SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name:	Aortic valve, prosthesis, percutaneously delivered
Device Trade Name:	Edwards SAPIEN XT™ Transcatheter Heart Valve, model 9300TFX, 23, 26, and 29 mm, and accessories (NovaFlex+ delivery system, models 9355FS23, 9355FS26, and 9355FS29, with crimp stopper and Qualcrimp crimping accessory [laminated model or cloth model 9300QC]; Edwards Expandable Introducer Sheath Set, models 916ES23, 918ES26, and 920ES29; Ascendra+ delivery system with crimp stopper, models 9355AS23, 9355AS26, and 9355AS29; Ascendra+ introducer sheath set, models 9350IS23, 9350IS26, and 9350IS29; Edwards crimper, model 9350CR)
Device Procode:	NPT
Applicant Name and Address:	Edwards Lifesciences LLC One Edwards Way Irvine, CA 92614
Date of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P130009/S034
Date of FDA Notice of Approval:	October 9, 2015

The Edwards SAPIEN XT Transcatheter Heart Valve (THV) was approved under PMA P130009 on June 16, 2014 with an indication for relief of aortic stenosis in patients with symptomatic heart disease due to severe native calcific aortic stenosis (aortic valve area ≤ 1.0 cm^2 or aortic valve area index ≤ 0.6 cm^2/m^2, a mean aortic valve gradient of ≥ 40 mmHg, or a peak aortic-jet velocity of ≥ 4.0 m/s), and with native anatomy appropriate for the 23, 26, or 29 mm valve system, who are judged by a heart team, including a cardiac surgeon, to be at high or greater risk for open surgical therapy (i.e., Society of Thoracic Surgeons (STS) operative risk score ≥ 8% or at a ≥ 15% risk of mortality at 30 days). The SSED supporting this indication is available on the FDA website

(http://www.accessdata.fda.gov/cdrh_docs/pdf13/P130009b.pdf) and is incorporated by reference herein. The current supplement was submitted to expand the indication for the Edwards SAPIEN XT THV and accessories to include the treatment of a failed surgical bioprosthesis ("TAV-in-SAV").

II. INDICATIONS FOR USE

The Edwards SAPIEN XT Transcatheter Heart Valve is indicated for patients with symptomatic heart disease due to either severe native calcific aortic stenosis or failure (stenosed, insufficient, or combined) of a surgical bioprosthetic aortic valve who are judged by a heart team, including a cardiac surgeon, to be at high or greater risk for open surgical therapy (i.e., Society of Thoracic Surgeons operative risk score ≥8% or at a ≥15% risk of mortality at 30 days).

III. CONTRAINDICATIONS

The Edwards XT Transcatheter Heart Valve (THV) and accessories are contraindicated in patients who cannot tolerate an anticoagulation/antiplatelet regimen or who have active bacterial endocarditis or other active infections.

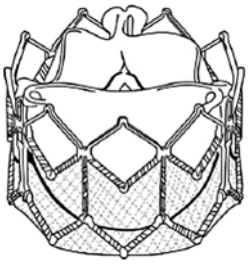
IV. WARNINGS AND PRECAUTIONS

Warnings and precautions are provided in the Edwards SAPIEN XT THV and accessories labeling.

V. DEVICE DESCRIPTION

The Edwards SAPIEN XT THV, shown in **Figure 1**, is comprised of a balloon-expandable, radiopaque, cobalt-chromium frame, trileaflet bovine pericardial tissue valve and polyethylene terephthalate (PET) fabric skirt. The leaflets are treated according to the Edwards ThermaFix™ process, and the valve is packaged and terminally sterilized in glutaraldehyde.

Figure 1: SAPIEN XT Transcatheter Heart Valve

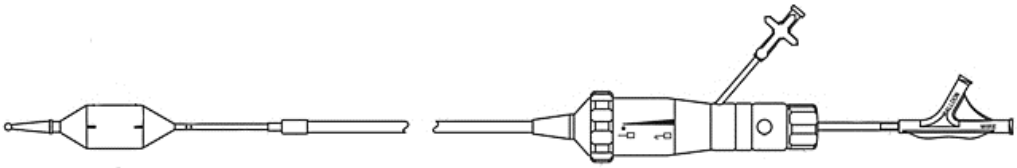


23mm and 26mm

29mm

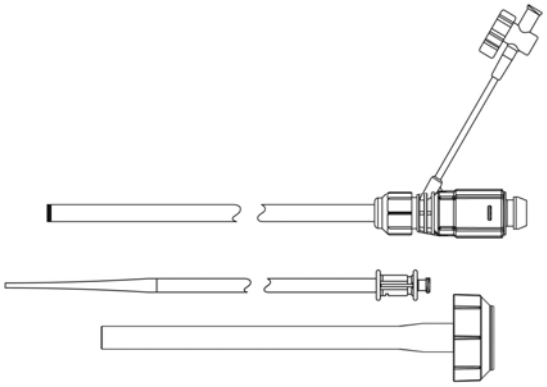
The NovaFlex+ delivery system, shown in **Figure 2**, includes a handle that provides a flex wheel for articulation of the flex catheter, a tapered tip at the distal end of the delivery system to facilitate crossing the valve, a balloon catheter for deployment of the THV, and radiopaque markers.

Figure 2: NovaFlex+ Delivery System



The Edwards Expandable Introducer Sheath Set, shown in **Figure 3**, consists of a sheath, an introducer, and a loader.

Figure 3: Edwards Expandable Introducer Sheath Set



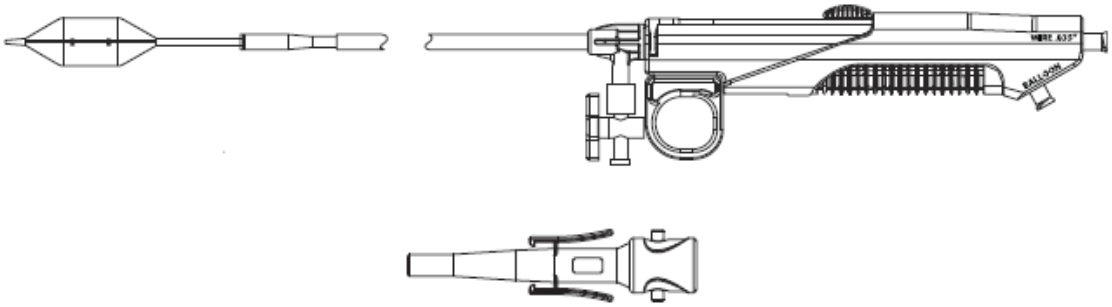
The Qualcrimp crimping accessory, shown in **Figure 4**, is a non patient-contacting device that is placed around the Edwards SAPIEN XT THV to protect the leaflets during the crimping process. It is available in two models. The cloth model is manufactured from ester-based polyurethane compressed foam encapsulated in a single piece of knitted polyester cloth that is wrapped around the foam and sutured at the top. The laminated model is manufactured of tubular polyester polyurethane foam that is laminated cylindrically on both the inner and outer surfaces with a polyether urethane material.

Figure 4: Qualcrimp Crimping Accessory

Cloth Model | Laminated Model

The Ascendra+ delivery system, shown in **Figure 5**, has radiopaque markers for visualization under fluoroscopy, a balloon for deployment of the THV and a handle. The system comes with a loader that is used to cover the THV during delivery. An extension tube is supplied for use with the delivery system during balloon inflation.

Figure 5: Ascendra+ Delivery System



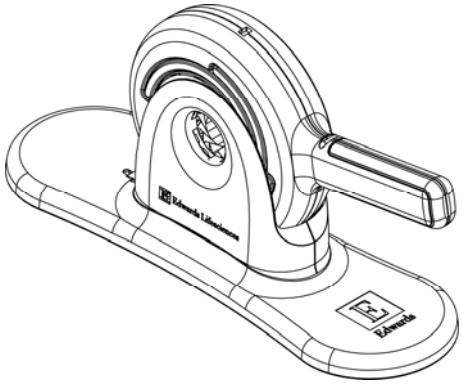
The Ascendra+ introducer sheath set, shown in **Figure 6**, consists of an introducer and a sheath.

Figure 6: Ascendra+ Introducer Sheath Set

The Edwards crimper, shown in **Figure 7**, is comprised of various molded plastic components which compress the valve to a controlled aperture. The aperture is created by rotating the handle until it abuts the crimp stopper. The Edwards crimper includes a 2-piece crimp stopper (packaged with the NovaFlex+ delivery system) or a one-piece

crimp stopper (packaged with the Ascendra+ delivery system) used to correctly crimp the THV.

Figure 7: Edwards Crimper



VI. ALTERNATIVE PRACTICES AND PROCEDURES

Alternatives for patients with surgical bioprosthetic aortic valve failure (stenosed, insufficient, or combined) include: temporary relief using percutaneous balloon aortic valvuloplasty (BAV), medical therapy (non obstruction-relieving intervention), or other commercial transcatheter aortic valve replacement (TAVR) device approved for this indication. For patients who are operable, redo surgical aortic valve replacement (SAVR) is an established safe and effective treatment option. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the treatment that best meets his/her expectations and lifestyle.

