The PARTNER II Trial: Placement of AoRTic TraNscathetER Valves: Continued Access Program for SAPIEN 3 Intermediate Risk (S3iCAP)

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The PARTNER II Trial for SAPIEN 3 Intermediate Continued Access

The Safety and Effectiveness of the SAPIEN 3 Transcatheter Heart Valve with Associated Delivery Systems in Intermediate Patients with Severe Symptomatic Aortic Stenosis

Study 2010-12-US Amendment H

IDE G090216

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1.0 Purpose

The purpose of this protocol is to provide continued access of the Edwards SAPIEN 3 Transcatheter Heart Valve Model 9600TFX (20, 23, 26, 29 mm) and delivery systems (transfemoral, transapical and transaortic), which are intended for use in patients with symptomatic, calcific, severe aortic stenosis for patients with intermediate risk for standard aortic valve replacement.

2.0 Device Description

The Edwards SAPIEN 3 transcatheter heart valve (THV) is comprised of a balloon-expandable, radiopaque, cobalt-chromium alloy frame, trileaflet bovine pericardial tissue valve, and polyethylene terephthalate (PET) internal fabric skirt, and a PET outer skirt. The valve is treated according to the Edwards ThermaFix process, and is packaged and terminally sterilized in glutaraldehyde.

Refer to the instructions for use for descriptions of the following SAPIEN 3 Edwards accessory devices:

- Edwards Commander Delivery System, models 9610TF23, 9610TFX23, 9610TF29 for the transfemoral procedure
- Edwards Expandable Introducer Sheath Set, models 9610ES14, 916ES23 for the transfemoral procedure
- Edwards Certitude Delivery System, models 9620TA23, 9620TA26, and 9620TA29 for transapical and transaortic procedure
- Edwards Certitude Introducer Sheath Set, models 9620IS18 and 9620IS21 for the transapical and transaortic procedure
- Ascendra Balloon Aortic Valvuloplasty Catheter model 9100BAVC for the transapical and transaortic procedure
- Crimper, model 9600CR

3.0 Background

A total of 1,078 intermediate risk patients were enrolled in the PARTNER II SAPIEN 3 intermediate (PIIS3i) cohort. Edwards has received strong feedback from the PARTNER Community that further research for both the SAPIEN 3 valve as well as the intermediate risk group is warranted to expand the device and procedural related learning as well as to address the needs of patients that are in the screening process or could present at the investigating centers.

4.0 Design

All data from Screening through 1 year; including adverse events (AE) will be entered in The Society of Thoracic Surgeons (STS) and the American College of Cardiology (ACC), TVT Registry™ (TVTR). Data excerpts of the TVTR data entered by enrolling sites will be transferred to the Sponsor on a monthly basis. All patient personal identifiers will be redacted prior to data transfer. The annual one year follow-up visit data will be entered in the TVTR, and data from years 2-5 will be obtained from the Centers for Medicare and Medicaid Services (CMS) via TVTR linkage.

Edwards or designee will monitor the patient 30-day follow up visit data.

The TVTR is a benchmarking tool developed to track patient safety and real-world outcomes related to transcatheter valve replacement, repair procedures and emerging treatments for valve disease patients. It is designed to monitor the safety and efficacy of these new technologies for the treatment of valve disease.

Patients in PIIS3i continued access must be covered by Medicare. This will enable Edwards to link to the CMS database for long term follow-up through 5 years. No other insurance provider will be accepted for enrollment.

Participating sites will maintain patient files in the same manner as they do for the initial Investigational Device Exemption (IDE) study patient populations. Refer to the PARTNER II protocol version 6.0 or most current protocol version for additional information.

5.0 Continued Access Protocol Endpoints

The primary safety and effectiveness endpoint is stroke, aortic valve reintervention and death at the 30-day follow-up visit.

Summary statistic reports for the primary safety and effectiveness endpoint will be provided at the 1 year follow-up visit.

