Edwards SAPIEN Transcatheter Heart Valve Model 9000 and RetroFlex 3 Delivery System

FDA Review of P100041

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Office of Device Evaluation
Food and Drug Administration

Circulatory System Devices Panel Meeting
July 20, 2011
FDA Team Presenters

Lisa Kennell
  *Introduction and Pre-Clinical*

Chenguang Wang, PhD
  *Statistical Summary*

Julie Swain, MD
  *Clinical Summary*

Mary Beth Ritchey, PhD
  *Post-Approval Study*

Matthew Hillebrenner, MSE
  *Summary*
Outline

- Regulatory History
- Proposed Indications for use
- Device Description
- Pre-Clinical Testing
- Overview of PARTNER study
- Statistical Review
- Clinical Review
- Post-Approval Study
- FDA Summary
Regulatory History

- **SAPIEN IDE Study G030069**
  - *Pivotal PARTNER study began in 2007*

- **Premarket Approval (PMA) Application**
  - *PMA application received November 2010*
  - *Data “freeze” or “lock” date November 1, 2010*

- **Ongoing Study (Continued Access)**
  - *Currently approved for 1680 patients at 23 sites*
Proposed Indications for Use

• The Edwards SAPIEN Transcatheter Heart Valve (THV) is indicated for use in the following clinical conditions:

  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.
Proposed Indications for Use (continued)

• Consistent with patient selection process used in the PARTNER study to define “inoperable” patient
  – Most important to have surgeon assess operability of patient

• Language added to improve patient selection process by identifying “inoperable” patients who are likely to benefit from this treatment option
  – Several patients enrolled in trial who may have been too sick to benefit from isolated treatment of severe aortic stenosis
Device Description

- The Edwards SAPIEN THV
  - Heterologous (bovine) tissue sutured within a stainless steel stent
  - Aortic Sizes: 23 and 26 mm
  - Polyethylene terephthalate (PET) cuff
- RetroFlex 3 or RetroFlex delivery system available in sizes 20 and 23 mm for pre-dilating to ease crossing size 23 and 26 mm valve
- Sheath Set with Introducer, Sheath, and Loader with Cap
- A dilator kit
FDA Pre-Clinical Review Team

• **Team Leader**
  – Lisa Kennell

• **Engineering**
  – Changfu Wu PhD
  – Nandini Duraiswamy PhD
  – Sandy Stewart PhD
  – Stephen Retta MS
  – Albert Rodriguez

• **Animal Study**
  – Michael John, MPH

• **Patient Labeling Review**
  – David Windt, MPH

• **MRI**
  – Terry Woods PhD
  – Wolfgang Kainz PhD

• **Microbiology**
  – Lisa Kennell BS

• **Bio-Research Monitoring**
  – Adam Donat MS

• **Manufacturing**
  – Andrea P. Artman MS
  – Daniel Walter
Pre-Clinical Testing

- Biocompatibility
- Sterility & Packaging
- Magnetic Resonance Imaging (MRI)
- Delivery system
- Manufacturing
- Bio-research monitoring

- Corrosion resistance evaluation of the valve stent
- Fatigue evaluation of the valve stent
- Hydrodynamic and durability testing of the whole valve
- Valve migration potential evaluation
- In Vivo sheep studies

No further concerns about the majority of testing.

However, no testing was conducted on valve-in-valve implantation.
Valve-in-Valve

• 4 cases of valve-in-valve in Cohort B study
• Many more cases outside of the U.S., as reported in the literature
• Different valve positions
  – Aortic, mitral, tricuspid, and pulmonic
• Different configurations
  – TAV-in-TAV
  – TAV-in-SAV
  – TAV-in-Ring
Valve-in-Valve: Potential Risks

• Size mismatch
  – 2-3 sizes for current transcatheter valves vs. various sizes for surgically placed bioprosthetic valves
  – Impact on stable anchoring and uncompromised hemodynamic performance