VII. MARKETING HISTORY

Currently, the SAPIEN XT THV and accessories are commercially available for "TAV-in-SAV" use in the 28 member states under the European Union (i.e., Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, The Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, United Kingdom) and other countries including Albania, Armenia, Azerbaijan, Chile, Egypt, Georgia, Hong Kong, Iceland, Iran, Jordan, Kuwait, Lebanon, Liechtenstein, Maghreb (Algeria, Morocco, Tunisia), Malaysia, Moldova, Monaco, Montenegro, Norway, Oman, Panama, South Africa, Switzerland, Turkey, and United Arab Emirates. It has not been withdrawn from marketing for any reason related to its safety or effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The adverse effects listed below are associated with access complications associated with standard cardiac catheterization, balloon valvuloplasty, potential risks of conscious sedation and/or general anesthesia, and use of angiography:

- Death
- Stroke/transient ischemic attack, clusters or neurological deficit
- Paralysis
- Permanent disability
- Respiratory insufficiency or respiratory failure
- Hemorrhage requiring transfusion or intervention
- Cardiovascular injury including perforation or dissection of vessels, ventricle, myocardium or valvular structures that may require intervention
- Pericardial effusion or cardiac tamponade
- Embolization including air, calcific valve material or thrombus
- Infection including septicemia and endocarditis
- Heart failure
- Myocardial infarction
- Renal insufficiency or renal failure
- Conduction system defect which may require a permanent pacemaker
- Arrhythmia
- Retroperitoneal bleed
- Femoral AV fistula or pseudoaneurysm
- Reoperation
- Peripheral ischemia or nerve injury
- Restenosis
- Pulmonary edema
- Pleural effusion
- Bleeding
- Anemia
- Abnormal lab values (including electrolyte imbalance)
- Hypertension or hypotension
- Allergic reaction to anesthesia, contrast media, or device materials
- Hematoma
- Syncope
- Pain or changes at the access site
- Exercise intolerance or weakness
- Inflammation
- Angina
- Heart murmur
- Fever

Additional potential risks associated with the use of the THV, delivery system and/or accessories include:

- Cardiac arrest
- Cardiogenic shock
- Emergency cardiac surgery
- Cardiac failure or low cardiac output
- Coronary flow obstruction/transvalvular flow disturbance
- Device thrombosis requiring intervention
- Valve thrombosis
- Device embolization
- Device migration or malposition requiring intervention
- Valve deployment in unintended location
- Valve stenosis
- Structural valve deterioration (wear, fracture, calcification, leaflet tear/tearing from surgical valve's stent posts, leaflet retraction, suture line disruption of components of a prosthetic valve, leaflet thickening, stenosis)
- Device degeneration
- Paravalvular or transvalvular leak
- Valve regurgitation
- Hemolysis
- Device explants
- Nonstructural dysfunction
- Mechanical failure of delivery system, and/or accessories
- Non-emergent reoperation

See Section X for specific adverse events that occurred in the clinical studies.

IX. SUMMARY OF PRECLINICAL STUDIES

A summary of previously reported preclinical studies is provided in the SSED for the original PMA (http://www.accessdata.fda.gov/cdrh_docs/pdf13/P130009b.pdf).

Additional preclinical bench testing was performed on the SAPIEN XT THV in the "TAV-in-SAV" configuration, as summarized in Table 1.

Table 1: Summary of *In Vitro* Studies for SAPIEN XT in a "TAV-in-SAV" Configuration

Test	Applicable Standards	Test Description	Results
Hydrodynamic Testing	ISO 5840:2005, ISO 5840-3:2013	This test evaluated the hydrodynamic performance of the Edwards SAPIEN XT THV in appropriately sized surgical valves.	Pass
Accelerated Wear Testing	ISO 5840:2005, ISO 5840-3:2013	Valves underwent durability testing to 200 million cycles without excessive structural damage and/or functional impairment and met the minimum effective orifice area (EOA) and total regurgitation fraction requirements.	Pass

Test	Applicable Standards	Test Description	Results
Corrosion Testing	ISO 5840:2005, ISO 5840-3:2013	This test evaluated the potential for galvanic corrosion of the SAPIEN XT THV in a "TAV-in-SAV" configuration.	Pass
MR Compatibility	ASTM F2182-11a ASTM F2213-06 IEC 60601-2-33 ASTM F2119-07 ASTM 2052-06e1 FDA Stent Guidance (2005) ISO 5840-3:2013	This test evaluated MR compatibility of the Edwards SAPIEN XT THV in a "TAV-in-SAV" configuration.	MR conditional
Balloon Burst Testing	N/A	This test evaluated balloon burst in a constrained configuration	Pass

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study in the U.S. to establish a reasonable assurance of safety and effectiveness of transcatheter aortic valve replacement with the Edwards SAPIEN XT THV in patients with a failing surgical bioprosthetic aortic valve (i.e., "TAV-in-SAV"). The study was carried out as a single-arm registry nested in IDE G090216 (i.e., the PARTNER II Trial), which was designated as "NR3." NR3 was originally approved for 100 patients and later expanded under a Continued Access Protocol (CAP). The pooled data from the original NR3 cohort and the NR3 CAP (CANR3) cohort were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

Patients were treated at 40 investigational sites between June 12, 2012 and December 10, 2013. The database for this PMA supplement reflected data collected through February 26, 2015 and included 199 patients, of which 2 withdrew prior to treatment. The last database extract was performed on February 26, 2015. All 197 remaining patients were included in the 30-day data analysis and 97 patients were included in the 1-year analysis.

The NR3 study was a single arm, prospective, observational, descriptive study without formal hypothesis testing. The patients were limited to those who were deemed by a heart team to have a mortality or major morbidity rate of ≥ 50% for redo surgical aortic valve replacement surgery and met the sizing requirements for the 23 mm or 26 mm SAPIEN XT THV. The specific sizing requirements were imposed because the 29 mm SAPIEN XT THV was not available when the study was initiated.

Contractors were utilized for analysis and interpretation of the clinical data, including an independent Data Safety Monitoring Board (DSMB) that was instructed to notify the applicant of any safety or compliance issues, a Clinical Event Committee (CEC) that was responsible for adjudicating endpoint-related events reported during the trial per definitions established *a priori*, an Electrocardiography (ECG) Core Lab for independent

analysis of rhythm and occurrence of myocardial infarction, and an Echocardiography Core Lab for independent analysis of all echocardiograms.

1. Clinical Inclusion and Exclusion Criteria

In the absence of a specific tool for assessing patient operability, high-risk patients were deemed "inoperable" based on a consensus assessment by two cardiovascular surgeons and a cardiac interventionalist. At least one surgeon who deemed the patient inoperable was required to have performed a physical assessment of the patient. Most inoperable patients had elevated STS risk scores including one or more STS risk elements that exceeded the thresholds considered safe for surgery, e.g., respiratory disease, for which the STS risk-scoring threshold usually signaled increased risk in operable patients, but which was severe enough in a given patient to explain inoperability. Other "inoperable" patients, regardless of the STS score, were rendered inoperable by severe co-morbidities of the low-prevalence, high-heterogeneity variety that are difficult to represent statistically and are not part of the STS risk model, such as liver disease, porcelain aorta, chest wall abnormalities, and frailty.

To minimize subjective influences, patients declared "inoperable" were presented for case review to one or more surgeons from the Executive Committee and/or the Patient Selection and Procedure Steering Committee, who confirmed patient eligibility or ineligibility.

The inclusion and exclusion criteria are summarized below:

Inclusion criteria:

- Stenosed or insufficient surgically implanted bioprosthetic valve in the aortic position.
- New York Heart Association (NYHA) Functional Class > II.
- The heart team agreed that the risk of surgical mortality or major morbidity ≥ 50%.

Exclusion criteria:

- Labeled external diameter of the bioprosthetic valve < 21mm.
- Surgical or transcatheter valve in another position on the same side of the heart (mitral and tricuspid rings were not an exclusion).
- Hemodynamic instability defined as requiring inotropic, pressor, or mechanical support.
- Infectious endocarditis within 6 months.
- Bacteremia within 1 month.
- Intra-cardiac thrombus or vegetation.
- Acute myocardial infarction ≤ 1 month (30 days) before the intended treatment [defined as: Q wave MI, or non-Q wave MI with total CK elevation ≥ twice normal in the presence of MB elevation and/or troponin level elevation (WHO definition)].

- Percutaneous coronary intervention or implantation of a permanent pacemaker within 7 days of the index procedure.
- Leukopenia (WBC < 3000 cell/mL), acute anemia (Hgb < 9 g/dL), thrombocytopenia (Plt < 50,000 cell/mL).
- Hypertrophic cardiomyopathy with obstruction.
- Severe ventricular dysfunction with left ventricular injection fraction (LVEF) < 20%.
- Active upper gastro-intestinal (GI) bleeding within 3 months (90 days) prior to procedure requiring transfusion.
- Inability to be anticoagulated for the study procedure.
- Stroke or transient ischemic attack within 6 months (180 days).
- Renal Insufficiency (creatinine > 3.0 mg/dL) and/or renal replacement therapy at the time of screening.
- Estimated life expectancy < 24 months.
- Participating in an investigational drug or another device study. Note: Trials requiring extended follow-up for products that were investigational, but have since become commercially available, are not considered investigational trials.
- The patient requires emergency surgery for any reason.
- Xenograft or THV in another position.
- Index valve has moderate or severe paravalvular regurgitation.
- Index valve is unstable or rocking.
- Extensive, severe non-revascularized coronary disease.
- Increased risk of coronary obstruction by prosthetic leaflets (non-stented or internally stented valve which might extend above a coronary ostium).
- Increased risk of embolization (non-stented and non-calcified valve).

2. Follow-up Schedule

   All patients were scheduled for follow-up examinations at discharge or 7 days, whichever comes first, 30 days, 6 months, 12 months, and annually thereafter to a minimum of 5 years post procedure.

3. Clinical Endpoints

   The primary effectiveness endpoint was a composite event that included all-cause mortality, all stroke, moderate or severe obstruction (defined as Doppler Velocity Index [DVI] < 0.25), and moderate or severe paravalvular leak at 30 days and 1 year. The analyses were not hypothesis driven.

   Additional safety and effectiveness endpoints were as follows:

   - All-cause mortality at 30 days, 1 year, and annually thereafter up to 5 years
   - All stroke or transient ischemic attack (TIA) at 30 days, 1 year, and annually thereafter up to 5 years
   - All-cause mortality or major stroke at 30 days, 1 year, and annually thereafter up to 5 years
   - All stroke, major vascular complication, or aortic valve reintervention at 30 days, 1 year, and annually thereafter up to 5 years

- NYHA at 30 days, 6 months, 1 year, and annually thereafter up to 5 years
- Change in distance walked during 6 minute walk test (6MWT) from baseline at 30 days and 1 year
- Echocardiographic assessment of valve performance at 30 days, 1 year, and annually thereafter up to 5 years using the following measures:
  - DVI
  - Total aortic regurgitation
  - Paravalvular leak
  - Transvalvular mean and peak gradients
- Clinical improvement per Quality of Life (QoL) instrument (KCCQ) at 30 days, 1 year, and annually thereafter up to 5 years
- Index hospitalization length of stay

The above additional endpoints were assessed at 30 days, 6 month (where applicable), and 1 year in this application.

