify or are notified of the event.
ADVERSE DEVICE EFFECT *Ref: ISO 14155:2011* (ADE)	Adverse event related to the use of an investigational medical device Note 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. Note 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

Table 26.2-1: Definitions

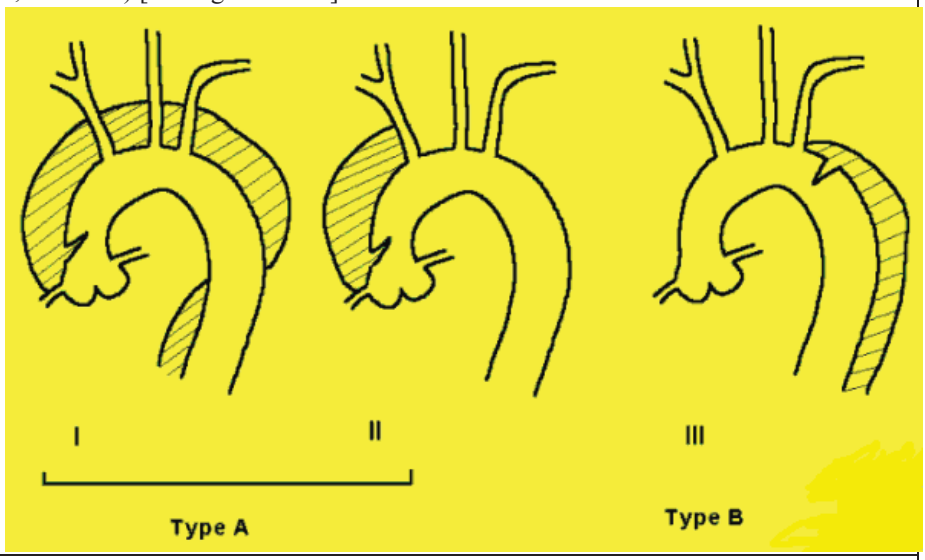
Term	Definition
AORTIC DISSECTION	Intimal tear resulting in blood splitting the aortic media and producing a false lumen that can progress in an antegrade or retrograde direction Aortic dissection is further classified using Stanford classification (Types A and B depending on whether ascending or descending aorta involved) or DeBakey classification (Types I, II and III) [see Figure below]. 
AORTIC REGURGITATION (AR)	The leaking of the aortic valve that causes blood to flow in the reverse direction during ventricular diastole, from the aorta into the left ventricle. The echocardiographic findings in severe aortic regurgitation include the following. • An AR color jet dimension >60% of the left ventricular outflow tract diameter (may not be true if the jet is eccentric) • The pressure half-time of the regurgitant jet is <250 msec • Early termination of the mitral inflow (due to increase in LV pressure due to the AR) • Early diastolic flow reversal in the descending aorta. • Regurgitant volume >60 mL • Regurgitant fraction >55%
ARRHYTHMIA	Any variation from the normal rhythm of the heartbeat, including sinus arrhythmia, premature beat, heart block, atrial fibrillation, atrial flutter and tachycardia. Complete heart block, ventricular tachycardia and ventricular fibrillation are considered major arrhythmias. Data should be collected on any new arrhythmia resulting in hemodynamic instability or requiring therapy (therapy includes electrical/medical cardioversion or initiation of a new medication [oral anticoagulation, rhythm or rate controlling therapy]). New onset atrial fibrillation or atrial flutter (AF) is diagnosed as any arrhythmia within hospitalization that has the ECG characteristics of AF and lasts sufficiently long to be recorded on a 12-lead ECG, or at least 30 seconds on a rhythm strip. The therapeutic approach to new-onset AF (spontaneous conversion, electrical or medical cardioversion, initiation of oral anticoagulation, and rate or rhythm control medications) and any clinical consequences should be documented. Note: See also definitions for conductance disturbance and permanent pacemaker.
AS-TREATED	This population includes all subjects who sign an Informed Consent Form, are

Table 26.2-1: Definitions

Term	Definition
ANALYSIS SET	enrolled in the trial, are randomized, and receive a study device, but subjects are analyzed based on the treatment actually received. For example, if a subject is assigned to receive a test device but instead receives a control device, that subject will be considered a control subject for the as-treated analyses of implant subgroups. **Note**: If a subject receives 2 valves, the subject is assigned to the group corresponding to the first valve received.
BLEEDING[70,71]	Life-threatening or Disabling Bleeding • Fatal bleeding (Bleeding Academic Research Consortium [BARC] type 5[99,100]) • Bleeding in a critical organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome (BARC type 3b and 3c) • Bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery (BARC type 3b) • Overt source of bleeding with drop in hemoglobin of ≥5 g/dL or whole blood or packed red blood cells (RBC) transfusion ≥4 units (BARC type 3b)* Major Bleeding (BARC type 3a) • Overt bleeding either associated with a drop in the hemoglobin level of at least 3.0g/dL or requiring transfusion of 2 or 3 units of whole blood/RBC, or causing hospitalization or permanent injury, or requiring surgery AND does not meet criteria of life-threatening or disabling bleeding Minor Bleeding (BARC type 2 or 3a, depending on the severity) • Any bleeding worthy of clinical mention (e.g., access site hematoma) that does not qualify as life-threatening, disabling, or major * Given one unit of packed RBC typically will raise blood hemoglobin concentration by 1 g/dL, an estimated decrease in hemoglobin will be calculated.
CARDIAC DECOMPENSATION	Inability of the heart to maintain adequate circulation
CARDIAC TAMPONADE	Evidence of a new pericardial effusion associated with hemodynamic instability and clearly related to the TAVR procedure. Clinical syndrome caused by the accumulation of fluid in the pericardial space, resulting in reduced ventricular filling and subsequent hemodynamic compromise.
CARDIOGENIC SHOCK	An insufficient forward cardiac output to maintain adequate perfusion of vital organs to meet ongoing demands for oxygenation and metabolism. Cardiogenic shock is due to either inadequate left ventricular pump function (such as in congestive heart failure) or inadequate left ventricular filling (such as in cardiac tamponade). Cardiogenic shock is defined as sustained hypotension (>30 minutes) with evidence of tissue hypoperfusion including oliguria (<30 mL/h), cool extremities, cyanosis, and altered mental status.
CEREBRAL INFARCTION	Evidence of brain cell death from imaging studies or pathological examination. If there are clinical symptoms, then it is a stroke; otherwise, it is an asymptomatic cerebral infarction.
CHRONIC RENAL INSUFFICIENCY	Subject has chronic impairment of kidney function.
CLINICAL PROCEDURAL SUCCESS	Implantation of the device in the absence of death, disabling stroke, major vascular complications, and life-threatening or major bleeding

Table 26.2-1: Definitions

Term	Definition
(IN-HOSPITAL)	
CONDUCTION DISTURBANCES[70,71]	Implant-related new or worsened cardiac conduction disturbances include new or worsened first degree atrioventricular (AV) block, second degree AV block (Mobitz I or Mobitz II), third degree AV block, incomplete right bundle branch block (RBBB), RBBB, intraventricular conduction delay, left bundle branch block (LBBB), left anterior fascicular block, or left posterior fascicular block, including block requiring permanent pacemaker implant Note 1: High grade AV block is considered persistent if it is present every time the underlying rhythm is checked. Note 2: See also definitions for arrhythmia and permanent pacemaker.
CONVERSION TO OPEN SURGERY	Conversion to open sternotomy during the TAVR procedure secondary to any procedure-related complications
CORONARY OBSTRUCTION	Angiographic or echocardiographic evidence of a new, partial or complete, obstruction of a coronary ostium, either by the valve prosthesis itself, the native leaflets, calcifications, or dissection, occurring during or after the TAVR procedure. Mechanical coronary artery obstruction following TAVR or surgical AVR that typically occurs during the index procedure. Possible mechanisms for mechanical coronary obstruction include the following. • Impingement of the coronary ostia by the valve support structure in the setting of suboptimal valve positioning and/or 'small aortic root' anatomy • Embolization from calcium, thrombus, air, or endocarditis displacement of native aortic valve leaflets towards the coronary ostia during TAVR • Suture-related kinking or obstruction or cannulation related obstruction of the coronary ostia associated with surgical AVR The diagnosis of TAVR-associated coronary obstruction can be determined by imaging studies (coronary angiography, intravascular ultrasound, multi-slice CT angiography, or echocardiography), surgical exploration, or autopsy findings. Cardiac biomarker elevations and ECG changes indicating new ischemia provide corroborative evidence.
DEATH	All-cause Death Death from any cause after a valve intervention. Cardiovascular Death Any one of the following criteria is met. • Any death due to proximate cardiac cause (e.g., myocardial infarction, cardiac tamponade, worsening heart failure) • Sudden or unwitnessed death • Death of unknown cause • Death caused by noncoronary vascular conditions such as neurological events, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular disease • All procedure-related deaths, including those related to a complication of the procedure or treatment for a complication of the procedure • All valve-related deaths including structural or nonstructural valve dysfunction or other valve-related adverse events Non-cardiovascular Death • Any death in which the primary cause of death is clearly related to another condition (e.g. trauma, cancer, suicide)

Table 26.2-1: Definitions

Term	Definition
DEVICE DEFICIENCY *Ref: ISO 14155:2011* *Ref: MEDDEV 2.7/3 12/2010*	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Note 1: Device deficiencies include malfunctions, use errors, and inadequate labeling.
DEVICE FAILURE	A device failure is identified whenever the criteria for device success are not met.
DEVICE MIGRATION	Device migration is defined as an upward or downward displacement of the implanted valve from its original implant location, after initial correct positioning within the aortic annulus from its initial position, with or without consequences. This can be confirmed by X-ray, echocardiography, CT scan or MRI or valve migration demonstrated by direct assessment during open heart surgery or at autopsy.
DEVICE RELATED COMPLICATIONS	Complications associated with the device as it relates to delivery, placement, efficacy or durability; these may involve the implanted device or the delivery system.
ECTOPIC VALVE DEPLOYMENT	Permanent deployment of the valve prosthesis in a location other than the aortic root.
EMBOLISM	Examples include a free flowing blood clot or lesion material that is located in the systemic or pulmonary circulation. Embolism may be manifested by a neurological event or a noncerebral embolic event.
ENCEPHALOPATHY	Altered mental state (e.g., seizures, delirium, confusion, hallucinations, dementia, coma, psychiatric episode, etc.)
ENDOCARDITIS	**Infective endocarditis** is diagnosed based on Duke criteria[101] and necessitates the following. • Two major criteria -OR- • One major and three minor criteria -OR- • Five minor criteria Major Criteria • Positive blood culture for infective endocarditis o Typical microorganism consistent with infective endocarditis from 2 separate blood cultures, as noted below. ▪ Viridans streptococci, *Streptococcus bovis*, or HACEK group (*Haemophilus* [*Haemophilus parainfluenzae, Haemophilus aphrophilus, and Haemophilus paraphrophilus*], *Actinobacillus actinomycetemcomitans* [*Aggregatibacter actinomycetemcomitans*], *Cardiobacterium hominis, Eikenella corrodens, Kingella kingae* -OR- ▪ Community-acquired *Staphylococcus aureus* or enterococci, in the absence of a primary focus -OR- o Microorganisms consistent with infective endocarditis from persistently positive blood cultures defined as noted below. ▪ Two (2) positive cultures of blood samples drawn >12 hours apart -OR- ▪ All of 3 or a majority of 4 separate cultures of blood (with first and last sample drawn 1 hour apart) • Evidence of endocardial involvement o Positive echocardiogram for infective endocarditis defined as noted below. ▪ Oscillating intracardiac mass on valve or supporting structures, in the path

Table 26.2-1: Definitions

Term	Definition
	of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation -OR- ▪ Abscess -OR- ▪ New partial dehiscence of prosthetic valve -OR- o New valvular regurgitation (worsening or changing of preexisting murmur not sufficient) Minor Criteria • Predisposition: predisposing heart condition or intravenous drug use • Fever: temperature >38.0° C (100.4° F) • Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway lesions • Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth spots, and rheumatoid factor • Microbiological evidence: positive blood culture but does not meet a major criterion as noted above or serological evidence of active infection with organism consistent with infective endocarditis • Echocardiographic findings: consistent with infective endocarditis but do not meet a major criterion as noted above **Implanted valve endocarditis** includes any infection involving an implanted valve. The diagnosis of operated valvular endocarditis is based on one of the following criteria. • Fulfillment of the Duke endocarditis criteria as defined above • Evidence of abscess, paravalvular leak, pus, or vegetation confirmed as secondary to infection by histological or bacteriologic studies during a re-operation • Findings of abscess, pus, or vegetation involving a repaired or replaced valve during an autopsy.
EXPLANT	Removal of the investigational valve implant for any reason.
FRAILTY	Slowness, weakness, exhaustion, wasting and malnutrition, poor endurance and inactivity, loss of independence.
HEMOLYSIS	Two plasma free hemoglobin values >40 mg/dL with the two readings taken within a single 48-hour period. If the second plasma free hemoglobin assessment is not performed within 48 hours following an initial determination of >40 mg/dL, this would qualify as an AE.
HOSTILE CHEST	Any of the following or other reasons that make redo operation through sternotomy or right anterior thoracotomy prohibitively hazardous: • Abnormal chest wall anatomy due to severe kyphoscoliosis or other skeletal abnormalities (including thoracoplasty, Potts' disease) • Complications from prior surgery • Evidence of severe radiation damage (e.g. skin burns, bone destruction, muscle loss, lung fibrosis or esophageal stricture) • History of multiple recurrent pleural effusions causing internal adhesions
IMPLANTED ANALYSIS SET	This population includes all subjects who sign an Informed Consent Form, are enrolled in the trial, and are implanted with the assigned, randomized study device. **Note**: If a subject receives 2 valves, the subject is assigned to the group

Table 26.2-1: Definitions

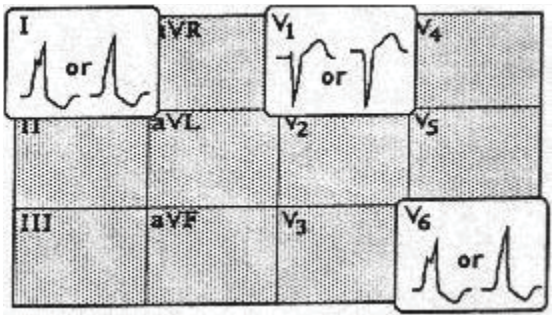
Term	Definition
	corresponding to the first valve received.
INTENT TO TREAT (ITT) ANALYSIS SET	This population includes all subjects who sign an Informed Consent Form, are enrolled in the trial, and are randomized, whether or not an assigned study device is implanted. Subjects in the ITT population will be followed with their ITT cohort. **Note**: If a subject receives 2 valves, the subject is assigned to the group corresponding to the first valve received.
INTERNAL MAMMARY ARTERY OR OTHER CRITICAL CONDUIT(S) CROSSING MIDLINE AND/OR ADHERENT TO POSTERIOR TABLE OF STERNUM	A patent IMA graft that is adherent to the sternum such that injuring it during reoperation is likely. A patient may be considered extreme risk if any of the following are present: • The conduit(s) are radiographically indistinguishable from the posterior table of the sternum. • The conduit(s) are radiographically distinguishable from the posterior table of the sternum but lie within 2-3mm of the posterior table.
INTRACRANIAL HEMORRHAGE	Collection of blood between the brain and skull; subcategorized as epidural, subdural, and subarachnoid bleeds.
LEFT BUNDLE BRANCH BLOCK (LBBB)	The appearance of typical complete LBBB in the three KEY leads (I, V1, and V6) with the following diagnostic criteria [see Figure below]. • The heart rhythm must be supraventricular in origin • QRS widening to at least 0.12 sec • An upright (monophasic) QRS complex in leads I and V6; the QRS may be notched, but there should not be any q wave in either lead I or lead V6. • A predominantly negative QRS complex in lead V1; there may or may not be an initial small r wave in lead V1, that is, lead V1 may show either a QS or RS complex. 
LIVER DISEASE (SEVERE) /CIRRHOSIS	Any of the following: • Child-Pugh class C • MELD score ≥10 • Portal-caval, spleno-renal, or transjugular intrahepatic portal shunt • Biopsy proven cirrhosis with portal hypertension or hepatocellular dysfunction
MITRAL VALVE APPARATUS DAMAGE	Angiographic or echocardiographic evidence of a new damage to the mitral valve apparatus (chordae papillary muscle, or leaflet) during or after the TAVR procedure.
MODIFIED DEVICE SUCCESS	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 mm

Table 26.2-1: Definitions

Term	Definition
	Hg or a peak velocity <3m/sec with no moderate or severe prosthetic valve aortic regurgitation)
MYOCARDIAL INFARCTION (MI)	**Periprocedural MI (≤72 hours after the index procedure)** • New ischemic symptoms (e.g., chest pain or shortness of breath) or new ischemic signs (e.g., ventricular arrhythmias, new or worsening heart failure, new ST-segment changes, hemodynamic instability, new pathological Q waves in at least two contiguous leads, or imaging evidence of new loss of viable myocardium or new wall motion abnormality) -AND- • Elevated cardiac biomarkers (preferably CK-MB) within 72 h after the index procedure, consisting of at least one sample post-procedure with a peak value exceeding 15× upper reference limit (troponin) or 5× for CK-MB. If cardiac biomarkers are increased at baseline (>99th percentile), a further increase of at least 50% post-procedure is required AND the peak value must exceed the previously stated limit. **Spontaneous MI (>72 hours after the index procedure)** Any one of the following criteria applies. • Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile URL, together with evidence of myocardial ischemia with at least one of the following o Symptoms of ischemia o ECG changes indicative of new ischemia [new ST-T changes or new LBBB] o New pathological Q waves in at least two contiguous leads o Imaging evidence of new loss of viable myocardium or new wall motion abnormality • Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST-segment elevation, or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/ or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood. • Pathological findings of an acute myocardial infarction[102].
NEUROLOGICAL EVENT	Any central, new neurological deficit, whether temporary or permanent and whether focal or global, that occurs after the subject emerges from anesthesia

Table 26.2-1: Definitions

<table>
<tr><th>Term</th><th>Definition</th></tr>
<tr><td>NEW YORK HEART ASSOCIATION CLASSIFICATION (NYHA)</td><td>Classification system for defining cardiac disease and related functional limitations into four broad categorizations:
<table>
<tr><td>Class I</td><td>Subject with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.</td></tr>
<tr><td>Class II</td><td>Subjects with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.</td></tr>
<tr><td>Class III</td><td>Subjects with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.</td></tr>
<tr><td>Class IV</td><td>Subjects with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.</td></tr>
</table></td></tr>
<tr><td>NONSTRUCTURAL DYSFUNCTION</td><td>Any abnormality not intrinsic to the valve itself that results in stenosis or regurgitation of the operated valve or hemolysis. The term nonstructural dysfunction refers to problems (exclusive of thrombosis and infection) that do not directly involve valve components yet result in dysfunction of an operated valve, as diagnosed by re-operation, autopsy, or clinical investigation. Nonstructural dysfunction includes the following.
Entrapment by pannus, tissue, or suture
Paravalvular leak
Inappropriate sizing or positioning
Residual leak or obstruction after valve implantation or repair
Clinically important intravascular hemolytic anemia
Development of aortic or pulmonic regurgitation as a result of technical errors
Dilatation of the sinotubular junction
Dilatation of the valve annulus after either valve replacement with stentless prostheses, new onset of coronary ischemia from coronary ostial obstruction, or paravalvular aortic regurgitation</td></tr>
<tr><td>OPERATIVE RISK</td><td>Operative risk is determined by a center cardiac surgeon and must be confirmed by the Case Review Committee (including a cardiac surgeon).
Extreme Risk: Predicted operative mortality or serious, irreversible morbidity risk ≥50% at 30 days
High Risk: Predicted operative mortality or serious, irreversible morbidity risk ≥15% at 30 days</td></tr>
<tr><td>PARAVALVULAR REGURGITATION</td><td>Leakage due to a separation of the prosthetic valve from the annulus. Any evidence of leakage of blood around the device. Diagnosis of paravalvular regurgitation may be obtained from TEE/TTE, however, definitive diagnosis is obtained at re-operation, explant, or autopsy.</td></tr>
</table>

Table 26.2-1: Definitions

Term	Definition
PERMANENT PACEMAKER (PPM) IMPLANTATION[89]	Implantation of new PPM after the index procedure resulting from new or worsened conduction disturbances • Procedure-related: PPM is implanted in subjects with new onset or worsened conduction disturbances occurring post index procedure • Not related to procedure: PPM is implanted in subjects with known conduction disturbances that did not advance after the index procedure. Note: See also definitions for arrhythmia and conductance disturbance.
PORCELAIN AORTA	Heavy circumferential calcification of the entire ascending aorta extending to the arch such that aortic cross-clamping is not feasible
PROCEDURE RELATED COMPLICATIONS	Complications associated with any part of the vascular access procedure, associated treatments or necessary secondary interventions that do not necessarily involve the device. This includes morbidity associated with either pre-medication, or anesthesia, or other adjunct to the surgical procedure. Other technical errors including inappropriate subject selection, inappropriate operator techniques, measurements, or judgment that do not involve the device itself are also included.
PROCEDURE-RELATED EVENTS	Events occurring during or as a direct result of the index procedure.
REPEAT PROCEDURE FOR VALVE-RELATED DYSFUNCTION	Any surgical or percutaneous interventional catheter procedure that repairs, otherwise alters or adjusts, or replaces a previously implanted valve. In addition to surgical re-operations, enzymatic, balloon dilatation, interventional manipulation, repositioning, or retrieval, and other catheter-based interventions for valve-related complications are also considered re-interventions. Cardiac re-interventions will be categorized as repeat TAVR, valvuloplasty, or surgical AVR. • Conversion to open surgery • Conversion to open sternotomy during the TAVR procedure secondary to any procedure-related complications. • Unplanned use of CPB • Unplanned use of CPB for hemodynamic support at any time during the TAVR procedure.
RESPIRATORY INSUFFICIENCY	Inadequate ventilation or oxygenation
RESPIRATORY FAILURE	The need for ventilatory support for >72 hours associated with an inability to wean from the respirator for any reason.
RIGHT VENTRICULAR INSUFFICIENCY	• Defined as sequelae of right ventricular failure including the following. o Significantly decreased right ventricular systolic and/or diastolic function o Tricuspid valvular regurgitation secondary to elevated pressure • Clinical symptoms to include the following. o Hepatic congestion o Ascites o Anasarca o Presence of “hepato-jugular reflux” o Edema Severe right ventricular dysfunction or severe pulmonary hypertension is primary or secondary pulmonary hypertension with PA systolic pressures greater than 2/3 of systemic pressure.
SAFETY ANALYSIS SET	This population includes all subjects in the ITT analysis set who have a study device implanted, regardless of the assigned treatment group.

Table 26.2-1: Definitions

Term	Definition
SERIOUS ADVERSE EVENT *Ref: ISO 14155:2011* (SAE)	Adverse event that resulted in the following. • Led to a death • Led to serious deterioration in the health of the subject, that resulted in one or more of the following. o Life-threatening illness or injury o Permanent impairment of a body structure or a body function o In-patient or prolonged hospitalization o Medical or surgical intervention to prevent life- threatening illness or injury or permanent impairment to a body structure or a body function, • Led to fetal distress, fetal death or a congenital abnormality or birth defect Note 1: Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered a serious adverse event.
SERIOUS ADVERSE DEVICE EFFECT *Ref: ISO 14155:2011* (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event
SOURCE DATA (per ISO 14155:2011)	All information in original records of clinical findings, observations, or other activities in a clinical investigation, necessary for the reconstruction and evaluation of the clinical investigation
SOURCE DOCUMENT (per ISO 14155:2011)	Printed, optical or electronic document containing source data. Examples: Hospital records, laboratory notes, device accountability records, photograhic negatives, radiographs, records kept at the investigation center, at the laboratories and at the medico-technical departments involvced in the clinical investigation.
STROKE[70,71]	Stroke is defined as an acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction **Stroke Classification** • Ischemic Stroke is defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by an infarction of central nervous system tissue. • Hemorrhagic Stroke is defined as an acute episode of focal or global cerebral or spinal dysfunction caused by an intraparenchymal, intraventricular, or subarachnoid hemorrhage Note 1: The CEC will adjudicate ischemic versus hemorrhagic stroke. Note 2: A stroke may be classified as undetermined if there is insufficient information to allow categorization as ischemic or hemorrhagic **Stroke Diagnostic Criteria** • Rapid onset of a focal or global neurological deficit with at least one of the following: change in level of consciousness, hemiplegia, hemiparesis, numbness or sensory loss affecting one side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke • Duration of a focal or global neurological deficit ≥24 h; OR <24 h, if available neuroimaging documents a new hemorrhage or infarct; OR the neurological deficit results in death • No other readily identifiable nonstroke cause for the clinical presentation (e.g., brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences), to be determined by or in conjunction with designated neurologist

Table 26.2-1: Definitions

Term	Definition

	• Confirmation of the diagnosis by at least one of the following.
	  o Neurology or neurosurgical specialist
	  o Neuroimaging procedure (MRI or CT scan), but stroke may be diagnosed on clinical grounds alone
	Note 3: Subjects with non-focal global encephalopathy will not be reported as a stroke without unequivocal evidence based upon neuroimaging studies (CT scan or brain MRI).
	Stroke Definitions
	Diagnosis as above, preferably with positive neuroimaging study
	• Non-disabling: Modified Rankin Scale (mRS) score <2 at 90 days OR one that does not result in an increase of at least one mRS category from an individual's pre-stroke baseline
	• Disabling: Modified Rankin Scale score ≥2 at 90 days AND an increase of at least one mRS category from an individual's pre-stroke baseline
	Note 4: Modified Rankin Scale assessments should be made by qualified individuals according to a certification process.
	Note 5: Assessment of the mRS score should occur at all scheduled visits in a study; mRS also should be performed after a stroke and at 90 days after the onset of any stroke.

STRUCTURAL VALVE DETERIORATION	Component of time-related valve safety defined as follows. • Valve-related dysfunction: Mean aortic valve gradient ≥20 mmHg, EOA ≤0.9-1.1 cm^2, and/or DVI <0.35 AND/OR moderate or severe prosthetic valve regurgitation (per VARC definition) • Requiring repeat procedure (TAVR or SAVR).
TAV-IN-TAV DEPLOYMENT	An additional valve prosthesis is implanted within a previously implanted prosthesis because of suboptimal device position and/or function during or after the index procedure.
TRANSIENT ISCHEMIC ATTACK (TIA)	• Transient episode of focal neurological dysfunction caused by brain, spinal cord, or retinal ischemia, without acute infarction • Duration of a focal or global neurological deficit is <24 h • Neuroimaging does not demonstrate a new hemorrhage or infarct (if performed) Note: The difference between TIA and ischemic stroke is the presence of tissue damage or new sensory-motor deficit persisting >24 hours. By definition, TIA does not produce lasting disability.
UNANTICIPATED ADVERSE DEVICE EFFECT *Ref: 21CFR Part 812* (UADE)	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the protocol or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.
UNANTICIPATED SERIOUS ADVERSE DEVICE EFFECT *Ref: ISO 14155:2011* (USADE)	Serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report Note: An anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity, or outcome has been identified in the risk analysis report.
UNPLANNED USE OF CARDIOPULMONARY	Unplanned use of cardiopulmonary bypass for hemodynamic support at any time during the TAVR procedure

Table 26.2-1: Definitions

Term	Definition
BYPASS	
VALVE EMBOLIZATION	The valve prosthesis moves during or after deployment such that it loses contact with the aortic annulus.
VALVE MALPOSITIONING	Includes valve migration, valve embolization, or ectopic valve deployment
VALVE MIGRATION	After initial correct positioning the valve prosthesis moves upward or downward within the aortic annulus from its initial position, with or without consequences (e.g., regurgitation).
VALVE-RELATED DYSFUNCTION	Mean aortic valve gradient ≥20 mmHg, EOA ≤0.9-1.1 cm^2, and/or DVI <0.35 AND/OR moderate or severe prosthetic valve aortic regurgitation (per VARC definition)
VALVE-RELATED SYMPTOMS/CHF REQUIRING HOSPITALIZATION	The need for hospitalization associated with valve-related symptoms or worsening CHF (NYHA Class III or IV) is intended to serve as a basis for calculation of a "days alive outside the hospital" endpoint. Included are heart failure, angina, or syncope due to aortic valve disease requiring intervention or intensified medical management; clinical symptoms of CHF with objective signs including pulmonary edema, hypoperfusion, or documented volume overload AND administration of intravenous diuresis or inotropic therapy, performance of aortic valvuloplasty, institution of mechanical support (intra-aortic balloon pump or ventilation for pulmonary edema), or hemodialysis for volume overload; clear documentation of anginal symptoms AND no clinical evidence that angina was related to coronary artery disease or acute coronary syndrome; documented loss of consciousness not related to seizure or tachyarrhythmia.
VALVE THROMBOSIS	Any thrombus attached to or near an implanted valve that occludes part of the blood flow path, interferes with valve function, or is sufficiently large to warrant treatment. Note that valve-associated thrombus identified at autopsy in a patient whose cause of death was not valve-related or at operation for an unrelated indication should not be reported as valve thrombosis.
VASCULAR ACCESS SITE AND ACCESS RELATED COMPLICATIONS	**Major Vascular Complications** • Any aortic dissection, aortic rupture, annulus rupture, left ventricle perforation, or new apical aneurysm/pseudoaneurysm • Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, hematoma, irreversible nerve injury, compartment syndrome, percutaneous closure device failure*) ***leading to*** death, life-threatening or major bleeding**, visceral ischaemia, or neurological impairment • Distal embolization (non-cerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage • The use of unplanned endovascular or surgical intervention ***associated*** with death, major bleeding, visceral ischaemia or neurological impairment • Any new ipsilateral lower extremity ischemia documented by patient symptoms, physical exam, and/or decreased or absent blood flow on lower extremity angiogram • Surgery for access site-related nerve injury • Permanent access site-related nerve injury **Minor Vascular Complications** • Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysms , hematomas, percutaneous

Table 26.2-1: Definitions

Term	Definition
	closure device failure*) not leading to death, life-threatening or major bleeding**, visceral ischaemia or neurological impairment • Distal embolization treated with embolectomy and/or thrombectomy and not resulting in amputation or irreversible end-organ damage • Any unplanned endovascular stenting or unplanned surgical intervention not meeting the criteria for a major vascular complication • Vascular repair or the need for vascular repair (via surgery, ultrasound-guided compression, transcatheter embolization, or stent-graft) ***Percutaneous Closure Device Failure** Failure of a closure device to achieve hemostasis at the arteriotomy site leading to alternative treatment (other than manual compression or adjunctive endovascular ballooning) Note 1**:** Pre-planned surgical access or a planned endovascular approach to vascular closure (e.g., "pre-closure")[103,104] should be considered as part of the TAVR procedure and not as a complication, unless untoward clinical consequences are documented (e.g., bleeding complications, limb ischemia, distal embolization, or neurological impairment). Note 2: If unplanned percutaneous or surgical intervention does not lead to adverse outcomes this is not considered a major vascular complication. ** Refers to VARC bleeding definitions[70,71]
VENTRICULAR SEPTAL PERFORATION	Angiographic or echocardiographic evidence of a new septal perforation during or after the TAVR procedure
VESSEL PERFORATION	Unexpected puncture of the vessel with evidence of extravasation into extraluminal surrounding tissue or space requiring treatment using interventional or surgical techniques

Abbreviations: ADE=adverse device effect; AE=adverse event; AR=aortic regurgitation; AVA=aortic valve area; AVR= aortic valve replacement; CEC= Clinical Events Committee; CK= creatine kinase; CT=computed tomography; DVI=Doppler velocity index; ECG=electrocardiogram; EOA=effective orifice area; FEV= forced expiratory volume; LBBB=left bundle branch block; LV= left ventricle; MI=myocardial infarction; MRI=magnetic resonance imaging; NYHA=New York Heart Association; PPM=permanent pacemaker; RBC=red blood cell; SADE=serious adverse device effect; SAE=serious adverse event; TAV=transcatheter aortic valve; TAVR=transcatheter aortic valve replacement; TEE=transesophageal Doppler echocardiography; TIA=transient ischemic attack; USADE= unanticipated serious adverse device effect; URL=upper reference limit (defined as 99th percentile of normal reference range); VARC=Valve Academic Research Consortium

27. Appendices

27.1. *Changes in Protocol Versions*

27.1.1. Protocol Version AA to Version AB

Table 27.1-1 lists changes between protocol versions AA and AB

Table 27.1-1: Table of Changes for REPRISE III Protocol Version AB (Compared to REPRISE III Protocol Version AA)

Section Modified	Text as Written in REPRISE III Protocol Version AA	Text as Written in REPRISE III Protocol Version AB	Justification for Modification
Page 1	Parc d'Affaires, Le Val Saint-Quentin 2 rue René Caudron, 78960 Voisins le Bretonneux, France	55 Av. des Champs Pierreux, TSA 51101, 92729 Nanterre Cedex, France	Corrected Sponsor contact address for Europe

REPRISE III: REpositionable Percutaneous Replacement of Stenotic Aortic Valve through Implantation of Lotus™ Valve System – Randomized Clinical Evaluation

CLINICAL PROTOCOL

Protocol Number: S2282

Sponsor:	Boston Scientific Corporation 300 Boston Scientific Way Marlborough, MA 01752 USA International Representative Boston Scientific Limited Ballybrit Business Park Galway, Ireland Australian Representative Boston Scientific Pty. Ltd. Suite 5.01, Level 5 247 Coward Street Mascot, NSW 2020, Australia

This protocol contains confidential information for use by the Investigators and their designated representatives participating in this clinical investigation. It should be held confidential and maintained in a secure location.

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Original Release: 27-Jun-2014
Current Version: 05-May-2016

Revision History

Revision Number	Release Date	Template Version	Reason for Change
AB	25-Jul-2014	90702637 Rev/Ver AD	See Table 27.1-1
AC*	25-Sep-2014	90702637 Rev/Ver AD	See Table 27.1-2
AD	23-Apr-2015	90702637 Rev/Ver AD	See Table 27.1-3
AE*	19-Aug-2015	90702637 Rev/Ver AE	See Table 27.1-4
AF	07-Dec-2015	90702637 Rev/Ver AE	See Table 27.1-5
AG	22-Dec-2015	90702637 Rev/Ver AE	See Table 27.1-6
AH	05-May-2016	90702637 Rev/Ver AF	See Table 27.1-7

*Boston Scientific Corporation (BSC) internal update only; Versions AC and AE were not implemented or distributed outside of BSC.

2. Protocol Synopsis

REPRISE III: REpositionable Percutaneous Replacement of Stenotic Aortic Valve through Implantation of Lotus™ Valve System – Randomized Clinical Evaluation	
Objective(s)	To evaluate the safety and effectiveness of the Lotus™ Valve System for transcatheter aortic valve replacement (TAVR) in symptomatic subjects with calcific, severe native aortic stenosis who are considered at extreme or high risk for surgical valve replacement.
Intended Use	The Lotus Valve System is intended to improve aortic valve function for symptomatic subjects with calcific, severe native aortic stenosis who are at extreme or high risk for standard surgical valve replacement.
Test Device and Sizes	The Lotus Valve System consisting of two main components: - a bioprosthetic bovine pericardial aortic valve, and - a delivery system. Devices sizes include 21 mm, 23 mm, 25 mm, and 27 mm diameter.
Control Device and Sizes	Commercially available self-expanding CoreValve® Transcatheter Aortic Valve Replacement System (CoreValve) that is introduced percutaneously via the femoral artery using conventional catheterization techniques (Medtronic, Inc., Minneapolis, MN, USA). Devices sizes include 26 mm, 29 mm, and 31 mm diameter. ***Note 1:*** Every subject in the randomized cohort must be deemed treatable with an available size of both the test (Lotus) device and the control (CoreValve) device. The CoreValve device in the planned size must be approved for use and commercially available at the investigational center where the implant procedure is being performed. ***Note 2:*** A center may use the CoreValve® Evolut™ R Recapturable TAVR System with the aforementioned size matrix if it is approved and commercially available, but only if the center no longer has access to CoreValve.
Study Design	REPRISE III is designed to evaluate the safety and effectiveness of the Lotus Valve System for TAVR in symptomatic subjects who have calcific, severe native aortic stenosis and who are at high or extreme risk for surgical aortic valve replacement (SAVR). Study cohorts include the following. - A prospective, multicenter, 2:1 randomized (Lotus Valve System [23 mm, 25 mm, and 27 mm valve sizes] versus a commercially

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	available CoreValve Transcatheter Aortic Valve Replacement System [26 mm, 29 mm, and 31 mm valve sizes]), controlled trial - A non-randomized roll-in phase with only the test device (23 mm, 25 mm, and 27 mm valve sizes) for centers that do not have previous experience implanting the Lotus valve; each of these centers will perform at least 2 roll-in cases before commencing randomization. Data from roll-in subjects will be summarized separately from the randomized population. - A non-randomized, nested registry cohort of subjects who will receive the 21 mm Lotus Valve (Lotus 21 mm Nested Registry). Participating centers will be centers that have enrolled subjects in REPRISE III – An additional cohort of subjects who will receive the Lotus Valve (23 mm, 25 mm, and 27 mm valve sizes) beginning after enrollment of the randomized cohort is completed (U.S. Continued Access Study cohort). This cohort will be used to further assess performance and safety. Participating centers will be United States centers that have enrolled subjects in REPRISE III. Selected centers with the ability to perform high quality 4D computed tomography (CT) scans will include U.S. Continued Access Study subjects in a CT Imaging Substudy to assess the prevalence of reduced leaflet mobility and its relationship, if any, to clinical events. The REPRISE III study will be conducted in accordance with the relevant parts of the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practices (GCP) or the International Standard ISO 14155: 2011; ethical principles that have their origins in the Declaration of Helsinki; and pertinent individual country/state/local laws and regulations.
Planned Subjects/ Centers/ Countries	Subjects will be enrolled at up to 60 centers in the United States, Canada, Western Europe, and Australia. There will be up to 2052 subjects in REPRISE III. Up to 120 subjects will be enrolled and included in a roll-in phase (test device only) among centers that do not have previous experience implanting the Lotus Valve (a minimum of 2 roll-in subjects per center) before randomization begins. There will be 912 subjects enrolled and randomized. Up to 20 subjects will be enrolled in the Lotus 21 mm Nested Registry. After enrollment in the randomized cohort is completed, up to 1000 subjects will be enrolled in the U.S. Continued Access Study cohort to receive the Lotus Valve (23 mm, 25 mm, and 27 mm valve sizes); participating centers will be United States centers that have enrolled

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	subjects in REPRISE III. Approximately 200 of the 1000 subjects enrolled in the U.S. Continued Access Study will be included in a CT Imaging Substudy.
Primary Endpoints	Primary Safety Endpoint: 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 Primary Effectiveness Endpoint: Composite of all-cause mortality, disabling stroke, or moderate or greater paravalvular aortic regurgitation (based on core lab assessment) at 1 year Powered statistical analyses for the primary safety endpoint and the primary effectiveness endpoint will be carried out on the randomized cohort.
Secondary Endpoint	Moderate or greater paravalvular aortic regurgitation (based on core lab assessment) at 1 year Powered statistical analysis for the secondary endpoint will be carried out on the randomized cohort.
Additional Measurements	Additional measurements based on the VARC[a,b] endpoints and definitions (see **Note 1** below) will be 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): o Mortality: all-cause, cardiovascular, and non-cardiovascular o Stroke: disabling and non-disabling o Myocardial infarction (MI): periprocedural (≤72 hours post index procedure) and spontaneous (>72 hours post index procedure) o Bleeding: life-threatening (or disabling) and major o Acute kidney injury (≤7 days post index procedure): based on the AKIN System Stage 3 (including renal replacement therapy) or Stage 2 o Major vascular complication o Repeat procedure for valve-related dysfunction (surgical or interventional therapy) o Hospitalization for valve-related symptoms or worsening congestive heart failure (NYHA class III or IV)

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	○ New permanent pacemaker 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 (see **Note 2** below) ○ Grade of aortic valve regurgitation: paravalvular, central, and combined • 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, 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 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 mm Hg 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; see **Note 3** below)

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	and assessed by an independent core laboratory, including effective orifice area, 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 mm Hg or a peak velocity <3m/sec with no moderate or severe prosthetic valve aortic regurgitation) • For subjects who received a permanent pacemaker related to the index procedure, results of pacemaker interrogation at 30 days and 1 year • Functional status as evaluated by the following: o 5-m gait speed test (at 1 year compared to baseline) o New York Heart Association (NYHA) classification • Neurological status (see **Note 4** below) as determined by the following: o Neurological physical exam at discharge and 1 year (conducted by a neurologist, neurology fellow, neurology physician assistant, or neurology nurse practitioner) o National Institutes of Health Stroke Scale (NIHSS) at discharge and 1 year o Modified Rankin Scale (mRS) at all time points • Health status as evaluated by Kansas City Cardiomyopathy and SF-12 Quality of Life questionnaires at baseline; 1 and 6 months; and 1, 3, and 5 years Additionally, assessment of leaflet mobility using 4D CT will be carried out at 30 days and 1 year for subjects in the CT Imaging Substudy of the U.S. Continued Access Study. The data will be evaluated by an independent CT core lab. ***Note 1:*** The most current VARC definitions and endpoints available at the beginning of the trial were used. ***Note 2:*** For the Lotus Valve (test), repositioning may be achieved with partial or full resheathing of the valve. ***Note 3:*** At least 1 echocardiogram must be obtained before discharge or 7 days (whichever comes first); if multiple echocardiographic studies are performed prior to discharge and within 7 days of the procedure, the latest

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	study performed will be used for analysis. ***Note 4:*** For subjects diagnosed with a neurological event (e.g., stroke, transient ischemic attack), a neurological physical exam (conducted by a neurologist, neurology fellow, neurology physician assistant, or neurology nurse practitioner), NIHSS assessment, and mRS must be performed after the event; mRS must also be administered 90±14 days post-neurological event. a: Kappetein AP, *et al*. *J Am Coll Cardiol*. 2012;60:1438 b: Leon M, *et al. J Am Coll Cardiol.* 2011;57:253
Follow-up Schedule	All subjects implanted with a test or control device will be assessed at baseline, peri- and post-procedure, at discharge or 7 days post-procedure (whichever comes first), 30 days, 6 months, 1 year, and then annually for up to 5 years post-procedure. Subjects who are enrolled but not implanted with a test or control device at the time of the procedure will be followed for safety through 1 year.
Study Duration	Subjects implanted with a test or control device will be followed for 5 years after the procedure.
Adjunctive Pharmacologic Therapy	**Anticoagulant Therapy** Anticoagulant therapy (e.g., unfractionated heparin) per local standard of care must be administered during the implant procedure, with a recommended target activated clotting time of ≥250 seconds during the index procedure. **Anti-Platelet Therapy** Per society guidelines[c], antiplatelet therapy with aspirin and clopidogrel[d] is recommended after TAVR to decrease the risk of thrombotic or thromboembolic complications if there are no contraindications to these medications. Aspirin A loading dose of aspirin (recommended dose of 75–325 mg) is required for subjects who have not been taking aspirin for ≥72 hours at the time of the index procedure. The loading dose must be administered prior to the implant procedure. Subjects who have been taking aspirin daily for ≥72 hours at the time of the index procedure do not require a loading dose. After the valve implant procedure, aspirin (recommended dose of ≥75 mg daily) must be given for at least 1 month. It is recommended that daily

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	aspirin be given indefinitely thereafter as per local standard of care. Clopidogrel A loading dose of clopidogrel (recommended dose of ≥300 mg) is required for subjects who have not been taking clopidogrel for ≥72 hours at the time of the index procedure. The loading dose must be administered prior to the implant procedure. After the valve implant procedure, clopidogrel[d] (recommended dose of 75 mg daily) is required for at least 1 month. ***Note*:** If a subject requires chronic anticoagulation, either clopidogrel or aspirin is required prior to and after the implant procedure in addition to the anticoagulant therapy (but both aspirin and clopidogrel are not required). After the implant procedure, the subject must be treated with warfarin (other anticoagulants are not permitted in the first month) and either clopidogrel (other $P2Y_{12}$ inhibitors are not permitted in combination with warfarin) or aspirin for at least 1 month. After 1 month, subjects requiring chronic anticoagulation may be switched from warfarin to a new oral anticoagulant (NOAC) at the discretion of the treating physician. The subject should not receive a $P2Y_{12}$ inhibitor in combination with a NOAC but may be treated with a NOAC plus aspirin.. c: Holmes, D. R., et al. *J Am Coll Cardiol*. 2012;59:1200-1254 Nishimura, R., et al. *J Am Coll Cardiol*. 2014;63:2438-88 d: An alternative $P2Y_{12}$ inhibitor may be prescribed if subject is allergic to or intolerant of clopidogrel.
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 mm Hg or jet velocity ≥4.0 m/s, as measured by echocardiography and/or invasive hemodynamics. IC2. Subject has a documented aortic annulus size of ≥18 mm and ≤27 mm based on the center's assessment of pre-procedure diagnostic imaging (and confirmed by the Case Review Committee [CRC]) and, for the randomized cohort, is deemed treatable with an available size of both test and control device. For the U.S. Continued Access Study cohort the acceptable aortic annulus size is ≥20 mm and ≤27 mm. 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

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	investigator interventionalist and a site investigator cardiac surgeon) that subject is at high or extreme operative risk for surgical valve replacement (see note 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%, or other evidence of severe pulmonary dysfunction) o Neuromuscular disease that creates risk for mechanical ventilation or rehabilitation 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

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	subject is capable of returning to the study hospital for all required scheduled follow up visits. ***Note:*** Extreme operative risk and high operative risk are defined as follows: **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. Risk of operative mortality and morbidity must be assessed via an in-person evaluation by a center cardiac surgeon and must be confirmed by the CRC (which must include an experienced cardiac surgeon).
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 aortic or mitral valve. 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. EC12. Subject has had a gastrointestinal bleed requiring hospitalization or transfusion within the past 3 months, or has other clinically

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	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. 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

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	implantation. Enrollment is permissible after permanent pacemaker implantation. EC26. Subject has severe incapacitating dementia. Additional exclusion criteria apply for subjects considered for enrollment in the CT Imaging substudy of the U.S. Continued Access Study as listed below. AEC1. Subject has eGFR <30 mL/min (chronic kidney disease stage IV or stage V). AEC2. Subject has atrial fibrillation that cannot be rate controlled to ventricular response rate < 60 bpm. AEC3. Subject is expected to undergo chronic anticoagulation therapy after the TAVR procedure. ***Note*:** Subjects treated with short-term anticoagulation post-procedure can be included in the imaging substudy; in these subjects the 30-day imaging will be performed 30 days after discontinuation of anticoagulation.
Statistical Methods	
Analysis Sets	Analysis sets for the randomized cohort are listed below. As-Treated: This population includes all subjects who sign an Informed Consent Form, are enrolled in the trial, are randomized, and received a study device, but is based on the treatment actually received. Intention-To-Treat (ITT): This population includes all subjects who sign an Informed Consent Form, are enrolled in the trial, and are randomized, whether or not an assigned study device is implanted. Implanted: This population includes all subjects who sign an Informed Consent Form, are enrolled in the trial, and are implanted with the assigned, randomized study device. For all randomized cohort analysis sets, if a subject receives 2 valves, the subject is assigned to the group corresponding to the first valve received. Among the roll-in, Lotus 21 mm Nested Registry, and U.S. Continued Access cohorts, for ITT analyses all subjects who sign an Informed Consent Form and are enrolled in the study will be included in the analysis sample, regardless of whether the study device was implanted. The As-Treated population is the same as the Implanted population for these cohorts and includes all subjects who sign an Informed Consent Form and are implanted with the Lotus Valve.

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Primary Safety Endpoint Statistical Hypothesis	The primary safety endpoint (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) rate for the Lotus Valve is non-inferior to that for CoreValve.
Statistical Test Method for the Primary Safety Endpoint	A Farrington-Manning standardized test will be used to test the one-sided hypothesis of non-inferiority of the Lotus Valve versus CoreValve: H_0: P_{S_Lotus} minus $P_{S\_Control} \geq \Delta$ (Inferior) H_1: P_{S_Lotus} minus $P_{S\_Control} < \Delta$ (Non-inferior) where P_{S_Lotus} and $P_{S\_Control}$ are the rates of the primary safety endpoint for the Lotus Valve group (test) and the CoreValve group (control), respectively, and Δ (delta) is the non-inferiority margin. The primary analysis set for the primary safety endpoint is the implanted analysis set. This endpoint will also be analyzed for the ITT and as-treated analysis sets.
Sample Size Parameters for the Primary Safety Endpoint	• Expected Lotus Valve (test) rate = 40% • Expected CoreValve (control) rate = 40% • Non-inferiority margin (Δ) = 10.5% • Test significance level (α) = 0.025 (1-sided) • Test : Control ratio = 2:1 • Expected rate of attrition = 5% • Given enrollment of 912 subjects (608 Lotus Valve, 304 CoreValve) and 5% attrition, there is approximately 85% power to show non-inferiority with the given expected rates
Success Criteria for the Primary Safety Endpoint	If the *P* value from the Farrington-Manning standardized test is <0.025, the rate of the primary safety endpoint for the Lotus Valve will be concluded to be non-inferior to the CoreValve rate. This corresponds to the one-sided upper 97.5% confidence bound on the difference between treatment groups (Lotus Valve minus CoreValve) for the observed rate of the primary safety endpoint being less than delta.
Primary Effectiveness Endpoint	The primary effectiveness endpoint (composite of all-cause mortality, disabling stroke, or moderate or greater paravalvular aortic regurgitation [based on core lab assessment] at 1 year) rate for the Lotus Valve group is

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Statistical Hypothesis	noninferior to that for the CoreValve group. If non-inferiority is shown for the Lotus group for the primary safety and primary effectiveness endpoints, superiority is shown for the secondary endpoint, and the rate for the Lotus group is less than the rate for the CoreValve group for the primary effectiveness endpoint, then a test of superiority will be performed for the primary effectiveness endpoint.
Statistical Test Method for the Primary Effectiveness Endpoint – Non-Inferiority	A Farrington-Manning standardized test will be used to test the one-sided hypothesis of non-inferiority of the Lotus Valve versus CoreValve: H_0: P_{E_Lotus} minus $P_{E\_Control} \geq \Delta$ (Inferior) H_1: P_{E_Lotus} minus $P_{E\_Control} < \Delta$ (Non-inferior) where P_{E_Lotus} and $P_{E\_Control}$ correspond to the rates of the primary effectiveness endpoint for the Lotus Valve group (test) and the CoreValve group (control), respectively. The primary analysis set for the primary effectiveness endpoint is the implanted analysis set. This endpoint will also be analyzed for the ITT and as-treated analysis sets.
Sample Size Parameters for the Primary Effectiveness Endpoint – Non-Inferiority	• Expected Lotus Valve (test) rate $P_{E\_Lotus} = 32\%$ • Expected CoreValve (control) rate $P_{E\_Control} = 32\%$ • Non-inferiority margin (Δ) = 9.5% • Test significance level (α) = 0.025 (1-sided) • Test : Control ratio = 2:1 • Power ($1-\beta$) = 80% • Total number of evaluable subjects = 819 • Expected rate of attrition = 10% N = 912 subjects (608 Lotus Valve, 304 CoreValve)
Success Criteria for the Primary Effectiveness Endpoint – Non-Inferiority	If the *P* value from the Farrington-Manning standardized test is <0.025, the rate of the primary effectiveness endpoint for the Lotus Valve will be concluded to be non-inferior to the CoreValve rate. This corresponds to the one-sided upper 97.5% confidence bound on the difference between treatment groups (Lotus Valve minus CoreValve) for the observed rate of the primary effectiveness endpoint being less than delta.

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Statistical Test Method for the Primary Effectiveness Endpoint – Superiority	A chi-square test will be used to test the two-sided hypothesis of superiority of the Lotus Valve versus CoreValve: H_0: $P_{E\_Lotus} = P_{E\_Control}$ H_1: $P_{E\_Lotus} \neq P_{E\_Control}$ where P_{E_Lotus} and $P_{E\_Control}$ correspond to the rates of the primary effectiveness endpoint for the Lotus Valve group (test) and the CoreValve group (control), respectively. The primary analysis set for superiority test of the primary effectiveness endpoint is the ITT analysis set. This endpoint will also be analyzed for the as-treated and implanted analysis sets.
Sample Size Parameters for the Primary Effectiveness Endpoint – Superiority	• Expected Lotus Valve (test) rate $P_{E\_Lotus} = 22\%$ • Expected CoreValve (control) rate $P_{E\_Control} = 32\%$ • Test significance level (α) = 0.05 (2-sided) • Test : Control ratio = 2:1 • Power ($1-\beta$) = 80% • Total number of evaluable subjects = 684 • Expected rate of attrition = 10% • Given enrollment of 912 subjects (608 Lotus Valve, 304 CoreValve) and 10% attrition, there is approximately 86% power to show superiority with the given expected rates
Success Criteria for the Primary Effectiveness Endpoint – Superiority	If the *P* value from the chi-square test is <0.05 and the rate of the Lotus Valve group is less than the rate of the CoreValve group, the rate of the primary effectiveness endpoint for the Lotus Valve will be concluded to be superior to the CoreValve rate. This corresponds to the two-sided upper 95% confidence bound on the difference between treatment groups (Lotus Valve minus CoreValve) for the observed rate of the primary effectiveness endpoint being less than zero.
Secondary Endpoint Statistical Hypothesis	The secondary endpoint of moderate or greater paravalvular aortic regurgitation rate at 1 year (based on core lab assessment) for the Lotus Valve group is superior to that for the CoreValve group.
Statistical Test Method for the	A chi-square test will be used to test the two-sided hypothesis of superiority:

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Secondary Endpoint	H_0: $P_{AR\_Lotus} = P_{AR\_Control}$ H_1: $P_{AR\_Lotus} \neq P_{AR\_Control}$ where P_{AR_Lotus} and $P_{AR\_Control}$ correspond to the moderate or greater paravalvular aortic regurgitation rates at 1 year for the Lotus Valve group (test) and the CoreValve group (control), respectively. The primary analysis set for the secondary endpoint is the ITT analysis set. This endpoint will also be analyzed for the as-treated and implanted analysis sets.
Sample Size Parameters for the Secondary Endpoint	• Expected Lotus Valve (test) rate $P_{AR\_Lotus} = 1.1\%$ • Expected CoreValve (control) rate $P_{AR\_Control} = 5.3\%$ • Test significance level (α) = 0.05 (2-sided) • Test : Control ratio = 2:1 • Expected rate of attrition = 25% • Given enrollment of 912 subjects (608 Lotus Valve, 304 CoreValve) and 25% attrition, there is approximately 86% power to show superiority with the given expected rates
Success Criteria for the Secondary Endpoint	If the *P* value from the chi square test is <0.05, and the rate of moderate or greater paravalvular aortic regurgitation at 1 year for the Lotus Valve group is less than the rate of the CoreValve group, the moderate or greater paravalvular aortic regurgitation rate at 1 year for the Lotus Valve group will be concluded to be superior to that of the CoreValve group. This corresponds to the two-sided upper 95% confidence bound on the difference between treatment groups (Lotus Valve minus CoreValve) for the observed rate of the secondary endpoint being less than zero.

