FDA Executive Summary

Prepared for the
July 20, 2011 meeting of the
Circulatory System Devices Panel

P100041

Edwards SAPIEN™ Transcatheter Heart Valve, model 9000TFX, sizes 23mm and 26mm and accessories (RetroFlex 3™ Delivery System, models 9120FS23 and 9120FS26; RetroFlex™ Balloon Catheter, models 9120BC20 and 9120BC23; and Crimper, models 9100CR23 and 9100CR26)

INTRODUCTION

This is the FDA Executive Summary for a first-of-a-kind transcatheter aortic heart valve, the Edwards SAPIEN Transcatheter Heart Valve, model 9000TFX, sizes 23mm and 26mm and accessories. This device has been reviewed by the Division of Cardiovascular Devices within the Center for Devices and Radiological Health of the Food and Drug Administration under Premarket Approval (PMA) application P100041, which is the subject of this Advisory Panel meeting.

This memorandum will summarize the FDA’s review of the PMA up to this point, highlighting the particular areas for which we are seeking your expertise and input. These topics will include the proposed indications for use, pre-clinical study findings, the results of the randomized clinical study conducted by the sponsor, and the proposed post-approval study. At the conclusion of your review and discussion of the data presented, the Agency will ask for your recommendation regarding whether or not the data demonstrate a reasonable assurance of safety and effectiveness.
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1 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 pre-dilatation of a stenotic cardiac valve prior to implantation of a transcatheter heart valve.

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

2 DEVICE DESCRIPTION

The Edwards SAPIEN Transcatheter Heart Valve, model 9000TFX, sizes 23mm and 26mm and accessories implant system consists of eight components and sub-components.

The Edwards SAPIEN Transcatheter Heart Valve consists of a heterologous (bovine) pericardium leaflet valve sutured within a stainless steel mesh frame, with a polyester skirt. It is offered in two sizes, 23 mm and 26 mm.

For a description of the other components of the system, please refer to the sponsor’s Briefing Document.
3 REGULATORY HISTORY

The SAPIEN Transcatheter Heart Valve (THV) was originally manufactured by Percutaneous Valve Technologies (PVT), and was called the PHV Model 9000. Edwards Lifesciences acquired PVT in January 2004, changing the name of the device to Cribier-Edwards Aortic Bioprosthesis before changing the name again to SAPIEN THV. The first U.S. implant occurred in the REVIVAL I feasibility study on March 10, 2005. The REVIVAL I study was intended to compare the new valve versus balloon aortic valvuloplasty (BAV) and allowed either a retrograde (transfemoral) or antegrade implantation technique of a size 23 mm valve at two investigational sites. After 7 antegrade implants, the study was suspended while a root cause analysis of the early failures and deaths was performed, major design modifications were made, and a comprehensive training program was instituted. The device modifications included the addition of a 26 mm size valve, a new retrograde delivery catheter, replacement of equine tissue with bovine tissue valve leaflets, and the addition of the TFX anti-calcification treatment used on other Edwards valves.

The protocol was completely redrafted as the REVIVAL II study, a non-randomized study to involve only the retrograde implantation approach via a transfemoral cut down in 55 subjects. The first REVIVAL II subject was enrolled on December 15, 2005.

After all of the transfemoral subjects were entered, the transapical approach was proposed for subjects with inadequate vessel size or ileo-femoral occlusive disease that did not allow transfemoral implantation of the valve, to involve 40 subjects at 6 sites. As the transapical portion of the feasibility study was nearing completion, FDA allowed the sponsor to begin the pivotal PARTNER study, with only transfemoral implantation at the start. The pivotal trial consisted of two independent studies; an arm randomizing high risk operative patients to either open surgical aortic valve replacement or the SAPIEN device (Cohort A), and an arm randomizing inoperable patients to either “standard” therapy control arm or the SAPIEN device (Cohort B). As will be discussed later, the control arm patients in Cohort B had a variety of treatments. The pivotal study was later expanded to include the transapical subjects in the arm of the study enrolling operative patients (Cohort A), but not in the inoperable arm (Cohort B) at the request of the sponsor.

The PARTNER study was approved to begin in March 2007 (transfemoral only) for up to 40 subjects in Cohorts A and B, and was later expanded to add transapical insertion in December 2007, with an ultimate sample size of 1040 subjects (690 in Cohort A, 350 in Cohort B), at up to 30 sites. The PARTNER trial was a prospective, randomized (1:1), controlled, multi-center pivotal trial evaluating the safety and effectiveness of the Edwards SAPIEN THV in a stratified population of high risk patients. The Cohort B trial was designed to demonstrate superiority of the device to “standard” therapy for the primary endpoint of all cause death. After trial enrollment had begun, a second co-primary endpoint was added. Cohort B study enrollment ended in March 2009.

The PMA addressed by this document contains the results of the Cohort B study only; a separate PMA has been submitted covering the Cohort A study.
4 PRE-CLINICAL STUDIES

4.1 In Vitro Testing

The sponsor conducted in vitro performance and characterization studies of the SAPIEN THV:

- Test results demonstrated that the device is compliant with FDA recognized international standards for biocompatibility.
- Packaging and sterilization processes were validated according to FDA recognized international standards as well.
- The valve was evaluated for MRI compatibility.
- FDA performed a comprehensive review of the pre-clinical bench testing performed under challenging conditions to verify the design of the SAPIEN THV.
  - The testing was conducted in accordance with the international heart valve standard (ISO 5840) and the draft FDA heart valve guidance document.
  - Testing included fatigue (15 years of simulated use) and corrosion evaluation of the stainless steel valve frame as well as an assessment of hydrodynamic performance and durability (5 years of simulated use) of the whole valve.
  - Scope of the bench testing performed exceeded that for traditional surgical bioprosthetic heart valves, and the results supported device safety in the anticipated clinical environment for the intended patient population.
  - Design verification testing of the accessories associated with transfemoral delivery was done using various voluntary standards, and was found to be acceptable.

The only unresolved issue raised by the FDA engineering review team is the safety associated with valve-in-valve implantation. According to ISO 5840, surface damage (i.e., fretting corrosion) may occur between two surfaces that are in close contact, under pressure, and are subjected to slight relative motion, and corrosion (i.e., galvanic corrosion) could occur between two dissimilar materials. In response to FDA’s request to investigate the effects of valve-in-valve implantation, especially fretting corrosion and galvanic corrosion, the sponsor has stated that “[t]he SAPIEN valves are not deployed in an overlapping condition with other vascular implants, nor do they contain multiple metallic components as the implant is composed entirely of 316L stainless steel and therefore this testing is not applicable to the Edwards system.”

FDA disagrees with this statement. The literature has reported many cases of valve-in-valve implantation involving the SAPIEN valve, such as SAPIEN in SAPIEN, SAPIEN in another transcatheter valve, and SAPIEN in a previously implanted surgical bioprosthesis. In the present study, the valve-in-valve configuration was used four times. The FDA is concerned that if the SAPIEN becomes commercially available, widespread use of the valve-in-valve technique might occur. However, without any pre-clinical testing, the FDA is unable to draw conclusions regarding the short- and long-term safety of valve-in-valve implantation. In addition to fretting corrosion and galvanic corrosion, other unknowns associated with valve-in-valve implantation may include long-term durability, valve migration/embolization, and access to the coronary ostia. We would appreciate the Panel’s perspective regarding ways to address this issue, such as labeling, training or other testing that may be warranted.
### 4.2 In Vivo Animal Testing of SAPIEN TPV

The sponsor conducted in vivo performance and characterization studies of the SAPIEN valve and delivery system, which included the following:

- Several feasibility studies, using the equine tissue version of the valve, in various animal models to determine the optimal model.
- A Good Laboratory Practices (GLP) study, involving 19 sheep with induced aortic insufficiency (Hufnagel Model), into which the SAPIEN valve was implanted (either percutaneously or surgically) in the proximal descending aorta. Six animals survived to 21 weeks. The gross findings and histopathology results suggest that the valve is capable of long-term implant. This study also involved the equine version of the valve.
- A second GLP study involving 21 sheep into which the SAPIEN was balloon deployed in an open chest operation into a modified Cosgrove Annuloplasty ring presewn at the aortic annulus supra-annular position. The control valve (Carpentier-Edwards PERIMOUNT) was implanted in the same position. Both the test valve and the control valve had acceptable hemodynamic performance, normal healing with pliable leaflets, and no thrombus. In addition, there was no evidence of infection or calcification. These two valve models were comparable in all parameters evaluated. This final GLP study utilized the current bovine version of the valve which was studied in the PARTNER trial and is the subject of this PMA.

### 4.3 Device Modifications

The valve was significantly modified, as noted above, prior to starting the pivotal trial. During the pivotal trial, the design of the delivery components continually evolved but the changes made to the delivery system were minor. As a result, FDA believes that the clinical data collected in the PARTNER trial are applicable to the current design of the device and delivery system proposed in this PMA application.