B. Accountability of Study Cohort

Since identical protocols were used in the pivotal and CAP cohort investigations, data from the two cohorts were pooled.

The "Attempted Implant" population consisted of all screen success patients for whom the index procedure was started. The "Valve Implant" population consisted of those patients for whom the valve implant process was completed. A total of 199 patients were screened for study participation. Two patients withdrew consent prior to treatment; therefore, there were 197 "Attempted Implant" patients. Two "Attempted Implant" patients were excluded from the "Valve Implant" population, because in one patient, intra-procedural TEE demonstrated a low transvalvular jet velocity (2.6 m/s) and gradient of 24 mmHg which did not meet the inclusion criteria, and in the other patient, the procedure was aborted due to inability to place the purse string sutures for transapical access. The patient disposition is summarized in Table 2.

Table 2: Patient Disposition

	Attempted Implant[1]	Valve Implant[2]
Number of Patients	197	195

[1]Attempted Implant: All screen success patients for whom the Index Procedure was started. Patients were analyzed according to the valve used in the initial implant attempt.
[2]Valve Implant: This population was a subset of the Attempted Implant group, consisting of those patients for whom the valve implant process was completed.

C. Study Population Demographics and Baseline Parameters

The demographics of the pooled study population are summarized in Table 3. The mean age was 78.5 years, and 60.4% were male. A high proportion of patients had significant comorbidities, frailty, and prior cardiac interventions. The mean STS score was 9.7, and 95.4% of all patients were in NYHA classes III or IV.

Table 3: Demographic and Baseline Characteristics - Attempted Implant Population

Characteristic	Results[1] (N=197)
Age – yr	78.5 ± 11.00[1]
Male sex	119/197 (60.4%)
STS score	9.7 ± 5.09
New York Heart Association (NYHA) class	
I/II	9/197 (4.6%)
III/IV	188/197 (95.4%)
Coronary artery disease	139/197 (70.6%)
Previous myocardial infarction	25/197 (12.7%)
Previous intervention	
Coronary artery bypass grafting (CABG)	97/197 (49.2%)
Percutaneous coronary intervention (PCI)	39/197 (19.8%)
Prior aortic valvuloplasty	17/197 (8.6%)
Cerebral vascular accident (CVA)	29/197 (14.7%)
Peripheral vascular disease	49/197 (24.9%)
Chronic obstructive pulmonary disease (COPD)	
Any	65/197 (33.0%)
Oxygen-dependent	14/197 (7.1%)
Creatinine > 2 mg/dL (177 μmol/liter)[2]	25/197 (12.7%)
Atrial fibrillation	98/197 (49.7%)
Permanent pacemaker	51/197 (25.9%)
Pulmonary hypertension	26/197 (13.2%)
Frailty[3]	65/197 (33.0%)
Extensively calcified aorta	12/197 (6.1%)
Chest-wall deformity	4/197 (2.0%)
Liver disease	14/197 (7.1%)
Reason for Valve Replacement	
Mixed Lesion	45/192 (23.4%)
Insufficiency/regurgitation Only	43/192 (22.4%)
Stenosis Only	104/192 (54.2%)
Echocardiographic findings	
Doppler Velocity Index (DVI)[4]	0.27 ± 0.10
Mean aortic-valve gradient — mmHg	35.9 ± 16.42
Mean left ventricular ejection fraction (LVEF) — %	49.8 ± 13.87
Moderate or severe mitral regurgitation[5]	62/171 (36.3%)

[1] Quantitative data are expressed as mean ± SD (n). Categorical data are expressed as no./total no. (%).
[2]To convert the value for creatinine to micromoles per liter, multiply by 88.4.
[3]Frailty was determined by the surgeons according to pre-specified criteria.
[4]DVI is a flow-dependent measure of orifice stenosis. A DVI < 0.25 suggests significant stenosis.
[5]Moderate or severe mitral regurgitation was defined as regurgitation of grade 3+ or higher.

Table 4 provides a summary of the failed surgical valves treated, which consisted of 94.4% bioprosthesis, 4.6% homografts, and 1.0% other valve types. Aortic stenosis was the predominant cause of prosthetic failure (54.2%), followed by mixed lesion (23.4%) and insufficiency/regurgitation (22.4%).

Table 4: Summary of Failed Bioprosthetic Surgical Valves - Attempted Implant Population

	Results[1] (N=197)
Type of Failed Surgical Valve	
Bioprosthesis	184 / 195 (94.4%)
Homograft	9 / 195 (4.6%)
Other [2]	2 / 195 (1.0%)
Reason for Valve Replacement	
Mixed Lesion	45/192 (23.4%)
Insufficiency/regurgitation Only	43/192 (22.4%)
Stenosis Only	104/192 (54.2%)

[1] Categorical data are expressed as no./total no. (%).

[2] Other included an unidentified manufactured tissue valve and a St. Jude mechanical composite.

D. Safety and Effectiveness Results

The 30-day results reported herein were from the pooled data (NR3/CANR3), and the 1-year results from only the NR3 cohort.

1. Primary Endpoint

The primary endpoint of all-cause mortality, all stroke, moderate or severe obstruction, or moderate or severe paravalvular leak was 16.9% at 30 days and 38.0% at 1 year, as shown in Table 5.

Table 5: All-Cause Mortality, All Stroke, Moderate or Severe Obstruction, or Moderate or Severe Paravalvular Leak – Valve Implant Population

	30 Days (N=195)		1 Year (N=96)	
Events	**Patients with Event**	**95% Confidence Interval[3]**	**Patients with Event**	**95% Confidence Interval**
Composite Event[1]	28/166 (16.9%)	[11.5%, 23.4%]	27/71 (38.0%)	[26.8%, 50.3%]
All-Cause Mortality	8/195 (4.1%)	[1.8%, 7.9%]	19/96 (19.8%)	[12.4%, 29.2%]
All Stroke	5/195 (2.6%)	[0.8%, 5.9%]	3/96 (3.1%)	[0.6%, 8.9%]
Moderate or Severe Obstruction[2]	12/169 (7.1%)	[3.7%, 12.1%]	6/54 (11.1%)	[4.2%, 22.6%]
Moderate or Severe PV Leak	4/162 (2.5%)	[0.7%, 6.2%]	1/53 (1.9%)	[0.0%, 10.1%]

[1]Composite of all-cause mortality, all stroke, moderate or severe obstruction, moderate or severe paravalvular leak. Mortality and stroke are calculated at 30 days. The moderate or severe obstruction and paravalvular leak use the Echo core lab's determination at the 30-day follow-up visit.

[2]Doppler velocity index (DVI) < 0.25 per the echo core lab read.

[3]Confidence intervals calculated using exact binomial calculations. The confidence intervals are calculated without multiplicity adjustment. The adjusted confidence intervals could be wider than presented here. As such, confidence intervals are provided to illustrate the variability only and should not be used to draw any statistical conclusion.

2. Additional Endpoints

Adverse Events

No unanticipated adverse device effects (UADEs) were reported throughout the trial. Three explants have been reported to date; one explant occurred at autopsy, and two during surgical aortic valve replacement due to severe aortic insufficiency on postoperative day 5 and day 18, respectively. No CEC adjudicated endocarditis was reported.

The key safety outcomes adjudicated by the CEC for this study are presented in Table 6 through Table 8.

Table 6: CEC Adjudicated Adverse Events - Attempted Implant Population

Adverse Events	Rate (no./total no. (%))	
	30 Days (N=197)	1 Year (N=97)
Death[1]		
From any cause	8/197 (4.1%)	19/97 (19.6%)
From cardiovascular cause	7/197 (3.6%)	15/97 (15.5%)
Major Stroke	5/197 (2.5%)	3/97 (3.1%)
Myocardial Infarction	5/197 (2.5%)	3/97 (3.1%)
Major Vascular Complications	8/197 (4.1%)	6/97 (6.2%)
Acute Kidney Injury, Stage III[2]	2/197 (1.0%)	N/A
Disabling Bleeding[3]	19/197 (9.6%)	16/97 (16.5%)
Cardiac Reintervention[4]	4/197 (2.0%)	2/97 (2.1%)
Endocarditis	0/197 (0.0%)	0/97 (0.0%)
New Atrial Fibrillation	4/135 (3.0%)	2/45 (4.4%)
New Pacemaker	3/197 (1.5%)	1/97 (1.0%)

[1]Deaths from unknown causes were assumed to be deaths from cardiovascular causes.

[2]Acute kidney injury, stage III is defined as an increase in serum creatinine to >=300% (3 x increase compared with baseline) or serum creatinine of >= 4 mg/d (>=354 µmol/L) with an acute increase of at least 0.5 mg/dl (44 µmol/L) within 72 hours of the procedure (per the VARC-1 definition).

[3]Disabling bleeding: Fatal bleeding OR bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome OR bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery OR overt source of bleeding with drop in hemoglobin of ≥ 5 g/dL or whole blood of packed red blood cells (RBC) transfusion ≥ 4 units (Life-threatening per VARC-1 definitions).

[4]Cardiac reintervention includes any intervention that repairs, alters or replaces a previously operated valve OR balloon aortic valvuloplasty OR Surgical aortic valve replacement OR valve in valve.

