SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Replacement Heart Valve

Device Trade Name: EDWARDS INTUITY Elite Valve System:
Aortic Valve, Model 8300AB
Delivery System, Model 8300DB
(Aortic sizes 19, 21, 23, 25, and 27 mm)

Device Procode: LWR

Applicant's Name and Address: Edwards Lifesciences, LLC
One Edwards Way
Irvine, CA 92614

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P150036

Date of FDA Notice of Approval: August 12, 2016

II. INDICATIONS FOR USE

The EDWARDS INTUITY Elite valve is indicated for the replacement of diseased, damaged, or malfunctioning native or prosthetic aortic valves.

III. CONTRAINDICATIONS

The EDWARDS INTUITY Elite Valve System is contraindicated for patients with the following conditions:

- pure aortic insufficiency
- aneurysms of the aortic root or ascending aorta

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Edwards INTUITY Elite Valve System labeling.

V. DEVICE DESCRIPTION

The EDWARDS INTUITY Elite Valve System consists of the aortic valve, model 8300AB, and the delivery system, model 8300DB.

The EDWARDS INTUITY Elite Aortic Valve (**Figure 1**) is a stented trileaflet valve comprised of bovine pericardium treated with the Carpentier-Edwards ThermaFix process. The leaflets are mounted on a flexible cobalt-chromium alloy wireform. A balloon expandable stainless steel cloth-covered frame is incorporated into the inflow aspect of the valve. The system reduces the number of sutures required to secure the valve, while establishing the seal between the aortic annulus and the frame. A holder is attached to the valve by means of sutures to facilitate handling, deployment, and suturing the valve during the implant procedure.

Figure 1: EDWARDS INTUITY Elite Aortic Valve

The EDWARDS INTUITY Elite Delivery System (**Figure 2**) is designed to introduce the EDWARDS INTUITY Elite Valve to the surgical site after removal of the diseased native leaflets. The delivery system includes an integrated balloon catheter and malleable tubular handle shaft through which the catheter extends. The distal end of the handle shaft includes an adapter, which mates with the holder of the valve, and a locking sleeve for rapidly connecting the delivery system to the valve holder. The balloon portion of the delivery system resides within the adapter, and advances distally into position for expanding the frame. A tubular balloon introducer is attached, when removing the valve from a storage jar and facilitates passage of the balloon through the valve.

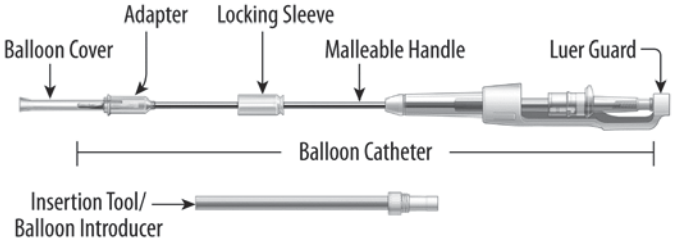

Figure 2: EDWARDS INTUITY Elite Delivery System

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the correction of diseased and malfunctioning heart valves. Alternative treatments include palliative medical therapy, aortic balloon valvuloplasty (opening the narrowed aortic valve with a balloon catheter), transcatheter valve replacement and surgical replacement of the aortic valve with another commercially available mechanical or bioprosthetic valve. The choice of replacement depends on an assessment of patient factors which include age, preoperative condition, anatomy and the patient's ability to tolerate long-term anticoagulant therapy. Each

alternative has its own advantages and disadvantages. Patients should fully discuss these alternatives with his or her physician to select the method that best meets expectations and lifestyles.

VII. MARKETING HISTORY

Commercial distribution of the EDWARDS INTUITY Elite Valve System outside the U.S. began in April 2014. Currently, the device is approved 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, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, United Kingdom) and other countries, including Australia, Brazil, Colombia, Norway, Saudi Arabia, South Korea, Switzerland and Turkey. The device has not been withdrawn from marketing for any reason related to its safety and effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device.

- Allergic reaction to valve materials
- Annulus (damage, dissection, tear)
- Aorta (damage, dissection, tear)
- Blood - Coagulopathy
- Blood - Hemolysis
- Blood - Hemorrhage/anemia
- Blood pressure alteration (hypotension, hypertension)
- Cardiac arrest/Asystole
- Cardiac arrhythmias/conduction disturbances
- Cardiac failure (heart failure)
- Chordae tendineae damage (mitral valve)
- Coronary artery ostia blockage
- Death
- Endocarditis
- Explant/Reoperation
- Infection - Local and/or Systemic
- Leaflet impingement (aortic or mitral valve)
- Left Ventricular outflow tract damage
- Myocardial Infarction (MI)
- Neurologic Events
- Stroke
- Transient ischemic attack (TIA)
- Patient prosthesis mismatch (PPM) (due to inappropriate sizing)
- Pericardial Tamponade

- Reduced exercise tolerance/shortness of breath
- Tissue Leaflet damage (from instruments or sutures)
- Thromboembolism
- Valve instability/migration/embolization
- Valvular leaking
- Aortic insufficiency - regurgitation
- Paravalvular leak
- Transvalvular leak
- Valve - Nonstructural dysfunction
- Valve - Structural dysfunction/deterioration
- Valve stent fracture
- Valve stent separation
- Annulus frame fracture
- Annulus frame separation
- Valve - Thrombosis
- Valve frame distortion (from chest compression or trauma)

For the specific adverse events that occurred in the clinical study, please see Section X below.

IX. SUMMARY OF PRECLINICAL STUDIES

A. Laboratory Studies

1. Biocompatibility

Biocompatibility evaluations were completed on the EDWARDS INTUITY valve and delivery system in accordance with EN ISO 10993-1:2009/Cor:1-2010 Biological Evaluation of Medical Devices Part 1: Evaluation and Testing, American Society for Test Reports and Materials (ASTM), and U.S. FDA Blue Book Memorandum No. G95-1 (1995) guidelines.

Summaries of the biocompatibility test results for Edwards INTUITY Elite Valve and Delivery System are provided in **Table 1** and **Table 2.** Test samples for the studies consisted of all patient-contacting portions of the devices (direct and indirect) after all manufacturing processes, including sterilant exposure.