### 5 U.S. FEASIBILITY STUDIES

The REVIVAL I feasibility study was conditionally approved on January 26, 2005. A total of 5 roll-in subjects were enrolled at the William Beaumont Hospital and two at the Columbia University Medical Center, all with the antegrade approach. Of these, three expired, two valves migrated, and there was one stroke. The study was stopped because of these adverse events. The device was redesigned, a second size (size 26 mm) was developed, and the REVIVAL II study was then proposed.

The REVIVAL II study involved 55 transfemoral and 40 transapical subjects enrolled into a registry study. The first subject was enrolled on December 15, 2005. This study was performed to develop a greater understanding of the patient population and implant technique prior to beginning a pivotal study.
6 THE PARTNER TRIAL – BACKGROUND

6.1 Study Design

The PARTNER trial was a prospective, unblinded, randomized, controlled, multi-center pivotal trial evaluating the safety and effectiveness of the Edwards SAPIEN THV, via transfemoral or transapical (Cohort A only) delivery, in a stratified population of high risk (Cohort A) or inoperable (Cohort B) patients. Because the study enrolled two distinct populations, the two Cohorts were separately-powered and analyzed. As depicted in the diagram below, an initial stratification based on operability for aortic valve replacement (AVR) surgery was used to assign the patients to Cohort A or B. Assignment to Cohorts was followed by determination of vascular access for transfemoral delivery. Patients who were considered high surgical risk and eligible for transfemoral access were stratified into Cohort A and randomized to treatment (transfemoral AVR) or control (surgical AVR). Cohort A patients who were not eligible for transfemoral access were evaluated as candidates for transapical delivery and, if appropriate, randomized to treatment (transapical AVR) or control (surgical AVR). Those patients who were considered non-surgical candidates were stratified into Cohort B and randomized to treatment (transfemoral AVR) or control (“standard” therapy). Those assigned to Cohort B who did not meet the criteria for transfemoral delivery were not enrolled in the study because the sponsor declined to have a transapical arm in Cohort B.

PARTNER Trial Enrollment Diagram

AVR=aortic valve replacement surgery, TA=transapical, TAVR=transcatheter aortic valve replacement, TF=transfemoral.

Note: the “standard” therapy control group predominantly consisted of subjects receiving BAV (78.2%); other patients received medical therapy alone (7.9%), AVR (6.1%), apical-aortic conduits (3.3%), or TAVR outside of the U.S. (2.2%)
A total of 1057 subjects were enrolled at 27 sites in the PARTNER study in the two arms – 699 patients in Cohort A (transfemoral or transapical insertion of the SAPIEN compared to surgical aortic valve replacement); 358 patients in Cohort B (transfemoral insertion of the SAPIEN versus “standard” therapy). As mentioned above, the Cohort A and Cohort B studies were separately powered. The PMA under consideration by this Panel contains data from only the Cohort B study.

Changes in the protocol were made after this unblinded study had started enrollment, the most significant of which was the addition of a co-primary composite endpoint of mortality and hospitalization. The 6-minute walk test endpoint was also added after the start of the trial. The protocol was fully approved in March 2009 (Version 3.2) coincident with completion of enrollment into the Cohort B study, and approval to begin a Continued Access study. At the onset, the Cohort B continued access study protocol was the same as the randomized PARTNER study until Cohort A enrollment was completed. In August 2009, enrollment into the Cohort A study was completed, and the Continued Access study was expanded to allow enrollment of Cohort A subjects in a non-randomized protocol. Randomization for the Cohort B group was also discontinued at that time.

6.2 Patient Selection Process and Enrollment Criteria

Much effort was spent by both FDA and the sponsor to define the inoperable patient. The existing risk assessment tools, such as the STS risk calculator, were deemed inadequate as a stand-alone mechanism for patient selection in the population; therefore, it was decided to have a minimum of two surgeons and a cardiologist make the initial inoperable decision, taking into account risk factors not covered by the STS risk calculator. This decision was then reviewed by a central study committee.

The major inclusion and exclusion criteria for the Cohort B study are summarized below; the full list is in the protocol and covered by the sponsor’s clinical report:

Inclusion Criteria

The major inclusion criteria for patient entry into the study included the following:

- Patient has senile degenerative aortic valve stenosis with echocardiographically derived criteria: mean gradient >40 mmHg or jet velocity greater than 4.0 m/s or an initial aortic valve area (AVA) of < 0.8 cm² (indexed EOA < 0.5 cm²/m²). (Qualifying AVA baseline measurement must be within 45 days prior to randomization).
- Patient is symptomatic from his/her aortic valve stenosis, as demonstrated by NYHA Functional Class II or greater.
- The subject, after formal consults by a cardiologist and two cardiovascular surgeons agree that medical factors preclude operation, based on a conclusion that the probability of death or serious, irreversible morbidity exceeds the probability of meaningful improvement. Specifically, the probability of death or serious, irreversible morbidity should exceed 50%. The surgeons' consult notes shall specify the medical
or anatomic factors leading to that conclusion and include a printout of the calculation of the STS score to additionally identify the risks in these patients.

Exclusion Criteria

The major exclusion criteria for patient entry into the study included the following:

- Evidence of an acute myocardial infarction ≤ 1 month 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).
- Mixed aortic valve disease (aortic stenosis and aortic regurgitation with predominant aortic regurgitation >3+).
- Any therapeutic invasive cardiac procedure performed within 30 days of the index procedure, (or 6 months if the procedure was a drug eluting coronary stent implantation).
- Pre-existing prosthetic heart valve in any position, prosthetic ring, severe mitral annular calcification (MAC), severe (greater than 3+) mitral insufficiency, or Gorlin syndrome
- Need for emergency surgery for any reason.
- Native aortic annulus size < 18mm or > 25mm as measured by echocardiogram.
- Patient has been offered surgery but has refused surgery.
- Recent (within 6 months) cerebrovascular accident (CVA) or a transient ischemic attack (TIA).

There was not a specific exclusion criterion for patients with critical aortic stenosis who had co-morbid conditions limiting the length or quality of their life.

6.3 Study Endpoints

Primary Safety and Effectiveness Endpoints

There were two co-primary endpoints in this study:

1. Freedom from death, over the duration of the trial (superiority)

A log-rank test p-value is reported by the sponsor. The hypotheses corresponding to the log-rank test are as follows:

$$H_0: \text{Survival function of SAPIEN} = \text{Survival function of Control}$$

$$H_1: \text{Survival function of SAPIEN} \neq \text{Survival function of Control}.$$
2. Hierarchical composite of death and recurrent hospitalization (superiority)

The Finkelstein-Schoenfeld method\(^1\) is used for the analysis of this endpoint. The hypotheses corresponding to the Finkelstein-Schoenfeld method are:

- **H\(_0\):** Neither survival nor the re-hospitalization is different between SAPIEN and Control arm;
- **H\(_1\):** At least one and possibly both are different between SAPIEN and Control arm.

A brief explanation of the Finkelstein-Schoenfeld (FS) analysis method is provided here for your information. The FS method is a non-parametric rank sum test where each patient is compared to every other patient in a pairwise manner. Specifically, all patient pairs are compared first on survival if this comparison is possible. If not, patients are then compared on time to first hospitalization. Rejection of the null hypothesis for this test implies that there is a difference between the two groups in either mortality, time to hospitalization or both.

More formally, for each pair of patients i and j, a score \(u_{ij}\) is defined as follows:

- If patient i is known to have lived longer than patient j, then \(u_{ij} = 1\). If patient j is known to have lived longer, then \(u_{ij} = -1\).
- If it is not known which patient has lived longer, then compare the time to first recurrent hospitalization using the same methodology as for survival. If patient i is known to have a longer time to first rehospitalization than patient j, then \(u_{ij} = 1\). If patient j is known to have a longer time to first rehospitalization, then \(u_{ij} = -1\).
- If it is not known which patient has lived longer or had longer time to recurrent hospitalization, then \(u_{ij} = 0\).

To summarize, the score looks first for a difference in survival. If there is no difference in survival, then the score looks for improvement in the time to first hospitalization. The final test statistic is based on the sum of the scores for patients in the treatment group.

Note that the hierarchical co-primary composite endpoint of death and recurrent hospitalization was added to the protocol after the study was begun, due to the sponsor’s concern that the primary endpoint would not be met. The FDA had concerns about adding hospitalization to the endpoint because of the potential for assessment bias, treatment bias, and placebo/nocebo effects, as well as concerns about evaluation of hospitalization events, since a considerable number of the patients appear to have been nursing home/rehabilitation patients. However, FDA approved this change to the protocol based on our belief that this endpoint would provide a meaningful contribution to the totality of the data and our overall evaluation of safety and effectiveness.

The trial was designed to demonstrate superiority of the SAPIEN device to “standard” therapy (see discussion below regarding various treatments received by the control group) for either of the co-primary endpoints.

To control the type I error rate at the 0.05-level for the trial, multiplicity was handled by the Hochberg method. Applying the Hochberg method in this particular case, the Cohort B study would be deemed a success if both of the co-primary endpoints favored SAPIEN with a p-value of less than 0.05. Alternatively, the Cohort B study would also be successful if either of the co-primary endpoints were met with a p-value of less than 0.025.