Table 7: Kaplan-Meier (KM) Event Rate for CEC Adjudicated Major Vascular Complications, Major Stroke, Minor Stroke, TIA, and Acute Kidney Injury - Attempted Implant Population

	30 Days (N=197)				1 Year (N=97)			
VARC Event[1]	**Events**	**Patients with Event**	**KM Estimate[2]**	**95% CI[3]**	**Events**	**Patients with Event**	**KM Estimate**	**95% CI**
Major Vascular Complications and/or Major Stroke and/or Minor Stroke and/or TIA and/or Acute Kidney Injury, Stage III	15	14	0.071	(0.043, 0.117)	14	12	0.127	(0.074, 0.213)
Major Vascular Complications	8	8	0.041	(0.021, 0.080)	6	6	0.062	(0.029, 0.134)
Major Stroke	5	5	0.025	(0.011, 0.060)	5	3	0.032	(0.010, 0.096)
Minor Stroke	0	0	0.000	N/A	0	0	0.000	N/A
TIA	0	0	0.000	N/A	1	1	0.013	(0.002, 0.089)
Acute Kidney Injury, Stage III	2	2	0.010	(0.003, 0.040)				

[1]Standardized endpoint definitions for transcatheter aortic valve implantation clinical trials consensus from the Valve Academic Research Consortium (VARC). Events with missing or incomplete onset dates were excluded from the analysis.

[2]Kaplan-Meier estimates used the first event per patient. Events occurring after day 30 and day 365 were not included in the analysis of the 30-day and 1-year results, respectively.

[3]Confidence intervals calculated using Greenwood's formula. The confidence intervals are calculated without multiplicity adjustment. The adjusted confidence intervals could be wider than presented here. As such, confidence intervals are provided to illustrate the variability only and should not be used to draw any statistical conclusion.

Table 8: Conduction Disturbance Requiring New Permanent Pacemaker - Attempted Implant Population

	30 Days (N=197)		1 Year (N=97)	
	Events	**Patients with Event**	**Events**	**Patients with Event**
New Permanent Pacemaker- All Patients[1]	3	3/197 (1.5%)	1	1/97 (1.0%)
New Permanent Pacemaker – Patients without preexisting pacemaker[2]	3	3/146 (2.1%)	1	1/70 (1.4%)

[1]Subjects with pacemaker or ICD at baseline were included (all patients included in denominator).

[2]Subjects with pacemaker or ICD at baseline were excluded (patients with baseline pacemaker/ICD subtracted from denominator).

Valve Performance

Valve hemodynamics as assessed by echocardiography is summarized in Table 9 and Figure 9 through Figure 13. The mean DVI increased from 0.27 ± 0.10 at baseline to 0.37 ± 0.09 at 30 days and 0.39 ± 0.11 at 1 year. The mean gradient decreased from 36.1 ± 16.38 mmHg at baseline to 17.4 ± 7.37 mmHg at 30 days, which was maintained at 1 year. The mean peak gradient decreased from 65.0 ± 26.76 mmHg at baseline to 32.7 ± 12.90 mmHg at 30 days, which was maintained at 1 year. Moderate/severe aortic regurgitation was present in 43.7% of subjects at baseline, which decreased to 2.5% at 30 days and 1.9% at 1 year. Moderate/severe paravalvular leak was present in 6.8% of subjects at baseline, 2.5% at 30 days, and 1.9% at 1 year.

It is important to note that although mean and peak gradients were significantly reduced as compared to baseline for the "TAV-in-SAV" procedure, the residual mean and peak gradients were numerically higher than those observed for TAVR procedures performed for native valve stenosis.

Table 9: Valve Hemodynamics Measured by Echocardiography - Valve Implant Population

	Baseline (N=195)	**Discharge (N=195)**	**30 Days (N=195)**	**1 Year (N=96)**
Doppler Velocity Index - mean ± SD (n)				
All Valve Sizes	0.27 ± 0.10 (173)	0.37 ± 0.09 (161)	0.37 ± 0.09 (169)	0.39 ± 0.11 (54)
23 mm (N=140)	0.26 ± 0.09 (123)	0.36 ± 0.10 (114)	0.36 ± 0.09 (118)	0.38 ± 0.11 (38)
26 mm (N=55)	0.29 ± 0.13 (50)	0.40 ± 0.08 (47)	0.41 ± 0.11 (51)	0.44 ± 0.11 (16)
Mean Gradient (mmHg) - mean ± SD (n)				
All Valve Sizes	36.1 ± 16.38 (179)	18.2 ± 7.79 (168)	17.4 ± 7.37 (176)	17.3 ± 8.76 (56)
23 mm (N=140)	37.2 ± 16.86 (129)	19.5 ± 8.19 (120)	19.0 ± 7.64 (125)	18.8 ± 9.32 (40)
26 mm (N=55)	33.2 ± 14.84 (50)	15.0 ± 5.51 (48)	13.4 ± 4.79 (51)	13.7 ± 5.91 (16)
Peak Gradient (mmHg) - mean ± SD (n)				
All Valve Sizes	65.0 ± 26.76 (179)	34.3 ± 13.67 (168)	32.7 ± 12.90 (176)	32.8 ± 15.58 (56)
23 mm (N=140)	66.9 ± 27.49 (129)	36.5 ± 14.36 (120)	35.4 ± 13.30 (125)	35.2 ± 16.80 (40)
26 mm (N=55)	60.1 ± 24.34 (50)	29.0 ± 10.05 (48)	26.2 ± 9.09 (51)	26.7 ± 10.04 (16)
Total Aortic Regurgitation - no./total no. (%)				
All Valve Sizes				
None	22/174 (12.6%)	74/164 (45.1%)	86/163 (52.8%)	34/53 (64.2%)
Trace	34/174 (19.5%)	64/164 (39.0%)	58/163 (35.6%)	15/53 (28.3%)
Mild	42/174 (24.1%)	21/164 (12.8%)	15/163 (9.2%)	3/53 (5.7%)
Moderate	47/174 (27.0%)	4/164 (2.4%)	3/163 (1.8%)	1/53 (1.9%)
Severe	29/174 (16.7%)	1/164 (0.6%)	1/163 (0.6%)	0/53 (0.0%)
23 mm				
None	21/124 (16.9%)	55/116 (47.4%)	63/115 (54.8%)	23/37 (62.2%)
Trace	29/124 (23.4%)	43/116 (37.1%)	39/115 (33.9%)	12/37 (32.4%)

	Baseline (N=195)	Discharge (N=195)	30 Days (N=195)	1 Year (N=96)
Mild	32/124 (25.8%)	14/116 (12.1%)	10/115 (8.7%)	2/37 (5.4%)
Moderate	29/124 (23.4%)	3/116 (2.6%)	2/115 (1.7%)	0/37 (0.0%)
Severe	13/124 (10.5%)	1/116 (0.9%)	1/115 (0.9%)	0/37 (0.0%)
26 mm				
None	1/50 (2.0%)	19/48 (39.6%)	23/48 (47.9%)	11/16 (68.8%)
Trace	5/50 (10.0%)	21/48 (43.8%)	19/48 (39.6%)	3/16 (18.8%)
Mild	10/50 (20.0%)	7/48 (14.6%)	5/48 (10.4%)	1/16 (6.3%)
Moderate	18/50 (36.0%)	1/48 (2.1%)	1/48 (2.1%)	1/16 (6.3%)
Severe	16/50 (32.0%)	0/48 (0.0%)	0/48 (0.0%)	0/16 (0.0%)
Paravalvular Leak - no./total no. (%)				
All Valve Sizes				
None	121/162 (74.7%)	76/164 (46.3%)	91/162 (56.2%)	35/53 (66.0%)
Trace	18/162 (11.1%)	66/164 (40.2%)	56/162 (34.6%)	15/53 (28.3%)
Mild	12/162 (7.4%)	17/164 (10.4%)	11/162 (6.8%)	2/53 (3.8%)
Moderate	8/162 (4.9%)	4/164 (2.4%)	3/162 (1.9%)	1/53 (1.9%)
Severe	3/162 (1.9%)	1/164 (0.6%)	1/162 (0.6%)	0/53 (0.0%)
23 mm				
None	92/121 (76.0%)	55/116 (47.4%)	68/114 (59.6%)	24/37 (64.9%)
Trace	15/121 (12.4%)	47/116 (40.5%)	36/114 (31.6%)	11/37 (29.7%)
Mild	10/121 (8.3%)	10/116 (8.6%)	7/114 (6.1%)	2/37 (5.4%)
Moderate	2/121 (1.7%)	3/116 (2.6%)	2/114 (1.8%)	0/37 (0.0%)
Severe	2/121 (1.7%)	1/116 (0.9%)	1/114 (0.9%)	0/37 (0.0%)
26 mm				
None	29/41 (70.7%)	21/48 (43.8%)	23/48 (47.9%)	11/16 (68.8%)
Trace	3/41 (7.3%)	19/48 (39.6%)	20/48 (41.7%)	4/16 (25.0%)
Mild	2/41 (4.9%)	7/48 (14.6%)	4/48 (8.3%)	0/16 (0.0%)
Moderate	6/41 (14.6%)	1/48 (2.1%)	1/48 (2.1%)	1/16 (6.3%)
Severe	1/41 (2.4%)	0/48 (0.0%)	0/48 (0.0%)	0/16 (0.0%)