3. Table of Contents

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4. Introduction

This protocol specifies procedures and contains information relevant to the clinical evaluation of the Lotus™ Valve System, a transfemoral aortic valve replacement device designed and manufactured by Boston Scientific Structural Heart a Division of Boston Scientific Corporation (BSC). The Lotus Valve System consists of a pre-loaded, stent-mounted tissue valve prosthesis and catheter delivery system designed to enable predictable and precise placement of the valve during transcatheter aortic valve replacement (TAVR). Early leaflet function during valve deployment and the presence of a radiopaque tantalum marker on the braided frame facilitate optimal initial positioning of the valve. If needed, the valve may be partially or fully resheathed for repositioning prior to final release or can be fully retrieved if during the procedure the decision is made not to implant. The valve also has a polycarbonate-based urethane outer seal (Adaptive Seal™) designed to minimize paravalvular leakage. Additional device information can be found in Section 5. Study subjects will be entered into the roll-in cohort, randomized (test versus control) cohort, a single-arm, nested registry cohort of subjects who receive the 21 mm Lotus Valve (Lotus 21 mm Nested Registry), or the U.S. Continued Access Study cohort (which will include a 4D computed tomography [CT] substudy cohort). Additional information on study design can be found in Section 8.

4.1. *Justification for the Use of the Investigational Device in Human Subjects*

4.1.1. Treatments for Aortic Stenosis

The incidence of aortic stenosis (AS), which most commonly occurs in the very elderly, is increasing due to the aging of the world-wide population and the lack of drug therapies to prevent, halt, or effectively slow the stenotic process[1-3]. It is estimated that nearly 5% of elderly ≥75 years of age have AS and its prevalence is expected to increase as a result of an aging population[4-6]. Aortic stenosis is associated with high rates of death and complications after the appearance of symptoms[7,8].

The standard of care for AS in patients who do not have serious comorbidities is surgical aortic valve replacement (SAVR), which has been shown to reduce symptoms and improve survival[5,7,9-11]. Between 1999 and 2011, the rate of surgical AVR for elderly subjects in the United States has increased and outcomes have improved[11]. However, up to one-third of patients with severe AS are not treated with SAVR because of their comorbidities and consequent peri-operative risk (e.g., advanced age, left ventricular dysfunction, etc.)[5,12-14]. With standard medical therapy, mortality after 1 year among these patients may be as high as 50%[13-15]. Percutaneous transluminal aortic valvuloplasty, which was introduced as an alternative to SAVR in elderly and/or high-surgical-risk subjects, can provide symptomatic relief and/or temporary improvement but does not provide definitive treatment in subjects with severe calcific AS. It is also associated with relatively high mortality and complication rates[16].

Transcatheter aortic valve replacement (TAVR) has recently emerged as a less invasive treatment strategy in subjects who are not suitable candidates for open-heart surgery[17-21] and more than 60,000 transcatheter aortic valve prostheses have been implanted worldwide[22]. Patients with severe aortic stenosis undergo a joint interdisciplinary screening process, including comprehensive multimodality imaging[23-26], prior to procedure recommendation. Because existing surgical risk scores imperfectly characterize risk[27-30], center Heart Teams also consider other co-morbidities and patient frailty. While not captured well by any of the standard risk scores, these added measures help to more fully characterize a patient population that potentially benefits from TAVR[31].

Transcatheter aortic valve replacement was initially performed through a retrograde transfemoral approach and an antegrade transapical approach. Two additional retrograde approaches, transaortic through the ascending aorta and trans-subclavian, were subsequently described[19,32]. Evidence of the safety of the procedure using either a balloon expandable or a self-expanding bioprosthetic heart valve has rapidly accumulated through observational studies[33-39], device-specific registries[40-54], and national registries[55-62]. In the randomized Placement of Aortic Transcatheter Valves (PARTNER) trial, patients unsuitable for surgical valve replacement who underwent TAVR with a balloon-expandable device experienced significant reductions in mortality and repeat hospitalization compared to those receiving conventional medical therapy at 1 and 2 years[14,63] and high-surgical-risk patients receiving either TAVR or surgical replacement had a similar mortality risk[64,65]. In the randomized U.S. CoreValve High Risk Study, TAVR with a self-expanding transcatheter aortic-valve bioprosthesis was associated with a significantly higher rate of survival at 1 year compared to SAVR[66].

Recently, reduced aortic valve leaflet motion, mainly asymptomatic, has been identified with follow-up CT among some TAVR subjects[67,68]. Therapeutic anticoagulation with warfarin was associated with a decreased incidence and leaflet motion could be restored with anticoagulation. This phenomenon has not been definitively linked with abnormal clinical symptoms. Studies to assess its prevalence and determine any relationship to patient, procedural, or pharmacologic factors or clinical events are ongoing.

A recently published expert consensus document lists TAVR as a reasonable alternative to SAVR in AS patients with high surgical risk[8] and a subsequent consensus document outlines patient selection for TAVR.[69] The potential of TAVR to be a treatment option for a considerable number of patients with AS has resulted in significant advances in the technology aiming to simplify the procedure and minimize adverse events[70,71]. Standardized endpoint definitions were published by the Valve Academic Research Consortium (VARC) in 2011 (VARC-1[72]) and updated in 2012 (VARC-2[73]).

Table 4.1-1 summarizes the peri-operative event rates through 30 days post-procedure from several TAVR studies that enrolled subjects similar to those planned for this study, as well as results from inoperable and high risk subjects in PARTNER, the U.S. CoreValve Extreme Risk Pivotal Trial, and the U.S. CoreValve High Risk Study. A more detailed summary of the available literature is presented in the Investigator Brochure.

Table 4.1-1: Events from Peri-Operative to 30 Days (Transfemoral Approach)

Study	Device/N	Death (%)	MI (%)	Stroke* (%)	Bleeding (%)	AKI (%)	VC (%)
Webb, et al. 2009[33]	EW/113[a]	8	N/A	5.3	11.6	4.4	8
Rodés-Cabau, et al. 2010[41]	EW/168[a]	9.5	0.6	3.0	N/A	N/A	N/A
Thomas, et al. 2010[42]	EW/463[a]	6.3	N/A	2.4	9.9	1.3	22.9
Leon, et al. 2010[14]	EW/267[b]	5	0	5	16.8	1.1	16.2[c] 30.7
Smith, et al. 2011[64]	EW/244[a,d]	3.4	0	3.8	9.3	2.9	14[c] 22.7
Piazza, et al. 2008[40]	CV/646	8	0.6	1.9[e]	N/A	N/A	1.2
Munoz-Garcia, et al. 2012[74]	CV/133[f]	4.5	0.8	1.5	N/A	N/A	2.2[c]
Buchanan, et al. 2011[35]	CV, EW/305	4.7	1.3	1.0	33.1	10.2[g]	15.7[c]
Moat, et al. 2011[57]	CV, EW/599	5.5	1.0	4.0[h]	N/A	N/A	6.2
Zahn, et al. 2011[56]	CV, EW/697[i]	12.4	0.3	2.8[e]	N/A	N/A	17.1[j]
Bosmans, et al. 2011[58]	CV/133[a] EW/99[a]	8 CV; 6 EW	N/A	5[e,k]	N/A	6[k,l]	N/A
Tamburino, et al. 2012[36]	CV, EW/218[m]	6.9	0.0	2.3	5.5	N/A	N/A
Gilard, et al. 2012[59]	CV, EW/2361[a]	8.5	0.8	2.2	1.2[n]	N/A	5.5[c]
Spargias, et al. 2013[60]	CV/67, EW/59	1.0	N/A	0.0[e]	2.0[c]	N/A	9.0[o]
Mack, et al. 2013[62]	EW/3833[a,d,h] EW/1139[a,b,h] EW/1687[a,d] EW/489[a,b]	3.8[a,d,h] 5.4[a,b,h] 5.0[a,d] 6.7[a,b]	0.5[a,d,h] 0.8[a,b,h] N/A[a,b,d]	3.8[a,d,e,h] 5.4[a,b,e,h] 3.2[a,d,e] 1.6[a,b,e]	3.2[a,c,d,h] 3.6[a,b,c,h] N/A[a,b,d]	1.3[a,d,h,l] 1.7[a,b,h,l] 1.5 [a,d,l] 1.6 [a,b,l]	6.4[c,h,k]
Popma, et al. 2014[75]	CV/489[b]	8.4	1.2	2.3	12.7[n] 24.9[c]	11.8	8.2[c]
Adams, et al. 2014[66]	CV/390[a,d]	3.3	0.8	3.9	13.6[n] 28.1[c]	6.0	5.9[c]
Van Mieghem, et al. 2013[38]	EW&XT/281 CV/361	6.1	1.2	2.2	13.2[n] 19.6[c]	7.3[p]	11.5[c]
Testa, et al. 2014[76]	CV/1531[m]	5.9	2.0	2.0	15.0[c]	N/A	2.7[c]
Abdel-Wahab, et al. 2014[77]	CV/117; EW/121	5.1 CV; 4.1 EW	0 CV; 0.8 EW	2.6[e] CV; 5.8[e] EW	12.0[n] CV 8.3[n] EW 14.5[c] CV 19.0[c] EW	9.4 CV 4.1 EW	11.1[c] CV 9.9[c] EW
Webb, et al. 2014[78]	S3/96	2.1	2.1	0.0	3.1[n] 19.8[c]	1.0[p]	4.2[c]

Table 4.1-1: Events from Peri-Operative to 30 Days (Transfemoral Approach)

Study	Device/N	Death (%)	MI (%)	Stroke* (%)	Bleeding (%)	AKI (%)	VC (%)
Wenaweser, et al. 2014[79]	CV/336[q] SXT/317[q]	4.8	0.4	2.5	6.3[n] 8.4[c]	2.5[g]	6.3[c,h]
Tarsia, et al. 2014[80]	CV/53 EW&SXT/56	1.9 CV 14.3 EW&SXT	N/A	1.9 CV 0.0 EW&SXT	7.5 CV 8.9 EW%SXT	N/A	1.9 CV 7.1 EW & SXT
De Brito, et al. 2015[81]	CV/360[f] SXT/58[f]	9.1	0.7	2.2	7.6[n] 7.3[c]	5.6[g]	8.5[c]

* Disabling or major stroke
a: Transfemoral approach population only
b: Inoperable subjects
c: Major
d: High risk subjects
e: All stroke
f: Femoral access in >90% of cases
g: Stage 3
h: In hospital
i: 92.4% transfemoral and 3.2% subclavian; 84% of all procedures were CV
j: Groin problem with need of transfusion
k: All subjects
l: Dialysis
m: Femoral access in 84% of cases
n: Life-threatening bleeding
o: All vascular complications
p: Stage 2/3
q: 93% of subjects received either SXT or CV; 79% of subjects had transfemoral access
Abbreviations: AKI=acute kidney injury; CV=CoreValve; EW=Edwards; MI=myocardial infarction; N/A=not available; S3=SAPIEN 3 (Edwards); SXT=SAPIEN XT (Edwards);VC=vascular complications

4.1.2. REPRISE I Study

As discussed above, TAVR in patients unsuitable for SAVR has reduced mortality[14,75] and treatment of selected patients at high surgical risk has resulted in similar[64] or better[66] survival at 1 year. These results notwithstanding, TAVR with early generation devices has been associated with increased stroke risk and vascular complications when compared to surgical valve replacement[64-66], which have been significant predictors of mortality[82,83]. There are also other infrequent but substantial complications that impact long-term outcomes and may limit the use of TAVR in lower risk subjects. Precise valve positioning can be challenging with first-generation devices, and valve misplacement can lead to severe problems, including coronary occlusion and valve embolization [84]. Incomplete apposition of the prosthesis with the native valve can occur in the presence of significant amounts of calcium or with suboptimal implantation, resulting in paravalvular regurgitation[85,86]. This has been associated with increased mortality in several longitudinal registries[45,87,88]. While careful patient

selection may serve to mitigate these risks[89-91], device design improvements such as seen with the Lotus Valve System (including the ability to fully reposition and retrieve the valve and a unique adaptive seal to prevent leakage, see Section 5.1) may enable more precise placement and minimize or eliminate paravalvular regurgitation.

The prospective, single arm, multicenter REPRISE I (REpositionable Percutaneous Replacement of Stenotic Aortic Valve through Implantation of Lotus™ Valve SystEm) feasibility study (N=11) assessed the acute safety and performance of the Lotus Valve System in symptomatic subjects with calcific aortic stenosis who were considered high risk for surgical valve replacement[92]. The primary endpoint was clinical procedural success, defined as successful implantation of a Lotus Valve (per the VARC-1 definitions[72]) without in-hospital major adverse cardiovascular and cerebrovascular events (MACCE, defined as all-cause mortality, periprocedural myocardial infarction ≤72 hours after the index procedure, major stroke, urgent/emergent conversion to surgery or repeat procedure for valve-related dysfunction) through discharge or 7 days post-procedure, whichever came first. Clinical follow-up will extend through 5 years. Safety endpoints are adjudicated by an independent Clinical Events Committee (CEC); prosthetic valve function and cardiac function endpoints are assessed by independent echocardiography and electrocardiography core labs. The study is registered at ClinicalTrials.gov, Identifier NCT01383720.

To ensure proper use of the Lotus Valve System and mitigate any procedural complication that could be secondary to misuse or misinterpretation of the Instructions For Use, a comprehensive training and proctorship program was implemented in this study supported by an experienced proctoring physician assigned by Boston Scientific. Given the importance of selecting appropriate subjects, a Case Review Committee (CRC) comprised of the Principal Investigators, other investigators experienced with TAVR, and the Sponsor was established. This committee was responsible for reviewing and confirming subject eligibility across study sites during the screening process.

The primary endpoint was achieved in 9/11 subjects[92]. The device was successfully implanted in all 11 subjects but there was a device failure in 1 subject based on not meeting one of four VARC-1 criteria[72] for device success (the mean gradient of 22 mmHg in this subject was greater than the VARC-1 cutoff of 20 mmHg). The Echocardiography Core Lab concluded that the device failure resulted from a hyperdynamic state in the subject and noted that the prosthetic valve appeared to be functioning well. Ten (10) of 11 subjects had no in-hospital MACCE; there were no deaths and 1 major stroke. Paravalvular regurgitation at discharge TTE was mild in 2 subjects, trivial in 1 subject, and absent in the other 8 subjects; these outcomes compare favorably with published data[14,40,56,64,93].

To date, data are available through 3 years[92,94]. There were no additional MACCE events beyond the primary endpoint through 2 years and 1 noncardiovascular death in the interval between 2 and 3 years. The 3-year VARC-1[72] combined safety endpoint, including MACCE, life threatening/disabling bleeding, major vascular complications, and Stage 3 acute kidney injury, was 4/11; the aforementioned subject with the major stroke also had a small left femoral dissection treated with balloon inflation during the procedure and there were 2 life-threatening/disabling bleeds through 30 days that were unrelated to valve implantation and

resolved, and there was 1 noncardiovascular death due to uncontrolled sepsis. Conduction disturbances led to implantation of a permanent pacemaker (PPM) before discharge in 4 subjects; 2 of these 4 subjects had paced rhythms at 1 year. While all REPRISE I subjects were NYHA Class II (n=6) or III (n=5) at baseline, this distribution was significantly improved between baseline and 30 days (3 in Class I, 7 in Class II, 1 in Class III; *P*=0.02), baseline and 1 year (5 in Class I, 6 in Class II; *P*=0.004), baseline and 2 years (6 in Class I, 5 in Class II; *P*=0.004), and baseline and 3 years (5 in Class I, 1 in Class II, 2 in Class III; *P*=0.004). The mean aortic valve gradient was 11.7±3.0 mmHg for the cohort at 30 days, 15.4±4.6 mmHg at 1 year, 15.4±4.4 mmHg at 2 years, and 15.6±4.4 mmHg at 3 years. Paravalvular aortic regurgitation was mild (2/11) or absent (9/11) at 30 days, mild (1/11) or absent/trivial (10/11) at 1 year, absent/trivial (11/11) at 2 years, and absent (7/8) or mild (1/8) at 3 years; there was no moderate or severe paravalvular aortic regurgitation at any time post implantation of the Lotus Valve. The results of the REPRISE I feasibility study support the safety and performance of the Lotus Valve System.

4.1.3. REPRISE II Study

The REpositionable Percutaneous Replacement of Stenotic Aortic Valve through Implantation of Lotus™ Valve System – Evaluation of Safety and Performance (REPRISE II) clinical trial was designed to evaluate the safety and performance of the Lotus Valve System for TAVR in symptomatic subjects with calcific stenotic aortic valves who were considered high risk for surgical valve replacement. This prospective, single-arm, multicenter, CE-Mark study enrolled 120 subjects in the main cohort at 14 investigative centers in Australia, France, Germany and the United Kingdom. As noted above for REPRISE I (Section 0), a comprehensive training and proctorship program was implemented and a CRC was responsible for reviewing and confirming subject eligibility across study sites during the screening process. The study is registered at ClinicalTrials.gov, Identifier NCT01627691.

Safety endpoints in the ongoing REPRISE II study are adjudicated by an independent CEC; prosthetic valve function and cardiac function endpoints are assessed by independent echocardiography and electrocardiography core labs. The primary device performance endpoint was the mean aortic valve pressure gradient at 30 days post implant as measured by echocardiography. This endpoint was analyzed on an as-treated (subjects who received the Lotus Valve) basis. A one-sample *t*-test was used to test the one-sided hypothesis that the primary device performance endpoint is less than the prespecified performance goal (PG) of 18 mmHg. Two interim analyses were conducted on the first 40 and 60 subjects; the alpha-adjustment for multiple comparisons was 0.01123 and 0.00792, respectively. The alpha level adjustment for the final analysis conducted on the fully enrolled cohort of 120 subjects was 0.01305.The primary safety endpoint was all-cause mortality at 30 days after the implant procedure and was evaluated on an intent-to-treat basis.

The 30-day mean aortic valve pressure gradient was 11.45±5.20 mmHg with a one-sided 98.695% upper confidence bound of 12.64. The *P* value from the one-sample *t*-test was <0.0001 and so the Lotus Valve was concluded to have a 30-day mean aortic pressure

gradient <18 mmHg and the primary device performance endpoint was met. Table 4.1-2 shows device performance endpoints, clinical outcomes, and echocardiographic outcomes through 30 days[95]. Successful vascular access, delivery and deployment of the Lotus Valve along with successful retrieval of the delivery system was achieved in all 120 subjects. Repositioning and/or retrieval was successful in all patients in whom it was attempted. Mortality was 4.2% and the disabling stroke rate was 1.7%. There were no repeat procedures for valve-related dysfunction. Core lab assessment of paravalvular aortic regurgitation at 30 days indicated no severe regurgitation and 1 case of moderate regurgitation; in 83.3% (80/96) of subjects there was trace/trivial or no paravalvular regurgitation. The observed clinical results are consistent with other TAVR studies (see Table 4.1-1) and the rates of paravalvular regurgitation are lower[14,64,66,75,77]. Table 4.1-3 shows 1-year[96] and 2-year[97] clinical (time-to-event analysis) and echocardiographic outcomes. At 2 years, mortality was 17% and the disabling stroke rate was 3.5%. The low paravalvular aortic regurgitation rate observed at 30 days was maintained at 2 years as most subjects (91%) had none/trivial paravalvular aortic regurgitation and there was no moderate or severe paravalvular regurgitation. The results of the REPRISE II study support the safety and performance of the Lotus Valve System.

Table 4.1-2: 30-Day Outcomes in REPRISE II Main Cohort (N=120)

Outcomes	REPRISE II (N=120)
Clinical Outcomes at 30 Days (CEC Adjudicated)	
All-cause mortality	4.2% (5/119)
Cardiovascular	4.2% (5/119)
All stroke	6.1% (7/115)
Disabling stroke	1.7% (2/115)
Major vascular complications	2.6% (3/116)
Life-threatening or disabling bleeding	5.1% (6/117)
Major bleeding	17.9% (21/117)
Acute kidney injury – Stage 2 or 3	3.5% (4/115)
Coronary obstruction (periprocedural)	0.9% (1/115)
Valve-related dysfunction requiring repeat procedure (surgical/interventional)	0.0% (0/115)
New permanent pacemaker implantation resulting from new or worsened conduction disturbances	29.1% (34/117)
Periprocedural MI (≤72 hours after index procedure)	3.4% (4/117)
Hospitalization for valve-related symptoms or worsening congestive heart failure	4.3% (5/115)
Atrial fibrillation or atrial flutter (new onset)	5.2% (6/115)
Ventricular septal perforation (periprocedural)	0.0% (0/115)
Mitral apparatus damage (periprocedural)	2.6% (3/115)
Cardiac tamponade (periprocedural)	4.3% (5/117)
Prosthetic aortic valve malpositioning	0.0% (0/115)
Prosthetic aortic valve thrombosis	0.0% (0/115)
Prosthetic aortic valve endocarditis	0.0% (0/115)

Table 4.1-2: 30-Day Outcomes in REPRISE II Main Cohort (N=120)

Outcomes	REPRISE II (N=120)
Device Performance Endpoints	
Successful vascular access, delivery, and deployment of the Lotus Valve System, and successful retrieval of the delivery system	100.0% (120/120)
Successful repositioning (partial or complete resheathing of the Lotus Valve in the catheter and redeployment in a more accurate position within the aortic valve annulus) of the Lotus Valve System if repositioning is attempted for the last valve attempted	100.0% (32/32)
Successful retrieval (complete resheathing of the Lotus Valve in the catheter and removal from the body) of the Lotus Valve System if retrieval is attempted	100.0% (6/6)
Valve Performance by Transthoracic Echocardiography (30 Days-Core Lab Assessment)	
Aortic valve area (effective orifice area) (cm^2)	1.67±0.43 (78)
Mean aortic valve gradient (mmHg)	11.45±5.20 (97)
Peak aortic gradient (mmHg)	21.30±9.26 (97)
Peak aortic velocity (cm/s)	2.25±0.48 (97)
Paravalvular Aortic Regurgitation	
None	78.1% (75/96)
Trace/trivial	5.2% (5/96)
Mild	15.6% (15/96)
Moderate	1.0% (1/96)
Severe	0.0% (0/96)

Values are % (count/sample size) or mean±SD (n)
Note: Denominators for clinical event rates are based on the number of subjects who have either had an event within 30 days post-procedure or who were event-free with last follow-up at least 23 days post-procedure.
Reference: Meredith, 2014[95]

Table 4.1-3: 1-Year and 2-Year Outcomes in REPRISE II Main Cohort (N=120)

Outcomes	REPRISE II 1 Year	REPRISE II 2 Years
Clinical Outcomes at 1 Year and 2 Years (CEC Adjudicated)		
All-cause mortality	11.0% (13)	16.9% (20)
Cardiovascular	6.7% (8)	10.4% (12)
All stroke	9.5% (11)	9.5% (11)
Disabling stroke	3.5% (4)	3.5% (4)
Major vascular complications	2.5% (3)	2.5% (3)
Life-threatening or disabling bleeding	5.9% (7)	7.8% (9)
Major bleeding	21.4% (25)	23.3% (27)
Acute kidney injury – Stage 2 or 3	3.4% (4)	3.4% (4)
Valve-related dysfunction requiring repeat procedure (surgical/interventional)	0.0% (0)	0.0% (0)
New permanent pacemaker implantation resulting from new or worsened conduction disturbances	32.2% (38)	34.2% (40)
Spontaneous MI (> 72 hours after index procedure)	0.0% (0)	0.0% (0)

Table 4.1-3: 1-Year and 2-Year Outcomes in REPRISE II Main Cohort (N=120)

Outcomes	REPRISE II 1 Year	REPRISE II 2 Years
Hospitalization for valve-related symptoms or worsening congestive heart failure	5.2% (6)	8.0% (9)
Atrial fibrillation or atrial flutter (new onset)	6.0% (7)	6.0% (7)
Prosthetic aortic valve malpositioning	0.0% (0)	0.0% (0)
Prosthetic aortic valve thrombosis	0.0% (0)	0.0% (0)
Prosthetic aortic valve endocarditis	0.9% (1)	2.8% (3)
Valve Performance by Transthoracic Echocardiography (1 Year and 2-Years -Core Lab Assessment)		
Aortic valve area (effective orifice area) (cm^2)	1.65±0.51 (79)	1.66±0.45 (69)
Mean aortic valve gradient (mmHg)	12.58±5.66 (92)	12.30±6.18 (75)
Peak aortic gradient (mmHg)	23.09±10.14 (92)	21.25±11.03 (75)
Peak aortic velocity (cm/s)	2.35±0.50 (92)	2.23±0.56 (75)
Paravalvular Aortic Regurgitation		
None	86.4% (76/88)	87.8% (65/74)
Trace/trivial	2.3% (2/88)	2.7% (2/74)
Mild	11.4% (10/88)	9.5% (7/74)
Moderate	0.0% (0/88)	0.0% (0/74)
Severe	0.0% (0/88)	0.0% (0/74)

Values are % (n); % (count/sample size), or mean±SD (n)
Clinical event rates are presented as Kaplan-Meier estimates.
References: Meredith, 2015[96,97]

The REPRISE II study was subsequently expanded to enroll 130 additional subjects in the REPRISE II extended trial cohort at centers in Australia and Europe; enrollment in this extended cohort was completed in April 2014. The main trial cohort and the extended trial cohort had the same overall study design. The main trial cohort received additional neurologic evaluation and annual imaging assessments to determine valve frame integrity. Per the protocol, a statistically powered analysis based on the combined main and extended trial cohorts (full cohort, N=250) was performed for the primary safety endpoint (mortality at 30 days). The primary safety endpoint was analyzed on an intent-to-treat basis (all subjects enrolled, whether or not a study device is implanted). A one-sample z test was used to test the one-sided hypothesis that 30-day all-cause mortality is less than the prespecified PG of 16% (based on an expected rate of 9.8% plus a testing margin of 6.2%). All-cause mortality at 30 days was 4.4% with an upper confidence bound of 6.97% and the primary safety endpoint was met[98].

Table 4.1-4 shows device performance endpoints, clinical outcomes, and echocardiographic outcomes through 30 days and 1 year for the full cohort (N=250)[98,99]. Outcomes at 30 days in the full cohort were similar to that reported for the main cohort (see Table 4.1-2) with a mean aortic valve gradient of 11.70±6.77 mmHg. Mortality was 4.4% and the disabling stroke rate was 3.3%. The new PPM implant rate was 29.6%. Reported rates for early conduction abnormalities and the need for PPM implantation after TAVR have ranged from 3% to 8%

with SAPIEN and 14% to 40% with CoreValve[100]. In a recent report, 12-month clinical outcomes were similar among subjects with and without periprocedural PPM[101]. Another study (mean follow-up of 22±17 months) found that PPM implantation post TAVR had a negative effect on left ventricular function but was not associated with any increase in overall or cardiovascular death or rehospitalization for heart failure and was a protective factor for the occurrence of sudden or unknown death (*P*=0.023)[102]. Implantation of a new PPM following TAVR with SAPIEN (retrospective analysis from the combined PARTNER trial and NRCA registry) was associated with a higher rate of repeat hospitalization at 30 days and 1 year (10.6% vs. 5.9%, *P*=0.02 at 30 days; 23.9% vs. 18.2%, *P*=0.05 at 1 year) but not mortality (7.5% vs. 5.8%, *P*=0.40 at 30 days; 26.3% vs. 20.8%, *P*=0.08 at 1 year)[103]. There was no severe paravalvular regurgitation and trace/trivial or no paravalvular regurgitation in 85.8% of REPRISE II subjects. Reported moderate or severe aortic regurgitation after TAVR has ranged from 6% to 21%[104] and has been associated with increased mortality in several longitudinal registries[45,59,87,88]. Through 1 year, mortality was 12% and the disabling stroke rate was 3.6%. Valve endocarditis (N=2) and thrombosis (N=3) were successfully resolved with antibiotics and anticoagulant therapy, respectively, without sequelae. The low paravalvular aortic regurgitation rate observed at 30 days was maintained at 1 year as most subjects (91%) had none/trivial paravalvular aortic regurgitation and there was no moderate or severe paravalvular regurgitation.

In summary, the observed clinical results are consistent with other TAVR studies and the PVR rates are lower. The results of the REPRISE II study support the safety and performance of the Lotus Valve System.

Table 4.1-4: 30-Day and 1-Year Outcomes in the REPRISE II Full Cohort (N=250)

Outcomes	**REPRISE II 30 Days**	**REPRISE II (1 Year)**
Clinical Outcomes at 30 Days and 1 Year (CEC Adjudicated)		
All-cause mortality	4.4% (11/249)	11.6% (29/249)
Cardiovascular	4.0% (10/249)	7.6% (19/249)
All stroke	7.1% (17/241)	8.4% (21/249)
Disabling stroke	3.3% (8/241)	3.6% (9/249)
Major vascular complications	5.4% (13/241)	5.2% (13/249)
Life-threatening or disabling bleeding	7.3% (18/247)	9.2% (23/249)
Major bleeding	21.5% (53/247)	23.3% (58/249)
Acute kidney injury – Stage 2 or 3	2.9% (7/240)	2.9% (7/240)
Coronary obstruction (periprocedural)	0.8% (2/241)	–
Valve-related dysfunction requiring repeat procedure (surgical/interventional)	0.0% (0/240)	0.0% (0/249)
New permanent pacemaker implantation resulting from new or worsened conduction disturbances	29.6% (72/243)	32.5% (81/249)
Periprocedural MI (≤72 hours after index procedure)	2.9% (7/243)	–
Spontaneous MI (>72 hours after index procedure)	–	0.0% (0/249)
Hospitalization for valve-related symptoms or worsening congestive heart failure	2.9% (7/240)	6.8% (17/249)

Table 4.1-4: 30-Day and 1-Year Outcomes in the REPRISE II Full Cohort (N=250)

Outcomes	REPRISE II 30 Days	REPRISE II (1 Year)
Atrial fibrillation or atrial flutter (new onset)	6.6% (16/241)	6.8% (17/249)
Ventricular septal perforation (periprocedural)	0.0% (0/240)	–
Mitral apparatus damage (periprocedural)	1.7% (4/240)	–
Cardiac tamponade (periprocedural)	3.7% (9/246)	–
Prosthetic aortic valve malpositioning	0.0% (0/240)	0.0% (0/249)
Prosthetic aortic valve thrombosis	0.0% (0/240)	1.2% (3/249)
Prosthetic aortic valve endocarditis	0.0% (0/240)	0.8% (2/249)
Device Performance Endpoints		
Successful vascular access, delivery, and deployment of the Lotus Valve System, and successful retrieval of the delivery system	98.8% (247/250)	–
Successful repositioning (partial or complete resheathing of the Lotus Valve in the catheter and redeployment in a more accurate position within the aortic valve annulus) of the Lotus Valve System if repositioning is attempted for the last valve attempted	100.0% (85/85)	–
Successful retrieval (complete resheathing of the Lotus Valve in the catheter and removal from the body) of the Lotus Valve System if retrieval is attempted	92.3% (12/13)	–
Valve Performance by Transthoracic Echocardiography (30 Days-Core Lab Assessment)		
Aortic valve area (effective orifice area) (cm^2)	1.74±0.45 (149)	1.68±0.49 (157)
Mean aortic valve gradient (mmHg)	11.70±6.77 (183)	12.49±5.35 (176)
Peak aortic gradient (mmHg)	20.75±9.05 (183)	21.90±9.40 (176)
Peak aortic velocity (cm/s)	2.23±0.47 (183)	2.29±0.47 (176)
Paravalvular Aortic Regurgitation		
None	80.2% (142/177)	83.4% (136/163)
Trace/trivial	5.6% (10/177)	8.0% (13/163)
Mild	13.6% (24/177)	8.6% (14/163)
Moderate	0.6% (1/177)	0.0% (0/163)
Severe	0.0% (0/177)	0.0% (0/163)

Values are % (count/sample size) or mean±SD (n)

Note: For 30-day outcomes, denominators for clinical event rates are based on the number of subjects who have either had an event within 30 days post-procedure or who were event-free with last follow-up at least 23 days post-procedure. Outcomes at 1 year are based on the as-treated group (N=249).

Reference: Meredith, 2014[98]; Meredith, 2015[99]

4.2. *Justification for the Study*

As noted above, the Lotus Valve System potentially provides a number of performance and safety features beyond that of earlier TAVR devices. These include an enhanced ability to place the valve correctly at the first attempt, the capacity to reposition the device if the initial deployment is considered to be suboptimal, the ability to retrieve the device if during the

procedure the decision is made to replace it with another valve to optimize implant or not to implant, and the aforementioned outer seal designed to minimize paravalvular leakage. The anticipated risks and benefits associated both with the Lotus Valve System and with participation in this clinical investigation are summarized in the Investigator Brochure and in Section 19 of this document. The conclusion of this risk-benefit analysis demonstrates that the known risks associated with the procedure, and specifically the use of the Lotus Valve System, have been mitigated to acceptable limits. It was also concluded that the aforementioned design features may improve procedural safety and longer term clinical outcomes. The available Sponsor-provided training program and proctorship for physicians further mitigates risk. The result is a procedure with residual subject risk comparable to that of currently available transcatheter aortic valves and potential benefit compared with other alternatives.

It is therefore determined that:

- All applicable risks have been addressed through appropriate testing and any residual risks are acceptable when weighed against the potential benefits to the subject.
- The potential benefits of the use of the device out-weigh the risks.

5. Device Description

The study devices are intended to improve aortic valve function for symptomatic subjects with calcific, severe native aortic stenosis who are at extreme or high risk for standard surgical valve replacement. Every subject in the randomized cohort must be deemed treatable with an available size of both the test and the control device. The control device in the planned size must be approved for use and commercially available at the investigational center where the implant procedure is being performed.

5.1. *Lotus Valve System Investigational Device (Test)*

The Lotus Valve System (Figure 5.1-1) has two main parts: a bioprosthetic aortic valve implant and a catheter-based delivery system for introduction and delivery of the valve implant. The device is introduced percutaneously via the femoral artery using conventional catheterization techniques. Femoral access using the surgical cut-down approach can also be performed to gain access into the aortic vessel. Device sizes used in the randomized cohort include 23 mm, 25 mm, and 27 mm diameter. Devices in the Lotus 21 mm Nested Registry cohort are 21 mm in diameter. More detailed product information is contained in the Investigator Brochure and Instructions For Use (IFU).

Figure 5.1-1: Lotus™ Valve System

5.1.1. Lotus Valve

The Lotus Valve (Figure 5.1-2) consists of 3 bovine pericardial leaflets. The commissures of the leaflets are attached to the valve frame through portions of the locking components. The valve frame is made of a single nitinol wire strand woven into a braid. The wire ends of this frame are encapsulated by a tantalum crimp that is used as a radiopaque marker, and which is located in the center of the frame height. The braided structure is designed to foreshorten and expand radially when delivered, and is then locked in this position using a post and buckle locking mechanism.

The Adaptive Seal™ is made of a polycarbonate-based urethane and is located on the outside bottom half of the frame. This seal provides a barrier between the native annulus and the frame to help reduce paravalvular leakage.

The valve is deployed in a beating heart and rapid pacing is not required during valve deployment. The valve begins to function early in the deployment process, facilitating maintenance of cardiac output and hemodynamic stability during deployment.

The device is designed to produce a final diameter of 21 mm, 23 mm, 25 mm, or 27 mm (depending on valve size) when the valve is locked. In the deployed state, the frame height of the 21mm valve is approximately 15 mm; the frame height of the three larger valve sizes is approximately 19 mm.

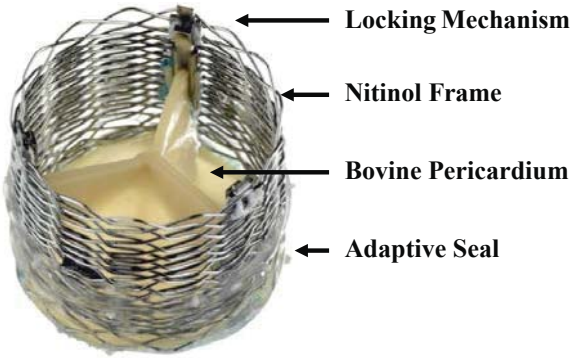

Figure 5.1-2: Lotus Valve Implant

5.1.2. Lotus Delivery System

The Lotus Delivery System is made of the catheter and the Lotus Controller.

- The catheter is a sheath in which mandrels allowing the shortening, locking, unlocking, and elongation of the valve, as well as its releasing, connect from the Lotus Controller to the valve. The catheter has a hydrophilic coating to facilitate the insertion. The tip of the catheter seats on the shoulder of a nosecone to provide a smooth transition.
- The Lotus Controller is shown in Figure 5.1-3.
  - The Lotus Controller has 3 ports; 2 of the ports are for flushing purposes and one is the Guidewire Port.
  - The Control Knob at the proximal end of the Lotus Controller is the primary control used to deploy the valve. It operates both the sheathing/unsheathing function as well as the locking/unlocking function.
    - The sheathing/unsheathing capability allows the implant to be pulled into or pushed out of the outer sheath.
    - The locking function shortens the valve implant into the locked configuration; the unlocking function elongates the valve.
  - The Release Ring is used when the operator is ready to release the valve. A Safety Cover covers the Release Ring to avoid inadvertent premature release.

Figure 5.1-3: Lotus Controller

5.1.3. Lotus Introducer Set

The Lotus Introducer Set will be used as an accessory to the Lotus Valve System during the procedure. It is composed of a dilator and an introducer sheath manufactured with materials commonly used in medical devices having contact with circulating blood. The Lotus Introducer is suitable for use in subjects requiring the 21 mm or 23 mm valve with femoral artery lumen diameter ≥6.0 mm or for use in subjects requiring the 25 mm or 27 mm valve with femoral artery lumen diameter ≥6.5 mm. In countries where the Lotus Introducer Set is approved, the commercial devices will be used. In countries where it is not approved, it will be considered an investigational device.

5.2. *CoreValve Transcatheter Aortic Valve Replacement System (Control)*

The control device is the commercially available self-expanding CoreValve® Transcatheter Aortic Valve Replacement System (CoreValve) that is introduced percutaneously via the femoral artery using conventional catheterization techniques (Medtronic, Inc., Minneapolis, MN, USA).

Devices sizes include the CoreValve 26 mm, 29 mm, and 31 mm diameter.

Note 1: Every subject in the randomized cohort must be deemed treatable with an available size of both the test (Lotus) device and the control (CoreValve) device. The CoreValve device in the planned size must be approved for use and commercially available at the investigational center where the implant procedure is being performed.

Note 2: A center may use the CoreValve® Evolut™ R Recapturable TAVR System with the aforementioned size matrix if it is approved and commercially available, but only if the center no longer has access to CoreValve.

5.3. *Device Labeling*

5.3.1. Test Device

The study Manual of Operations includes the IFU for the Lotus Valve System. Study devices are labeled on the top and one side (one label wraps around the top and side) of the outer carton and on the sterile pouch. Packaging will include peelable, self-adhesive labels for each unit shipped. The labeling will include the following information.

- Product Name
- Part/Reference number
- Lot number
- Expiration (use by) date (labeled as month/year, device not to be used after the last day of the indicated month)

The following statement appears on the label.

Caution: Investigational Device. Limited by Federal Law (USA) to Investigational Use.

In addition, the following statements appear on the product labeling.

CAUTION: Exclusively for Clinical Investigations.

Device labeling will be provided in local language(s) as per respective national regulations.

5.3.2. Control Device

Information is provided in the IFU supplied with the commercially available CoreValve® or CoreValve® Evolut™ R System (if used because a center no longer has access to CoreValve).

6. Objectives

The objective of the REPRISE III trial is to evaluate the safety and effectiveness of the Lotus™ Valve System for transcatheter aortic valve replacement (TAVR) in symptomatic subjects with calcific, severe native aortic stenosis who are considered at extreme or high risk for surgical valve replacement.

7. Endpoints

Outcomes will be assessed on an intention-to-treat (ITT) basis, an implanted basis, and an as-treated basis. The ITT analysis population of the randomized cohort includes subjects who sign an Informed Consent Form (see Section 20), are enrolled in the trial (see Section 10.1 for point of enrollment), and are randomized, whether or not an assigned study device is implanted. The implanted analysis population includes ITT subjects who are implanted with an assigned, randomized study device. The as-treated population includes subjects who sign an Informed Consent Form, are enrolled in the trial, are randomized, and received a study device, with the analysis based on the treatment actually received. For all analysis sets, if a subject receives 2 valves, the subject is assigned to the group corresponding to the first valve received. Among the roll-in, Lotus 21 mm Nested Registry, and U.S. Continued Access Study cohorts, for ITT analyses, all subjects who sign the IRB/IEC-approved study ICF and are enrolled in the trial will be included in the analysis sample, regardless of whether the study device was implanted. For these cohorts, the as-treated population includes all subjects implanted with the Lotus valve. Endpoint definitions can be found in Table 26.2-1.

7.1. *Primary Endpoints*

7.1.1. Primary Safety Endpoint

The primary safety endpoint is 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 analysis set for the primary safety endpoint is the implanted analysis set.

7.1.2. Primary Effectiveness Endpoint

The primary effectiveness endpoint is a composite of all-cause mortality, disabling stroke, or moderate or greater paravalvular aortic regurgitation (based on core lab assessment) at 1 year. The primary analysis set for the primary effectiveness endpoint is the implanted analysis set.

7.1.3. Secondary Endpoint

The secondary endpoint is the rate of moderate or greater paravalvular aortic regurgitation based on core lab assessment at 1 year. The primary analysis set for the secondary endpoint is the ITT analysis set.

7.2. *Additional Measurements*

Additional measurements based on the VARC endpoints and definitions[72,73] (see **Note 1** below) will be 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 (see **Note 2** below) adjudicated by an independent Clinical Events Committee (CEC; Section 22.1.1):
  - 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 System[105,106] 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 CHF (NYHA class III or IV)
  - New permanent pacemaker implantation resulting from new or worsened conduction disturbances (definitions in Table 26.2-1; see **Note 3** below)
  - 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 (see **Note 4** below)
  - Grade of aortic valve regurgitation: paravalvular, central and combined; the overall distribution of paravalvular aortic regurgitation (none, trace/trivial, mild, moderate, severe) will be determined as well as the percentage of subjects who have moderate or severe paravalvular regurgitation and the percentage of subjects who have mild, moderate or severe paravalvular regurgitation
- 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 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 mm Hg 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; see **Note 5** below) and assessed by an independent core laboratory, including effective orifice area, mean and peak aortic gradients, peak aortic velocity, and grade of aortic regurgitation (see **Note 6** below).
- 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 mm Hg 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[107] (at 1 year compared to baseline)
  - New York Heart Association (NYHA) classification
- Neurological status (see **Note 7** below) 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[108] and SF-12[109] Quality of Life (QOL) questionnaires at baseline; 1 and 6 months; and 1, 3, and 5 years
- Resource utilization associated with the procedure and/or follow-up.

Additionally, assessment of leaflet thickening and mobility using 4D CT will be carried out at 30 days and 1 year post index procedure for subjects in the CT Imaging Substudy of the U.S. Continued Access Study. The CT scans will be evaluated by an independent CT Core Laboratory and should be blinded to local investigators for cardiac valve findings (local reading should be only for non-cardiac valve findings such as unexpected lung pathology; see Section 11.10.1 for additional information).

Note 1: The most current VARC definitions and endpoints available at the beginning of the trial were used.

Note 2: The VARC-2[72,73] safety composite at 30 days includes all-cause mortality, all stroke (disabling and non-disabling), life-threatening bleeding, acute kidney injury (Stage 2 or 3), coronary artery obstruction requiring intervention, major vascular complication, and repeat procedure for valve-related dysfunction. The VARC-2 time-related valve safety composite includes structural valve deterioration (valve-related dysfunction requiring repeat procedure [TAVR or SAVR]), prosthetic valve endocarditis, prosthetic valve thrombosis, thromboembolic events (e.g., stroke), and VARC bleeding (unless clearly unrelated to valve therapy based on investigator assessment)

Note 3: Clinical indications for permanent pacemaker implantation are outlined in the ACCF/AHA/HRS Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities[110]. Permanent pacemaker implantation should generally be performed only for accepted Class I indications.

Note 4: For the Lotus Valve System, repositioning may be achieved with partial or full resheathing of the valve; the proportion of subjects with partial valve resheathing and full valve resheathing will be determined.

Note 5: At least 1 echocardiogram must be obtained before discharge or 7 days (whichever comes first); if multiple echocardiographic studies are performed prior to discharge and within 7 days of the procedure, the latest study performed will be used for analysis.

Note 6: The VARC-2[72,73] clinical efficacy composite (after 30 days) includes all-cause mortality, all stroke, required hospitalization for valve-related symptoms or worsening CHF (NYHA class III or IV), and prosthetic heart valve dysfunction (mean aortic valve gradient ≥20 mmHg, effective orifice area ≤0.9-1.1 cm^2 and/or Doppler velocity index [DVI] <0.35, AND/OR moderate or severe prosthetic valve aortic regurgitation [per VARC definition]). The need for hospitalization associated with valve-related symptoms or worsening CHF serves as a basis for calculation of a "days alive outside the hospital" endpoint. This includes heart failure, angina, or syncope due to aortic valve disease requiring intervention or intensified medical management; clinical symptoms of CHF with objective signs including

pulmonary edema, hypoperfusion, or documented volume overload AND administration of intravenous diuresis or inotropic therapy, performance of aortic valvuloplasty, institution of mechanical support (intra-aortic balloon pump or ventilation for pulmonary edema), or hemodialysis for volume overload; clear documentation of anginal symptoms AND no clinical evidence that angina was related to coronary artery disease or acute coronary syndrome; documented loss of consciousness not related to seizure or tachyarrhythmia.

Note 7: For subjects diagnosed with a neurological event (e.g., stroke, transient ischemic attack), a neurological physical exam (conducted by a neurologist, neurology fellow, neurology physician assistant, or neurology nurse practitioner), NIHSS assessment, and mRS must be performed after the event. Additionally, mRS must be administered at 90±14 days post-neurological event (see Table 11.1-1). If a subject who has not received a study device (investigational or control) experiences a neurological event within the first 1 year after the index procedure, mRS must be performed on that subject after the event and at 90±14 days _ENREF_113post-neurological event and the results must be reported to the Sponsor.

8. Design

8.1. *Scale and Duration*

The REPRISE III clinical study includes a prospective, multicenter, randomized controlled trial designed to evaluate the safety and efficacy of the Lotus Valve System for TAVR in symptomatic subjects who have calcific, severe native aortic stenosis and who are at extreme or high risk for surgical valve replacement. There will be a non-randomized roll-in phase with only the test device for centers that do not have previous experience implanting the Lotus Valve. There will also be a single-arm, non-randomized, nested registry cohort of subjects who receive the 21 mm Lotus Valve to assess safety and effectiveness (Lotus 21 mm Nested Registry); participating centers will be centers that have enrolled subjects in REPRISE III. After enrollment of the randomized cohort is completed, an additional cohort of subjects will be enrolled in a U.S. Continued Access Study cohort with the Lotus Valve (23 mm, 25 mm, and 27 mm valve sizes) to further assess performance and safety. Selected centers with the ability to perform high quality 4D CT scans will include U.S. Continued Access Study subjects in a CT Imaging Substudy to assess the prevalence of reduced leaflet mobility and its relationship, if any, to clinical events. Centers participating in the CT Imaging Substudy should ask all subjects eligible for enrollment in the U.S. Continued Access Study to consider participation in the substudy. Enrollment in the substudy will end after approximately 200 consecutive subjects who provide consent for participation are enrolled.

All subjects implanted will be followed at baseline, peri- and post-procedure, at discharge or 7 days post-procedure (whichever comes first), 30 days, 6 months, and then annually for up to 5 years post-procedure. Implanted subjects participating in the CT Imaging Substudy will undergo additional 4D CT assessment at 30 days and 1 year. Enrolled subjects who do not

have a study device implanted will be assessed through 1 year post procedure for safety/adverse events.

The REPRISE III study will be conducted in accordance with the relevant parts of the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practices (GCP) or the International Standard ISO 14155: 2011; ethical principles that have their origins in the Declaration of Helsinki; and pertinent individual country/state/local laws and regulations. See Section 11 below for additional information on study design and data collection.

The REPRISE III study will be registered at ClinicalTrials.gov prior to enrollment of the first subject.

8.2. *Treatment Assignment*

Screening materials from eligible subjects who are identified by the investigators as having met the inclusion and exclusion criteria (see below Table 9.2-1 and Table 9.3-1, respectively) and who provide written informed consent, will be reviewed by a Case Review Committee (CRC; see Section 22.2) to assess and confirm suitability of subjects for enrollment.

For the randomized cohort, eligible subjects will be randomized in a 2:1 allocation to receive either the Lotus Valve System (test) or a commercially available self-expanding CoreValve® Transcatheter Aortic Valve Replacement System (control). The randomization schedules will be computer-generated, using a pseudo-random number generator. Randomization will be stratified by center and by high or extreme risk status (see Section 26.2 for definitions). All randomized subjects will have unique identification numbers. Random permuted blocks will be employed to ensure approximate balance of treatment allocation within each stratum. Instructions on randomization are provided in the Manual of Operations. Subject should be randomized within 7 calendar days of CRC approval. Subjects should be treated within 14 calendar days of randomization and no later than 30 calendar days after randomization.

Note: There will be a non-randomized roll-in phase with only the test device for centers that do not have previous experience implanting the Lotus Valve; each of these centers will perform at least 2 roll-in cases before commencing randomization. All roll-in subjects will have unique identification numbers. Subjects receiving the 21 mm Lotus Valve will be enrolled in a non-randomized, nested registry cohort to assess safety and effectiveness. After enrollment of the randomized cohort is completed, subjects will be enrolled in a U.S. Continued Access Study cohort with the Lotus Valve (23 mm, 25 mm, and 27 mm valve sizes) to further assess performance and safety.

8.2.1. Treatment

See Section 5 for a detailed description of the devices and information on device sizes.

The test device is the Lotus Valve System, which consists of a bioprosthetic bovine pericardial aortic valve and a delivery system. The Lotus Introducer Set is used as an accessory in the procedure.

The control device is the commercially available CoreValve Transcatheter Aortic Valve Replacement System.

8.3. *Study Design Justification*

There will be up to 2052 subjects in REPRISE III. In order to support the stated objectives of this study (see Section 6) while also limiting the potential exposure of study subjects to risk, up to 120 subjects will be enrolled in the roll-in phase of this study (at centers without previous Lotus Valve experience), 912 subjects will be randomized and enrolled, up to 20 subjects will be enrolled in the Lotus 21 mm Nested Registry, and up to 1000 subjects will be enrolled in the U.S. Continued Access Study cohort. Up to 60 centers in the United States, Canada, Western Europe, and Australia will participate in the study. Centers in the United States that enrolled subjects in the randomized cohort will be eligible to enroll subjects in the U.S. Continued Access Study cohort. Safety and effectiveness results will be reported on all enrolled subjects (see Section 21 for information on safety reporting). Selected centers with the ability to perform high quality 4D CT scans will include approximately 200 U.S. Continued Access Study subjects in a CT Imaging Substudy to assess the prevalence of reduced leaflet mobility and its relationship, if any, to clinical events. In addition to the risk-benefit analysis noted in Section 4.2 (see also Section 19), ongoing dynamic data safety monitoring will be performed throughout the trial to minimize risk to subjects (see Section 22.1). All implanted subjects will be followed for up to 5 years post index procedure. Per society guidelines[8,111] antiplatelet therapy with aspirin and clopidogrel is recommended after TAVR to decrease the risk of thrombotic or thromboembolic complications if there are no contraindications to these medications.

9. Subject Selection

9.1. *Study Population and Eligibility*

The study will include subjects presenting with symptomatic calcific, severe native aortic stenosis who are considered at extreme or high risk for surgical valve replacement (see definitions of operative risk in Section 26.2). Traditionally underrepresented populations are expected to be included in the subject population. Because aortic stenosis most commonly occurs in the very elderly, women represent the majority of subjects enrolled in many TAVR trials. All efforts will be made to minimize attrition in REPRISE III. Since the very elderly will represent the majority of subjects enrolled in the trial, these efforts are by definition targeted to traditionally under-represented groups.

Prior to being eligible for the REPRISE III study, a subject must meet all of the inclusion criteria (Section 9.2) and none of the exclusion criteria (Section 9.3). The inclusion and exclusion criteria are not expected to have a negative effect on recruitment or retention of traditionally under-represented populations.

9.2. *Inclusion Criteria*

Subjects who meet all of the following criteria (Table 9.2-1) may be given consideration for inclusion in this clinical investigation, provided no exclusion criterion (Table 9.3-1) is met. Centers participating in the 4D CT substudy of the U.S. Continued Access Study must have the ability to perform high quality 4D CT scans; subjects in this substudy must meet none of the additional exclusion criteria listed in Table 9.3-2.

Table 9.2-1: 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 mm Hg or jet velocity ≥4.0 m/s, as measured by echocardiography and/or invasive hemodynamics.
IC2.	Subject has a documented aortic annulus size of ≥18 mm and ≤27 mm based on the center's assessment of pre-procedure diagnostic imaging (and confirmed by the Case Review Committee [CRC]) and, for the randomized cohort, is deemed treatable with an available size of both test and control device. For the U.S. Continued Access Study cohort the acceptable aortic annulus size is ≥20 mm and ≤27 mm.
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 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

Table 9.2-1: REPRISE III Inclusion Criteria

	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*:**	Extreme operative risk and high operative risk are defined as follows: **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. Risk of operative mortality and morbidity must be assessed via an in-person evaluation by a center cardiac surgeon and must be confirmed by the CRC (which must include an experienced cardiac surgeon).

Abbreviations: AVA=aortic valve area; CRC=Clinical Review Committee; NYHA=New York Heart Association; STS=Society of Thoracic Surgeons

9.3. *Exclusion Criteria*

Subjects who meet any one of the following criteria (Table 9.3-1) will be excluded from this clinical study.

Table 9.3-1: 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.
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.
EC12.	Subject has had a gastrointestinal bleed requiring hospitalization or transfusion within the past 3 months,

Table 9.3-1: REPRISE III Exclusion Criteria

	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.
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.

* An alternative $P2Y_{12}$ inhibitor may be prescribed if subject is allergic to or intolerant of clopidogrel.
Abbreviations: AV= atrioventricular; CK=creatine kinase; MI=myocardial infarction; PCI=percutaneous coronary intervention

Additional exclusion criteria apply for subjects considered for enrollment in the CT Imaging substudy of the U.S. Continued Access Study as shown in Table 9.3-2.

Table 9.3-2: Additional Exclusion Criteria for the 4D CT Imaging Substudy of the U.S. Continued Access Study

AEC1. Subject has eGFR <30 mL/min (chronic kidney disease stage IV or stage V).
AEC2. Subject has atrial fibrillation that cannot be rate controlled to ventricular response rate < 60 bpm.
AEC3. Subject is expected to undergo chronic anticoagulation therapy after the TAVR procedure. ***Note*:** Subjects treated with short-term anticoagulation post-procedure can be included in the imaging substudy; in these subjects the 30-day imaging will be performed 30 days after discontinuation of anticoagulation.

Abbreviations: AEC=additional exclusion criterion; CT=computed tomography; eGFR=estimated glomerular filtration rate; TAVR=transcatheter aortic valve replacement

10. Subject Accountability

10.1. *Point of Enrollment*

10.1.1. Roll-in Subjects

There will be a non-randomized roll-in phase with only the test device for centers that do not have previous experience implanting the Lotus Valve. For this roll-in phase, subjects confirmed eligible for the study by the CRC (see Section 22.2) and who provided written informed consent are considered enrolled in the study as soon as an attempt is made to insert the Lotus Valve System into the subject's femoral artery.