Secondary Safety and Effectiveness Endpoints

This study included a number of secondary safety and effectiveness endpoints. For a complete accounting of these results, please refer to the sponsor’s Briefing Document. This memo will summarize the endpoints that FDA believes are most critical to the evaluation of safety and effectiveness for this device.

Key secondary safety endpoints included the following:

- Time from randomization to the first occurrence of a Major Adverse Cardiac and Cerebrovascular Event (MACCE) within 1 year. The MACCE definition included:
  - Death
  - Myocardial infarction (MI)
  - **All** stroke
  - Renal failure

- Serious Adverse Events
  - Deaths
  - Neurological Events
  - Aortic Insufficiency/Paravalvular Leak
  - Bleeding Event/Hemorrhage/Vascular Complications
  - Aortic Valve Regurgitation
  - Myocardial Infarction
  - Renal failure (patient requires chronic dialysis for greater than 30 days) or Renal Insufficiency (creatinine >3.5)
  - Endocarditis
  - Cardiac Reintervention
  - Bradyarrhythmic Event
  - Mitral valve compromise

Key secondary effectiveness endpoints included the following:

- Hospitalization
  - Total hospital days through one year
  - Days alive out of the hospital through 1 year
- New York Heart Association (NYHA) functional classification
- 6-Minute Walk Test
- Effective Orifice Area Responder Analysis
6.4  Issues Related to Analysis and Interpretation of Study Results

Analysis Populations

The sponsor has analyzed the study results based on two populations: Intent-To-Treat (ITT) and As Treated (AT). Of the 358 patients in the inoperable cohort, 179 were randomized to SAPIEN and 179 randomized to Control, forming the Intent To Treat (ITT) population. The As Treated (AT) population was based on the treatment actually received. Therefore, the As Treated population is defined as follows:

- **AT SAPIEN**: Randomized Treatment patients for whom the study valve implant procedure is begun, defined as the “time the study catheter is placed in the patient in the catheterization laboratory.”
- **AT Control**: Randomized Control patients as well as patients randomized to the Treatment arm who did not receive a valve implant (SAPIEN or open surgery).

**NOTE**: The AT Control group does not include randomized Treatment patients who received open surgery in lieu of the SAPIEN.

Based on the definition of the AT population, the FDA has concerns regarding bias in favor of the SAPIEN group. Specifically, those patients who died before receiving the SAPIEN device or had complications prior to the SAPIEN device implant attempt were not counted against the SAPIEN group in the sponsor’s safety analyses. However, all of these events were counted against the Control group. In addition, patients in the SAPIEN group who underwent open AVR were not counted in the safety analysis, but patients in the control group who underwent open AVR were counted. Therefore, complications from the open AVR were differentially assigned to the arms.

The following two patients were randomized to SAPIEN but analyzed as Control patients in the As Treated analysis. The accompanying text is an excerpt from the CEC narrative for each patient.

- **– “Although randomized to the test arm, the pt was later deemed too high risk for the procedure, due to his pulmonary disease, bicuspid valve, and large annulus. He instead underwent successful percutaneous balloon aortic valvuloplasty on 27 Aug 08.”**
- **– “…underwent attempted percutaneous aortic valve replacement on 05Dec2007, but the procedure was aborted. Instead, percutaneous balloon aortic valvuloplasty was performed.”**

The following two patients were not counted in the As Treated analysis for the SAPIEN group.

- **– “The patient was randomized to Cohort B test on 20Jun2008 and underwent successful percutaneous balloon aortic valvuloplasty the same day. A subsequent CT scan revealed multiple pulmonary metastases which were not present one month prior.” The patient died 10 days later.**
- **– “TF case was scheduled, but patient had a hip fracture and underwent surgery. Post op suffered second hip fracture, rapidly deteriorated and expired on Feb 5, 2009.”**

The resulting As Treated population consisted of 175 SAPIEN and 181 Control patients. The patient examples listed above underline FDA’s concern regarding the bias associated with the
As Treated safety analysis conducted by the sponsor. In the first two cases, both of whom may have been too sick to receive the SAPIEN device were analyzed as Controls. The second two cases highlight the disparity in how adverse events were counted in the two AT populations.

As a result, FDA believes that the analyses based on the ITT population are the most relevant in evaluating the safety and effectiveness of the SAPIEN THV.

**Heterogeneity of the Control Group**

The Cohort B arm of the PARTNER trial was designed to demonstrate superiority of the SAPIEN device to “standard” therapy. During the trial, however, the control group received several different treatments, as outlined here:

- 78.2% of the control patients received balloon aortic valvuloplasty (BAV), 2/3 of these were within 30 days of randomization and 20% underwent repeat BAV
- Eleven (6.1%) of the control patients underwent open surgical aortic valve replacement (AVR)
  - 5 of these 11 patients underwent concomitant cardiac operations such as MVR, TVR, CAB, or ICD
  - 8/11 (73%) survived >200 days after operation (5/8 were alive at data lock at an average 453 days. Of the 3 who died after hospital discharge, the average length of life was 291 days
- 6 patients received apical-aortic conduits (4/6 died within 62 days post-op, 2/6 are ongoing at an average of 658 days)
- 4 patients underwent transcatheter aortic valve implantation in Germany and all are ongoing with an average survival of 480 days
- Only 14 (7.9%) of the control patients underwent no invasive procedure and had medical therapy alone

Based on these data, it is clear that there is no “standard” therapy for this patient cohort as evidenced by the various treatments received. The Panel will be asked to consider the impact of this heterogeneity of treatment options on the evaluation of safety and effectiveness of the SAPIEN THV in this patient population.
Adverse Event Definitions

FDA would like to provide clarification regarding the adverse event definitions used in the safety analyses presented by the sponsor. The CEC conducted an appropriate original review of the adverse events that occurred in this trial using the pre-specified event definitions. However, after the study was complete and data were unblinded, the Executive Committee of the trial and the sponsor requested that the CEC reassess adverse event definitions. The CEC letter regarding this readjudication process states:

“The sponsor, Executive Committee and the PARTNER CEC agree that this adjudication is an adjunctive process to the primary adjudication process for PARTNER. This review is occurring after the unblinded assessment has been completed and as such there is clear variation from the primary adjudication process for PARTNER as described in the CEC Charter.”

The FDA was not notified of the adjunctive readjudication. The last approved Statistical Analysis Plan (SAP, Version 10, Feb 28, 2010) states that MACCE is comprised of death, MI, stroke, and renal failure. The post hoc adjudication process incorrectly states the components of MACCE in that they include only “Major stroke” instead of “stroke.” It is important to note that the CEC did not distinguish between Major and Minor stroke until this post hoc request by the sponsor to re-adjudicate the neurological events (and other adverse events) after the data were analyzed and the results were known. This is particularly problematic since Modified Rankin assessments were not performed in any patients during the PARTNER trial and there is no validated method of retrospectively determining the Modified Rankin score.

The FDA maintains that the primary safety analyses should be based on the pre-specified adverse event definitions, not the post hoc adjunctive analyses. Therefore, all safety analyses presented by FDA in conjunction with this Advisory Panel meeting will rely on the pre-specified adverse event definitions, which we have included in the pertinent adverse event section of this memo.
7 THE PARTNER TRIAL – COHORT B STUDY RESULTS