Figure 9: Doppler Velocity Index by Visit - Valve Implant Population

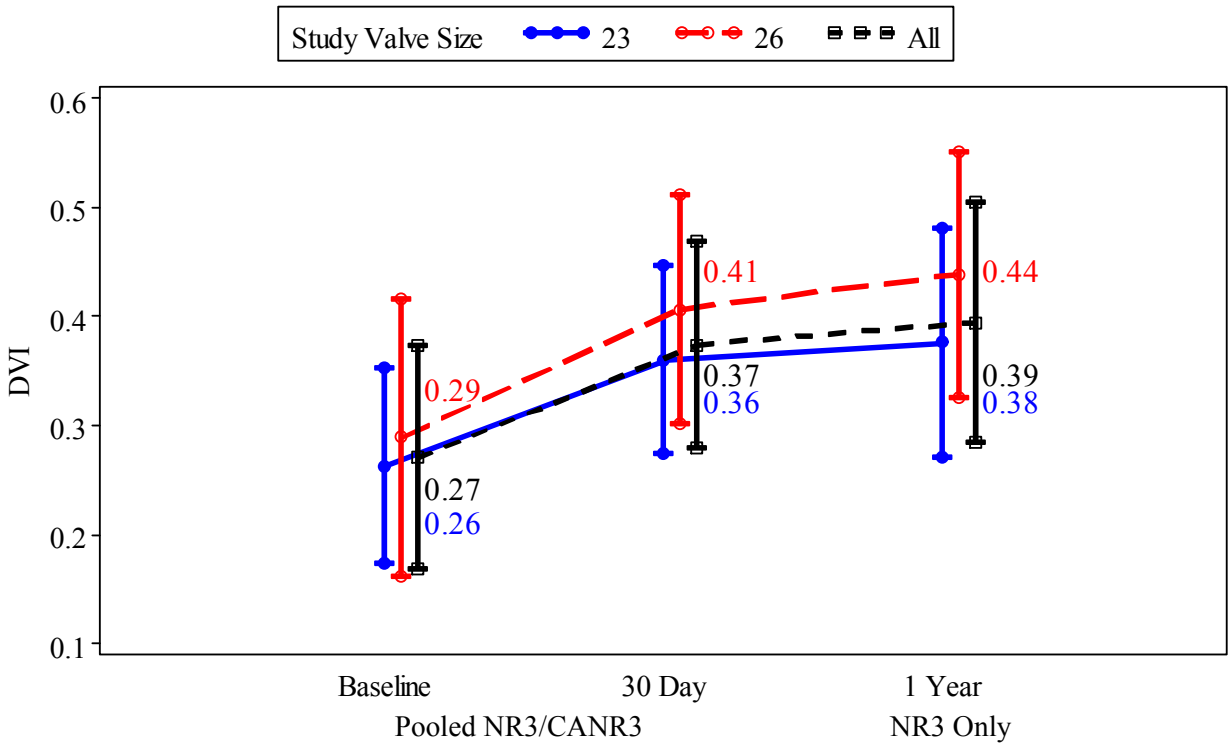


Figure 10: Mean Gradient by Visit - Valve Implant Population

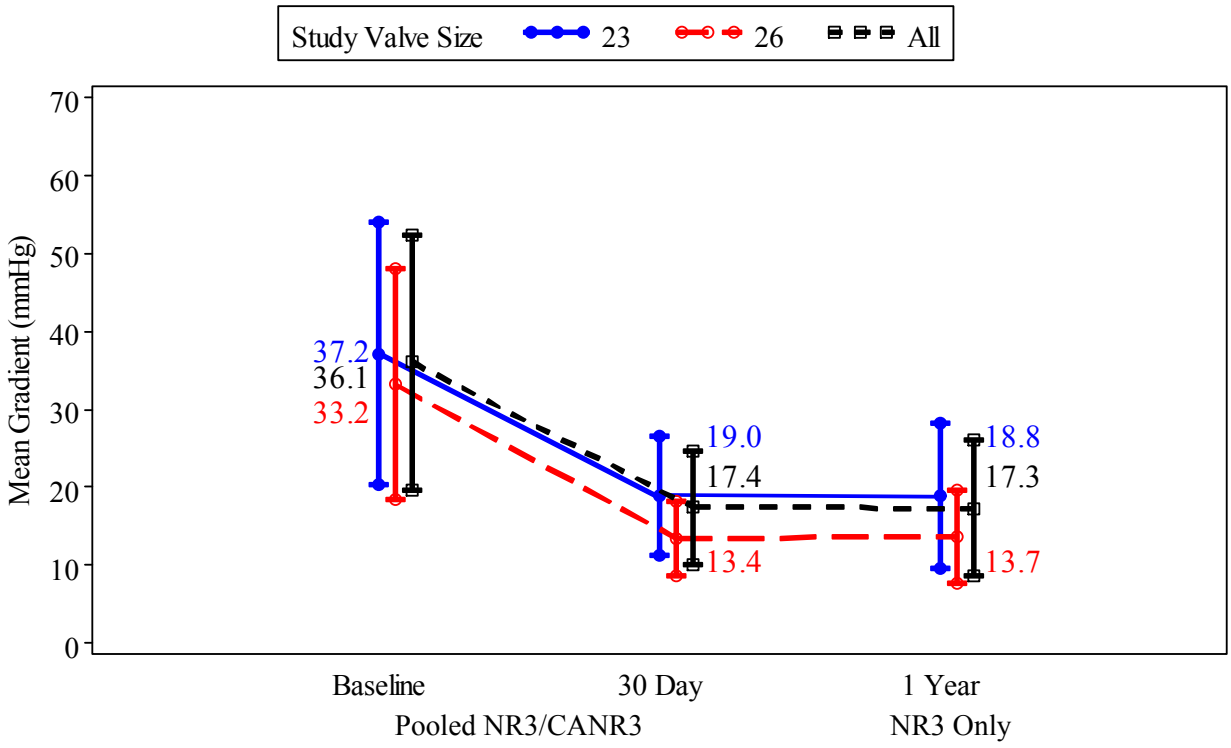


Figure 11: Peak Gradient by Visit - Valve Implant Population

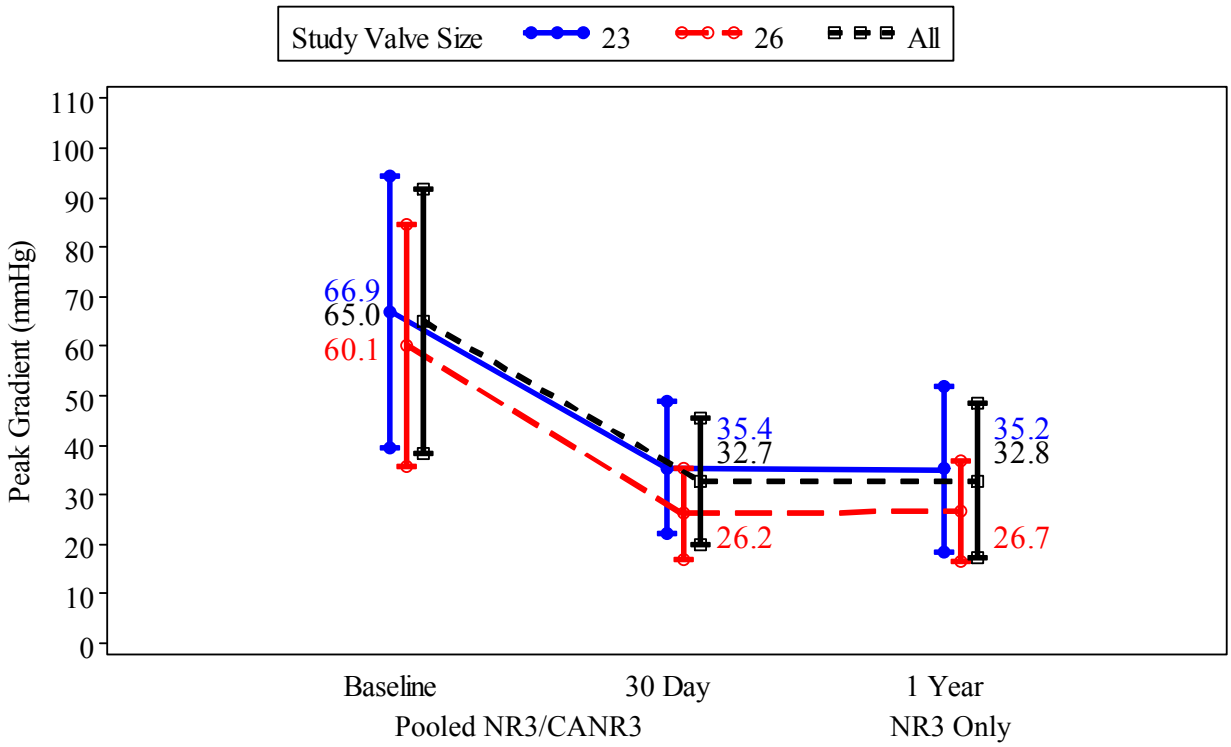


Figure 12: Total Aortic Regurgitation by Visit - Valve Implant Population

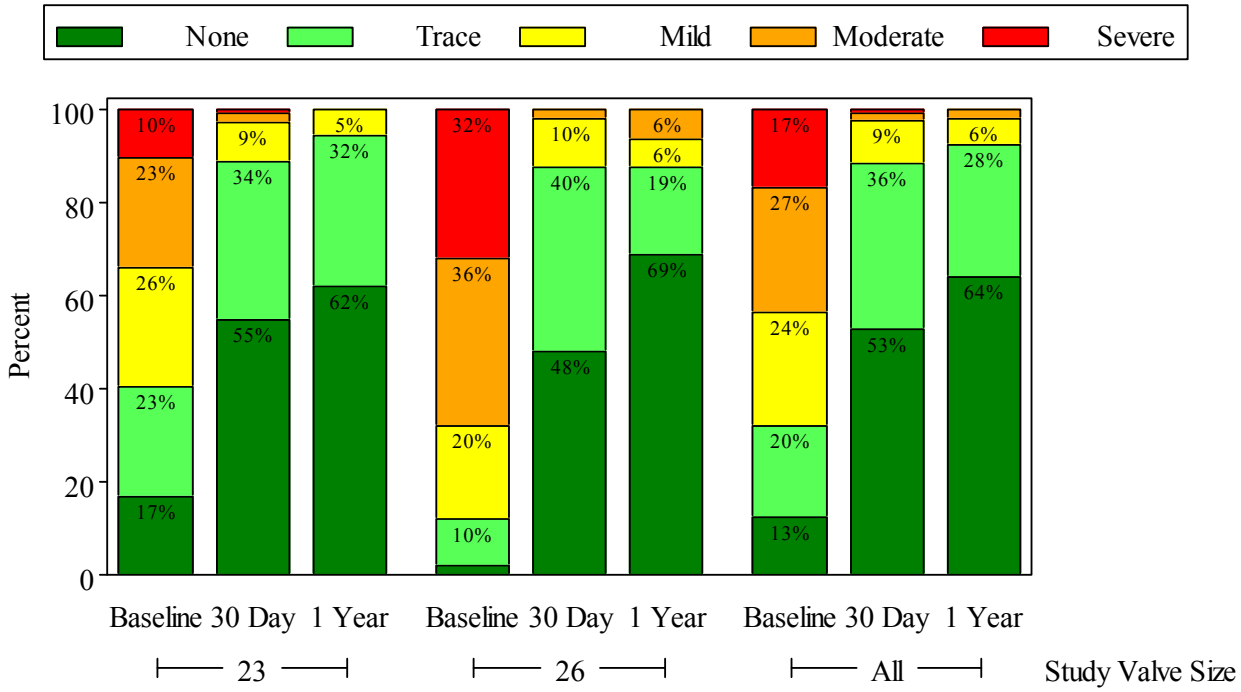
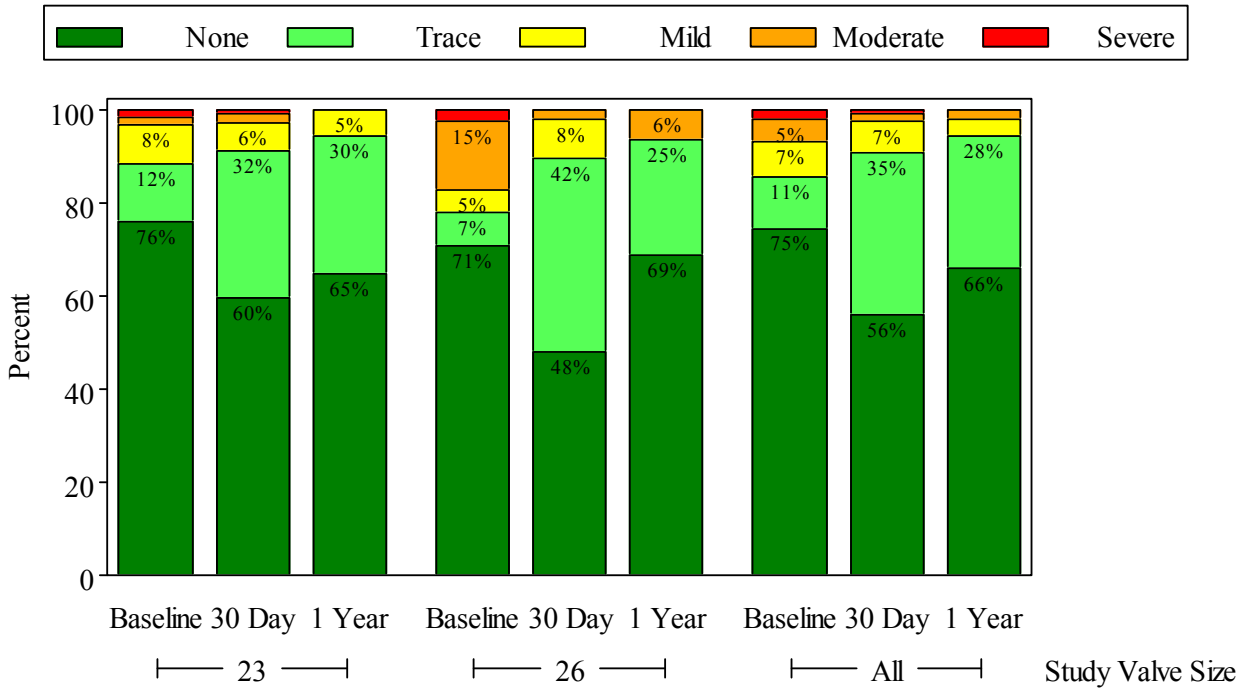


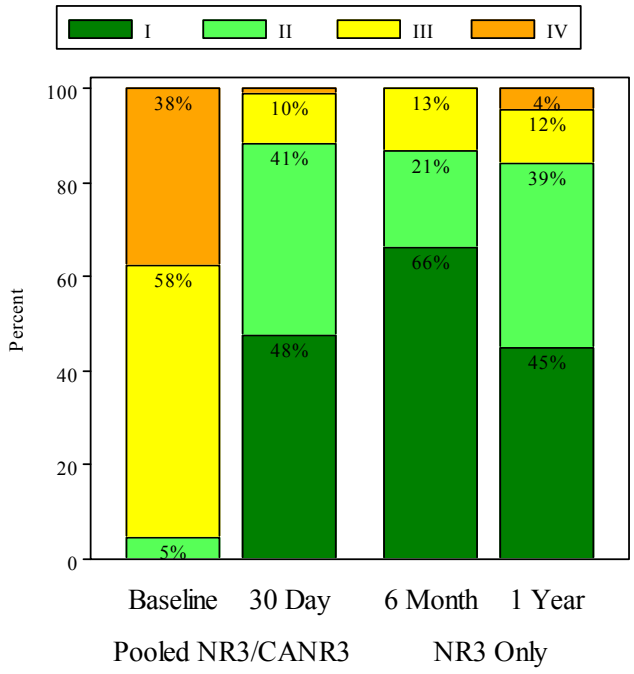
Figure 13: Paravalvular Leak by Visit - Valve Implant Population



NYHA

The NYHA class by visit is shown in Figure 14. About 89% of subjects were in NYHA I/II at 30 days and 84% at 1 year as compared to 5% at baseline.

Figure 14: NYHA Class by Visit - - Attempted Implant Population



Six Minute Walk Distance (6MWD)

The mean improvement in 6MWD among the Attempted Implant population was 49.8 ± 169.9 meters from baseline to 30 days and 86.1 ± 142.0 meters from baseline to 1 year.

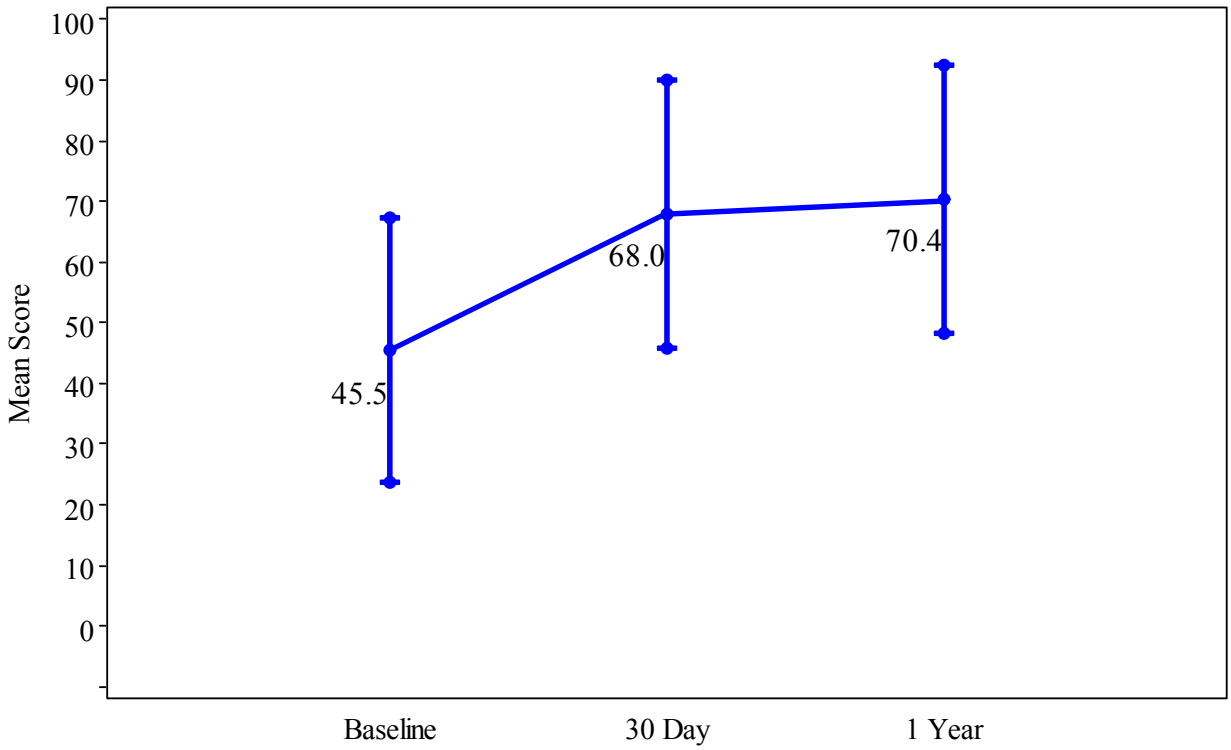
Length of Stay

The mean hospitalization stay among the Attempted Implant population was 7.9 ± 7.0 days, which included 2.9 ± 5.0 days in the ICU.

Quality of Life (QoL)

The QoL at different time points as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ) clinical summary score is shown in Figure 15. The mean KCCQ summary score among the Attempted Implant population improved from 45.5 ± 21.8 at baseline to 68.0 ± 22.0 at 30 days and 70.4 at 1 year.

Figure 15: KCCQ Clinical Summary Score - Attempted Implant Population



Device Success

Device success was defined as successful vascular access, delivery and deployment and retrieval of delivery system; correct positioning, intended performance (aortic valve area > 1.2 cm^2 and mean aortic valve gradient < 20 mmHg or peak velocity < 3 m/s, without moderate or severe prosthetic valve aortic regurgitation. It was achieved in 61.5 % of patients, as summarized in Table 10. In the vast majority of device failure subjects, the failure was due to unintended performance of the valve; specifically, mean gradient ≥ 20

mmHg or peak velocity ≥ 3m/s was observed in 62 cases and moderate/severe aortic regurgitation in 5 cases.