Table 1: Summary of Biocompatibility Testing - EDWARDS INTUITY Elite Aortic Valve Model 8300AB

Biological Effect per ISO 10993-1	Test Method	Results
Cytotoxicity	Percent Inhibition of Cell Growth (%ICG)	Pass
Cytotoxicity	Medium Eluate Method (MEM)	Pass
Cytotoxicity	Agar Overlay Test	Pass
Sensitization	Guinea Pig Maximization Test	Pass
Irritation / Intracutaneous toxicity	Rabbit Intracutaneous Reactivity Test	Pass
Systemic Toxicity	Mouse Systemic Injection	Pass
Systemic Toxicity	Rabbit Pyrogen (Material-Mediated) Test	Pass
Genotoxicity	In-Vitro Ames Plate Incorporation Test and Spot Test	Pass
Genotoxicity	In-Vitro Chromosomal Aberration in Chinese Hamster Ovary (CHO) Cells Test	Pass
Genotoxicity	In-Vivo Mouse Micronucleus Test (MMT)	Pass
Implantation / Subchronic Toxicity / Chronic Toxicity	Rabbit Implantation Test with Histological Evaluation – 7, 30, and 90 day implant durations	Pass
Hemocompatibility	ASTM Blood Compatibility Test (Hemolysis and Clotting Time Coagulation Assessment) – New Zealand White rabbits	Pass
Hemocompatibility	Complement Activation Test	Pass

Table 2: Summary Biocompatibility Testing – EDWARDS INTUITY Elite Delivery System Model 8300DB

Biological Effect per ISO 10993-1	Test Method	Results
Cytotoxicity	Medium Eluate Method (MEM)	Pass
Cytotoxicity	Agar Overlay-Solid Sample	Pass
Sensitization	Guinea Pig Maximization Test	Pass

Biological Effect per ISO 10993-1	Test Method	Results
Irritation / Intracutaneous Toxicity	Rabbit Intracutaneous Reactivity Test	Pass
Systemic toxicity	Mouse Systemic Injection Test	Pass
Systemic Toxicity	Rabbit Pyrogen (Material-Mediated) Test	Pass
Hemocompatibility	ASTM Blood Compatibility Test (Hemolysis and Clotting Time Coagulation Assessment) New Zealand White rabbits	Pass
Hemocompatibility	Complement Activation Test	Pass

2. Hydrodynamic Performance

In vitro hydrodynamic testing was conducted on the Edwards INTUITY Elite Valve System. Studies were conducted in accordance with ISO 5840: Cardiovascular Implants-Cardiac Valve Prostheses (2005). Tests are summarized in **Table 3** below.

Table 3: Hydrodynamic Testing and Results

Test	Purpose/ Objective	Test and reference articles	Results
Flow Visualization	Qualitatively investigate flow characteristics in the vicinity of the valve.	Test: INTUITY size 19 mm Reference: Carpentier Edwards PERIMOUNT Magna Ease size 19 mm.	The EDWARDS INTUITY valve offers acceptable aortic flow patterns throughout the entire cardiac cycle. Broad central jet-like flows during opening were observed. No retrograde jets or valvular incompetence was observed during valve closure. Throughout the complete cardiac cycle no regions of stasis or continuous recirculation were observed.
Steady Forward Flow Test	To determine pressure drop at various steady forward flow	Test: INTUITY sizes 19, 21, 23, 25 and 27 mm. Reference: PERIMOUNT Magna	The INTUITY valve offers acceptable hydrodynamics with pressure gradients and

Test	Purpose/ Objective	Test and reference articles	Results
	rates.	Ease sizes 19, 21, 23, 25 and 27 mm.	effective orifice areas (EOA) that are comparable to the reference valves.
Steady Back Flow Test	To determine the leakage rate at various steady back flow pressures.	Test: INTUITY sizes 19, 21, 23, 25 and 27 mm. Reference: PERIMOUNT Magna Ease sizes 19, 21, 23, 25 and 27 mm.	The INTUITY valve offers acceptable performance in terms of its competency to prevent significant transvalvular aortic backflow during the diastolic phase, with results that are comparable to the reference valves.
Pulsatile Flow Pressure Drop	To determine pressure drop and effective orifice area performance under pulsatile flow conditions.	Test: INTUITY sizes 19, 21, 23, 25 and 27 mm. Reference: PERIMOUNT Magna Ease sizes 19, 21, 23, 25 and 27 mm.	The INTUITY valve offers acceptable hydrodynamics with a larger effective orifice area than required by ISO 5840:2005, with results that are comparable to the reference valves.
Pulsatile Flow Regurgitation	To determine regurgitation performance under pulsatile flow conditions.	Test: INTUITY sizes 19, 21, 23, 25 and 27 mm. Reference: PERIMOUNT Magna Ease sizes 19, 21, 23, 25 and 27 mm.	The INTUITY valve offers acceptable hydrodynamics with regurgitant fractions lower than required by ISO 5840:2005, with results that are comparable to the reference valves.
Bernoulli Coefficient	Use pressure drop testing to demonstrate that the EDWARDS INTUITY valve and the PERIMOUNT Magna Ease valve 3300TFX are both correlated with the	Test: INTUITY sizes 19, 21, 23, 25, 27 and 29 mm.* Reference: Edwards PERIMOUNT Magna Ease valve sizes 19mm, 25 mm and 29 mm.	Pressure drop testing for the EDWARDS INTUITY test valves show no statistically significant differences from the Carpentier Edwards PERIMOUNT Magna Ease reference valves that previously

Test	Purpose/ Objective	Test and reference articles	Results
	Bernoulli relationship.		demonstrated correlation with the Bernoulli relationship. These data justify using a Bernoulli coefficient of four with the INTUITY valve.

*A 29 mm valve test article was used for several tests but was not pursued as a commercial device.

3. Structural Performance

The structural performance of the Edwards INTUITY Elite Valve was evaluated per the testing listed in **Table 4**. Studies were conducted in accordance with ISO 5840: Cardiovascular Implants-Cardiac Valve Prostheses (2005).