10.1.2. Randomized Subjects

Subjects confirmed eligible for the study by the CRC (see Section 22.2) and who provided written informed consent are considered enrolled in the study upon randomization.

10.1.3. Lotus 21 mm Nested Registry Subjects

For the Lotus 21 mm Nested Registry, subjects confirmed eligible for the study by the CRC (see Section 22.2) and who provided written informed consent are considered enrolled in the study as soon as an attempt is made to insert the Lotus Valve System into the subject's femoral artery.

10.1.4. U.S. Continued Access Study Subjects

For the U.S. Continued Access Study cohort, subjects confirmed eligible for the study by the CRC (see Section 22.2) and who provided written informed consent are considered enrolled in the study as soon as an attempt is made to insert the Lotus Valve System into the subject's femoral artery.

10.2. *Withdrawal*

All subjects enrolled in the clinical study (including those withdrawn from the clinical study or lost to follow-up) shall be accounted for and documented. If a subject withdraws from the clinical investigation, the reason(s) shall be reported. If such withdrawal is due to problems related to investigational device safety or performance, the investigator shall ask for the subject's permission to follow his/her status/condition outside of the clinical study.

11. Study Methods

11.1. *Data Collection*

The study event schedule is shown diagrammatically in Figure 11.1-1 and discussed in Table 11.1-1 and Sections 11.2 through 11.12. The methods are based on recommendations in the 2012 ACCF/AATS/SCAI/STS Expert Consensus Document on Transcatheter Aortic Valve Replacement[8] and the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease[111].

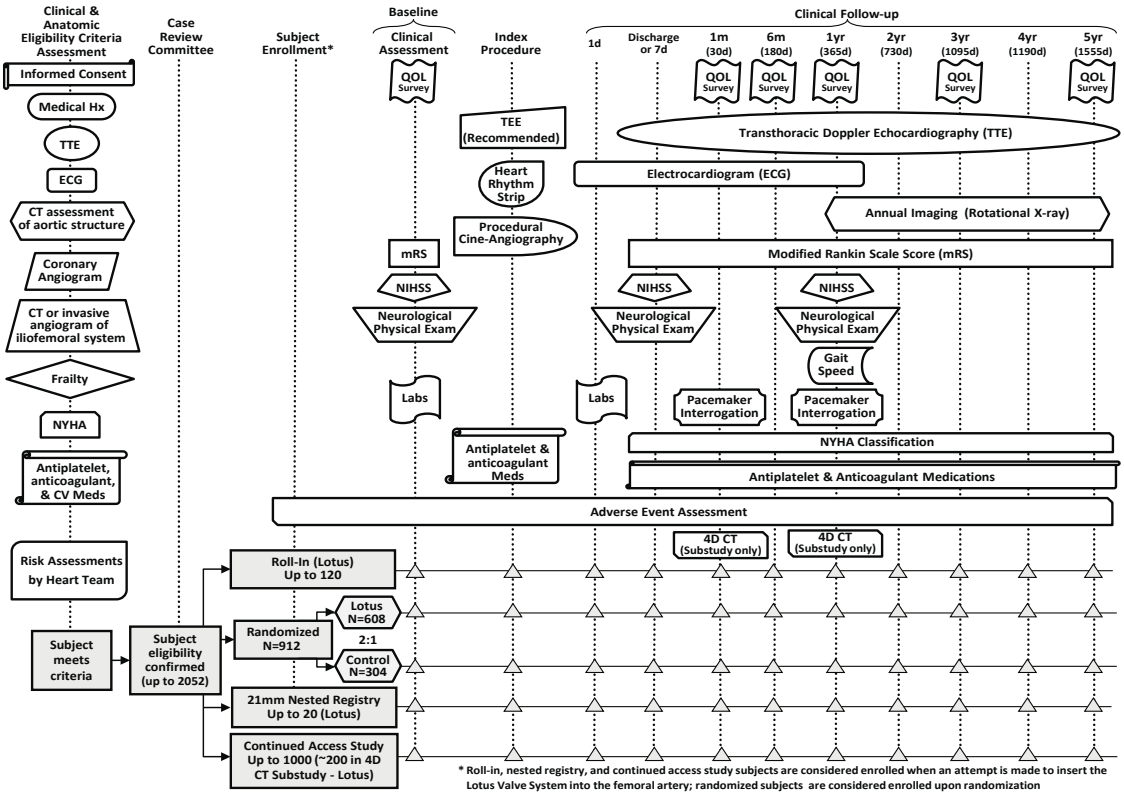

Figure 11.1-1: REPRISE III Study Design

Table 11.1-1: Study Event Schedule

Assessment	Screening[a]	Baseline	Procedure	Within 1 Day Post-procedure	Prior to Discharge or 7 Days Post-Procedure	30 Days[b] (±7 Days) Office Visit	6 Months[b] (±30 Days) Office Visit	12 Months[b] (±30 Days) Office Visit	24–60 Months[b] [Annual] (±45 Days) Office Visit
Signed Informed Consent Form[c]	X								
Demographics and medical history, including cardiac, neurological, renal (e.g., creatinine) and peripheral disease	X								
NYHA Classification	X				X	X	X	X	X
Neurological physical exam[d]		X			X			X	
NIHSS[d]		X			X			X	
Modified Rankin Scale[d]		X			X	X	X	X	X
12-lead ECG[e]	X			X	X	X	X	X	
Heart rhythm strip[e]			X[e]						
Laboratory tests[f]		X		X					
Risk assessments[g]	X								
Frailty, disability and comorbidity[h]	X							X	
Antiplatelet and anticoagulant (if applicable) medications	X		X		X	X	X	X	X
Other CV medications	X								
TTE[i]	X				X	X	X	X	X
TEE[j]			X						
Coronary angiogram[k]	X								

Table 11.1-1: Study Event Schedule

Assessment	Screening[a]	Baseline	Procedure	Within 1 Day Post-procedure	Prior to Discharge or 7 Days Post-Procedure	30 Days[b] (±7 Days) Office Visit	6 Months[b] (±30 Days) Office Visit	12 Months[b] (±30 Days) Office Visit	24–60 Months[b] [Annual] (±45 Days) Office Visit
CT angiogram of aortic structure[l]	X								
CT angiogram of iliofemoral system[m]	X								
Annual imaging (rotational X-ray)[n]								X	X
QOL surveys[o]		X				X	X	X	X[p]
Procedural cine-angiography (including post-deployment aortogram)[q]			X						
Pacemaker interrogation[r]						X		X	
AE and ADE assessments[s]			X	X	X	X	X	X	
Device deficiencies, SAE, SADE, USADE, UADE and CEC event assessments[t]			X	X	X	X	X	X	X
4D CT imaging of prosthetic valve[u]						X		X	

a: It is recommended that screening materials for CRC review be submitted electronically within 5 days of a scheduled CRC call in order to be considered for review (unless otherwise specified).

b: All follow-up dates will be calculated from the date of the (attempted) index procedure (or randomization in randomized subjects where no implant is attempted). Visits must be an office/clinical visit, but may be done in-hospital should the subject be admitted at the time. Subjects who are enrolled but do not receive a study device (test or control) will be followed for 1 year to assess for safety but do not need to have protocol required TTE or ECG.

c: Study-specific consent includes screening consent to perform required assessments that will be evaluated by the CRC to confirm subject eligibility. If the study Informed Consent Form is modified during the course of the study, study subjects will be re-consented as necessary.

d: Neurological physical examination must be performed by a neurologist, neurology fellow, neurology physician assistant, or neurology nurse practitioner. NIHSS and mRS must be performed by a neurology professional or certified personnel (external certification for NIHSS; internal or external certification for mRS). The assessors

Table 11.1-1: Study Event Schedule

Assessment	Screening[a]	Baseline	Procedure	Within 1 Day Post-procedure	Prior to Discharge or 7 Days Post-Procedure	30 Days[b] (±7 Days) Office Visit	6 Months[b] (±30 Days) Office Visit	12 Months[b] (±30 Days) Office Visit	24–60 Months[b] [Annual] (±45 Days) Office Visit

should be independent (not involved with the care of study subjects). For subjects diagnosed with a neurological event (e.g., stroke, transient ischemic attack), a neurological physical exam, mRS, and NIHSS must be performed after the event; mRS must also be administered at 90±14 days post-neurological event. If a subject who has not received a study device (investigational or control) experiences a neurological event within the first 1 year after the index procedure, mRS must be performed on that subject after the event and at 90±14 days post-neurological event and the results must be reported to the Sponsor.

e: All screening and post-procedure 12-lead ECGs must be performed according to the ECG Core Laboratory guidelines (see study Manual of Operations). Heart rhythm strip should be obtained after BAV and before study valve insertion (12-lead ECG is not required during the procedure).

f: Laboratory tests at baseline include CBC with platelets, albumin, serum creatinine, and cardiac enzymes. Cardiac enzymes (CK is required, CK-MB or troponin if CK is elevated) must be collected twice at intervals per standard of care within 6-24 hours post-procedure. Acute kidney injury (AKI) should be assessed through discharge/7 days based on the AKIN system.

g: Consists of STS score, euroSCORE II (2011), and heart team assessment including an in-person evaluation by a center cardiac surgeon that must be confirmed by the CRC (which must include an experienced cardiac surgeon). In the United States, the Centers for Medicare and Medicaid Services require independent evaluations by 2 cardiac surgeons for reimbursement.

h: Frailty, disability, and comorbidity risk assessments must be captured at screening: height, weight, cognitive function (Mini-Cognitive Assessment for Dementia), strength and balance (use of wheelchair, gait speed to walk 5 meters, number of falls in the past 6 months, maximal grip strength), and activities of daily living (Katz Index); at 1 year, gait speed to walk 5 meters must be assessed again.

i: Transthoracic echocardiogram (TTE) is required for all subjects who have a valve implanted in the aortic position. This includes assessment of EOA, peak and mean aortic valve pressure gradients, aortic regurgitation assessment, and LVEF. Screening TTE must be performed within 60 days prior to CRC review. At least 1 echocardiogram must be obtained before discharge or 7 days (whichever comes first); if multiple echocardiographic studies are performed prior to discharge and within 7 days of the procedure, the latest study performed will be used for analysis. All TTEs must be performed according to the Echocardiography Core Laboratory procedure guidelines (see study Manual of Operations). If a subject does not receive an implanted valve, then no follow-up TTE is required.
Note: In cases of low flow low gradient aortic stenosis, dobutamine can be used to assess the grade of aortic stenosis; the subject may be enrolled if echocardiographic criteria are met with this augmentation. In cases where a subject who has met the echocardiographic criteria for enrollment receives BAV prior to the index procedure and subsequently no longer meets the REPRISE III aortic valve pressure gradient or EOA criteria, the subject may still be enrolled based on the pre-BAV echocardiographic data. In such cases, the most recent echocardiogram done prior to the index procedure (even if after BAV) must be submitted to the Echocardiography Core Laboratory to be included in the baseline data.

j: TEE is recommended but not required during the implant procedure.

k: A coronary angiogram must be performed within 365 days prior to CRC review. If there is concern regarding the current extent of coronary artery disease or aortic stenosis, the CRC may recommend a repeat study closer to the time of enrollment.

l: A CT angiogram of the aortic complex must be performed within 180 days prior to CRC review (and should be performed within 90 days if possible) to evaluate the aortic valve anatomy and aortic root dimensions for device sizing. CT angiogram must be performed according to the CT/X-ray Core Laboratory procedure guidelines

Table 11.1-1: Study Event Schedule

Assessment	Screening[a]	Baseline	Procedure	Within 1 Day Post-procedure	Prior to Discharge or 7 Days Post-Procedure	30 Days[b] (±7 Days) Office Visit	6 Months[b] (±30 Days) Office Visit	12 Months[b] (±30 Days) Office Visit	24–60 Months[b] [Annual] (±45 Days) Office Visit

(see study Manual of Operations). It must be sent to the Core Laboratory for detailed measurements and analyses in advance of the CRC meeting where results will be reviewed to confirm subject's eligibility.

m: An assessment of the iliofemoral system must be performed within 180 days prior to CRC review (and should be performed within 90 days if possible). A CT angiogram of the iliofemoral system should be performed for complete visualization of the iliac and femoral arteries to assess for dimensions, tortuosity, and calcification. The CT angiogram should be performed per the procedure guidelines (see study Manual of Operations) and sent to the CT Core Laboratory with the screening CT angiogram of the aortic structure. An iliofemoral invasive angiogram may be substituted for the iliofemoral CT angiogram.

n: Annual imaging using rotational x-ray to assess for structural valve frame integrity must be performed on subjects who receive the Lotus Valve. Please refer to the Imaging Core Laboratory procedure guidelines (see study Manual of Operations). Results must be forwarded to the CT/X-Ray Core Laboratory for analysis. If additional imaging is performed (e.g., cardiac CT or MRI scan), data may be provided for analysis.

o: Includes the Kansas City Cardiomyopathy and SF-12 QOL questionnaires. Baseline QOLs should be performed within 30 days prior to the index procedure.

p: QOL survey at 36 and 60 months.

q: Procedural cine-angiogram including final post-deployment aortogram of the ascending aorta must be done and sent to the CT/X-Ray Core Laboratory for analysis.

r: For subjects who received a permanent pacemaker related to the index procedure, pacemaker dependence must be captured at the 30-day and 1-year visits via pacemaker interrogation. Pacemaker interrogation should also include assessment of the percentage of beats where the ventricles are paced.

s: AEs and ADEs will be monitored and collected from the time of enrollment through 12-month follow-up. For subjects who do not receive the study device, AEs will be monitored through 1-year follow-up.

t: Information on device deficiencies for the test and the control devices, as well as all SAEs, SADEs, UADEs, USADEs, and CEC events will be monitored and reported to Boston Scientific for all enrolled subjects from the time of enrollment through termination of the study. For subjects who do not receive a study device (test or control), the mentioned events will be monitored through 1 year post-index procedure. Please refer to Section 7.2 for a list of CEC events and Table 26.2-1 for definitions of these events, which specify data required for CEC adjudication. Complaint reporting of any device deficiencies for any commercially available products used should also be carried out using the manufacturer's processes.

u: This applies to subjects in the CT Imaging Substudy of the U.S. Continued Access Study. Please refer to the CT Core Laboratory procedure guidelines (see study Manual of Operations). Results must be sent to the CT Core Laboratory (Section 13.3.2).

Abbreviations: AE=adverse event; ADE=adverse device effect; AKI=acute kidney injury; BAV=balloon aortic valvuloplasty; CBC=complete blood count; CEC=Clinical Events Committee; CK-MB=creatine kinase-myoglobin band; CRC=Case Review Committee; CT=computed tomography; CV=cardiovascular; ECG=electrocardiogram; EOA=effective orifice area; LDH=lactate dehydrogenase; LV=left ventricle; MRI=magnetic resonance imaging; mRS=modified Rankin Scale; NIHSS=National Institutes of Health Stroke Scale; NYHA=New York Heart Association; QOL=Quality of Life; SAE=serious adverse event; SADE=serious adverse device effect; STS=Society of Thoracic Surgery; TEE=transesophageal Doppler echocardiography; TTE=transthoracic Doppler echocardiography; UADE=unanticipated adverse device effect; USADE=unanticipated serious adverse device effect

11.2. *Study Candidate Screening*

Subjects will be evaluated for eligibility by the center heart team (which must include a cardiac interventionalist and an experienced cardiac surgeon). Assessment will be based on results from the Society of Thoracic Surgeons (STS) score (≥8%) and/or agreement by the heart team that the subject is at extreme or high operative risk of serious morbidity or mortality with surgical valve replacement (see Table 9.2-1 for inclusion criteria and operative risk definitions). Risk of operative mortality and morbidity is to be assessed via an in-person evaluation by a center cardiac surgeon and must be confirmed by the CRC (which must include an experienced cardiac surgeon). In the United States, the Centers for Medicare and Medicaid Services (CMS) require independent evaluations by 2 cardiac surgeons for reimbursement. The heart team must also agree that the subject is likely to benefit from valve replacement.

Clinical assessment and evaluation as well as all collected tests and images (e.g., echocardiography, computerized tomography [CT], angiography) performed in preparation for TAVR will be reviewed by the CRC (see Section 8.2 and Section 22.2). The CRC will be comprised of experienced cardiac surgeons, interventional cardiologists, and Sponsor staff proficient with the Lotus Valve System and will confirm subject eligibility for enrollment.

11.3. *Subject Informed Consent*

Informed consent (see Section 20) must be obtained from a potential subject prior to conducting any preoperative assessments that are not part of the local routine preparation and evaluation of a subject for TAVR, even if the subject's eligibility has not yet been completely determined.

The Investigator/designee, who has been trained on the protocol, will explain the nature and scope of the study, potential risks and benefits of participation, and answer questions for the subject. If the subject agrees to participate, the Informed Consent form (ICF) must be signed and personally dated by the subject or his/her legally authorized representative. The Investigator/designee must also sign the ICF prior to subject enrollment. Any additional persons required by the center's Institutional Review Board (IRB)/Independent Ethics Committee (IEC) to sign the ICF must also comply. Study personnel should explain to the subject that even if the subject agrees to participate in the study and signs the ICF, the heart team and/or the CRC may determine that the subject is not a suitable candidate for the study and/or TAVR procedure.

If during the course of the preoperative evaluations, the subject is found not to be eligible for inclusion in the study, the subject should be notified. Reason for ineligibility will be accounted for as "screening failure" and will be documented as such in the screening module. If the subject has signed the ICF, but is found not eligible for inclusion in the study prior to or during the procedure, the subject should receive the appropriate treatment as identified by the clinical investigator. Information regarding the screening failure will be captured on the screening module and subject will be included in the "screening cohort" accountability.

11.4. *Screening Assessments*

The following screening tests and procedures must be performed and submitted to the CRC (Section 22.2) for evaluation to confirm a subject's eligibility for the study. Screening assessment documentation should be provided at least 5 days in advance of a scheduled CRC meeting via electronic upload. It is planned that CRC meetings will take place at least weekly or as needed to ensure timely review and confirmation of subject eligibility. For the randomized cohort, only after CRC approval of a subject's suitability for enrollment should the subject be randomized (within 7 calendar days).

Sites will be trained on the screening process as detailed in the REPRISE III Training Plan (see Section 17.4.1). Specific data points will be collected in the REPRISE III electronic Case Report Forms (eCRFs) as shown below.

- Clinical assessments
  - Demographics including age and gender
  - Medical history (general medical; cardiac [including previous cardiac surgery]; neurological, renal [including creatinine] and peripheral disease; and other medical conditions)
  - Physical examination including weight and height
  - NYHA classification
  - Current antiplatelet and other cardiovascular medications
  - 12-lead electrocardiogram (ECG) at screening must be performed according to the ECG Core Laboratory guidelines (see study Manual of Operations) and forwarded to Core Laboratory for analysis
  - Risk assessments: STS Score, euroSCORE II (2011), heart team assessment including an in-person evaluation by a center cardiac surgeon and any frailty assessments (detailed in next bullet). In the United States, CMS requires independent evaluations by 2 cardiac surgeons for reimbursement.
- Frailty, disability, and comorbidity assessments (collected prospectively)
  - Body Mass Index from the physical exam
  - Cognitive function: Mini-Cognitive Assessment for Dementia[112,113] (see study Manual of Operations).
  - Strength and balance
    - Use of wheelchair
    - Gait speed as measured by a stopwatch for a subject to walk 5 meters (3 measures averaged)[114-116]
    - Number of falls in the past 6 months
    - Maximal grip strength (kg) in the dominant hand (3 measures averaged), using a Jamar hand-held dynamometer[117]
  - Activities of daily living: Katz Index[113,118] is based on an evaluation of the functional independence or dependence of a subject in bathing, dressing, going to toilet,

transferring, continence, and feeding. A point is assigned for independence in each of the 6 functions, and 0 points if there is any dependence in these 6 categories.

- Imaging assessments
  - Within 60 days prior to CRC review, TTE (2-D, M-Mode, and color) must be carried out. The evaluation should include assessment of effective orifice area (EOA), peak systolic and mean aortic valve gradient pressure, aortic regurgitation assessment, mitral regurgitation, LVEF, left ventricular end-diastolic and end-systolic diameter, tricuspid regurgitation (TR) jet velocity, and left atrial (LA) volume. The TTEs must be performed according to the Echocardiography Core Laboratory procedure guidelines (see study Manual of Operations). All TTEs for enrolled subjects must be sent to the Echocardiography Core Laboratory for independent analyses. In cases of low flow, low gradient aortic stenosis dobutamine can be used to assess the grade of aortic stenosis (maximum dobutamine dose of 20 mcg/kg/min recommended)[8]; the subject may be enrolled if echocardiographic criteria are met with this augmentation. In cases where a subject who has met the echocardiographic criteria for enrollment receives balloon aortic valvuloplasty (BAV) prior to the index procedure and subsequently no longer meets the REPRISE III aortic valve pressure gradient or EOA criteria, the subject may still be enrolled based on the pre-BAV echocardiographic data. In such cases, the most recent echocardiogram done prior to the index procedure (even if after BAV) must be submitted to the Echocardiography Core Laboratory to be included in the baseline data.
  - A coronary angiogram must be performed within 365 days prior to CRC review. If there is concern regarding the current extent of coronary artery disease or aortic stenosis, the CRC may recommend a repeat study closer to the time of enrollment. An aortogram and hemodynamics including simultaneous ascending aorta and left ventricle pressure measurements should be performed.
  - A CT angiogram of the aortic complex must be performed 180 days prior to the CRC review and should be performed within 90 days, if possible, to evaluate the aortic valve anatomy and aortic root dimensions to determine eligibility and device sizing. It must meet the CT Core Laboratory procedure guidelines (see study Manual of Operations) and forwarded in advance to the Core Laboratory for detailed measurements and independent analyses, which will be reviewed by the CRC to confirm subject's eligibility.
  - An assessment of the iliofemoral system must be performed within 180 days prior to the CRC review (and should be performed within 90 days if possible). A CT angiogram of the iliofemoral system should be performed for complete visualization of the iliac and femoral arteries to assess for dimensions, tortuosity, and calcification. The CT angiogram of the iliofemoral system should be performed per the procedure guidelines (see study Manual of Operations) and sent to the CT Core Laboratory with the screening CT angiogram of the aortic structure for independent measurements and review by the CRC to confirm subject's eligibility. An iliofemoral invasive angiogram may be substituted for the iliofemoral CT angiogram.

11.5. *Baseline Assessments*

The following assessments must be completed within 30 days prior to the index procedure, unless otherwise specified below. The REPRISE III electronic eCRFs identify the specific data points to be collected.

- Confirmation of eligibility criteria
- Neurological physical examination, which must be performed by a neurologist, neurology fellow, neurology physician assistant, or neurology nurse practitioner (see Table 11.1-1); assessors should be independent (not involved with the care of study subjects).
- NIH Stroke Scale (NIHSS), which must be performed by a neurology professional or certified personnel (external certification); assessors should be independent (not involved with the care of study subjects)
- Modified Rankin Scale score, which must be performed by a neurology professional or certified personnel (external or internal certification); assessors should be independent (not involved with the care of study subjects)
- Laboratory tests
  - Complete blood count (CBC) with platelets
  - Albumin
  - Serum creatinine
  - Cardiac enzymes (CK is required, CKMB or troponin if CK is elevated)
- Quality Of Life (QOL) Surveys: Kansas City Cardiomyopathy[108] and SF-12[109] QOL Questionnaires must be administered to the subject within 30 days prior to the procedure.

Note: In cases where a subject who has met the echocardiographic criteria for enrollment receives BAV prior to the index procedure and subsequently no longer meets the REPRISE III aortic valve pressure gradient or EOA criteria, the subject may still be enrolled based on the pre-BAV echocardiographic data. In such cases, the most recent echocardiogram done prior to the index procedure (even if after BAV) must be submitted to the Echocardiography Core Laboratory to be included in the baseline data.

11.6. *Preprocedure Medications*

- Antiplatelet Therapy:

  Subjects must be treated with aspirin and a thienopyridine prior to valve implantation.

  <u>Aspirin</u>

  A loading dose of aspirin (recommended dose of 75–325 mg) is required for subjects who have not been taking aspirin for ≥72 hours at the time of the index procedure. The loading dose must be administered prior to the implant procedure. Subjects who have

been taking aspirin daily for ≥72 hours at the time of the index procedure do not require a loading dose.

Clopidogrel

A loading dose of clopidogrel (recommended dose of ≥300 mg) is required for subjects who have not been taking clopidogrel for ≥72 hours at the time of the index procedure. The loading dose must be administered prior to the implant procedure.

Note 1: An alternative $P2Y_{12}$ inhibitor (e.g., ticlopidine) may be prescribed if subject is allergic to or intolerant of clopidogrel.

Note 2: If the study-specific dosages and durations for antiplatelet medications conflict with country-specific labeling for the medications, the country-specific labeling should take precedence.

Note 3: If a subject requires chronic anticoagulation, either clopidogrel or aspirin is required prior to the implant procedure (but both aspirin and clopidogrel are not required). The subject should not receive a $P2Y_{12}$ inhibitor aside from clopidogrel.

- Anticoagulant therapy (e.g., unfractionated heparin) must be administered per local standard of care during the implant procedure, with a recommended target activated clotting time of ≥250 seconds during the implantation procedure.
- Additionally, the subject should be given prophylactic antibiotic therapy according to the local practice. The choice of antibiotic drug is left to the investigator's discretion.

11.7. *Index Procedure*

For sites in the US, CMS coverage criteria require that both the cardiac surgeon and interventional cardiologist members of the heart team participate in the technical aspects of the index procedure.

The preparation of the subject for the percutaneous procedure will be performed following standard techniques.

11.7.1. Medtronic CoreValve (Control) Cohort

The IFU associated with the control device (CoreValve) should be followed. A final post-deployment aortogram of the ascending aorta must be performed and forwarded to the Core Laboratory with the procedural cine-angiogram for analysis.

Labels from devices used during the procedure (e.g., CoreValve, Introducer, etc.) should be retained so that they can be included in the appropriate source documents and reported in the eCRFs. During the procedure, designated center study personnel must capture necessary information on acute device/delivery system performance and procedure. The following information will be collected during the procedure.

- Date of procedure
- Specifics of device type (such as size and model)

- Time of first vascular puncture (femoral) and time of vascular closure (skin-to-skin time)
- Introducer insertion and removal time
- Descriptive information on balloon valvuloplasty (e.g., size of balloon, number of balloon inflations)
- Any devices used and adjunctive procedures performed during implant procedure
- Heart rhythm after balloon valvuloplasty with rhythm strip should be recorded (12-lead ECG is not required).
- Valve catheter insertion and removal time
- Descriptive information on valve implantation procedure
- Adverse event (AE) assessment and associated treatment (including AE, serious adverse event [SAE], serious adverse device effect [SADE], unanticipated adverse device effect [UADE]/unanticipated serious adverse device effect [USADE], adverse device effect [ADE] and Clinical Events Committee [CEC] events; see Section 21).
- Device deficiencies assessment

11.7.2. Lotus Valve (Test) Cohort

The Lotus Introducer is prepared and introduced in the patient's femoral artery, as described in the Lotus Introducer IFU.

11.7.2.1. Valvuloplasty

A balloon valvuloplasty on the native valve following standard techniques must be performed with an appropriately sized valvuloplasty balloon (avoid oversizing). Careful attention should be paid to the position of the guidewire throughout the procedure. Prior to introduction of the Lotus Valve System, the subject's hemodynamic status and heart rhythm must be assessed, and a heart rhythm strip should be obtained (12-lead ECG is not required).

Information on the balloon valvuloplasty, including number of inflations, should be documented in the source data and will be captured in the eCRFs.

Note: If the subject becomes hemodynamically unstable after the valvuloplasty for reasons unrelated to the aortic valve annulus and/or leaflets, the Lotus Valve implantation should be interrupted until the subject is stable.

11.7.2.2. Preparing and Using the Lotus Valve System

The Lotus Valve implantation procedure requires two operators: First and Second Operators. Both operators must comply with the IFU and must be adequately trained and certified by BSC personnel in accordance with the training plan before performing the procedure (see Section 17.4.1 for additional information on training). Guidelines provided by the Sponsor for valve size selection should be followed.

The Lotus Valve System must be prepared in accordance with the IFU. Device preparation should only be performed by persons who have completed appropriate training with the Lotus Valve.

Prior to insertion of the Lotus Valve catheter into the Lotus Introducer, the recommended target ACT of ≥250 seconds should be confirmed, with additional boluses of heparin administered if needed.

The Lotus Valve IFU should be followed. The following summarizes the Lotus Valve System procedure.

1) The Lotus delivery catheter is back-loaded onto a 0.035 in (0.89 mm) Super/Extra Stiff guidewire, maintaining proper guidewire positioning across the native valve and into the ventricle.
2) The Lotus catheter is inserted in the Lotus Introducer and carefully advanced through the aorta and the aortic arch under fluoroscopy.
3) The catheter is then advanced slowly through the aortic annulus. The valve is then mechanically expanded into the desired position.
4) Prior to the release of the Lotus Valve, assessment of its position and function is performed using contrast injection and/or TEE.
5) If the position of the valve is deemed too aortic or too ventricular, the valve is then partially or completely resheathed inside the catheter, with a repositioning made by either pulling or pushing the catheter carefully, using the radiopaque marker as a guide. The valve can then be re-expanded.
6) Once the Lotus Valve position is deemed satisfactory and the valve is fully locked, the release process is then initiated and the Lotus Valve is detached from the catheter.
7) The nosecone is recaptured and the system pulled out of the body.
8) A final post-deployment aortogram of the ascending aorta (including rotational angiography of the valve frame, required only for Lotus) must be performed and forwarded to the Core Laboratory with the procedural cine-angiogram for analysis.
9) The Lotus Introducer is then removed.
10) The femoral access is then closed according to standard practice.

Labels from the devices used during the procedure (e.g., the Lotus Valve System, Lotus Introducer) should be retained so that they can be included in the appropriate source documents and reported in the eCRFs.

During the procedure, designated center study personnel must capture necessary information on acute device/delivery system performance and procedure. The following information will be collected during the procedure.

- Date of procedure
- Device size (21 mm, 23 mm, 25 mm, or 27 mm) and model

- Time of first vascular puncture (femoral) and time of vascular closure (skin-to-skin time)
- Lotus Introducer insertion and removal time
- Descriptive information on balloon valvuloplasty (e.g., size of balloon, number of balloon inflations)
- Any devices used and adjunctive procedures performed during implant procedure
- Heart rhythm after balloon valvuloplasty with rhythm strip should be recorded (12-lead ECG is not required).
- Lotus Valve catheter insertion and removal time
- Descriptive information on Lotus Valve implantation procedure and information on valve repositioning or retrieval (if performed)
- Adverse event (AE) assessment and associated treatment (including AE, serious adverse event [SAE], serious adverse device effect [SADE], unanticipated adverse device effect [UADE]/unanticipated serious adverse device effect [USADE], adverse device effect [ADE] and Clinical Events Committee [CEC] events; see Section 21).
- Device deficiencies assessment (for the Lotus Valve System)

Note: All Lotus Valve implantation procedures will be performed with the support/presence of trained BSC personnel.

11.8. *Post-Procedure*

The following are to be performed post-procedure.

- Per society guidelines, antiplatelet therapy with aspirin and a thienopyridine is recommended to reduce the risk of thrombotic or thromboembolic complications if there are no contraindications to these medications[8,111]. Subjects must be treated with aspirin and clopidogrel for at least 1 month following valve implantation. Extended dual antiplatelet therapy may be administered per physician choice.
  - After the valve implant procedure, aspirin (recommended dose of ≥75 mg daily) must be given for at least 1 month. It is recommended that daily aspirin be given indefinitely thereafter as per local standard of care. Aspirin dose may be adjusted to the closest approximation based on local tablet formulation availability.
  - After the valve implant procedure, clopidogrel (recommended dose of 75 mg daily) is required for at least 1 month.

    Note: An alternative $P2Y_{12}$ inhibitor (e.g., ticlopidine) may be prescribed if subject is allergic to or intolerant of clopidogrel.
  - If a subject requires chronic anticoagulation, either clopidogrel or aspirin is required after the implant procedure in addition to the anticoagulant therapy (but both aspirin and clopidogrel are not required). The subject must be treated with warfarin (other

anticoagulants are not permitted in the first month) and either clopidogrel (other $P2Y_{12}$ inhibitors are not permitted in combination with warfarin) or aspirin for at least 1 month. After 1 month, subjects requiring chronic anticoagulation may be switched from warfarin to a new oral anticoagulant (NOAC) at the discretion of the treating physician. The subject should not receive a $P2Y_{12}$ inhibitor in combination with a NOAC but may be treated with a NOAC plus aspirin.

- Prophylactic antibiotic regimen should be completed as per local practice.
- Additional medications may be used at the investigator's discretion.
- It is recommended that the subject's heart rhythm be monitored using telemetry for at least 48 hours after the index procedure.
- 12-lead ECG must be completed within 24 hours post-procedure per the ECG Core Laboratory guidelines (see study Manual of Operations) and must be forwarded to the Core Laboratory for analysis.
- Cardiac enzymes (CK is required, CK-MB or troponin if CK is elevated) must be collected twice at intervals per standard of care within 6-24 hours post-procedure.

11.9. *Prior to Discharge or 7 Days Post-Procedure (Whichever Comes First)*

Subjects must be evaluated prior to discharge or 7 days post-procedure (whichever comes first) based on the assessments below. The REPRISE III eCRFs identify the specific data points to be collected.

- Weight and height
- NYHA classification
- Neurological physical examination, which must be performed by a neurologist, neurology fellow, neurology physician assistant, or neurology nurse practitioner; assessors should be independent (not involved with the care of study subjects).
- NIHSS, which must be performed by a neurology professional or certified personnel (external certification); assessors should be independent (not involved with the care of study subjects).
- Modified Rankin Scale score, which must be performed by a neurology professional or certified personnel (external or internal certification); assessors should be independent (not involved with the care of study subjects).
- 12-lead ECG per the Core Laboratory guidelines (see study Manual of Operations) and must be forwarded for analysis.
- TTE, including assessment of effective orifice area, peak systolic and mean aortic valve gradient pressure, aortic regurgitation assessment, mitral regurgitation, LVEF, left ventricular end-diastolic and end-systolic diameter, TR jet velocity and LA volume, per the Echocardiography Core Laboratory procedure guidelines (see study Manual of

Operations). All TTEs for enrolled subjects must be sent to the Echocardiography Core Laboratory for independent analyses.

Note: For all subjects who have a valve implanted in the aortic position during the index procedure at least 1 echocardiogram must be obtained before discharge or 7 days (whichever comes first); if multiple echocardiographic studies are performed prior to discharge and within 7 days of the procedure, the latest study performed will be used for analysis. Subjects who do not receive a transcatheter valve during the index procedure are not required to have follow-up TTE.

- Current antiplatelet and anticoagulant (if applicable) medications
- Complete adverse event (AE, SAE, SADE, UADE/USADE, ADE, and CEC events) and device deficiencies assessment (with associated treatment)

11.10. *Follow-up*

All implanted subjects will be evaluated at 30 days, 6 months, 12 months, 24 months, 36 months, 48 months, and 60 months post index procedure. Subjects who do not have a study device implanted will be assessed through 1 year post procedure for safety/adverse events. Physical clinic visits or follow-up visits are scheduled for appointed times after the date of the procedure. It is important that this schedule be maintained as closely as possible for all subjects. Boston Scientific Corporation recognizes that subjects may not be able to return for all scheduled visits at precisely the date required, and therefore, a period of time in which each visit is allowed is indicated in Table 11.1-1. Visits not completed will be considered missed and recorded as protocol deviations. Visits completed outside these windows will be recorded as protocol deviations. After 6 months, visits will be scheduled on an annual basis from 1 through 5 years. Each follow-up visit must be performed by study personnel; data from the required tests and images as well as medical assessments will be recorded in source documentation and captured in the eCRFs. The determination of specified study endpoints and measurements such as valve function and CEC events will require data from images and tests as outlined in the event definitions (Table 26.2-1).

In the event that study personnel learn of a subject's hospitalization outside the study center, the center should make every effort to obtain copies of reports or results based on tests (e.g., echocardiogram) and/or procedures performed on the study subject.

Note: A subject who has received a study valve should not be enrolled in a clinical trial of an investigational drug/device/treatment until the subject has reached the REPRISE III primary effectiveness endpoint (1 year).

11.10.1.30-Day Follow-up (30±7 Days)

All enrolled subjects must be evaluated 30 days after the index procedure. During the 30-day follow-up, the following assessments must be completed. The REPRISE III eCRFs identify the specific data points to be collected.

- Weight and height

- NYHA classification
- Modified Rankin Scale score, which must be performed by a neurology professional or certified personnel (external or internal certification); assessors should be independent (not involved with the care of study subjects).
- 12-lead ECG per the Core Laboratory guidelines (see study Manual of Operations) and must be forwarded to the Core Laboratory for analysis.
- Current antiplatelet, anticoagulant (if applicable) medications
- TTE including assessment of effective orifice area, peak systolic and mean aortic valve gradient pressure, aortic regurgitation assessment, mitral regurgitation, LVEF, left ventricular end-diastolic and end-systolic diameter, TR jet velocity and LA volume. TTE must be performed per the Echocardiography Core Laboratory procedure guidelines (see study Manual of Operations). All TTEs for enrolled subjects must be sent to the Echocardiography Core Laboratory for independent analyses.

  Note: TTE must be done for all subjects who have a valve implanted in the aortic position during the index procedure. Subjects who do not receive a transcatheter valve during the index procedure are not required to have follow-up TTE.
- Quality of Life Surveys: Kansas City Cardiomyopathy and SF-12 Quality of Life Questionnaires
- Complete adverse event (AE, SAE, SADE, UADE/USADE, ADE and CEC events) and device deficiencies assessment (with associated treatment)
- For subjects who received a permanent pacemaker related to the index procedure, pacemaker dependence and percentage of beats where the ventricles are paced via pacemaker interrogation; please see the study Manual of Operations for determining pacemaker dependency.
- For subjects enrolled in the CT Imaging Substudy of the U.S. Continued Access Study, assessment of prosthetic valve leaflet mobility using 4D CT must be performed per the CT Core Laboratory procedure guidelines (see study Manual of Operations). All 4D CT scans for subjects enrolled in the CT Imaging Substudy must be sent to the CT Core Laboratory for independent analyses.

  Note: The CT scans will be read by the CT Core Laboratory and will not be provided to local investigators except as per below. Local reading should be done only for non-cardiac valve findings such as unexpected lung pathology. A study CT scan can be unblinded upon investigator request based on any of the following if the event occurs within 2 weeks of the study CT scan.
  - Any neurological event
  - Any potential embolic event
  - Any MI (ST segment elevation MI or non-ST segment elevation MI)
  - Increase in aortic regurgitation to moderate or severe

- A change in echocardiographic parameters including an increase in mean gradient of >10 mmHg or a change in DVI of >0.05.

If any of the above events occurs outside of the 2-week window around the study CT scan, the investigator must not be unblinded to the core laboratory assessment of the study CT scan and instead should perform a separate CT scan if clinically indicated. If an additional CT scan is performed for clinical indications, it should be sent to the CT Core Laboratory for analysis.

11.10.2. 6-Month (180±30 Days) Follow-up

All implanted subjects must be evaluated at 6 months after the index procedure. During the 6-month follow-up, the following assessments must be completed. The REPRISE III eCRFs identify the specific data points to be collected.

- Weight and height
- NYHA classification
- Modified Rankin Scale score, which must be performed by a neurology professional or certified personnel (external or internal certification); assessors should be independent (not involved with the care of study subjects).
- 12-lead ECG per the Core Laboratory guidelines (see study Manual of Operations) and must be forwarded for analysis
- Current antiplatelet, anticoagulant (if applicable) medications
- TTE, including assessment of effective orifice area, peak systolic and mean aortic valve gradient pressure, aortic regurgitation assessment, mitral regurgitation, LVEF, left ventricular end-diastolic and end-systolic diameter, TR jet velocity and LA volume, per the Echocardiography Core Laboratory procedure guidelines (see study Manual of Operations). It must be sent to the Core Laboratory for independent analysis.
  Note: TTE must be done for all subjects who have a valve implanted in the aortic position during the index procedure. Subjects who do not receive a transcatheter valve during the index procedure are not required to have follow-up TTE.
- Complete adverse event (AE, SAE, SADE, UADE/USADE, ADE and CEC events) and device deficiencies assessment (with associated treatment)
- Quality of Life Surveys: Kansas City Cardiomyopathy and SF-12 Quality of Life Questionnaires

11.10.3.12-Month (365±30 Days) Follow-up

All implanted subjects must be evaluated at 12 months after the index procedure. During the 12-month follow-up, the following assessments must be completed. The REPRISE III eCRFs identify the specific data points to be collected.

- Physical examination including weight and height

- NYHA classification
- Modified Rankin Scale score, which must be performed by a neurology professional or certified personnel (external or internal certification); assessors should be independent (not involved with the care of study subjects).
- Neurological physical examination, which must be performed by a neurologist, neurology fellow, neurology physician assistant, or neurology nurse practitioner (see Table 11.1-1); assessors should be independent (not involved with the care of study subjects).
- NIHSS, which must be performed by a neurology professional or certified personnel (external certification); assessors should be independent (not involved with the care of study subjects).
- Gait speed to walk 5 meters
- Rotational x-ray angiography performed on subjects who received the Lotus Valve to assess for structural valve frame integrity per the Imaging Core Laboratory procedure guidelines (see study Manual of Operations). It must be forwarded to the Core Laboratory for analysis.
- 12-lead ECG per the Core Laboratory Guidelines (see study Manual of Operations) and must be forwarded for analysis
- Current antiplatelet and anticoagulant (if applicable) medications
- TTE, including assessment of effective orifice area, peak systolic and mean aortic valve gradient pressure, aortic regurgitation assessment, mitral regurgitation, LVEF, left ventricular end-diastolic and end-systolic diameter, TR jet velocity and LA volume, per the Echocardiography Core Laboratory procedure guidelines (see study Manual of Operations). It must be forwarded to the Core Laboratory for independent analysis. **Note**: TTE must be done for all subjects who have a valve implanted in the aortic position during the index procedure. Subjects who do not receive a transcatheter valve during the index procedure are not required to have follow-up TTE.
- Complete adverse event (AE, SAE, SADE, UADE/USADE, ADE and CEC events) and device deficiencies assessment (with associated treatment)
- Quality of Life Surveys: Kansas City Cardiomyopathy and SF-12 Quality of Life Questionnaires
- For subjects who received a permanent pacemaker related to the index procedure, pacemaker dependence and percentage of beats where the ventricles are paced via pacemaker interrogation; please see the study Manual of Operations for determining pacemaker dependency.
- For subjects enrolled in the CT Imaging Substudy of the U.S. Continued Access Study, assessment of prosthetic valve leaflet mobility using 4D CT must be performed per the CT Core Laboratory procedure guidelines (see study Manual of Operations). The 4D

CT scans done for the CT Imaging Substudy must be sent to the CT Core Laboratory for independent analyses.

Note: The CT scans will be read by the CT Core Laboratory and findings will not be provided to local investigators except as noted above. Local reading should be done only for non-cardiac valve findings such as unexpected lung pathology. A study CT scan can be unblinded upon investigator request based on the conditions described in Section 11.10.1 if the event occurs within 2 weeks of the study CT scan.

11.10.4. Annual Follow-up (±45 Days)

All enrolled subjects implanted with a Lotus Valve must be evaluated at 24, 36, 48, and 60 months after the index procedure. During the annual follow-up, the following assessments must be completed. The REPRISE III eCRFs identify the specific data points to be collected.

- Physical examination including weight and height
- NYHA classification
- Modified Rankin Scale score, which must be performed by a neurology professional or certified personnel (external or internal certification); assessors should be independent (not involved with the care of study subjects).
- Current antiplatelet, anticoagulant (if applicable)
- TTE, including assessment of effective orifice area, peak systolic and mean aortic valve gradient pressure, aortic regurgitation assessment, mitral regurgitation, LVEF, left ventricular end-diastolic and end-systolic diameter, TR jet velocity, and LA volume, per the Echocardiography Core Laboratory procedure guidelines. All TTEs must be forwarded to the Core Laboratory for independent analyses.
  Note: TTE must be done for all subjects who have a valve implanted in the aortic position during the index procedure.
- Rotational x-ray angiography performed on subjects who received the Lotus Valve to assess for structural valve frame integrity per the Imaging Core Laboratory procedure guidelines (see study Manual of Operations). It must be forwarded to the Core Laboratory for analysis. If additional imaging is performed (e.g., cardiac CT or MRI scan), data may also be provided for analysis.
- Complete serious adverse event (SAE, SADE, USADE, and CEC events) and device deficiencies assessment (with associated treatment).
- Quality of Life Surveys: Kansas City Cardiomyopathy and SF-12 Quality of Life Questionnaires at 3 years and 5 years

11.10.5. Management of Missed or Late Visits

Missed or late visits will be recorded as protocol deviations and will be reviewed as such by the Sponsor or designee on a regular basis in accordance with applicable standard operating procedures.

Note: An in-person visit is required. If an in-person assessment cannot be performed, follow-up by telephone should be attempted. Subject or subject's physician should provide rationale for why the subject cannot come in for the follow-up visit.

11.10.6. Procedure for Determining when a Subject is Lost to Follow-up

A subject will be considered "lost to follow-up" and terminated from the study when all of the following criteria have been met.

- Failure to complete 2 consecutive visits without due cause (beginning with the 6-month and 1-year visits, i.e., subjects should not be considered lost to follow-up prior to the 1-year follow-up visit)
- Documentation of 3 unsuccessful attempts, one of which must be in written communication, by the Investigator or his/her designee to contact the subject or next of kin
- Notification from the Investigator to Sponsor reporting subject as lost to follow up

11.10.7. Withdrawal and Replacement of Subjects

While all efforts will be made to minimize attrition, subjects may withdraw from the study at any time, with or without reason and without prejudice to further treatment. Withdrawn subjects will not undergo any additional study follow-up, nor will they be replaced. The reason for withdrawal will be recorded (if given) in all cases of withdrawal. The investigator may discontinue a subject from participation in the study if the investigator feels that the subject can no longer fully comply with the requirements of the study or if any of the study procedures are deemed potentially harmful to the subject. Data that have already been collected on withdrawn subjects will be retained and used for analysis but no new data will be collected after withdrawal.

11.10.8. Explant Procedure

If a Lotus Valve test device is explanted during conventional scheduled or emergent surgical valve replacement or during an autopsy, if possible, the explanted valve should be sent to an independent histopathology core laboratory for macroscopic and microscopic analyses. Please refer to the study Manual of Operations for recommendations on the explant procedure and shipment of the explanted valve.

If a control device is explanted during conventional scheduled or emergent surgical valve replacement or during an autopsy, please follow the directions in the associated IFU.

Information on the explant procedure must be documented in source notes and captured in the Explant Form of the eCRFs.

11.11. *Study Completion*

All subjects who receive a test or control device will be evaluated at 30 days, 6 months, 12 months, 24 months, 36 months, 48 months, and 60 months post index procedure. All visits are office visits. A subject's participation in the study will be considered complete after the 60-month visit. For subjects who do not receive a test or control device, participation in the study will be considered complete after the 1-year visit.

11.12. *Source Documents*

It is preferable that original source documents (see Table 26.2-1 for definition) are maintained, when available. Where copies of the original source document as well as printouts of original electronic source documents are retained, it is recommended that these be signed and dated by a member of the investigation center team with a statement that it is a true reproduction of the original source document.

12. Statistical Considerations

12.1. *Endpoints*

Data will be summarized separately from subjects in the roll-in (up to 120 subjects), randomized, Lotus 21 mm Nested Registry, and U.S. Continued Access Study populations. Descriptive statistics will be used to summarize the data from subjects in the roll-in, Lotus 21 mm Nested Registry, and U.S. Continued Access Study cohorts and no statistical inference will be made.

In the randomized cohort, testing of endpoints will be carried out in a hierarchal manner in order to ensure the experiment-wise type I error rate is controlled. Testing will be done in 3 steps with each step needing to reject the null hypothesis in order to proceed to the next step:

1. Test the primary safety endpoint (Section 12.1.1) and the primary hypothesis of the primary effectiveness endpoint (Section 12.1.2.1.1). If the null hypothesis for both endpoints is rejected to show non-inferiority of the Lotus group to the CoreValve group, then proceed to step 2.
2. Test the secondary endpoint (Section 12.1.3); if the null hypothesis is rejected to show superiority of the Lotus group over the CoreValve group, then proceed to step 3.
3. Test the secondary hypothesis of the primary effectiveness endpoint (Section 12.1.2.1.2).

12.1.1. Primary Safety Endpoint

The primary safety endpoint is the composite of all-cause mortality, stroke, life-threatening and major bleeding events, stage 2 or 3 acute kidney injury, or major vascular complications evaluated at 30 days after the implant procedure.

12.1.1.1. Statistical Hypothesis for the Primary Safety Endpoint

The statistical hypothesis is that the rate of the primary safety endpoint (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) for the Lotus Valve is non-inferior to that for CoreValve.

The primary safety endpoint is expressed as the proportion of subjects who experience mortality, stroke, life-threatening and major bleeding events, stage 2 or 3 acute kidney injury, or major vascular complications within 30 days after the index procedure among all subjects who either experience mortality/stroke/life-threatening or major bleeding events/stage 2 or 3 acute kidney injury/major vascular complications within 30 days after the index procedure or are followed for at least 23 days after the index procedure.

The null and alternative hypotheses for the primary safety endpoint are as follows:

H_0: P_{S_Lotus} minus $P_{S\_Control} \geq \Delta$ (Inferior)

H_1: P_{S_Lotus} minus $P_{S\_Control} < \Delta$ (Non-inferior)

where P_{S_Lotus} and $P_{S\_Control}$ are the rates of the primary safety endpoint at 30 days for the Lotus Valve (test) group and the CoreValve group (control), respectively, and Δ (delta) is the non-inferiority margin.

A Farrington-Manning standardized test will be used to test the one-sided hypothesis of noninferiority in the difference between the rates of the two treatment groups, as described in the Statistical Analysis Plan. If the *P* value from the Farrington-Manning standardized test is <0.025, the rate of the primary safety endpoint for the Lotus Valve will be concluded to be non-inferior to the CoreValve rate. This corresponds to the one-sided upper 97.5% confidence bound on the difference between treatment groups (Lotus Valve minus CoreValve) for the observed rate of the primary safety endpoint at 1 year being less than the non-inferiority margin.

12.1.1.2. Sample Size Parameters for the Primary Safety Endpoint

The sample size calculation for the primary safety endpoint is based on the following assumptions.

- Expected Lotus Valve (test) rate = 40%
- Expected CoreValve (control) rate = 40%
- Non-inferiority margin (Δ) = 10.5%
- Test significance level (α) = 0.025 (1-sided)

- Test : Control ratio = 2:1
- Expected rate of attrition = 5%

Given enrollment of 912 subjects (608 Lotus Valve, 304 CoreValve) and 5% attrition, there is approximately 85% power to show non-inferiority with the given expected rates.

12.1.1.3. Statistical Methods – Primary Safety Endpoint

All subjects who are enrolled and randomized will be eligible for evaluation. Any events or hospitalizations occurring after enrollment but prior to the index procedure should be entered in the electronic data capture system; events with onset date starting from the time of the index procedure will be included in the primary endpoint analysis.

Handling of dropouts and missing data will depend on their frequency and the nature of the outcome measure. Sensitivity analyses (e.g., tipping-point analysis) will be performed to assess the impact of subjects with inadequate follow-up (i.e., missing data) on the primary endpoint and to assess the robustness of the conclusion of the primary analysis. The sensitivity analysis of the primary endpoint, including events occurring after enrollment but prior to the index procedure, will be performed. Statistical models that account for censored data will be employed in appropriate circumstances (e.g., for time-to-event outcomes). Suspected invalid data will be queried and corrected in the database prior to statistical analysis. Additional information may be found in the Statistical Analysis Plan.

12.1.2. Primary Effectiveness Endpoint

The primary effectiveness endpoint is the composite of all-cause mortality, disabling stroke, or moderate or severe paravalvular aortic regurgitation (based on independent core lab assessment) at 1 year.

12.1.2.1. Statistical Hypothesis for the Primary Effectiveness Endpoint

12.1.2.1.1 Primary Hypothesis

The primary statistical hypothesis is that the rate of the primary effectiveness endpoint (composite of all-cause mortality, disabling stroke, or moderate or severe paravalvular aortic regurgitation [based on independent core lab assessment] at 1 year) for the Lotus Valve group is non-inferior to that for the CoreValve group.

The null and alternative hypotheses for the primary hypothesis of the primary effectiveness endpoint are as follows:

H_0: P_{E_Lotus} minus $P_{E\_Control} \geq \Delta$ (Inferior)

H_1: P_{E_Lotus} minus $P_{E\_Control} < \Delta$ (Non-inferior)

where P_{E_Lotus} and $P_{E\_Control}$ correspond to the rates of the primary effectiveness endpoint for the Lotus Valve group (test) and the CoreValve group (control), respectively, and Δ (delta) is the non-inferiority margin.

A Farrington-Manning test will be used to test the one-sided hypothesis of non-inferiority in the difference between the rates of the two treatment groups, as described in the Statistical Analysis Plan. If the *P* value from the Farrington-Manning standardized test is <0.025, the rate of the primary effectiveness endpoint for the Lotus Valve will be concluded to be non-inferior to the CoreValve rate. This corresponds to the one-sided upper 97.5% confidence bound on the difference between treatment groups (Lotus Valve minus CoreValve) for the observed rate of the primary effectiveness endpoint being less than the noninferiority margin.

12.1.2.1.2 Secondary Hypothesis

The secondary statistical hypothesis is that the rate of the primary effectiveness endpoint (composite of all-cause mortality, disabling stroke, or moderate or severe paravalvular aortic regurgitation [based on independent core lab assessment] at 1 year) for the Lotus Valve group is superior to that for the CoreValve group. This test will be carried out only if the null hypothesis from the statistical hypothesis is rejected for the primary safety endpoint (Section 12.1.1), the primary hypothesis of the primary effectiveness endpoint (Section 12.1.2), and the secondary endpoint (Section 12.1.3), and the rate for the primary effectiveness endpoint for the Lotus group is less than that of the CoreValve group.

The null and alternative hypotheses for the secondary hypothesis of the primary effectiveness endpoint are as follows:

H_0: $P_{E\_Lotus} = P_{E\_Control}$

H_1: $P_{E\_Lotus} \neq P_{E\_Control}$

where P_{E_Lotus} and $P_{E\_Control}$ correspond to the rates of the primary effectiveness endpoint for the Lotus Valve group (test) and the CoreValve group (control), respectively.

A chi-square test will be used to test the two-sided hypothesis of superiority between the rates of the two treatment groups, as described in the Statistical Analysis Plan. If the *P* value from the chi-square test is <0.05 and the rate of the Lotus Valve group is less than the rate of the CoreValve group, the rate of the primary effectiveness endpoint for the Lotus Valve will be concluded to be superior to the CoreValve rate. This corresponds to the two-sided upper 95% confidence bound on the difference between treatment groups (Lotus Valve minus CoreValve) for the observed rate of the primary effectiveness endpoint being less than zero.

12.1.2.2. Sample Size Parameters for the Primary Effectiveness Endpoint

12.1.2.2.1 Primary Hypothesis

The sample size calculation for the primary hypothesis of the primary effectiveness endpoint at 1 year is based on the following assumptions.