7.1 Baseline Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>SAPIEN N=179</th>
<th>Control N=179</th>
<th>P-value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr), mean±SD</td>
<td>83.1±8.6</td>
<td>83.2±8.3</td>
<td>0.95</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>82 (45.8)</td>
<td>84 (46.9)</td>
<td>0.92</td>
</tr>
<tr>
<td>STS score&lt;sup&gt;b&lt;/sup&gt;, mean±SD</td>
<td>11.2±5.8</td>
<td>11.9±4.8</td>
<td>0.21</td>
</tr>
<tr>
<td>NYHA class, n (%):</td>
<td></td>
<td></td>
<td>0.68</td>
</tr>
<tr>
<td>II</td>
<td>14 (7.8)</td>
<td>11 (6.1)</td>
<td></td>
</tr>
<tr>
<td>III or IV</td>
<td>165 (92.2)</td>
<td>168 (93.9)</td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease, n (%)</td>
<td>121 (67.6)</td>
<td>133 (74.3)</td>
<td>0.2</td>
</tr>
<tr>
<td>Previous myocardial infarction, n/total n (%)</td>
<td>33/177 (18.6)</td>
<td>47/179 (26.3)</td>
<td>0.10</td>
</tr>
<tr>
<td>Previous intervention, n/total n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CABG</td>
<td>58/179 (32.4)</td>
<td>73/179 (40.8)</td>
<td>0.12</td>
</tr>
<tr>
<td>PCI</td>
<td>47/179 (26.3)</td>
<td>39/179 (21.8)</td>
<td>0.39</td>
</tr>
<tr>
<td>Balloon aortic valvuloplasty</td>
<td>25/154 (16.2)</td>
<td>39/160 (24.4)</td>
<td>0.09</td>
</tr>
<tr>
<td>Cerebral vascular disease, n/total n (%)</td>
<td>48/175 (27.4)</td>
<td>46/171 (26.9)</td>
<td>1.00</td>
</tr>
<tr>
<td>Peripheral vascular disease, n/total n (%)</td>
<td>55/178 (30.9)</td>
<td>45/179 (25.1)</td>
<td>0.24</td>
</tr>
<tr>
<td>COPD, n (%):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>74 (41.3)</td>
<td>94 (52.5)</td>
<td>0.04</td>
</tr>
<tr>
<td>Oxygen-dependent</td>
<td>38 (21.2)</td>
<td>46 (25.7)</td>
<td>0.38</td>
</tr>
<tr>
<td>Creatinine &gt;2 mg/dl (177 µmol/liter), n/total n (%)</td>
<td>8/179 (4.5)</td>
<td>16/178 (9.0)</td>
<td>0.10</td>
</tr>
<tr>
<td>Atrial fibrillation, n/total n (%)</td>
<td>28/85 (32.9)</td>
<td>39/80 (48.8)</td>
<td>0.04</td>
</tr>
<tr>
<td>Permanent pacemaker, n/total n (%)</td>
<td>35/179 (19.6)</td>
<td>31/179 (17.3)</td>
<td>0.68</td>
</tr>
<tr>
<td>Pulmonary hypertension, n/total n (%)</td>
<td>50/118 (42.4)</td>
<td>53/121 (43.8)</td>
<td>0.9</td>
</tr>
<tr>
<td>Extensively calcified aorta, n (%)</td>
<td>34 (19.0)</td>
<td>20 (11.2)</td>
<td>0.05</td>
</tr>
<tr>
<td>Deleterious effects of chest-wall irradiation, n (%)</td>
<td>16 (8.9)</td>
<td>15 (8.4)</td>
<td>1</td>
</tr>
<tr>
<td>Chest-wall deformity, n (%)</td>
<td>15 (8.4)</td>
<td>9 (5.0)</td>
<td>0.29</td>
</tr>
</tbody>
</table>

FDA would like to point out that 16% of the SAPIEN patients had a previous BAV before enrollment compared to 24% of the control patients. The control group had numerically higher percentages of patients with the following significant risk factors: coronary artery disease, previous MI, previous CABG, COPD, O₂ dependence, elevated creatinine, and atrial fibrillation. The SAPIEN group had numerically higher percentages for the following significant risk factors: peripheral vascular disease, extensively calcified aorta, and chest wall deformity. Note that, although the mean age was 83, there were some relatively young
patients included (e.g. 46 year old). Although not presented in the above table, FDA also notes that these patients were generally large (BSA 1.79) and Caucasian (91.3%).

### 7.2 Primary and Co-Primary Safety and Effectiveness Endpoints

#### Primary Safety and Effectiveness Endpoint

*Freedom from death over the duration of the trial*

The primary analysis was a comparison of survival through the full duration of the study. The figure below shows the mortality results in Cohort B for the ITT population. All-cause mortality risk over the full duration of the study was significantly less for those assigned to SAPIEN compared to Control (p-value < 0.0001 from 2-sided log-rank test). The survival rate at one year is 69.3% and 50.3% for SAPIEN and Control, respectively.

![All Cause Mortality](image)

<table>
<thead>
<tr>
<th>Number at Risk</th>
<th>Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test 179</td>
<td>103</td>
</tr>
<tr>
<td></td>
<td>61</td>
</tr>
<tr>
<td></td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Control 179</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>
As can be seen, there was an impressive reduction of mortality with this device relative to the heterogenous control group, and the endpoint was met. A careful review of the death narratives for this study did not raise any specific concerns regarding the cause of death in this study. We note that there are limited data beyond 2 years from the PARTNER trial and the long-term mortality benefit of the SAPIEN THV remains unclear. Therefore, the Agency believes that continued long-term follow-up is warranted in a Post-Approval Study should this device be approved.
Co-Primary Safety and Effectiveness Endpoint

*Hierarchical composite of death and recurrent hospitalization*

The additional co-primary endpoint was defined as a hierarchical analysis of the time from randomization to death from any cause or to the first occurrence of recurrent hospitalization, which was analyzed according to the Finkelstein-Schoenfeld method. The analysis was statistically significant (p-value <0.0001 from 2-sided Finkelstein-Schoenfeld test) in favor of the SAPIEN group.

The Kaplan-Meier survival curve is below. This endpoint also shows a clinically important difference between arms of this trial over the first two years of follow-up.

All Cause Mortality or Recurrent Hospitalization

<table>
<thead>
<tr>
<th>Number at Risk</th>
<th>Test 179</th>
<th>116</th>
<th>101</th>
<th>Years 85</th>
<th>49</th>
<th>11</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control 179</td>
<td>87</td>
<td>49</td>
<td>29</td>
<td>10</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
7.3 Secondary Safety Endpoints

Major Adverse Cardiac and Cerebrovascular Events (MACCE)

Time from randomization to the first occurrence of a MACCE event within 1 year

For the purposes of this analysis, MACCE includes all-cause death, myocardial infarction (MI), all stroke, and renal failure. The comparison was performed by the log-rank test and a two-sided p-value was reported. All data were truncated at one year for the analysis; patients alive and MACCE free at that time point were censored. The log-rank test favors the Test arm with p-value 0.0176.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>SAPIEN (N = 179)</th>
<th>Control (N = 179)</th>
<th>SAPIEN (N = 179)</th>
<th>Control (N = 179)</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of patients (%)</td>
<td>no. of patients (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death (all cause)</td>
<td>9 (5.0)</td>
<td>5 (2.8)</td>
<td>55 (30.7)</td>
<td>89 (49.7)</td>
</tr>
<tr>
<td>Stroke</td>
<td>13 (7.3)</td>
<td>3 (1.7)</td>
<td>20 (11.2)</td>
<td>8 (4.5)</td>
</tr>
<tr>
<td>Myocardial Infarction (MI)</td>
<td>0</td>
<td>0</td>
<td>1 (0.6)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Renal failure</td>
<td>2 (1.1)</td>
<td>2 (1.1)</td>
<td>4 (2.2)</td>
<td>5 (2.8)</td>
</tr>
</tbody>
</table>

The above table shows that the higher death rate in the control group drove this endpoint, since stroke was higher in the SAPIEN group and there was no difference in MI and renal failure. The early stroke rate was 4.3 times higher in the SAPIEN group and the 1 year stroke rate was 2.5 times higher than the control group, who were primarily treated with balloon aortic valvuloplasty. Death is counted as a component of the primary endpoints as well as the MACCE, thus resulting in double counting of this component.

The figure below presents the cumulative MACCE rate over the first year of follow-up. As you can see in both the table and figure, the SAPIEN had a higher incidence of events <30 days, but lower incidence of death after 30 days.
Number at Risk

Test 179 144 130 125 119 114
Control 179 149 128 103 88 81

Probability

Years

0.0 0.2 0.4 0.6 0.8 1.0

Control (n=179)
Test (n=179)
Serious Adverse Events

The following is a summary of the Serious Adverse Events (SAEs) that occurred in this study:

### Table 6 (updated 11Jun2011): Clinical Outcomes at 30 Days and 1 Year.*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>30 Days</th>
<th>1 Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TAVR (N = 179)</td>
<td>Standard Therapy (N = 179)</td>
</tr>
<tr>
<td>Death From any cause</td>
<td>9 (5.0)</td>
<td>5 (2.8)</td>
</tr>
<tr>
<td>From cardiovascular cause‡</td>
<td>8 (4.5)</td>
<td>3 (1.7)</td>
</tr>
<tr>
<td>Repeat hospitalization∫</td>
<td>10 (5.6)</td>
<td>18 (10.1)</td>
</tr>
<tr>
<td>Death from any cause or repeat hospitalization∫</td>
<td>20 (11.2)</td>
<td>22 (12.3)</td>
</tr>
<tr>
<td>Stroke</td>
<td>13 (7.3)</td>
<td>3 (1.7)</td>
</tr>
<tr>
<td>TIA</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Periprocedural</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hemorrhagic Vascular Complication</td>
<td>90 (50.7)</td>
<td>25 (14.0)</td>
</tr>
<tr>
<td>Renal failure</td>
<td>2 (1.1)</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>Renal Insufficiency‡</td>
<td>1 (0.6)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Bleeding Event</td>
<td>29 (16.2)</td>
<td>4 (2.2)</td>
</tr>
<tr>
<td>Cardiac re-intervention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Balloon aortic valvuloplasty</td>
<td>1 (0.6)**</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>Repeat TAVR‡‡</td>
<td>3 (1.7)</td>
<td>NA</td>
</tr>
<tr>
<td>Aortic-valve replacement</td>
<td>0</td>
<td>3 (1.7)</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>New atrial fibrillation</td>
<td>1 (0.6)</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>New pacemaker</td>
<td>6 (3.4)</td>
<td>9 (5.0)</td>
</tr>
</tbody>
</table>