Table 4. Structural Performance Evaluation

Test	Purpose/ Objective	Test and reference articles	Results
Accelerated Wear Testing	To assess long-term performance of the valve through accelerated wear.	Test: INTUITY sizes 19, 25 and 29 mm.* Reference: PERIMOUNT Magna Ease sizes 19, 25 and 29 mm.	All valves survived durability testing to 200 million cycles in accelerated wear testers without functional impairment. After 200 million cycles all valves met the EOA and regurgitation fraction requirements of ISO 5840:2005.
Dynamic Failure Mode	To obtain information about the failure modes affecting the durability of the valve.	Test: INTUITY sizes 19, 25 and 29 mm.* Reference: PERIMOUNT Magna Ease sizes 19, 25 and 29 mm.	All of the failures of the test valves occurred at pressures well beyond what would be expected *in vivo.*
Stent Fatigue Testing	Assess long-term performance of the INTUITY frame.	Test: Worst-case INTUITY size 25 mm stainless steel frame.	Testing demonstrates greater than 600 million cycle life under worst-case conditions
Frame Stress Analysis	To characterize the mechanical	FEA and life analysis for all sizes using worst-case in vitro	Results indicate that all sizes of the INTUITY

Test	Purpose/ Objective	Test and reference articles	Results
(FEA) and Fatigue Life Analysis	behavior of the INTUITY frame during collapsing, deployment and operation.	and clinical data from size 19, 21, 23, 25 and 27 mm frames, compared to stainless steel fatigue test data.	frames should not fracture for 600 million cycles, even under the unlikely simultaneous combination of all the worst-case conditions.
Valve Stent Deflection	To determine the relationship between peak pressure difference and valve stent post deflection.	Test: INTUITY valve sizes 19, 21, 23, 25, 27 and 29 mm*. Reference: PERIMOUNT Magna Ease sizes 19, 21, 23, 25 and 27, and 29 mm mm.	Stent post deflections of the INTUITY valve were lower than or equivalent to those of the reference valve.
Corrosion Resistance	To characterize the corrosion resistance of metallic components in accordance with ASTM F2129 and ASTM G71.	Test: INTUITY valve size 19 mm and 29 mm* stainless steel frames, cobalt-chromium stiffener bands and cobalt-chromium wireforms..	Test results show high corrosion resistance of the stainless steel frame. The coupled galvanic tests showed that there is not accelerated corrosion due to the coupling of the stainless steel frame and the cobalt chromium stiffener band/wireform in the INTUITY valve
Frame Radial Stiffness	To determine radial stiffness and radial strength of the stainless steel frame.	Test: INTUITY size 19, 21, 23, 25, 27 and 29 mm* stainless steel frames Reference: SAPIEN THV size 23 and 26 stainless steel frames.	Radial stiffness for all sizes of the INTUITY frames exceeds the mean radial stiffness of the reference frames.
Suture Retention	To determine the sewing ring suture retention strength.	Test: INTUITY sizes 19, 21, 23, 25, 27 and 29 mm.*	Test results for all sizes of the INTUITY valve showed that the sewing ring suture retention strength is acceptable
Frame Separation	To evaluate the integrity of the cloth covered INTUITY frame attachment to the sewing ring.	Test: INTUITY sizes 19, 21, 23, 25 27 and 29 mm.*	Test results for all sizes of INTUITY showed that the cloth covered frame to sewing ring separation force is acceptable

Test	Purpose/ Objective	Test and reference articles	Results
Sewing Ring Integrity.	To determine the force required to separate the sewing ring from the stent subassembly of the INTUITY valve.	Test: INTUITY sizes 19, 21, 23, 25 27 and 29 mm.*	Test results for all sizes of the INTUITY valve show that the sewing ring integrity is acceptable

*A 29 mm valve test article was used for several tests but was not pursued as a commercial device.

4. Accessory Performance Testing

The Edwards INTUITY Elite delivery system was evaluated through several pre-clinical tests as outlined in **Table 5**.

Table 5. Accessory Performance Testing

Test	Purpose/ Objective	Test and reference articles	Results
Bond Strength and Snap Fit tensile strength	To evaluate all bonds and snap-fit mechanisms of the delivery system against their design requirements.	Test: INTUITY sizes 19, 21, 23, 25, and 27 mm	Delivery systems met all design requirements and acceptance criteria for bond strength and snap fit.
Compatibility with Inflation Device	To evaluate the compatibility of the inflation device with the INTUITY valve system.	Test: custom inflation syringes	Test articles met all design requirements and acceptance criteria
Dimensional and Assembly Verification	To verify all component dimensional and functional fit requirements.	Test: INTUITY sizes 19, 21, 23, 25, and 27 mm	Delivery system components met design requirements and acceptance criteria for dimensional and functional fit.
Frame Expansion at Nominal Pressure	To verify that the INTUITY delivery system expands the INTUITY frame within required limits.	Test: INTUITY size 19, 21, 23, 25, and 27 mm frames and delivery systems	Test results show that the INTUITY delivery system expands the frame within the required limits.
ISO 594	To evaluate the	Test: INTUITY delivery	Test results show the

Test	Purpose/ Objective	Test and reference articles	Results
Female Luer Testing	female Luer fitting used in the INTUITY delivery system in accordance with ISO 594-1 and ISO 594-2.	system female Luer fitting	INTUITY female Luer fitting meets the requirements of ISO 594-1 and ISO 594-2

B. Animal Studies

The performance of the EDWARDS INTUITY Valve System was evaluated in the aortic position in the young adult ovine model. A total of 10 test articles (8300AB) and three (3) control articles (3300TFX) were implanted in the aortic position for 20 weeks.

The performance of the test and control valves was assessed by evaluating the general health of each animal, *in vivo* hemodynamics, and an examination of both the animal and valve at explant.

Study results demonstrated that the Model 8300AB and 3300TFX had similar healing response (including normal inflammation), tissue overgrowth, no material wear, good suture integrity, no sewing ring dehiscence, no structural valve deterioration on all the valves and no mineralization, thrombus, significant vegetative growths or significant leaflet damage when implanted at 20 weeks in adult sheep. The EDWARDS INTUITY 8300AB valve performance results were comparable to the Model 3300TFX control valve.

C. Additional Studies

1. Sterilization

   The EDWARDS INTUITY Elite Aortic Valve model 8300AB is sterilized by terminal liquid sterilization (TLS) in buffered glutaraldehyde solution. The EDWARDS INTUITY Elite delivery system, model 8300DB is sterilized by electron beam (E-beam). After sterilization, the devices are held in quarantine until sterility is verified per process specifications. TLS and E-beam processes have demonstrated Sterility Assurance Levels (SAL) of 10^{-6} in validation studies.

2. Shelf life and Package Integrity

   The packaging for the EDWARDS INTUITY Elite Valve consists of a 3.8 oz jar, a lid and gasket closure system and shelf and shipping containers.

The EDWARDS INTUITY Elite Delivery System is secured in a double sterile barrier tray sealed with a Tyvek® lid (inner and outer) and placed inside a shelf carton and shipping carton.

The shelf life for the EDWARDS INTUITY Elite Valve model 8300AB and delivery system model 8300DB is two (2) years as demonstrated by package and functional product integrity testing on aged samples.

