REPRISE II: Repositionable Percutaneous Replacement of Stenotic Aortic Valve through Implantation of Lotus Valve System - Evaluation of Safety and Perfomance

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To evaluate the safety and performance of the Lotus Valve system for transcathether aortic valve replacment (TAVR) in symptomatic subjects with severe calcific aortic stenosis who are considered high risk for surgical valve replacement.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Cardiac valve disorders
Study type	Interventional

Summary

ID

NL-OMON40520

Source
ToetsingOnline

Brief title
REPRISE II

Condition

- Cardiac valve disorders
- Cardiac therapeutic procedures

Synonym
Symptomatic Aortic Heart Valve Stenosis; Narrowed Aortic Heart Valve

Research involving
Human

Sponsors and support

Primary sponsor: Boston Scientific International
Source(s) of monetary or material Support: Sponsor van het onderzoek is Boston Scientific Structural Heart;a division of Boston Scientific Corporation

Intervention

Keyword: Aortic Lotus Valve System, Percutaneous, Replacement, Repositionable

Outcome measures

Primary outcome

- Primary Device Performance Endpoint: mean aortic valve pressure gradient at

30 days post implant procedure as measured by echocardiography and assessed by

an independent core laboratory

- Primary Safety Endpoint: all-cause mortality at 30 days post implant

procedure

Secondary outcome

- Effective orifice area at 30 days as measured by echocardiography and

assessed by an independent core laboratory

- Device performance endpoints peri- and post-procedure:

*successful vascular access, delivery and deployment of the Lotus Valve System,

and successful retrieval of the delivery system

*successful repositioning of the Lotus Valve System if repositioning is

attempted

*successful retrieval of the Lotus Valve System if retrieval is attempted

*grade of aortic valve regurgitation: paravalvular, central and combined

- Device success based on the Valve Academic Research Consortium definitions

(VARC)

- Additional measurements based on the VARC endpoints and definitions will be collected throughout the study:

*safety endpoints adjudicated by an independent Clinical Events Committee: mortality, stroke, myocardial infarction, bleeding, etc.

*proesthetic aortic valve performance as measured by transthoracic echocardiography (TTE) and assessed by an independent core laboratory

*functional status

*neurological status

*health status

Study description

Background summary

Justification for the use of the investigational device in human subjects
The incidence of aortic stenosis (AS) 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. Nearly 5% of individuals >75 years of age have some degree of AS. Once symptoms manifest, the prognosis is poor, especially when associated with congestive heart failure. Successful treatment of aortic valve obstruction can result in the improvement of symptoms, hemodynamic parameters, systolic function, and cardiac hypertrophy along with increased survival.
Surgical aortic valve replacement (SAVR) remains the gold standard treatment for the management of subjects with severe AS. However, the operative risk is increased in elderly subjects, in subjects with concomitant coronary artery disease or severely reduced left ventricular (LV) function, and in subjects with associated comorbidities such as cerebral and peripheral vascular disease, renal failure, and respiratory dysfunction. Percutaneous transluminal aortic valvuloplasty, which was introduced as an alternative to SAVR in elderly and/or high-risk subjects, can provide symptomatic relief and/or temporary improvement but does not provide definitive treatment in subjects with severe calcified AS. It is also associated with relatively high mortality and complication rates.
Transcatheter aortic valve replacement has recently emerged as an alternative to the surgical approach in the treatment of severe AS in subjects who are not suitable candidates for open-heart surgery. This technology is generally

restricted to subjects considered at prohibitive or high surgical risk.
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, device-specific registries, national registries, and randomized controlled trials. Through 2-year follow-up in the PARTNER US IDE trial there have been significant reductions in mortality and repeat hospitalization rates compared to standard medical therapy in subjects unsuitable for SAVR29, and similar mortality rates compared to surgical valve replacement in high-surgical-risk subjects. An expert consensus document on TAVR was recently published.
Related literature is referenced in the full-text study protocol.
Table 4.1 1 in the protocol summarizes the peri-operative event rates through 30 days post-procedure from several TAVR studies that enrolled similar subjects as those planned for this study, as well as the results from the inoperable (Cohort B) and high risk (Cohort A) subjects with severe aortic stenosis enrolled in the PARTNER US IDE trial. A more detailed summary of the available literature is presented in the Investigator Brochure.

REPRISE I Study
The aforementioned results notwithstanding, TAVR with early generation devices has been associated with increased stroke risk versus surgical valve replacement. Cerebrovascular accidents and vascular complications associated with TAVR have been significant predictors of mortality. The paravalvular regurgitation more commonly seen with TAVR compared to surgery has also been accompanied by higher early and late mortality. While careful subject selection may serve to mitigate these risks, device design improvements such as seen with the Lotus Valve System (Section 5.1) may enable more precise placement, minimize or eliminate paravalvular regurgitation, and obviate the need for valve-in-valve repeat intervention.
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. The primary endpoint was clinical procedural success, defined as successful implantation of a Lotus Valve (per the Valve Academic Research Consortium [VARC] definitions44) 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.
To date, the study has reached the primary endpoint, which was achieved in 9/11 subjects. 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 criteria for device success. The Echocardiography Core Lab concluded that the device failure (mean aortic valve gradient >20 mmHg) 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, which was based on preliminary adjudication by the CEC and is pending full adjudication based on an assessment to be performed at 90-day follow-up. 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 data16,24,27,28,46.
To date, data are available through 6 months47. There were no additional MACCE events beyond the primary endpoint. While all REPRISE I subjects were NYHA Class II (n=6) or Class III (n=5) at baseline, this distribution was significantly improved at 6 months (6 in Class I, 4 in Class II, 1 in Class III; P=0.004). The mean aortic valve gradient was 13.9±3.8 mmHg for the cohort at 6 months, which was below the VARC criterion of 20 mmHg, and there was no moderate or severe paravalvular aortic regurgitation. The results of the REPRISE I feasibility study support the acute safety and performance of the Lotus Valve System.