Secondary safety endpoints will include death, annular dissection, aortic dissection, major access vascular site complication, unplanned vascular surgery or intervention, and retroperitoneal, GI and GU bleeds, and bleeding at access sites collected through the 30 day follow-up visit.

Summary statistic reports for individual rates of death and all other safety endpoints included in the TVTR data collection form in sections F, I, and on the adjudicated event rates (section J) for stroke and aortic reintervention will be provided.

6.0 Sites

Up to a total of 60 actively enrolling sites.

7.0 Enrollment

A total of 1,078 intermediate risk patients were implanted in the PIIS3i cohort. Enrollment in this continued access protocol will consist of up to a maximum of 2,000 PIIS3i patients. Patients enrolled under the PIIS3i continued access will become part of the TVTR database. Edwards will receive data excerpts from the TVTR on a monthly basis through the first year of patient registration and then yearly through follow-up year 5. Edwards will provide annual reports to the FDA based on this data through year 5 of follow up.

To ensure enrollment is representative and balanced across study sites, no site will enroll more than 15 percent of the total enrollment or implant approach.

8.0 Continued Access Study Duration

Enrollment will continue up to a maximum of 2,000 continued access patients.

Initial Enrollment: January 2015

Anticipated Enrollment Close: August 2016

9.0 Patient Population

Inclusion Criteria

All candidates for this study must meet the following criteria:

1. Patients must be covered by Medicare. This will enable Edwards to link to the CMS database for long term follow-up through 5 years. No other insurance provider will be accepted.
2. Assessment of intermediate surgical risk defined as STS 4-8% or heart team assessment of intermediate risk factors.
3. Patient has senile degenerative aortic valve stenosis with echocardiographically derived criteria: mean gradient > 40 mmHg or jet velocity greater than 4.0 m/s and an initial aortic valve area (AVA) of $\leq$ 0.8 cm^2 or indexed EOA < 0.5 cm^2/m^2. Qualifying echo must be within 60 days of the date of the procedure.
4. Aortic valve annulus area range (273mm^2-680 mm^2) per 3D imaging (echo, CT, or MRI).
5. Patient is symptomatic from his/her aortic valve stenosis, as demonstrated by NYHA Functional Class II or greater.
6. The heart team agrees (and verified in the case review process) that valve implantation will likely benefit the patient.
7. Heart team agrees (a priori) on treatment strategy for concomitant coronary disease (if present).
8. The study patient or the study patient's legal representative has been informed of the nature of the study, agrees to its provisions and has provided written informed

consent as approved by the Institutional Review Board (IRB) of the respective clinical site.

9. The study patient agrees to comply with all required post-procedure follow-up visits including annual visits through 5 years and analysis close date visits, which will be conducted as a phone follow-up.

Exclusion Criteria

Candidates will be excluded from the study if any of the following conditions are present:

1. Heart team assessment of inoperability (including examining cardiac surgeon).
2. Evidence of an acute myocardial infarction ≤ 1 month (30 days) before the intended treatment [(defined as: Q wave MI, or non-Q wave MI with total CK elevation of CK-MB ≥ twice normal in the presence of MB elevation and/or troponin level elevation (WHO definition)].
3. Aortic valve is a congenital unicuspid or congenital bicuspid valve, or is non-calcified.
4. Mixed aortic valve disease (aortic stenosis and aortic regurgitation with predominant aortic regurgitation >3+).
5. Pre-existing mechanical or bioprosthetic valve in any position.
6. Complex coronary artery disease:
   a) Unprotected left main coronary artery
   b) Syntax score > 32 (in the absence of prior revascularization)
7. Any therapeutic invasive cardiac procedure resulting in a permanent implant that is performed within 30 days of the index procedure (unless part of planned strategy for treatment of concomitant coronary artery disease). Implantation of a permanent pacemaker or ICD is not considered exclusion criteria.
8. Any patient with a balloon valvuloplasty (BAV) < 30 days of the procedure (unless BAV is a bridge to procedure after a qualifying ECHO).
9. Patients with planned concomitant surgical or transcatheter ablation for atrial fibrillation.
10. Leukopenia (WBC < 3000 cell/mL), acute anemia (Hgb < 9 g/dL), thrombocytopenia (Plt < 50,000 cell/mL).
11. Hypertrophic cardiomyopathy with or without obstruction (HOCM).
12. Hemodynamic or respiratory instability requiring inotropic support, mechanical ventilation or mechanical heart assistance within 30 days of screening evaluation.
13. Need for emergency surgery for any reason.
14. Severe ventricular dysfunction with LVEF < 20%.
15. Echocardiographic evidence of intracardiac mass, thrombus or vegetation.