• Valve migration/embolization

• Long term durability

• Fretting fatigue

• Galvanic corrosion

• Access to the coronary ostia
PARTNER IDE Trial

Cohort A (High Risk)
- Open AVR
- SAPIEN

Cohort B (Inoperable)
- Control*
- SAPIEN

CONTROL = BAV, Open AVR, Apico-aortic conduit, TAVR, and/or optimum medical therapy
Study Endpoints

• Primary endpoints of freedom from all cause death and composite of death and recurrent hospitalization were met

• FDA will focus mainly on totality of the data/key secondary endpoints
Secondary Safety Endpoints

• Key secondary safety endpoints
  – Time from randomization to first MACCE (death, MI, all stroke, renal failure)
  – Serious adverse events
    • Neurological Events
    • Vascular Complications
    • Aortic Regurgitation
Secondary Effectiveness Endpoints

• Key secondary effectiveness endpoints
  – 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
FDA Statistical Review of P100041

Chenguang Wang, PhD

Cardiovascular and Ophthalmic Devices Branch
Division of Biostatistics
Office of Surveillance and Biometrics
Outline

1. Study Design and Progression
2. Patient Accountability
3. Primary Endpoint Results
4. Secondary Endpoint Results
5. Summary
Study Design and Progression

- Design
  - Prospective, nonblinded, randomized, controlled, multi-center clinical trial
  - Calculated sample size 350 with estimated power 85%

- Enrollment
  - First enrollment 5/11/2007
  - 358 patients (179 Control, 179 SAPIEN) enrolled by 3/16/2009
  - 22 Centers (4 OUS)
  - Final statistical analysis plan on 2/18/2010.
  - Data cut-off date 11/1/2010
    - All events after the cut-off date excluded
Patient Accountability

- Control
  - 5/179 (2.8%) withdrawals by the data cut-off date
  - 14/86 (16.3%) eligible patients missing one-year in-window visit

- SAPIEN
  - 1/179 (0.6%) withdrawal by the data cut-off date
  - 12/124 (9.7%) eligible patients missing one-year in-window visit
  - 9/179 (5.0%) did not receive the device
Patient Demographics and Baseline Characteristics

• No statistically significant difference detected for the distributions of patient demographics and baseline characteristics between Control and SAPIEN.

• Potential clinically significant difference
  • Percentage numerically higher in Control:
    - coronary artery disease
    - previous MI
    - previous CABG
    - COPD
  • Percentage numerically higher in SAPIEN:
    - peripheral vascular disease
    - extensively calcified aorta
    - O₂ dependence
    - elevated creatinine
    - atrial fibrillation
    - chest-wall deformity
Analysis Population

Protocol specified analysis populations:

- Intent-To-Treat (ITT)
  - All randomized patients

- “As Treated” (AT)
  - AT Control: Randomized control patients and patients randomized to SAPIEN who did not receive the implant
  - AT SAPIEN: Randomized Treatment patients for whom the study valve implant procedure is begun

The analyses of the primary and secondary endpoints based on the ITT population, which was pre-specified in the protocol, will be presented.
Primary Safety and Effectiveness Endpoint

- **Definition**
  - *Freedom from death (over the duration of the trial)*

- **Null and alternative hypotheses:**
  - $H_0$: Survival function of SAPIEN = Survival function of Control
  - $H_1$: Survival function of SAPIEN $\neq$ Survival function of Control

- **Superiority test of SAPIEN over Control**

- **All-cause mortality significantly lower for SAPIEN.** (log-rank test, two-sided p-value < 0.0001).
**Primary Safety and Effectiveness Endpoint**

- **Proportion Survival At One Year:**
  - Control: 50.3%
  - SAPIEN: 69.3%

- **Median Survival (Years):**
  - Control: 0.97
  - SAPIEN: 2.18

<table>
<thead>
<tr>
<th>Number at Risk</th>
<th>Years</th>
<th>Control (n=179)</th>
<th>SAPIEN (n=179)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td></td>
<td>179 122 85 56 24 4 1</td>
<td>SAPIEN 179 138 124 103 61 13 0</td>
</tr>
</tbody>
</table>