3. MRI Compatibility

Testing of this device in magnetic fields of 1.5 and 3.0 Tesla showed that the device is MR Conditional. The INTUITY Elite Valve can be scanned safely under the following conditions:

- Static magnetic field of 1.5 T or 3 T
- Maximum spatial field gradient of 2670 Gauss/cm; and
- Maximum Whole-Body averaged Specific Absorption Rate (SAR) of 2.0 W/kg (Normal Operating mode) for 15 minutes of continuous scanning.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of heart valve replacement with the INTUITY Elite Valve System in the US under IDE # G110189. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

Patients were treated between September 26, 2012 and December 2, 2015. The database for this PMA reflected data collected through December 3, 2015 and included 889 patients. There were 29 investigational sites.

The study was a prospective, non-randomized, multi-center trial for the Edwards Intuity Elite Valve System implanted in patients requiring native or prosthetic aortic valve replacement. Adverse Event (AE) rates as compared to a set of Objective Performance Criteria (OPC) and to literature-based control data were used for the design and analysis of this study. New York Heart association (NYHA) functional classification status and hemodynamic performance of the valve by echocardiography were evaluated using a comparison to literature-based control data.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the TRANSFORM study was limited to patients who met the following inclusion criteria:

1. Subject is male or female, age 18 years or older
2. Subject has aortic stenosis or stenosis-insufficiency of an aortic valve requiring a planned replacement as indicated in the preoperative evaluation
3. Subject is scheduled to undergo planned aortic valve replacement with or without concomitant coronary bypass surgery
4. Subject has provided written informed consent
5. Subject is geographically stable and agrees to attend follow-up assessments until all subjects have completed 5 years of follow up

Patients were not permitted to enroll in the TRANSFORM study if they met any of the following exclusion criteria:

1. Subject has pure aortic insufficiency
2. Subject requires emergency surgery
3. Subject has had previous aortic valve replacement
4. Subject has had prior mitral, tricuspid or pulmonic valve surgery, which included implant of a bioprosthetic valve, mechanical valve, or annuloplasty ring that will remain in situ
5. Subject requires multiple valve replacement/repair
6. Subject requires a surgical procedure outside of the cardiac area (e.g., vascular endarterectomy, vascular bypass, tumor removal)
7. Subject has an aneurysm of the aortic root and/or ascending aorta requiring surgical intervention
8. Subject has active endocarditis/myocarditis or endocarditis/myocarditis within 3 months prior to the scheduled AVR surgery
9. Subject has had a myocardial infarction (MI) within thirty (30) days prior to valve replacement surgery
10. Subject has renal insufficiency as determined by creatinine ≥ mg/dL at screening or end-stage renal disease requiring chronic dialysis
11. Subject has hyperparathyroidism
12. Subject has had a MRI or CT-scan confirmed cerebrovascular accident(CVA), or transient ischemic attack (TIA) within 6 months (180 days) of the procedure
13. Subject has a non-cardiac disease limiting life expectancy to less than 12 months
14. Subject has hypertrophic obstructive cardiomyopathy (HOCM)
15. Subject has a left ventricular ejection fraction of ≤25%
16. Subject has a documented history of substance (drug or alcohol) abuse within the last 5 years
17. Subject has echocardiographic evidence of an intra-cardiac mass, thrombus, or vegetation

18. Subject has hemodynamic or respiratory instability requiring inotropic support, mechanical circulatory support, or mechanical ventilation within 30 days prior to the procedure
19. Subject is pregnant, lactating, or planning to become pregnant;
20. Subject is currently incarcerated or unable to give voluntary informed consent
21. Subject has leucopenia (WBC < 3.5x 103/μL), or acute anemia (Hgb < 10.0 gm/dL or 6 mmol/L), or thrombocytopenia (platelet count < 50x 10^3 or history of bleeding diathesis or coagulopathy
22. Subject has a history of myxomatous disease/connective tissue disorders (e.g., Marfan's Syndrome)
23. Subject is a current or recent participant (within 6 weeks prior to surgery) in an investigational drug or device trial

Otherwise qualified candidates may also have been excluded from participation in the trial during the surgical procedure. Specifically, anatomic variances may have contraindicated implant of the trial valve, such as:

- anomalous coronary arteries
- annular deformation or extensive calcification of the annulus or aortic root which cannot be removed
- significant calcium on the anterior mitral leaflet
- pronounced septal calcification
- position of coronary ostia relative to EDWARDS INTUITY Elite Valve that would result in obstruction of blood flow

Finally, in the event that the INTUITY Elite valve sizes were unsuitable for a particular subject's annulus, the candidate was excluded from participation in the trial.

2. Follow-up Schedule

All patients were scheduled to return for follow-up examinations at discharge, 3 months, 1 year, and annually thereafter for a minimum of 5 years postoperatively.

Preoperatively, demographic and baseline data were collected. Postoperatively, the objective parameters measured during the study included echocardiographic data and NYHA functional classification. Adverse events and complications were recorded at all visits.

3. Clinical Endpoints

With regards to safety, the following criteria were evaluated:

1) complication and survival rates for the INTUITY Elite Valve System compared to the OPCs defined in ISO 5840:2009 and compared to values reported in the literature for other bioprosthetic valves.

With regards to effectiveness, the following criteria were evaluated:

1) hemodynamic performance evaluated by echocardiography;
2) New York Heart Association (NYHA) functional classification status; and
3) average cardiopulmonary bypass time (CPBT) and aortic cross clamp time (XCT).

Success was defined by comparing OPC category event rates with 2x the OPC values listed in ISO 5840:2009 as well as a comparison of literature controls from commercially available devices.

B. Accountability of PMA Cohort

At the time of database lock, of 889 patients enrolled in the PMA study, 839 patients received the INTUITY Elite Valve and were available for analysis. Forty-nine (49) subjects were classified as implant failures, received a non-study valve, and were not included in the main analysis. Subject compliance is detailed in **Table 6.**

Table 6: Subject Compliance

Visit Interval	Eligible Subjects (N_1)	Follow-up Compliance %[1] (n)	Censored[2] (N_2)
Preoperative	839	100.0% (839)	0
Discharge	831	99.9% (830)	8
3 Month	778	97.0% (755)	61
1 Year	573	96.3% (552)	266
2 Year	215	94.4% (203)	624

[1]% compliance = $100*n/N_1$

[2]Censoring due to pending visit, explant, study exit, death or lost to follow-up.