- Expected Lotus Valve (test) rate = 32%
- Expected CoreValve (control) rate = 32%
- Non-inferiority margin (Δ) = 9.5%

- Test significance level (α) = 0.025 (1-sided)
- Test : Control ratio = 2:1
- Power ($1-\beta$) = 80%
- Total number of evaluable subjects = 819
- Expected rate of attrition = 10%

Given the above assumptions, at least 912 randomized subjects (608 Lotus Valve, 304 CoreValve) are needed to account for attrition.

12.1.2.2.2 Secondary Hypothesis

The sample size calculation for the secondary hypothesis of the primary effectiveness endpoint at 1 year is based on the following assumptions.

- Expected Lotus Valve (test) rate = 22%
- Expected CoreValve (control) rate = 32%
- Test significance level (α) = 0.05 (2-sided)
- Test : Control ratio = 2:1
- Expected rate of attrition = 10%

Given enrollment of 912 subjects (608 Lotus Valve, 304 CoreValve) and 10% attrition, there is approximately 86% power to show superiority with the given expected rates.

12.1.2.3. Statistical Methods – Primary Effectiveness Endpoint

Procedures similar to that described in Section 12.1.1.3 and discussed in the Statistical Analysis Plan will be applied to analysis of the primary effectiveness endpoint.

12.1.3. Secondary Endpoint

The secondary endpoint is the rate of moderate or greater paravalvular aortic regurgitation (based on review by an independent core lab) at 1 year. To control for experiment-wise type I error, testing for the secondary endpoint will be conducted only if the null hypotheses for the primary safety and the primary analysis of the primary effectiveness endpoints are rejected. That is, non-inferiority must be shown for the primary safety endpoint and the primary effectiveness endpoint for testing to be conducted for the secondary endpoint.

12.1.3.1. Statistical Hypothesis for the Secondary Endpoint

The statistical hypothesis is that the secondary endpoint of moderate or greater paravalvular aortic regurgitation rate at 1 year (based on review by an independent core lab) for the Lotus Valve is superior to that for the CoreValve group.

The null and alternative hypotheses for the secondary endpoint are as follows:

H_0: $P_{AR\_Lotus} = P_{AR\_Control}$

H_1: $P_{AR\_Lotus} \neq P_{AR\_Control}$

where P_{AR_Lotus} and $P_{AR\_Control}$ correspond to the rates of moderate or greater paravalvular aortic regurgitation at 1 year for the Lotus Valve group (test) and the CoreValve group (control), respectively.

A chi-square test will be used to test the two-sided hypothesis of superiority between the rates of the two treatment groups, as described in the Statistical Analysis Plan. If the *P* value from the chi-square test is <0.05 and the rate of the Lotus Valve group is less than the rate of the CoreValve group, the rate of moderate or greater paravalvular aortic regurgitation for the Lotus Valve group will be concluded to be superior to that of the CoreValve group.

12.1.3.2. Sample Size Parameters for the Secondary Endpoint

The sample size calculation for the secondary endpoint (moderate/severe paravalvular aortic regurgitation rate at 1 year) is based on the following assumptions.

- Expected Lotus Valve (test) rate P_{AR_Lotus} = 1.1%
- Expected CoreValve (control) rate $P_{AR\_Control}$ = 5.3%
- Test significance level (α) = 0.05 (2-sided)
- Test : Control ratio = 2:1
- Expected rate of attrition = 25%

Given enrollment of 912 subjects (608 Lotus Valve, 304 CoreValve) and 25% attrition, there is approximately 86% power to show superiority with the given expected rates.

12.1.3.3. Statistical Methods – Secondary Endpoint

Procedures similar to that described in Section 12.1.1.3 and discussed in the Statistical Analysis Plan will be applied to analysis of the secondary endpoint.

12.1.4. Baseline Comparability

Baseline data will be summarized by treatment group for the randomized subjects and separately for subjects in the roll-in, Lotus 21 mm Nested Registry, and U.S. Continued Access Study cohorts. Subject demographics, clinical and neurological history, risk factors, and preprocedure characteristics will be summarized using descriptive statistics (e.g., mean, standard deviation, n, minimum, maximum) for continuous variables and frequency tables or proportions for discrete variables. Treatments for the randomized subjects will be compared with a chi-square or Fisher exact test for discrete variables and a Student *t*-test for continuous variables. Treatment differences for the randomized subjects and their 95% confidence intervals will be presented. Procedural characteristics will be summarized similarly. No formal statistical testing will be done for the roll-in, Lotus 21 mm Nested Registry, or U.S. Continued Access Study subjects.

12.1.5. Post-procedure Measurements

Post-procedure information will be collected at regularly scheduled follow-up examinations as detailed in the clinical study schedule (Table 11.1-1) and will be summarized using descriptive statistics for continuous variables (e.g., mean, standard deviation, n, minimum, maximum) and frequency tables or proportions for discrete variables. Estimates will be reported by treatment group and, for randomized subjects, differences between treatment groups and their 95% confidence intervals will be presented. Treatments for the randomized subjects will be compared with the chi-square or Fisher exact test for discrete variables and the Student t-test for continuous variables. No inferences are planned on the additional measurements and, therefore, alpha-adjustments for multiple comparisons will not be used. The Kaplan-Meier product-limit method will be used to estimate rates for time-to-event endpoints and treatment groups will be compared using the Log-rank and Wilcoxon tests. Adverse event and SAE rates will be reported. No formal statistical testing will be done for the roll-in, Lotus 21 mm Nested Registry, or U.S. Continued Access Study subjects.

12.1.6. Subgroup Analyses for Randomized Subjects

Primary and pre-specified additional endpoints will be summarized and treatment groups will be compared for the following subgroups of randomized subjects.

- Gender (male and female)
- Extreme risk and high risk (see Table 26.2-1 for definitions of extreme and high operative risk)
- Region (North America, outside North America)

No adjustments for multiple comparisons will be made. Additional analyses may be performed as appropriate.

12.1.7. Subgroup Analyses for U.S. Continued Access Study Subjects

Primary and pre-specified additional endpoints will be summarized and treatment groups will be compared for the following subgroups of U.S. Continued Access Study subjects.

- Gender (male and female)
- Extreme risk and high risk (see Table 26.2-1 for definitions of extreme and high operative risk)

No adjustments for multiple comparisons will be made. Additional analyses may be performed as appropriate.

12.2. *General Statistical Methods*

All statistical analyses will be performed using the SAS System software, version 9.2 or later (Copyright© 2000 SAS Institute Inc., SAS Campus Drive, Cary, North Carolina 27513, USA. All rights reserved).

All statistical analyses will be conducted according to applicable Standard Operating Procedures, Work Instructions, and the study-specific Statistical Analysis Plan.

12.2.1. Analysis Sets

The primary endpoints and additional measurements will be analyzed on an ITT, an as-treated, and an implanted basis. Among the randomized cohort, for ITT analyses, all subjects who sign the IRB/IEC-approved study ICF (see Section 11.3), are enrolled in the trial, and are randomized will be included in the analysis, whether or not an assigned study valve (Lotus Valve or CoreValve) was implanted. The as-treated population includes all subjects who sign the IRB/IEC-approved study ICF, are enrolled in the trial, and are randomized, with the analysis based on the treatment actually received (for example, if a subject is assigned to receive a test device but instead receives a control device, that subject will be considered a control subject for the as-treated analyses). For implanted analyses, ITT subjects who had the assigned, randomized study valve (Lotus Valve or CoreValve) implanted will be included in the analysis. For all analysis sets, if a subject receives 2 valves, the subject is assigned to the group corresponding to the first valve received. Among the roll-in, Lotus 21 mm Nested Registry, and U.S. Continued Access Study cohorts, for ITT analyses, all subjects who sign the IRB/IEC-approved study ICF and are enrolled in the trial will be included in the analysis sample, regardless of whether the study device was implanted. For these 3 cohorts, the as-treated population includes all subjects implanted with the Lotus Valve. The as-treated and implanted analysis sets are the same for these 3 cohorts.

For the randomized cohort, the primary safety endpoint, primary effectiveness endpoint (both hypotheses), and the secondary endpoint will all be analyzed for the ITT, as-treated, and implanted analysis sets. The primary analysis for the primary hypothesis of the primary effectiveness endpoint and the primary safety endpoint will be based on the implanted analysis set. The primary analysis set for the secondary hypothesis of the primary effectiveness endpoint and the secondary endpoint will be based on the ITT analysis set.

After 1 year, all analyses will be based on the safety analysis set. All subjects who sign the written ICF, are enrolled in the study, and have a study device implanted regardless of the device and treatment assignment will be included in the safety analysis set.

12.2.2. Control of Systematic Error/Bias

All subjects who have met the inclusion/exclusion criteria, received a positive recommendation from the CRC, and signed the Informed Consent Form will be eligible for enrollment in the study. The center heart team's assessment of TTE measurements before device placement will contribute to the determination of subject eligibility for the study.

To control for inter-observer variability, data from independent core laboratories (see Section 13.3) will be used for analysis. These include an echocardiography core lab, a CT and rotational X-ray angiography core laboratory to assess all CT and rotational X-ray data using standard techniques, and an electrocardiography core laboratory to independently analyze protocol-required 12-lead ECGs performed for each subject.

12.2.3. Randomization Scheme

A computer generated list of random treatment allocations (i.e., a randomization schedule) will be used to assign subjects to treatment in a 2:1 ratio of Lotus Valve to CoreValve. Randomization will be stratified by center and risk factor (extreme and high operative risk with a targeted enrollment of at least 30% of subjects in each group; see Table 26.2-1 for operative risk definitions). Additional information is provided in the study Manual of Operations.

12.2.4. Reporting Events

For all subjects in the roll-in, Lotus 21 mm Nested Registry, and U.S. Continued Access Study cohorts, all events that occur from the start of the index procedure will be reported. For all randomized subjects, events from the time of randomization onward will be reported. For randomized subjects who do not have an attempted procedure, events from the date of randomization to 1 year post-randomization will be reported. For time based clinical events, the cut-off for events for 30-day endpoints will be 30 days, for 6-month endpoints will be 180 days, for 1-year endpoints will be 365 days, and for 2-5 year endpoints will be 365 days times the number of years. For events at discharge or 7 days post-procedure, the cut-off for events will be the earlier of the date of discharge or 7 days post-procedure for each subject.

12.3. *Data Analyses*

Baseline and outcome variables will be summarized using descriptive statistics for continuous variables (mean, standard deviation, number of observations, minimum and maximum) and discrete variables (percentage and count/sample). See Section 12.1 for a discussion on analysis of the primary safety endpoint, primary effectiveness endpoint, secondary endpoint, and additional measurements.

12.3.1. Other Measurements

Other measurements not driven by statistical hypotheses are listed in Section 7.2.

12.3.2. Interim Analyses

No formal interim analyses are planned for the purpose of stopping this trial early for effectiveness or futility.

An administrative analysis of 30-day data for the first 300 randomized subjects will be performed by a statistician independent of BSC for regulatory agency review after these 300 subjects have completed their 30-day follow-up visits.

An administrative analysis of 30-day data for subjects in the Lotus 21 mm Nested Registry will be performed for regulatory agency review after these subjects have completed their 30-day follow-up visits.

12.3.3. Justification of Pooling

Analyses for the primary safety and effectiveness endpoints and the secondary endpoint will be presented using data pooled across institutions and surgical (high or extreme) risk groups. An assessment of the poolability of subjects across centers and surgical risk groups will be made using logistic regression. Main effects for the center (risk group) and treatment and the interaction of the center (risk group) by treatment will be included in separate logistic regression models with the primary safety endpoint, the primary effectiveness endpoint, and the secondary endpoint as the outcome. If the *P* value for center (risk group) by treatment interaction is ≥0.15, it can be concluded that the treatment effect is not different across the centers (risk groups) and the data can be pooled. In the analysis to justify pooling across centers, the centers with fewer than 6 subjects enrolled in the study will be combined into "virtual centers" based on geographic region so that "virtual centers" have ≥6 subjects but no more than the largest enrolling center.

12.3.4. Multivariable Analyses

Univariate and multivariate analyses will be performed to assess the effect of potential predictors on the primary safety and effectiveness endpoints and the secondary endpoint as described in the Statistical Analysis Plan.

12.3.5. Changes to Planned Analyses

Any changes to the planned statistical analyses made prior to performing the analyses will be documented in an amended Statistical Analysis Plan approved before performing the analyses. Changes from the planned statistical methods after performing the analyses will be documented in the clinical study report along with a reason for the deviation.

13. Data Management

13.1. *Data Collection, Processing, and Review*

Subject data will be recorded in a limited access secure electronic data capture (EDC) system. Only personnel trained and authorized will have access to the system.

The clinical database will reside on a production server hosted by Medidata. All changes made to the clinical data will be captured in an electronic audit trail and available for review

by BSC or its representative. The associated RAVE software and database have been designed to meet regulatory compliance for deployment as part of a validated system compliant with laws and regulations applicable to the conduct of clinical studies pertaining to the use of electronic records and signatures. Database backups are performed regularly.

The Investigator provides his/her electronic signature on the appropriate eCRFs in compliance with local regulations. A written signature on printouts of the eCRFs must also be provided if required by local regulation. Changes to data previously submitted to the Sponsor require a new electronic signature by the Investigator acknowledging and approving the changes.

Visual and/or electronic data review will be performed to identify possible data discrepancies. Manual and/or automatic queries will be created in the EDC system and will be issued to the center for appropriate response. Center staff will be responsible for resolving all queries in the database.

13.2. *Data Retention*

The Investigator will maintain at the investigative center all essential study documents and source documentation that support the data collected on the study subjects in compliance with ICH/GCP guidelines. Documents must be retained for at least 2 years after the last approval of a marketing application or until at least 2 years have elapsed since the formal discontinuation of the clinical investigation of the product. These documents will be retained for a longer period of time by agreement with BSC or in compliance with other local regulations. It is BSC's responsibility to inform the Investigator when these documents no longer need to be maintained. The Investigator will take measures to ensure that these essential documents are not accidentally damaged or destroyed. If for any reason the Investigator withdraws responsibility for maintaining these essential documents, custody must be transferred to an individual who will assume responsibility and BSC must receive written notification of this custodial change.

13.3. *Core Laboratories*

13.3.1. Transthoracic Echocardiography (TTE) Core Laboratory

An independent Core Laboratory will review echocardiography images from all centers and every subject enrolled in this study for qualitative and quantitative analysis. These analyses will minimize bias and inconsistencies by providing an independent interpretation of all measurements using standard techniques. The TTE procedure guideline is provided by the core laboratory in the study Manual of Operations.

13.3.2. CT and Rotational X-Ray Angiography Core Laboratory

An independent Core Laboratory will centrally assess all of the CT and rotational X-ray angiography data in this study to reduce variability. These analyses will minimize bias and inconsistencies by providing an independent interpretation of all measurements using

standard techniques. The screening CT Angiogram procedure guidelines and annual imaging acquisition protocol are provided by the core laboratory in the study Manual of Operations. Data from subjects in the 4D CT Imaging Substudy will also be evaluated by the independent CT Core Laboratory; procedure guidelines for 4D CT scanning are provided by the core laboratory in the Manual of Operations.

13.3.3. Electrocardiography (ECG) Core Laboratory

All 12-lead ECGs performed at each of the required protocol visits will be sent to an ECG core laboratory (see study Manual of Operations) for independent analyses. These analyses will minimize bias and will provide consistent interpretation of the ECGs.

13.3.4. Histopathology Core Laboratory

If a Lotus Valve (test device) is explanted during conventional scheduled or emergent surgical valve replacement or during an autopsy, please refer to the study Manual of Operations for recommendations on the explant procedure and shipment of the explanted valve to an independent histopathology laboratory for analyses.

14. Amendments

If a protocol revision is necessary which affects the rights, safety or welfare of the subjects or scientific integrity of the data, an amendment is required. Appropriate approvals (e.g., IRB/EC/FDA/CA) of the revised protocol must be obtained prior to implementation.

15. Deviations

An Investigator must not make any changes or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency. An investigator shall notify the Sponsor and the reviewing IRB/EC of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency, and those deviations which affect the scientific integrity of the clinical investigation. Such notice shall be given as soon as possible, but no later than 5 working days after the emergency occurred, or per prevailing local requirements, if sooner than 5 working days.

All deviations from the investigational plan, with the reason for the deviation and the date of occurrence, must be documented and reported to the Sponsor using the EDC CRF. Centers may also be required to report deviations to the IRB/EC, per local guidelines and government regulations.

Deviations will be reviewed and evaluated on an ongoing basis and, as necessary, appropriate corrective and preventive actions (including notification, center re-training, or discontinuation) will be put into place by the Sponsor.

16. Device Accountability

16.1. *Investigational Device*

The Lotus Valve System (investigational device) will be released by the Sponsor to the clinical center only after the center has been initiated and all regulatory approvals as well as required documentation have been collected from the center.

The Lotus Valve System shall be securely maintained, controlled, and used only in this clinical study. Additionally, the study personnel must follow the instructions related to the storage of the test and control devices as noted in the corresponding IFUs. Device Accountability Logs for the Lotus Valve System will be provided to the centers and will be used to track subjects and device allocations during the study.

The Sponsor shall keep records to document the physical location of all investigational devices from shipment of investigational devices to the investigation centers until return or disposal.

Centers must not dispose of any investigational devices for any reason at the center unless instructed to do so by BSC. Any investigational device that is disposed of at the center must be recorded in the Device Accountability Log. The PI must document the reasons for any discrepancy noted in device accountability.

The principal investigator or an authorized designee shall keep records documenting the receipt, use, return and disposal of the investigational devices, which shall include the following; this will be verified by personnel from BSC or its designee.

- Date of receipt
- Identification of each investigational device (Part/Reference, Lot numbers, valve size)
- Expiry date, as applicable
- Date of use
- Subject identification
- Date on which the investigational device was returned/explanted from subject, if applicable
- Date of return of unused, expired, or malfunctioning investigational devices, if applicable

Written procedures may be required by national regulations.

Once the Investigator and Center are notified in writing by BSC that subject enrollment is complete, all unused investigational devices must be returned to BSC or its designee. A copy of the Device Accountability Logs must also be provided to BSC.

16.2. *Control Device*

Appropriate information on control device size and model will be collected.

17. Compliance

17.1. *Statement of Compliance*

The REPRISE III study will be conducted in accordance with the relevant parts of the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practices (GCP) or the International Standard ISO 14155: 2011; ethical principles that have their origins in the Declaration of Helsinki; and pertinent individual country/state/local laws and regulations.

17.2. *Investigator Responsibilities*

The Principal Investigator of an investigational center is responsible for ensuring that the study is conducted in accordance with the Clinical Study Agreement, the investigational plan/protocol, ISO 14155 or ICH/GCP, ethical principles that have their origins in the Declaration of Helsinki, any conditions of approval imposed by the reviewing IRB/EC, and prevailing local and/or country laws and/or regulations, whichever affords the greater protection to the subject.

The Principal Investigator's responsibilities include, but are not limited to, the following.

- Prior to beginning the study, sign the Investigator Agreement and Protocol Signature page documenting his/her agreement to conduct the study in accordance with the protocol.
- Provide his/her qualifications and experience to assume responsibility for the proper conduct of the study and that of key members of the center team through up-to-date curriculum vitae or other relevant documentation and disclose potential conflicts of interest, including financial, that may interfere with the conduct of the clinical study or interpretation of results.
- Complete training requirements associated with the CoreValve device.
- Complete all Lotus Valve (investigational device) training requirements as detailed in the REPRISE III Training Plan (see Section 17.4.1).
- Make no changes in or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency; document and explain any deviation from the approved protocol that occurred during the course of the clinical investigation.
- Create and maintain source documents throughout the clinical study and ensure their availability with direct access during monitoring visits or audits; ensure that all clinical-investigation-related records are retained per requirements.

- Ensure the accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor in the CRFs and in all required reports.
- Record, report, and assess (seriousness and relationship to the device/procedure) every adverse event and observed device deficiency.
- Report to BSC, per the protocol requirements, all SAEs and device deficiencies that could have led to a SADE.
- Report to the IRB/EC and regulatory authorities any SAEs and device deficiencies that could have led to a SADE, if required by the national regulations or this protocol or by the IRB/EC, and supply BSC with any additional requested information related to the safety reporting of a particular event.
- Maintain the device accountability records and control of the investigational device, ensuring that the investigational device is used only by authorized/designated users and in accordance with this protocol and instructions/directions for use.
- Allow the Sponsor and Sponsor representatives to perform monitoring and auditing activities, and be accessible to the monitor and respond to questions during monitoring visits.
- Allow and support regulatory authorities and the IRB/EC when performing auditing activities.
- Ensure that informed consent is obtained in accordance with this protocol and local IRB/EC requirements.
- Provide adequate medical care to a subject during and after a subject's participation in a clinical study in the case of adverse events, as described in the ICF.
- Inform the subject of the nature and possible cause of any adverse events experienced.
- Inform the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required.
- Provide the subject with well-defined procedures for possible emergency situations related to the clinical study, and make the necessary arrangements for emergency treatment as needed.
- Ensure that clinical medical records are clearly marked to indicate that the subject is enrolled in this clinical study.
- Ensure that, if appropriate, subjects enrolled in the clinical investigation are provided with some means of showing their participation in the clinical investigation, together with identification and compliance information for concomitant treatment measures (contact address and telephone numbers shall be provided).
- Inform, with the subject's approval or when required by national regulations, the subject's personal physician about the subject's participation in the clinical investigation.

- Make all reasonable efforts to ascertain the reason(s) for a subject's premature withdrawal from clinical investigation while fully respecting the subject's rights.
- Ensure that an adequate investigation center team and facilities exist and are maintained and documented during the clinical investigation.
- Ensure that maintenance and calibration of the equipment relevant for the assessment of the clinical investigation is appropriately performed and documented, where applicable.

17.2.1. Delegation of Responsibility

When specific tasks are delegated by an investigator, included but not limited to conducting the informed consent process, the investigator is responsible for providing appropriate training and adequate supervision of those to whom tasks are delegated. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

17.3. *Institutional Review Board/ Ethics Committee*

Prior to gaining Approval-to-Enroll status, the investigational center will provide to the Sponsor documentation verifying that their IRB/EC is registered or that registration has been submitted to the appropriate agency, as applicable according to national/regulatory requirements.

A copy of the written IRB/EC and/or competent authority approval of the protocol (or permission to conduct the study) and Informed Consent Form, must be received by the Sponsor before recruitment of subjects into the study and shipment of investigational product/equipment. Prior approval must also be obtained for other materials related to subject recruitment or which will be provided to the subject.

Annual IRB/EC approval and renewals will be obtained throughout the duration of the study as required by local/country or IRB/EC requirements. Copies of the Investigator's reports and the IRB/EC continuance of approval must be provided to the Sponsor.

17.4. *Sponsor Responsibilities*

All information and data sent to BSC and its authorized designee concerning subjects or their participation in this study will be considered confidential by BSC. Only authorized BSC personnel, representatives, or designees will have access to these confidential records. Authorized regulatory personnel have the right to inspect and copy all records pertinent to this study. Study data collected during this study may be used by BSC for the purposes of this study, publication, and to support future research and/or other business purposes. Data used in the analysis and reporting of this study will not be identified by specific subject name.

Note: Boston Scientific may utilize a contract research organization (CRO) or other contractors to act as its representative for carrying out designated tasks.

Boston Scientific Corporation will keep subjects' health information confidential in accordance with all applicable laws and regulations. Boston Scientific Corporation may use subjects' health information to conduct this research, as well as for additional purposes, such as overseeing and improving the performance of its device, new medical research and proposals for developing new medical products or procedures, and other business purposes. Information received during the study will not be used to market to subjects; subject names will not be placed on any mailing lists or sold to anyone for marketing purposes.

17.4.1. Training with the Lotus Valve System

The Sponsor is responsible for providing Investigators with the information and training on the Lotus Valve System they need to conduct the study properly. The Sponsor is responsible for maintaining documentation of attendance at each of the training sessions provided.

A Lotus Training Plan has been developed for this study that meets the requirements of ISO 5840-3:2013 and includes the following elements.

- Device Description: A detailed description of all components of the device including a summary of the basic principle of operation.
- CT and Procedural Angiography: A detailed review of pre-procedural and procedural imaging techniques to aid in sizing decisions and implantation of the Lotus valve.
- Step by Step Procedure: A detailed description of each step of the procedure. The training describes any warnings associated with any steps, and tips and tricks for a Lotus valve implantation.
- Implantation Techniques and Sizing: A detailed review of specific implantation techniques and valve sizing based on clinical cases.
- Device Demonstration: A hands-on training using standard Lotus valve components to practice the implantation procedure in a bench model or a robotic simulation system.
- Proctoring: The investigator and co-investigators as well as the scrub team will be proctored by an experienced TAVR physician on a minimum of 6 Lotus Valve implantation procedures. These are to be performed in the investigator's institution with his/her staff. If the proctor or investigators (First Operator and Second Operator) are not satisfied that these initial proctored procedures are sufficient preparation, then subsequent proctoring sessions may be added as needed.

Note: The training requirements listed above apply to centers that do not have previous experience implanting the Lotus Valve. For these centers there will be a roll-in phase with at least 2 roll-in subjects per center treated under the supervision of a proctor. The roll-in subjects will count towards the 6 required proctored cases.

17.4.2. Role of Boston Scientific Corporation Representatives

Boston Scientific Corporation personnel (including field clinical engineers) will provide training and technical support to the investigator and other health care personnel (collectively

HCP) as needed during Lotus Valve implant and testing required by the protocol. Boston Scientific Corporation is also responsible for ensuring investigators are trained on the Directions for Use. Support may include addressing HCP questions or providing clarifications to HCPs concerning the operation of BSC equipment/devices. In addition, BSC personnel may perform certain activities to ensure study quality. These activities may include the following.

- Observing testing or medical procedures to provide information relevant to protocol compliance
- Reviewing collected data and study documentation for completeness and accuracy.

17.5. *Insurance*

Where required by local/country regulation, proof and type of insurance coverage by BSC for subjects in the study will be obtained.

18. Monitoring

Monitoring will be performed during the study according to the monitoring plan to assess continued compliance with the protocol and applicable regulations. In addition, the monitor verifies that study records are adequately maintained, that data are reported in a satisfactory manner with respect to timeliness, adequacy, and accuracy, and that the Investigator continues to have sufficient staff and facilities to conduct the study safely and effectively. The Investigator/institution guarantees direct access to original source documents by BSC personnel, their designees, and appropriate regulatory authorities.

The study may also be subject to a quality assurance audit by BSC or its designees, as well as inspection by appropriate regulatory authorities. It is important that the Investigator and relevant study personnel are available during on-site monitoring visits or audits and that sufficient time is devoted to the process.

19. Potential Risks and Benefits

Risks to clinical subjects associated with their participation in this clinical investigation, arising from the clinical procedures set out in the study protocol, have been identified from prior studies conducted by Boston Scientific Corporation and review of relevant literature, most recently from the Edwards Lifesciences' Placement of Aortic Transcatheter Valves (PARTNER) Trial[14,63-65], the PARTNER II trial[119], the SAPIEN 3 CE Mark study[78], the CoreValve Extreme Risk Study[75], the CoreValve High Risk Study[66], and the PORTICO IDE randomized trial/RESOLVE registry/SAVORY registry[68].

Benefits to subjects anticipated to arise from the use of the investigational device have also been identified. These clinical risks and benefits are summarized below, with an assessment of the balance of risks and benefits to subjects.

Potential risks and benefits have been included in the study-specific template of the ICF provided to the study centers (see Section 20).

19.1. *Risks Associated with Transcatheter Aortic Valve Implantation Procedure*

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 Valve System and/or CoreValve include but may not be limited to the following.

- Abnormal lab values (including anemia and electrolytes)
- Allergic reaction (including to medications, anesthesia, contrast, or device materials)
- Angina
- Arrhythmia or new conduction system injury (including need for pacemaker insertion)
- Bleeding or hemorrhage (possibly requiring transfusion or intervention)
- Cardiac arrest
- Cardiac failure/low cardiac output
- Cerebrovascular accident, stroke or transient ischemic attack
- Coronary obstruction
- Death
- Device misplacement or migration
- Endocarditis
- Emboli (including air, calcium, tissue, thrombus or device materials)
- Fever
- Heart failure
- Hemolysis and/or hemolytic anemia
- Hematoma or lymphatic problems at the access sites
- Hemodynamic instability or shock
- Hypertension/hypotension
- Infection (local and/or systemic, including septicemia)
- Inflammation
- Mitral valve insufficiency

- Myocardial infarction
- Myocardial or valvular injury (including perforation or rupture)
- Nerve injury
- Pain
- Pericardial effusion or cardiac tamponade
- Peripheral ischemia or infarction
- Permanent disability
- Pleural effusion
- Pulmonary edema
- Renal insufficiency or failure
- Respiratory insufficiency or failure
- Valve dysfunction, deterioration or failure
- Valvular stenosis or regurgitation (central or paravalvular)
- Valve or device thrombosis
- Vessel injury (including spasm, trauma, dissection, perforation, rupture, arteriovenous fistula, or pseudoaneurysm)

As a result of these complications, the subject may require medical, percutaneous or surgical intervention, including re-operation and replacement of the implanted valve. Such complications can be fatal.

As the Lotus valve is an investigational device, uncertainty remains over risks of experiencing some or all of the complications listed above. There may be risks that are unknown at this time.

19.2. *Risk Minimization Actions*

Additional risks may exist. Risks can be minimized through compliance with this protocol, performing procedures in the appropriate hospital environment, adherence to subject selection criteria, close monitoring of the subject's physiologic status during research procedures and/or follow-ups and by promptly supplying BSC with all pertinent information required by this protocol.

- Boston Scientific Corporation will employ measures throughout the course of this investigation consistent with the best practices and lessons learned from other ongoing TAVR trials and commercial use to minimize risk for subjects choosing to participate. All efforts will be made to minimize risks by selecting centers that are experienced and skilled in TAVR procedures.

- Risk mitigation will be accomplished through the following actions.
  - Clearly defining the inclusion/exclusion criteria to ensure only appropriate subjects are enrolled
  - Confirmation of eligible subjects by a Case Review Committee, including experienced investigators in TAVR
  - Ensuring that treatment and follow-up of the subject are consistent with current medical practices
  - Selection of investigators who are experienced and skilled in TAVR procedures
  - Completion of training and proctorship provided by the Sponsor
  - Performing all procedures in accordance with the IFU, including the preparation of the valve and delivery system
  - Dynamic safety review processes, including assessment by the Data Monitoring Committee (DMC, Section 22.1) and CEC (Section 22.1) adjudication of specified events as recommended by VARC[72,73].

In addition to its repositioning and self-centering features designed to facilitate optimal positioning, the Lotus Valve System provides physicians with control throughout the procedure by allowing them to pause, assess, lock, un-lock, incrementally reverse, resheath and, if needed, retrieve the valve prior to final release. These features help the physician to do the following: place the valve correctly with the first attempt, reposition the device if the initial deployment is considered to be suboptimal, and retrieve the device if during the procedure the decision is made not to implant. The valve's outer seal is also designed to minimize paravalvular leakage.

Anticoagulation medication (e.g., heparin) will be administered during the procedure to reduce the risk of embolism and stroke. Additionally, post-procedure anti-platelet therapy is recommended to minimize any risk of thrombus formation, stroke, or transient ischemic attack. Neurological assessments will be performed at each required follow-up visit to identify any change in the neurological status of the subjects as recommended by VARC[72,73].

Cardiac enzyme measurements as well as ECGs post-procedure will be performed to detect periprocedural MI.

Subjects will be carefully monitored during the procedure, hospitalization, and throughout the follow-up period. Serial echocardiograms and electrocardiograms will be used to evaluate valve and general cardiac function. Any abnormal rhythm will be assessed and, if needed, the implantation of a permanent pacemaker will be performed. Annual imaging will also be performed to assess for structural valve frame integrity.

Subjects who are converted to standard surgical aortic valve replacement will be carefully monitored in a method appropriate for their surgical procedure.

Data will be monitored as they are submitted to BSC. Qualified employees of BSC, or a designee under contract, will conduct monitoring visits at the initiation of the study and at

interim intervals described in the monitoring plan throughout the course of the study to evaluate protocol compliance and determine if there are any issues that could affect the safety or welfare of any subject in the study.

19.3. *Anticipated Benefits*

19.3.1. Potential Benefits to the TAVR Procedure

Transcatheter aortic valve replacement (TAVR) may offer certain advantages when compared to surgical replacement of the stenotic native aortic valve, particularly in high risk subjects. Known benefits associated with TAVR, as described in the scientific literature (see summary in Section 4.1 of this document and details in Sections 2 and 3 of the investigator brochure), potentially include the following.

- Minimally invasive procedure and reduced risks related to open heart surgery
- Shorter stay in the intensive care unit and overall hospital stay
- Reduced blood loss
- More rapid recovery
- Reduced need for general anesthesia and associated risks
- Opportunity to receive a new aortic prosthesis in spite of having been refused surgery or being of high surgical risk profile

19.3.2. Potential Benefit Using the Lotus Valve System

Potential benefits that may be associated specifically with use of the Lotus™ Valve System compared to other TAVR systems include the following.

- Pre-loaded delivery system minimizing time required and potential issues with preparing the device
- Accurate valve placement due to the ability to reposition the valve during deployment
- Device is minimally obstructive to the blood flow and maintains hemodynamic stability through the annulus during delivery because there is no balloon or other obstructive device required for deployment and due to early valve leaflet function
- Reduced need for post-dilation
- Reduced or obviated need for valve-in-valve repeat intervention
- Lower risk of ectopic valve placement and valve migration
- Reduced incidence of paravalvular aortic regurgitation due to the Adaptive Seal

19.4. *Risk to Benefit Rationale*

Review of the aforementioned clinical benefits versus risks takes into account the known risks/benefits that have been identified in the published literature on other TAVR devices. The estimation of risk also includes prior limited clinical experience with the Lotus Valve System including earlier generations of the device design. When used according to the IFU, all known risks associated with the TAVR procedure and the specific use of the Lotus Valve System are mitigated to acceptable limits comparable to existing TAVR devices. The design features of full repositioning and retrievability may improve TAVR procedural safety. The Adaptive Seal may provide long term benefit as it is designed to minimize paravalvular regurgitation, which has been associated with long term mortality in TAVR.

20. Informed Consent

Subject participation in this clinical study is voluntary. Informed Consent is required from all subjects or their legally authorized representative. The Investigator is responsible for ensuring that Informed Consent is obtained prior to the use of any investigational devices, study-required procedures and/or testing, or data collection.

The obtaining and documentation of Informed Consent must be in accordance with the principles of the Declaration of Helsinki; the relevant parts of ISO 14155: 2011 and the ICH guidelines for GCP; any applicable national regulations; and local Ethics Committee and/or Regulatory authority body, as applicable. The ICF must be approved by the center's IRB/EC, or central IRB, if applicable.

Boston Scientific Corporation will provide a study-specific template of the ICF to investigators participating in this study. The ICF template may be modified to meet the requirements of the investigative center's IRB/EC. Any modification requires approval from BSC or authorized representative prior to use of the form. The ICF must be in a language understandable to the subject and if needed, BSC will assist the center in obtaining a written consent translation. Translated consent forms must also have IRB/EC approval prior to their use. Privacy language shall be included in the body of the form or as a separate form as applicable.

The process of obtaining Informed Consent shall:

- be conducted by the Principal Investigator or designee authorized to conduct the process,
- include a description of all aspects of the clinical study that are relevant to the subject's decision to participate throughout the clinical study,
- avoid any coercion of or undue influence of subjects to participate,
- not waive or appear to waive subject's legal rights,
- use native language that is non-technical and understandable to the subject or his/her legal representative,

- provide ample time for the subject to consider participation and ask questions if necessary,
- ensure important new information is provided to new and existing subjects throughout the clinical study.

The ICF shall always be signed and personally dated by the subject or legal representative and by the investigator or an authorized designee responsible for conducting the informed consent process. If a legal representative signs, the subject shall be asked to provide informed consent for continued participation as soon as his/her medical condition allows. The original signed ICF will be retained by the center and a copy of the signed and dated document and any other written information must be given to the person signing the form.

Failure to obtain subject consent will be reported by BSC to the applicable regulatory body according to their requirements. Any violations of the informed consent process must be reported as deviations to the Sponsor and local regulatory authorities (e.g. IRB/EC), as appropriate.

If new information becomes available that can significantly affect a subject's future health and medical care, that information shall be provided to the affected subject(s) in written form via a revised ICF or, in some situations, enrolled subjects may be requested to sign and date an addendum to the ICF. In addition to new significant information during the course of a study, other situations may necessitate revision of the ICF, such as if there are amendments to the protocol, a change in Principal Investigator, administrative changes, or following annual review by the IRB/EC. The new version of the ICF must be approved by the IRB/EC. Boston Scientific Corporation approval is required if changes to the revised ICF are requested by the center's IRB/EC. The IRB/EC will determine the subject population to be re-consented.

21. Safety Reporting

21.1. *Definitions and Classification*

Adverse event definitions are provided in Table 21.1-1.

Table 21.1-1: Adverse Event Definitions

Term	Definition[a]
Adverse Event (AE) *Ref: ISO 14155:2011*	Any untoward medical occurrence, unintended disease or injury or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device **Note 1**: This definition includes events related to the investigational medical device or the comparator. **Note 2**: This definition includes events related to the procedures involved. **Note 3**: For users or other persons, this definition is restricted to events related to investigational medical devices.

Table 21.1-1: Adverse Event Definitions

Term	Definition[a]
Adverse Device Effect (ADE) *Ref: ISO 14155:2011*	Adverse event related to the use of an investigational medical device **Note 1**: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. **Note 2**: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.
Serious Adverse Event (SAE) *Ref: ISO 14155:2011*	Adverse event that: • Led to a death • Led to serious deterioration in the health of the subject, that either resulted in: o a life-threatening illness or injury, or o a permanent impairment of a body structure or a body function, or o in-patient or prolonged hospitalization, or o medical or surgical intervention to prevent life- threatening illness or injury or permanent impairment to a body structure or a body function, • Led to fetal distress, fetal death or a congenital abnormality or birth defect **Note**: Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered a serious adverse event.
Serious Adverse Device Effect (SADE) *Ref: ISO 14155:2011*	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated Adverse Device Effect (UADE) *Ref: 21 CFR Part 812*	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.
Unanticipated Serious Adverse Device Effect (USADE) *Ref: ISO 14155:2011*	Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report **Note**: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.
Device Deficiency *Ref: ISO 14155:2011* *Ref: MEDDEV 2.7/3 12/2010*	A device deficiency is Any inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. **Note 1**: Device deficiencies include malfunctions, use errors, and inadequate labeling. **Note 2**: All device deficiencies that could have led to a SADE if a) suitable action had not been taken or b) if intervention had not been made or c) if circumstances had been less fortunate shall be reported as required by the local IRB/EC, national regulations, or the protocol.

Table 21.1-1: Adverse Event Definitions

Term	Definition[a]

a: Other definitions may apply per local reporting requirements.

Underlying diseases are not reported as AEs unless there is an increase in severity or frequency during the course of the investigation. Death should not be recorded as an AE, but should only be reflected as an outcome of a specific SAE (see Table 21.1-1 for AE definitions).

In-patient hospitalization is defined as the subject being admitted to the hospital, with the following exceptions.

- A hospitalization that is uncomplicated and elective/planned (i.e., planned prior to enrollment) does not have to be reported as an SAE.
- If complications or AEs occur during an elective/planned (i.e., planned prior to enrollment) hospitalization after enrollment, the complications and AEs must be reported as AEs or SAEs if they meet the protocol-specified definitions.

For the randomized cohort, event reporting (eCRF) is required beginning from the time of randomization.

For the roll-in, Lotus 21 mm Nested Registry, and U.S. Continued Access Study cohorts, event reporting (eCRF) is required beginning from the time an attempt is made to insert the Lotus Valve System into the subject's femoral artery.

Refer to Section 19 for the known risks associated with the study devices (test and control).

Based on the VARC[72,73] recommendations and definitions, the adverse events and/or safety endpoints requiring adjudication by the CEC include the following.

- 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 events: life-threatening (or disabling) and major
- Acute kidney injury (≤7 days post index procedure): based on the AKIN System[105,106] Stage 3 (including renal replacement therapy) or Stage 2
- Vascular complications: major
- Repeat procedure for valve-related dysfunction (surgical or interventional therapy)
- Hospitalization for valve-related symptoms or worsening congestive heart failure (NYHA class III or IV)

- New permanent pacemaker 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
- TAV-in-TAV deployment
- Prosthetic aortic valve thrombosis
- Prosthetic aortic valve endocarditis

Details on the CEC events and procedures are outlined in the CEC charter. Tests and images required to adjudicate these events are specified in the event definitions (see Table 26.2-1).

21.2. *Relationship to Study Device(s)*

The Investigator must assess the relationship of the AE/SAE to the study device as related or unrelated. See criteria in Table 21.2-1.

Table 21.2-1: Criteria for Assessing Relationship of Study Device to Adverse Event

Classification	Description
Unrelated	The adverse event is determined to be due to a concurrent illness or effect of another device/drug and is not related to the investigational product.
Related	• The adverse event is determined to be potentially related to the investigational product, and an alternative etiology is equally or less likely compared to the potential relationship to investigational product. • There is a strong relationship to investigational product, or recurs on re-challenge, and another etiology is unlikely. • There is no other reasonable medical explanation for the event.

21.3. *Investigator Reporting Requirements*

The communication requirements for reporting to BSC are as shown in Table 21.3-1.

Note: The "become aware date" for an event that requires reporting per the protocol is the date that study personnel listed on the Delegation of Authority Log identify or are notified of the event.

Centers should report control device-related deficiencies as per requirements in the control-device Instructions For Use.

Table 21.3-1: Investigator Reporting Requirements

Event Classification	Communication Method	Communication Timeline
Unanticipated Adverse Device Effect / Unanticipated Serious Adverse Device Effect (UADE/USADE)	Complete adverse event (AE) electronic case report form (eCRF) page with all available new and updated information	• Within 1 business day of first becoming aware of the event • Beginning from time of enrollment for all subjects • Terminating at the end of the study
	Provide copies of all relevant source documents requested by BSC	• As soon as possible after reporting the event
Serious Adverse Event (SAE) including Serious Adverse Device Effects (SADE)	Complete AE eCRF page with all available new and updated information	• Within 2 business days of first becoming aware of the event or as per local/regional regulations. • Beginning from time of enrollment for all subjects • Reporting required through the end of the study
	Provide all relevant source documentation (unidentified) for reported event	• When documentation is available
Adverse Event (AE)	Complete AE eCRF page	• As soon as possible before the next planned monitoring visit • Beginning from time of enrollment for all subjects • Reporting required through 12 months
Device Deficiencies, Failures, Malfunctions, and Product Nonconformities	Complete applicable eCRF fields/pages with all available new and updated information.	Investigational Device: • Within 1 business day of first becoming aware of the event and as per local/regional regulations • Beginning from time of Lotus Introducer sheath insertion for all subjects • Reporting required through the end of the study Control Device: • As required per IFU and as per local/regional regulations

Note: The AE eCRF page contains information such as date of AE, treatment of AE resolution, assessment of seriousness, and relationship to the device.

Abbreviations: AE=adverse event; BSC=Boston Scientific Corporation; eCRF=electronic case report form; IFU=Instructions for Use

21.4. *Device Deficiencies*

21.4.1. Boston Scientific Device Deficiencies

All Lotus Valve System device deficiencies (including but not limited to failures, malfunctions, use errors, product nonconformities, and labeling errors) must be documented on the appropriate eCRF and, if possible, the device should be returned to BSC for analysis. Instructions for returning the investigational device will be provided in the study Manual of Operations. If it is not possible to return the device, the investigator should document why the device was not returned and the final disposition of the device. Device deficiencies should also be documented in the subject's medical record.

Device deficiencies and other device issues should not be reported as AEs. Instead, they should be reported on the appropriate eCRF. If an AE results from a device deficiency or other device issue, the AE must be reported on the appropriate eCRF.

Device deficiencies that did not lead to an AE but could have led to a SAE if a) suitable action had not been taken, or b) intervention had not been made, or c) circumstances had been less fortunate must be reported as described in Table 21.3-1.

21.4.2. Control Device Deficiencies

Device deficiencies related to use of the control device (CoreValve) should be reported per the IFU and per applicable local/regional requirements. If an AE results from a device deficiency or other device issue, the AE must be reported on the appropriate eCRF.

21.5. *Reporting to Regulatory Authorities / IRBs / ECs / Investigators*

Boston Scientific Corporation will notify all participating study centers if UADEs, USADEs, SAEs, SADEs, or investigational device deficiencies occur which imply a possible increase in the anticipated risk of the procedure or use of the device or if the occurrence of certain SAEs/SADEs requires changes to the protocol or the conduct of the study in order to further minimize the unanticipated risks.

Boston Scientific Corporation is responsible for reporting AE information to all participating investigators and regulatory authorities as applicable according to local reporting requirements.

The PI is responsible for informing the IRB/EC, and regulatory authorities of UADEs, USADEs, SADEs, SAEs, Device Deficiencies and/or other CEC events as applicable according to local reporting requirements. A copy of the Investigator's reports and other relevant reports (if applicable) to the IRB/IEC must be provided to BSC in accordance with local requirements.

22. Committees

22.1. *Safety Monitoring Process*

To promote early detection of safety issues, the Clinical Events Committee (CEC) and Data Monitoring Committee (DMC; see below) will provide evaluations of safety events. Success of this program requires dynamic collection of unmonitored data as soon as the event is reported. This is expedited through the Sponsor or designee, which is responsible for coordinating the collection of information for the subject dossier from the centers and core laboratories. During regularly scheduled monitoring visits, clinical research monitors will support the dynamic reporting process through their review of source document information.

22.1.1. Clinical Events Committee

A CEC will be used in this study. A CEC is an independent group of individuals with pertinent expertise, including cardiovascular interventional therapy, cardiovascular surgery, and neurology, which reviews and adjudicates important endpoints and relevant adverse events reported by study investigators. The CEC will review a safety event dossier, which may include copies of subject source documents provided by study sites, and adjudicate study endpoint related clinical events. The responsibilities, qualifications, membership, and committee procedures of the CEC are outlined in the CEC charter.

22.1.2. Data Monitoring Committee

The DMC is responsible for the oversight review of all AEs and all SAEs in the roll-in, randomized, and Lotus 21 mm Nested Registry cohorts. The DMC will include leading experts in cardiovascular interventional therapy, cardiovascular surgery, and biostatistics who are not participating in the study and who have no affiliation with BSC. During the course of the study, the DMC will review accumulating safety data to monitor the incidence of CEC events and other trends that would warrant modification or termination of the study. Responsibilities, qualifications, membership, and committee procedures are outlined in the DMC Charter.

22.2. *Case Review Committee*

A Case Review Committee (CRC) will be comprised of experienced cardiac surgeons and interventional cardiologists, including the Study Coordinating PIs, Center PIs, other Investigators, Proctors and Medical Consultants experienced in TAVR for their clinical/medical expertise, and the Sponsor for technical expertise on the Lotus Valve System requirements. This committee will be responsible for the review of subject screening data to confirm eligibility given the increased surgical risk of the subject population being studied and to ensure consistency of subjects enrolled across study centers. Responsibilities, qualifications, membership, and committee procedures are outlined in the CRC Charter.

22.3. *Steering Committee*

A Steering Committee consisting of Sponsor Clinical Management, the Study Coordinating PIs, cardiac surgeons, and other investigators experienced in TAVR will be convened. Responsibilities may include oversight of the overall conduct of the study with regard to protocol development, study progress, subject safety, overall data quality and integrity, as well as disseminating any study results through appropriate scientific sessions and publications. Steering Committee members may participate in the review and approval of all requests for data analysis, abstract and manuscript preparation and submission.

23. Suspension or Termination

23.1 Premature Termination of the Study

Boston Scientific Corporation reserves the right to terminate the study at any stage but intends to exercise this right only for valid scientific or administrative reasons and reasons related to protection of subjects. Investigators, associated IRBs/ECs, and regulatory authorities, as applicable, will be notified in writing in the event of study termination.

23.1.1 Criteria for Premature Termination of the Study

Possible reasons for premature study termination include, but are not limited to, the following.

- The occurrence of unanticipated adverse device effects that present a significant or unreasonable risk to subjects enrolled in the study.
- An enrollment rate far below expectation that prejudices the conclusion of the study.
- A decision on the part of BSC to suspend or discontinue development of the device.

23.2 Termination of Study Participation by the Investigator or Withdrawal of IRB/EC Approval

Any investigator or IRB/EC in the REPRISE III study may discontinue participation in the study or withdrawal approval of the study, respectively, with suitable written notice to BSC. Investigators, associated IRBs/ECs, and regulatory authorities, as applicable, will be notified in writing in the event of these occurrences.

23.3 Requirements for Documentation and Subject Follow-up

In the event of premature study termination a written statement as to why the premature termination has occurred will be provided to all participating centers by BSC. The IRB/EC and regulatory authorities, as applicable, will be notified. Detailed information on how enrolled subjects will be managed thereafter will be provided.

In the event an IRB/EC terminates participation in the study, participating investigators, associated IRBs/ECs, and regulatory authorities, as applicable, will be notified in writing. Detailed information on how enrolled subjects will be managed thereafter will be provided by BSC.

In the event an investigator terminates participation in the study, study responsibility will be transferred to a co-investigator, if possible. In the event there are no opportunities to transfer investigator responsibility; detailed information on how enrolled subjects will be managed thereafter will be provided by BSC. The investigator must return all documents and investigational product to BSC, unless this action would jeopardize the rights, safety, or welfare of the subjects.

23.4 Criteria for Suspending/Terminating a Study Center

Boston Scientific Corporation reserves the right to stop the inclusion of subjects at a study center at any time after the study initiation visit if no subjects have been enrolled or if the center has multiple or severe protocol violations/noncompliance without justification and/or fails to follow remedial actions.

In the event of termination of investigator participation, all study devices and testing equipment, as applicable, will be returned to BSC unless this action would jeopardize the rights, safety or well-being of the subjects. The IRB/EC and regulatory authorities, as applicable, should be notified. All subjects enrolled in the study at the center will continue to be followed per this protocol. The Principal Investigator at the center must make provision for these follow-up visits unless BSC notifies the investigational center otherwise.

24. Publication Policy

In accordance with the Global SOP – Human Subject Data and Research Controls, BSC requires disclosure of its involvement as a sponsor or financial supporter in any publication or presentation relating to a BSC study or its results. In accordance with the Global SOP – Human Subject Data and Research Controls, BSC will submit study results for publication (regardless of study outcome) in a timely manner. Boston Scientific Corporation follows authorship principals as set forth in the Uniform Requirements of the International Committee of Medical Journal Editors (ICMJE; http://www.icmje.org). In order to ensure the public disclosure of study results in a timely manner, while maintaining an unbiased presentation of study outcomes, BSC personnel may assist authors and investigators in publication preparation provided the following guidelines are followed.

- All authorship and contributorship requirements as described above must be followed.
- BSC involvement in the publication preparation and the BSC Publication Policy should be discussed with the Coordinating Principal Investigator(s) and/or Steering Committee at the onset of the project.

- The First and Senior authors are the primary drivers of decisions regarding publication content, review, approval, and submission.

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26. Abbreviations and Definitions

26.1. *Abbreviations*

Abbreviations are shown in Table 26.1-1.

Table 26.1-1: Abbreviations and Acronyms

Abbreviation/Acronym	Definition
ADE	adverse device effect
AE	adverse event
AKIN	Acute Kidney Injury Network
AR	aortic regurgitation
AS	aortic stenosis
AV	atrioventricular
AVA	aortic valve area
AVR	aortic valve replacement
BARC	Bleeding Academic Research Consortium
BMI	body mass index
BSA	body surface area
BSC	Boston Scientific Corporation
CBC	complete blood count
CEC	Clinical Events Committee
CK	creatine kinase
CK-MB	creatine kinase-myoglobin band, a fraction of creatine kinase
CRC	Case Review Committee
CT	computed tomography
CVA	cerebrovascular accident
DVI	Doppler velocity index
ECG	Electrocardiogram
eCRF	electronic case report form
EOA	effective orifice area
eGFR	estimated glomerular filtration rate
GCP	Good Clinical Practices
ICF	Informed Consent form
ICH	International Conference on Harmonisation
IEC/IRB	Independent Ethics Committee/Institutional Review Board
IFU	Instructions for Use
ISO	International Organization For Standardization
ITT	intention to treat
LBBB	left bundle branch block
LDH	lactate dehydrogenase
LV	left ventricle
LVEF	left ventricular ejection fraction
MACCE	major adverse cardiovascular and cerebrovascular events

Table 26.1-1: Abbreviations and Acronyms

Abbreviation/Acronym	Definition
MI	myocardial infarction
MRI	magnetic resonance imaging
mRS	Modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
NOAC	new oral anticoagulant
NYHA	New York Heart Association classification
PPM	permanent pacemaker
QOL	quality of life
SADE	serious adverse device effect
SAE	serious adverse event
SAVR	surgical aortic valve replacement
TAVR	transcatheter aortic valve replacement
TEE	transesophageal Doppler echocardiography
TIA	transient ischemic attack
TTE	transthoracic Doppler echocardiography
UADE	unanticipated adverse device effect
USADE	unanticipated serious adverse device effect
URL	upper reference limit (defined as 99th percentile of normal reference range)
VARC	Valve Academic Research Consortium

26.2. *Definitions*

Terms are defined in Table 26.2-1. See Table 26.1-1 for abbreviations.