Table 10: Device Success and Reason for Device Failure - Valve Implant Population

Device Success[1]	Rate[2]
Success	115/187 (61.5%)
Failure	72/187 (38.5%)
Factor 1: Unsuccessful access, delivery, deployment, or retrieval of delivery system	11/72 (15.3%)
Factor 2: Position - Too Aortic or Too Ventricular	2/72 (2.8%)
Factor 3a: mean gradient ≥ 20mmHg or peak velocity ≥ 3 m/s	62/70 (88.6%)
Factor 3b: Moderate/ Severe Aortic Regurgitation	5/71 (7.0%)
Factor 4: More than 1 valve implanted	3/72 (4.2%)

[1]Device success was defined as successful vascular access, delivery and deployment and retrieval of delivery system; correct positioning of the THV, intended performance (mean aortic valve gradient < 20 mmHg or peak velocity < 3 m/s, without moderate or severe prosthetic valve AR), only one THV implanted. Each participant who failed could experience a failure in more than one factor. If a patient failed one factor, the device was considered a failure even if other factors were undetermined due to missing data.
[2]The results are expressed as no. / total no. (%). The denominator for each factor was equal to the patients with an overall failure and non-missing data for that factor.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conduction clinical studies covered by the regulation.

NR3 and CANR3 included 274 investigators, of which none were full-time or part-time employees of the sponsor and 24 had disclosable financial interests/ arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0
- Significant payment of other sorts: 24
- Proprietary interest in the product tested held by the investigator: 0
- Significant equity interest held by investigator in sponsor of covered study: 0

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. The information provided does not raise any questions about the reliability of the data.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

The clinical results presented in section X were obtained from patients who were deemed inoperable and who received the 23 and 26 mm SAPIEN XT THV. The applicant provided supplemental clinical information to support the approval of the 29 mm SAPIEN XT THV for the "TAV-in-SAV" indication and approval of all three valve sizes

(23, 26, and 29 mm) for the "TAV-in-SAV" indication in high risk patients. This supplemental clinical information came from the SOURCE XT registry.

A. Study Design

SOURCE XT was the first post-approval study conducted outside the U.S. with the size 23, 26 and 29mm SAPIEN XT THV following commercial availability of the device in the European Union. It was an international, multi-center, observational registry study of consecutive patients undergoing transcatheter aortic valve replacement (TAVR) with the SAPIEN XT THV, including "TAV-in-SAV" implantations.

Patients were treated between July 20, 2010 and November 9, 2011. The database reflected data collected through December 15, 2014. Data were collected at discharge, 30 days, and 12 months post-implant, and annually thereafter for up to 5 years.

B. Safety and Effectiveness Results

A total of 2688 patients were enrolled in SOURCE XT. The results summarized in this section only involve the 57 patients in SOURCE XT that underwent the "TAV-in-SAV" procedure. The implanted valve size was 23 mm in 38 patients (66.7%), 26 mm in 14 patients (24.6%), and 29 mm in 5 patients (8.8%).

Demographic and baseline characteristics are described in Table 11.

Table 11: Demographics and Baseline Characteristics of the SOURCE XT "TAV-in-SAV" Subjects (Attempted Implant Population)

Characteristics	Results[1] (N=57)
Age[1] - yr	77.7 ± 9.5 (57)
Male sex[2]	34/57 (59.6%)
STS score	7.3 ±5.7 (55)
Logistic EuroSCORE	28.8 ±15.8 (57)
NYHA class	
I/II	16/56 (28.6%)
III/IV	40/56 (71.4%)
Coronary artery disease	20/57 (35.1%)
Previous myocardial infarction	7/57 (12.3%)
Previous intervention	
Coronary artery bypass grafting (CABG)	22/57 (38.6%)
Percutaneous coronary intervention (PCI)	7/57 (12.3%)
Balloon aortic valvuloplasty	1/57 (1.8%)
Cerebral vascular disease[2]	10/57 (17.5%)

Characteristics	Results[1] (N=57)
Peripheral vascular disease	15/57 (26.3%)
Chronic obstructive pulmonary disease (COPD)	
Pulmonary Disease COPD	5/57 (8.8%)
Pulmonary Disease Oxygen Dependent	0/57 (0.0%)
Creatinine > 2 mg/dL (177 µmol/liter)	7/57 (12.3%)
Atrial fibrillation	12/56 (21.4%)
Permanent pacemaker	10/57 (17.5%)
Pulmonary hypertension	9/57 (15.8%)
Frailty[3]	5.4 ±1.4 (44)
Extensively calcified aorta	2/57 (3.5%)
Chest-wall deformity	2/57 (3.5%)
Liver disease	2/57 (3.5%)
Echocardiographic findings	
Aortic-valve area - cm^2	0.8 ±0.3 (43)
Mean aortic-valve gradient - mmHg	39.9 ±15.8 (51)
Mean left ventricular ejection fraction (LVEF) - %	51.8 ±10.3 (55)
Moderate or severe mitral regurgitation[4]	19/57 (33.3%)

[1]Quantitative data are expressed as mean ± SD (n). Categorical data are expressed as no./total no. (%).

[2]Cerebral vascular disease is derived from CVA Stroke with Residual Deficit, CVA Stroke without Residual Sequela and CVA TIA.

[3]Frailty was determined by the surgeons according to prespecified criteria.

[4]Moderate or severe mitral regurgitation was defined as regurgitation of grade 3+ or higher.

The key safety outcomes for the SOURCE XT "TAV-in-SAV" subjects are presented in Table 12.

Table 12: CEC Adjudicated Adverse Events for SOURCE XT "TAV-in-SAV" Subjects – Attempted Implant Population

Events	Results[1]		
	30 Days (N= 57)	1-Year (N= 57)	2-Year (N= 57)
All-cause death	3 (5.3%)	10 (17.5%)	16 (28.5%)
Cardiac death	1 (1.8%)	7 (12.9%)	11 (21.0%)
Stroke			
All Stroke	1 (1.8%)	2 (3.8%)	2 (3.8%)
Major Stroke	1 (1.8%)	1 (1.8%)	1 (1.8%)
Repeat hospitalization[2]	5 (9.0%)	17 (31.9%)	24 (47.0%)

Events	Results[1]		
	30 Days (N= 57)	1-Year (N= 57)	2-Year (N= 57)
Myocardial Infarction	1 (1.8%)	1 (1.8%)	1 (1.8%)
Major Vascular Complications	2 (3.5%)	3 (5.5%)	3 (5.5%)
Acute Kidney Injury[3]	6 (10.5%)	NA	NA
Life-threatening bleeding[4]	3 (5.3%)	3 (5.3%)	3 (5.3%)
Endocarditis	0 (0.0%)	2 (4.2%)	3 (6.6%)
New Atrial Fibrillation	0 (0.0%)	2 (3.7%)	5 (10.1%)
New pacemaker	4 (7.0%)	5 (8.9%)	5 (8.9%)

[1]Results are presented as n (%) where % is the Kaplan-Meier event rate.
[2]Repeat hospitalizations were included if they were due to aortic stenosis or complications of the valve procedure (e.g., TAVR).
[3]Life-threatening bleeding: Fatal bleeding OR bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome OR bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery OR overt source of bleeding with drop in hemoglobin of =5 g/dL or whole blood of packed red blood cells (RBC) transfusion =4 units.
[4]Renal failure is defined as stage III acute kidney injury: Increase in serum creatinine to =300% (3 x increase compared with baseline) or serum creatinine of = 4 mg/d (=354 µmol/L) with an acute increase of at least 0.5 mg/dl (44 µmol/L)

Valve hemodynamics as assessed by echocardiography is summarized in Table 13.

Table 13: Valve Hemodynamics Measured by Echocardiography for SOURCE XT "TAV-in-SAV" Subjects - Valve Implant Population

	Baseline (N=57)	Discharge (N=48)	30 Days (N=46)	1 Year (N=34)	2 Year (N=21)
Doppler Velocity Index (DVI)					
All Valve Sizes	0.5 ± 0.9 (28)	0.5 ± 0.4 (18)	0.3 ± 0.1 (18)	0.4 ± 0.1 (10)	0.4 ± 0.1 (6)
23 mm	0.5 ± 1.1 (19)	0.5 ± 0.5 (14)	0.3 ± 0.1 (12)	0.4 ± 0.1 (8)	0.4 ± 0.1 (3)
26 mm	0.3 ± 0.2 (7)	0.4 ± 0.0 (4)	0.3 ± 0.2 (3)	0.3 ± 0.1 (2)	0.4 ± 0.1 (3)
29 mm	0.3 ± 0.1 (2)	N/A (0)	0.2 ± 0.2 (3)	N/A (0)	N/A (0)
Mean Gradient (mmHg)					
All Valve Sizes	39.9 ± 15.8 (51)	21.0 ± 9.6 (45)	19.2 ± 7.4 (36)	17.2 ± 6.0 (30)	17.6 ± 6.6 (18)
23 mm	41.8 ± 17.0 (36)	24.0 ± 10.0 (30)	20.0 ± 8.2 (23)	19.0 ± 6.1 (18)	16.3 ± 6.5 (11)
26 mm	37.4 ± 12.2 (10)	15.7 ± 5.4 (11)	18.9 ± 5.5 (10)	15.6 ± 4.3 (9)	21.2 ± 7.5 (5)
29 mm	31.0 ± 10.0 (5)	13.0 ± 2.6 (4)	14.3 ± 7.0 (3)	11.0 ± 6.1 (3)	16.0 ± 2.8 (2)
Total Aortic Regurgitation					
All Valve Sizes					
None	10/52 (19.2%)	28/46 (60.9%)	30/45 (66.7%)	25/34 (73.5%)	12/19 (63.2%)
Trace	11/52 (21.2%)	10/46 (21.7%)	8/45 (17.8%)	4/34 (11.8%)	4/19 (21.1%)
Mild	6/52 (11.5%)	7/46 (15.2%)	7/45 (15.6%)	5/34 (14.7%)	3/19 (15.8%)