* NA denotes not applicable, TAVR transcatheter aortic-valve implantation, and TIA transient ischemic attack.
† P values are for between-group comparisons of the frequency of the event at each time point.
‡ Deaths from unknown causes were assumed to be deaths from cardiovascular causes.
∫ Repeat hospitalizations were included if they were due to aortic stenosis or complications of the valve procedure (e.g., TAVR).
¶ Patients who received renal-replacement therapy were not included.
|| Patients who received renal-replacement therapy after randomization were included.
** One patient in the TAVR group did not receive TAVR (because of failed access) and subsequently underwent balloon aortic valvuloplasty, followed by aortic-valve replacement.
†† A total of 30 patients underwent a repeat balloon aortic valvuloplasty after the index balloon aortic valvuloplasty procedure that had been performed in the first 30 days after randomization, and 36 patients underwent a first balloon aortic valvuloplasty more than 30 days after randomization.
‡‡ Three patients underwent a repeat TAVR within 24 hours after the index TAVR procedure; four patients in the standard-therapy group who underwent TAVR at a nonparticipating site outside the United States are not included here.
Neurological Events

The pre-specified definition of stroke was as follows:

**Stroke**: A neurological deficit lasting ≥ 24 hours, or lasting < 24 hours with a brain imaging study showing infarction

The sponsor reports stroke as Major and Minor in the *post hoc* adjunctive analysis. This determination of stroke severity was not part of the original CEC Charter and was performed at the request of the Executive Committee. The CEC performed a retrospective review of source data to determine Rankin Score. The sponsor has stated that “this (Modified Rankin) score is not validated for retrospective use.” The FDA was not informed of this adjunctive *post hoc* readjudication until November 2010, when the PMA was submitted. Therefore, FDA requested that the sponsor present the data using the agreed upon definition of stroke, which is included in the table below:

**All Neurological Events at 30 Days, 1 Year, and Total Study (ITT Population)**

<table>
<thead>
<tr>
<th>Follow-Up Window</th>
<th>Control # events (% patients)</th>
<th>SAPIEN # events (% patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-30 days</td>
<td>3 (1.7%)</td>
<td>13 (7.3%)</td>
</tr>
<tr>
<td>[ &lt;5 days from SAPIEN]</td>
<td></td>
<td>[11/13]</td>
</tr>
<tr>
<td>31 days - 1 year</td>
<td>5 (2.8%)</td>
<td>8 (4.5%)</td>
</tr>
<tr>
<td>&gt;1 year</td>
<td>0</td>
<td>4 (2.2%)</td>
</tr>
<tr>
<td>Total in study</td>
<td>8 (4.5%)</td>
<td>25 (14.0%)</td>
</tr>
</tbody>
</table>

This table shows that the acute neurological event risk is 4.3 times higher in the SAPIEN arm compared to Control, noting that the majority of controls had BAV. The total neurological event rate in the study was 3.1 times higher in SAPIEN than Control. Interpretation of this increased late stroke rate is complicated because of the higher mortality rate in the Control group.

The types of neurological events that occurred during the course of the study are listed in the table below:

**All Neurological Events Through Duration of Study (ITT Population)**

<table>
<thead>
<tr>
<th>Neurological Event</th>
<th>Control</th>
<th>SAPIEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic/unclassified Stroke</td>
<td>7</td>
<td>16</td>
</tr>
<tr>
<td>Hemorrhagic Stroke</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Intracranial Hemorrhage</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>TIA</td>
<td>0</td>
<td>3 (2 patients)</td>
</tr>
<tr>
<td><strong>Total Events</strong></td>
<td>8</td>
<td>25</td>
</tr>
</tbody>
</table>
Neurological Events in the Control Group

There were 7 ischemic/unclassified strokes:

- 1 after open AVR
- 4 after BAV (5 days, 2 weeks, 2 months, 6 months)
- 2 in patients who only received medical management (one on the day of randomization, and another 3 days after randomization)

There was one hemorrhagic stroke 8 months after BAV.

Only 14 control patients had optimal medical therapy without an interventional procedure throughout the trial. As mentioned above, two of these 14 patients had strokes within 3 days of randomization, but there were no further strokes. Fourteen additional patients had either open AVR or apico-aortic conduits. One of these 14 patients had a stroke on the day of surgery. There were no further strokes throughout the trial in the Control group. Therefore, the control group had minimal neurological events over 60 days after invasive procedures and there does not appear to be a continuing risk of neurological events. As a result, there is no evidence that the patients in this study were a high risk stroke population.

Neurological Events in the SAPIEN Group

There were 16 ischemic/unclassified strokes:

- 1 occurred after randomization and before SAPIEN
- 10/16 were recognized within 6 days of SAPIEN implantation or attempted implantation
- 2/16 occurred from 23-180 days (23, 75 days)
- 3/16 occurred late (361, 650, 875 days)

There were 3 hemorrhagic strokes (2, 39, and 120 days)

There were 3 intracranial hemorrhages (51, 136, 151 days)

There were 3 TIAs (143 days in one patient; 386 and 831 days in a second patient)

This shows that 12/25 (48%) of the neurological events occurred > 30 days after the procedure – thus indicating a continued risk of neurological events with the device.

Comparing BAV (5/150; 3.3%) and SAPIEN (24/175; 13.8%), there is a higher neurological event rate in the SAPIEN patients, both in the acute periprocedural period and during longer-term follow-up. Neurological adverse events remain an important safety consideration for this device, and should be weighed by the Panel in their overall determination of safety and effectiveness for the SAPIEN device.
Bleeding Events/Hemorrhage/Vascular Complications

The PARTNER protocol prospectively defined adverse events relating to bleeding and vascular complications as follows:

**Bleeding Event** Any episode of major internal or external bleeding that causes death, hospitalization or permanent injury (e.g., vision loss) or necessitates transfusion of greater than 3 units PRBCs or pericardiocentesis procedure. The complication *bleeding event* applies to all patients whether or not they are taking anticoagulants or antiplatelet drugs, since bleeding events can occur in patients who are not receiving anticoagulants. Embolic stroke complicated by bleeding is classified as a neurologic event under *embolism* and is not included as a separate bleeding event. Hemorrhage that requires 2 or more units of transfusion within the index procedure shall be reported as serious adverse events.

**Aortic Dissection:**
Aortic dissection defined as Type A or B dissections that require surgical or percutaneous intervention.

**Hemorrhage** See “Bleeding event”
Events which are excluded are: those due to liver disease, myocardial infarction, or systemic infection.
Reported as major or minor as defined below:
Major: Requires intervention.
Minor: Does not require intervention.

**Hemorrhagic Vascular Complication**
Vascular complications include the following:
1. Hematoma at access site >5 cm
2. False aneurysm
3. Arterio-venous fistula
4. Retroperitoneal bleeding
5. Peripheral ischemia/nerve injury
6. Any transfusion required will be reported as a vascular complication unless for a clinical indication clearly other than catheterization complication.
7. Vascular surgical repair

It appears that half (55.9%) of the SAPIEN patients had serious adverse events relating to the access procedure. The table below, which FDA created based on a review of the CEC narratives, lists the most serious of the vascular complications.

<table>
<thead>
<tr>
<th>Acute Vascular complication</th>
<th># patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic dissection</td>
<td>1</td>
</tr>
<tr>
<td>Iliac artery/distal aortic injury</td>
<td>17</td>
</tr>
<tr>
<td>Femoral artery injury</td>
<td>13</td>
</tr>
<tr>
<td>Pseudoaneurysm</td>
<td>2</td>
</tr>
<tr>
<td>Hematoma</td>
<td>6</td>
</tr>
<tr>
<td>Unknown injury</td>
<td>2</td>
</tr>
</tbody>
</table>

These injuries often resulted in the need for prosthetic material and/or graft repair of the injuries. These patients remain at risk of graft thrombosis and infection throughout the remainder of their lives, a long-term risk that should be closely monitored in the post-approval setting.
**Aortic Regurgitation**

The table below presents the total amount of aortic regurgitation (moderate or greater) reported from the core laboratory at the listed follow-up points in both treatment arms. Note that these totals include all sources of regurgitation, including both central regurgitation and paravalvular leak.

<table>
<thead>
<tr>
<th>Follow-up Visit</th>
<th>Control (% patients)</th>
<th>SAPIEN (% patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 days</td>
<td>16.5%</td>
<td>15.2%</td>
</tr>
<tr>
<td>6 month</td>
<td>16.8%</td>
<td>9.9%</td>
</tr>
<tr>
<td>1 yr</td>
<td>16.7%</td>
<td>15.6%</td>
</tr>
</tbody>
</table>

These data show that the amount of aortic regurgitation (AR) is appreciable and does not decrease over time in the SAPIEN group. Because of the heterogeneity of treatments received in the Control group, comparison to the Control group is of little value. The amount of AR and its clinical significance over time in the SAPIEN group remains a concern and will need to be monitored in the potential post-approval setting if the device is approved.

**Endocarditis**

There were no endocarditis events reported in the Control group. In the SAPIEN group, 3/175 (1.7%) patients experienced endocarditis. Two of these patients died and the third had an explant and open AVR. This explant patient had a difficult post-SAPIEN implant course with septicemia then returned 19 months later with acute decompensation and a stenotic valve. He underwent open operation and was discharged from the hospital after a complicated course. Pathologic evaluation of the valve showed endocarditis and severe calcification of all three leaflets of the SAPIEN. These cases confirm the need for longer-term (>1-2 years) monitoring of this device in this patient group, as the patients are at risk over the life of the valve.