**Distribution of Time to Death**

- Probability vs. Years graph showing the survival distribution for Control and SAPIEN groups.
Co-primary Endpoint: Death and Re-hospitalization

- Hierarchical composite of death and recurrent hospitalization
- Endpoint proposed after the initiation of study
- Null and alternative hypotheses
  \[ H_0: \text{Neither survival nor the re-hospitalization is different} \]
  \[ H_1: \text{At least one and possibly both components are different} \]
- Finkelstein-Schoenfeld test
- Statistical significance achieved in favor of SAPIEN (two-sided p-value <0.0001)
Finkelstein-Schoenfeld (FS) Method

• Non-parametric rank sum test where each patient is compared to every other patient in a pairwise manner.

• All patient pairs are compared first on survival if this comparison is possible. If not, patients are then compared on time to first recurrent hospitalization.
Secondary Endpoint: MACCE

- **Definition:**
  - *Time from randomization to the first occurrence of a MACCE event (death, MI, all strokes and renal failure) within one year*

- MACCE beyond one year not included

- Nominal two-side p-value 0.0176 (log-rank test) favoring SAPIEN

- FDA clinical reviewer will discuss the MACCE components
Secondary Endpoint: Hospitalization

**Definition:**

- *Total Hospital Days Through One Year*
  - Control Median: 8 days
  - SAPIEN Median: 12 days
  - Nominal two-sided p-value 0.019 (Bootstrap test)

**Additional Analysis**

- *Days Alive and Out of the Hospital Through One Year*
  - Proposed after the study was begun
  - Control Median: 233 days
  - SAPIEN Median: 348 days
Secondary Endpoint: NYHA at One Year

<table>
<thead>
<tr>
<th></th>
<th>Missing</th>
<th>Dead</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>11</td>
<td>89</td>
<td>2</td>
<td>29</td>
<td>37</td>
<td>11</td>
<td>179</td>
</tr>
<tr>
<td>SAPIEN</td>
<td>7</td>
<td>55</td>
<td>45</td>
<td>44</td>
<td>23</td>
<td>5</td>
<td>179</td>
</tr>
<tr>
<td>Total</td>
<td>18</td>
<td>144</td>
<td>47</td>
<td>73</td>
<td>60</td>
<td>16</td>
<td>358</td>
</tr>
</tbody>
</table>

- Sensitivity analyses regarding missing data conducted
- Results favored SAPIEN
- Possible systematic bias for nonblinded trials
Secondary Endpoint: Six-Minute Walk Test at One Year

- Observed
  - Control: 151 ± 78 meters
  - SAPIEN: 216 ± 132 meters

- Missing
  - Control: 59/90 (66%)
  - SAPIEN: 68/124 (55%)

- Sensitivity analyses regarding missing data conducted
- Results indefinite
- Difficult to draw firm conclusion because of missing data
Summary of FDA Statistical Review

- The study met its pre-specified primary endpoint
- This presentation highlights the primary and secondary endpoints with pre-specified hypotheses
- FDA clinical reviewer will discuss key effectiveness and safety issues
FDA Clinical Review of P100041

Julie A. Swain, MD
Cardiovascular Surgeon
Circulatory Support & Prosthetics Branch
Division of Cardiovascular Devices
Office of Device Evaluation
SAPIEN Clinical Experience

- 1st US Feasibility
- 2nd US Feasibility
- Roll-in Registry IDE Trial
- **Randomized, Controlled IDE Trial**
  - Randomized Continued Access Registry
  - Continued Access Registry
- European data 7000+ patients
  - EuroScore as inclusion (invalid for isolated valves, overpredicts mortality 3-7 times)
  - Surgeon determination of inoperability not required
PARTNER IDE Trial

Cohort A (High Risk)
- Open AVR
- SAPIEN

Cohort B (Inoperable)
- Control*
- SAPIEN

CONTROL = BAV, Open AVR, Apico-aortic conduit, TAVR, and/or optimum medical therapy
Randomized IDE Trial
Cohort B