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for an aortic heart valve study performed in the US. Baseline demographics are shown in **Table 7**.

Table 7: Preoperative Subject Demographics

Age at Implant	**N: Mean ± SD (Min - Max)**
Age (years)	839: 73.5 ± 8.3 (34 – 95)
Sex	**% (n / N)**
Female	35.5% (298 / 839)
Male	64.5% (541 / 839)
NYHA Classification[1]	**% (n/N)**
Class I	15.6% (130 / 836)
Class II	52.2% (436 / 836)
Class III	30.5% (255 / 836)
Class IV	1.8% (15 / 836)
Risk Scores	**N: Mean ± SD (Min - Max)**
STS risk of mortality (%)[2]	733: 2.5 ± 1.8 (0.4 – 14.6)
EuroSCORE II (%)	839: 3.3 ± 3.4 (0.5 – 31.6)

[1]Preoperative NYHA class unavailable for 3 subjects.

[2]STS scores only calculated for subjects undergoing isolated AVR or AVR+CABG.

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the 839 patients that received the INTUITY Elite Valve System over the course of 912 total patient-years. The key safety outcomes for this study are presented below in **Table 8**. Simple proportions are presented to describe early event rates, linearized rates (%/patient-year) are presented for late events, and "freedom from event" at 1-year based on Kaplan-Meier analysis are provided based on all reported events both "early" and "late".

Table 8: Observed Adverse Event Rates

Adverse Event or Outcome	**Early[1] (N=839) n, m (%)**	**Late[2] (LPY[3] = 844.5) n, m, (%/pt-yr)**	**Freedom-from Event at 1 Year (SE)[4]**
All mortality	7, 7 (0.8)	25, 25 (3.0)	0.964 (0.007)
Valve-related mortality	4, 4 (0.5)	9, 9 (1.1)	0.985 (0.005)
Reoperation	2, 2 (0.2)	7, 8 (0.9)	0.993 (0.003)
Explant	1, 1 (0.1)	4, 4 (0.5)	0.996 (0.002)
Thromboembolism	29, 29 (3.5)	22, 22 (2.6)	0.939 (0.009)
Stroke	22, 22 (2.6)	11, 11 (1.3)	0.961 (0.007)

Adverse Event or Outcome	Early[1] (N=839) n, m (%)	Late[2] (LPY[3] = 844.5) n, m, (%/pt-yr)	Freedom-from Event at 1 Year (SE)[4]
Valve thrombosis	0, 0 (0.0)	0, 0 (0.0)	1.000 (0.000)
Endocarditis	0, 0 (0.0)	0, 0 (0.0)	1.000 (0.000)
All bleeding	13, 13 (1.5)	37, 43 (5.1)	0.941 (0.009)
Major bleeding	11, 11 (1.3)	19, 21 (2.5)	0.962 (0.007)
All Paravalvular Leak	9, 9 (1.1)	15, 15 (1.8)	0.977 (0.005)
Major PVL	2, 2 (0.2)	7, 7 (0.8)	0.993 (0.003)
Hemolysis	0, 0 (0.0)	3, 3 (0.4)	0.997 (0.0024)
Non-Structural Valve Dysfunction (non-PVL)	6, 6 (0.7)	3, 3 (0.4)	0.989 (0.004)
Valve migration	0, 0 (0.0)	0, 0 (0.0)	1.000 (0.000)
Valve malposition[5]	2, 2 (0.2)	1, 1 (0.1)	0.996 (0.002)
Valve instability[5]	2, 2 (0.2)	1, 1 (0.1)	0.996 (0.002)
Valve dislodgement	0, 0 (0.0)	0, 0 (0.0)	1.000 (0.000)
Valve Stenosis[6]	4, 4 (0.5)	2, 2 (0.2)	0.992 (0.003)
Structural Valve Deterioration	0, 0 (0.0)	0, 0 (0.0)	1.000 (0.000)
Site-reported permanent pacemaker implant[7] (n=785, LPY =786.7)	111, 111 (14.1)	15, 15 (1.9)	0.845 (0.013)

[1]For 'Early Events' (events occurring thru post-implant day 30): For 'Early' m is the number of events; n is the number of subjects experiencing an event; % = n/N.

[2]For 'Late Events' (events occurring after post-implant day 30): m is the number of events; n is the number of subjects experiencing an event; and % = m/LPY.

[3]LPY: Late patient-years; LPY are calculated from post-implant day 31 until the last patient contact

[4]Based on Kaplan-Meier analysis of time to first occurrence (early or late). Standard Error (SE) based on Greenwood's formula.

[5]Echo Core Lab findings of mild rocking or dehiscence count as both valve malposition and valve instability, but only count once in the overall counts of NSVD (non-PVL).

[6]Valve stenosis includes all site-reported events independent of clinical sequelae and without evidence of calcification. For the 6 cases noted, all patients were asymptomatic at the time of the data lock.

[7]Includes permanent pacemaker implant required for treatment of cardiac arrhythmia(s) or conduction disturbance(s) as reported by the investigational site. If multiple PPI for the same subject were reported, the event with the earliest onset date is summarized. Excludes patients with pre-existing PPIs.

The results of the TRANSFORM study were compared to the OPC per ISO 5840 requirements and detailed in **Table 9**. The study valve successfully met the OPC requirements with the exception of all and major paravalvular leak and all and major bleeding where values for the 95% confidence limits exceeded two (2) times the OPC. However, linearized rates for the study valve were within 2 times the OPC for all performance criteria.

Table 9. Linearized Late Rates Compared to the OPC

Adverse Event	Late[1] (LPY[2] = 844.5) N, m, (%/pt-yr)	95% UCL[3]	2X OPC[4]
Thromboembolism	22, 22 (2.6)	3.7	5.0
Valve thrombosis	0, 0 (0.0)	0.2	0.4
All bleeding	37, 43 (5.1)	6.5	2.8
Major bleeding	19, 21 (2.5)	3.5	1.8
All paravalvular leak	15, 15 (1.8)	2.7	2.4
Major PVL	7, 7 (0.8)	1.5	1.2
Endocarditis	0, 0 (0.0)	0.2	2.4

[1]For 'Late Events' (events occurring after post-implant day 30): m is the number of events; n is the number of subjects experiencing an event; and % = m/LPY.
[2]LPY: Late patient-years; LPY are calculated from post-implant day 31 until the last patient contact.
[3]UCL is the one-sided 95% Upper Confidence Limit for the linearized rate.
[4]FDA Objective Performance Criteria for tissue valves as described in Table R.1 of EN ISO 5840:2009, Annex R.1.