Table 26.2-1: Definitions

Term	Definition
ACUTE KIDNEY INJURY (AKI) (AKIN System[105,106])	Change in serum creatinine (up to 7 days) compared to baseline: • Stage 1: Increase in serum creatinine to 150–199% (1.5–1.99 × increase compared with baseline) OR increase of ≥0.3 mg/dl (≥26.4 mmol/L) • Stage 2: Increase in serum creatinine to 200–299% (2.0–2.99 × increase compared with baseline) • Stage 3: Increase in serum creatinine to ≥300% (>3 × increase compared with baseline) OR serum creatinine of ≥4.0 mg/dL (≥354 mmol/L) with an acute increase of at least 0.5 mg/dL (44 mmol/L) -OR- Based on urine output (up to 7 days): • Stage 1: <0.5 ml/kg per hour for >6 but <12 hours • Stage 2: <0.5 ml/kg per hour for >12 but <24 hours • Stage 3: <0.3 ml/kg per hour for ≥24 hours or anuria for ≥12 hours Note 1: Subjects receiving renal replacement therapy are considered to meet Stage 3 criteria irrespective of other criteria.
ACUTE VESSEL	The state of complete luminal obstruction with no antegrade blood flow

Table 26.2-1: Definitions

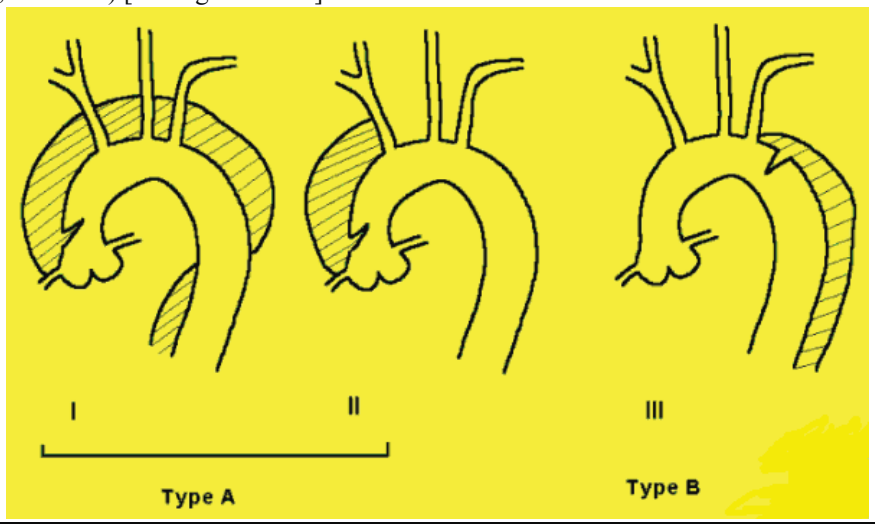
Term	Definition
OCCLUSION	
ADVERSE EVENT *Ref: ISO 14155:2011* (AE)	Any untoward medical occurrence, unintended disease or injury or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device. Note 1: This definition includes events related to the investigational medical device or the comparator. Note 2: This definition includes events related to the procedures involved. Note 3: For users or other persons, this definition is restricted to events related to investigational medical devices.
ADVERSE EVENT BECOME AWARE DATE	The become aware date for an adverse event that requires reporting per the protocol is the date that study personnel listed on the Delegation of Authority Log identify or are notified of the event.
ADVERSE DEVICE EFFECT *Ref: ISO 14155:2011* (ADE)	Adverse event related to the use of an investigational medical device Note 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. Note 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.
AORTIC DISSECTION	Intimal tear resulting in blood splitting the aortic media and producing a false lumen that can progress in an antegrade or retrograde direction Aortic dissection is further classified using Stanford classification (Types A and B depending on whether ascending or descending aorta involved) or DeBakey classification (Types I, II and III) [see Figure below]. 
AORTIC REGURGITATION (AR)	The leaking of the aortic valve that causes blood to flow in the reverse direction during ventricular diastole, from the aorta into the left ventricle. The echocardiographic findings in severe aortic regurgitation include the following. • An AR color jet dimension >60% of the left ventricular outflow tract diameter (may not be true if the jet is eccentric) • The pressure half-time of the regurgitant jet is <250 msec • Early termination of the mitral inflow (due to increase in LV pressure due to the AR)

Table 26.2-1: Definitions

Term	Definition
	• Early diastolic flow reversal in the descending aorta. • Regurgitant volume >60 mL • Regurgitant fraction >55%
ARRHYTHMIA	Any variation from the normal rhythm of the heartbeat, including sinus arrhythmia, premature beat, heart block, atrial fibrillation, atrial flutter and tachycardia. Complete heart block, ventricular tachycardia and ventricular fibrillation are considered major arrhythmias. Data should be collected on any new arrhythmia resulting in hemodynamic instability or requiring therapy (therapy includes electrical/medical cardioversion or initiation of a new medication [oral anticoagulation, rhythm or rate controlling therapy]). New onset atrial fibrillation or atrial flutter (AF) is diagnosed as any arrhythmia within hospitalization that has the ECG characteristics of AF and lasts sufficiently long to be recorded on a 12-lead ECG, or at least 30 seconds on a rhythm strip. The therapeutic approach to new-onset AF (spontaneous conversion, electrical or medical cardioversion, initiation of oral anticoagulation, and rate or rhythm control medications) and any clinical consequences should be documented. Note 1: See also definitions for conductance disturbance and permanent pacemaker.
AS-TREATED ANALYSIS SET	This population includes all subjects who sign an Informed Consent Form, are enrolled in the trial, are randomized, and receive a study device, but subjects are analyzed based on the treatment actually received. For example, if a subject is assigned to receive a test device but instead receives a control device, that subject will be considered a control subject for the as-treated analyses of implant subgroups. Note 1: If a subject receives 2 valves, the subject is assigned to the group corresponding to the first valve received.
BLEEDING[72,73]	Life-threatening or Disabling Bleeding • Fatal bleeding (Bleeding Academic Research Consortium [BARC] type 5[120,121]) • Bleeding in a critical organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome (BARC type 3b and 3c) • Bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery (BARC type 3b) • Overt source of bleeding with drop in hemoglobin of ≥5 g/dL or whole blood or packed red blood cells (RBC) transfusion ≥4 units (BARC type 3b)* Major Bleeding (BARC type 3a) • Overt bleeding either associated with a drop in the hemoglobin level of at least 3.0g/dL or requiring transfusion of 2 or 3 units of whole blood/RBC, or causing hospitalization or permanent injury, or requiring surgery AND does not meet criteria of life-threatening or disabling bleeding Minor Bleeding (BARC type 2 or 3a, depending on the severity) • Any bleeding worthy of clinical mention (e.g., access site hematoma) that does not qualify as life-threatening, disabling, or major * Given one unit of packed RBC typically will raise blood hemoglobin concentration by 1 g/dL, an estimated decrease in hemoglobin will be calculated.
CARDIAC DECOMPENSATION	Inability of the heart to maintain adequate circulation

Table 26.2-1: Definitions

Term	Definition
CARDIAC TAMPONADE	Evidence of a new pericardial effusion associated with hemodynamic instability and clearly related to the TAVR procedure. Clinical syndrome caused by the accumulation of fluid in the pericardial space, resulting in reduced ventricular filling and subsequent hemodynamic compromise.
CARDIOGENIC SHOCK	An insufficient forward cardiac output to maintain adequate perfusion of vital organs to meet ongoing demands for oxygenation and metabolism. Cardiogenic shock is due to either inadequate left ventricular pump function (such as in congestive heart failure) or inadequate left ventricular filling (such as in cardiac tamponade). Cardiogenic shock is defined as sustained hypotension (>30 minutes) with evidence of tissue hypoperfusion including oliguria (<30 mL/h), cool extremities, cyanosis, and altered mental status.
CEREBRAL INFARCTION	Evidence of brain cell death from imaging studies or pathological examination. If there are clinical symptoms, then it is a stroke; otherwise, it is an asymptomatic cerebral infarction.
CHRONIC RENAL INSUFFICIENCY	Subject has chronic impairment of kidney function.
CLINICAL PROCEDURAL SUCCESS (IN-HOSPITAL)	Implantation of the device in the absence of death, disabling stroke, major vascular complications, and life-threatening or major bleeding
CONDUCTION DISTURBANCES[72,73]	Implant-related new or worsened cardiac conduction disturbances include new or worsened first degree atrioventricular (AV) block, second degree AV block (Mobitz I or Mobitz II), third degree AV block, incomplete right bundle branch block (RBBB), RBBB, intraventricular conduction delay, left bundle branch block (LBBB), left anterior fascicular block, or left posterior fascicular block, including block requiring permanent pacemaker implant Note 1: High grade AV block is considered persistent if it is present every time the underlying rhythm is checked. Note 2: See also definitions for arrhythmia and permanent pacemaker.
CONVERSION TO OPEN SURGERY	Conversion to open sternotomy during the TAVR procedure secondary to any procedure-related complications
CORONARY OBSTRUCTION	Angiographic or echocardiographic evidence of a new, partial or complete, obstruction of a coronary ostium, either by the valve prosthesis itself, the native leaflets, calcifications, or dissection, occurring during or after the TAVR procedure. Mechanical coronary artery obstruction following TAVR or surgical AVR that typically occurs during the index procedure. Possible mechanisms for mechanical coronary obstruction include the following. • Impingement of the coronary ostia by the valve support structure in the setting of suboptimal valve positioning and/or 'small aortic root' anatomy • Embolization from calcium, thrombus, air, or endocarditis displacement of native aortic valve leaflets towards the coronary ostia during TAVR • Suture-related kinking or obstruction or cannulation related obstruction of the coronary ostia associated with surgical AVR The diagnosis of TAVR-associated coronary obstruction can be determined by imaging studies (coronary angiography, intravascular ultrasound, multi-slice CT angiography, or echocardiography), surgical exploration, or autopsy findings.

Table 26.2-1: Definitions

Term	Definition
	Cardiac biomarker elevations and ECG changes indicating new ischemia provide corroborative evidence.
DEATH	All-cause Death Death from any cause after a valve intervention. Cardiovascular Death Any one of the following criteria is met. • Any death due to proximate cardiac cause (e.g., myocardial infarction, cardiac tamponade, worsening heart failure) • Sudden or unwitnessed death • Death of unknown cause • Death caused by noncoronary vascular conditions such as neurological events, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular disease • All procedure-related deaths, including those related to a complication of the procedure or treatment for a complication of the procedure • All valve-related deaths including structural or nonstructural valve dysfunction or other valve-related adverse events Non-cardiovascular Death • Any death in which the primary cause of death is clearly related to another condition (e.g. trauma, cancer, suicide)
DEVICE DEFICIENCY *Ref: ISO 14155:2011* *Ref:MEDDEV 2.7/3 12/2010*	inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Note 1: Device deficiencies include malfunctions, use errors, and inadequate labeling.
DEVICE FAILURE	A device failure is identified whenever the criteria for device success are not met.
DEVICE MIGRATION	Device migration is defined as an upward or downward displacement of the implanted valve from its original implant location, after initial correct positioning within the aortic annulus from its initial position, with or without consequences. This can be confirmed by X-ray, echocardiography, CT scan or MRI or valve migration demonstrated by direct assessment during open heart surgery or at autopsy.
DEVICE RELATED COMPLICATIONS	Complications associated with the device as it relates to delivery, placement, efficacy or durability; these may involve the implanted device or the delivery system.
ECTOPIC VALVE DEPLOYMENT	Permanent deployment of the valve prosthesis in a location other than the aortic root.
EMBOLISM	Examples include a free flowing blood clot or lesion material that is located in the systemic or pulmonary circulation. Embolism may be manifested by a neurological event or a noncerebral embolic event.
ENCEPHALOPATHY	Altered mental state (e.g., seizures, delirium, confusion, hallucinations, dementia, coma, psychiatric episode, etc.)
ENDOCARDITIS	**Infective endocarditis** is diagnosed based on Duke criteria[122] and necessitates the following. • Two major criteria -OR- • One major and three minor criteria -OR- • Five minor criteria

Table 26.2-1: Definitions

Term	Definition
	Major Criteria • Positive blood culture for infective endocarditis o Typical microorganism consistent with infective endocarditis from 2 separate blood cultures, as noted below. ▪ Viridans streptococci, *Streptococcus bovis*, or HACEK group (*Haemophilus* [*Haemophilus parainfluenzae, Haemophilus aphrophilus, and Haemophilus paraphrophilus*], *Actinobacillus actinomycetemcomitans* [*Aggregatibacter actinomycetemcomitans*], *Cardiobacterium hominis, Eikenella corrodens, Kingella kingae* -OR- ▪ Community-acquired *Staphylococcus aureus* or enterococci, in the absence of a primary focus -OR- o Microorganisms consistent with infective endocarditis from persistently positive blood cultures defined as noted below. ▪ Two (2) positive cultures of blood samples drawn >12 hours apart -OR- ▪ All of 3 or a majority of 4 separate cultures of blood (with first and last sample drawn 1 hour apart) • Evidence of endocardial involvement o Positive echocardiogram for infective endocarditis defined as noted below. ▪ Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation -OR- ▪ Abscess -OR- ▪ New partial dehiscence of prosthetic valve -OR- o New valvular regurgitation (worsening or changing of preexisting murmur not sufficient) Minor Criteria • Predisposition: predisposing heart condition or intravenous drug use • Fever: temperature >38.0° C (100.4° F) • Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway lesions • Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth spots, and rheumatoid factor • Microbiological evidence: positive blood culture but does not meet a major criterion as noted above or serological evidence of active infection with organism consistent with infective endocarditis • Echocardiographic findings: consistent with infective endocarditis but do not meet a major criterion as noted above **Implanted valve endocarditis** includes any infection involving an implanted valve. The diagnosis of operated valvular endocarditis is based on one of the following criteria. • Fulfillment of the Duke endocarditis criteria as defined above • Evidence of abscess, paravalvular leak, pus, or vegetation confirmed as secondary to infection by histological or bacteriologic studies during a re-operation

Table 26.2-1: Definitions

Term	Definition
	• Findings of abscess, pus, or vegetation involving a repaired or replaced valve during an autopsy.
EXPLANT	Removal of the investigational valve implant for any reason.
FRAILTY	Slowness, weakness, exhaustion, wasting and malnutrition, poor endurance and inactivity, loss of independence.
HEMOLYSIS	Two plasma free hemoglobin values >40 mg/dL with the two readings taken within a single 48-hour period. If the second plasma free hemoglobin assessment is not performed within 48 hours following an initial determination of >40 mg/dL, this would qualify as an AE.
HOSTILE CHEST	Any of the following or other reasons that make redo operation through sternotomy or right anterior thoracotomy prohibitively hazardous: • Abnormal chest wall anatomy due to severe kyphoscoliosis or other skeletal abnormalities (including thoracoplasty, Potts' disease) • Complications from prior surgery • Evidence of severe radiation damage (e.g. skin burns, bone destruction, muscle loss, lung fibrosis or esophageal stricture) • History of multiple recurrent pleural effusions causing internal adhesions
IMPLANTED ANALYSIS SET	This population includes all subjects who sign an Informed Consent Form, are enrolled in the trial, and are implanted with the assigned, randomized study device. Note 1: If a subject receives 2 valves, the subject is assigned to the group corresponding to the first valve received.
INTENT TO TREAT (ITT) ANALYSIS SET	This population includes all subjects who sign an Informed Consent Form, are enrolled in the trial, and are randomized, whether or not an assigned study device is implanted. Subjects in the ITT population will be followed with their ITT cohort. Note 1: If a subject receives 2 valves, the subject is assigned to the group corresponding to the first valve received.
INTERNAL MAMMARY ARTERY OR OTHER CRITICAL CONDUIT(S) CROSSING MIDLINE AND/OR ADHERENT TO POSTERIOR TABLE OF STERNUM	A patent IMA graft that is adherent to the sternum such that injuring it during reoperation is likely. A patient may be considered extreme risk if any of the following are present: • The conduit(s) are radiographically indistinguishable from the posterior table of the sternum. • The conduit(s) are radiographically distinguishable from the posterior table of the sternum but lie within 2-3mm of the posterior table.
INTRACRANIAL HEMORRHAGE	Collection of blood between the brain and skull; subcategorized as epidural, subdural, and subarachnoid bleeds.

Table 26.2-1: Definitions

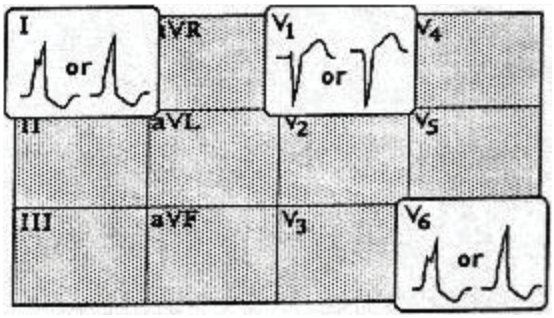
Term	Definition
LEFT BUNDLE BRANCH BLOCK (LBBB)	The appearance of typical complete LBBB in the three KEY leads (I, V1, and V6) with the following diagnostic criteria [see Figure below]. • The heart rhythm must be supraventricular in origin • QRS widening to at least 0.12 sec • An upright (monophasic) QRS complex in leads I and V6; the QRS may be notched, but there should not be any q wave in either lead I or lead V6. • A predominantly negative QRS complex in lead V1; there may or may not be an initial small r wave in lead V1, that is, lead V1 may show either a QS or RS complex. 
LIVER DISEASE (SEVERE) /CIRRHOSIS	Any of the following: • Child-Pugh class C • MELD score ≥10 • Portal-caval, spleno-renal, or transjugular intrahepatic portal shunt • Biopsy proven cirrhosis with portal hypertension or hepatocellular dysfunction
MITRAL VALVE APPARATUS DAMAGE	Angiographic or echocardiographic evidence of a new damage to the mitral valve apparatus (chordae papillary muscle, or leaflet) during or after the TAVR procedure.
MODIFIED DEVICE SUCCESS	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 mm Hg or a peak velocity <3m/sec with no moderate or severe prosthetic valve aortic regurgitation)
MYOCARDIAL INFARCTION (MI)	**Periprocedural MI (≤72 hours after the index procedure)** • New ischemic symptoms (e.g., chest pain or shortness of breath) or new ischemic signs (e.g., ventricular arrhythmias, new or worsening heart failure, new ST-segment changes, hemodynamic instability, new pathological Q waves in at least two contiguous leads, or imaging evidence of new loss of viable myocardium or new wall motion abnormality) -AND- • Elevated cardiac biomarkers (preferably CK-MB) within 72 h after the index procedure, consisting of at least one sample post-procedure with a peak value exceeding 15× upper reference limit (troponin) or 5× for CK-MB. If cardiac biomarkers are increased at baseline (>99th percentile), a further increase of at least 50% post-procedure is required AND the peak value must exceed the previously stated limit.

Table 26.2-1: Definitions

<table>
<tr><th>Term</th><th>Definition</th></tr>
<tr><td></td><td>Spontaneous MI (>72 hours after the index procedure)
Any one of the following criteria applies.
• Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile URL, together with evidence of myocardial ischemia with at least one of the following
o Symptoms of ischemia
o ECG changes indicative of new ischemia [new ST-T changes or new LBBB]
o New pathological Q waves in at least two contiguous leads
o Imaging evidence of new loss of viable myocardium or new wall motion abnormality
• Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST-segment elevation, or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/ or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.
• Pathological findings of an acute myocardial infarction[123].</td></tr>
<tr><td>NEUROLOGICAL EVENT</td><td>Any central, new neurological deficit, whether temporary or permanent and whether focal or global, that occurs after the subject emerges from anesthesia</td></tr>
<tr><td>NEW YORK HEART ASSOCIATION CLASSIFICATION (NYHA)</td><td>Classification system for defining cardiac disease and related functional limitations into four broad categorizations:

<table><tr><td>Class I</td><td>Subject with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.</td></tr><tr><td>Class II</td><td>Subjects with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.</td></tr><tr><td>Class III</td><td>Subjects with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.</td></tr><tr><td>Class IV</td><td>Subjects with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.</td></tr></table></td></tr>
<tr><td>NONSTRUCTURAL DYSFUNCTION</td><td>Any abnormality not intrinsic to the valve itself that results in stenosis or regurgitation of the operated valve or hemolysis. The term nonstructural dysfunction refers to problems (exclusive of thrombosis and infection) that do not directly involve valve components yet result in dysfunction of an operated valve, as diagnosed by re-operation, autopsy, or clinical investigation. Nonstructural dysfunction includes the following.
• Entrapment by pannus, tissue, or suture
• Paravalvular leak
• Inappropriate sizing or positioning
• Residual leak or obstruction after valve implantation or repair
• Clinically important intravascular hemolytic anemia</td></tr>
</table>

Table 26.2-1: Definitions

Term	Definition
	• Development of aortic or pulmonic regurgitation as a result of technical errors • Dilatation of the sinotubular junction • Dilatation of the valve annulus after either valve replacement with stentless prostheses, new onset of coronary ischemia from coronary ostial obstruction, or paravalvular aortic regurgitation
OPERATIVE RISK	Operative risk is determined by a center cardiac surgeon and must be confirmed by the Case Review Committee (including a cardiac surgeon). **Extreme Risk**: Predicted operative mortality or serious, irreversible morbidity risk ≥50% at 30 days **High Risk**: Predicted operative mortality or serious, irreversible morbidity risk ≥15% at 30 days
PARAVALVULAR REGURGITATION	Leakage due to a separation of the prosthetic valve from the annulus. Any evidence of leakage of blood around the device. Diagnosis of paravalvular regurgitation may be obtained from TEE/TTE, however, definitive diagnosis is obtained at re-operation, explant, or autopsy.
PERMANENT PACEMAKER (PPM) IMPLANTATION[110]	Implantation of new PPM after the index procedure resulting from new or worsened conduction disturbances • Procedure-related: PPM is implanted in subjects with new onset or worsened conduction disturbances occurring post index procedure • Not related to procedure: PPM is implanted in subjects with known conduction disturbances that did not advance after the index procedure. Note 1: See also definitions for arrhythmia and conductance disturbance.
PORCELAIN AORTA	Heavy circumferential calcification of the entire ascending aorta extending to the arch such that aortic cross-clamping is not feasible
PROCEDURE RELATED COMPLICATIONS	Complications associated with any part of the vascular access procedure, associated treatments or necessary secondary interventions that do not necessarily involve the device. This includes morbidity associated with either pre-medication, or anesthesia, or other adjunct to the surgical procedure. Other technical errors including inappropriate subject selection, inappropriate operator techniques, measurements, or judgment that do not involve the device itself are also included.
PROCEDURE-RELATED EVENTS	Events occurring during or as a direct result of the index procedure.
REPEAT PROCEDURE FOR VALVE-RELATED DYSFUNCTION	Any surgical or percutaneous interventional catheter procedure that repairs, otherwise alters or adjusts, or replaces a previously implanted valve. In addition to surgical re-operations, enzymatic, balloon dilatation, interventional manipulation, repositioning, or retrieval, and other catheter-based interventions for valve-related complications are also considered re-interventions. Cardiac re-interventions will be categorized as repeat TAVR, valvuloplasty, or surgical AVR. • Conversion to open surgery • Conversion to open sternotomy during the TAVR procedure secondary to any procedure-related complications. • Unplanned use of CPB • Unplanned use of CPB for hemodynamic support at any time during the TAVR procedure.
RESPIRATORY INSUFFICIENCY	Inadequate ventilation or oxygenation

Table 26.2-1: Definitions

Term	Definition
RESPIRATORY FAILURE	The need for ventilatory support for >72 hours associated with an inability to wean from the respirator for any reason.
RIGHT VENTRICULAR INSUFFICIENCY	• Defined as sequelae of right ventricular failure including the following. o Significantly decreased right ventricular systolic and/or diastolic function o Tricuspid valvular regurgitation secondary to elevated pressure • Clinical symptoms to include the following. o Hepatic congestion o Ascites o Anasarca o Presence of "hepato-jugular reflux" o Edema Severe right ventricular dysfunction or severe pulmonary hypertension is primary or secondary pulmonary hypertension with PA systolic pressures greater than 2/3 of systemic pressure.
SAFETY ANALYSIS SET	This population includes all subjects in the ITT analysis set who have a study device implanted, regardless of the assigned treatment group.
SERIOUS ADVERSE DEVICE EFFECT *Ref: ISO 14155:2011* (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event
SERIOUS ADVERSE EVENT *Ref: ISO 14155:2011* (SAE)	Adverse event that resulted in the following. • Led to a death • Led to serious deterioration in the health of the subject, that resulted in one or more of the following. o Life-threatening illness or injury o Permanent impairment of a body structure or a body function o In-patient or prolonged hospitalization o Medical or surgical intervention to prevent life- threatening illness or injury or permanent impairment to a body structure or a body function, • Led to fetal distress, fetal death or a congenital abnormality or birth defect Note 1: Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered a serious adverse event.
SOURCE DATA (per ISO 14155:2011)	All information in original records of clinical findings, observations, or other activities in a clinical investigation, necessary for the reconstruction and evaluation of the clinical investigation
SOURCE DOCUMENT (per ISO 14155:2011)	Printed, optical or electronic document containing source data. Examples: Hospital records, laboratory notes, device accountability records, photograhic negatives, radiographs, records kept at the investigation center, at the laboratories and at the medico-technical departments involvced in the clinical investigation.
STROKE[72,73]	Stroke is defined as an acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction **Stroke Classification** • Ischemic Stroke is defined as an acute episode of focal cerebral, spinal, or retinal

Table 26.2-1: Definitions

Term	Definition
	dysfunction caused by an infarction of central nervous system tissue. • Hemorrhagic Stroke is defined as an acute episode of focal or global cerebral or spinal dysfunction caused by an intraparenchymal, intraventricular, or subarachnoid hemorrhage Note 1: The CEC will adjudicate ischemic versus hemorrhagic stroke. Note 2: A stroke may be classified as undetermined if there is insufficient information to allow categorization as ischemic or hemorrhagic **Stroke Diagnostic Criteria** • Rapid onset of a focal or global neurological deficit with at least one of the following: change in level of consciousness, hemiplegia, hemiparesis, numbness or sensory loss affecting one side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke • Duration of a focal or global neurological deficit ≥24 h; OR <24 h, if available neuroimaging documents a new hemorrhage or infarct; OR the neurological deficit results in death • No other readily identifiable nonstroke cause for the clinical presentation (e.g., brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences), to be determined by or in conjunction with designated neurologist • Confirmation of the diagnosis by at least one of the following. o Neurology or neurosurgical specialist o Neuroimaging procedure (MRI or CT scan), but stroke may be diagnosed on clinical grounds alone Note 3: Subjects with non-focal global encephalopathy will not be reported as a stroke without unequivocal evidence based upon neuroimaging studies (CT scan or brain MRI). **Stroke Definitions** Diagnosis as above, preferably with positive neuroimaging study • Non-disabling: Modified Rankin Scale (mRS) score <2 at 90 days OR one that does not result in an increase of at least one mRS category from an individual's pre-stroke baseline • Disabling: Modified Rankin Scale score ≥2 at 90 days AND an increase of at least one mRS category from an individual's pre-stroke baseline Note 4: Modified Rankin Scale assessments should be made by a neurology professional or by qualified individuals according to a certification process. Note 5: Assessment of the mRS score should occur at all scheduled visits in a study; mRS also should be performed after a stroke and at 90 days after the onset of any stroke.
STRUCTURAL VALVE DETERIORATION	Component of time-related valve safety defined as follows. • Valve-related dysfunction: Mean aortic valve gradient ≥20 mmHg, EOA ≤0.9-1.1 cm^2, and/or DVI <0.35 AND/OR moderate or severe prosthetic valve regurgitation (per VARC definition) • Requiring repeat procedure (TAVR or SAVR).
TAV-IN-TAV DEPLOYMENT	An additional valve prosthesis is implanted within a previously implanted prosthesis because of suboptimal device position and/or function during or after the index procedure.
TRANSIENT ISCHEMIC ATTACK	• Transient episode of focal neurological dysfunction caused by brain, spinal cord,

Table 26.2-1: Definitions

Term	Definition
(TIA)	or retinal ischemia, without acute infarction • Duration of a focal or global neurological deficit is <24 h • Neuroimaging does not demonstrate a new hemorrhage or infarct (if performed) Note: The difference between TIA and ischemic stroke is the presence of tissue damage or new sensory-motor deficit persisting >24 hours. By definition, TIA does not produce lasting disability.
UNANTICIPATED ADVERSE DEVICE EFFECT *Ref: 21CFR Part 812* (UADE)	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the protocol or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.
UNANTICIPATED SERIOUS ADVERSE DEVICE EFFECT *Ref: ISO 14155:2011* (USADE)	Serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report Note 1: An anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity, or outcome has been identified in the risk analysis report.
UNPLANNED USE OF CARDIOPULMONARY BYPASS	Unplanned use of cardiopulmonary bypass for hemodynamic support at any time during the TAVR procedure
VALVE EMBOLIZATION	The valve prosthesis moves during or after deployment such that it loses contact with the aortic annulus.
VALVE MALPOSITIONING	Includes valve migration, valve embolization, or ectopic valve deployment
VALVE MIGRATION	After initial correct positioning the valve prosthesis moves upward or downward within the aortic annulus from its initial position, with or without consequences (e.g., regurgitation).
VALVE-RELATED DYSFUNCTION	Mean aortic valve gradient ≥20 mmHg, EOA ≤0.9-1.1 cm^2, and/or DVI <0.35 AND/OR moderate or severe prosthetic valve aortic regurgitation (per VARC definition)
VALVE-RELATED SYMPTOMS/CHF REQUIRING HOSPITALIZATION	The need for hospitalization associated with valve-related symptoms or worsening CHF (NYHA Class III or IV) is intended to serve as a basis for calculation of a "days alive outside the hospital" endpoint. Included are heart failure, angina, or syncope due to aortic valve disease requiring intervention or intensified medical management; clinical symptoms of CHF with objective signs including pulmonary edema, hypoperfusion, or documented volume overload AND administration of intravenous diuresis or inotropic therapy, performance of aortic valvuloplasty, institution of mechanical support (intra-aortic balloon pump or ventilation for pulmonary edema), or hemodialysis for volume overload; clear documentation of anginal symptoms AND no clinical evidence that angina was related to coronary artery disease or acute coronary syndrome; documented loss of consciousness not related to seizure or tachyarrhythmia.
VALVE THROMBOSIS	Any thrombus attached to or near an implanted valve that occludes part of the blood flow path, interferes with valve function, or is sufficiently large to warrant treatment. Note that valve-associated thrombus identified at autopsy in a patient whose cause of death was not valve-related or at operation for an unrelated indication should not be reported as valve thrombosis.

Table 26.2-1: Definitions

Term	Definition
VASCULAR ACCESS SITE AND ACCESS RELATED COMPLICATIONS	**Major Vascular Complications** • Any aortic dissection, aortic rupture, annulus rupture, left ventricle perforation, or new apical aneurysm/pseudoaneurysm • Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, hematoma, irreversible nerve injury, compartment syndrome, percutaneous closure device failure*) ***leading to*** death, life-threatening or major bleeding**, visceral ischaemia, or neurological impairment • Distal embolization (non-cerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage • The use of unplanned endovascular or surgical intervention ***associated*** with death, major bleeding, visceral ischaemia or neurological impairment • Any new ipsilateral lower extremity ischemia documented by patient symptoms, physical exam, and/or decreased or absent blood flow on lower extremity angiogram • Surgery for access site-related nerve injury • Permanent access site-related nerve injury **Minor Vascular Complications** • Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysms , hematomas, percutaneous closure device failure*) not leading to death, life-threatening or major bleeding**, visceral ischaemia or neurological impairment • Distal embolization treated with embolectomy and/or thrombectomy and not resulting in amputation or irreversible end-organ damage • Any unplanned endovascular stenting or unplanned surgical intervention not meeting the criteria for a major vascular complication • Vascular repair or the need for vascular repair (via surgery, ultrasound-guided compression, transcatheter embolization, or stent-graft) ***Percutaneous Closure Device Failure** Failure of a closure device to achieve hemostasis at the arteriotomy site leading to alternative treatment (other than manual compression or adjunctive endovascular ballooning) Note 1**:** Pre-planned surgical access or a planned endovascular approach to vascular closure (e.g., "pre-closure")[124,125] should be considered as part of the TAVR procedure and not as a complication, unless untoward clinical consequences are documented (e.g., bleeding complications, limb ischemia, distal embolization, or neurological impairment). Note 2: If unplanned percutaneous or surgical intervention does not lead to adverse outcomes this is not considered a major vascular complication. ** Refers to VARC bleeding definitions[72,73]
VENTRICULAR SEPTAL PERFORATION	Angiographic or echocardiographic evidence of a new septal perforation during or after the TAVR procedure
VESSEL PERFORATION	Unexpected puncture of the vessel with evidence of extravasation into extraluminal surrounding tissue or space requiring treatment using interventional or surgical techniques

Abbreviations: ADE=adverse device effect; AE=adverse event; AR=aortic regurgitation; AVA=aortic valve

Table 26.2-1: Definitions

Term	Definition

area; AVR= aortic valve replacement; CEC= Clinical Events Committee; CK= creatine kinase; CT=computed tomography; DVI=Doppler velocity index; ECG=electrocardiogram; EOA=effective orifice area; FEV= forced expiratory volume; LBBB=left bundle branch block; LV= left ventricle; MI=myocardial infarction; MRI=magnetic resonance imaging; NYHA=New York Heart Association; PPM=permanent pacemaker; RBC=red blood cell; SADE=serious adverse device effect; SAE=serious adverse event; TAV=transcatheter aortic valve; TAVR=transcatheter aortic valve replacement; TEE=transesophageal Doppler echocardiography; TIA=transient ischemic attack; USADE= unanticipated serious adverse device effect; URL=upper reference limit (defined as 99th percentile of normal reference range); VARC=Valve Academic Research Consortium

27. Appendices

27.1. *Changes in Protocol Versions*

27.1.1. Protocol Version AA to Version AB

Table 27.1-1 lists changes between protocol versions AA and AB.

27.1.2. Protocol Version AB to Version AC

Table 27.1-2 lists changes between protocol versions AB and AC.

27.1.3. Protocol Version AC to Version AD

Table 27.1-3 lists changes between protocol versions AC and AD.

27.1.4. Protocol Version AD to Version AE

Table 27.1-4 lists changes between protocol versions AD and AE.

27.1.5. Protocol Version AE to Version AF

Table 27.1-5 lists changes between protocol versions AE and AF.

27.1.6. Protocol Version AF to Version AG

Table 27.1-6 lists changes between protocol versions AF and AG.

27.1.7. Protocol Version AG to Version AH

Table 27.1-7 lists changes between protocol versions AG and AH.

Table 27.1-1: Table of Changes for REPRISE III Protocol Version AB (Compared to REPRISE III Protocol Version AA)

Section Modified	Text as Written in REPRISE III Protocol Version AA	Text as Written in REPRISE III Protocol Version AB	Justification for Modification
Page 1	Parc d'Affaires, Le Val Saint-Quentin 2 rue René Caudron, 78960 Voisins le Bretonneux, France	55 Av. des Champs Pierreux, TSA 51101 92729 Nanterre Cedex, France	Corrected Sponsor contact address for Europe

Table 27.1-2: Table of Changes for REPRISE III Protocol Version AC (Compared to REPRISE III Protocol Version AB)

Section Modified	Text as Written in REPRISE III Protocol Version AB	Text as Written in REPRISE III Protocol Version AC	Justification for Modification
Page 2	Current Version: 25-Jul-2014	Current Version: 25-Sep-2014 Inserted Table of Revision History	Updated for clarity and to account for local practice.
2. Protocol Synopsis, Test Devices and Sizes	The Lotus Valve System consisting of two…	The Lotus Valve System is an investigational device consisting of two…	
2. Protocol Synopsis, Control Device and Sizes	Commercially available self-expanding CoreValve® Transcatheter Aortic Valve Replacement System (CoreValve) that is introduced… ***Note 1:*** Every subject... control (CoreValve) valve size approved for use and commercially available at the investigational center... ***Note 2:*** A center…size matrix if it is approved and commercially available, but only…	Although commercially available in other countries, the self-expanding CoreValve® Transcatheter Aortic Valve Replacement System (CoreValve) is an unapproved medical device available to Authorized Prescribers in Australia. It is introduced… ***Note 1:*** Every subject... control (CoreValve) valve size available to Authorized Prescribers in Australia at the investigational center... ***Note 2:*** A center…size matrix if it is available, but only…	
2. Protocol Synopsis, study Design	REPRISE III is a prospective, multicenter, 2:1 randomized (Lotus Valve System versus a commercially available CoreValve…	REPRISE III is a prospective, multicenter, 2:1 randomized (Lotus Valve System versus CoreValve…	
5.2 CoreValve… System	The control device is the commercially available self-expanding CoreValve® Transcatheter Aortic Valve Replacement System (CoreValve) that is introduced…	The control device is the self-expanding CoreValve® Transcatheter Aortic Valve Replacement System (CoreValve), which is an unapproved medical device available to Authorized	

Table 27.1-2: Table of Changes for REPRISE III Protocol Version AC (Compared to REPRISE III Protocol Version AB)

Section Modified	Text as Written in REPRISE III Protocol Version AB	Text as Written in REPRISE III Protocol Version AC	Justification for Modification
(Control)	***Note1***: Every subject… and the control (CoreValve) valve approved for use and commercially available at the investigational center where… ***Note 2***: A center… size matrix if it is approved and commercially available, but…	Prescribers in Australia. It is introduced… ***Note 1***: Every subject… and the control (CoreValve) valve available to Authorized Prescribers at the investigational center where… ***Note 2***: A center…size matrix if it is available, but…	
5.3.2 Control Device	Information is provided in the IFU supplied with the commercially available CoreValve…	Information is provided in the IFU supplied with the CoreValve…	
8.2 Treatment Assignment	Eligible subjects… or a commercially available self-expanding CoreValve® Transcatheter Aortic Valve Replacement System (control).	Eligible subjects… or the self-expanding CoreValve® Transcatheter Aortic Valve Replacement System (control).	
8.2.1 Treatment	The control device is the commercially available CoreValve…	The control device is the CoreValve….	
11.7.1 Medtronic…	• Descriptive information on balloon valve annuloplasty (e.g., size of balloon…	• Descriptive information on balloon valvuloplasty (e.g., size of balloon…	Updated for clarity
11.7.2.2 Preparing…	• Descriptive information on balloon valve annuloplasty (e.g., size of balloon…	• Descriptive information on balloon valvuloplasty (e.g., size of balloon…	
27 Appendices	—	Added Section 27.1-2 and Table 27.1-2	

Note: Version AC was a Boston Scientific Corporation (BSC) internal update only; Version AC was not implemented and was not distributed outside of BSC.

Table 27.1-3: Table of Changes for REPRISE III Protocol Version AD (Compared to REPRISE III Protocol Version AC)

Section Modified	Text as Written in REPRISE III Protocol Version AC	Text as Written in REPRISE III Protocol Version AD	Justification for Modification
Page 2	Current Version: 25-Sep-2014 Inserted Table of Revision History	Added Clinical Contact: Sarah Zanon, Senior Clinical Trial Manager, Structural Heart – Interventional Cardiology, Boston Scientific Corporation, Dornacherplatz 7, 4500 Solothurn, Switzerland Current Version: dd-Mar-2015 Updated Table of Revision History	Updated for clarity

Table 27.1-3: Table of Changes for REPRISE III Protocol Version AD (Compared to REPRISE III Protocol Version AC)

Section Modified	Text as Written in REPRISE III Protocol Version AC	Text as Written in REPRISE III Protocol Version AD	Justification for Modification
2. Protocol Synopsis, Test Devices and Sizes	The Lotus Valve System is an investigational device consisting of two…	The Lotus Valve System consists of two…	
2. Protocol Synopsis, Control Device and Sizes	Although commercially available in other countries, the self-expanding CoreValve® Transcatheter Aortic Valve Replacement System (CoreValve) is an unapproved medical device available to Authorized Prescribers in Australia. It is introduced… ***Note 1:*** Every subject... control (CoreValve) valve size available to Authorized Prescribers in Australia at the investigational center... ***Note 2:*** A center…size matrix if it is available, but only…	Commercially available self-expanding CoreValve® Transcatheter Aortic Valve Replacement System (CoreValve) that is introduced… ***Note 1:*** Every subject... test (Lotus) device and the control (CoreValve) device. The CoreValve device in the planned size must be approved for use and commercially available at the investigational center... ***Note 2:*** A center…size matrix if it is approved and commercially available, but only…	
2. Protocol Synopsis, Study Design	REPRISE III is a prospective, multicenter, 2:1 randomized (Lotus Valve System versus CoreValve…	REPRISE III is a prospective, multicenter, 2:1 randomized (Lotus Valve System versus a commercially available CoreValve…	
2. Protocol Synopsis, Additional Measurements	○ Neurological physical exam at discharge and 1 year (conducted by a neurologist or neurology fellow) ***Note 4:*** For subjects diagnosed with a neurological event... a neurological physical exam (conducted by a neurologist or neurology fellow), NIHSS assessment…	○ Neurological physical exam at discharge and 1 year (conducted by a neurologist, neurology fellow, neurology physician assistant, or neurology nurse practitioner) ***Note 4:*** For subjects diagnosed with a neurological event... a neurological physical exam (conducted by a neurologist, neurology fellow, neurology physician assistant, or neurology nurse practitioner), NIHSS assessment…	
2. Protocol Synopsis, Adjunctive Pharmacologic Therapy	***Note*:** If a subject requires chronic anticoagulation with warfarin (other anticoagulants are not permitted), either clopidogrel or aspirin is required prior to and after the implant procedure in addition to the anticoagulant therapy (but both aspirin and clopidogrel are not required). Subjects treated with warfarin should not be treated with a $P2Y_{12}$ inhibitor other than clopidogrel. c: Holmes, D. R., et al. *J Am Coll Cardiol*. 2012;59:1200-1254 Nishimura, R., et al. *J Am Coll Cardiol*. 2014;doi:	***Note*:** If a subject requires chronic anticoagulation, either clopidogrel or aspirin is required prior to and after the implant procedure in addition to the anticoagulant therapy (but both aspirin and clopidogrel are not required). After the implant procedure, the subject must be treated with warfarin (other anticoagulants are not permitted in the first month) and either clopidogrel (other $P2Y_{12}$ inhibitors are not permitted in combination with warfarin) or aspirin for at least 1 month. After 1 month, subjects requiring chronic anticoagulation may be switched from warfarin to a new oral anticoagulant (NOAC) at	

Table 27.1-3: Table of Changes for REPRISE III Protocol Version AD (Compared to REPRISE III Protocol Version AC)

Section Modified	Text as Written in REPRISE III Protocol Version AC	Text as Written in REPRISE III Protocol Version AD	Justification for Modification
	10.1016/j.jacc.2014.02.536	the discretion of the treating physician. The subject should not receive a $P2Y_{12}$ inhibitor in combination with a NOAC but may be treated with a NOAC plus aspirin. c: Holmes, D. R., et al. *J Am Coll Cardiol*. 2012;59:1200-1254 Nishimura, R., et al. *J Am Coll Cardiol*. 2014;63:2438-88	
2. Protocol Synopsis, Inclusion Criteria	IC1. Subject has… 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… echocardiography.	IC1. Subject has… 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… echocardiography and/or invasive hemodynamics.	To be consistent with approved control (CoreValve) Instructions For Use
	IC4. ● If STS <8, subject has…	IC4. ● If STS <8, subject has… ○ Age ≥90 years (Added text)	In-hospital mortality rate of heart valve surgery in patients ≥90 years is >10%*, which is above the 8% risk set for study inclusion. *Assmann A. Interactive CardioVascular Thor Surg 2013;17:340 Speziale G. J Thorac Cardiovasc Surg 2011;141:725 Bridges C. J Am Coll Surg 2003:197:347
2. Protocol Synopsis, Exclusion Criteria	EC6. Subject has severe (≥3+) aortic… EC11. Subject is being treated with chronic anticoagulation therapy other than warfarin. ***Note***: Subjects who require chronic anticoagulation with warfarin must be able to be treated additionally with either aspirin or clopidogrel.	EC6. Subject has severe (4+) aortic… 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. ~~***Note***: Subjects who require chronic anticoagulation with warfarin must be able to be treated additionally with either aspirin or~~	Updated for clarity

Table 27.1-3: Table of Changes for REPRISE III Protocol Version AD (Compared to REPRISE III Protocol Version AC)

Section Modified	Text as Written in REPRISE III Protocol Version AC	Text as Written in REPRISE III Protocol Version AD	Justification for Modification
		~~clopidogrel.~~ (text removed)	
	EC9. Subject has echocardiographic evidence of new intra-cardiac mass, thrombus or vegetation or one requiring treatment.	EC9. Subject has echocardiographic evidence of new intra-cardiac vegetation or intraventricular or paravalvular thrombus.	Some intra-cardiac masses increase risk of TAVR complications whereas others do not; this update clarifies which should be included as exclusion criteria
	EC12. Subject has active peptic ulcer disease or gastrointestinal bleed… within the past 3 months, other clinically…	EC12. Subject has had a gastrointestinal bleed… within the past 3 months, or has other clinically significant bleeding diathesis or coagulopathy that would preclude treatment with required antiplatelet regimen, or will …	Definition of active peptic ulcer disease is considered ambiguous by some centers (i.e., are subjects who are well controlled on medical therapy considered to have the active disease). This modification clarifies this and limits the exclusion to those with increased risk of adverse events.
	EC20. Subject has severe peripheral vascular disease including aneurysm defined as maximal luminal diameter ≥5 cm or with documented presence of thrombus, marked tortuosity, narrowing…	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… or vertebral disease).	Updated text is clearer about conditions that would increase the risk of adverse events.
Table 4.1-1	-	The table was updated with 6 new references.	Provided additional current literature information.
4.1.2	The aforementioned results notwithstanding, TAVR with early	As discussed above, TAVR in patients unsuitable for SAVR has	Provided additional

Table 27.1-3: Table of Changes for REPRISE III Protocol Version AD (Compared to REPRISE III Protocol Version AC)

Section Modified	Text as Written in REPRISE III Protocol Version AC	Text as Written in REPRISE III Protocol Version AD	Justification for Modification
REPRISE I Study	generation devices has been associated with increased stroke risk and vascular complications when compared to surgical valve replacement[64-66]. Cerebrovascular accidents and vascular complications associated with TAVR have been significant predictors of mortality[75,76]. The paravalvular regurgitation more commonly seen with TAVR compared to surgery has also been accompanied by higher early and late mortality[45,65,77]. While careful patient selection may serve to mitigate these risks[87-89], device design improvements such as seen with the Lotus Valve System (Section 5.1) … …subjects with calcified stenotic aortic valves who… To date, data are available through 1 year[81]… The 1-year VARC-1… …and 1 year (5 in Class I, 6 in Class II; P=0.004). The mean… and 15.4±4.6 mmHg at 1 year. Paravalvular… or absent/trivial (10/11) at 1 year…	reduced mortality[14, 73] and treatment of selected patients at high surgical risk has resulted in similar[64] or better[66] survival at 1 year. These results notwithstanding, TAVR with early generation devices has been associated with increased stroke risk and vascular complications when compared to SAVR[64-66], which have been significant predictors of mortality[80,81]. There are also other infrequent but substantial complications that impact long-term outcomes and may limit the use of TAVR in lower risk subjects. Precise valve positioning can be challenging with first-generation devices, and valve misplacement can lead to severe problems, including coronary occlusion and valve embolization[82]. Incomplete apposition of the prosthesis with the native valve can occur in the presence of significant amounts of calcium or with suboptimal implantation, resulting in paravalvular regurgitation[83,84]. This has been associated with increased mortality in several longitudinal registries[45,85,86]. While careful patient selection may serve to mitigate these risks[87-89], device design improvements such as seen with the Lotus Valve System (including the ability to fully reposition and retrieve the valve and a unique adaptive seal to prevent leakage, see Section 5.1)… … subjects with calcific aortic stenosis who… To date, data are available through 2 years[90,92]… The 2-year VARC-1… …and baseline and 2 years (6 in Class I, 5 in Class II; P=0.004). The mean… and 15.4±4.4 mmHg at 2 years. Paravalvular… and absent/trivial (11/11) at 2 years…	current literature information and updated REPRISE I with data from 2 years to include the most current data.
4.1.3 REPRISE II Study	…enrolled 120 subjects at 14 investigative… …shows 6 month[94] clinical... Mortality was 8.4% and the disabling stroke rate was 3.5%. Most subjects (81%) had none/trivial paravalvular aortic regurgitation at 6 months…	…enrolled 120 subjects in the main cohort at 14 investigative… …shows 6 month[94] and 1 year[95] clinical. .. At 1 year, mortality was 11.0% and the disabling stroke rate was 3.5%. The low paravalvular aortic regurgitation rate observed at 30 days was maintained at 1 year as most subjects (86%) had none/trivial paravalvular aortic regurgitation… Table 4.1-3 updated with 1-year data in addition to 6-month data.	Updated with data from 1 year for the main cohort (N=120) and with 30-day data from the full cohort (N=250) to include the most current data available.

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		The REPRISE II study was subsequently expanded to enroll 130 additional subjects in the REPRISE II extended trial cohort at centers in Australia and Europe; enrollment in this extended cohort was completed in April 2014. The main trial cohort and the extended trial cohort had the same overall study design. The main trial cohort received additional neurologic evaluation and annual imaging assessments to determine valve frame integrity. Per the protocol, a statistically powered analysis based on the combined main and extended trial cohorts (full cohort, N=250) was performed for the primary safety endpoint (mortality at 30 days). The primary safety endpoint was analyzed on an intent-to-treat basis (all subjects enrolled, whether or not a study device is implanted). A one-sample z test was used to test the one-sided hypothesis that 30 day all-cause mortality is less than the prespecified PG of 16% (based on an expected rate of 9.8% plus a testing margin of 6.2%). Table 4.1 4 shows device performance endpoints, clinical outcomes, and echocardiographic outcomes through 30 days for the full cohort (N=250)[96]. Outcomes in the full cohort were similar to that reported for the main cohort (see Table 4.1 2) with a mean aortic valve gradient of 11.70±6.77 mmHg. Mortality was 4.4% and the disabling stroke rate was 3.3%. The new PPM implant rate was 29.6%. Reported rates for early conduction abnormalities and the need for PPM implantation after TAVR have ranged from 3% to 8% with SAPIEN and 14% to 40% with CoreValve[97]. In a recent report, 12-month clinical outcomes were similar among subjects with and without periprocedural PPM[98]. Another study (mean follow-up of 22±17 months) found that PPM implantation post TAVR had a negative effect on left ventricular function but was not associated with any increase in overall or cardiovascular death or rehospitalization for heart failure and was a protective factor for the occurrence of sudden or unknown death (P=0.023)[99]. Implantation of a new PPM following TAVR with SAPIEN (retrospective analysis from the combined PARTNER trial and NRCA registry) was associated with a higher rate of repeat hospitalization at 30 days and 1 year	

Table 27.1-3: Table of Changes for REPRISE III Protocol Version AD (Compared to REPRISE III Protocol Version AC)

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		(10.6% vs. 5.9%, P=0.02 at 30 days; 23.9% vs. 18.2%, P=0.05 at 1 year) but not mortality (7.5% vs. 5.8%, P=0.40 at 30 days; 26.3% vs. 20.8%, P=0.08 at 1 year)[100]. There was no severe paravalvular regurgitation and trace/trivial or no paravalvular regurgitation in 85.8% of REPRISE II subjects. Reported moderate or severe aortic regurgitation after TAVR has ranged from 6% to 21%[101] and has been associated with increased mortality in several longitudinal registries[45,59,85,86]. In summary, the observed clinical results are consistent with other TAVR studies and the PVR rates are lower… Table 4.1 4 was added.	
5. Device Description	…both the test and the control device approved for use and commercially available at…	…both the test and the control device. The control device in the planned size must be approved for use and commercially available at…	Updated for clarity
5.2 CoreValve… System (Control)	The control device is the self-expanding CoreValve® Transcatheter Aortic Valve Replacement System (CoreValve), which is an unapproved medical device available to Authorized Prescribers in Australia. It is introduced… ***Note 1***: Every subject… both the test (Lotus) and the control (CoreValve) valve available to Authorized Prescribers at the investigational center where… ***Note 2***: A center…size matrix if it is available, but…	The control device is the commercially available self-expanding CoreValve® Transcatheter Aortic Valve Replacement System (CoreValve) that is introduced… ***Note1***: Every subject… both the test (Lotus) device and the control (CoreValve) device. The CoreValve device in the planned size must be approved for use and commercially available at the investigational center where… ***Note 2***: A center… size matrix if it is approved and commercially available, but…	
5.3.2 Control Device	Information is provided in the IFU supplied with the CoreValve…	Information is provided in the IFU supplied with the commercially available CoreValve…	
7.2 Additional Measurements	• Neurological status… by the following: ○ Neurological physical exam by a neurologist or neurology fellow at discharge and 1 year ***Note 7:*** For subjects diagnosed with a neurological event … a neurological physical exam (conducted by a neurologist or neurology fellow), NIHSS assessment… …If a subject who has not received a study device… within the first 30 days after the index…	• Neurological status… by the following: ○ Neurological physical exam by a neurologist, neurology fellow, neurology physician assistant, or neurology nurse practitioner at discharge and 1 year ***Note 7:*** For subjects diagnosed with a neurological event … a neurological physical exam (conducted by a neurologist, neurology fellow, neurology physician assistant, or neurology nurse practitioner), NIHSS assessment…	Updated for clarity and a correction

Table 27.1-3: Table of Changes for REPRISE III Protocol Version AD (Compared to REPRISE III Protocol Version AC)

Section Modified	Text as Written in REPRISE III Protocol Version AC	Text as Written in REPRISE III Protocol Version AD	Justification for Modification
		…If a subject who has not received a study device… within the first 1 year after the index…	
8.2 Treatment Assignment	Eligible subjects… or the self-expanding CoreValve® Transcatheter Aortic Valve Replacement System (control).	Eligible subjects… or a commercially available self-expanding CoreValve® Transcatheter Aortic Valve Replacement System (control).	Updated for clarity
8.2.1 Treatment	The control device is the CoreValve….	The control device is the commercially available CoreValve…	
Table 9.2-1	IC1. Subject has… 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… echocardiography…	IC1. Subject has… 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… echocardiography and/or invasive hemodynamics.	To be consistent with approved control (CoreValve) Instructions For Use
	IC4. ● If STS <8, subject has…	IC4. ● If STS <8, subject has… ○ Age ≥90 years (Added text)	In-hospital mortality rate of heart valve surgery in patients ≥90 years is >10%*, which is above the 8% risk set for study inclusion. *Assmann A. Interactive CardioVascular Thor Surg 2013;17:340. Speziale G. J Thorac Cardiovasc Surg 2011;141:725. Bridges C. J Am Coll Surg 2003:197:347.
Table 9.3-1	EC6. Subject has severe (≥3+) aortic… EC11. Subject is being treated with chronic anticoagulation therapy other than warfarin. Subject requires chronic anticoagulation therapy (warfarin) and cannot tolerate concomitant therapy with either aspirin or clopidogrel.	EC6. Subject has severe (4+) aortic… 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. ~~***Note***: Subjects who require chronic anticoagulation with warfarin~~	Updated for clarity

Table 27.1-3: Table of Changes for REPRISE III Protocol Version AD (Compared to REPRISE III Protocol Version AC)

Section Modified	Text as Written in REPRISE III Protocol Version AC	Text as Written in REPRISE III Protocol Version AD	Justification for Modification
	Note: Subjects who require chronic anticoagulation with warfarin must be able to be treated additionally with either aspirin or clopidogrel.	~~must be able to be treated additionally with either aspirin or clopidogrel.~~ (text removed)	
	EC9. Subject has echocardiographic evidence of new intra-cardiac mass, thrombus or vegetation or one requiring treatment.	EC9. Subject has echocardiographic evidence of new intra-cardiac vegetation or intraventricular or paravalvular thrombus.	Some intra-cardiac masses increase risk of TAVR complications whereas others do not; this update clarifies which should be exclusion criteria.
	EC12. Subject has active peptic ulcer disease or gastrointestinal bleed… clinically significant bleeding diathesis or coagulopathy or will refuse transfusions.	EC12. Subject has gastrointestinal bleed… clinically significant bleeding diathesis or coagulopathy that would preclude treatment with required antiplatelet regimen, or will refuse transfusions.	Definition of active peptic ulcer disease is considered ambiguous by some centers (i.e., are subjects who are well controlled on medical therapy considered to have the active disease). This modification clarifies this and limits the exclusion to those with increased risk of adverse events.
	EC20. Subject has severe peripheral vascular disease including aneurysm defined as maximal luminal diameter ≥5 cm or with documented presence of thrombus, marked…	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).	Updated text is clearer about conditions that would increase the risk of adverse events.
Figure 11.1-1	Figure says “Heart Rhythm.”	Updated figure to say “Heart Rhythm Strip”	Updated for clarity

Table 27.1-3: Table of Changes for REPRISE III Protocol Version AD (Compared to REPRISE III Protocol Version AC)

Section Modified	Text as Written in REPRISE III Protocol Version AC	Text as Written in REPRISE III Protocol Version AD	Justification for Modification
Table 11.1-1	b: All follow-up dates will be calculated from the date of the index procedure. Visits… d: Neurological physical exam… neurologist or neurology fellow. NIHSS…performed by certified personnel... …If a subject who has not received a study device… within the first 30 days after the index…	b: All follow-up dates will be calculated from the date of the (attempted) index procedure (or randomization in randomized subjects where no implant is attempted). Visits… d: Neurological physical exam… neurologist, neurology fellow, neurology physician assistant, or neurology nurse practitioner. NIHSS…performed by a neurology professional or certified personnel... …If a subject who has not received a study device… within the first 1 year after the index…	Updated for clarity and a correction
	e: All baseline and post-procedure 12-lead …Lotus Valve insertion. Baseline column of the 12-lead ECG[e] row has the following: X Procedure column of the 12-lead ECG[e] row has the following: X[e]	e: All screening and post-procedure 12-lead …study valve insertion (12-lead ECG is not required during the procedure). Removed from the Baseline column of the 12-lead ECG[e] row the following: X Removed from the Procedure column of the 12-lead ECG[e] row the following: X[e] Added a new row labeled "Heart rhythm strip[e]" which has the following in the Procedure column: X[e]	Updated for clarity
	g: Consists of STS score (v2.73), euroSCORE II… i: …on the pre-BAV echocardiographic data.	g: Consists of STS score ~~(v2.73)~~, euroSCORE II… (removed version number) i: …on the pre-BAV echocardiographic data. In such cases, the most recent echocardiogram done prior to the index procedure (even if after BAV) must be submitted to the Echocardiography Core Laboratory to be included in the baseline data.	g: To allow for updated STS score calculator i: Updated for clarity
11.4 Screening Assessments	○ 12-lead electrocardiogram (ECG) at screening and/or baseline must… ○ Risk assessments: STS Score (2.73), euroSCORE II…	○ 12-lead electrocardiogram (ECG) at screening must… ○ Risk assessments: STS Score ~~(2.73)~~, euroSCORE II… (removed version number)	Updated for clarity
	• Frailty, disability, and comorbidity assessments (collected prospectively) O Nutritional assessment ☐Albumin O Body Mass Index…	• Frailty, disability, and comorbidity assessments (collected prospectively) ~~O Nutritional assessment~~ (removed the 2 bullets) ~~☐Albumin~~ O Body Mass Index…	

Table 27.1-3: Table of Changes for REPRISE III Protocol Version AD (Compared to REPRISE III Protocol Version AC)

Section Modified	Text as Written in REPRISE III Protocol Version AC	Text as Written in REPRISE III Protocol Version AD	Justification for Modification
	• Imaging… ○ Within 60 days… pre-BAV echocardiographic data.	• Imaging… ○ Within 60 days… pre-BAV echocardiographic data. In such cases, the most recent echocardiogram done prior to the index procedure (even if after BAV) must be submitted to the Echocardiography Core Laboratory to be included in the baseline data.	
11.5 Baseline Assessments	• Neurological physical… by a neurologist or neurology fellow (see Table 11.1-1)… • NIH …performed by certified personnel (external… • Modified Rankin …performed by certified personnel (external… • Laboratory tests O Complete blood count (CBC) with platelets O Serum creatinine… • 12-lead electrocardiogram (ECG) at screening and/or baseline must be performed…	• Neurological physical… by a neurologist, neurology fellow, neurology physician assistant, or neurology nurse practitioner (see Table 11.1-1)… • NIH …performed by a neurology professional or certified personnel (external… • Modified Rankin …performed by a neurology professional or certified personnel (external… • Laboratory tests O Complete blood count (CBC) with platelets O Albumin O Serum creatinine… ~~• 12-lead electrocardiogram (ECG) at screening and/or baseline must be performed…~~ (removed the bullet) ***Note:*** In cases where a subject who has met the echocardiographic criteria for enrollment receives BAV prior to the index procedure and subsequently no longer meets the REPRISE III aortic valve pressure gradient or EOA criteria, the subject may still be enrolled based on the pre-BAV echocardiographic data. In such cases, the most recent echocardiogram done prior to the index procedure (even if after BAV) must be submitted to the Echocardiography Core Laboratory to be included in the baseline data.	
11.6 Preprocedure Medications	***Note 3***: If a subject requires chronic anticoagulation with warfarin (other anticoagulants are not permitted), either clopidogrel or aspirin is required prior to the implant procedure in addition to the anticoagulant therapy (but both aspirin and clopidogrel are not required). Subjects treated with warfarin	***Note 3***: If a subject requires chronic anticoagulation, either clopidogrel or aspirin is required prior to the implant procedure (but both aspirin and clopidogrel are not required). The subject should not receive a $P2Y_{12}$ inhibitor aside from clopidogrel.	

