1.0 Executive Summary

Proposed Indications for Use:

The Edwards SAPIEN Transcatheter Heart Valve, model 9000TFX, sizes 23mm and 26mm, and RetroFlex 3 Delivery System are indicated for transfemoral delivery in patients with severe aortic stenosis who have been determined by a cardiac surgeon to be inoperable for open aortic valve replacement and in whom existing co-morbidities would not preclude the expected benefit from correction of the aortic stenosis.

The RetroFlex Balloon Catheter is indicated for predilatation of a stenotic cardiac valve prior to implantation of a transcatheater heart valve.

The Crimper is indicated for preparing the Edwards SAPIEN Transcatheter Heart Valve for implantation.

2.0 Device Description

The Edwards SAPIEN Transcatheter Heart Valve (bioprosthesis), shown in Figure 1, is comprised of a balloon-expandable, radiopaque, stainless steel (316L) frame, three bovine pericardial tissue leaflets, and a polyethylene terephthalate (PET) fabric. The bioprosthesis is treated according to the Carpentier-Edwards ThermaFix process, packaged, and terminally sterilized in glutaraldehyde.

The RetroFlex 3 Delivery System, shown in Figure 2, includes a rotating wheel within the handle for articulation of flex catheter, a tapered tip at the distal end of the delivery system to facilitate crossing the native valve, a balloon for deployment of the bioprosthesis, and radiopaque markers.
The RetroFlex Balloon Catheter, shown in Figure 3, is used to predilate stenotic cardiac valves. The device consists of a shaft and balloon with radiopaque markers indicating working length of the balloon. At the proximal end of the device, there is a standard “Y-connector” for balloon inflation and guidewire insertion.

![Figure 3: RetroFlex Balloon Catheter](image)

The Crimper, shown in Figure 4, is comprised of a housing and a compression mechanism, creating an aperture that is opened and closed by means of a handle located on the housing. The crimper includes a balloon gauge to verify diameter of an inflated balloon catheter and a crimp gauge to verify collapsed diameter of the device.

![Figure 4: Crimper](image)

## 3.0 Summary of Nonclinical Studies

### 3.1 In vitro Testing

*In vitro* studies were performed for the Edwards SAPIEN Transcatheter Heart Valve Model 9000TFX and non-implantable accessories as recommended in the FDA’s *Draft Replacement Heart Valve Guidance* (1994) and ISO 5840: *Cardiovascular Implants-Cardiac Valve Prostheses* (2005). It included fatigue and corrosion evaluation of the stainless steel valve frame and hydrodynamic performance and durability assessment of the whole valve. The testing exceeded that for traditional surgical bioprosthetic heart valves. The results supported the intended performance of the device in the clinical environment.
Testing of the SAPIEN valve in magnetic fields of 1.5 and 3.0 Tesla has shown that this device is MR Conditional.

Design verification testing of the accessories associated with the transfemoral delivery was performed using various voluntary standards. The results supported the intended performance of the device in the clinical environment.

Packaging and sterilization processes were validated according to FDA recognized international standards. Packaging and product integrity studies were conducted to ensure that the shelf life for each package and product is maintained for a minimum of two (2) years for the SAPIEN Valve, RetroFlex 3 Delivery System, RetroFlex Balloon Catheter, and Crimper.

The SAPIEN Valve Model 9000TFX is sterilized by terminal liquid sterilization (TLS) in buffered glutaraldehyde solution. The RetroFlex 3 Delivery System, RetroFlex Balloon Catheter, and Crimper are sterilized by ethylene oxide (EO). The TLS and EO processes have demonstrated Sterility Assurance Levels (SAL) exceeding the industry standard of $10^{-6}$ in validation studies.

### 3.2 Biocompatibility Studies

Toxicology and biocompatibility testing for the SAPIEN Transcatheter Heart Valve Model 9000TFX and accessories was conducted in accordance with Good Laboratory Practices (21 CFR §58) and ISO 10993-1: 2003 *Biological Evaluation of Medical Devices Part 1: Evaluation and Testing*.