Table 10 and **Table 11**present the number of new or worsened cardiac conduction disturbances as reported by the investigational site, for device-related and procedure related events, respectively.

Table 10. Site-Reported Device-Related New or Worsened Cardiac Conduction Disturbances in AVR Patients in INTUITY Valve TRANSFORM Clinical Study [1, 2]

Device-Related[1] Adverse Event	Postoperative Onset Day			
	Early (Day 0) n[2]	Early (1-30 Days) n[2]	Late (>30 Days) n[2]	All Events n[2]
Requiring Permanent Pacemaker Implant (PPI)				
AV block I	0	1	0	**1**
AV block III	0	6	1	**7**

Device-Related[1] Adverse Event	Postoperative Onset Day			
	Early (Day 0) n[2]	Early (1-30 Days) n[2]	Late (>30 Days) n[2]	All Events n[2]
Tachy-bradycardia	0	1	0	**1**
Total requiring PPI[3]	**0**	**8**	**1**	**9**
Not requiring Permanent Pacemaker Implant (PPI)				
AV block I	1	5	3	**9**
AV block III	1	0	0	**1**
Atrial flutter	0	1	0	**1**
LBBB	11	9	1	**21**
RBBB	0	1	1	**2**
Other arrhythmia	2	4	2	**8**
Paroxysmal atrial fibrillation	0	2	0	**2**
Total not requiring PPI	**14**	**20**	**7**	**40**
Total	**14**	**27**	**8**	**47**

[1]Device-related includes those events considered related to the trial valve or trial delivery system. Eight (8) events were reported as both device- and procedure-related.
[2]n is the number of subjects experiencing an event; if multiple PPI for the same subject were reported, the event with the earliest onset date is summarized.
[3]Total does not include 38 PPI considered unrelated to the device or procedure and two (2) events where the relationship to the device or procedure could not be determined.

Table 11. Site-Reported Procedure-Related New or Worsened Cardiac Conduction Disturbances in AVR Patients in INTUITY Valve TRANSFORM Clinical Study [1, 2]

Procedure-Related[1] Adverse Event	Postoperative Onset Day			
	Early (Day 0) n[2]	Early (1-30 Days) n[2]	Late (>30 Days) n[2]	All Events n[2]
AV block I	0	4	0	**4**
AV block II[3]	0	4	2	**6**
AV block III	0	54	1	**55**
Bradycardia	0	2	1	**3**
LBBB	0	4	1	**5**

Procedure-Related[1] Adverse Event	Postoperative Onset Day			
	Early (Day 0) n[2]	Early (1-30 Days) n[2]	Late (>30 Days) n[2]	All Events n[2]
Other arrhythmia	0	6	1	**7**
Paroxysmal atrial fibrillation	0	2	0	**2**
Tachy-bradycardia	0	3	0	**3**
Total requiring PPI[3,4]	**0**	**79**	**6**	**85**

[1]Procedure-related includes those events considered related to the cardiac surgery or the trial procedure. Eight (8) events were reported as both device- and procedure-related.
[2]n is the number of subjects experiencing an event; if multiple PPI for the same subject were reported, the event with the earliest onset date is summarized.
[3]The date of onset for one AV block II event was unknown; this event is included in the 'All events' column.
[4]Total does not include 38 PPI considered unrelated to the device or procedure and two (2) events where the relationship to the device or procedure could not be determined.

2. Effectiveness Results

The analysis of effectiveness was based on the 839 evaluable patients that received the INTUITY Elite Valve System over the course of 912 total patient-years. Effectiveness of the INTUITY Elite Valve System was evaluated by NYHA functional class and echocardiographic assessment of the hemodynamic performance of the valve.

NYHA functional classification at baseline and at 1 year is shown in **Table 12**.

Table 12: NYHA Functional Classification

NYHA Class	Baseline NYHA% (n / N[1])	1-Year NYHA % (n / N[1])
Class I	14.5% (79 / 546)	77.1% (421 / 546)
Class II	51.1% (279 / 546)	19.6% (107 / 546)
Class III	32.6% (178 / 546)	2.7% (15 / 546)
Class IV	1.8% (10 / 546)	0.5% (3 / 546)

[1]N is the number of subjects who have both preoperative and 1 year NYHA data

Effective orifice area (EOA) and mean gradient at 1-year follow-up are presented in **Table 13**.

Table 13: Hemodynamic Results at 1-Year

Parameter	19 mm Mean±SD (n[1])	21 mm Mean±SD (n[1])	23 mm Mean±SD (n[1])	25 mm Mean±SD (n[1])	27 mm Mean±SD (n[1])
EOA (cm^2)	1.1 ± 0.1 (36)	1.3 ± 0.1 (113)	1.7 ± 0.2 (157)	1.9 ± 0.2 (127)	2.2 ± 0.2 (58)
Mean Gradient (mmHg)	13.9 ± 3.9 (36)	11.6 ±3.6 (115)	10.4±3.5 (165)	9.1 ± 3.2 (132)	8.3 ± 3.7 (61)

[1]n represents the number of subjects with evaluable data.

Total Aortic regurgitation at one and two years is shown in **Table 14**.
Paravalvular leak at one (1) and two (2) years is shown in **Table 15**.

Table 14. Total aortic regurgitation by follow-up visit

Visit / Size	None % (n/N[1])	Trace % (n/N[1])	Mild % (n/N[1])	Moderate % (n/N[1])	Severe % (n/N[1])
1 YEAR					
All subjects	46.8% (244 /521)	44.3% (231 /521)	7.3% (38 /521)	1.2% (6 /521)	0.4% (2 /521)
19 mm	21.1% (8 /38)	65.8% (25 /38)	13.2% (5 /38)	0.0% (0 /38)	0.0% (0 /38)
21 mm	45.8% (54 /118)	50.8% (60 /118)	2.5% (3 /118)	0.8% (1 /118)	0.0% (0 /118)
23 mm	44.6% (74 /166)	44.6% (74 /166)	7.8% (13 /166)	3.0% (5 /166)	0.0% (0 /166)
25 mm	55.5% (76 /137)	33.6% (46 /137)	10.2% (14 /137)	0.0% (0 /137)	0.7% (1 /137)
27 mm	51.6% (32 /62)	41.9% (26 /62)	4.8% (3 /62)	0.0% (0 /62)	1.6% (1 /62)
2 YEAR					
All subjects	44.8% (74 /165)	45.5% (75 /165)	9.7% (16 /165)	0.0% (0 /165)	0.0% (0 /165)
19 mm	18.8% (3 /16)	62.5% (10 /16)	18.8% (3 /16)	0.0% (0 /16)	0.0% (0 /16)
21 mm	40.9% (18 /44)	56.8% (25 /44)	2.3% (1 /44)	0.0% (0 /44)	0.0% (0 /44)