- Transfemoral TAVR vs “standard” treatment

- Inoperable, anatomically eligible for transfemoral
  - Transapical studied in Cohort A arm only

- “Inoperable” does not necessarily mean “short-lived”

- FDA asked that transapical be included – Sponsor declined (Limits population for labeling)
### Key Procedural Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (min-max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Procedure Time (min)</td>
<td>262 (139 – 616)</td>
</tr>
<tr>
<td>Fluoro time (min)</td>
<td>29 (10 – 68)</td>
</tr>
<tr>
<td>Contrast Vol (ml)</td>
<td>132 (10 – 450)</td>
</tr>
<tr>
<td>Gen. Anesthesia</td>
<td>100% of patients</td>
</tr>
<tr>
<td>Procedure Success (device success, no MACCE &lt;30d)</td>
<td>71.8%</td>
</tr>
</tbody>
</table>
Primary Safety and Effectiveness Endpoint

Proportion Survival At One Year:
- Control: 50.3%
- SAPIEN: 69.3%

Median Survival (Years):
- Control: 0.97
- SAPIEN: 2.18
Co-Primary Endpoint (free from mortality/hospitalization)

- Interpretation complicated by possible assessment bias, treatment bias, and placebo effect in this unblinded trial

<table>
<thead>
<tr>
<th></th>
<th>0-1 years (# at risk)</th>
<th>1-2 years (# at risk)</th>
<th>2-3 years (# at risk)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Con</td>
<td>TEST</td>
<td>CON</td>
</tr>
<tr>
<td></td>
<td>.282 (.179)</td>
<td>.564 (.179)</td>
<td>.120 (.49)</td>
</tr>
</tbody>
</table>
Days Alive Out of Acute Care Hospital in 1 year

# Days (median)

- **Control**: 233
- **SAPIEN**: 348
Other Secondary Endpoints

**NYHA**
- subject to placebo effect, assessment bias
- interpretation of results in an unblinded trial is difficult

**6 Minute Walk Test**
- subject to placebo effect
- >50% missing data - interpretation impossible
MACCE at 1 year
(all cause death, all stroke, MI, renal failure)

Note: Vascular complications not included
New Pacemaker

% patients

Pacer <30d
5.0 3.4

Pacer 1yr
7.8 4.5

Control  SAPIEN
Important Considerations

1. Heterogeneity of control
2. *Post hoc* adverse event definitions
3. Neurological damage
4. Vascular injury
5. Aortic Insufficiency
6. Patient selection
Control “Standard” Therapy

- Balloon Aortic Valvuloplasty: 78.2%
- Open Aortic Valve Replacement: 6.1%
- Apico-Aortic Conduit: 3.3%
- Transcath Aortic Valve Implant: 2.2%
- Optimal Medical Management only: 7.9%
Implications of Control Heterogeneity

- Superiority is to “no SAPIEN implant”

- Control treatment selection not protocolized, possible selection bias in determining control treatment

- Not powered to compare SAPIEN with individual treatments - No proof of superiority to:
  - BAV
  - medical therapy
  - open AVR
  - Apico-aortic conduit
Important Considerations

1. Heterogeneity of control
2. *Post hoc* adverse event definitions
3. Neurological damage
4. Vascular injury
5. Aortic Insufficiency
6. Patient selection
Adverse Event Definitions

- FDA/Sponsor defined adverse events prior to start, FDA will use these for labeling

- Data analyzed, results known, then CEC was asked to redefine some adverse events (stroke, vascular), FDA not informed

- CEC Letter:
  
  “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.”
Important Considerations

1. Heterogeneity of control
2. *Post hoc* adverse event definitions
3. **Neurological damage**
4. Vascular injury
5. Aortic Insufficiency
6. Patient selection
Definition of Stroke and MACCE

- **Prespecified Definition of Stroke:**
  A neurological deficit lasting \( \geq \) 24 hours, or lasting < 24 hours with a brain imaging study showing infarction