16. Active upper GI bleeding within 3 months (90 days) prior to procedure.
17. A known contraindication or hypersensitivity to all anticoagulation regimens, or inability to be anticoagulated for the study procedure.
18. Native aortic annulus size < 16 mm or > 28mm as measured by echocardiogram.
19. Clinically (by neurologist) or neuroimaging confirmed stroke or transient ischemic attack (TIA) within 6 months (180 days) of the procedure.
20. Renal insufficiency (creatinine > 3.0 mg/dL) and/or renal replacement therapy at the time of screening.
21. Estimated life expectancy < 24 months (730 days) due to carcinomas, chronic liver disease, chronic renal disease or chronic end stage pulmonary disease.
22. Expectation that patient will not improve despite treatment of aortic stenosis.
23. Significant aortic disease, including marked tortuosity (hyperacute bend), aortic arch atheroma [especially if thick (> 5 mm), protruding or ulcerated] or narrowing (especially with calcification and surface irregularities) of the abdominal or thoracic aorta, severe “unfolding” and tortuosity of the thoracic aorta. (Transfemoral)
24. Iliofemoral vessel characteristics that would preclude safe placement of 14F or 16F introducer sheath such as severe obstructive calcification, severe tortuosity or minimum average vessel size less than 5.5 mm. (Transfemoral).
25. Currently participating in an investigational drug or another device study. Note: Trials requiring extended follow-up for products that were investigational, but have since become commercially available, are not considered investigational trials.
26. Active bacterial endocarditis within 6 months (180 days) of procedure.
27. Evidence of intracardiac mass, thrombus, vegetation, active infection or endocarditis.
28. Inability to tolerate anticoagulation/antiplatelet therapy.
29. For transfemoral approach only: Femoro-iliac vessels < 5.5 mm for the 23 mm and the 26 mm system and < 6.0 mm for the 29 mm system.

10.0 Study Visits

The data in the following sections will be collected for all patients (see Table 1.0). Assessments listed throughout this section are an overview of key assessments; however, please refer to the TVTR data collection form for all required assessments.

10.1 Screening

The screening phase is designed to meet the following objectives:

1. Determine patient eligibility, operability risk assessment and access site for THV procedure.

2. Patient informed consent.

10.1.0 Screening Assessments

Screening assessments should be completed within 30 days of patient enrollment unless otherwise specified.

- Medical history
- STS Risk Score
- NYHA classification
- Syntax Score (conducted in the absence of prior revascularization)
- Hemoglobin, Platelet Count, Creatinine
- Transthoracic (TTE) or transesophageal echocardiogram (TEE)
- Cardiac Imaging (ECHO, CTA, or cardiac MRI) with 3D reconstruction of the aortic root to determine aortic valve annulus area must be completed within 180 days of patient enrollment.
- Reference S3 Sizing Guide (Protocol 6.0, Appendix U) for sizing recommendations
- Thoracic x-ray, an abdominal angiogram, and CT angiograms or MRI, and with complete visualization of both iliacs and femorals to the aorta. In the situation where patients have compromised renal function that precludes the use of contrast agents, MR imaging may be used as an alternative. CT scans are strongly recommended, particularly in patients with femoral arteries less than 7 mm; (must be within 180 days of patient enrollment). Patients with previously documented inadequate femoral access [(Iliofemoral vessel characteristics that would preclude safe placement of 22F or 24F introducer sheath (14F or 16F for S3) such as severe obstructive calcification, severe tortuosity or minimum average vessel size less than 6 mm (20, 23 and 26 mm THV minimum vessel size ≥ 5.5 mm / 29 mm THV minimum vessel size ≥ 6.0 mm for S3)] don't require repeat testing.
- Left and right cardiac catheterization to assess the severity of aortic stenosis and severity of coronary artery disease if applicable (< 90 days before procedure)