Visit Size	None % (n/N[1])	Trace % (n/N[1])	Mild % (n/N[1])	Moderate % (n/N[1])	Severe % (n/N[1])
23 mm	47.8% (22 /46)	43.5% (20 /46)	8.7% (4 /46)	0.0% (0 /46)	0.0% (0 /46)
25 mm	51.2% (22 /43)	30.2% (13 /43)	18.6% (8 /43)	0.0% (0 /43)	0.0% (0 /43)
27 mm	56.3% (9 /16)	43.8% (7 /16)	0.0% (0 /16)	0.0% (0 /16)	0.0% (0 /16)

[1]N represents the number of subjects with evaluable data.

Table 15. Paravalvular leak by follow-up visit

Visit Size	None % (n/N[1])	Trace % (n/N[1])	Mild % (n/N[1])	Moderate % (n/N[1])	Severe % (n/N[1])
1 YEAR					
All subjects	75.5% (392 /519)	16.0% (83 /519)	6.9% (36 /519)	1.2% (6 /519)	0.4% (2 /519)
19 mm	63.2% (24 /38)	26.3% (10 /38)	10.5% (4 /38)	0.0% (0 /38)	0.0% (0 /38)
21 mm	83.8% (98 /117)	12.8% (15 /117)	2.6% (3 /117)	0.9% (1 /117)	0.0% (0 /117)
23 mm	70.9% (117 /165)	18.2% (30 /165)	7.9% (13 /165)	3.0% (5 /165)	0.0% (0 /165)
25 mm	73.7% (101 /137)	15.3% (21 /137)	10.2% (14 /137)	0.0% (0 /137)	0.7% (1 /137)
27 mm	83.9% (52 /62)	11.3% (7 /62)	3.2% (2 /62)	0.0% (0 /62)	1.6% (1 /62)
2 YEAR					
All subjects	75.8% (125 /165)	14.5% (24 /165)	9.7% (16 /165)	0.0% (0 /165)	0.0% (0 /165)
19 mm	56.3% (9 /16)	25.0% (4 /16)	18.8% (3 /16)	0.0% (0 /16)	0.0% (0 /16)
21 mm	81.8% (36 /44)	15.9% (7 /44)	2.3% (1 /44)	0.0% (0 /44)	0.0% (0 /44)
23 mm	78.3% (36 /46)	13.0% (6 /46)	8.7% (4 /46)	0.0% (0 /46)	0.0% (0 /46)
25 mm	69.8% (30 /43)	11.6% (5 /43)	18.6% (8 /43)	0.0% (0 /43)	0.0% (0 /43)

Visit Size	None % (n/N[1])	Trace % (n/N[1])	Mild % (n/N[1])	Moderate % (n/N[1])	Severe % (n/N[1])
27 mm	87.5% (14 /16)	12.5% (2 /16)	0.0% (0 /16)	0.0% (0 /16)	0.0% (0 /16)

[1]N represents the number of subjects with evaluable data.

Average aortic cross clamp time (XCT) for the trial compared to surgical times entered into the STS Adult Cardiac Surgery Database between July 2011 and December 2012 for comparable procedures is presented in **Table 16**.

The XCTs for the enrolled cohort were statistically lower in five (5) out of the six (6) categories tested ($p<0.05$). Statistical significance was not achieved when more complex CABG procedures (≥4 grafts) were performed during the index surgery which may be attributed to higher relative time required for the concomitant procedure as well as the small sample size.

Table 16: Aortic cross-clamp times compared to the STS Database

Surgical Group	ENROLLED (n: mean ± SD)	STS Database (mean)[2]	*p*-value[1]
Isolated AVR, Full Sternotomy	221: 49.3 ± 26.9	76.35	<0.001
Isolated AVR, MIS	327: 63.1 ± 25.4	82.98	<0.001
AVR + CABG 1 graft	89: 66.6 ± 25.7	94.88	<0.001
AVR + CABG 2 grafts	76: 89.2 ± 27.3	111.60	<0.001
AVR + CABG 3 grafts	38: 113.1 ± 38.2	127.73	0.023
AVR + CABG 4+ grafts	7: 148.9 ± 40.0	141.99	0.666

[1]*p*-values are calculated using one-sample t-tests.
[2]Data from the STS Adult Cardiac Surgery Database is derived from the period of July 2011 - December 2012.

Average cardiopulmonary bypass time (CPBT) for procedures performed during the trial compared to surgical times entered into the STS Adult Cardiac Surgery Database between July 2011 and December 2012 for comparable procedures is presented in **Table 17**.

The CPBTs for the enrolled cohort were statistically lower in five (5) out of the six (6) categories tested ($p<0.05$). Statistical significance was not achieved when more complex CABG procedures (≥4 grafts) were performed during the index surgery which may be attributed to higher relative time required for the concomitant procedure as well as the small sample size.

Table 17: Cardiopulmonary bypass times compared to STS Database

Surgical Group	ENROLLED (n: mean ± SD)	STS Database (mean)[2]	*p*-value[1]
Isolated AVR, Full Sternotomy	222: 69.2 ± 34.7	104.23	<0.001
Isolated AVR, MIS	327: 84.6 ± 33.5	111.44	<0.001
AVR + CABG 1 graft	89: 87.1 ± 34.2	125.95	<0.001
AVR + CABG 2 grafts	76: 113.3 ± 38.4	144.95	<0.001
AVR + CABG 3 grafts	38: 140.6 ± 44.0	163.60	0.003
AVR + CABG 4+ grafts	7: 171.0 ± 44.4	180.49	0.592

[1] *p*-values are calculated using one-sample t-tests.
[2] Data from the STS Adult Cardiac Surgery Database is derived from the period of July 2011 - December 2012.

3. Subgroup Analyses

Gender was evaluated for potential association with outcomes. Among the 889 subjects enrolled, 64.5% were male and 35.5% were female. Analysis was performed on the 839 patients who were successfully implanted in order to assess potential differences between the sexes that may be relevant to the clinical evaluation of the INTUITY Elite Valve System. The TRANSFORM study was not designed nor powered to study safety and effectiveness differences between sexes, so this analysis is considered exploratory without definitive conclusions.