- *Post hoc* “adjunctive” definition uses Modified Rankin Score for disability (major vs minor)
  - No patient had a Modified Rankin assessment
  - Sponsor agrees that retrospective Rankin is not validated
  - Stroke patients poor at self-evaluation

- Prespecified definition of MACCE included ALL stroke
**Stroke (%) patients**

- **Stroke <30d**
  - Control: 1.7%
  - SAPIEN: 7.3%
  - **4.3 X higher**

- **Total Stroke at 1yr**
  - Control: 4.5%
  - SAPIEN: 11.2%
  - **2.5 X higher**

**Note:** No standardized anticoagulation/antiplatelet regimen
Neurological Events (Stroke + TIA, % pts)

- **Neuro Events <30d:**
  - Control: 1.7
  - SAPIEN: 4.3 x higher

- **Neuro Events 30d - 1yr:**
  - Control: 2.8
  - SAPIEN: 4.5

- **Neuro Events >1yr:**
  - Control: 0
  - SAPIEN: 2.2

- **Neuro Events Total Study:**
  - Control: 4.5
  - SAPIEN: 14
  - 3.1 x higher
## Neurological Events

<table>
<thead>
<tr>
<th>Neurological Event</th>
<th>Control # events</th>
<th>SAPIEN # events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic/unclassified stroke</td>
<td>7</td>
<td>16</td>
</tr>
<tr>
<td>TIA</td>
<td>0</td>
<td>3 (2pts)</td>
</tr>
<tr>
<td>Intracranial Hemorrhage</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td><strong>Total Events</strong></td>
<td><strong>8</strong></td>
<td><strong>25</strong></td>
</tr>
</tbody>
</table>
Control Neuro Events

- 7 ischemic/unclassified strokes:
  - 1 after open AVR
  - 4 after BAV (5 days, 2 weeks, 2 months, 6 months)
  - 2 medical management (day of random, 3 days after random)

- One hemorrhagic stroke 8 months after BAV

- No intracranial hemorrhages

- No TIAs
SAPIEN Neuro Events

- 16 ischemic/unclassified strokes:
  - 1 after randomization 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)

- 3 hemorrhagic strokes (2, 39, and 120 days)

- 3 intracranial hemorrhages (51, 136, 151 days)

- 3 TIAs in 2 patients (143 days; 386/831 days)
DW-MRI Lesions

% Patients

Cross AV (Omran) 22
AVR (Astarci) 8
AVR (Knipp) 48
Ghanem 73
Kahlert 84
Rodes-Cabau 68
Astarci 91
Arnold 68
Cerebral Infarction after TAVI

- ~ 60% scans not done (death, complications, refusal, etc.)
- Limitations in assessment of stroke, no long-term assessment
- Possible mechanisms of injury:
  - catheter in arch - crossing stenotic AV
  - Balloon valvuloplasty - TAVI positioning
  - TAVI expansion - Corrective manipulation

Future TAVI IDE studies – protocolized neurological assessment by neurologists in at least 50% of patients
Important Considerations

1. Heterogeneity of control
2. Post hoc adverse event definitions
3. Neurological damage
4. Vascular injury
5. Aortic Insufficiency
6. Patient selection
Hemorrhagic Vascular Complications

1. Hematoma at access site >5 cm
2. False aneurysm
3. Arterio-venous fistula
4. Retroperitoneal bleeding
5. Peripheral ischemia/nerve injury
6. Transfusion for cath complication
7. Vascular surgical repair

% SAPIEN patients

Hemorrhagic Vascular Complications <30 days

55.9

57
### Selected Vascular Complications (SAPIEN)

<table>
<thead>
<tr>
<th>Acute Vascular Complications</th>
<th># Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic Dissection</td>
<td>1</td>
</tr>
<tr>
<td>Iliac artery/distal aortic</td>
<td>17</td>
</tr>
<tr>
<td>Femoral artery</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>

FDA seeking Panel input on training program to minimize this complication
Important Considerations

1. Heterogeneity of control
2. *Post hoc* adverse event definitions
3. Neurological damage
4. Vascular injury
5. **Aortic Insufficiency**
6. Patient selection
# Aortic Regurgitation
(ACC/AHA Guidelines 2006)