	Baseline (N=57)	Discharge (N=48)	30 Days (N=46)	1 Year (N=34)	2 Year (N=21)
Moderate	13/52 (25.0%)	1/46 (2.2%)	0/45 (0.0%)	0/33 (0.0%)	0/17 (0.0%)
Severe	12/52 (23.1%)	0/45 (0.0%)	0/45 (0.0%)	0/33 (0.0%)	0/17 (0.0%)
23 mm					
None	9/33 (27.3%)	24/29 (82.8%)	26/31 (83.9%)	19/21 (90.5%)	9/10 (90.0%)
Trace	8/33 (24.2%)	2/29 (6.9%)	2/31 (6.5%)	0/21 (0.0%)	0/10 (0.0%)
Mild	4/33 (12.1%)	3/29 (10.3%)	3/31 (9.7%)	2/21 (9.5%)	1/10 (10.0%)
Moderate	7/33 (21.2%)	0/29 (0.0%)	0/31 (0.0%)	0/21 (0.0%)	0/10 (0.0%)
Severe	5/33 (15.2%)	0/29 (0.0%)	0/31 (0.0%)	0/21 (0.0%)	0/10 (0.0%)
26 mm					
None	3/12 (25.0%)	10/11 (90.9%)	9/9 (100.0%)	9/9 (100.0%)	7/7 (100.0%)
Trace	2/12 (16.7%)	1/11 (9.1%)	0/9 (0.0%)	0/9 (0.0%)	0/7 (0.0%)
Mild	0/12 (0.0%)	0/11 (0.0%)	0/9 (0.0%)	0/9 (0.0%)	0/7 (0.0%)
Moderate	2/12 (16.7%)	0/0 (0.0%)	0/9 (0.0%)	0/9 (0.0%)	0/7 (0.0%)
Severe	5/12 (41.7%)	0/11 (0.0%)	0/9 (0.0%)	0/9 (0.0%)	0/7 (0.0%)
29 mm					
None	1/5 (20.0%)	4/4 (100.0%)	5/5 (100.0%)	3/3 (100.0%)	1/1 (100.0%)
Trace	0/5 (0.0%)	0/4 (0.0%)	0/5 (0.0%)	0/3 (0.0%)	0/1 (0.0%)
Mild	1/5 (20.0%)	0/4 (0.0%)	0/5 (0.0%)	0/3 (0.0%)	0/1 (0.0%)
Moderate	1/5 (20.0%)	0/4 (0.0%)	0/5 (0.0%)	0/3 (0.0%)	0/1 (0.0%)
Severe	2/5 (40.0%)	0/4 (0.0%)	0/5 (0.0%)	0/3 (0.0%)	0/1 (0.0%)

Quantitative data are expressed as mean ± SD (n). Categorical data are expressed as no./total no. (%).

The changes in NYHA class are summarized in Table 14. Compared to baseline NYHA, 77.8% of patients improved, 19.4% remained in the same NHYA class and one single patient worsened at 2 years.

Table 14: NYHA Class Change for SOURCE XT "TAV-in-SAV" Subjects – Attempted Implant Population

Visit	Improved	Same	Worsened
Baseline to 30 Days	41/51 (80.4%)	9/51 (17.6%)	1/51 (2.0%)
Baseline to 1 Year	36/42 (85.7%)	6/42 (14.3%)	0/42 (0.0%)
Baseline to 2 Year	28/36 (77.8%)	7/36 (19.4%)	1/36 (2.8%)

Results are expressed as no./total no. (%).

The QoL as measured by EuroQoL (EQ-5D) is summarized in Table 15.

Table 15: ED-5Q Visual Analog Scale for SOURCE XT "TAV-in-SAV" Subjects – Attempted Implant Population

Visit	EQ- 5D Visual Analog Scale[1]
Baseline	50.5 ± 19.8 (47)
30 Days	71.5 ± 19.5 (43)
1 Year	72.6 ± 18.0 (35)
2 Year	65.3 ± 20.3 (24)

[1]Visual analog scale ranges from 0 to 100 points with 100 being "the best health you can imagine" and 0 being "the worst health you can imagine." Results are expressed as mean ± SD (n).

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(2) of the Act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory Systems Device panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Safety Conclusions

The results from the preclinical studies performed on the Edwards SAPIEN XT THV demonstrate that the device is suitable for long-term implantation in a "TAV-in-SAV" configuration.

In the pivotal clinical study, the observed rate for the composite endpoint of all-cause mortality, all stroke, moderate or severe obstruction, or moderate or severe paravalvular leak was 16.9% at 30 days and 38.0% at 1 year. The observed rate was 4.1% at 30 days and 19.8% at 1 year for all-cause mortality, 2.6% at 30 days and 3.1% at 1 year for all stroke, 7.1% at 30 days and 11.1% at 1 year for moderate or severe obstruction, and 2.5% at 30 days and 38.0% at 1 year for moderate/severe paravalvular leak. These results for all-cause mortality, all stroke, and moderate or severe paravalvular leak compared well with those of the SAPIEN XT THV implanted inside a native aortic annulus.

B. Effectiveness Conclusions

In the clinical study, the "TAV-in-SAV" subjects experienced an improvement in hemodynamics. The mean Doppler velocity index increased from 0.27 at baseline to 0.37 at 30 days and 0.39 at 1 year. The mean pressure gradient decreased from 36.1 mmHg to

17.4 mmHg at 30 days and 17.3 mmHg at 1 year. However, it is of note that the mean residual pressure gradient was higher than that observed in patients with a SAPIEN XT THV implanted inside a native aortic annulus (10.0 mmHg at 30 days and 11.4 mmHg at 1 year; see the SSED for PMA P130009). It is not clear whether this elevated pressure gradient will have any long-term impact on the patient outcome.

The improvement in hemodynamics is further demonstrated through functional classification as evaluated by NYHA classification and in cardiac symptoms as evaluated by KCCQ scores. About 89% of subjects were in NYHA I/II at 30 days and 84% at 1 year as compared to 5% at baseline. The mean KCCQ score was 68.0 at 30 days and 70.4 at 1 year, as compared to 45.5 at baseline.

C. Benefit-Risk Conclusions

The benefits of the Edwards SAPIEN XT THV for patients with a failed surgical bioprosthetic aortic valve included improved valve hemodynamic performance, improved functional status as measured by the NYHA classification, improved QoL, and reduced mortality.

The probable risks of the Edwards SAPIEN XT THV system included procedure related complications such as death, stroke, major vascular complications, bleeding, conduction disturbance, and acute kidney injury. However, most of these risks were lower in the "TAV-in-SAV" subjects as compared with those observed in subjects with a SAPIEN XT THV implanted inside a native aortic annulus.

Given the available information above, the data support that for patients with a failed (stenosed, regurgitant, or combined) surgical bioprosthetic aortic valve who are at high or greater risk for redo surgical aortic valve replacement, the probable benefits of implanting an Edwards SAPIEN XT THV outweigh the probable risks.

D. Overall Conclusions

The preclinical and clinical studies submitted in the PMA supplement provide reasonable assurance that the Edwards SAPIEN THV is safe and effective for the replacement of failed surgical bioprosthetic aortic valves in symptomatic severe aortic stenosis, aortic insufficiency, or combined patients who are deemed to be at high or greater risk for open surgical therapy (i.e., Society of Thoracic Surgeons operative risk score ≥8% or at a ≥15% risk of mortality at 30 days).

XIV. CDRH DECISION

CDRH issued an approval order on October 9, 2015. The final conditions of approval cited in the approval order are described below.

The applicant must conduct one post-approval study as well as participate in and support one surveillance study:

1. ***ODE Lead Post-Approval Study* (*Continued follow-up of the premarket cohort*)**: The study will consist of all living subjects who were enrolled under the IDE in NR3 and CANR3. The objective of this study is to characterize the cumulative clinical outcomes of all subjects at discharge or 7 days, whichever comes first, 30 days, 1 year, and annually thereafter through 5 years post procedure. The safety and effectiveness endpoints include all-cause mortality, all stroke, moderate or severe obstruction (defined as DVI < 0.25), or moderate or severe paravalvular leak (through 1 year only); all-cause mortality; all stroke or transient ischemic attack (TIA); all-cause mortality or major stroke; all stroke, major vascular complication, or aortic valve reintervention; NYHA classification (additional data point at 6 months); change in 6MWD from baseline (through 1 year only); echocardiographic assessment of valve performance; clinical improvement per QoL instrument KCCQ; and index hospitalization length of stay.

2. ***OSB Lead Surveillance* (*Comprehensive Linked Registry-Based Surveillance*)**: The applicant is required to support and actively participate as a stakeholder in the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry (TVTR) to ensure that surveillance occurs for the Edwards SAPIEN XT device over the next 5 years. This surveillance will monitor the following: (1) device success (intra-procedure); (2) all-cause mortality, all stroke, life-threatening (or disabling) bleeding, acute kidney injury-stage 3 (including renal replacement therapy, acute events associated with index TAVR procedure), peri-procedural myocardial infarction, and repeat procedure for valve-related dysfunction (surgical or interventional therapy) at 30 days and 12 months; (3) neurological (non-stroke), vascular complications, and QoL (KCCQ) outcomes at 30 days and 12 months; and (4) all-cause mortality, all stroke, and repeat procedure for valve-related dysfunction (surgical or interventional therapy) annually through 5 year post implantation.

FDA issued a Warning Letter to Edwards on May 24, 2013 that listed violations observed during an inspection of the firm's manufacturing facility in Draper, UT on January 22 through February 22, 2013. FDA conducted an additional inspection of the same facility on March 3 through April 11, 2014. At the conclusion of that inspection on April 15, 2014, an FDA 483 form was issued, followed by an "Official Action Indicated" (OAI) letter on May 1, 2014. FDA subsequently approved a variance plan on June 10, 2014 that met the requirements set forth in Section 520(f)(2)(A) of the Federal Food, Drug, and Cosmetic Act and 21 C.F.R. 820(e)(2). The variance plan provided controls for the manufacture, packing, and storage of the SAPIEN XT THV, delivery systems and accessories in lieu of the FDA's prescribed methods, facilities, and controls.

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.