Safety endpoints stratified by gender are listed in **Table 18**.

Table 18: Female vs. male freedom from safety outcomes at 1-year

	Probability Event Free at 1 Year[1]	
Adverse Event or Outcome	**Female**	**Male**
Death	96.6%	96.4%
Reoperation	99.2%	99.4%
Thromboembolism	93.9%	93.9%
Valve Thrombosis	100.0%	100.0%
All Bleeding	94.6%	93.7%
Major Bleeding	96.5%	96.0%
OPC All PVL	98.6%	97.2%
OPC Major PVL	99.2%	99.4%
Endocarditis	100.0%	100.0%
OPC Composite	87.8%	86.8%

[1] Probability event free based on Kaplan-Meier analysis; time to event truncated at 1 year (POD 365).

NYHA classification at 1-year was similar between males and females with results presented in **Table 19**.

Table 19: Female vs. male NYHA classification at 1-year

Post-operative NYHA	Female %(n/N[1])	Male %(n/N[1])
Class I/II	97.5% (197 / 202)	96.3% (334 / 347)
Class III/IV	2.5% (5 / 202)	3.7% (13 / 347)

[1]N is the number of subjects with available data at the 1-year visit.

EOA at 1-year was also comparable between sexes (**Table 20**).

Table 20: Female vs. male hemodynamic performance at 1-year

Parameter	Female Mean±SD (n[1])	Male Mean±SD (n[1])
EOA (cm^2)	1.42 ± 0.25 (185)	1.80 ± 0.28 (306)
Mean Gradient (mmHg)	11.04 ± 3.77 (189)	9.90 ± 3.75 (320)

[1]n represents the number of subjects with evaluable data.

The comparisons of safety and effectiveness data support the conclusion that the results of the overall study can be applied equally well to males and females.

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 conducting clinical studies covered by the regulation. The pivotal clinical study included 29 principal investigators and 59 sub-investigators totaling 88 investigators of which none were full-time or part-time employees of the sponsor and 18 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: none
- Significant payment of other sorts: 18 investigators
- Proprietary interest in the product tested held by the investigator: none
- Significant equity interest held by investigator in sponsor of covered study: none

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study

outcome. The information provided does not raise any questions about the reliability of the data.

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

In accordance with the provisions of section 515(c)(3) 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.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

In the clinical study, the analysis of effectiveness is based on NYHA functional classification and echocardiography data at one (1) year. Improvement in NYHA classification from baseline to the one year visit was observed based on subjects with available data at both time intervals.

Based on core lab assessments of echocardiography data, mean effective orifice areas (EOA) and mean gradients are consistent with current literature regarding other stented aortic bioprostheses and indicate acceptable hemodynamic performance of the INTUITY Elite Valve System.

The clinical study analysis demonstrated a significant reduction (in minutes) for cross-clamp and cardiopulmonary bypass times for the enrolled cohort in comparison to surgical times entered into the STS Adult Cardiac Surgery Database. Reductions in cross-clamp and bypass times varied with concomitant procedures but demonstrated a reduction of approximately 20 to 35 minutes for isolated aortic valve replacement.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and animal studies as well as data collected in a clinical study conducted to support PMA approval as described above. The results from the pre-clinical laboratory studies performed on the Edwards INTUITY Elite Valve system for biocompatibility, hydrodynamic performance and structural performance demonstrate that this device is suitable for long-term implant.

In-vivo animal studies in sheep demonstrate that the Edwards INTUITY Elite Valve System is safe for aortic valve replacement.

The results of the TRANSFORM clinical investigation demonstrates that the adverse event rates for the major safety endpoints are significantly lower than the established standard of twice the FDA's Objective Performance Criteria for a bioprosthetic valve,

with exception of bleeding and paravalvular leak. Detailed analyses of the bleeding rates do not suggest direct relation to the Edwards INTUITY Elite Valve System.

In the TRANSFORM study the upper 95% confidence limit for the linearized rate for all paravalvular leak was 2.7% which exceeds the FDA criterion of twice the OPC (2.4%). Analyses correlated the occurrence of increased paravalvular leak with valve under-sizing that was observed during the trial. Furthermore, the frequency of valve under-sizing observed during the study suggests that the Edwards INTUITY Elite Valve System may present challenges for proper sizing. When isolating data from properly sized valves, the INTUITY Elite Valve System performs within two (2) times the OPC for all and major paravalvular leak.

Data suggested that the use of the INTUITY Valve System may be associated with new or worsening conduction system disturbances which may require permanent cardiac pacemaker implantation. However, the benefits of receiving the device outweigh the risks associated with implantation of a permanent pacemaker.

C. Benefit-Risk Determination

The probable benefits of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. The probable benefits of the Edwards INTUITY Valve System included improved aortic valve hemodynamic performance, improved NYHA functional classification compared to baseline values, as well as reduction in average cross-clamp time and average cardiopulmonary bypass time when compared to standard surgical valve replacement. The device design allows implantation through smaller incisions in comparison to typical surgical prosthetic aortic valves that are sutured into place.

The risks of the Edwards INTUITY Elite Valve System include complications such as valvular thrombosis, thromboembolism, paravalvular leak, endocarditis, structural valve deterioration, nonstructural dysfunction, reoperation, explant, and death. However, these risks are similar to those observed with other surgical prosthetic aortic valves.

The data presented from the TRANSFORM trial indicate relatively high percentages of paravalvular leak. However, analyses suggested a correlation between large paravalvular leak and implant under-sizing. The probable benefits of receiving the INTUITY Elite Valve System to restore aortic valve function outweigh the risks of paravalvular leak when care is taken to properly fit the valve to patient anatomy.

1. Patient Perspectives
   This submission did not include specific information on patient perspectives for this device. However, attributes of the Edwards INTUITY Elite Valve System allow for minimally invasive surgery in comparison to standard surgical valve replacement. Minimally invasive procedures may be associated with smaller incisions, less pain, and faster return to normal activities.

In conclusion, given the available information above, the data support that for replacement of diseased, damaged, or malfunctioning native or prosthetic aortic valves, the probable benefits of implanting the Edwards INTUITY Elite Valve System outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. Preclinical and clinical studies provided in the PMA application demonstrate reasonable assurance that the Edwards INTUITY Elite Valve System is safe and effective for replacement of diseased, damaged, or malfunctioning native or prosthetic aortic heart valves.

XIII. CDRH DECISION

CDRH issued an approval order on August 12, 2016.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XIV. 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.