<table>
<thead>
<tr>
<th></th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Qualitative</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angiographic grade</td>
<td>1+</td>
<td>2+</td>
<td>3-4+</td>
</tr>
<tr>
<td>Color Doppler jet width</td>
<td>Central jet, width less than 25% of LVOT</td>
<td>Greater than mild but no signs of severe AR</td>
<td>Central jet, width greater than 65% LVOT</td>
</tr>
<tr>
<td>Doppler vena contracta width (cm)</td>
<td>Less than 0.3</td>
<td>0.3–0.6</td>
<td>Greater than 0.6</td>
</tr>
<tr>
<td><strong>Quantitative (cath or echo)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regurgitant volume (ml per beat)</td>
<td>Less than 30</td>
<td>30–59</td>
<td>Greater than or equal to 60</td>
</tr>
<tr>
<td>Regurgitant fraction (%)</td>
<td>Less than 30</td>
<td>30–49</td>
<td>Greater than or equal to 50</td>
</tr>
<tr>
<td>Regurgitant orifice area (cm²)</td>
<td>Less than 0.10</td>
<td>0.10–0.29</td>
<td>Greater than or equal to 0.30</td>
</tr>
</tbody>
</table>

**Additional essential criteria**
- Left ventricular size: Increased
SAPIEN Aortic Regurgitation
Moderate (2+) or Greater
Central + Paravalvular

% SAPIEN patients

30d  6mos  1yr

15.2  9.9  15.6
Important Considerations

1. Heterogeneity of control
2. *Post hoc* adverse event definitions
3. Neurological damage
4. Vascular injury
5. Aortic Insufficiency
6. Patient selection
Patient Selection Issues

Inclusion:
6. 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%.

Exclusion:
19. Life expectancy < 12 months due to non-cardiac co-morbid conditions.
Patient Selection Issues

• Qualitative judgement at individual sites – In-person assessment only at the center

• Enthusiasm for devices tests limits of patient selection – refined during trials

• Inclusion/Exclusion criteria did not address patients in long-term care facilities; no measure of return home vs rehab facility

• Need to consider when transcatheter valve implantation may not have a positive impact on a patient’s quality of life

• The following 3 patients are not unique examples of patients with comorbidities – obtained from CEC narratives
87-year-old male

- non-ischemic cardiomyopathy, pacemaker, EF 20%, HTN
- Paget’s disease, debilitating rheumatoid arthritis with multiple exacerbations and peripheral myopathy, post-herpetic neuralgia with severe chronic pain
- Randomized to SAPIEN, post-procedure complications (transient delirium, probable aspiration pneumonia, episodes of hypotension in the setting of volume overload/overdiuresis, laryngeal edema)
- discharged to a rehab facility POD #20, readmitted due to probable aspiration pneumonia, sepsis and death
95 YO male

- CAD (prior PCI, CABG), afib (warfarin), HTN, HL, renal insufficiency
- **COPD (home O2), macular degeneration (legally blind), history of CVA, subdural hematoma**
- SAPIEN implant, post-procedure stroke, reintubation, pneumonia, renal insufficiency, etc.;
  Transferred to acute rehab on POD#21, difficulty swallowing, pneumonia;
  Transferred home and died
88 YO female

- CHF, CAD, afib (coumadin), HTN, severe Pulm HTN (72/32)

- Severe COPD with multiple admissions, home O₂, FEV1 0.53; monoclonal gammaglobulinemia, osteoporosis, spinal stenosis
  - Left sided weakness (recurrent TIA’s);
  - transferred from outside hosp. where she had transient left arm clumsiness (dx. TIA)
  - left arm became clumsy again - MRI = acute subacute stroke
    (MRA = decreased flow in right ICA, right MCA, b/l ACA, L PCA and stenosis R PCA, R proximal ICA)

- SAPIEN implanted, died 11 days later from progression of her stroke
Patient Selection Issues

- No active consideration given to specifying patients who **should not** have transcatheter valve implantation due to extensive comorbidities.