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	should not be treated with a $P2Y_{12}$ inhibitor other than clopidogrel.		
11.7.1 Medtronic…	A final post-deployment aortogram of the ascending aorta and rotational angiography of the valve frame must be performed…	A final post-deployment aortogram of the ascending aorta must be performed…	Valve frame angiogram is unnecessary as do not expect fracture at procedure.
11.7.1 Medtronic…	• Heart rhythm… recorded	• Heart rhythm… recorded (12-lead ECG is not required)	Updated for clarity
11.7.2.1 Valvuloplasty	Prior to…heart rhythm strip should be obtained.	Prior to…heart rhythm strip should be obtained (12-lead ECG is not required).	
11.7.2.2 Preparing…	8) A final … (including recommended rotational angiography of the valve frame) must be performed… • Heart rhythm… recorded	8) A final … (including ~~recommended~~ rotational angiography of the valve frame, required only for Lotus) must be performed… • Heart rhythm… recorded (12-lead ECG is not required)	The rotational angiography is required for Lotus to allow comparison with required annual assessment; updated heart rhythm bullet for clarity.
11.8 Post-Procedure	○ If a subject requires chronic anticoagulation with warfarin (other anticoagulants are not permitted), either clopidogrel or aspirin is required after the implant procedure in addition to the anticoagulant therapy (but both aspirin and clopidogrel are not required). Subjects treated with warfarin should not be treated with a $P2Y_{12}$ inhibitor other than clopidogrel.	○ If a subject requires chronic anticoagulation, either clopidogrel or aspirin is required after the implant procedure in addition to the anticoagulant therapy (but both aspirin and clopidogrel are not required). The subject must be treated with warfarin (other anticoagulants are not permitted in the first month) and either clopidogrel (other $P2Y_{12}$ inhibitors are not permitted in combination with warfarin) or aspirin for at least 1 month. After 1 month, subjects requiring chronic anticoagulation may be switched from warfarin to a new oral anticoagulant (NOAC) at the discretion of the treating physician. The subject should not receive a $P2Y_{12}$ inhibitor in combination with a NOAC but may be treated with a NOAC plus aspirin.	Updated for clarity
11.9 Prior to Discharge	• Neurological physical… by a neurologist or neurology fellow… • NIH …performed by certified personnel (external...	• Neurological physical… by a neurologist, neurology fellow, neurology physician assistant, or neurology nurse practitioner…	

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	• Modified Rankin …performed by certified personnel (external…	• NIH …performed by a neurology professional or certified personnel (external... • Modified Rankin …performed by a neurology professional or certified personnel (external…	
11.10.1 30-Day	• Modified Rankin …performed by certified personnel (external…	• Modified Rankin …performed by a neurology professional or certified personnel (external…	
11.10.2 6-Month	• Modified Rankin …performed by certified personnel (external…	• Modified Rankin …performed by a neurology professional or certified personnel (external…	
11.10.3 12-Month ...	• Modified Rankin …performed by certified personnel (external... • Neurological physical… by a neurologist or neurology fellow (see Table 11.1-1)… • NIH …performed by certified personnel (external...	• Modified Rankin …performed by a neurology professional or certified personnel (external.. • Neurological physical… by a neurologist, neurology fellow, neurology physician assistant, or neurology nurse practitioner (see Table 11.1-1)... • NIH …performed by a neurology professional or certified personnel (external…	
11.10.4 Annual…	• Modified Rankin …performed by certified personnel (external…	• Modified Rankin …performed by a neurology professional or certified personnel (external…	
12.2.1 Analysis Sets	…For ITT analyses…enrolled in the trial, are randomized, and received a study device, will be included…	…For ITT analyses…enrolled in the trial, and are randomized will be included…	Updated for clarity and correction
12.2.4 Reporting Events	For subjects who have a procedure or an attempted procedure, all events that occur from the date of the (attempted) procedure onward will be reported. For subjects who do not have a (attempted) procedure, events from the date of randomization to 30 days post-randomization will be reported.	For all roll-in subjects, all events that occur from the start of the index procedure will be reported. For all randomized subjects, events from the time of randomization onward will be reported. For randomized subjects who do not have an attempted procedure, events from the date of randomization to 1 year post-randomization will be reported.	
12.3.2 Interim Analyses	No formal interim analyses... for European regulatory agency review after these 300 patients…	No formal interim analyses... for regulatory agency review after these 300 patients…	Updated for clarity
17.4.1 Training with the Lotus…	• Directions for Use: An overview of the current Instructions for Use (IFU) manual.	~~• Directions for Use: An overview of the current Instructions for Use (IFU) manual.~~ (text removed)	Clarification of training.
17.4.2 Role of Boston	…testing required by the protocol. Support may…	…testing required by the protocol. Boston Scientific Corporation is also responsible for ensuring investigators are trained on the	

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Section Modified	Text as Written in REPRISE III Protocol Version AC	Text as Written in REPRISE III Protocol Version AD	Justification for Modification
Scientific…		Directions for Use. Support may…	
19. Potential Risks…	…the PARTNER II trial[119], the CoreValve Extreme Risk Study[75] and…	…the PARTNER II trial[119], the SAPIEN 3 CE Mark study[75], the CoreValve Extreme Risk Study[73] and…	Including most current data.
Table 26.1-1	-	Added the abbreviation "NOAC" – new oral anticoagulant	Updated for clarity
Table 26.2-1 STROKE	Note 4: Modified Rankin Scale assessments should be made by by qualified individuals according to a certification process.	Note 4: Modified Rankin Scale assessments should be made by a neurology professional or by qualified individuals according to a certification process.	
27 Appendices	-	Added Section 27.1-3 and Table 27.1-3	List changes made.

Note: Version AC was a Boston Scientific Corporation (BSC) internal update only; Version AC was not implemented and was not distributed outside of BSC.

Table 27.1-4: Table of Changes for REPRISE III Protocol Version AE (Compared to REPRISE III Protocol Version AD)

Section Modified	Text as Written in REPRISE III Protocol Version AD	Text as Written in REPRISE III Protocol Version AE	Justification for Modification
Page 2	Current Version: 23-Apr-2015	Current Version: 19-Aug-2015 Updated Table of Revision History	Updated for clarity
2. Protocol Synopsis, Test Devices and Sizes	The Lotus Valve System consisting of two… Devices sizes include 23 mm, 25 mm, and 27 mm diameter.	The Lotus Valve System consisting of two… Devices sizes include 21 mm, 23 mm, 25 mm, and 27 mm diameter.	Addition of the 21 mm Lotus Valve to the test matrix and the 23 mm CoreValve Evolut to the control matrix
2. Protocol Synopsis, Control Device and Sizes	Commercially available self-expanding CoreValve® Transcatheter Aortic Valve Replacement System (CoreValve) that is introduced… Devices sizes include 26 mm, 29 mm, and 31 mm diameter.	Commercially available self-expanding CoreValve® Transcatheter Aortic Valve Replacement System (CoreValve) that is introduced… Devices sizes include 23 mm (CoreValve® Evolut™ 23mm), 26 mm, 29 mm, and 31 mm diameter.	
2. Protocol Synopsis, Inclusion Criteria	IC2. Subject has a documented aortic annulus size of ≥20 mm and ≤27 mm…	IC2. Subject has a documented aortic annulus size of ≥18 mm and ≤27 mm…	Smaller valve size can be used with smaller annulus sizes
5.1 Lotus Valve	Device sizes include 23 mm, 25 mm, and 27 mm diameter.	Device sizes include 21 mm, 23 mm, 25 mm, and 27 mm	Addition of the

Table 27.1-4: Table of Changes for REPRISE III Protocol Version AE (Compared to REPRISE III Protocol Version AD)

Section Modified	Text as Written in REPRISE III Protocol Version AD	Text as Written in REPRISE III Protocol Version AE	Justification for Modification
System… (Test)		diameter.	21 mm Lotus Valve to the test matrix and the 23 mm CoreValve Evolut to the control matrix
5.1.1 Lotus Valve	The device is designed to produce a final diameter of 23 mm, 25 mm, or 27 mm… The frame height of all valve sizes in the deployed state is approximately 19 mm.	The device is designed to produce a final diameter of 21 mm, 23 mm, 25 mm, or 27 mm… In the deployed state, the frame height of the 21mm valve is approximately 15 mm; the frame height of the three larger valve sizes is approximately 19 mm.	
5.1.3 Lotus Introducer Set	The Lotus Introducer is suitable for use in subjects requiring the 23 mm valve with femoral artery lumen diameter ≥6.0 mm or…	The Lotus Introducer is suitable for use in subjects requiring the 21 mm or 23 mm valve with femoral artery lumen diameter ≥6.0 mm or…	
5.2 CoreValve …System (Control)	Devices sizes include 26 mm, 29 mm, and 31 mm diameter.	Devices sizes include the CoreValve® Evolut™ 23 mm diameter and the CoreValve 26 mm, 29 mm, and 31 mm diameter.	
5.3.2 Control Device	Information is provided in the IFU supplied with the commercially available CoreValve…	Information is provided in the IFU supplied with the commercially available CoreValve and CoreValve® Evolut™ 23mm …	
Table 9.2-1	IC2. Subject has a documented aortic annulus size of ≥20 mm and ≤27 mm…	IC2. Subject has a documented aortic annulus size of ≥18 mm and ≤27 mm…	Smaller valve size can be used with smaller annulus sizes
11.7.2.2 Preparing…	• Device size (23 mm, 25 mm, or 27 mm) and model	• Device size (21 mm, 23 mm, 25 mm, or 27 mm) and model	Addition of the 21 mm Lotus Valve to the test matrix
27 Appendices	-	Added Section 27.1-4 and Table 27.1-4	List changes made.

Table 27.1-5: Table of Changes for REPRISE III Protocol Version AF (Compared to REPRISE III Protocol Version AE)

Section Modified	Text as Written in REPRISE III Protocol Version AE	Text as Written in REPRISE III Protocol Version AF	Justification for Modification
Page 1 Sponsor:	Boston Scientific Corporation 160 Knowles Drive Los Gatos, CA 95032 USA International Representative Boston Scientific International SA European Headquarters, Paris	Boston Scientific Corporation 300 Boston Scientific Way Marlborough, MA 01752, USA International Representative Boston Scientific Limited Ballybrit Business Park	Updated addresses

Table 27.1-5: Table of Changes for REPRISE III Protocol Version AF (Compared to REPRISE III Protocol Version AE)

Section Modified	Text as Written in REPRISE III Protocol Version AE	Text as Written in REPRISE III Protocol Version AF	Justification for Modification
	55 Av. des Champs Pierreux, TSA 51101 92729 Nanterre Cedex, France	Galway, Ireland	
Page 2	Current Version: 19-Aug-2015	Current Version: 07-Dec-2015 Updated Table of Revision History	Updated for clarity
2. Protocol Synopsis – Control Device and Sizes	Devices sizes include 23 mm (CoreValve® Evolut™ 23mm), 26 mm, 29 mm, and 31 mm diameter. ***Note 1:*** Every subject must be deemed treatable…	Devices sizes include 26 mm, 29 mm, and 31 mm diameter. ***Note 1:*** Every subject in the randomized cohort must be deemed treatable…	
2. Protocol Synopsis – Study Design	REPRISE III is a prospective, multicenter, 2:1 randomized (Lotus Valve System versus a commercially available CoreValve Transcatheter Aortic Valve Replacement System), controlled trial designed to evaluate the safety and effectiveness of the Lotus Valve System for TAVR in symptomatic subjects who have calcific, severe native aortic stenosis and who are at high or extreme risk for surgical aortic valve replacement (SAVR). There will be a non-randomized roll-in phase… Roll-in subjects will not be included in the endpoint analyses. The REPRISE III study will…	REPRISE III is designed to evaluate the safety and effectiveness of the Lotus Valve System for TAVR in symptomatic subjects who have calcific, severe native aortic stenosis and who are at high or extreme risk for surgical aortic valve replacement (SAVR). Study cohorts include the following. – A prospective, multicenter, 2:1 randomized (Lotus Valve System [23 mm, 25 mm, and 27 mm valve sizes] versus a commercially available CoreValve Transcatheter Aortic Valve Replacement System [26 mm, 29 mm, and 31 mm valve sizes]), controlled trial - A non-randomized roll-in phase with only the test device (23 mm, 25 mm, and 27 mm valve sizes) for centers… randomized population. – A non-randomized, nested registry cohort of subjects who will receive the 21 mm Lotus Valve (Lotus 21 mm Nested Registry). Participating centers will be centers that have enrolled subjects in REPRISE III. The REPRISE III study will…	Updated to include the 21mm Nested Registry
2. Protocol Synopsis – Planned Subjects/…	Subjects will be enrolled at up to 60 centers in the United States, Canada, Western Europe, and Australia. There will be up to 1032 subjects in REPRISE III… and randomized.	Subjects will be enrolled at up to 60 centers in the United States, Canada, Western Europe, and Australia. There will be up to 1052 subjects in REPRISE III… and randomized. Up to 20 subjects will be enrolled in the Lotus 21 mm Nested Registry.	
2. Protocol Synopsis – Primary Endpoints	Primary Safety Endpoint: … at 30 days. Primary Effectiveness Endpoint:… at 1 year	Primary Safety Endpoint: … at 30 days. Primary Effectiveness Endpoint:… at 1 year Powered statistical analyses for the primary safety endpoint and the primary effectiveness endpoint will be carried out on the	Updated for clarity

Table 27.1-5: Table of Changes for REPRISE III Protocol Version AF (Compared to REPRISE III Protocol Version AE)

Section Modified	Text as Written in REPRISE III Protocol Version AE	Text as Written in REPRISE III Protocol Version AF	Justification for Modification
		randomized cohort.	
2. Protocol Synopsis – Secondary Endpoint	Moderate or greater paravalvular aortic regurgitation (based on core lab assessment) at 1 year	Moderate or greater paravalvular aortic regurgitation (based on core lab assessment) at 1 year Powered statistical analysis for the secondary endpoint will be carried out on the randomized cohort.	
2. Protocol Synopsis – Inclusion…	IC2. Subject… and is deemed treatable with an available size of both test and control device.	IC2. Subject… and, for the randomized cohort, is deemed treatable with an available size of both test and control device.	
2. Protocol Synopsis – Analysis Sets	As-Treated: This population… For all analysis sets… first valve received.	Analysis sets for the randomized cohort are listed below. As-Treated: This population… For all randomized cohort analysis sets… first valve received. Among the roll-in and the Lotus 21 mm Nested Registry cohorts, for ITT analyses all subjects who sign an Informed Consent Form and are enrolled in the study will be included in the analysis sample, regardless of whether the study device was implanted. The As-Treated population is the same as the Implanted population for these two cohorts and includes all subjects who sign an Informed Consent Form and are implanted with the Lotus valve.	Updated for clarity and to include the Lotus 21 mm Nested Registry cohort.
4.0 Introduction	Additional device information can be found in found in Section 5.	Additional device information can be found in Section 5. Study subjects will be entered into the roll-in cohort, randomized (test versus control) cohort, or a single-arm, non-randomized, nested registry cohort of subjects who receive the 21 mm Lotus Valve (Lotus 21 mm Nested Registry). Additional information on study design can be found in Section 8.	Updated for clarity
4.1.2 REPRISE I Study	To date, data are available through 2 years… There were no additional MACCE events beyond the primary endpoint. The 2-year… was 3/11… resolved… While… baseline and 2 years… The mean… at 2 years. Paravalvular… at 2 years…	To date, data are available through 3 years… There were no additional MACCE events beyond the primary endpoint through 2 years and 1 noncardiovascular death in the interval between 2 and 3 years. The 3-year… was 4/11… resolved, and there was 1 noncardiovascular death due to uncontrolled sepsis. … While… baseline and 2 years… and baseline and 3 years (5 in Class I, 1 in Class II, 2 in Class III; *P*=0.004). The mean… at 2 years, and 15.6±4.4 mmHg at 3 years. Paravalvular… at 2 years and absent	Updated REPRISE I data to 3 years

Table 27.1-5: Table of Changes for REPRISE III Protocol Version AF (Compared to REPRISE III Protocol Version AE)

Section Modified	Text as Written in REPRISE III Protocol Version AE	Text as Written in REPRISE III Protocol Version AF	Justification for Modification
		(7/8) or mild (1/8) at 3 years…	
4.1.3 REPRISE II Study	The 30 day mean aortic valve pressure gradient was… Table 4.1-3 shows 6-month and 1-year clinical… At 1 year, mortality was 11.0% and the disabling stroke rate was 3.5%. The low paravalvular aortic regurgitation rate observed at 30 days was maintained at 1 year as most subjects (86%) had none/trivial paravalvular aortic regurgitation; there was no severe paravalvular regurgitation.. Table 4.1-3 with 6-month and 1-year data for the REPRISE II main cohort (N=120). The REPRISE II study was subsequently expanded… plus a testing margin of 6.2%). Table 4.1 4 shows device performance endpoints, clinical outcomes, and echocardiographic outcomes through 30 days for the full cohort (N=250). Outcomes in the full cohort …several longitudinal registries. Table 4.1-4 with 30-day data for the REPRISE II full cohort (N=250).	The 30 day mean aortic valve pressure gradient was… Table 4.1-3 shows 1-year and 2-year clinical… At 2 years, mortality was 17% and the disabling stroke rate was 3.5%. The low paravalvular aortic regurgitation rate observed at 30 days was maintained at 2 years as most subjects (91%) had none/trivial paravalvular aortic regurgitation and there was no moderate or severe paravalvular regurgitation… Table 4.1-3 updated to show 1-year and 2-year data for the REPRISE II main cohort (N=120). The REPRISE II study was subsequently expanded… plus a testing margin of 6.2%). %). All-cause mortality at 30 days was 4.4% with an upper confidence bound of 6.97% and the primary safety endpoint was met… Table 4.1 4 shows device performance endpoints, clinical outcomes, and echocardiographic outcomes through 30 days and 1 year for the full cohort (N=250. Outcomes at 30 days in the full cohort… several longitudinal registries. Through 1 year, mortality was 12% and the disabling stroke rate was 3.6%. Valve endocarditis (N=2) and thrombosis (N=3) were successfully resolved with antibiotics and anticoagulant therapy, respectively, without sequelae. The low paravalvular aortic regurgitation rate observed at 30 days was maintained at 1 year as most subjects (91%) had none/trivial paravalvular aortic regurgitation and there was no moderate or severe paravalvular regurgitation. Table 4.1-4 updated to include 1-year data for the REPRISE II full cohort (N=250).	Updated REPRISE II main cohort data to 2 years and REPRISE II full cohort data to 1 year
5. Device Description	… Every subject must be deemed…	… Every subject in the randomized cohort must be deemed…	Updated for clarity

Table 27.1-5: Table of Changes for REPRISE III Protocol Version AF (Compared to REPRISE III Protocol Version AE)

Section Modified	Text as Written in REPRISE III Protocol Version AE	Text as Written in REPRISE III Protocol Version AF	Justification for Modification
5.1 Lotus Valve System…	… Device sizes include 21 mm, 23 mm, 25 mm, and 27 mm diameter. More detailed…	… Device sizes used in the randomized cohort include 23 mm, 25 mm, and 27 mm diameter. Devices in the Lotus 21 mm Nested Registry cohort are 21 mm in diameter. More detailed…	Updated to include the Lotus 21 mm Nested Registry
5.2 CoreValve Transcatheter…	Devices sizes include the CoreValve® Evolut™ 23 mm diameter and the CoreValve 26 mm… **Note 1:** Every subject must be deemed treatable…	Devices sizes include the CoreValve 26 mm… **Note 1:** Every subject in the randomized cohort must be deemed treatable…	Updated for clarity; no CoreValve 23 mm device is used.
5.3.2 Control Device	Information… available CoreValve® and CoreValve® Evolut™ 23 mm diameter or…	Information… available CoreValve® or…	
7. Endpoints	Outcomes will be assessed… The ITT analysis population includes…first valve received. Endpoint definitions…	Outcomes will be assessed… The ITT analysis population of the randomized cohort includes …first valve received. Among the roll-in and Lotus 21 mm Nested Registry cohorts, for ITT analyses, all subjects who sign the IRB/IEC-approved study ICF and are enrolled in the trial will be included in the analysis sample, regardless of whether the study device was implanted. For these two cohorts, the as-treated population includes all subjects implanted with the Lotus valve. Endpoint definitions…	Clarify analysis populations for roll-in, randomized, and Lotus 21 mm Nested Registry cohorts.
8.1 Scale and Duration	The REPRISE III clinical study includes a prospective, multicenter, randomized controlled trial … previous experience implanting the Lotus Valve.	The REPRISE III clinical study includes a prospective, multicenter, randomized controlled trial … previous experience implanting the Lotus Valve. There will also be a single-arm, non-randomized nested registry cohort of subjects who receive the 21 mm Lotus Valve to assess safety and effectiveness (Lotus 21 mm Nested Registry); participating centers will be centers that have enrolled subjects in REPRISE III.	Clarification of overall study design.
8.2 Treatment Assignment	Eligible subjects will be randomized… ***Note:*** There will be… numbers.	For the randomized cohort, eligible subjects will be randomized… ***Note:*** There will be… numbers. Subjects receiving the 21 mm Lotus Valve will be enrolled in a non-randomized, nested registry cohort to assess safety and effectiveness.	
8.3 Study Design Justification	There will be up to 1032 subjects in REPRISE III. In order to support… 912 subjects will be randomized and enrolled. Up to 60…	There will be up to 1052 subjects in REPRISE III. In order to support… 912 subjects will be randomized and enrolled, and up to 20 subjects will be enrolled in the Lotus 21 mm Nested Registry. Up to 60…	
9.2 Inclusion Criteria	IC2. Subject… and is deemed…	IC2. Subject … and, for the randomized cohort, is deemed…	Updated for clarity

Table 27.1-5: Table of Changes for REPRISE III Protocol Version AF (Compared to REPRISE III Protocol Version AE)

Section Modified	Text as Written in REPRISE III Protocol Version AE	Text as Written in REPRISE III Protocol Version AF	Justification for Modification
10.1.3 Lotus 21 mm Nested Registry Subjects	—	For the Lotus 21 mm Nested Registry cohort, subjects confirmed eligible for the study by the CRC (see Section 22.2) and who provided written informed consent are considered enrolled in the study as soon as an attempt is made to insert the Lotus Valve System into the subject's femoral artery.	New section added to clarify point of enrollment for the Lotus 21 mm Nested Registry cohort.
11.1 Data Collection	Figure 11.1-1 REPRISE III Study Design	Updated Figure 11.1-1 REPRISE III Study Design to include the 21 mm Nested Registry	Clarify that there will be up to 20 additional subjects enrolled in the study.
11.4 Screening Assessments	The following screening… subject eligibility. Only after CRC approval…	The following screening… subject eligibility. For the randomized cohort, only after CRC approval…	Updated for clarity
12.1 Endpoints	Data from roll-in subjects (up to 120 subjects) will be summarized separately from the randomized population. Roll-in subjects will not be included in the endpoint analyses. Testing of endpoints… 12.1.4 Baseline Comparability Baseline data will be summarized… and separately for the roll-in subjects. … No formal statistical testing will be done for the roll-in subjects. 12.1.5 Post-procedure Measurements … No formal statistical testing will be done for the roll-in subjects.	Data will be summarized separately from subjects in the roll-in (up to 120 subjects), randomized, and Lotus 21 mm Nested Registry populations. Descriptive statistics will be used to summarize the data from subjects in the roll-in and Lotus 21 mm Nested Registry and no statistical inference will be made. In the randomized cohort, testing of endpoints… 12.1.4 Baseline Comparability Baseline data will be summarized… and separately for the roll-in subjects and subjects in the Lotus 21 mm Nested Registry. … No formal statistical testing will be done for the roll-in or Lotus 21 mm Nested Registry subjects. 12.1.5 Post-procedure Measurements … No formal statistical testing will be done for the roll-in or Lotus 21 mm Nested Registry subjects.	Updated for clarity including analyses for Lotus 21 mm Nested Registry cohort.
12.2.1 Analysis Sets	The primary endpoints… and an implanted basis. For ITT analyses… first valve received. The primary safety endpoint…	The primary endpoints… and an implanted basis. Among the randomized cohort, for ITT analyses… first valve received. Among the roll-in and Lotus 21 mm Nested Registry cohorts, for ITT analyses, all subjects who sign the IRB/IEC-approved study ICF and are enrolled in the trial will be included in the analysis sample, regardless of whether the study device was implanted. For these two cohorts, the As-Treated population includes all	

Table 27.1-5: Table of Changes for REPRISE III Protocol Version AF (Compared to REPRISE III Protocol Version AE)

Section Modified	Text as Written in REPRISE III Protocol Version AE	Text as Written in REPRISE III Protocol Version AF	Justification for Modification
		subjects implanted with the Lotus Valve. The As-Treated and Implanted analysis sets are the same for these two cohorts. For the randomized cohort, the primary safety endpoint…	
12.2.4 Reporting Events	For all roll-in subjects, all events… For all randomized…	For all subjects in the roll-in and Lotus 21 mm Nested Registry cohorts, all events… For all randomized…	Updated for clarity
12.3.2 Interim Analyses	… after these 300 patients have completed their 30-day follow-up visits.	… after these 300 subjects have completed their 30-day follow-up visits. An administrative analysis of 30-day data for subjects in the Lotus 21 mm Nested Registry will be performed for regulatory agency review after these subjects have completed their 30-day follow-up visits.	Clarification of interim analyses
19. Potential Risks…	Risks… review of relevant literature, most recently… and the CoreValve High Risk Study.	Risks… review of relevant literature, most recently… the CoreValve High Risk Study[66], and the PORTICO IDE randomized trial/RESOLVE registry/SAVORY registry.	Additional literature reference
21.1 Definitions and Classification	• If complications… protocol-specified definitions. Any AE experienced by the study subject beginning from the time of randomization must be recorded in the eCRF.	• If complications… protocol-specified definitions. For the randomized cohort, event reporting (eCRF) is required beginning from the time of randomization. For the roll-in cohort and the Lotus 21 mm Nested Registry cohort, event reporting (eCRF) is required beginning from the time an attempt is made to insert the Lotus Valve System into the subject's femoral artery.	Clarify timing for the different cohorts.
21.2 Relationship…	The Investigator must assess the relationship of the AE to the study device…	The Investigator must assess the relationship of the AE/SAE to the study device…	Updated for clarity
27.1.5 Protocol Version AE to Version AF	—	Table 27.1-5 lists changes between protocol versions AE and AF. New Table 27.1-5.	Provide list of changes between version AE and version AF.

Note: Version AE was a BSC internal update only and was not implemented.
Abbreviations: BSC=Boston Scientific Corporation; ICF=Informed Consent form; ITT=intent-to-treat; SAE=serious adverse event; TAVR=transcatheter aortic valve replacement

Table 27.1-6: Table of Changes for REPRISE III Protocol Version AG (Compared to REPRISE III Protocol Version AF)

Section Modified	Text as Written in REPRISE III Protocol Version AF	Text as Written in REPRISE III Protocol Version AG	Justification for Modification
Page 2	Current Version: 07-Dec-2015	Current Version: 22-Dec-2015 Updated Table of Revision History	Updated for clarity
2. Protocol Synopsis – Study Design	-	– An additional cohort of subjects who will receive the Lotus Valve (23 mm, 25 mm, and 27 mm valve sizes) beginning after enrollment of the randomized cohort is completed (U.S. Continued Access Study cohort). This cohort will be used to further assess performance and safety. Participating centers will be United States centers that have enrolled subjects in REPRISE III.	Updated to include the U.S. Continued Access study
2. Protocol Synopsis – Planned Subjects/…	Subjects will be enrolled at up to 60 centers in the United States, Canada, Western Europe, and Australia. There will be up to 1032 subjects in REPRISE III… Nested Registry.	Subjects will be enrolled at up to 60 centers in the United States, Canada, Western Europe, and Australia. There will be up to 2052 subjects in REPRISE III… Nested Registry. After enrollment in the randomized cohort is completed, up to 1000 subjects will be enrolled in the U.S. Continued Access Study cohort to receive the Lotus Valve (23 mm, 25 mm, and 27 mm valve sizes); participating centers will be United States centers that have enrolled subjects in REPRISE III.	
2. Protocol Synopsis – Inclusion…	IC2. Subject… control device.	IC2. Subject… control device. For the U.S. Continued Access Study cohort the acceptable aortic annulus size is ≥20 mm and ≤27 mm.	Updated for clarity, the U.S. Continued Access study
2. Protocol Synopsis – Analysis Sets	Among the roll-in and the Lotus 21 mm Nested Registry cohorts, for ITT analyses…	Among the roll-in, Lotus 21 mm Nested Registry, and U.S. Continued Access Study cohorts, for ITT analyses…	Updated to include the U.S. Continued Access study cohort
4.0 Introduction	…Valve (Lotus 21 mm Nested Registry). Additional…	…Valve (Lotus 21 mm Nested Registry), or the U.S. Continued Access Study cohort. Additional…	
5.2 CoreValve Transcatheter…	Devices sizes include the CoreValve® Evolut™ 23 mm diameter and the CoreValve 26 mm… **Note 1:** Every subject must be deemed treatable…	Devices sizes include the CoreValve 26 mm… **Note 1:** Every subject in the randomized cohort must be deemed treatable…	Updated for clarity; no CoreValve 23 mm device is used.
5.3.2 Control Device	Information… available CoreValve® and CoreValve® Evolut™ 23 mm diameter or…	Information… available CoreValve® or…	
7. Endpoints	Outcomes will be assessed… The ITT analysis population includes…first valve received. Endpoint definitions…	Outcomes will be assessed… The ITT analysis population of the randomized cohort includes …first valve received. Among the roll-in and Lotus 21 mm Nested Registry cohorts, for ITT analyses, all subjects who sign the IRB/IEC-approved study ICF	Clarify analysis populations for roll-in, randomized, and Lotus 21 mm Nested

Table 27.1-6: Table of Changes for REPRISE III Protocol Version AG (Compared to REPRISE III Protocol Version AF)

Section Modified	Text as Written in REPRISE III Protocol Version AF	Text as Written in REPRISE III Protocol Version AG	Justification for Modification
		and are enrolled in the trial will be included in the analysis sample, regardless of whether the study device was implanted. For these two cohorts, the as-treated population includes all subjects implanted with the Lotus valve. Endpoint definitions…	Registry cohorts.
8.1 Scale and Duration	… that have enrolled subjects in REPRISE III.	… that have enrolled subjects in REPRISE III. After enrollment of the randomized cohort is completed, an additional cohort of subjects will be enrolled in a U.S. Continued Access Study cohort with the Lotus Valve (23 mm, 25 mm, and 27 mm valve sizes) to further assess performance and safety.	Updated to include the U.S. Continued Access study cohort
8.2 Treatment Assignment	***Note:*** There will be… to assess safety and effectiveness.	***Note:*** There will be… to assess safety and effectiveness. After enrollment of the randomized cohort is completed, subjects will be enrolled in a U.S. Continued Access Study cohort with the Lotus Valve (23 mm, 25 mm, and 27 mm valve sizes) to further assess performance and safety.	
8.3 Study Design Justification	There will be up to 1052 subjects in REPRISE III… Nested Registry. Up to 60… in the study. Safety…	There will be up to 2052 subjects in REPRISE III… Nested Registry, and up to 1000 subjects will be enrolled in the U.S. Continued Access Study cohort. Up to 60… in the study. Centers in the United States that enrolled subjects in the randomized cohort will be eligible to enroll subjects in the U.S. Continued Access Study cohort. Safety…	
9.2 Inclusion Criteria	IC2. Subject… control device.	IC2. Subject … control device. For the U.S. Continued Access Study cohort the acceptable aortic annulus size is ≥20 mm and ≤27 mm.	U.S. Continued Access Study includes only 23mm, 25mm, and 27mm Lotus Valve sizes.
10.1.4 U.S. Continued Access Subjects	—	For the U.S. Continued Access Study cohort, subjects confirmed eligible for the study by the CRC (see Section 22.2) and who provided written informed consent are considered enrolled in the study as soon as an attempt is made to insert the Lotus Valve System into the subject's femoral artery.	New section added to clarify point of enrollment for the U.S. Continued Access Study cohort.
11.1 Data Collection	Figure 11.1-1 REPRISE III Study Design	Updated Figure 11.1-1 REPRISE III Study Design to include the U.S. Continued Access Study.	Clarify that there will be up to 1000 additional subjects

Table 27.1-6: Table of Changes for REPRISE III Protocol Version AG (Compared to REPRISE III Protocol Version AF)

Section Modified	Text as Written in REPRISE III Protocol Version AF	Text as Written in REPRISE III Protocol Version AG	Justification for Modification
			enrolled in the study.
12.1 Endpoints	Data will be summarized separately… Nested Registry populations. Descriptive statistics will be used to summarize the data from subjects in the roll-in and Lotus 21 mm Nested Registry and no statistical inference will be made. 12.1.4 Baseline Comparability Baseline data will be summarized… and separately for the roll-in subjects and subjects in the Lotus 21 mm Nested Registry. … No formal statistical testing will be done for the roll-in or Lotus 21 mm Nested Registry subjects. 12.1.5 Post-procedure Measurements … No formal statistical testing will be done for the roll-in or Lotus 21 mm Nested Registry subjects.	Data will be summarized separately… Nested Registry, and U.S. Continued Access Study populations. Descriptive statistics will be used to summarize the data from subjects in the roll-in, Lotus 21 mm Nested Registry, and U.S. Continued Access Study cohorts and no statistical inference will be made. 12.1.4 Baseline Comparability Baseline data will be summarized… and separately for subjects in the roll-in, Lotus 21 mm Nested Registry, and U.S. Continued Access Study cohorts. … No formal statistical testing will be done for the roll-in, Lotus 21 mm Nested Registry, or U.S. Continued Access Study subjects. 12.1.5 Post-procedure Measurements … No formal statistical testing will be done for the roll-in, Lotus 21 mm Nested Registry, or U.S. Continued Access Study subjects.	Updated for clarity including analyses for U.S. Continued Access Study cohort.
12.1.7 Subgroup Analyses for U.S. Continued Access Study Subjects	—	Primary and pre-specified additional endpoints will be summarized and treatment groups will be compared for the following subgroups of U.S. Continued Access Study subjects. • Gender (male and female) • Extreme risk and high risk (see Table 26.2 1 for definitions of extreme and high operative risk) No adjustments for multiple comparisons will be made. Additional analyses may be performed as appropriate.	
12.2.1 Analysis Sets	Among the roll-in and Lotus 21 mm Nested Registry cohorts, for ITT analyses… For these two cohorts, the As-Treated… same for these two cohorts.	Among the roll-in, Lotus 21 mm Nested Registry, and U.S. Continued Access Study cohorts, for ITT analyses… For these 3 cohorts, the As-Treated… same for these 3 cohorts.	
12.2.4 Reporting Events	For all subjects in the roll-in and Lotus 21 mm Nested Registry cohorts, all events…	For all subjects in the roll-in, Lotus 21 mm Nested Registry, and U.S. Continued Access Study cohorts, all events…	
21.1 Definitions and	For the roll-in cohort and the Lotus 21 mm Nested Registry cohort, event reporting…	For the roll-in, Lotus 21 mm Nested Registry, and U.S. Continued Access Study cohorts, event reporting…	Updated to include the U.S. Continued

Table 27.1-6: Table of Changes for REPRISE III Protocol Version AG (Compared to REPRISE III Protocol Version AF)

Section Modified	Text as Written in REPRISE III Protocol Version AF	Text as Written in REPRISE III Protocol Version AG	Justification for Modification
Classification			Access Study
22.1.2 Data Monitoring Committee	The DMC is responsible for the oversight review of all AEs. The DMC will…	The DMC is responsible for the oversight review of all AEs and all SAEs in the roll-in, randomized, and Lotus 21 mm Nested Registry cohorts. The DMC will…	Updated for clarity
24. Publication Policy	In accordance with the Corporate Policy for the Conduct of Human Subject Research, BSC requires disclosure of its involvement as a sponsor or financial supporter in any publication or presentation relating to a BSC study or its results. In accordance with the Corporate Policy for the Conduct of Human Subject Research, BSC will submit…	In accordance with the Global SOP – Human Subject Data and Research Controls, BSC requires disclosure of its involvement as a sponsor or financial supporter in any publication or presentation relating to a BSC study or its results. In accordance with the Global SOP – Human Subject Data and Research Controls, BSC will submit…	Global SOP replaced Corporate Policy
27.1.6 Protocol Version AF to Version AG	—	Table 27.1-6 lists changes between protocol versions AF and AG. New Table 27.1-6.	Provide list of changes between version AF and version AG.

Abbreviations: BSC=Boston Scientific Corporation; DMC=Data Monitoring Committee; ITT=intent-to-treat; SAE=serious adverse event; SOP=Standard Operating Procedure.

Table 27.1-7: Table of Changes for REPRISE III Protocol Version AH (Compared to REPRISE III Protocol Version AG)

Section Modified	Text as Written in REPRISE III Protocol Version AG	Text as Written in REPRISE III Protocol Version AH	Justification for Modification
Page 2	Current Version: 22-Dec-2015	Current Version: 03-May -2016 Updated Table of Revision History	Updated to include the CT Imaging substudy of the U.S. Continued Access study
2. Protocol Synopsis – Study Design	-An additional... in REPRISE III.	-An additional... in REPRISE III. Selected centers with the ability to perform high quality 4D computed tomography (CT) scans will include U.S. Continued Access Study subjects in a CT Imaging Substudy to assess the prevalence of reduced leaflet mobility and its relationship, if any, to clinical events.	
2. Protocol Synopsis – Planned Subjects/…	Subjects… in REPRISE III.	Subjects… in REPRISE III. Up to 200 of the 1000 subjects enrolled in the U.S. Continued Access Study will be included in a CT Imaging Substudy.	

Table 27.1-7: Table of Changes for REPRISE III Protocol Version AH (Compared to REPRISE III Protocol Version AG)

Section Modified	Text as Written in REPRISE III Protocol Version AG	Text as Written in REPRISE III Protocol Version AH	Justification for Modification
2. Protocol Synopsis – Additional Measurements	… and 5 years.	… and 5 years. Additionally, assessment of leaflet mobility using 4D CT will be carried out at 30 days and 1 year for subjects in the CT Imaging Substudy of the U.S. Continued Access Study. The data will be evaluated by an independent CT core lab.	
2. Protocol Synopsis – Exclusion Criteria	–	Additional exclusion criteria apply for subjects considered for enrollment in the CT Imaging substudy of the U.S. Continued Access Study as listed below: AEC1. Subject has eGFR <30 mL/min (chronic kidney disease stage IV or stage V). AEC2. Subject has atrial fibrillation that cannot be rate controlled to ventricular response rate < 60 bpm. AEC3. Subject is expected to undergo chronic anticoagulation therapy after the TAVR procedure. ***Note*:** Subjects treated with short-term anticoagulation post-procedure can be included in the imaging substudy; in these subjects the 30-day imaging will be performed 30 days after discontinuation of anticoagulation.	
4. Introduction	…or the U.S. Continued Access Study cohort.	…or the U.S. Continued Access Study cohort (which will include a 4D computed tomography [CT] substudy cohort).	
4.1.1 Treatments for Aortic Stenosis	…higher rate of survival at 1 year compared to SAVR. A recently published expert consensus...	…higher rate of survival at 1 year compared to SAVR. Recently, reduced aortic valve leaflet motion, mainly asymptomatic, has been identified with follow-up CT among some TAVR subjects. Therapeutic anticoagulation with warfarin was associated with a decreased incidence and leaflet motion could be restored with anticoagulation. This phenomenon has not been definitively linked with abnormal clinical symptoms. Studies to assess its prevalence and determine any relationship to patient, procedural, or pharmacologic factors or clinical events are ongoing. A recently published expert consensus …	

Table 27.1-7: Table of Changes for REPRISE III Protocol Version AH (Compared to REPRISE III Protocol Version AG)

Section Modified	Text as Written in REPRISE III Protocol Version AG	Text as Written in REPRISE III Protocol Version AH	Justification for Modification
7.2 Additional Measurements	• Resource utilization associated with the procedure and/or follow-up	• Resource utilization associated with the procedure and/or follow-up Additionally, assessment of leaflet thickening and mobility using 4D CT will be carried out at 30 days and 1 year post index procedure for subjects in the CT Imaging Substudy of the U.S. Continued Access Study. The CT scans will be evaluated by an independent CT Core Laboratory and should be blinded to local investigators for cardiac valve findings (local reading should be only for non-cardiac valve findings such as unexpected lung pathology; see Section 11.10.1 for additional information).	
8.1 Scale and Duration	… a U.S. Continued Access Study cohort … to further assess performance and safety. All subjects implanted... Enrolled…	… a U.S. Continued Access Study cohort … to further assess performance and safety. Selected centers with the ability to perform high quality 4D CT scans will include U.S. Continued Access Study subjects in a CT Imaging Substudy to assess the prevalence of reduced leaflet mobility and its relationship, if any, to clinical events. Centers participating in the CT Imaging Substudy should ask all subjects eligible for enrollment in the U.S. Continued Access Study to consider participation in the substudy. Enrollment in the substudy will end after approximately 200 consecutive subjects who provide consent for participation are enrolled. All subjects implanted... Implanted subjects participating in the CT Imaging Substudy will undergo additional 4D CT assessment at 30 days and 1 year. Enrolled…	
8.3 Study Design Justification	There will be up to 2052 subjects in REPRISE III… Centers in the United States that enrolled subjects in the randomized cohort will be eligible to enroll subjects in the U.S. Continued Access Study cohort… safety reporting). In addition to… medications.	There will be up to 2052 subjects in REPRISE III… Centers in the United States that enrolled subjects in the randomized cohort will be eligible to enroll subjects in the U.S. Continued Access Study cohort… safety reporting). Selected centers with the ability to perform high quality 4D CT scans will include approximately 200 U.S. Continued Access Study subjects in a CT Imaging Substudy to assess the prevalence of reduced leaflet mobility and	

Table 27.1-7: Table of Changes for REPRISE III Protocol Version AH (Compared to REPRISE III Protocol Version AG)

Section Modified	Text as Written in REPRISE III Protocol Version AG	Text as Written in REPRISE III Protocol Version AH	Justification for Modification
		its relationship, if any, to clinical events. In addition to…medications.	
9.2 Inclusion Criteria	…provided no exclusion criterion (Table 9.3-1) is met.	…provided no exclusion criterion (Table 9.3-1) is met. Centers participating in the 4D CT substudy of the U.S. Continued Access Study must have the ability to perform high quality 4D CT scans; subjects in this substudy must meet none of the additional exclusion criteria listed in Table 9.3-2.	
9.3 Exclusion Criteria	-	Additional exclusion criteria apply for subjects considered for enrollment in the CT Imaging substudy of the U.S. Continued Access Study as shown in Table 9.3 2. Added Table 9.3-2	
11.1 Data Collection	Figure 11.1-1 REPRISE III Study Design	Updated Figure 11.1-1 REPRISE III Study Design to include the 4D CT assessment at 30 days and 1 year for the CT Imaging substudy	
	Table 11.1-1 Study Event Schedule	Updated Table 11.1-1 Study Event Schedule to include a row for the 4D CT assessment at 30 days and 1 year for the CT Imaging substudy Footnote u: This applies to subjects in the CT Imaging Substudy of the U.S. Continued Access Study. Please refer to the CT Core Laboratory procedure guidelines (see study Manual of Operations). Results must be sent to the CT Core Laboratory (Section 13.3.2).	
11.10.1 30-Day Follow-up	• For subjects… pacemaker dependency.	• For subjects… pacemaker dependency. • For subjects enrolled in the CT Imaging Substudy of the U.S. Continued Access Study, assessment of prosthetic valve leaflet mobility using 4D CT must be performed per the 4D CT Core Laboratory procedure guidelines (see study Manual of Operations). All 4D CT scans for subjects enrolled in the CT Imaging Substudy must be sent to the CT Core Laboratory for independent analyses. **Note:** The CT scans will be read by the CT Core Laboratory and will not be provided to local investigators except as per below. Local reading should be done only for non-cardiac valve findings such as unexpected lung pathology. A study CT scan can be	

Table 27.1-7: Table of Changes for REPRISE III Protocol Version AH (Compared to REPRISE III Protocol Version AG)

Section Modified	Text as Written in REPRISE III Protocol Version AG	Text as Written in REPRISE III Protocol Version AH	Justification for Modification
		unblinded upon investigator request based on any of the following if the event occurs within 2 weeks of the study CT scan. o Any neurological event o Any potential embolic event o Any MI (ST segment elevation MI or non-ST segment elevation MI) o Increase in aortic regurgitation to moderate or severe o A change in echocardiographic parameters including an increase in mean gradient of >10 mmHg or a change in DVI of >0.05. If any of the above events occurs outside of the 2 week window around the study CT scan, the investigator must not be unblinded to the core laboratory assessment of the study CT scan and instead should perform a separate CT scan if clinically indicated. If an additional CT scan is performed for clinical indications, it should be sent to the CT Core Laboratory for analysis.	
11.10.3 12-Month Follow-up	• For subjects… pacemaker dependency.	• For subjects… pacemaker dependency. • For subjects enrolled in the CT Imaging Substudy of the U.S. Continued Access Study, assessment of prosthetic valve leaflet mobility using 4D CT must be performed per the 4D CT Core Laboratory procedure guidelines (see study Manual of Operations). All 4D CT scans for subjects enrolled in the CT Imaging Substudy must be sent to the CT Core Laboratory for independent analyses. **Note:** The CT scans will be read by the CT Core Laboratory and findings will not be provided to local investigators except as noted above. Local reading should be done only for non-cardiac valve findings such as unexpected lung pathology. A study CT scan can be unblinded upon investigator request based on the conditions described in Section 11.10.1 if the event occurs within 2 weeks of the study CT scan.	
13.3.2 CT and Rotational X-Ray…	An independent Core Laboratory… of Operations.	An independent Core Laboratory… of Operations. Data from subjects in the 4D CT Imaging Substudy will also be evaluated by an independent CT Core Laboratory; procedure guidelines for 4D	

Table 27.1-7: Table of Changes for REPRISE III Protocol Version AH (Compared to REPRISE III Protocol Version AG)

Section Modified	Text as Written in REPRISE III Protocol Version AG	Text as Written in REPRISE III Protocol Version AH	Justification for Modification
		CT scanning are provided by the core laboratory in the Manual of Operations	
26.1 Abbreviations	Table 26.1-1	Added abbreviation “eGFR” (estimated glomerular filtration rate)	
27.1.7 Protocol Version AG to Version AH	—	Table 27.1-7 lists changes between protocol versions AG and AH. New Table 27.1-7.	

Abbreviations: BSC=Boston Scientific Corporation; DMC=Data Monitoring Committee; ITT=intent-to-treat; SAE=serious adverse event; SOP=Standard Operating Procedure.

The table below provides a list of changes to the REPRISE III Clinical Investigational Protocol.

Clinical Investigational Plan Revision	**Reason for Update**
AA*	Initial release of clinical study protocol. Version AA was not released to REPRISE III clinical study sites.
AB	Update to correct Sponsor contact address in Europe
AC**	REPRISE III protocol updated to address control device status and use in REPRISE III in Australia
AD	REPRISE III protocol updated for inclusion/exclusion criteria changes and other administrative changes. The clinical DFU was updated to align the 'Inclusion Criteria' and 'Exclusion Criteria' with the revised clinical study protocol.
AE***	REPRISE III protocol updated to add the 21mm Lotus Valve size to the randomized controlled trial.
AF	REPRISE III protocol updated to add a single-arm nested registry for the 21mm Lotus Valve. The clinical DFU was updated to align the 'Inclusion Criteria' and 'Exclusion Criteria' with the revised clinical study protocol.
AG	REPRISE III protocol updated to add a single-arm US Continued Access Study cohort to further assess performance and safety.
AH	REPRISE III protocol updated to add a CT Imaging Substudy to the US Continued Access Study Cohort to assess the prevalence of reduced leaflet mobility and its relationship, if any, to clinical events. The clinical DFU was updated to align the 'Inclusion Criteria' and 'Exclusion Criteria' with the revised clinical study protocol.

* Protocol version AA was not released to REPRISE III clinical study sites.
** Protocol version AC was an internal Boston Scientific update, which was not implemented. Version AC was not submitted to FDA or to any agency.
*** Protocol version AE was released to a single site in Australia (0201, Monash Medical Center). It was approved by the site's Ethics Committee, but was not implemented. Enrollment in the 21mm nested registry was initiated upon the approval of protocol version AF.