Data must be entered in the STS/ACC TVT Registry. Data in the TVTR data forms will be included in monthly data transfers from the TVTR to the Sponsor. All patient personal identifiers will be redacted prior to data transfer.

10.2 Case Review Process

Patients must meet the fundamental enrollment criteria of severe, symptomatic, calcific aortic stenosis. Upon meeting these eligibility criteria, the site investigators (per site heart team assessment) shall then determine the patient's risk for operative morbidity and mortality. Patients determined to be operable must have a STS score of 4 - 8% or a defensible

intermediate risk profile determined by the heart team and approved by the case review board process.

The PARTNER II trial operations include a case review process prior to enrollment of patients. After screening assessments are made, the patient's qualifying criteria are reviewed by the case review board where the members will assess patient eligibility and access approach. Upon approval, the patient may be enrolled into the study. The case approval decision will be documented by the Sponsor.

The study procedure should occur within two weeks (14 days) of case approval.

10.3 Pre-Procedure Assessments

The following data will be collected for all patients prior to the procedure (see Table 1.0). Assessments must be completed within 30 days of patient enrollment unless otherwise specified.

- Height and weight closest to the time of the procedure
- Medication classification (anticoagulants, anti-platelet/anti-thrombins, inotropes)
- STS Score
- 5 Meter Walk Test
- KCCQ
- Pulmonary Function Test (FEV1, DCLO); optional
- Albumin
- Bilirubin, total
- INR

Data must be entered in the STS/ACC TVT Registry. Data in the TVTR data forms will be included in monthly data transfers from the TVTR to the Sponsor. All patient personal identifiers will be redacted prior to data transfer.

10.4 Procedure Assessments

The following procedural data should be collected:

- Intra-procedure medications (inotropes)
- AV gradients (post-implant)
- Calculated aortic valve area (post-implant)
- Radiation dosage
- AE Assessment. For those events considered UADE, refer to protocol 6.0 or the most current protocol version (Section 11.0) for reporting requirements.

Device accountability will be retained on the Sponsor Device Accountability Forms.

Data must be entered in the STS/ACC TVT Registry. Data in the TVTR data forms will be included in monthly data transfers from the TVTR to the Sponsor. All patient personal identifiers will be redacted prior to data transfer.

10.5 Post Procedure Assessments

The post procedure time period is within 48 hours from the time the patient exits the cath lab or operating room unless otherwise noted. The following post procedure data will be collected:

- Hemoglobin (lowest)
- Creatinine (highest)
- 12 Lead ECG
- TTE or TEE
- AE Assessment. For those events considered UADE, refer to protocol 6.0 or the most current protocol version (Section 11.0) for reporting requirements.

Data must be entered in the STS/ACC TVT Registry. Data in the TVTR data forms will be included in monthly data transfers from the TVTR to the Sponsor. All patient personal identifiers will be redacted prior to data transfer.

10.6 Discharge Assessments

The following data will be collected for all patients for the index hospitalization:

- RBC/Whole blood transfusions
- Medications (cardiac, anticoagulants, anti-platelet/anti-thrombins)

- AE Assessment. For those events considered UADE, refer to protocol 6.0 or the most current protocol version (Section 11.0) for reporting requirements.

Data must be entered in the STS/ACC TVT Registry. Data in the TVTR data forms will be included in monthly data transfers from the TVTR to the Sponsor. All patient personal identifiers will be redacted prior to data transfer.