**Aortic Valve Reintervention**

The SAPIEN group had a 2.3% incidence of this SAE while the control group had a 66.9% incidence. This reflects expected BAV in control patients and is not really an adverse event. If a control patient had a BAV more than 30 days after randomization, it is counted as an aortic valve reintervention.

**Other Serious Adverse Events**

Data were also collected for the following important adverse events: myocardial infarction, renal failure (chronic dialysis for >30 days), renal insufficiency (creatinine >3.5), bradyarrhythmic event, and mitral valve compromise. Based on the available data, these potential procedure-related complications did not appear to be a problem in this study.
7.4 Secondary Effectiveness Endpoints

Hospitalization

Hospitalization for any reason is a valuable measure of quality of life for patients and is therefore considered an important secondary endpoint. Hospitalization was analyzed two different ways in this trial in an attempt to describe the differences between the Treatment and Control groups.

Total Hospital Days Through 1 Year

This endpoint captured the total hospital days from the index procedure (SAPIEN arm) or randomization (Control arm) to one year post-procedure or randomization. For the purposes of analyzing this endpoint, it should be noted that the hospitalization for the valve implantation procedure in the SAPIEN arm was not counted. The sponsor reported the SAPIEN and Control arm results (mean±SD) to be 18.4±20.3 and 13.8±17.9, respectively. The bootstrap test yielded p-value of 0.019 favoring the Control arm.

Days Alive and Out of the Hospital (DAOH) Through One Year

An analysis of DAOH allows for an assessment of two important objectives of the device therapy – improvement in mortality and quality of life. Note that the index hospitalization for SAPIEN implantation was included in this analysis. The sponsor reported the SAPIEN and Control arm results to be 273.8±128.5 and 210.2±146.9, respectively.

New York Heart Association Functional Class

An evaluation of cardiac symptom severity based on NYHA classification was conducted at several evaluation time points during the first year of the trial. At baseline, patients presented with the following breakdown of NYHA class:

<table>
<thead>
<tr>
<th>NYHA at Baseline</th>
<th>Total N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>11 87 81 179</td>
</tr>
<tr>
<td>SAPIEN</td>
<td>14 87 78 179</td>
</tr>
<tr>
<td>Total</td>
<td>25 174 159 358</td>
</tr>
</tbody>
</table>

At 1 year, the following results of the NYHA evaluation were reported:

<table>
<thead>
<tr>
<th>PMA: NYHA at One Year</th>
<th>Total N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>11 89 2 29 37 11 179</td>
</tr>
<tr>
<td>SAPIEN</td>
<td>7 55 45 44 23 5 179</td>
</tr>
<tr>
<td>Total</td>
<td>18 144 47 73 60 16 358</td>
</tr>
</tbody>
</table>

In the ITT population, more patients in the SAPIEN group had less severe cardiac symptoms (NYHA class I or II) as compared to patients in the Control group (49.7% vs. 17.9%,
respectively). The between-group difference remained statistically significant, favoring SAPIEN, across a number of sensitivity analyses using various methods for imputing missing data other than death. Specifically, the analysis that imputes test arm NYHA missing for reasons other than death to NYHA IV, control arm with NYHA missing for reasons other than death to have NYHA I, and death to have NYHA V yields p-value 0.0005 that favors the SAPIEN arm.

Despite the statistically significant result, it is important to note the limitations of subjective measures such as NYHA in this unblinded study due to the influence of placebo/nocebo effects and assessment bias.

6-Minute Walk Test

Based on the available data from the test performed at 1 year, patients in the SAPIEN group were able to walk further during a 6-minute walk test (6MWT) than those in the Control group (mean ± SD, 118.93 ± 147.3 vs 84.40 ± 96.83 meters).

The most important observation is that only 45.2% (56/124) of the alive SAPIEN patients and 34.4% (31/90) of the alive Control patients completed the 6MWT at one year. Although the sponsor conducted multiple sensitivity analyses to assess the impact of missing data, the fact that such a significant amount of the data were missing makes it impossible to draw any firm conclusions regarding these results.

Effective Orifice Area (EOA) Responder Analysis

For the purpose of this analysis, a responder was defined as maintenance of >50% of the EOA at the follow-up time periods. The following results were noted for the SAPIEN group (based on the As Treated population):

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>30 days</td>
<td>n=133</td>
</tr>
<tr>
<td>6 months</td>
<td>n=93</td>
</tr>
<tr>
<td>1 year</td>
<td>n=82</td>
</tr>
<tr>
<td>92%</td>
<td>85%</td>
</tr>
<tr>
<td>90%</td>
<td></td>
</tr>
</tbody>
</table>

This shows that the reduction in stenosis was maintained at least at a reasonable level for the first year in the SAPIEN group.
7.5 Additional Study Observations

Procedure Data

The following table provides data on the transcatheter valve implantation procedure for patients in the SAPIEN arm of Cohort B. These data demonstrate that the procedure took, on average, over 4 hours and required general anesthesia in all patients. Also, 10% of the patients either did not get a valve or got more than one valve. There was a relatively even distribution of the two valve sizes. We do not have comparable data for the majority of control patients who underwent balloon valvuloplasty.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean or % of patients (min – max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total time of procedure (min)</td>
<td>262 (139-616)</td>
</tr>
<tr>
<td>Skin to skin time (min)</td>
<td>150 (34 – 553)</td>
</tr>
<tr>
<td>Fluoroscopy time (min)</td>
<td>29 (10-68)</td>
</tr>
<tr>
<td>Volume of contrast (ml)</td>
<td>132 (10-450)</td>
</tr>
<tr>
<td>Use of CPB</td>
<td>1.1%</td>
</tr>
<tr>
<td>Use of general anesthesia</td>
<td>100%</td>
</tr>
<tr>
<td># of devices used</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>4.6%</td>
</tr>
<tr>
<td>1</td>
<td>89.1%</td>
</tr>
<tr>
<td>2</td>
<td>5.7%</td>
</tr>
<tr>
<td>3</td>
<td>0.6%</td>
</tr>
<tr>
<td>Valve in Valve procedure</td>
<td>2.3%</td>
</tr>
<tr>
<td>Emergent operation due to device or procedure</td>
<td>1.1%</td>
</tr>
<tr>
<td>Valve Size</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>56.6%</td>
</tr>
<tr>
<td>26</td>
<td>43.4%</td>
</tr>
<tr>
<td>Adverse event during procedure</td>
<td>39.4%</td>
</tr>
<tr>
<td>Device malfunction</td>
<td>3.4%</td>
</tr>
<tr>
<td>Device Success (deployment, AVA &gt;0.9, AI&lt;3+, 1 valve)</td>
<td>78.2%</td>
</tr>
<tr>
<td>Procedure Success (Device success, no MACCE &lt;30d)</td>
<td>71.8%</td>
</tr>
</tbody>
</table>

Valve-in-Valve Experience

Four patients underwent valve-in-valve procedures in the Cohort B study. A brief description of these cases is included here:

- During deployment of the SAPIEN, the valve moved up above the annulus. The second valve was implanted in the correct position.
- During the index procedure, after deployment of the SAPIEN valve, it was noted that the patient had a central leak, which was treated with a second SAPIEN valve. When
pushing the second valve, it came loose at the aortic level and dislodged from the
delivery system. A third valve was implanted.

- Following the index procedure, the patient was noted to have 2-3+ aortic
regurgitation, which worsened to 4+ on the next day. Re-intervention with a second
SAPIEN was performed on postoperative day 3.
- During the index procedure the SAPIEN was implanted too high in the aorta causing
perivalvular leak, requiring implantation of a second SAPIEN.

As stated earlier in this memo, FDA is concerned that if the SAPIEN becomes commercially
available, widespread use of the valve-in-valve technique might occur. While this only
occurred four times in the Cohort B study, there have been many reports of valve-in-valve
usage in Europe. Without any pre-clinical testing, and limited clinical data, the FDA is
unable to draw conclusions regarding the short- and long-term safety of SAPIEN valve-in-
valve implantation. The FDA would appreciate Panel input regarding the appropriate way to
address this issue, such as labeling, training or other testing that may be warranted.

Patient Selection Issues

The FDA worked extensively with sponsor to define “inoperable” or “extreme high risk” for
this randomized study of inoperable patients so as not to enroll less sick patients who could
reasonably have open AVR. However, active consideration was not given to specifying
patients who should not have transcatheter valve implantation due to extensive comorbidities.
There were no specific inclusion/exclusion criteria in this study to eliminate patients too sick
to benefit from isolated treatment of severe aortic stenosis.

Based on a review of the CEC narratives, it is clear that one needs also to consider when
transcatheter valve implantation may not have a positive impact on a patient’s quality of life.
In addition, SAPIEN implantation requires general anesthesia, 4+ hours of procedure time,
radiographic contrast, invasive TEE, often an operative procedure for vascular access or
closure, etc.; therefore, it is a highly invasive interventional cardiology procedure.