Justification for the Study Design
As noted above, the Lotus Valve System potentially provides a number of performance and safety features beyond that of earlier TAVR devices. These include a pre-loaded delivery system, early leaflet function to maintain hemodynamic stability during valve deployment, an enhanced ability to place the valve correctly at the first attempt using the radiopaque marker to aid in valve positioning, the capacity to reposition the device if the initial deployment is considered to be suboptimal, the capability of to retrieveing the device if during the procedure the decision is made 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 the specific use of the Lotus Valve System have been mitigated to acceptable limits and are comparable to that associated with existing transcatheter aortic valves. It was also concluded that the aforementioned design features may improve procedural safety. The available sponsor-provided training program and proctorship for physicians further mitigates the risk. The result is a procedure with residual subject risk comparable to that of currently available transcatheter aortic valves and significant 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.

Study objective

To evaluate the safety and performance of the Lotus Valve system for transcathether aortic valve replacment (TAVR) in symptomatic subjects with severe calcific aortic stenosis who are considered high risk for surgical valve replacement.

Study design

The REPRISE II clinical study is a prospective, single-arm, multicenter study designed to evaluate the safety and performance of the Lotus Valve System for TAVR in symptomatic subjects who have severe calcific aorta valve stenosis and who are at high risk for surgical aortic valve replacement (SAVR).

Intervention

The procedure consists of :
- preparation of the subject for the percutaneous procedure following standard techniques. The commercially approved Lotus Introducer Set will be used as an accessory to the Lotus Valve System during the procedure.
- a balloon valvuloplasty on the native valve following standard techniques must be performed with an adequately sized valvuloplasty balloon.
- preparing and using the Lotus Valve System: the implantation procedure requires 2 operators: first and second operators. Both operators must comply with the IFU and must be trained and certified by BSC personnel in accordance with the training plan before performing the procedure.

Study burden and risks

The burden of participating in this trial could be related to the yearly follow-up visit throughout 5 years after the implantation. On the one hand these planned follow-up visits are positive for the patients since they will be followed very closely, on the other hand these yearly follow-up visits can be experienced as a burden since they are planned up to 5 years after the implant in a strict timewindow. Patients will also be requested to complete on regular timepoints (baseline, 30 days, 6 month, 1 year, 3 year and 5 year) Quality of Life questionnaires. This can also be experienced as a burden for the patients enrolled in the study. The burden of other planned examinations depends on routine practice within the hospital. As far as planned examinations per study protocol are part of the routine examinations in daily practice, they are no extra burden for the patients enrolled in the trial.

The possible risks and side effects of taking part in this study are listed above in section E. Patients who take part in this study are subject to similar risks shared by all patients who receive a similar type of device but are not in this study. There may also be additional risks or side effects which are unknown at this time.
As a result of the complications listed above, you may require medical,

percutaneous or surgical intervention, including re-operation and replacement of the Lotus* 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.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

IC1. Subject is >=70 years of age
IC2. Subject has documented calcific native aortic valve stenosis with an initial aortic valve area (AVA) of <1.0 cm2 (or AVA index of <0.6 cm2/m2) and either a mean pressure gradient >40 mm Hg or a jet velocity >4 m/s, as measured by echocardiography
IC3. Subject has a documented aortic annulus size between >=20 and <=27 mm based on

pre-procedure diagnostic imaging
IC4. Symptomatic aortic valve stenosis with NYHA Functional Class >= II
IC5. Subject is considered high risk for surgical valve replacement based on at least one of the following:
a. Society of Thoracic Surgeons (STS) score >=8%, AND/OR
b. Agreement by the heart team (which must include an in-person evaluation by an experienced cardiac surgeon) that subject is at high operative risk of serious morbidity or mortality with surgical valve replacement
IC6. Heart team (which must include an experienced cardiac surgeon) assessment that the subject is likely to benefit from valve replacement.
IC7. Subject (or legal representative) understands the study requirements and the treatment procedures, and provides written informed consent.
IC8. 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.

Exclusion criteria

EC1. Subject has a congenital unicuspid or bicuspid aortic valve.
EC2. Subject with an acute myocardial infarction within 30 days of 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, or has any permanent neurologic defect prior to study enrollment.
EC4. Subject is on dialysis or has serum creatinine level >3.0 mg/dL or 265 µmol/L.
EC5. Subject has a pre-existing prosthetic heart valve (aortic or mitral) or a prosthetic ring in any position.
EC6. Subject has >=3+ mitral regurgitation, >=3+ aortic regurgitation or >=3+ tricuspid regurgitation (i.e., subject cannot have more than moderate mitral, aortic or tricuspid regurgitation).
EC7. Subject has a need for emergency surgery for any reason.
EC8. Subject has a history of endocarditis within 12 months of index procedure or evidence of an active systemic infection or sepsis.
EC9. Subject has echocardiographic evidence of intra-cardiac mass, thrombus or vegetation.
EC10. Subject has Hgb <9 g/dL, platelet count <50,000 cells/mm3 or >700,000 cells/mm3, or white blood cell count <1,000 cells/mm3.
EC24. 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.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	11-09-2013
Enrollment:	20
Type:	Actual

Medical products/devices used

Generic name:	Aortic Valve System
Registration:	No

Ethics review

Approved WMO Date:	09-09-2013
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-04-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
ClinicalTrials.gov	NCT01627691
CCMO	NL44883.078.13