10.7 30 Day Follow-Up Visit Assessments

The following data will be collected:

- Hemoglobin
- Creatinine
- NYHA
- 5 Meter Walk
- 12 Lead ECG
- TTE or TEE
- KCCQ

- Medications (cardiac, anticoagulants, anti-platelet/anti-thrombins)
- AE Assessment. For those events considered UADE, refer to protocol 6.0 or the most current protocol version (Section 11.0) for reporting requirements.

Data must be entered in the STS/ACC TVT Registry. Data in the TVTR data forms will be included in monthly data transfers from the TVTR to the Sponsor. All patient personal identifiers will be redacted prior to data transfer.

10.8 1 Year Follow-Up Visit Assessments

The following data will be collected:

- Hemoglobin
- Creatinine
- NYHA
- 5 Meter Walk
- 12 Lead ECG
- TTE or TEE
- KCCQ
- Medications (cardiac, anticoagulants, anti-platelet/anti-thrombins)
- AE Assessment. For those events considered UADE, refer to protocol 6.0 or the most current protocol version (Section 11.0) for reporting requirements.

Data must be entered in the STS/ACC TVT Registry database. Data in the TVTR data forms will be included in monthly data transfers from the TVTR to the Sponsor. All patient personal identifiers will be redacted prior to data transfer.

10.9 Annual Follow-Up, Years 1-5

Annual follow-up 1 through 5 years will be obtained for all patients through TVTR linkage to the CMS database. Determination of outcomes for death, stroke and rehospitalization will utilize data from this linkage.

11.0 Monitoring of Study

Edwards or designee will conduct source data verification through the 30-day follow-up visit.

12.0 Protocol Deviations

The sponsor will check inclusion/exclusion for violations during the monthly extract receipt from the TVTR as well as during source document verification monitoring.

Table 1.0 - Schedule of Events

	Screening	Pre-Procedure	During procedure	Post Procedure	Discharge	30 D Follow-Up	1 yr Follow-Up
Assessments							
Informed Consent	**X**						
Medical History	**X**						
Height/Weight		**X**					
Medications		**X**	**X**		**X**	**X**	**X**
Screening Assessments	Screening	Pre-Procedure	During procedure	Post Procedure	Discharge	30 D Follow-Up	1 yr Follow-Up
STS	**X**						
NYHA	**X**					**X**	**X**
CCS							
Syntax Score	**X**						
5 Meter Walk		**X**				**X**	**X**
KCCQ		**X**				**X**	**X**
AE / UADE Assessment			**X**	**X**	**X**	**X**	**X**
Lab Measurements	Screening	Pre-Procedure	During procedure	Post Procedure	Discharge	30 D Follow-Up	1 yr Follow-Up
WBC	**X**						
Hgb	**X**			**X**	**X**	**X**	**X**
Plt Ct	**X**						
Crt	**X**			**X**	**X**	**X**	**X**
Alb		**X**					
Bili		**X**					
INR		**X**					

	Screening	Pre-Procedure	During procedure	Post Procedure	Discharge	30 D Follow-Up	1 yr Follow-Up
Non-Invasive Tests							
TTE or TEE	**X**			**X**		**X**	**X**
Fluoroscopic imaging implanted valve			**X**				
Pulmonary Functions (optional)		**X**					
Radiation Dosage			**X**				
12 Lead ECG				**X**		**X**	**X**
Invasive Tests	Screening	Pre-Procedure	During procedure	Post Procedure	Discharge	30 D Follow-Up	1 yr Follow-Up
Cardiac Imaging	**X**						
CT Thoracic/Abdomen (or MRI) with visualization of iliac and femoral arteries	**X**						
Cardiac Catheterization	**X**						
Supra-aortic angiogram or TEE			**X**				
Hemodynamics (see section 9.4 of protocol 6.0 or most current protocol version)			**X**				