Below are a few representative narratives that were excerpted from the PMA submission as
examples. These narratives illustrate some of the problems with selecting patients who may
have too many comorbidities to be expected to reasonably benefit from this invasive
procedure. The Panel will be asked to comment as to whether the proposed labeling
adequately describes the patients in whom this therapy should be considered so that post-
procedure there will be a reasonable expectation of improved quality of life.

Subject

Patient is an 87-year-old male with a history of severe aortic stenosis (aortic valve area of 0.4
cm$^2$), non-ischemic cardiomyopathy, permanent pacemaker secondary to sick sinus syndrome, ejection
fraction of 20%, hypertension, Paget’s disease, debilitating rheumatoid arthritis with multiple exacerbations
and peripheral myopathy, post-herpetic neuralgia with severe chronic pain, history of duodenal ulcer,
cholecystectomy, left inguinal hernia repair, and transurethral resection of the prostate.

The patient was randomized to Cohort B test on 04Nov2008 and underwent percutaneous aortic valve
replacement on 06Nov2008. His postoperative course was complicated by transient delirium, probable
aspiration pneumonia, episodes of hypotension in the setting of volume overload/overdiuresis, laryngeal
edema and copious secretions, possibly in the setting of allergy to latex tubing for suction, and thrombocytopenia. The pt was discharged to a rehab facility on 26Nov2008. The patient was readmitted on 14Dec2008 due to probable aspiration pneumonia. The patient subsequently developed sepsis and his status continued to decline. He died on 30Jan2009.

Subject

Patient H-S is an 88 year old female with a history of severe aortic stenosis (Aortic valvular area 0.6cm²), congestive heart failure, on-obstructive coronary artery disease, severe COPD with multiple admissions for exacerbations, on home oxygen, pulmonary function tests show severe restrictive (FEV1 0.53) and moderate obstructive disease, paroxysmal atrial fibrillation (on coumadin), severe pulmonary hypertension (PA72/32), monoclonal gammaglobulinenia, hypertension, hyperlipidemia, essential tremor, osteoporosis, spinal stenosis, h/o umbilical hernia repair 2005, left sided weakness (recurrent TIA possibly due to small vessel disease). The patient was transferred in from an outside hospital to be evaluated for the percutaneous valve replacement. At the outside hospital the patient had left arm clumsiness. This was evaluated by neurology. Neurology felt that she had symptoms consistent with TIA, from small vessel disease. No further workup was done, as she returned to her baseline functioning. Three days ago, again she felt her left arm become clumsy, and that it has remained constant without fluctuation. Head CT done on 11/24/08 shows moderate cerebral and slight cerebella atrophy (which could be degenerative). On 11/25/08 the stroke fellow notes; the MRI shows acute subacute stroke in right frontal lobe at the border between the right ACA and MCA, GRE small b/l old microhemorrhages. The MRA of the head shows decreased flow in right ICA, right MCA, b/l ACA, decreased flow in L PCA and stenosis R PCA. The MRA of the neck showed decreased flow in R proximal ICA.

The patient was taken to the catheterization lab for her percutaneous aortic valve replacement on 03Dec2008. She died 14DEC2008 from progression of her stroke.

Subject

Patient CBM is a 95 year-old male with a history of critical aortic stenosis (AVA=0.45cm²), CAD (s/p LAD PCI, prior CABG), chronic afib (warfarin therapy), HTN, HL, history of CVA, subdural hematoma, macular degeneration (legally blind), mild iliac disease, CKI (baseline Cr=2.5), and COPD (home O2) who was randomized on 22Feb2008 to Test B.

Patient CBM underwent a transfemoral aortic valve implantation on 27Feb2008. Following the procedure he was immediately found to have a R hemiparesis with both upper and lower extremity weakness and slurred speech with intermittent aphasic periods. CT on 03Mar2008 revealed a non-hemorrhagic acute infarct in the paramedian left frontal lobe in the L anterior cerebral artery territory. The patient began working with speech therapy, was able to eat, and was recovering until 4Mar2008 when he required reintubation for respiratory distress involving coughing spells and hypoxemia. CXR on 4Mar2008 showed pulmonary edema, small bilateral pleural effusions, and bibasilar atelectasis/edema/infiltrate treated with ABX. Tube feeds were started at that time. While intubated the patient had a mild increase in his creatinine and was given intermittent IV lasix and hydration. On 7Mar2008 the patient was placed on IV Amio for chronic afib without cardioversion. Beta-blockers resulted in hypotension and slow heart rate. Patient was eventually extubated and transferred to telemetry floor on 14Mar2008. Coumadin was initially restarted, but discontinued due to Guaiac positive stool with an INR=6.0 for which he received 2U FFP on 18Mar2008. Patient was maintained on Aspirin and Ticlid.

On 21Mar2008 the patient was transferred to an acute rehab facility. At the rehab facility, the patient had difficulty swallowing and his PIC line was used for IV hydration and ABX for pneumonia. The patient was transferred to home in “weak” condition where he eventually died in his sleep.
8 EUROPEAN CLINICAL EXPERIENCE

The sponsor estimates that 7,054 SAPIEN devices have been implanted in the commercial use of this device since October 2007, over half of whom were enrolled in some form of trial or registry. While we do not have detailed follow-up data on these patients and clinical interpretation of these data are quite limited for the reasons outlined later in this section, the following mortality results have been presented by the sponsor:

Table 13-1: Worldwide Clinical Experience with the Edwards SAPIEN THV

<table>
<thead>
<tr>
<th>Trial</th>
<th>Number of Subjects Enrolled</th>
<th>Number of Subjects Receiving Valve</th>
<th>Surviving at 1 month %</th>
<th>Survival at 6 month %</th>
<th>Survival at one year %</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-REVIVE*</td>
<td>22**</td>
<td>17</td>
<td>67.2%</td>
<td>33.0%</td>
<td>28.0%</td>
</tr>
<tr>
<td>RECAST*</td>
<td>24***</td>
<td>20</td>
<td>72.3%</td>
<td>43.2%</td>
<td>43.4%</td>
</tr>
<tr>
<td>REVIVAL-1*</td>
<td>7</td>
<td>7</td>
<td>57.1%</td>
<td>25.5%</td>
<td>25.5%</td>
</tr>
<tr>
<td>REVIVAL-2 Transfemoral</td>
<td>55</td>
<td>48</td>
<td>92.7%</td>
<td>83.4%</td>
<td>75.8%</td>
</tr>
<tr>
<td>REVIVE -2</td>
<td>106</td>
<td>94</td>
<td>88.3%</td>
<td>73.9%</td>
<td>72.5%</td>
</tr>
<tr>
<td>REVIVAL-2 Transapical</td>
<td>40</td>
<td>35</td>
<td>82.5%</td>
<td>65.0%</td>
<td>59.5%</td>
</tr>
<tr>
<td>TRAVERSE</td>
<td>172</td>
<td>169</td>
<td>84.7%</td>
<td>69.0%</td>
<td>62.0%</td>
</tr>
<tr>
<td>PARTNER EU Transapical</td>
<td>69</td>
<td>65</td>
<td>81.2%</td>
<td>59.0%</td>
<td>46.0%</td>
</tr>
<tr>
<td>PARTNER EU Transfemoral</td>
<td>81</td>
<td>55</td>
<td>91.8%</td>
<td>90.2%</td>
<td>79.7%</td>
</tr>
<tr>
<td>SOURCE Registry Transapical – Cohort 1</td>
<td>575</td>
<td>523</td>
<td>89.7%</td>
<td>NAP</td>
<td>72.1%</td>
</tr>
<tr>
<td>SOURCE Registry Transapical – Cohort 1</td>
<td>403</td>
<td>443</td>
<td>93.7%</td>
<td>NAP</td>
<td>61.1%</td>
</tr>
<tr>
<td>SOURCE Registry Cohort 1</td>
<td>1038</td>
<td>966</td>
<td>91.2%</td>
<td>NAP</td>
<td>NAP</td>
</tr>
<tr>
<td>SOURCE Registry Cohort 2</td>
<td>1306</td>
<td>1296</td>
<td>89.9%</td>
<td>NAP</td>
<td>NAP</td>
</tr>
<tr>
<td>PARTNER IDE Cohort B Transfemoral</td>
<td>358 randomized</td>
<td>173</td>
<td>95.0%</td>
<td>NAP</td>
<td>69.3%</td>
</tr>
<tr>
<td>PARTNER IDE Cohort B Standard Therapy</td>
<td>358 randomized</td>
<td>0</td>
<td>97.2%</td>
<td>NAP</td>
<td>49.3%</td>
</tr>
<tr>
<td>TOTAL</td>
<td>4296</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

The PARTNER EU trial (130 patients), and all of the registries in Europe (SOURCE Registries, n=3382), used the EuroScore risk prediction system as defining high risk and inoperability (i.e., predicted mortality >50%). The EuroScore was developed primarily using data from coronary bypass patients with a relatively small contribution from isolated aortic and mitral valve patients. Several studies have compared the validated STS Risk predictor
score for aortic valve replacements with the EuroScore in the aortic stenosis population and have found the EuroScore to be invalid, noting that the EuroScore can over predict risk by three (or more) times the actual risk.2,3

As a result, the trial results in Europe are very difficult to interpret because it is unclear who the patients were who were enrolled in these registries. One can only surmise from the inclusion criteria that the European trials were not trials primarily of “inoperable” patients. For example, surgeon input as to operability was not required in these trials. Other significant limitations include the lack of a concurrent control or clinical plans for longer-term follow-up.