Statistical Analysis Plan

Repositionable Percutaneous Replacement of Stenotic Aortic Valve through Implantation of Lotus™ Valve System – Evaluation of Safety and Performance

REPRISE III

Protocol Number: S2282

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TABLE OF CONTENTS

1 PROTOCOL SUMMARY

Objective(s)	To evaluate the safety and effectiveness of the Lotus™ Valve System for transcatheter aortic valve replacement (TAVR) in symptomatic subjects with calcific, severe native aortic stenosis who are considered at extreme or high risk for surgical valve replacement.
Intended Use	The Lotus Valve System is intended to improve aortic valve function for symptomatic subjects with calcific, severe native aortic stenosis who are at extreme or high risk for standard surgical valve replacement.
Test Device and Sizes	The Lotus Valve System consisting of two main components: - a bioprosthetic bovine pericardial aortic valve, and - a delivery system. Devices sizes include 23 mm, 25 mm, and 27 mm diameter.
Control Device and Sizes	Commercially available self-expanding CoreValve® Transcatheter Aortic Valve Replacement System (CoreValve) that is introduced percutaneously via the femoral artery using conventional catheterization techniques (Medtronic, Inc., Minneapolis, MN, USA). Devices sizes include 26 mm, 29 mm, and 31 mm diameter. ***Note 1:*** Every subject must be deemed treatable with an available size of both the test (Lotus) and the control (CoreValve) valve size approved for use and commercially available at the investigational site where the implant procedure is being performed. ***Note 2:*** A center may use the CoreValve® Evolut™ R Recapturable TAVR System with the aforementioned size matrix if it is approved and commercially available, but only if the center no longer has access to CoreValve.
Study Design	REPRISE III is a prospective, multicenter, 2:1 randomized (Lotus Valve System versus a commercially available CoreValve Transcatheter Aortic Valve Replacement System), controlled trial designed to evaluate the safety and effectiveness of the Lotus Valve System for TAVR in symptomatic subjects who have calcific, severe native aortic stenosis and who are at high or extreme risk for surgical aortic valve replacement (SAVR). There will be a non-randomized roll-in phase with only the test device for centers that do not have previous experience implanting the Lotus Valve; each of these centers will perform at least 2 roll-in cases before commencing randomization. Data from roll-in subjects will be summarized separately from the randomized population. Roll-in subjects will not be included in the

	endpoint analyses. The REPRISE III study will be conducted in accordance with the relevant parts of the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practices (GCP) or the International Standard ISO 14155: 2011; ethical principles that have their origins in the Declaration of Helsinki; and pertinent individual country/state/local laws and regulations.
Planned Subjects/ Centers/ Countries	Subjects will be enrolled at up to 60 centers in the United States, Canada, Western Europe, and Australia. There will be up to 1032 subjects in REPRISE III. Up to 120 subjects will be enrolled and included in a roll-in phase (test device only) among centers that do not have previous experience implanting the Lotus Valve (a minimum of 2 roll-in subjects per center) before randomization begins. There will be 912 subjects enrolled and randomized.
Primary Endpoints	Primary Safety Endpoint: 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 Primary Effectiveness Endpoint: Composite of all-cause mortality, disabling stroke, or moderate or greater paravalvular aortic regurgitation (based on core lab assessment) at 1 year
Secondary Endpoint	Moderate or greater paravalvular aortic regurgitation (based on core lab assessment) at 1 year
Additional Measurements	Additional measurements based on the VARC[a,b] endpoints and definitions (see **Note 1** below) will be 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): o Mortality: all-cause, cardiovascular, and non-cardiovascular o Stroke: disabling and non-disabling o Myocardial infarction (MI): periprocedural (≤72 hours post index procedure) and spontaneous (>72 hours post index procedure) o Bleeding: life-threatening (or disabling) and major o Acute kidney injury (≤7 days post index procedure): based on the AKIN System Stage 3 (including renal replacement therapy) or Stage 2 o Major vascular complication o Repeat procedure for valve-related dysfunction (surgical or

	interventional therapy) o Hospitalization for valve-related symptoms or worsening congestive heart failure (NYHA class III or IV) o New permanent pacemaker implantation resulting from new or worsened conduction disturbances o New onset of atrial fibrillation or atrial flutter o Coronary obstruction: periprocedural (≤72 hours post index procedure) o Ventricular septal perforation: periprocedural (≤72 hours post index procedure) o Mitral apparatus damage: periprocedural (≤72 hours post index procedure) o Cardiac tamponade: periprocedural (≤72 hours post index procedure) o Prosthetic aortic valve malpositioning, including valve migration, valve embolization, or ectopic valve deployment o Transcatheter aortic valve (TAV)-in-TAV deployment o Prosthetic aortic valve thrombosis o Prosthetic aortic valve endocarditis • Device Performance endpoints peri- and post-procedure: o Successful vascular access, delivery and deployment of the study valve, and successful retrieval of the delivery system o Successful retrieval of the study valve if retrieval is attempted o Successful repositioning of the study valve if repositioning is attempted (see **Note** 2 below) o Grade of aortic valve regurgitation: paravalvular, central, and combined • 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, 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 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 mm Hg 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; see **Note 3** below) and assessed by an independent core laboratory, including effective orifice area, 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 mm Hg or a peak velocity <3m/sec with no moderate or severe prosthetic valve aortic regurgitation) • For subjects who received a permanent pacemaker related to the index procedure, results of pacemaker interrogation at 30 days and 1 year • Functional status as evaluated by the following: o 5-m gait speed test (at 1 year compared to baseline) o New York Heart Association (NYHA) classification • Neurological status (see **Note 4** below) as determined by the following: o Neurological physical exam at discharge and 1 year (conducted by a neurologist or neurology fellow) o National Institutes of Health Stroke Scale (NIHSS) at discharge and 1 year o Modified Rankin Scale (mRS) at all time points • Health status as evaluated by Kansas City Cardiomyopathy and SF-12 Quality of Life questionnaires at baseline; 1 and 6 months; and 1, 3, and 5 years ***Note 1:*** The most current VARC definitions and endpoints available at the beginning of the trial were used. ***Note 2:*** For the Lotus Valve (test), repositioning may be achieved with partial or full resheathing of the valve. ***Note 3:*** At least 1 echocardiogram must be obtained before discharge or 7 days (whichever comes first); if multiple echocardiographic studies are performed prior to discharge and within 7 days of the procedure, the latest study performed will be used for analysis. ***Note 4:*** For subjects diagnosed with a neurological event (e.g., stroke, transient ischemic attack), a neurological physical exam (conducted by a neurologist or neurology fellow), NIHSS assessment, and mRS must be performed after the event; mRS must also be administered 90±14 days post-neurological event. a: Kappetein AP, *et al*. *J Am Coll Cardiol*. 2012;60:1438 b: Leon M, *et al. J Am Coll Cardiol.* 2011;57:253
Follow-up	All subjects implanted with a test or control device will be assessed at

Schedule	baseline, peri- and post-procedure, at discharge or 7 days post-procedure (whichever comes first), 30 days, 6 months, 1 year, and then annually for up to 5 years post-procedure. Subjects who are enrolled but not implanted with a test or control device at the time of the procedure will be followed for safety through 1 year.
Study Duration	Subjects implanted with a test or control device will be followed for 5 years after the procedure.

2 INTRODUCTION

This statistical plan addresses the planned analyses for the REPRISE III Trial based on the protocol with PDM # 90899936. Specified analyses may be used for scientific presentations and/or manuscripts and may not all be provided to Regulatory Authorities.

3 ENDPOINT ANALYSIS

Testing of endpoints will be carried out in a hierarchal manner in order to ensure the experiment-wise type I error rate is controlled. Testing will be done in three steps with each step needing to reject the null hypothesis in order to proceed to the next step:

1. Test the primary safety endpoint (Section 3.1) and the primary hypothesis of the primary effectiveness endpoint (Section 3.2.1.1). If the null hypothesis for both endpoints is rejected to show non-inferiority of the Lotus group to the CoreValve group, then proceed to step 2.
2. Test the secondary endpoint (Section 3.3); if the null hypothesis is rejected to show superiority of the Lotus group over the CoreValve group, then proceed to step 3.
3. Test the secondary hypothesis of the primary effectiveness endpoint (Section 3.2.1.2).

3.1 Primary Safety Endpoint

3.1.1 Hypotheses

The primary safety endpoint is the composite of all-cause mortality, all stroke, life-threatening and major bleeding events, acute kidney injury (stage 2 or 3), or major vascular complications evaluated at 30 days after the implant procedure. The primary analysis for the primary safety endpoint will be based on the implanted analysis set.

The null and alternative hypotheses for the primary safety endpoint are as follows:

H_0: $P_{S\_Lotus} - P_{S\_Control} \geq \Delta$ (Inferior)

H_1: $P_{S\_Lotus} - P_{S\_Control} < \Delta$ (Non-inferior)

where P_{S_Lotus} and $P_{S\_Control}$ are the rate of primary safety endpoint at 30 days for the Lotus Valve (test) group and the CoreValve group, respectively, and Δ (delta) is the non-inferiority margin.

A Farrington-Manning standardized test will be used to test the one-sided hypothesis of non-inferiority in the difference between the rates of the two treatment groups. If the *P* value from the Farrington-Manning standardized test is <0.025, the primary safety endpoint rate at 30 days for the Lotus Valve will be concluded to be non-inferior to that of the CoreValve rate. This corresponds to the one-sided upper 97.5% confidence bound on the difference in observed rates between treatment groups (Lotus Valve minus CoreValve) in the primary safety endpoint rate at 30 days being less than the non-inferiority margin.

3.1.2 Sample Size

The sample size calculation for the primary safety endpoint at 30 days is based on the following assumptions:

- Expected Lotus Valve (test) rate = 40%
- Expected CoreValve (control) rate = 40%
- Non-inferiority margin (Δ) = 10.5%
- Test significance level (α) = 0.025 (1-sided)
- Test : Control ratio = 2:1
- Expected rate of attrition = 5%

Given enrollment of 912 subjects (608 Lotus Valve, 304 CoreValve) and 5% attrition, there is approximately 85% power to show non-inferiority with the expected rates

3.2 Primary Effectiveness Endpoint

3.2.1 Hypothesis

3.2.1.1 Primary Hypothesis

The primary hypothesis is that the rate of the primary effectiveness endpoint (composite of all-cause mortality, disabling stroke, and moderate or greater paravalvular aortic regurgitation [based on core lab assessment] evaluated at 1 year [365 days]) for the Lotus Valve group is non-inferior to that for the CoreValve group. The primary analysis for the primary hypothesis of the primary effectiveness endpoint will be based on the implanted analysis set.

The null and alternative hypotheses for the primary hypothesis of the primary effectiveness endpoint are as follows:

H_0: $P_{E\_Lotus} - P_{E\_Control} \geq \Delta$ (Inferior)

H_1: $P_{E\_Lotus} - P_{E\_Control} < \Delta$ (Non-inferior)

where P_{E_Lotus} and $P_{E\_Control}$ are the primary effectiveness endpoint rates at 1 year for the Lotus Valve (test) group and the CoreValve group, respectively, and Δ (delta) is the non-inferiority margin.

A Farrington-Manning standardized test will be used to test the one-sided hypothesis of non-inferiority in the difference between the rates of the two treatment groups. If the *P* value from the Farrington-Manning standardized test is <0.025, the primary effectiveness endpoint rate at 1 year for the Lotus Valve will be concluded to be non-inferior to that of the CoreValve rate. This corresponds to the one-sided upper 97.5% confidence bound on the difference in observed rates between treatment groups (Lotus Valve minus CoreValve) in the primary effectiveness endpoint rate at 1 year being less than the non-inferiority margin.

3.2.1.2 Secondary Hypothesis

The secondary statistical hypothesis is that the rate of the primary effectiveness endpoint for the Lotus Valve group is superior to that for the CoreValve group. This test will be carried out only if the null hypothesis from the statistical hypothesis is rejected for all of the primary safety endpoint (Section 3.1), primary hypothesis of the primary effectiveness endpoint (Section 3.2.1.1), and the secondary endpoint (Section 3.3) and the rate for the primary effectiveness endpoint for the Lotus group is less than that of the CoreValve group. The primary analysis for

the secondary hypothesis of the primary effectiveness endpoint will be based on the ITT analysis set.

The null and alternative hypotheses for the secondary hypothesis of the primary effectiveness endpoint are as follows:

H_0: $P_{E\_Lotus} = P_{E\_Control}$

H_1: $P_{E\_Lotus} \neq P_{E\_Control}$

where P_{E_Lotus} and $P_{E\_Control}$ correspond to the rates of the primary effectiveness endpoint for the Lotus Valve group (test) and the CoreValve group (control), respectively.

A chi-square test will be used to test the two-sided hypothesis of superiority between the rates of the two treatment groups. If the *P* value from the chi-squared test is <0.05 and the rate of the Lotus group is less than the rate of the CoreValve, the rate of the primary effectiveness endpoint for the Lotus Valve will be concluded to be superior to the CoreValve. This corresponds to the two-sided upper 95% confidence bound on the difference between treatment groups (Lotus Valve minus CoreValve) for the observed rate of the primary effectiveness endpoint being less than zero.

3.2.2 Sample Size

3.2.2.1 Primary Hypothesis

The sample size calculation for the primary hypothesis of the primary effectiveness endpoint at 1 year is based on the following assumptions:

- Expected Lotus Valve (test) rate = 32%
- Expected CoreValve rate = 32%
- Non-inferiority margin (Δ) = 9.5%
- Test significance level (α) = 0.025 (1-sided)
- Test : Control ratio = 2:1
- Power ($1-\beta$) = 80%
- Total number of evaluable subjects = 819
- Expected rate of attrition = 10%

Given the above assumptions, the planned enrollment is 912 subjects (608 Lotus Valve, 304 CoreValve).

3.2.2.2 Secondary Hypothesis

The sample size calculation for the secondary hypothesis of the primary effectiveness endpoint at 1 year is based on the following assumptions:

- Expected Lotus Valve (test) rate = 22%
- Expected CoreValve rate = 32%
- Test significance level (α) = 0.05 (2-sided)

- Test : Control ratio = 2:1
- Expected rate of attrition = 10%

Given enrollment of 912 subjects (608 Lotus Valve, 304 CoreValve) and 10% attrition, there is approximately 86% power to show superiority with the given expected rates.

3.3 Secondary Endpoint

3.3.1 Hypothesis

The statistical hypothesis is that the secondary endpoint of moderate or greater paravalvular aortic regurgitation (AR) rate at 1 year (based on review by an independent core lab) for the Lotus Valve is superior to that for the CoreValve group. The primary analysis for the secondary endpoint will be based on the ITT analysis set.

To control for experiment-wise type I error, testing for the secondary endpoint will be conducted only if the null hypotheses for the primary safety and the primary analysis of the primary effectiveness endpoints are rejected. That is, non-inferiority must be shown for the primary safety endpoint and the primary effectiveness endpoint for testing to be conducted for the secondary endpoint.

The null and alternative hypotheses for the secondary endpoint are as follows:

H_0: $P_{AR\_Lotus} = P_{AR\_Control}$

H_1: $P_{AR\_Lotus} \neq P_{AR\_Control}$

where P_{AR_Lotus} and $P_{AR\_Control}$ correspond to the moderate or greater paravalvular aortic regurgitation rates at 1 year for the Lotus Valve group (test) and the CoreValve group (control), respectively.

A chi-square test will be used to test the two-sided hypothesis of superiority between the rates of the two treatment groups. If the *P* value from the chi-square test is <0.05 and the rate of the Lotus group is less than the rate of the CoreValve group, the rate of the secondary endpoint for the Lotus Valve will be concluded to be superior to the CoreValve rate. This corresponds to the two-sided upper 95% confidence bound on the difference between treatment groups (Lotus Valve minus CoreValve) for the observed rate of the secondary endpoint being less than zero.

3.3.2 Sample Size

The sample size calculation for the secondary endpoint (moderate or greater paravalvular aortic regurgitation rate at 1 year) is based on the following assumptions.

- Expected Lotus Valve (test) rate $P_{AR\_Lotus} = 1.1\%$
- Expected CoreValve (control) rate $P_{AR\_Control} = 5.3\%$
- Test significance level (α) = 0.05 (2-sided)
- Test : Control ratio = 2:1
- Expected rate of attrition = 25%

Given enrollment of 912 subjects (608 Lotus Valve, 304 CoreValve) and 25% attrition, there is approximately 86% power to show superiority with the given expected rates.

3.4 Statistical Methods for the Primary Effectiveness, Primary Safety, and Secondary Endpoints

3.4.1 Non-Inferiority Testing

The following methodology will be used for the non-inferiority testing of the primary safety endpoint and the primary hypothesis of the primary effectiveness endpoint.

All subjects who are enrolled will be eligible for evaluation. The primary safety and effectiveness endpoints will be analyzed for patients in the ITT, as-treated, and implanted analysis sets.

If the *P* value from the one-sided Farrington-Manning test comparing the treatment groups is <0.025, the Lotus group will be concluded to be non-inferior to the CoreValve group. This corresponds to the one-sided upper 97.5% confidence bound for the difference in rates (Lotus – CoreValve) being less than the non-inferiority margin (Δ). That is,

$$(p_{Lotus}\text{-}p_{Control}) + Z_{0.025}\tilde{\sigma}_{MLE} < \Delta$$

where

$$\tilde{\sigma}^2_{MLE} = \frac{\tilde{p}_{Lotus}(1\text{-}\tilde{p}_{Lotus})}{n_{Lotus}} + \frac{\tilde{p}_{Control}(1\text{-}\tilde{p}_{Control})}{n_{Control}}$$

$$\tilde{p}_{Lotus} = 2u\cos(w)\text{-}b/3a$$

$$\tilde{p}_{Control} = \tilde{p}_{Lotus}\text{-}\Delta$$

$$w = \frac{\pi + cos^{-1}(v/u^3)}{3}$$

$$v = \frac{b^3}{27a^3}\text{-}\frac{bc}{6a^2} + \frac{d}{2a}$$

$$u = sign(v)\sqrt{\frac{b^2}{9a^2}\text{-}\frac{c}{3a}}$$

$$a = 1 + R$$

$$b = \text{-}(1 + R + p_{Lotus} + Rp_{Control} + R\Delta + 2\Delta)$$

$$c = \Delta^2 + \Delta(2p_{Lotus} + R + 1) + p_{Lotus} + Rp_{Control}$$

$$d = \text{-}p_{Lotus}\Delta(1 + \Delta)$$

$$R = n_{Control} / n_{Lotus}$$

and p_{Lotus} is the observed rate of primary safety endpoint at 30 days (primary effectiveness endpoint at 30 days) for Lotus patients,

$p_{Control}$ is the observed rate of primary safety endpoint at 30 days (primary effectiveness endpoint at 1 year) for CoreValve patients,

n_{Lotus} is the number of Lotus patients evaluated for primary effectiveness endpoint at 30 days (primary safety endpoint at 1 year),

$n_{Control}$ is the number of CoreValve patients evaluated for primary effectiveness endpoint at 30 days (primary safety endpoint at 1 year), and

$Z_{0.025}$ is upper 2.5th percentile of the standard normal distribution.

The test statistic for the Farrington-Manning test is

$$Z = \frac{(p_{Lotus} - p_{Control}) - \Delta}{\tilde{\sigma}_{MLE}}.$$

A sensitivity analysis (e.g. tipping-point analysis) will be performed to assess the impact of subjects not evaluable for the primary safety and effectiveness endpoints and to assess the robustness of the conclusion of the primary analysis. Assuming no loss to follow-up and given the observed number of patients with primary safety endpoint/primary effectiveness endpoint evaluable for both treatment groups, for all combinations of success/failure for patients with missing data, the endpoints will be evaluated until the point at which the conclusion of the study changes. For each endpoint, a plot with the number of patients with missing values for the Lotus group on the x-axis and the number of patients with missing values for the CoreValve group on y-axis will be provided. There will be shaded regions on the plot which represent the cases where the p-value from the test of non-inferiority is <0.025 and ≥0.025 to demonstrate which combinations of successes and failures among the patients missing data change the conclusion of the study.

3.4.2 Superiority Testing

The following methodology will be used for the superiority testing of the secondary hypothesis of the primary effectiveness endpoint and the secondary endpoint.

All subjects who are enrolled will be eligible for evaluation. The primary effectiveness and secondary endpoints will be analyzed for patients in the ITT, as-treated, and implanted analysis sets.

If the *P* value from the chi-square test comparing the treatment groups is <0.05 and the Lotus group has lower rate than the CoreValve group, the Lotus group will be concluded to be superior to the CoreValve group. This corresponds to the two-sided upper 95% confidence bound for the difference in rates (Lotus – CoreValve) being less than zero. That is,

$$(p_{Lotus} - p_{Control}) + z_{0.025}\sigma_{MLE} < 0$$

where

$$\sigma^2_{MLE} = \frac{p_{Lotus}(1-p_{Lotus})}{n_{Lotus}} + \frac{p_{Control}(1-p_{Control})}{n_{Control}}$$

and p_{Lotus} is the observed rate for Lotus patients,

$p_{Control}$ is the observed rate for CoreValve patients,

n_{Lotus} is the number of Lotus patients evaluated for the endpoint,

$n_{Control}$ is the number of CoreValve patients evaluated the endpoint,
σ^2_{MLE} is the variance from the Pearson chi-square test, and
$z_{0.025}$ is upper 2.5th percentile of the standard normal distribution.

A sensitivity analysis (e.g. tipping-point analysis) will be performed to assess the impact of subjects not evaluable for the primary effectiveness and secondary endpoints and to assess the robustness of the conclusion of the primary analysis. Assuming no loss to follow-up and given the observed number of patients with primary effectiveness endpoint/secondary evaluable for both treatment groups, for all combinations of success/failure for patients with missing data, the endpoints will be evaluated until the point at which the conclusion of the study changes. For each endpoint, a plot with the number of patients with missing values for the Lotus group on the x-axis and the number of patients with missing values for the CoreValve group on y-axis will be provided. There will be shaded regions on the plot which represent the cases where the p-value from the test of non-inferiority is <0.025 and ≥0.025 to demonstrate which combinations of successes and failures among the patients missing data change the conclusion of the study.

4 GENERAL STATISTICAL METHODS

4.1 Description of Statistical Methods

Descriptive statistics will be presented on the trial results by treatment group for randomized patients and separately for roll-in patients. For continuous variables, summaries will include the sample size (N), mean, standard deviation, minimum, and maximum. Frequency tables will be used to summarize discrete variables. Treatment groups will be compared for randomized patients using the chi-square test or Fisher's exact test for binary variables and Student's t-test for continuous variables. Alpha-adjustments for multiple comparisons on the additional measures will not be used. The Kaplan-Meier product-limit method will be used to determine rates for time-to-event endpoints. Adverse event and SAE rates will be reported.

4.2 Analysis Sets

The primary safety endpoint, primary effectiveness endpoint, and all additional endpoints up to 1 year will be analyzed on an intent-to-treat (ITT), as-treated, and implanted basis. After 1-year, all analyses will be based on the safety analysis set.

For the ITT analysis set, all subjects who sign the written ICF and are enrolled in the study will be included in the analysis sample, regardless of whether or not the study device was implanted. The primary analysis for the superiority testing of the second hypothesis of the primary effectiveness endpoint and the secondary endpoint will be based on the ITT analysis set.

For the as-treated analysis set, all ITT subjects who received a study device will be included in this analysis sample and analyzed based on the treatment actually received. For example, if a subject is assigned to receive a test device but instead receives a control device, that subject will be considered a control subject for the as-treated analyses of implant subgroups. Note that if a

subject receives 2 valves, the subject is assigned to the group corresponding to the first valve received.

For the implanted analysis set, all ITT subjects who have the assigned study device implanted will be included in the analysis sample. The primary analysis for the primary safety endpoint and primary effectiveness endpoint will be based on the implanted analysis set.

For the safety analysis set, all ITT subjects who have a study device implanted regardless of the device and treatment assignment will be included in the analysis sample.

4.3 Eligibility of Subjects, Exclusions, and Missing Data

All subjects who are enrolled will be eligible for evaluation. Handling of dropouts and missing data will depend on their frequency and the nature of the outcome measure. The distribution of prognostic factors between subjects with and without data will be examined. Methods to eliminate or minimize bias will be implemented and are described in Section 4.4. Statistical models that account for censored data will be employed in appropriate circumstances (e.g., for time-to-event outcomes). Sensitivity analyses for the primary safety, primary effectiveness, and secondary endpoints, described in Section 3.4, will be conducted to assess the impact of different assumptions on interpretation of the results. Outlier values will be evaluated for their validity. Suspected invalid data will be queried and corrected in the database prior to statistical analysis.

When calculating rates of adverse events, missing and partial dates will be handled as shown below:

Partial Date Description	**Action Taken**
Entire onset date is missing	The procedure date will be used for the onset date.
The month and the day of the month are missing but the year is available	January 1 will be used for the month and day of the onset date. However, if the imputed date falls before the procedure date, then the procedure date will be used for the onset date.
Day is missing, but the month and year are available	The 1st will be used as the day of the onset date. However, if the imputed date falls before the procedure date, then the procedure date will be used for the onset date.

4.4 Control of Systematic Error/Bias

All subjects who have met the inclusion/exclusion criteria (including a positive recommendation from the Case Review Committee) and have signed the ICF will be eligible for enrollment in the study. The center heart team's assessment of transthoracic echocardiography (TTE) measurements before device placement will then determine subject eligibility for the study.

To control for inter-observer variability, an Echocardiography Core Laboratory will independently analyze echocardiography images collected for each subject during the study. Echocardiographic data obtained from the core laboratory will be used for analyses.

An independent Core Laboratory will centrally assess all CT's and rotational X-ray data for all patients to reduce variability. These analyses will minimize bias and inconsistencies by providing an independent interpretation of all measurements using standard techniques. Angiographic data obtained from the core laboratory will be used for analyses.

Similarly, an Electrocardiography Core Laboratory will independently analyze protocol-required 12-lead ECGs performed for each subject. Data obtained from the ECG core laboratory will be used for analyses.

5 ADDITIONAL DATA ANALYSES

5.1 Other Endpoints/Measurements

5.1.1 Additional Measures

Additional measurements based on the VARC endpoints and definitions (see **Note 1** below) will be 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 (see **Note 2** below) adjudicated by an independent Clinical Events Committee (CEC; Section 7.7):
  - 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 System 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 CHF (NYHA class III or IV)
  - New permanent pacemaker implantation resulting from new or worsened conduction disturbances (definitions in Table 26.2-1 of the protocol; see **Note 3** below)
  - 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 (see **Note 4** below)
  - Grade of aortic valve regurgitation: paravalvular, central and combined; the overall distribution of paravalvular aortic regurgitation (none, trace/trivial, mild, moderate, severe) will be determined as well as the percentage of subjects who have moderate or severe paravalvular regurgitation and the percentage of subjects who have mild, moderate or severe paravalvular regurgitation
- 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 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 mm Hg 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; see **Note 5** below) and assessed by an independent core laboratory, including effective orifice area, mean and peak aortic gradients, peak aortic velocity, and grade of aortic regurgitation (see **Note 6** below).
- 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 mm Hg 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)
  - New York Heart Association (NYHA) classification
- Neurological status (see **Note 7** below) as determined by the following:
  - Neurological physical exam by a neurologist or neurology fellow 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
- Resource utilization associated with the procedure and/or follow-up.

Note 1: The most current VARC definitions and endpoints available at the beginning of the trial were used.

Note 2: The VARC-2 safety composite at 30 days includes all-cause mortality, all stroke (disabling and non-disabling), life-threatening bleeding, acute kidney injury (Stage 2 or 3), coronary artery obstruction requiring intervention, major vascular complication, and repeat procedure for valve-related dysfunction. The VARC-2 time-related valve safety composite includes structural valve deterioration (valve-related dysfunction requiring repeat procedure [TAVR or SAVR]), prosthetic valve endocarditis, prosthetic valve thrombosis, thromboembolic events (e.g., stroke), and VARC bleeding (unless clearly unrelated to valve therapy based on investigator assessment)

Note 3: Clinical indications for permanent pacemaker implantation are outlined in the ACCF/AHA/HRS Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities. Permanent pacemaker implantation should generally be performed only for accepted Class I indications.

Note 4: For the Lotus Valve System, repositioning may be achieved with partial or full resheathing of the valve; the proportion of subjects with partial valve resheathing and full valve resheathing will be determined.

Note 5: At least 1 echocardiogram must be obtained before discharge or 7 days (whichever comes first); if multiple echocardiographic studies are performed prior to discharge and within 7 days of the procedure, the latest study performed will be used for analysis.

Note 6: The VARC-2 clinical efficacy composite (after 30 days) includes all-cause mortality, all stroke, required hospitalization for valve-related symptoms or worsening CHF (NYHA class III or IV), and prosthetic heart valve dysfunction (mean aortic valve gradient ≥20 mmHg, effective orifice area ≤0.9-1.1 cm and/or Doppler velocity index [DVI] <0.35, AND/OR moderate or severe prosthetic valve aortic regurgitation [per VARC definition]). The need for hospitalization associated with valve-related symptoms or worsening CHF serves as a basis for calculation of a "days alive outside the hospital" endpoint. This includes heart failure, angina, or syncope due to aortic valve disease requiring intervention or intensified medical management; clinical symptoms of CHF with objective signs including pulmonary edema, hypoperfusion, or documented volume overload AND administration of intravenous diuresis or inotropic therapy, performance of aortic valvuloplasty, institution of mechanical support (intra-aortic balloon pump or ventilation for pulmonary edema), or hemodialysis for volume overload; clear documentation of anginal symptoms AND no clinical evidence that angina was related to coronary artery disease or acute coronary syndrome; documented loss of consciousness not related to seizure or tachyarrhythmia.

Note 7: For subjects diagnosed with a neurological event (e.g., stroke, transient ischemic attack), a neurological physical exam (conducted by a neurologist or neurology fellow), NIHSS assessment, and mRS must be performed after the event. Additionally, mRS must be administered at 90±14 days post-neurological event (see Table 11.1-1 of the protocol). If a subject who has not received a study device (investigational or control) experiences a neurological event within the first 30 days after the index procedure, mRS must be performed on that subject after the event and at 90±14 days post-neurological event and the results must be reported to the Sponsor.

Data will be summarized as described in Section 4.1.

5.2 Interim Analyses

There are no planned interim analyses for stopping the trial early for effectiveness or futility. An administrative analysis based on 30-day data for the first 300 randomized (ITT) patients will be performed for European regulatory purposes after these 300 patients have completed their 30-day follow-up visits. This analysis will be conducted by a statistician independent to BSC.

Hypothesis testing for French Ministry of Health submission:
Aortic regurgitation rate (including both central and paravalvular regurgitation) as assessed by the echo core lab at 30 days for the Lotus Valve group is superior to that for the CoreValve group for implanted patients in the first 300 randomized patients.

The null and alternative hypotheses for the 30-day aortic regurgitation rate are as follows:

H_0: $P_{30Day\ AR\_Lotus} = P_{30Day\ AR\_Control}$

H_1: $P_{30Day\ AR\_Lotus} \neq P_{30Day\ AR\_Control}$

where $P_{30Day\ AR\_Lotus}$ and $P_{30Day\ AR\_Control}$ correspond to the rates of moderate or greater aortic regurgitation at 30 days for the Lotus Valve group (test) and the CoreValve group (control), respectively.

Sample Size Parameters for this 30-day aortic regurgitation rate analysis:

- Expected Lotus Valve (test) rate $P_{30Day\ AR\_Lotus}$ = 1.2%
- Expected CoreValve (control) rate $P_{30Day\ AR\_Control}$ = 12.0% (average from CoreValve IDE HR and ER data)
- Test significance level (α) = 0.05 (2-sided)
- Test : Control ratio = 2 : 1
- Power (1-β) = 0.91
- Number of evaluable subjects to detect 90% relative reduction = 240 (160 test and 80 control)
- Expected rate of attrition = 20%
- Number of subjects randomized = 300

If the *P* value from the chi-square test is <0.05, and the aortic regurgitation rate at 30 days for the Lotus Valve group is less than the rate of the CoreValve group, the aortic regurgitation rate at 30 days for the Lotus Valve group will be concluded to be superior to that of the CoreValve group.

Other testing

The following 30-day endpoints will be compared between the Lotus and CoreValve groups for the first 300 randomized (ITT) patients: all-cause mortality, disabling stroke, major bleeding events, and major vascular complications.

5.3 Subgroup Analyses

Subgroup analyses will be performed in the following subgroups:

- gender (male, female)
- surgical risk (high, extreme)
- region (North America, outside North America)

No adjustments for multiple comparisons will be made. Additional analyses may be performed as appropriate.

5.4 Justification of Pooling

The analyses will be presented using data pooled across regions, surgical risk (high or extreme) as well as by center for the primary safety, primary effectiveness, and secondary endpoints. An assessment of the poolability of subjects across centers, regions, and surgical risk group will be made using logistic regression to determine if there is a relationship between each factor and the primary safety, primary effectiveness, and secondary endpoints.

Main effects for the factor (site, region, surgical risk group) and treatment and the interaction of the factor by treatment will be included in separate logistic regression models with primary safety, /primary effectiveness, and secondary endpoints as the outcome. If the p-value for the coefficient for the factor by treatment interaction is ≥0.15, it can be concluded that the treatment effect is not significantly different across the different levels of the factor, and the data can be pooled across that factor.

In the analysis to justify pooling across centers, the centers with fewer than 6 subjects enrolled in the study will be combined into "virtual centers" based on geographic region so that "virtual centers" have ≥6 subjects in the study but no more than the largest enrolling center.

5.5 Multivariable Analyses

Univariate and multivariate analyses will be performed to assess the effect of potential predictors on the primary safety, primary effectiveness, and secondary endpoints.

Univariate and multivariate analyses will be performed to assess possible predictors of the primary safety, primary effectiveness, and secondary endpoints. Possible predictors (see below) will be modeled univariately; factors from the univariate models with p≤0.20 will also be modeled multivariately using a stepwise procedure in a logistic regression model. The significance level thresholds for entry and exit of independent variables into the multivariate model will be set at 0.1.

From the final models, predictors will be listed in ascending order of p-value. Univariate analyses will be performed overall as well as separately for each treatment group for randomized patients.

The following variables will be analyzed as possible predictors of primary safety, primary effectiveness, and secondary endpoints:

Category	Possible Predictors
Treatment	Group (CoreValve=0, Lotus=1)
Demographics	Sex, age, race (Caucasian)

Category	Possible Predictors
Baseline Characteristics	STS score, EuroSCORE, CHF, previous TIA or CVA, history of renal disease, medically-treated diabetes, hyperlipidemia, hypertension, current smoking at baseline, history of COPD, history of CAD, history of MI, history of CHF, prior balloon aortic valvuloplasty, history of atrial fibrillation, 5‑meter walk >6 seconds, Katz ADL score of 3/6 or less, body mass index <21, wheelchair bound, unable to live independently
Baseline Echocardiographic Characteristics (Core Lab)	LVEF, aortic valve area, mean pressure gradient, , Doppler velocity index
Baseline Computed Tomography (CT) (Core Lab)	Annulus area, LVOT area, annular calcification, LVOT calcification
Peri-Procedural Variables	Ratio of pre-dilation balloon diameter to annulus diameter (derived from area), post-dilation performed, repositioning performed, retrieval performed

5.6 Other Analyses

5.6.1 Baseline Characteristics

Baseline data will be summarized to assess subject demographics, clinical history, risk factors, and pre-procedure characteristics. Data will be summarized as described in Section 4.1.

5.6.2 Post-Procedure Endpoints

Post-procedure information will be collected at regularly scheduled follow-up examinations as detailed in the clinical trial schedule in the protocol. Data will be summarized as described in Section 4.1.

5.6.3 Subject Disposition

Subject disposition (e.g., number completing the study, number lost-to-follow-up) will be summarized with frequency tables.

5.6.4 Time-to-Event Methods

The Kaplan-Meier product-limit method will be used to estimate event rates for time-to-event endpoints. Kaplan-Meier plots of time-to-event endpoints will be constructed.

5.7 Changes to Planned Analyses

Any changes to the planned statistical analyses made prior to performing the analyses will be documented in an amended statistical analysis plan approved before performing the analyses.

Changes from the planned statistical methods after performing the analyses will be documented in the clinical study report along with a reason for the deviation.

6 Validation

All clinical data reports generated per this plan will follow the Global WI: Clinical Data Reporting Validation (PDM 90702587).

7 Programming Considerations

7.1 Statistical Software

Statistical data review will be performed by the sponsor. Statistical analyses will be performed using SAS System software, version 9.2 or later (Copyright © 2000 SAS Institute Inc., SAS Campus Drive, Cary, North Carolina 27513, USA. All rights reserved).

7.2 Format of Output

Results of analysis will be output programmatically to Word documents from SAS with no manual intervention. All output for the final statistical report will be in the form of a Word document containing tables, figures, graphs, and listings, as appropriate.

7.3 Rules and Definitions for Calculated Variables

7.3.1 Transthoracic Echocardiographic (TTE) Variables

Transthoracic echocardiograms will be assessed at each of the following visits: screening, 1 day post-procedure, discharge or 7 days post-procedure (whichever comes first), 30 days, 6 months, and then annually for up to 5 years post-procedure.

One transthoracic echocardiographic study will be performed for each visit. If multiple transthoracic echocardiographic studies are performed for the same visit, the latest study performed for each visit will be used for analysis.

7.3.1.1 Body Mass Index (BMI)

Valid Data Sources

- Assessment Form (Weight, Weight unit, Height, Height unit)
- Diss_FU_Assessment Form (Weight, Weight unit, Height, Height unit)

Valid Data Points

- Weight
- Weight unit
- Height
- Height unit

Analysis approach: Body Mass Index is calculated for each visit.

Weight (Kg) = Weight (lbs) / 2.20462262.
Height (cm) = Height (in) / 0.393700787

$$BMI = \frac{Weight\,(Kg) \times 10000}{\left(Height\,(cm)\right)^2}$$

7.3.1.2 Body Surface Area (BSA)

Valid Data Sources

- Assessment Form (Weight, Weight unit, Height, Height unit)
- Diss_FU_Assessment Form (Weight, Weight unit, Height, Height unit)

Valid Data Points

- Weight
- Weight unit
- Height
- Height unit

Analysis approach: Body Surface Area (BSA) is calculated using the following formula:

$$BSA(m^2) = \sqrt{(Height\,(cm)\,x\,Weight(Kg))/3600}$$

7.3.1.3 Indexed Aortic Valve Area (iAVA) or Indexed Effective Orifice Area (iEOA).

Effective Orifice Area (EOA) is synonymous with Aortic Valve Area (AVA). Both terms will be used in this SAP to easily follow either the protocol or the CRFs as reference documents.

Valid Data Sources

- Assessment Form (Weight, Weight unit, Height, Height unit)
- Diss_FU_Assessment Form (Weight, Weight unit, Height, Height unit)
- Echo Core Lab Form (AVA [TVI])

Valid Data Points

- Weight, Weight unit, Height, Height unit
- AVA (TVI)

Analysis approach:

Indexed Aortic Valve Area (iAVA) or Indexed Effective Orifice Area (iEOA) is calculated for each visit.

$$iAVA(cm2/m2) = iEOA(cm^2/m2) = AVA\ (TVI)\ (cm^2) / BSA\ (m^2),$$

where AVA (TVI) is the aortic valve area for a specific visit and BSA is the body surface area (calculated in Section 7.3.1.2) for the same specific visit under analysis.

7.3.2 ECG Variables

The following algorithm will be used to determine the ECG diagnosis codes for each time-point and subject.

If baseline ECG, then is ECG interpretable?

If No, then:

Rhythm/AV Conduction Abnormalities = Uninterpretable
IV Conduction Abnormalities = Uninterpretable
New Major ST-T Abnormalities = Uninterpretable

If Yes, then:

Rhythm/AV Conduction Abnormalities = 1.1, 1.2, 1.3, 1.4
IV Conduction Abnormalities = 2.1, 2.2, 2.3, 2.4
New Major ST-T Abnormalities = 4.1, 4.2, 4.3, 4.4

If not baseline ECG, then is ECG interpretable?

If No, then:

Rhythm/AV Conduction Abnormalities = Uninterpretable
IV Conduction Abnormalities = Uninterpretable
New Major ST-T Abnormalities = Uninterpretable

If Yes, then:

If No change is checked, then
Rhythm, IV Conduction, Major ST-T = their values from the most recent interpretable ECG

If No change is not checked, then

- Is a New Rhythm/AV Conduction Abnormality?
  - If Yes, then Rhythm = 1.1, 1.2, 1.3, 1.4
  - If No, then Rhythm = their values from the most recent interpretable ECG
- Is a New IV Conduction Abnormality?
  - If Yes, then IV Conduction = 2.1, 2.2, 2.3, 2.4

        - If No, then IV Conduction = their values from the most recent interpretable ECG
    - Is a New Major ST-T Abnormality?
        - If Yes, then Major ST-T = 4.1, 4.2, 4.3, 4.4
        - If No, then IV Conduction = their values from the most recent interpretable ECG.

7.3.3 Days to Last Follow-up

Valid Data Sources

- Adverse Event Form
- Hospitalization Form
- Procedure Form
- Date of Visit Form
- CEC data.

Valid Data Points

- Adverse event date is "Onset date" from the Adverse Event Form.
- Admission and Discharge dates are "Admission date" and "Discharge date" from the Hospitalization Form.
- Index procedure date is "Date of Procedure" from the Procedure Form.
- Follow-up visit date is "Date of Visit" from the Date of Visit Form at each of the visits (discharge or 7 days post-procedure, 30 days, 6 months, and 1 to 5 years post index procedure).
- CEC event date – date of event as adjudicated by the CEC.

Last follow-up date will be the latest of the following dates for each subject:

adverse event onset date,
admission and discharge dates from hospitalization,
index procedure date,
discharge or follow-up visit date, and
CEC event date.

Day 0 is the index procedure date.

Days to last follow-up = last follow-up date - index procedure date.

Days to (event or last known status) = (event or status) date – index procedure date.

7.3.4 Variable "Days alive outside the hospital"

Valid Data Sources

- Adverse Event Form.

- Hospitalization Form.
- Procedure Form.
- Date of Visit Form
- End of Study Form.

Analysis approach: Days alive outside the hospital is calculated for each visit.

$$Days\ alive\ within\ the\ hospital = \sum_{\substack{All\ Hospitalizations\ through \\ the\ visit\ under\ study}} (Dischage\ date - Admission\ date),$$

$$Days\ alive\ outside\ the\ hospital = Days\ to\ last\ \ follow\ up - Days\ alive\ within\ the\ hospital,$$

where *Days to last follow-up* is calculated as described in Section 7.3.3 at each visit under study.

7.3.5 Event Rates

7.3.5.1 Time-to-event Endpoints

This section describes the calculation of events for the safety endpoints adjudicated by the CEC as described in Section 7.7. Time-to-event safety endpoints are events that can occur at any time during the course of the study, for example all-cause mortality. For time-to-endpoints, the date of the event is expected to be known and the days from the index procedure can be calculated. In some cases, the exact date of the event will not be known however partial information should be available, e.g. missing date of month. Binary endpoints measured at pre-specified intervals during the study do not count as time-to-events endpoints. Examples of non-time-to-event binary endpoints are NYHA Class II at 30 days and aortic regurgitation at 12 months.

For the calculation of event rates for the primary safety, primary effectiveness, and secondary endpoints, see Sections 7.4, 7.5, and 7.6, respectively.

Binary event rates will be calculated only up to 1 year. After 1 year, events rates for time-to-event endpoints will be calculated using the Kaplan-Meier product-limit method.

The calculation of binary rates to 1 year will be the same for any endpoint and time point in regards to the appropriate numbers of days as indicated below in Table 1. As an example, for 30 days, the event must have occurred within 30 days of procedure (maximum days to event from procedure in Table 1) and the subject must have ≥ 23 days of follow-up (days for adequate follow-up from procedure in Table 1).

Table 1. Days Post-procedure to Event and for Adequate Follow-up.

Follow-up Visit	Maximum Days to Event from Procedure*	Days for Adequate Follow-up from Procedure**
30 Days	30	23
6 Months	180	150
12 Months	365	335
2 Years	730	

Follow-up Visit	Maximum Days to Event from Procedure*	Days for Adequate Follow-up from Procedure**
3 Years	1095	
4 Years	1460	
5 Years	1825	

* Target date for the follow-up visit.
** Start of the follow-up visit window. Not used after the 12-month follow-up

Rates in this section are described for all analysis sets. If the variable is calculated based on the ITT analysis set, "all subjects" refers to all subjects enrolled. If the variable is calculated based on the as-treated, implanted or safety analysis set, "all subjects" refers to all subjects within the respective analysis set.

Binary event rates (proportions) are calculated on a per subject basis.

All events through discharge or 7 days post-procedure (whichever comes first) are considered in-hospital. Event rates through discharge or 7 days post-procedure (whichever comes first) are calculated as the proportion of subjects who experience the specified event from index procedure through day of discharge or 7 days post-procedure (whichever comes first) out of all subjects in the analysis set.

Event rates through a follow-up visit through 1 year are calculated using the following for inclusion in the denominator and numerator:

- Denominator:

  Subjects in the analysis set count in the denominator with one of the following:

  - ***Subject experiences any CEC adjudicated event from Section 7.7 ≤ maximum number of days as specified in Table 1, or***
  - ***date of last follow-up ≥ days for adequate follow-up post-procedure from Table 1:***

- Numerator:

  Subjects in the analysis set count in the numerator if the subject experiences specified event ≤ maximum number of days as specified in Table 1.

Event rates from a previous visit to a current follow-up visit date are calculated as the proportion of "subjects in the analysis set who experience the specified event after the maximum number of days in the previous visit and through the maximum number of days of the current follow-up visit as specified in Table 1" out of "all subjects in the analysis set who have adequate follow-up as specified in Table 1 or have experienced the specified event in the time interval".

7.3.5.2 Other Binomial Endpoints

Binomial endpoints that are not time based will be presented as binary rates. Such endpoints include any binary measures that collected at baseline or at pre-specified intervals during the study such, for example medically-treated diabetes at baseline and NYHA Class II at 30 days.

For categorical variables, "unknown" and "not evaluated" responses and missing values will not be counted in rate denominators.

7.4 Calculation of Primary Safety Endpoint Rate

The Primary Safety Endpoint of all-cause mortality, all stroke, acute kidney injury (stage 2 or 3), life-threatening and major bleeding, and major vascular complications at 30 days is calculated on an ITT, as-treated, and implanted basis.

Valid Data Sources

- Procedure Form (Procedure date)
- CEC Adjudication Forms at 30 days (death, stroke, kidney injury stage 2 or 3, life-threatening or major bleeding, major vascular complication)
- Case report forms (CRFs) used in determining length of follow-up (see Section 7.3.3).

Valid Data Points

- Date of procedure.
- Date of death.
- Date of any stroke
- Date of acute kidney injury (stage 2 or 3)
- Date of life-threatening or major bleeding
- Date of major vascular complication
- Date of last follow-up (Section 7.3.3).

Analysis approach

- Denominator:

  Subjects in the analysis set count in the denominator with one of the following:

  - ***date of death ≤30 days post-procedure,***
  - ***date of any stroke ≤ 30 post-procedure,***
  - ***date of acute kidney injury (stage 2 or 3) ≤ 30 post-procedure,***
  - ***date of life-threatening or major bleeding ≤ 30 post-procedure,***
  - ***date of major vascular complications ≤ 30 post-procedure, or***
  - ***date of last follow-up ≥23 days post-procedure:***

- Numerator

  Subjects in the analysis set count in the numerator with <u>one</u> of the following:

  - ***Subject experiences death ≤30 days post-procedure,***
  - ***Subject experiences any stroke ≤ 30 post-procedure,***
  - ***Subject experiences acute kidney injury (stage 2 or 3) ≤ 30 post-procedure,***
  - ***Subject experiences life-threatening or major bleeding ≤ 30 post-procedure, or***
  - ***Subject experiences major vascular complication ≤ 30 post-procedure.***

Note that events occurring >30 days within the visit window of 30+7 days will not be included in the endpoint analysis.

7.5 Calculation of Primary Effectiveness Endpoint Rate

The Primary Effectiveness Endpoint of all-cause mortality, disabling stroke, and moderate or severe paravalvular aortic regurgitation (core lab assessment) at 12 months is calculated on an ITT, as-treated, and implanted basis.

Valid Data Sources

- Procedure Form (Procedure date)
- CEC Adjudication Forms at 1 year (Death, Disabling Stroke)
- Echocardiography Forms at 6 months and 1 year (Aortic Regurgitation)
- Case report forms (CRFs) used in determining length of follow-up (see Section 7.3.3).

Valid Data Points

- Date of procedure.
- Date of death.
- Date of disabling stroke
- Moderate or greater paravalvular aortic regurgitation present or not from the 12-month echocardiography form (use 6-month echocardiography form if aortic regurgitation is missing at 12 months or there is no 12 month echocardiography form and the patient has not died ≤365 days post-procedure).
- Date of last follow-up (Section 7.3.3).

Analysis approach

- Denominator:

  Subjects in the analysis set count in the denominator with <u>both</u> of the following:

  - ***Yes or No for moderate or greater paravalvular aortic regurgitation on the 12-month echocardiography form (or Yes or No for moderate or greater paravalvular aortic regurgitation on the 6-month echocardiography form when paravalvular aortic regurgitation is missing on the 12-month echocardiography form or the 12-month echocardiography is missing and the patient has not died ≤365 days post-procedure), and***
  - one of the following:
    - ***date of death ≤365 days post-procedure,***
    - ***date of disabling stroke ≤365 post-procedure, or***
    - ***date of last follow-up ≥335 days post-procedure.***

- Numerator

  Subjects in the analysis set count in the numerator with <u>one</u> of the following:

- ***Subject experiences death ≤365 days post-procedure,***
- ***Subject experiences disabling stroke ≤365 post-procedure, or***
- ***Subject has Yes for moderate or greater paravalvular aortic regurgitation on the 12-month echocardiography form (or Yes for moderate or greater paravalvular aortic regurgitation on the 6-month echocardiography form when paravalvular aortic regurgitation is missing on the 12-month echocardiography form or the 12-month echocardiography is missing and the patient has not died ≤365 days post-procedure)***

Note that deaths or disabling strokes occurring >365 days within the visit window of 365+45 days will not be included in the endpoint analysis.

7.6 Calculation of Secondary Endpoint Rate

The Secondary Endpoint of moderate or greater paravalvular aortic regurgitation (core lab assessment) at 12 months is calculated on an ITT, as-treated, and implanted basis.

Valid Data Sources

- Echocardiography Forms at 6 months and 1 year (Aortic Regurgitation).

Valid Data Points

- Moderate or greater paravalvular aortic regurgitation present or not from the 12-month echocardiography form (use 6-month echocardiography form if aortic regurgitation is missing at 12 months or there is no 12 month echocardiography form and the patient has not died ≤365 days post-procedure).

Analysis approach

- Denominator:

  Subjects in the analysis set count in the denominator with the following:

  - ***Yes or No for moderate or greater paravalvular aortic regurgitation on the 12-month echocardiography form (or Yes or No for moderate or greater paravalvular aortic regurgitation on the 6-month echocardiography form when paravalvular aortic regurgitation is missing on the 12-month echocardiography form or the 12-month echocardiography is missing and the patient has not died ≤365 days post-procedure).***

- Numerator

  Subjects in the analysis set count in the numerator with the following:

  - ***Subject has Yes for moderate or greater paravalvular aortic regurgitation on the 12-month echocardiography form (or Yes for moderate or greater paravalvular aortic regurgitation on the 6-month echocardiography form when paravalvular aortic regurgitation is missing on the 12-month echocardiography form or the 12-month echocardiography is missing and the patient has not died ≤365 days post-procedure)***

7.7 Clinical Events Committee (CEC)

A CEC will be used in this study. A CEC is an independent group of individuals with pertinent expertise that reviews and adjudicates important endpoints and relevant adverse events reported by study Investigators.

CEC events to be reported are:

- 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 System 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 CHF (NYHA class III or IV)
- New permanent pacemaker implantation resulting from new or worsened conduction disturbances (definitions in Table 26.2-1 of the protocol)
- 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

CEC periprocedural events are events that occur ≤72 hours after index procedure. The CEC will make the final adjudication and classification of all events mentioned above per the CEC charter, and the CEC determinations will supersede the site-reported data in all analyses of the events mentioned above.

7.8 Analysis of Site-Reported Serious and Non-Serious Adverse Events

Subject-based event rates will be calculated at various time points based on all events reported by the site regardless of whether or not they are ultimately adjudicated by the CEC. Rates will be calculated on an ITT basis through 1 year and on a safety basis from 2 years through the 5-year follow-up.

Non-Serious Adverse Events will be reported from the time of enrollment through 1-year follow-up.

Serious Adverse Events will be reported from the time of enrollment through termination of the study.

Statistical Analysis Plan

Repositionable Percutaneous Replacement of Stenotic Aortic Valve through Implantation of Lotus™ Valve System – Evaluation of Safety and Performance

REPRISE III

Protocol Number: S2282

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TABLE OF CONTENTS

1 PROTOCOL SUMMARY

Objective(s)	To evaluate the safety and effectiveness of the Lotus™ Valve System for transcatheter aortic valve replacement (TAVR) in symptomatic subjects with calcific, severe native aortic stenosis who are considered at extreme or high risk for surgical valve replacement.
Intended Use	The Lotus Valve System is intended to improve aortic valve function for symptomatic subjects with calcific, severe native aortic stenosis who are at extreme or high risk for standard surgical valve replacement.
Test Device and Sizes	The Lotus Valve System consisting of two main components: - a bioprosthetic bovine pericardial aortic valve, and - a delivery system. Devices sizes include 23 mm, 25 mm, and 27 mm diameter.
Control Device and Sizes	Commercially available self-expanding CoreValve® Transcatheter Aortic Valve Replacement System (CoreValve) that is introduced percutaneously via the femoral artery using conventional catheterization techniques (Medtronic, Inc., Minneapolis, MN, USA). Devices sizes include 26 mm, 29 mm, and 31 mm diameter. ***Note 1:*** Every subject must be deemed treatable with an available size of both the test (Lotus) and the control (CoreValve) device. The CoreValve device in the planned size must be approved for use and commercially available at the investigational center where the implant procedure is being performed. ***Note 2:*** A center may use the CoreValve® Evolut™ R Recapturable TAVR System with the aforementioned size matrix if it is approved and commercially available, but only if the center no longer has access to CoreValve.
Study Design	REPRISE III is a prospective, multicenter, 2:1 randomized (Lotus Valve System versus a commercially available CoreValve Transcatheter Aortic Valve Replacement System), controlled trial designed to evaluate the safety and effectiveness of the Lotus Valve System for TAVR in symptomatic subjects who have calcific, severe native aortic stenosis and who are at high or extreme risk for surgical aortic valve replacement (SAVR). There will be a non-randomized roll-in phase with only the test device for centers that do not have previous experience implanting the Lotus Valve; each of these centers will perform at least 2 roll-in cases before commencing randomization. Data from roll-in subjects will be summarized separately

	from the randomized population. Roll-in subjects will not be included in the endpoint analyses. The REPRISE III study will be conducted in accordance with the relevant parts of the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practices (GCP) or the International Standard ISO 14155: 2011; ethical principles that have their origins in the Declaration of Helsinki; and pertinent individual country/state/local laws and regulations.
Planned Subjects/ Centers/ Countries	Subjects will be enrolled at up to 60 centers in the United States, Canada, Western Europe, and Australia. There will be up to 1032 subjects in REPRISE III. Up to 120 subjects will be enrolled and included in a roll-in phase (test device only) among centers that do not have previous experience implanting the Lotus Valve (a minimum of 2 roll-in subjects per center) before randomization begins. There will be 912 subjects enrolled and randomized.
Primary Endpoints	Primary Safety Endpoint: 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 Primary Effectiveness Endpoint: Composite of all-cause mortality, disabling stroke, or moderate or greater paravalvular aortic regurgitation (based on core lab assessment) at 1 year
Secondary Endpoint	Moderate or greater paravalvular aortic regurgitation (based on core lab assessment) at 1 year
Additional Measurements	Additional measurements based on the VARC[a,b] endpoints and definitions (see **Note 1** below) will be 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): o Mortality: all-cause, cardiovascular, and non-cardiovascular o Stroke: disabling and non-disabling o Myocardial infarction (MI): periprocedural (≤72 hours post index procedure) and spontaneous (>72 hours post index procedure) o Bleeding: life-threatening (or disabling) and major o Acute kidney injury (≤7 days post index procedure): based on the AKIN System Stage 3 (including renal replacement therapy) or Stage 2 o Major vascular complication

	○ Repeat procedure for valve-related dysfunction (surgical or interventional therapy) ○ Hospitalization for valve-related symptoms or worsening congestive heart failure (NYHA class III or IV) ○ New permanent pacemaker 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 (see **Note** 2 below) ○ Grade of aortic valve regurgitation: paravalvular, central, and combined • 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, 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 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 mm Hg 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; see **Note 3** below) and assessed

	by an independent core laboratory, including effective orifice area, 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 mm Hg or a peak velocity <3m/sec with no moderate or severe prosthetic valve aortic regurgitation) • For subjects who received a permanent pacemaker related to the index procedure, results of pacemaker interrogation at 30 days and 1 year • Functional status as evaluated by the following: o 5-m gait speed test (at 1 year compared to baseline) o New York Heart Association (NYHA) classification • Neurological status (see **Note 4** below) as determined by the following: o Neurological physical exam at discharge and 1 year (conducted by a neurologist, neurology fellow, neurology physician assistant, or neurology nurse practitioner) o National Institutes of Health Stroke Scale (NIHSS) at discharge and 1 year o Modified Rankin Scale (mRS) at all time points • Health status as evaluated by Kansas City Cardiomyopathy and SF-12 Quality of Life questionnaires at baseline; 1 and 6 months; and 1, 3, and 5 years ***Note 1:*** The most current VARC definitions and endpoints available at the beginning of the trial were used. ***Note 2:*** For the Lotus Valve (test), repositioning may be achieved with partial or full resheathing of the valve. ***Note 3:*** At least 1 echocardiogram must be obtained before discharge or 7 days (whichever comes first); if multiple echocardiographic studies are performed prior to discharge and within 7 days of the procedure, the latest study performed will be used for analysis. ***Note 4:*** For subjects diagnosed with a neurological event (e.g., stroke, transient ischemic attack), a neurological physical exam (conducted by a neurologist, neurology fellow, neurology physician assistant, or neurology nurse practitioner), NIHSS assessment, and mRS must be performed after the event; mRS must also be administered 90±14 days post-neurological event. a: Kappetein AP, *et al*. *J Am Coll Cardiol*. 2012;60:1438

	b: Leon M, *et al. J Am Coll Cardiol.* 2011;57:253
Follow-up Schedule	All subjects implanted with a test or control device will be assessed at baseline, peri- and post-procedure, at discharge or 7 days post-procedure (whichever comes first), 30 days, 6 months, 1 year, and then annually for up to 5 years post-procedure. Subjects who are enrolled but not implanted with a test or control device at the time of the procedure will be followed for safety through 1 year.
Study Duration	Subjects implanted with a test or control device will be followed for 5 years after the procedure.