- SAPIEN implantation highly invasive (general anesthesia, 4+ hrs, contrast, TEE, + vascular operation).

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**Operable**

- High Risk Operable
- Inoperable (Benefit to Patient)
- Inoperable (No Benefit to Patient)

Need to appropriately bracket use.

***
Summary of FDA Clinical Review

• The inoperable patients who received the SAPIEN device had an impressive reduction in mortality compared to those randomized to not receive the device.

• This reduction in mortality in inoperable patients outweighed the significant safety issues with the device, most notably stroke and vascular injury.

• Long term issues with the SAPIEN relating to clinically significant aortic insufficiency and valve durability remain to be defined.

• Patient selection needs refinement.

• Residential status needs to be considered in the endpoint.
Post-Approval Study
Considerations for
SAPIEN Transcatheter Heart Valve

Mary Beth Ritchey, RN, MSPH, PhD
Division of Epidemiology
Office of Surveillance and Biometrics / CDRH

July 20, 2011
Reminder

• The discussion of a PAS prior to FDA determination of device approvability should not be interpreted to mean FDA is suggesting that the device is safe and effective
• The plan to conduct a PAS does not decrease the threshold of evidence required by FDA for device approval
• The premarket data submitted to the Agency and discussed today must stand on its own in demonstrating a reasonable assurance of safety and effectiveness and an appropriate risk/benefit balance
Post-Approval Study Components

- Fundamental study question or hypothesis
- Well specified study population and study design
- Safety endpoints and methods of assessment
- Short term and long term safety and effectiveness endpoints and methods of assessment
- Duration of follow-up
Important Postmarket Concerns for SAPIEN THV

- Long term device durability
- Long term patient quality of life
- Learning curve assessment
- Comparison of postmarket patients with premarket cohort, differences in patient populations and outcomes (including stroke), and device durability, and patient quality of life
Proposed Post-Approval Studies

• Extended Follow-up of the Premarket Cohort
  – “PAS 1”

• New Enrollment Study
  – “PAS 2”
Outline for Extended Follow-up of Premarket (PAS 1)

• Study Objectives
  – To assess: 1) long term (5-year) valve implant durability
    2) long term (5-year) quality of life

• Study Hypothesis
  – No hypotheses for: Durability or Quality of Life
Outline for Extended Follow-up of Premarket (PAS 1), cont

• Population and Sample Size
  – Includes IDE participants who remain alive and return for clinical visits
  – Limited long term data with 10-30% of Sapien patients and “virtually no” comparator patients expected to be alive at the 5 year visit

• Follow-up through 5 years post implant
  – Evaluation of data at 4 years and 5 years post implant

• Endpoints
  – Durability measured by echocardiography at 4 and 5 years post implant
  – Quality of Life measured by SF-12 at 4 and 5 years post implant
  – Only observed data included in evaluation
FDA Assessment – PAS 1

• Hypothesis and Power
  – Given long-term sample size, hypothesis and power calculation provide information regarding robustness of findings

• Outcomes
  – Collection of echo data included in current study
  – Modification of informed consent to collect quality of life data
  – Panel discussion requested
Outline for New Enrollment Study (PAS 2)

• Study Objectives
  To assess:
  1) safety (including stroke)
  2) adherence to indication and learning curve assessment (effectiveness)
  3) long-term valve durability and quality of life in the post approval population

• Study Hypotheses
  \[ H_0 : D=P_T-P_C \geq \delta \quad H_1 : D=P_T-P_C < \delta \]

  Where: \( P_T \) is event rate in registry, \( P_C \) is event rate comparison,
  \( \delta \) is non-inferiority margin (1.3 x performance goal)
Outline for New Enrollment Study (PAS 2), cont

• Population and Sample Size
  – 750-1000 participants at a minimum of 75 sites
  – Study does not include sites with < 50 implants per year because not intended to be included in first year of commercialization

• Follow-up
  – 5 years post implant
Primary Safety Composite Endpoint (PAS 2, 30-days post implant)