Therefore, the European experience cannot answer critical clinical questions regarding longer-term durability and outcomes. It is for this reason that FDA and the sponsor will be seeking key Panel input on a major US post-approval registry designed to assess, among other things, longer-term results and generalizability of IDE trial results to new centers.

9 FDA’s PERSPECTIVE & CONSIDERATIONS

The PARTNER trial met the pre-specified criteria for study success, as defined by the primary safety and effectiveness endpoint of all-cause mortality throughout the duration of the study, demonstrating superiority of the SAPIEN THV as compared to the Control group. When evaluating whether the results of the trial support the safety and effectiveness of the SAPIEN THV for the proposed indications, the following points should be considered.

9.1 Scope of Proposed Indications

The sponsor and the FDA propose the following 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.

This wording is intended to reflect the process by which patients were determined to be “inoperable” before entering the PARTNER trial. There were several patients enrolled in the trial who may have been too sick to benefit from isolated treatment of severe aortic stenosis, since there were no specific inclusion/exclusion criteria in this study to eliminate these patients. The proposed indications statement also attempts to address this concern. If there are other patient selection factors that can be addressed by refining the indications statement, these should also be considered.

9.2 Heterogeneity of the Control Group

The Cohort B arm of the PARTNER trial was designed to demonstrate superiority of the SAPIEN THV to “standard” therapy. During the trial, however, the control group received several different treatments according to practitioner judgment, including balloon aortic valvuloplasty, open aortic valve replacement, apical-aortic conduit, transcatheter aortic valve implantation (in Germany), or medical management alone. As a result, it is clear that there is no “standard” therapy for this patient cohort. It will be important to consider the impact of this heterogeneity of treatment options on the evaluation of safety and effectiveness of the SAPIEN THV in this patient population.

9.3 Adverse Event Definitions

FDA would like to provide clarification regarding the adverse event definitions used in the safety analyses presented by the sponsor. The CEC conducted an appropriate original review of the adverse events that occurred in this trial using pre-specified event definitions. However, after the study was complete and data were unblinded, the Executive Committee of the trial and the sponsor requested that the CEC reassess adverse event definitions. The CEC formally stated that this was a “clear variation from the primary adjudication process” and should be considered adjunctive.

Most importantly, the sponsor asked the CEC to categorize the stroke events as either Major or Minor. It is critical to note that the CEC did not distinguish between Major and Minor stroke until this post hoc request by the sponsor. This is particularly problematic since Modified Rankin assessments were not performed in any patients during the PARTNER trial and there is no validated method of retrospectively determining the Modified Rankin score.

The FDA maintains that the primary safety analyses should be based on the pre-specified adverse event definitions, not the post hoc adjunctive analyses. Therefore, all safety analyses presented by FDA in conjunction with this Advisory Panel meeting will rely on the pre-specified adverse event definitions.

9.4 Neurological Events

There was a significant increase in the neurological event risk in the SAPIEN arm compared to Control, noting that the majority of Controls had BAV, in both the acute periprocedural period and the longer-term follow-up phase of the PARTNER trial. While interpretation of the increased late event rate is complicated because of the higher mortality rate in the Control group, neurological adverse events remain an important safety consideration for this device and impact the overall risk-benefit profile of the SAPIEN THV.
Three published studies\textsuperscript{4-6} comparing cerebral imaging pre- and post-implantation in transcatheter aortic valve implantation patients showed cerebral infarction rates of 73\%, 84\%, and 68\%. The identification of stroke in the current study depended on recognition of symptoms by the cardiovascular team. Because of the elevated neurological event rate in this study and with consideration of the papers mentioned above, future FDA-regulated studies of transcatheter valve implantation will require more intense neurological evaluations.

The cause of neurological injury with transcatheter valve implantation is multifactorial. One important consideration is management of coagulation and platelet aggregation. The PARTNER trial did not require patients to be on a protocolized anticoagulation or antiplatelet regimen. In light of this, as well as the increased neurological event risk discussed above, the sponsor has proposed a protocolized anticoagulation/antiplatelet regimen to be used in the proposed post-approval study. While this may aid in reducing the neurological event risk for patients receiving the SAPIEN, other risk mitigation measures may also need to be taken into account.

\textbf{9.5 Vascular Complications}

The study results indicated that over half (57\%) of the SAPIEN patients had serious adverse events relating to the access procedure, resulting in both short- and long-term risks for patients receiving the SAPIEN. In an effort to address this risk, the sponsor has proposed a comprehensive training program for new practitioners. Compliance with this program, as well as an assessment of its effectiveness, will be important parameters in a potential post-approval study.

\textbf{9.6 Aortic Insufficiency}

The study data show that the amount of aortic regurgitation (moderate or greater) at 1-year follow-up (15.6\%) is appreciable in the patients who received the SAPIEN valve. Based on the available data, the clinical significance of aortic regurgitation in this patient population remains unknown and may impact evaluation of the long-term risks and benefits of the SAPIEN THV.

\textbf{9.7 Valve-in-Valve Experience}

While the valve-in-valve implant method was only utilized four times in the current trial, there are several reports in the literature regarding the use of this technique in Europe. In addition, no preclinical testing has been conducted to support the safety of this procedure. This is significant given the potential for corrosion (fretting and galvanic) as well as other unknown risks associated with valve-in-valve implantation may such as long-term durability.

valve migration/embolization, and access to the coronary ostia. Without any pre-clinical testing, and based on the limited clinical data available, it is difficult to draw conclusions regarding the short- and long-term safety of valve-in-valve implantation. Several risk mitigation measures, such as labeling, training, or requirements for additional testing may be appropriate in order to address this concern.

9.8 Availability of Long-term Data

While all Cohort B patients have been followed to at least 1 year, there are only 94 SAPIEN and 42 Control patients with 2-year follow-up. The feasibility studies and studies done outside of the U.S. have longer-term follow-up, but the comparability of these patients to those in the PARTNER trial is unknown. While not impacting the primary hypothesis testing for the PARTNER trial, the limited longer-term data available for this novel device and procedure supports the need for robust post-approval follow-up to bolster our understanding of device durability and longer-term performance if the device is approved.

9.9 Post-Approval Study Goals

The sponsor has proposed to conduct two post-approval studies if this PMA is approved. The first study proposes long-term follow-up of the patients remaining in the premarket cohort (referred to as the “Extended Follow-up of Premarket Cohort Study”). For the second study, the sponsor proposes a non-randomized, prospective, consecutively enrolled registry of new patients undergoing transcatheter heart valve replacement therapy with the SAPIEN THV (referred to as the “New Enrollment Study”).

Extended Follow-up of Premarket Cohort Study

This study will be designed to assess the long-term device performance, including evaluation of device durability and patient quality of life. This evaluation will be based on descriptive statistics – no hypothesis testing was proposed.

New Enrollment Study

This study will be designed to assess short-term and long-term evaluation of newly enrolled patients compared with premarket cohort; adherence to indications for use; differences in patient populations and outcomes (i.e., safety, including stroke); device durability; and patient quality of life. The primary hypotheses involve comparisons of:

- A safety composite endpoint at 30 days post-procedure (all-cause mortality, major stroke, life-threatening (or disabling) bleeding, peri-procedural MI, acute kidney injury - Stage 3, repeat procedure for valve-related dysfunction); and
- An effectiveness composite endpoint at 1 year post-procedure to newly developed objective performance criteria (all-cause mortality, failure of current therapy for AS, requiring hospitalization for symptoms of valve-related decompensation, prosthetic heart valve dysfunction).
In addition, this study includes a proposed learning curve analysis by evaluating the effect of rank order on the safety composite assessment at 30 days post-procedure. No hypothesis test was proposed. The effect of rank order of implant by physician and within site will be examined in separate analyses.

The design and goals of the post-approval studies should be carefully considered. Of particular interest to FDA is whether the composite primary endpoint should include all strokes, rather than only “major” strokes as captured in the proposed post-approval study. In addition, it may be important for the New Enrollment Study to include patients treated at smaller sites and at sites that are representative of real-world utilization, to assess if device performance is comparable to the premarket cohort. The New Enrollment Study provides an opportunity to further evaluate the learning curve by specifically comparing the results of the first patients treated by a newly trained interventionist to later patients of the same provider to determine patient risk as a function of operator experience level.

10 CONCLUSIONS

The data presented in the this PMA characterize the safety and effectiveness of the SAPIEN Transcatheter Heart Valve when used to treat 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 Panel will be asked to fully assess the significance of these results and comment on the risk to benefit ratio of using the SAPIEN Transcatheter Heart Valve to treat these patients.