2 INTRODUCTION

This statistical plan addresses the planned analyses for the REPRISE III Trial based on the protocol with PDM # 90899936. Specified analyses may be used for scientific presentations and/or manuscripts and may not all be provided to Regulatory Authorities.

3 ENDPOINT ANALYSIS

Testing of endpoints will be carried out in a hierarchal manner in order to ensure the experiment-wise type I error rate is controlled. Testing will be done in three steps with each step needing to reject the null hypothesis in order to proceed to the next step:

1. Test the primary safety endpoint (Section 3.1) and the primary hypothesis of the primary effectiveness endpoint (Section 3.2.1.1). If the null hypothesis for both endpoints is rejected to show non-inferiority of the Lotus group to the CoreValve group, then proceed to step 2.
2. Test the secondary endpoint (Section 3.3); if the null hypothesis is rejected to show superiority of the Lotus group over the CoreValve group, then proceed to step 3.
3. Test the secondary hypothesis of the primary effectiveness endpoint (Section 3.2.1.2).

3.1 Primary Safety Endpoint

3.1.1 Hypotheses

The primary safety endpoint is the composite of all-cause mortality, all stroke, life-threatening and major bleeding events, acute kidney injury (stage 2 or 3), or major vascular complications evaluated at 30 days after the implant procedure. The primary analysis for the primary safety endpoint will be based on the implanted analysis set.

The null and alternative hypotheses for the primary safety endpoint are as follows:

H_0: $P_{S\_Lotus} - P_{S\_Control} \geq \Delta$ (Inferior)

H_1: $P_{S\_Lotus} - P_{S\_Control} < \Delta$ (Non-inferior)

where P_{S_Lotus} and $P_{S\_Control}$ are the rate of primary safety endpoint at 30 days for the Lotus Valve (test) group and the CoreValve group, respectively, and Δ (delta) is the non-inferiority margin.

A Farrington-Manning standardized test will be used to test the one-sided hypothesis of non-inferiority in the difference between the rates of the two treatment groups. If the *P* value from the Farrington-Manning standardized test is <0.025, the primary safety endpoint rate at 30 days for the Lotus Valve will be concluded to be non-inferior to that of the CoreValve rate. This corresponds to the one-sided upper 97.5% confidence bound on the difference in observed rates between treatment groups (Lotus Valve minus CoreValve) in the primary safety endpoint rate at 30 days being less than the non-inferiority margin.

3.1.2 Sample Size

The sample size calculation for the primary safety endpoint at 30 days is based on the following assumptions:

- Expected Lotus Valve (test) rate = 40%
- Expected CoreValve (control) rate = 40%
- Non-inferiority margin (Δ) = 10.5%
- Test significance level (α) = 0.025 (1-sided)
- Test : Control ratio = 2:1
- Expected rate of attrition = 5%

Given enrollment of 912 subjects (608 Lotus Valve, 304 CoreValve) and 5% attrition, there is approximately 85% power to show non-inferiority with the expected rates

3.2 Primary Effectiveness Endpoint

3.2.1 Hypothesis

3.2.1.1 Primary Hypothesis

The primary hypothesis is that the rate of the primary effectiveness endpoint (composite of all-cause mortality, disabling stroke, and moderate or greater paravalvular aortic regurgitation* [based on core lab assessment] evaluated at 1 year [365 days]) for the Lotus Valve group is non-inferior to that for the CoreValve group. The primary analysis for the primary hypothesis of the primary effectiveness endpoint will be based on the implanted analysis set.

The null and alternative hypotheses for the primary hypothesis of the primary effectiveness endpoint are as follows:

H_0: $P_{E\_Lotus} - P_{E\_Control} \geq \Delta$ (Inferior)

H_1: $P_{E\_Lotus} - P_{E\_Control} < \Delta$ (Non-inferior)

where P_{E_Lotus} and $P_{E\_Control}$ are the primary effectiveness endpoint rates at 1 year for the Lotus Valve (test) group and the CoreValve group, respectively, and Δ (delta) is the non-inferiority margin.

A Farrington-Manning standardized test will be used to test the one-sided hypothesis of non-inferiority in the difference between the rates of the two treatment groups. If the *P* value from the Farrington-Manning standardized test is <0.025, the primary effectiveness endpoint rate at 1 year for the Lotus Valve will be concluded to be non-inferior to that of the CoreValve rate. This corresponds to the one-sided upper 97.5% confidence bound on the difference in observed rates between treatment groups (Lotus Valve minus CoreValve) in the primary effectiveness endpoint rate at 1 year being less than the non-inferiority margin.

***Note:** Moderate or greater indicates a regurgitation grade of moderate or severe.

3.2.1.2 Secondary Hypothesis

The secondary statistical hypothesis is that the rate of the primary effectiveness endpoint for the Lotus Valve group is superior to that for the CoreValve group. This test will be carried out only if the null hypothesis from the statistical hypothesis is rejected for all of the primary safety endpoint (Section 3.1), primary hypothesis of the primary effectiveness endpoint (Section 3.2.1.1), and the secondary endpoint (Section 3.3) and the rate for the primary effectiveness endpoint for the Lotus group is less than that of the CoreValve group. The primary analysis for

the secondary hypothesis of the primary effectiveness endpoint will be based on the ITT analysis set.

The null and alternative hypotheses for the secondary hypothesis of the primary effectiveness endpoint are as follows:

H_0: $P_{E\_Lotus} = P_{E\_Control}$

H_1: $P_{E\_Lotus} \neq P_{E\_Control}$

where P_{E_Lotus} and $P_{E\_Control}$ correspond to the rates of the primary effectiveness endpoint for the Lotus Valve group (test) and the CoreValve group (control), respectively.

A chi-square test will be used to test the two-sided hypothesis of superiority between the rates of the two treatment groups. If the *P* value from the chi-square test is <0.05 and the rate of the Lotus group is less than the rate of the CoreValve group, the rate of the primary effectiveness endpoint for the Lotus Valve will be concluded to be superior to the CoreValve. This corresponds to the two-sided upper 95% confidence bound on the difference between treatment groups (Lotus Valve minus CoreValve) for the observed rate of the primary effectiveness endpoint being less than zero.

3.2.2 Sample Size

3.2.2.1 Primary Hypothesis

The sample size calculation for the primary hypothesis of the primary effectiveness endpoint at 1 year is based on the following assumptions:

- Expected Lotus Valve (test) rate = 32%
- Expected CoreValve rate = 32%
- Non-inferiority margin (Δ) = 9.5%
- Test significance level (α) = 0.025 (1-sided)
- Test : Control ratio = 2:1
- Power ($1-\beta$) = 80%
- Total number of evaluable subjects = 819
- Expected rate of attrition = 10%

Given the above assumptions, the planned enrollment is 912 subjects (608 Lotus Valve, 304 CoreValve).

3.2.2.2 Secondary Hypothesis

The sample size calculation for the secondary hypothesis of the primary effectiveness endpoint at 1 year is based on the following assumptions:

- Expected Lotus Valve (test) rate = 22%
- Expected CoreValve rate = 32%
- Test significance level (α) = 0.05 (2-sided)

- Test : Control ratio = 2:1
- Expected rate of attrition = 10%

Given enrollment of 912 subjects (608 Lotus Valve, 304 CoreValve) and 10% attrition, there is approximately 86% power to show superiority with the given expected rates.

3.3 Secondary Endpoint

3.3.1 Hypothesis

The statistical hypothesis is that the secondary endpoint of moderate or greater* paravalvular aortic regurgitation (AR) rate at 1 year (based on review by an independent core lab) for the Lotus Valve is superior to that for the CoreValve group. The primary analysis for the secondary endpoint will be based on the ITT analysis set.

To control for experiment-wise type I error, testing for the secondary endpoint will be conducted only if the null hypotheses for the primary safety endpoint and the primary analysis of the primary effectiveness endpoint are rejected. That is, non-inferiority must be shown for the primary safety endpoint and the primary effectiveness endpoint for testing to be conducted for the secondary endpoint.

The null and alternative hypotheses for the secondary endpoint are as follows:

H_0: $P_{AR\_Lotus} = P_{AR\_Control}$

H_1: $P_{AR\_Lotus} \neq P_{AR\_Control}$

where P_{AR_Lotus} and $P_{AR\_Control}$ correspond to the moderate or greater paravalvular aortic regurgitation rates at 1 year for the Lotus Valve group (test) and the CoreValve group (control), respectively.

A chi-square test will be used to test the two-sided hypothesis of superiority between the rates of the two treatment groups. If the *P* value from the chi-square test is <0.05 and the rate of the Lotus group is less than the rate of the CoreValve group, the rate of the secondary endpoint for the Lotus Valve will be concluded to be superior to the CoreValve rate. This corresponds to the two-sided upper 95% confidence bound on the difference between treatment groups (Lotus Valve minus CoreValve) for the observed rate of the secondary endpoint being less than zero.

***Note:** Moderate or greater indicates a regurgitation grade of moderate or severe.

3.3.2 Sample Size

The sample size calculation for the secondary endpoint (moderate or greater paravalvular aortic regurgitation rate at 1 year) is based on the following assumptions.

- Expected Lotus Valve (test) rate $P_{AR\_Lotus} = 1.1\%$
- Expected CoreValve (control) rate $P_{AR\_Control} = 5.3\%$
- Test significance level (α) = 0.05 (2-sided)
- Test : Control ratio = 2:1
- Expected rate of attrition = 25%

Given enrollment of 912 subjects (608 Lotus Valve, 304 CoreValve) and 25% attrition, there is approximately 86% power to show superiority with the given expected rates.

3.4 Statistical Methods for the Primary Effectiveness, Primary Safety, and Secondary Endpoints

3.4.1 Non-Inferiority Testing

The following methodology will be used for the non-inferiority testing of the primary safety endpoint and the primary hypothesis of the primary effectiveness endpoint.

All subjects who are enrolled will be eligible for evaluation. The primary safety and effectiveness endpoints will be analyzed for patients in the ITT, as-treated, and implanted analysis sets.

If the *P* value from the one-sided Farrington-Manning test comparing the treatment groups is <0.025, the Lotus group will be concluded to be non-inferior to the CoreValve group. This corresponds to the one-sided upper 97.5% confidence bound for the difference in rates (Lotus – CoreValve) being less than the non-inferiority margin (Δ). That is,

$$(p_{Lotus}\text{-}p_{Control}) + Z_{0.025}\tilde{\sigma}_{MLE} < \Delta$$

where

$$\tilde{\sigma}^2_{MLE} = \frac{\tilde{p}_{Lotus}(1\text{-}\tilde{p}_{Lotus})}{n_{Lotus}} + \frac{\tilde{p}_{Control}(1\text{-}\tilde{p}_{Control})}{n_{Control}}$$

$$\tilde{p}_{Lotus} = 2u\cos(w)\text{-}b/3a$$

$$\tilde{p}_{Control} = \tilde{p}_{Lotus}\text{-}\Delta$$

$$w = \frac{\pi + cos^{-1}(v/u^3)}{3}$$

$$v = \frac{b^3}{27a^3}\text{-}\frac{bc}{6a^2} + \frac{d}{2a}$$

$$u = sign(v)\sqrt{\frac{b^2}{9a^2}\text{-}\frac{c}{3a}}$$

$$a = 1 + R$$

$$b = \text{-}(1 + R + p_{Lotus} + Rp_{Control} + R\Delta + 2\Delta)$$

$$c = \Delta^2 + \Delta(2p_{Lotus} + R + 1) + p_{Lotus} + Rp_{Control}$$

$$d = \text{-}p_{Lotus}\Delta(1 + \Delta)$$

$$R = n_{Control}/n_{Lotus}$$

and p_{Lotus} is the observed rate of primary safety endpoint at 30 days (primary effectiveness endpoint at 30 days) for Lotus patients,

$p_{Control}$ is the observed rate of primary safety endpoint at 30 days (primary effectiveness endpoint at 1 year) for CoreValve patients,

n_{Lotus} is the number of Lotus patients evaluated for primary effectiveness endpoint at 30 days (primary safety endpoint at 1 year),

$n_{Control}$ is the number of CoreValve patients evaluated for primary effectiveness endpoint at 30 days (primary safety endpoint at 1 year), and

$Z_{0.025}$ is upper 2.5th percentile of the standard normal distribution.

The test statistic for the Farrington-Manning test is

$$Z = \frac{(p_{Lotus} - p_{Control}) - \Delta}{\tilde{\sigma}_{MLE}}.$$

A sensitivity analysis (e.g. tipping-point analysis) will be performed to assess the impact of subjects not evaluable for the primary safety and effectiveness endpoints and to assess the robustness of the conclusion of the primary analysis. Assuming no loss to follow-up and given the observed number of patients with primary safety endpoint/primary effectiveness endpoint evaluable for both treatment groups, for all combinations of success/failure for patients with missing data, the endpoints will be evaluated until the point at which the conclusion of the study changes. For each endpoint, a plot with the number of patients with missing values for the Lotus group on the x-axis and the number of patients with missing values for the CoreValve group on y-axis will be provided. There will be shaded regions on the plot which represent the cases where the p-value from the test of non-inferiority is <0.025 and ≥0.025 to demonstrate which combinations of successes and failures among the patients missing data change the conclusion of the study.

3.4.2 Superiority Testing

The following methodology will be used for the superiority testing of the secondary hypothesis of the primary effectiveness endpoint and the secondary endpoint.

All subjects who are enrolled will be eligible for evaluation. The primary effectiveness and secondary endpoints will be analyzed for patients in the ITT, as-treated, and implanted analysis sets.

If the *P* value from the chi-square test comparing the treatment groups is <0.05 and the Lotus group has lower rate than the CoreValve group, the Lotus group will be concluded to be superior to the CoreValve group. This corresponds to the two-sided upper 95% confidence bound for the difference in rates (Lotus – CoreValve) being less than zero. That is,

$$(p_{Lotus} - p_{Control}) + z_{0.025}\sigma_{MLE} < 0$$

where

$$\sigma^2_{MLE} = \frac{p_{Lotus}(1-p_{Lotus})}{n_{Lotus}} + \frac{p_{Control}(1-p_{Control})}{n_{Control}}$$

and p_{Lotus} is the observed rate for Lotus patients,

$p_{Control}$ is the observed rate for CoreValve patients,

n_{Lotus} is the number of Lotus patients evaluated for the endpoint,

$n_{Control}$ is the number of CoreValve patients evaluated the endpoint,

σ^2_{MLE} is the variance from the Pearson chi-square test, and

$z_{0.025}$ is upper 2.5th percentile of the standard normal distribution.

A sensitivity analysis (e.g. tipping-point analysis) will be performed to assess the impact of subjects not evaluable for the primary effectiveness and secondary endpoints and to assess the robustness of the conclusion of the primary analysis. Assuming no loss to follow-up and given the observed number of patients with primary effectiveness endpoint/secondary evaluable for both treatment groups, for all combinations of success/failure for patients with missing data, the endpoints will be evaluated until the point at which the conclusion of the study changes. For each endpoint, a plot with the number of patients with missing values for the Lotus group on the x-axis and the number of patients with missing values for the CoreValve group on y-axis will be provided. There will be shaded regions on the plot which represent the cases where the p-value from the test of non-inferiority is <0.025 and ≥0.025 to demonstrate which combinations of successes and failures among the patients missing data change the conclusion of the study.

4 GENERAL STATISTICAL METHODS

4.1 Description of Statistical Methods

Descriptive statistics will be presented on the trial results by treatment group for randomized patients and separately for roll-in patients. For continuous variables, summaries will include the sample size (N), mean, standard deviation, minimum, and maximum. Frequency tables will be used to summarize discrete variables. Treatment groups will be compared for randomized patients using the chi-square test or Fisher's exact test for binary variables and Student's t-test for continuous variables. Alpha-adjustments for multiple comparisons on the additional measures will not be used. The Kaplan-Meier product-limit method will be used to determine rates for time-to-event endpoints. Adverse event and SAE rates will be reported.

4.2 Analysis Sets

The primary safety endpoint, primary effectiveness endpoint, and all additional endpoints up to 1 year will be analyzed on an intent-to-treat (ITT), as-treated, and implanted basis. After 1-year, all analyses will be based on the safety analysis set.

For the ITT analysis set, all subjects who sign the written ICF and are enrolled in the study will be included in the analysis sample, regardless of whether or not the study device was implanted. The primary analysis for the superiority testing of the second hypothesis of the primary effectiveness endpoint and the secondary endpoint will be based on the ITT analysis set.

For the as-treated analysis set, all ITT subjects who received a study device will be included in this analysis sample and analyzed based on the treatment actually received. For example, if a subject is assigned to receive a test device but instead receives a control device, that subject will be considered a control subject for the as-treated analyses of implant subgroups. Note that if a subject receives 2 valves, the subject is assigned to the group corresponding to the first valve received.

For the implanted analysis set, all ITT subjects who have the assigned study device implanted will be included in the analysis sample. The primary analysis for the primary safety endpoint and primary effectiveness endpoint will be based on the implanted analysis set.

For the safety analysis set, all ITT subjects who have a study device implanted regardless of the device and treatment assignment will be included in the analysis sample, which is identical to the as-treated analysis set.

For the intent-to-treat analysis set, events starting from the randomization date will be included in the analysis.

For the as-treated, safety and implanted analysis sets, events starting from the procedure date will be included in the analysis.

4.3 Eligibility of Subjects, Exclusions, and Missing Data

All subjects who are enrolled will be eligible for evaluation. Handling of dropouts and missing data will depend on their frequency and the nature of the outcome measure. The distribution of prognostic factors between subjects with and without data will be examined. Methods to eliminate or minimize bias will be implemented and are described in Section 4.4. Statistical models that account for censored data will be employed in appropriate circumstances (e.g., for time-to-event outcomes). Sensitivity analyses for the primary safety, primary effectiveness, and secondary endpoints, described in Section 3.4, will be conducted to assess the impact of different assumptions on interpretation of the results. Outlier values will be evaluated for their validity. Suspected invalid data will be queried and corrected in the database prior to statistical analysis.

When calculating rates of adverse events, missing and partial dates will be handled as shown below:

Partial Date Description	Action Taken
Entire onset date is missing	The procedure date will be used for the onset date.
The month and the day of the month are missing but the year is available	January 1 will be used for the month and day of the onset date. However, if the imputed date falls before the procedure date, then the procedure date will be used for the onset date.

Partial Date Description	Action Taken
Day is missing, but the month and year are available	The 1st will be used as the day of the onset date. However, if the imputed date falls before the procedure date, then the procedure date will be used for the onset date.

4.4 Control of Systematic Error/Bias

All subjects who have met the inclusion/exclusion criteria (including a positive recommendation from the Case Review Committee) and have signed the ICF will be eligible for enrollment in the study. The center heart team's assessment of transthoracic echocardiography (TTE) measurements before device placement will then determine subject eligibility for the study.

To control for inter-observer variability, an Echocardiography Core Laboratory will independently analyze echocardiography images collected for each subject during the study. Echocardiographic data obtained from the core laboratory will be used for analyses.

An independent Core Laboratory will centrally assess all CT's and rotational X-ray data for all patients to reduce variability. These analyses will minimize bias and inconsistencies by providing an independent interpretation of all measurements using standard techniques. Angiographic data obtained from the core laboratory will be used for analyses.

Similarly, an Electrocardiography Core Laboratory will independently analyze protocol-required 12-lead ECGs performed for each subject. Data obtained from the ECG core laboratory will be used for analyses.

5 ADDITIONAL DATA ANALYSES

5.1 Other Endpoints/Measurements

5.1.1 Additional Measures

Additional measurements based on the VARC (Leon M, *et al. J Am Coll Cardiol*. 2011;57:253 and Kappetein AP, *et al*. *J Am Coll Cardiol*. 2012;60:1438) endpoints and definitions (definitions in Table 26.2-1 of the protocol; see **Note 1** below) will be 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 (see **Note 2** below) adjudicated by an independent Clinical Events Committee (CEC; Section 7.7):
  - 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 System 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 CHF (NYHA class III or IV)
- New permanent pacemaker implantation resulting from new or worsened conduction disturbances (definitions in Table 26.2-1 of the protocol; see **Note 3** below)
- 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 (see **Note 4** below)
  - Grade of aortic valve regurgitation: paravalvular, central and combined; the overall distribution of paravalvular aortic regurgitation (none, trace/trivial, mild, moderate, severe) will be determined as well as the percentage of subjects who have moderate or severe paravalvular regurgitation and the percentage of subjects who have mild, moderate or severe paravalvular regurgitation
- 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 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 mm Hg 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; see **Note 5** below) and assessed by an independent core laboratory, including effective orifice area, mean and peak aortic gradients, peak aortic velocity, and grade of aortic regurgitation (see **Note 6** below).
- 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 mm Hg 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)
  - New York Heart Association (NYHA) classification
- Neurological status (see **Note 7** below) 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
- Resource utilization associated with the procedure and/or follow-up.

Note 1: The most current VARC definitions and endpoints available at the beginning of the trial were used.

Note 2: The VARC-2 safety composite at 30 days includes all-cause mortality, all stroke (disabling and non-disabling), life-threatening bleeding, acute kidney injury (Stage 2 or 3), coronary artery obstruction requiring intervention, major vascular complication, and repeat procedure for valve-related dysfunction. The VARC-2 time-related valve safety composite includes structural valve deterioration (valve-related dysfunction requiring repeat procedure [TAVR or SAVR]), prosthetic valve endocarditis, prosthetic valve thrombosis, thromboembolic events (e.g., stroke), and VARC bleeding (unless clearly unrelated to valve therapy based on investigator assessment)

Note 3: Clinical indications for permanent pacemaker implantation are outlined in the ACCF/AHA/HRS Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities (Epstein AE, *et al. J Am Coll Cardiol* 2013;61:e6). Permanent pacemaker implantation should generally be performed only for accepted Class I indications.

Note 4: For the Lotus Valve System, repositioning may be achieved with partial or full resheathing of the valve; the proportion of subjects with partial valve resheathing and full valve resheathing will be determined.

Note 5: At least 1 echocardiogram must be obtained before discharge or 7 days (whichever comes first); if multiple echocardiographic studies are performed prior to discharge and within 7 days of the procedure, the latest study performed will be used for analysis.

Note 6: The VARC-2 clinical efficacy composite (after 30 days) includes all-cause mortality, all stroke, required hospitalization for valve-related symptoms or worsening CHF (NYHA class III or IV), and prosthetic heart valve dysfunction (mean aortic valve gradient ≥20 mmHg, effective orifice area ≤0.9-1.1 cm and/or Doppler velocity index [DVI] <0.35, AND/OR moderate or severe prosthetic valve aortic regurgitation [per VARC definition]). The need for hospitalization associated with valve-related symptoms or worsening CHF serves as a basis for calculation of a "days alive outside the hospital" endpoint. This includes heart failure, angina, or syncope due to aortic valve disease requiring intervention or intensified medical management; clinical symptoms

of CHF with objective signs including pulmonary edema, hypoperfusion, or documented volume overload AND administration of intravenous diuresis or inotropic therapy, performance of aortic valvuloplasty, institution of mechanical support (intra-aortic balloon pump or ventilation for pulmonary edema), or hemodialysis for volume overload; clear documentation of anginal symptoms AND no clinical evidence that angina was related to coronary artery disease or acute coronary syndrome; documented loss of consciousness not related to seizure or tachyarrhythmia.

Note 7: For subjects diagnosed with a neurological event (e.g., stroke, transient ischemic attack), a neurological physical exam (conducted by a neurologist, neurology fellow, neurology physician assistant, or neurology nurse practitioner), NIHSS assessment, and mRS must be performed after the event. Additionally, mRS must be administered at 90±14 days post-neurological event (see Table 11.1-1 of the protocol). If a subject who has not received a study device (investigational or control) experiences a neurological event within the first 1 year after the index procedure, mRS must be performed on that subject after the event and at 90±14 days post-neurological event and the results must be reported to the Sponsor.

Data will be summarized as described in Section 4.1.

5.2 Interim Analyses

5.2.1 Analysis for Trial Discontinuation

There are no planned interim analyses for stopping the trial early for effectiveness or futility.

5.2.2 Administrative Analysis

An administrative analysis based on 30-day data for the implanted patients in the first 300 randomized (ITT) patients will be performed for review as required by designated regulatory agencies after these 300 patients have completed their 30-day follow-up visits. This analysis will be conducted by an independent statistician from a contract research organization (CRO; Quintiles) and will only be distributed to designated regulatory agencies and limited internal Boston Scientific personnel preparing for the submission. The study team executing the trial will remain blinded to the results from this analysis, which will not be disclosed publicly.

This administrative analysis will not include any analyses of the primary and secondary endpoints and thus will not affect the type I error of the analyses of those endpoints.

5.2.2.1 Administrative Analysis **Hypothesis testing**

Hypothesis: Moderate or greater aortic regurgitation rate (includes central plus paravalvular regurgitation) as assessed by the echocardiograph core lab at 30 days for the Lotus Valve group is non-inferior to that for the CoreValve group for implanted patients in the first 300 randomized patients.

If non-inferiority of the Lotus Valve group compared to the CoreValve group is demonstrated, then the superiority testing of the Lotus Valve group compared to the CoreValve group will be carried out.

Non-inferiority Testing:

The null and alternative hypotheses for the 30-day aortic regurgitation rate are as follows:

H_0: $P_{30Day\ All\ AR\_Lotus} - P_{30Day\ All\ AR\_Control} \geq \Delta$ (Inferior)

H_1: $P_{30Day\ All\ AR\_Lotus} - P_{30Day\ All\ AR\_Control} < \Delta$ (Non-inferior)

where $P_{30Day\ All\ AR\_Lotus}$ and $P_{30Day\ All\ AR\_Control}$ correspond to the rates of moderate or greater aortic regurgitation (includes central plus paravalvular) at 30 days for the Lotus Valve group (test) and the CoreValve group (control), respectively, and Δ (delta) is the non-inferiority margin.

Sample Size Parameters for this 30-day aortic regurgitation (includes central plus paravalvular) **rate non-inferiority testing:**

- Expected Lotus Valve (test) rate $P_{30Day\ All\ AR\_Lotus} = 1.2\%$
- Expected CoreValve (control) rate $P_{30Day\ All\ AR\_Control} = 12\%$ (average from CoreValve IDE High Risk [HR] and Extreme Risk [ER] study data)
- Non-inferiority margin (Δ) = 2%
- Test significance level (α) = 0.05 (1-sided)
- Test : Control ratio = 2 : 1
- Power ($1-\beta$) ≥ 0.98 using Farrington-Manning test
- Number of evaluable subjects = 240 (160 test and 80 control)
- Expected rate of attrition = 20%
- Number of subjects randomized = 300

A Farrington-Manning standardized test will be used to test the one-sided hypothesis of non-inferiority in the difference between the rates of the two treatment groups. If the *P* value from the Farrington-Manning standardized test is <0.05, the moderate or greater aortic regurgitation (central plus paravalvular) rate at 30 days for the Lotus Valve will be concluded to be non-inferior to the CoreValve rate. This corresponds to the one-sided 95% upper confidence bound on the difference between treatment groups (Lotus Valve minus CoreValve) in the moderate or greater aortic regurgitation at 30 days being less than the non-inferiority margin.
***Note:** Moderate or greater indicates a regurgitation grade of moderate or severe.

Superiority Testing:

The null and alternative hypotheses for the 30-day aortic regurgitation rate are as follows:

H_0: $P_{30Day\ All\ AR\_Lotus} = P_{30Day\ AR\_Control}$

H_1: $P_{30Day\ All\ AR\_Lotus} \neq P_{30Day\ AR\_Control}$

where $P_{30Day\ All\ AR\_Lotus}$ and $P_{30Day\ AR\_Control}$ correspond to the rates of moderate or greater aortic regurgitation (includes central plus paravalvular) at 30 days for the Lotus Valve group (test) and the CoreValve group (control), respectively.

Sample Size Parameters for this 30-day moderate or greater aortic regurgitation (includes central plus paravalvular) rate analysis:

- Expected Lotus Valve (test) rate $P_{30Day\ All\ AR\_Lotus}$ = 1.2%
- Expected CoreValve (control) rate $P_{30Day\ All\ AR\_Control}$ = 12.0% (average from CoreValve IDE HR and ER study data)
- Test significance level (α) = 0.05 (2-sided)
- Test : Control ratio = 2 : 1
- Power (1-β) = 0.91
- Number of evaluable subjects = 240 (160 test and 80 control)
- Expected rate of attrition = 20%
- Number of subjects randomized = 300

If the *P* value from the chi-square test is <0.05, and the aortic regurgitation rate at 30 days for the Lotus Valve group is less than the rate of the CoreValve group, the aortic regurgitation (includes central plus paravalvular) rate at 30 days for the Lotus Valve group will be concluded to be superior to that of the CoreValve group.

Other analyses

Descriptive statistics will be used to summarize the following 30-day endpoints for the Lotus and CoreValve groups for the first 300 randomized (ITT) patients: all-cause mortality, disabling stroke, major bleeding events, and major vascular complications.

5.3 Subgroup Analyses

Subgroup analyses will be performed in the following subgroups:

- gender (male, female)
- surgical risk (high, extreme)
- region (North America, outside North America)

No adjustments for multiple comparisons will be made. Additional analyses may be performed as appropriate.

5.4 Justification of Pooling

The analyses will be presented using data pooled across regions, surgical risk (high or extreme) as well as by center for the primary safety, primary effectiveness, and secondary endpoints. An assessment of the poolability of subjects across centers, regions, and surgical risk group will be made using logistic regression to determine if there is a relationship between each factor and the primary safety, primary effectiveness, and secondary endpoints.

Main effects for the factor (site, region, surgical risk group) and treatment and the interaction of the factor by treatment will be included in separate logistic regression models with primary safety, /primary effectiveness, and secondary endpoints as the outcome. If the p-value for the

coefficient for the factor by treatment interaction is ≥0.15, it can be concluded that the treatment effect is not significantly different across the different levels of the factor, and the data can be pooled across that factor.

In the analysis to justify pooling across centers, the centers with fewer than 6 subjects enrolled in the study will be combined into "virtual centers" based on geographic region so that "virtual centers" have ≥6 subjects in the study but no more than the largest enrolling center.

5.5 Multivariable Analyses

Univariate and multivariate analyses will be performed to assess the effect of potential predictors on the primary safety, primary effectiveness, and secondary endpoints.

Univariate and multivariate analyses will be performed to assess possible predictors of the primary safety, primary effectiveness, and secondary endpoints. Possible predictors (see below) will be modeled univariately; factors from the univariate models with p≤0.20 will also be modeled multivariately using a stepwise procedure in a logistic regression model. The significance level thresholds for entry and exit of independent variables into the multivariate model will be set at 0.1.

From the final models, predictors will be listed in ascending order of p-value. Univariate analyses will be performed overall as well as separately for each treatment group for randomized patients.

The following variables will be analyzed as possible predictors of primary safety, primary effectiveness, and secondary endpoints:

Category	**Possible Predictors**
Treatment	Group (CoreValve=0, Lotus=1)
Demographics	Sex, age, race (Caucasian)
Baseline Characteristics	STS score, EuroSCORE, CHF, previous TIA or CVA, history of renal disease, medically-treated diabetes, hyperlipidemia, hypertension, current smoking at baseline, history of COPD, history of CAD, history of MI, history of CHF, prior balloon aortic valvuloplasty, history of atrial fibrillation, 5‑meter walk >6 seconds, Katz ADL score of 3/6 or less, body mass index <21, wheelchair bound, unable to live independently
Baseline Echocardiographic Characteristics (Core Lab)	LVEF, aortic valve area, mean pressure gradient, , Doppler velocity index
Baseline Computed Tomography (CT) (Core Lab)	Annulus area, LVOT area, annular calcification, LVOT calcification

Category	Possible Predictors
Peri-Procedural Variables	Ratio of pre-dilation balloon diameter to annulus diameter (derived from area), post-dilation performed, repositioning performed, retrieval performed

5.6 Other Analyses

5.6.1 Baseline Characteristics

Baseline data will be summarized to assess subject demographics, clinical history, risk factors, and pre-procedure characteristics. Data will be summarized as described in Section 4.1.

5.6.2 Post-Procedure Endpoints

Post-procedure information will be collected at regularly scheduled follow-up examinations as detailed in the clinical trial schedule in the protocol. Data will be summarized as described in Section 4.1.

5.6.3 Subject Disposition

Subject disposition (e.g., number completing the study, number lost-to-follow-up) will be summarized with frequency tables.

5.6.4 Time-to-Event Methods

The Kaplan-Meier product-limit method will be used to estimate event rates for time-to-event endpoints. Kaplan-Meier plots of time-to-event endpoints will be constructed.

5.7 Changes to Planned Analyses

Any changes to the planned statistical analyses made prior to performing the analyses will be documented in an amended statistical analysis plan approved before performing the analyses. Changes from the planned statistical methods after performing the analyses will be documented in the clinical study report along with a reason for the deviation.

6 Validation

All clinical data reports generated per this plan will follow the Global WI: Clinical Data Reporting Validation (PDM 90702587).

7 Programming Considerations

7.1 Statistical Software

Statistical data review will be performed by the sponsor. Statistical analyses will be performed using SAS System software, version 9.2 or later (Copyright © 2000 SAS Institute Inc., SAS Campus Drive, Cary, North Carolina 27513, USA. All rights reserved).

7.2 Format of Output

Results of analysis will be output programmatically to Word documents from SAS with no manual intervention. All output for the final statistical report will be in the form of a Word document containing tables, figures, graphs, and listings, as appropriate.

7.3 Rules and Definitions for Calculated Variables

7.3.1 Transthoracic Echocardiographic (TTE) Variables

Transthoracic echocardiograms will be assessed at each of the following visits: screening, 1 day post-procedure, discharge or 7 days post-procedure (whichever comes first), 30 days, 6 months, and then annually for up to 5 years post-procedure.

One transthoracic echocardiographic study will be performed for each visit. If multiple transthoracic echocardiographic studies are performed for the same visit, the latest study performed for each visit will be used for analysis.

7.3.1.1 Body Mass Index (BMI)

Valid Data Sources

- Assessment Form (Weight, Weight unit, Height, Height unit)
- Diss_FU_Assessment Form (Weight, Weight unit, Height, Height unit)

Valid Data Points

- Weight
- Weight unit
- Height
- Height unit

Analysis approach: Body Mass Index is calculated for each visit.

Weight (Kg) = Weight (lbs) / 2.20462262.
Height (cm) = Height (in) / 0.393700787

$$BMI = \frac{Weight\,(Kg) \times 10000}{\left(Height\,(cm)\right)^2}$$

7.3.1.2 Body Surface Area (BSA)

Valid Data Sources

- Assessment Form (Weight, Weight unit, Height, Height unit)

- Diss_FU_Assessment Form (Weight, Weight unit, Height, Height unit)

Valid Data Points

- Weight
- Weight unit
- Height
- Height unit

Analysis approach: Body Surface Area (BSA) is calculated using the following formula:

$$BSA(m^2) = \sqrt{(Height\,(cm) x Weight(Kg))/3600}$$

7.3.1.3 Indexed Aortic Valve Area (iAVA) or Indexed Effective Orifice Area (iEOA).

Effective Orifice Area (EOA) is synonymous with Aortic Valve Area (AVA). Both terms will be used in this SAP to easily follow either the protocol or the CRFs as reference documents.

Valid Data Sources

- Assessment Form (Weight, Weight unit, Height, Height unit)
- Diss_FU_Assessment Form (Weight, Weight unit, Height, Height unit)
- Echo Core Lab Form (AVA [TVI])

Valid Data Points

- Weight, Weight unit, Height, Height unit
- AVA (TVI)

Analysis approach:

Indexed Aortic Valve Area (iAVA) or Indexed Effective Orifice Area (iEOA) is calculated for each visit.

iAVA(cm2/m2) = iEOA(cm^2/m2) = AVA (TVI) (cm^2) / BSA (m^2),

where AVA (TVI) is the aortic valve area for a specific visit and BSA is the body surface area (calculated in Section 7.3.1.2) for the same specific visit under analysis.

7.3.2 ECG Variables

The following algorithm will be used to determine the ECG diagnosis codes for each time-point and subject.

If baseline ECG, then is ECG interpretable?

If No, then:

Rhythm/AV Conduction Abnormalities = Uninterpretable
IV Conduction Abnormalities = Uninterpretable
New Major ST-T Abnormalities = Uninterpretable

If Yes, then:

Rhythm/AV Conduction Abnormalities = 1.1, 1.2, 1.3, 1.4
IV Conduction Abnormalities = 2.1, 2.2, 2.3, 2.4
New Major ST-T Abnormalities = 4.1, 4.2, 4.3, 4.4

If not baseline ECG, then is ECG interpretable?

If No, then:

Rhythm/AV Conduction Abnormalities = Uninterpretable
IV Conduction Abnormalities = Uninterpretable
New Major ST-T Abnormalities = Uninterpretable

If Yes, then:

If No change is checked, then
Rhythm, IV Conduction, Major ST-T = their values from the most recent interpretable ECG

If No change is not checked, then

- Is a New Rhythm/AV Conduction Abnormality?
  - If Yes, then Rhythm = 1.1, 1.2, 1.3, 1.4
  - If No, then Rhythm = their values from the most recent interpretable ECG
- Is a New IV Conduction Abnormality?
  - If Yes, then IV Conduction = 2.1, 2.2, 2.3, 2.4
  - If No, then IV Conduction = their values from the most recent interpretable ECG
- Is a New Major ST-T Abnormality?
  - If Yes, then Major ST-T = 4.1, 4.2, 4.3, 4.4
  - If No, then IV Conduction = their values from the most recent interpretable ECG.

7.3.3 Days to Last Follow-up

Valid Data Sources

- Adverse Event Form
- Hospitalization Form
- Procedure Form

- Date of Visit Form
- CEC data.

Valid Data Points

- Adverse event date is “Onset date” from the Adverse Event Form.
- Admission and Discharge dates are “Admission date” and “Discharge date” from the Hospitalization Form.
- Index procedure date is “Date of Procedure” from the Procedure Form.
- Randomization date is “Date of Randomization” from the Randomization Form
- Follow-up visit date is “Date of Visit” from the Date of Visit Form at each of the visits (discharge or 7 days post-procedure, 30 days, 6 months, and 1 to 5 years post index procedure).
- CEC event date – date of event as adjudicated by the CEC.

Last follow-up date will be the latest of the following dates for each subject:

adverse event onset date,
admission and discharge dates from hospitalization,
index procedure date,
randomization date
discharge or follow-up visit date, and
CEC event date.

Follow-up days will be calculated for as-treated and implanted analysis sets

Day 0 is the index procedure date.Days to last follow-up = last follow-up date - index procedure date. Days to (event or last known status) = (event or status) date – index procedure date.

Follow-up days will be calculated for intent-to-treat analysis set

Day 0 is the randomization date.

Days to last follow-up = last follow-up date - randomization date.

Days to (event or last known status) = (event or status) date - randomization date.

7.3.4 Variable “Days alive outside the hospital”

Valid Data Sources

- Adverse Event Form.
- Hospitalization Form.
- Procedure Form.
- Randomization Form

- Date of Visit Form
- End of Study Form.

Analysis approach: Days alive outside the hospital is calculated for each visit.

$$Days\ alive\ within\ the\ hospital = \sum_{\substack{All\ Hospitalizations\ through \\ the\ visit\ under\ study}} (Dischage\ date - Admission\ date),$$

$$Days\ alive\ outside\ the\ hospital = Days\ to\ last\ \ follow up - Days\ alive\ within\ the\ hospital,$$

where *Days to last follow-up* is calculated as described in Section 7.3.3 at each visit under study.

7.3.5 Event Rates

7.3.5.1 Time-to-event Endpoints

This section describes the calculation of events for the safety endpoints adjudicated by the CEC as described in Section 7.7. Time-to-event safety endpoints are events that can occur at any time during the course of the study, for example all-cause mortality. For time-to-endpoints, the date of the event is expected to be known and the days from the index procedure can be calculated. In some cases, the exact date of the event will not be known however partial information should be available, e.g. missing date of month. Binary endpoints measured at pre-specified intervals during the study do not count as time-to-events endpoints. Examples of non-time-to-event binary endpoints are NYHA Class II at 30 days and aortic regurgitation at 12 months.

For the calculation of event rates for the primary safety, primary effectiveness, and secondary endpoints, see Sections 7.4, 7.5, and 7.6, respectively.

Binary event rates will be calculated only up to 1 year. After 1 year, events rates for time-to-event endpoints will be calculated using the Kaplan-Meier product-limit method.

The calculation of binary rates to 1 year will be the same for any endpoint and time point in regards to the appropriate numbers of days as indicated below in Table 1.1 for as-treated and implanted analysis sets and Table 1.2 for ITT analysis set, respectively. As an example, for 30 days binary endpoint in the as-treated and implanted analysis sets, the event must have occurred within 30 days of procedure (maximum days to event from procedure) and the subject must have ≥ 23 days of follow-up (days for adequate follow-up from procedure as shown in Table 1.1).

Table 1.1 Days Post-procedure to Event and for Adequate Follow-up for As-Treated and Implanted Analysis Sets.

Follow-up Visit	Maximum Days to Event from Procedure*	Days for Adequate Follow-up from Procedure**
30 Days	30	23
6 Months	180	150
12 Months	365	335
2 Years	730	NA

Follow-up Visit	Maximum Days to Event from Procedure*	Days for Adequate Follow-up from Procedure**
3 Years	1095	NA
4 Years	1460	NA
5 Years	1825	NA

* Target date for the follow-up visit.
** Start of the follow-up visit window. Not used after the 12-month follow-up

Table 1.2 Days Post-randomization to Event and for Adequate Follow-up for ITT Analysis Set.

Follow-up Visit	Maximum Days to Event from Randomization*	Days for Adequate Follow-up from Randomization**
30 Days	30	23
6 Months	180	150
12 Months	365	335
2 Years	730	NA
3 Years	1095	NA
4 Years	1460	NA
5 Years	1825	NA

* Target date for the follow-up visit.
** Start of the follow-up visit window. Not used after the 12-month follow-up

Rates in this section are described for all analysis sets. If the variable is calculated based on the ITT analysis set, "all subjects" refers to all subjects enrolled/randomized. If the variable is calculated based on the as-treated, implanted or safety analysis set, "all subjects" refers to all subjects within the respective analysis set.

Binary event rates (proportions) are calculated on a per subject basis.

All events through discharge or 7 days post-procedure (whichever comes first) are considered in-hospital. Event rates through discharge or 7 days post-procedure (whichever comes first) are calculated as the proportion of subjects who experience the specified event from index procedure or randomization through day of discharge or 7 days post-procedure (whichever comes first) out of all subjects in the as-treated and implanted analysis sets or ITT analysis set, respectively.

Event rates through a follow-up visit through 1 year are calculated using the following for inclusion in the denominator and numerator:

- Denominator:

  Subjects in the specific analysis set count in the denominator with one of the following:

  - ***Subject experiences any CEC adjudicated event from Section 7.7 ≤ maximum number of days as specified in Table 1.1 and Table 1.2, as appropriate or***
  - ***date of last follow-up ≥ days for adequate follow-up post-procedure from Table 1.1 and Table 1.2, as appropriate:***

- Numerator:

Subjects in the specific analysis set count in the numerator if the subject experiences specified event ≤ maximum number of days as specified in Table 1.1 and Table 1.2, as appropriate.

Event rates from a previous visit to a current follow-up visit date are calculated as the proportion of "subjects in the analysis set who experience the specified event after the maximum number of days in the previous visit and through the maximum number of days of the current follow-up visit as specified in Table 1.1 and 1.2, as appropriate" out of "all subjects in the analysis set who have adequate follow-up as specified in Table 1.1 and 1.2, as appropriate or have experienced the specified event in the time interval".

7.3.5.2 Other Binomial Endpoints

Binomial endpoints that are not time based will be presented as binary rates. Such endpoints include any binary measures that collected at baseline or at pre-specified intervals during the study such, for example medically-treated diabetes at baseline and NYHA Class II at 30 days.

For categorical variables, "unknown" and "not evaluated" responses and missing values will not be counted in rate denominators.

7.4 Calculation of Primary Safety Endpoint Rate

The Primary Safety Endpoint of all-cause mortality, all stroke, acute kidney injury (stage 2 or 3), life-threatening and major bleeding, and major vascular complications at 30 days is calculated on an ITT, as-treated, and implanted basis.

Valid Data Sources

- Procedure Form (Procedure date)
- Randomization Form
- CEC Adjudication Forms at 30 days (death, stroke, kidney injury stage 2 or 3, life-threatening or major bleeding, major vascular complication)
- Case report forms (CRFs) used in determining length of follow-up (see Section 7.3.3).

Valid Data Points

- Date of procedure.
- Date of randomization
- Date of death.
- Date of any stroke
- Date of acute kidney injury (stage 2 or 3)
- Date of life-threatening or major bleeding
- Date of major vascular complication
- Date of last follow-up (Section 7.3.3).

Analysis approach

- Denominator for as-treated and implanted analysis sets:

  Subjects in the analysis set count in the denominator with one of the following:

- date of death ≤ 30 days post-procedure.
- date of any stroke ≤ 30 post-procedure.
- date of acute kidney injury (stage 2 or 3) ≤ 30 post-procedure.
- date of life-threatening or major bleeding ≤ 30 post-procedure.
- date of major vascular complications ≤ 30 post-procedure.
- date of last follow-up ≥ 23 days post-procedure.

- Numerator for as-treated and implanted analysis sets

  Subjects in the analysis set count in the numerator with <u>one</u> of the following:

  - Subject experiences death ≤ 30 days post-procedure.
  - Subject experiences any stroke ≤ 30 post-procedure.
  - Subject experiences acute kidney injury (stage 2 or 3) ≤ 30 post-procedure.
  - Subject experiences life-threatening or major bleeding ≤ 30 post-procedure.
  - Subject experiences major vascular complication ≤ 30 post-procedure.

- Denominator for ITT analysis set:

  Subjects in the analysis set count in the denominator with one of the following:

  - date of death ≤ 30 days post-randomization,
  - date of any stroke ≤ 30 post-randomization,
  - date of acute kidney injury (stage 2 or 3) ≤ 30 post-randomization,
  - date of life-threatening or major bleeding ≤ 30 post-randomization,
  - date of major vascular complications ≤ 30 post-randomization.
  - date of last follow-up ≥ 23 days post-randomization.

- Numerator for ITT analysis set

  Subjects in the analysis set count in the numerator with <u>one</u> of the following:

  - Subject experiences death ≤ 30 days post randomization,
  - Subject experiences any stroke ≤ 30 days post randomization,
  - Subject experiences acute kidney injury (stage 2 or 3) ≤ 30 days post randomization,
  - Subject experiences life-threatening or major bleeding ≤ 30 days post randomization,
  - Subject experiences major vascular complication ≤ 30 days post randomization.

Note that events occurring >30 days within the visit window of 30+7 days will not be included in the 30-day endpoint analysis.

7.5 Calculation of Primary Effectiveness Endpoint Rate

The Primary Effectiveness Endpoint of all-cause mortality, disabling stroke, and moderate or severe paravalvular aortic regurgitation (core lab assessment) at 12 months is calculated on an ITT, as-treated, and implanted basis.

Valid Data Sources

- Procedure Form (Procedure date)
- Randomization Form (Randomization date)
- CEC Adjudication Forms at 1 year (Death, Disabling Stroke)
- Echocardiography Forms at 6 months and 1 year (Aortic Regurgitation)
- Case report forms (CRFs) used in determining length of follow-up (see Section 7.3.3).

Valid Data Points

- Date of procedure.
- Date of randomization
- Date of death.
- Date of disabling stroke
- Moderate or greater paravalvular aortic regurgitation present or not from the 12-month echocardiography form (use 6-month echocardiography form if aortic regurgitation is missing at 12 months or there is no 12 month echocardiography form and the patient has not died ≤365 days post-procedure).
- Date of last follow-up (Section 7.3.3).

Analysis approach

- Denominator for as-treated and implanted analysis sets:

  Subjects in the analysis set count in the denominator with <u>both</u> of the following:

  - *Yes or No for moderate or greater paravalvular aortic regurgitation on the 12-month echocardiography form (or Yes or No for moderate or greater paravalvular aortic regurgitation on the 6-month echocardiography form when paravalvular aortic regurgitation is missing on the 12-month echocardiography form or the 12-month echocardiography is missing and the patient has not died ≤365 days post-procedure), and*
  - one of the following:
    - *date of death ≤365 days post-procedure.*
    - *date of disabling stroke ≤365 days post-procedure.*
    - *date of last follow-up ≥335 days post-procedure.*

- Numerator for as-treated and implanted analysis sets:

  Subjects in the analysis set count in the numerator with <u>one</u> of the following:

- *Subject experiences death ≤365 days post-procedure.*
- *Subject experiences disabling stroke ≤365 post-procedure.*
- *Subject has Yes for moderate or greater paravalvular aortic regurgitation on the 12-month echocardiography form (or Yes for moderate or greater paravalvular aortic regurgitation on the 6-month echocardiography form when paravalvular aortic regurgitation is missing on the 12-month echocardiography form or the 12-month echocardiography is missing and the patient has not died ≤365 days post-procedure)*

- Denominator for ITT analysis sets:

  Subjects in the analysis set count in the denominator with <u>both</u> of the following:

  - *Yes or No for moderate or greater paravalvular aortic regurgitation on the 12-month echocardiography form (or Yes or No for moderate or greater paravalvular aortic regurgitation on the 6-month echocardiography form when paravalvular aortic regurgitation is missing on the 12-month echocardiography form or the 12-month echocardiography is missing and the patient has not died ≤365 days post-radomization), and*
  - one of the following:
    - *date of death ≤365 days post-randomization.*
    - *date of disabling stroke ≤365 days post-randomization.*
    - *date of last follow-up ≥335 days post-randomization.*

- Numerator for ITT analysis sets:

  Subjects in the analysis set count in the numerator with <u>one</u> of the following:

  - *Subject experiences death ≤365 days post-randomization.*
  - *Subject experiences disabling stroke ≤365 post-randomization*
  - *Subject has Yes for moderate or greater paravalvular aortic regurgitation on the 12-month echocardiography form (or Yes for moderate or greater paravalvular aortic regurgitation on the 6-month echocardiography form when paravalvular aortic regurgitation is missing on the 12-month echocardiography form or the 12-month echocardiography is missing and the patient has not died ≤365 days post-randomization)*

Note that deaths or disabling strokes occurring >365 days within the visit window of 365+45 days will not be included in the endpoint analysis.

7.6 Calculation of Secondary Endpoint Rate

The Secondary Endpoint of moderate or greater paravalvular aortic regurgitation (core lab assessment) at 12 months is calculated on an ITT, as-treated, and implanted basis.

Valid Data Sources

- Echocardiography Forms at 6 months and 1 year (Aortic Regurgitation).

Valid Data Points

- Moderate or greater paravalvular aortic regurgitation present or not from the 12-month echocardiography form (use 6-month echocardiography form if aortic regurgitation is missing at 12 months or there is no 12 month echocardiography form and the patient has not died ≤365 days post-procedure).

Analysis approach

- Denominator:

  Subjects in the analysis set count in the denominator with the following:

  - *Yes or No for moderate or greater paravalvular aortic regurgitation on the 12-month echocardiography form (or Yes or No for moderate or greater paravalvular aortic regurgitation on the 6-month echocardiography form when paravalvular aortic regurgitation is missing on the 12-month echocardiography form or the 12-month echocardiography is missing and the patient has not died ≤365 days post-procedure).*

- Numerator

  Subjects in the analysis set count in the numerator with the following:

  - *Subject has Yes for moderate or greater paravalvular aortic regurgitation on the 12-month echocardiography form (or Yes for moderate or greater paravalvular aortic regurgitation on the 6-month echocardiography form when paravalvular aortic regurgitation is missing on the 12-month echocardiography form or the 12-month echocardiography is missing and the patient has not died ≤365 days post-procedure)*

7.7 Clinical Events Committee (CEC)

A CEC will be used in this study. A CEC is an independent group of individuals with pertinent expertise that reviews and adjudicates important endpoints and relevant adverse events reported by study Investigators.

CEC events (definitions in Table 26.2-1 of the protocol) to be reported are:

- 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 System 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 CHF (NYHA class III or IV)

- New permanent pacemaker implantation resulting from new or worsened conduction disturbances (definitions in Table 26.2-1 of the protocol)
- 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

CEC periprocedural events are events that occur ≤72 hours after index procedure. The CEC will make the final adjudication and classification of all events mentioned above per the CEC charter, and the CEC determinations will supersede the site-reported data in all analyses of the events mentioned above.

7.8 Analysis of Site-Reported Serious and Non-Serious Adverse Events

Subject-based event rates will be calculated at various time points based on all events reported by the site regardless of whether or not they are ultimately adjudicated by the CEC. Rates will be calculated on an ITT basis through 1 year and on a safety basis from 2 years through the 5-year follow-up.

Non-Serious Adverse Events will be reported from the time of enrollment through 1-year follow-up.

Serious Adverse Events will be reported from the time of enrollment through termination of the study.

8 Revision History

Revision Number	Section	Change	Reason for Change
AA	All	Original version	
AB	4.2, 5.2,7.3.3, 7.3.4, 7.4 and 7.5	Add the following details about the administrative analysis: • Updated neurological status and control device in section 1 for Protocol summary • who will receive the analysis • state that the analysis will not affect the type I error for the primary and secondary endpoints • state that descriptive statistics will be used to summarize endpoints for treatment groups. • Events collecting date for ITT analysis set • the randomization date as valid date if a subject wasn't implanted in section 7.3.3, 7.3.4, 7.4 and 7.5	Addressing comments from the FDA

8 Revision History

Revision Number	Section	Change	Reason for Change
AA	All	Original version	

The table below provides a list of changes to the REPRISE III Statistical Analysis Plan.

Statistical Analysis Plan Revision	**Reason for Update**
AA	Original version
AB	Add the following details about the administrative analysis: • Updated neurological status and control device in section 1 for Protocol summary • who will receive the analysis • state that the analysis will not affect the type I error for the primary and secondary endpoints • state that descriptive statistics will be used to summarize endpoints for treatment groups. • Events collecting date for ITT analysis set • the randomization date as valid date if a subject wasn't implanted in section 7.3.3, 7.3.4, 7.4 and 7.5 • Reasons for change: Addressing comments from the FDA