Testing results demonstrated that the devices are biocompatible for their intended use and compliant with the FDA recognized international standards for biocompatibility.

### 3.3 SAPIEN Valve Animal Studies

Feasibility studies were conducted in over 100 animals (porcine, bovine, canine and ovine) in an attempt to identify a suitable animal model and study feasibility of percutaneous delivery of the valve. A chronic study was performed with the equine version of the SAPIEN valve in which 19 juvenile sheep with induced aortic insufficiency were implanted. Six animals survived to 21 weeks. The gross findings and histopathology suggested the valve was capable of long-term implant.

A chronic *in vivo* animal implantation study was conducted using the SAPIEN Valve (final bovine version), Model 9000TFX in the adult ovine model. A total of eighteen test article Model 9000TFX valves were implanted in the aortic position of 18 adult male sheep for a 10 week (n=9) and 20 week (n=9) evaluation study; 3 of 9 animals survived to at least 10 weeks and 6 of 9 survived to at least 20 weeks. Three (3) control articles were implanted in the aortic position of 3 adult male sheep; 2 control animals survived to at least 20 weeks and were clinically normal prior to explant; 1 animal survived to less than 14 days. No control valves were evaluated at 10 weeks. The results of this study indicate that the 9000TFX valve model has acceptable hemodynamic performance. Normal healing with pliable leaflets and no thrombus were observed, with no evidence of infection or calcification when implanted for 20 weeks. The two valve models were comparable for all parameters evaluated.
4.0 Summary of Clinical Studies

Study Design
The PARTNER trial (Cohort B) was a prospective, stratified, randomized controlled, multi-center pivotal trial to evaluate the safety and effectiveness of the Edwards SAPIEN™ Transcatheter Heart Valve and accessories in non-surgical patients who were candidates for the transfemoral approach. The patients who were non-operable but were not eligible for transfemoral delivery were not eligible for randomization into the trial. A total of 358 patients with aortic stenosis who were not considered to be suitable candidates for surgery underwent randomization at 22 centers (18 in the United States).

Patients with severe aortic stenosis, whom surgeons considered not suitable candidates for surgery, were randomly assigned to standard therapy (including BAV) or SAPIEN implantation via the transfemoral approach. The primary study endpoint was the rate of death from any cause. All patients were followed for at least 1 year, and cross-over from the standard therapy group to the TAVR group was not permitted. The coprimary endpoint was the rate hierarchical composite of the time to death from any cause or the time to the first occurrence of repeat hospitalization (after the index procedure) due to valve-related or procedure related clinical deterioration. This composite endpoint was also reported with the use of more conventional Kaplan-Meier nonhierarchical analytical methods. Prespecified secondary end points included rate of death from cardiovascular causes, NYHA functional class, the rate of repeat hospitalization due to valve-related or procedural related clinical deterioration, the distance covered during a 6 minute walk test, valve performance (assessed by echocardiography), and the rates of myocardial infarction, stroke, acute kidney injury, vascular complications, and bleeding. A major stroke was defined as a focal or global neurologic deficit associated with a score of 2 or higher on the modified Rankin scale, which has a range of 0 to 6, with 0 indicating no symptoms and 6 indicating death. All patients were followed during the index hospitalization; at 30 days, 6 months, and 1 year; and yearly thereafter.

Study Results
Following in vitro, preclinical and clinical feasibly study, The PARTNER (Placement of AoRTic TraNscatheTER Valves) Trial was designed to affirm benefit of transfemoral TAVR in inoperable patients. The PARTNER Trial identified two cohorts of patients with symptomatic severe aortic stenosis: (1) Cohort A: patients at high risk for AVR and (2) Cohort B: patients who cannot undergo AVR (inoperable patients). After stratification by cohort, patients were randomized and studied separately within each cohort.