- All-cause mortality
- Major stroke
- Life-threatening (or disabling) bleeding
- Acute kidney injury - Stage 3
- Peri-procedural myocardial infarction
- Repeat procedure for valve-related dysfunction
Primary Effectiveness Composite Endpoint (PAS 2, 1-year post implant)

- All-cause mortality
- Failure of current therapy for aortic stenosis, requiring hospitalization for symptoms of valve-related decompensation
- Prosthetic heart valve dysfunction
FDA Assessment – PAS 2 Outcomes

• Composite endpoints:
  – could be heavily influenced by one component, such as death, or
  – this may not provide an accurate picture of the safety or effectiveness of the device for components of interest, such as major stroke

• Not all stroke specific hypothesis driven comparison proposed
  – only major stroke included in the composite primary safety analysis
  – all stroke is a secondary endpoint without specific hypothesis driven comparison
FDA Assessment – Further Consideration for PAS 2

• Notable secondary endpoint
  – All neurological events (major and minor stroke and TIA – VARC) at 30 days and 1 year

• Vascular complications not characterized within the study
  – High proportion of major vascular complications were observed in the Sapien arm of the premarket study.

• Anticoagulation protocol based on stroke risk in patients with atrial fibrillation
  – Not validated in this population
PAS 2 - Learning Curve

• Primary assessment via benchmarking of safety and effectiveness composite endpoints

• Secondary analyses of outcomes using analysis of patients ranked by order of implant in separate models by site and by interventionalist

\[
\frac{\text{expected}}{\text{observed}} = \text{performance}
\]
FDA Assessment – PAS 2 Learning Curve Evaluation

• Max of 20 patients per site with less patients expected for each interventionalist learning the procedure
  – patients per interventionalist may be inadequate for ROC curve evaluation
  – may prevent comparison of outcomes associated with “earlier” and “later” patients treated by the same interventionalist

• Learning curve consists of (1) technical aspects of procedure and (2) appropriate patient selection.
  – no assessment of learning appropriate patient selection was proposed
Panel Discussion

- Appropriateness of assessment of longer-term outcomes and quality of life, learning curve, and postmarket patient concerns
- Time frame, evaluation, and presentation of learning assessment to clinical community
- Use of VARC composite endpoints
- Use of performance goals derived from premarket data
- Recommended study questions and study design
Summary of FDA Review

Matthew Hillebrenner, MSE
Circulatory Support and Prosthetics Branch
Division of Cardiovascular Devices
Office of Device Evaluation
Summary of FDA Review

• Primary safety and effectiveness endpoint was met - The inoperable patients who received the SAPIEN device had an impressive reduction in mortality compared to those who did not receive the device

• A number of other factors should be considered in the evaluation of the overall risk-benefit profile of the device
  – These are the key areas where we are seeking panel input
Request for Panel Input

• Proposed indications for use
  – Does this language accurately describe the patient population where the risk-benefit profile is most favorable?

• Patient selection
  – How do you ensure that the appropriate patients get this device (inoperable patients who will benefit from correcting aortic stenosis)?

• Heterogeneity of the control group
  – How does this impact interpretation of the study results as well as labeling claims?
Request for Panel Input

- Neurological adverse events
  - Based on the PARTNER trial and worldwide experience, this remains a concern for TAVI
  - What measures can be taken to mitigate this risk?

- Vascular complications
  - 1st generation device/delivery system
  - Does the training program adequately address ways to minimize this risk?

- Aortic Insufficiency
  - Aortic regurgitation is appreciable at 1-year
  - The long-term clinical significance is unknown
Request for Panel Input

- Valve-in-valve technique
  - Widely used in worldwide experience
  - No preclinical testing and limited clinical data
  - How should this be addressed in the device labeling?

- Long-term valve durability remains unknown

- Need for post-approval study
  - Determine adverse event rate in “real world” use
  - Learning curve assessment
  - How do you interpret quality of life data in unblinded trials?
  - How long should these patients be followed?
Questions?