In the inoperable cohort, 358 inoperable AS patients (STS score 11.6±6.0%) were randomized at 22 centers (18 from the U.S.). At 1 year follow-up, based on a Kaplan-Meier analysis, all-cause mortality among intent to treat (ITT) patients in the TAVR arm was 30.7 % compared to 50.7% in the standard of care arm; hazard ratio, 0.51; 95% confidence interval, 0.39 to 0.68 (P<0.0001) from log-rank. The composite of all-cause mortality and repeat hospitalization, based on a Kaplan-Meier analysis, decreased from 71.6% with standard therapy to 43.6% with TAVR; hazard ratio, 0.45; 95% confidence interval, 0.35 to 0.59 (p<0.0001 from log-rank. In 1 year ITT survivors, TAVR reduced cardiac symptoms (NYHA class I or II, 76% vs. 39.2%, p<0.0001). At 30 days, TAVR was associated with more frequent major strokes (7.3% vs. 1.7%; p = 0.02) and major vascular complications (16.8% vs. 1.1%; P<0.001). Additional analyses were performed at the request of FDA and can be found in subsequent sections. In the
year after TAVI, there was no deterioration in bioprosthetic valve function (stenosis and regurgitation) assessed by echocardiography.

Three of the 4 secondary endpoints also favored TAVR including (1) time to first occurrence of major adverse cardiac and cerebrovascular events (MACCE) within one year, (2) New York Heart Association (NYHA) functional classification at one year, and (3) 6-minute walk test at one year. For the secondary endpoint of total hospital days during year 1, patients in the standard of care group of the ITT population spent fewer days hospitalized than did those in the transfemoral TAVR group. Sensitivity analyses of patients as they were treated, mortality at one year and cardiovascular mortality all favored TAVR. Mortality at 30 days was increased in the TAVR group. Over the first 30 days after randomization, 9 TAVR patients (5.0%) died vs. 5 standard of care patients (2.8%) in the ITT population. In the as-treated population, 11 TAVR patients (6.3%) died within 30 days of implant vs. 5 standard of care patients (2.8%) who died within 30 days of randomization. The increased mortality in the TAVR group was secondary to procedural complications and stroke.

Prespecified adverse events were defined by protocol and adjudicated by a clinical endpoint committee. The safety experience in high-risk (inclusive of inoperable patients) treated in feasibility studies (REVIVE, REVIVAL, PARTNER EU) and European post market registry (SOURCE) was consistent with that observed in The PARTNER Trial (1-3).

In The PARTNER Trial high-risk operable cohort, all-cause mortality at 1 year in ITT patients was 24.2% after TAVR and 26.8% after AVR in all patients ($P=0.44$), 22.2% and 26.4%, respectively, in the transfemoral TAVR and AVR subgroup ($P=0.29$), and 29.0% and 27.9%, respectively, in the transapical TAVR and AVR subgroup ($P=0.85$). The 30-day all-cause mortality was 3.4% after TAVR and 6.5% after AVR in all patients ($P=0.07$), 3.3% and 6.2%, respectively, in the transfemoral TAVR and AVR subgroup ($P=0.13$), and 3.8% and 7.0%, respectively, in the transapical TAVR and AVR subgroup ($P=0.32$). Neurological events (transient ischemic attack, stroke) were higher after TAVR (pooled transfemoral and transapical subgroups) at 30 days and 1 year. The data from this cohort further support the safety profile of the Edwards SAPIEN™ THV.

In summary, TAVR in inoperable patients with symptomatic severe aortic stenosis substantially increases survival compared to the standard of care. In addition, patient function characterized by Quality of Life instruments (Kansas City Cardiomyopathy Questionnaire, Short-Form-12 [SF-12], and EQ5D) as well as the 6-Minute Walk Test and NYHA Classification significantly improves at 30 days and 1 year after TAVR versus standard of care including balloon aortic valvuloplasty. TAVR is associated with an increased risk for stroke and procedure-related adverse events such as bleeding and vascular complications. Overall, the benefit from TAVR in inoperable patients with symptomatic severe aortic stenosis is substantially greater than the risk.