SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Replacement Heart Valve

Device Trade Name: Edwards Pericardial Aortic Bioprosthesis,
Model 11000A
Sizes: 19, 21, 23, 25, 27, and 29 mm

Edwards INSPIRIS RESILIA Aortic Valve
Model 11500A
Sizes: 19, 21, 23, 25, 27, and 29 mm

Device Product Code: LWR

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

Dates of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P150048

Date of FDA Notice of Approval: June 29, 2017

II. INDICATIONS FOR USE

The Pericardial Aortic Bioprosthesis, Model 11000A is indicated for the replacement of native or prosthetic aortic heart valves.

The INSPIRIS RESILIA Aortic Valve, Model 11500A, is indicated for the replacement of native or prosthetic aortic heart valves.

III. CONTRAINDICATIONS

There are no known contraindications with the use of the Edwards RESILIA Aortic Bioprosthesis.

There are no known contraindications with the use of the INSPIRIS RESILIA Aortic Valve.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Edwards Pericardial Aortic Bioprosthesis and Edwards INSPIRIS RESILIA Aortic Valve labeling.

V. DEVICE DESCRIPTION

The Edwards Pericardial Aortic Bioprosthesis, Model 11000A (**Figure 1**) and the Edwards INSPIRIS RESILIA Aortic Valve, Model 11500A (**Figure 2**) are stented trileaflet valves comprised of RESILIA bovine pericardial tissue. RESILIA tissue is created by treating bovine pericardial tissue with Edwards Integrity Preservation. The technology incorporates a stable capping anticalcification process, which blocks residual aldehyde groups that are known to bind with calcium. The technology also incorporates tissue preservation with glycerol, which allows the valve to be stored without a traditional liquid-based solution, such as glutaraldehyde. The valve is stored under dry packaging conditions and consequently does not require rinsing prior to implantation. Models 11000A and Model 11500A are available in sizes 19, 21, 23, 25, 27 and 29mm.

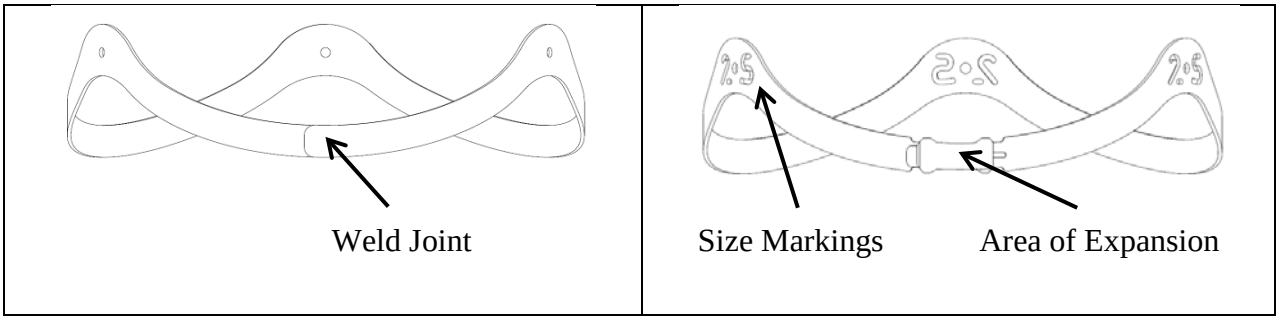
Figure 1: Edwards Pericardial Aortic Bioprosthesis, Model 11000A

Figure 2: INSPIRIS RESILIA Aortic Valve, Model 11500A

The three leaflets are mounted on a flexible cobalt-chromium alloy wireform. A thin cobalt-chromium alloy band and polyester support band surround the base of the valve below the wireform frame to provide structural support for the orifice. Model 11000A and Model 11500A are very similar in design. The main difference between the two models is the cobalt-chromium alloy band. The ends of the circular cobalt-chromium alloy band on Model 11000A sizes 19-29mm and Model 11500A sizes 27mm and 29mm are permanently secured by weld joint (**Figure 3**). On Model 11500A sizes 19-25mm, the ends of the cobalt-chromium alloy band are secured with a polyester shrink-sleeve (VFit Technology) (**Figure 4**). The polyester shrink-sleeve allows the band to expand under radial forces. The expandable band is intended for potential future valve-in-valve procedures. The band on Model 11000A sizes 19-29mm and Model 11500A sizes 27mm and 29mm is not designed to expand.

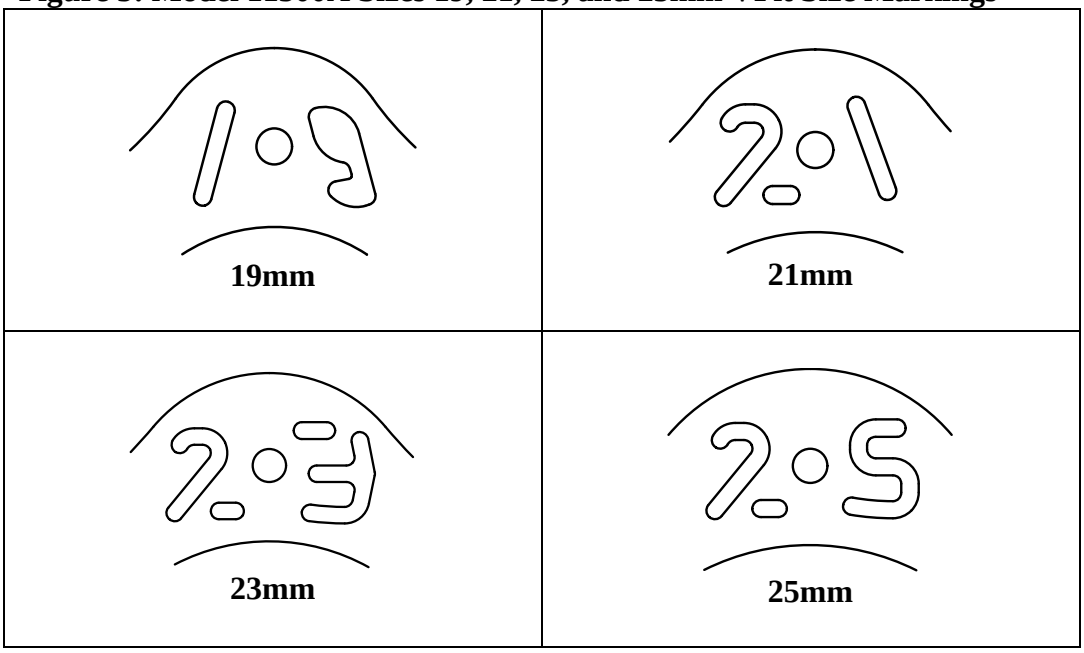
Figure 3: Model 11000A Sizes 19-29mm and Model 11500A Sizes 27mm and 29mm Band (Weld Joint)

Figure 4: Model 11500A Sizes 19, 21, 23, and 25mm VFit Technology (Expandable Band)



The sewing ring has three equally spaced black silk suture markers at the cusp centers to aid in valve orientation and suture placement. A holder is attached to the valve by means of sutures to facilitate handling, deployment, and suturing the valve during the implant procedure. Both Model 11000A and Model 11500A are visible under fluoroscopy to allow for identification of the valve's inflow and outflow edges. Additionally, the cobalt-chromium alloy band on Model 11500A sizes 19-25mm also contains labeled size markings at each commissure to aid in the identification of the surgical valve size under fluoroscopy. A representation of the commissure size markings for the sizes 19-25 mm is shown in **Figure 5**.

Figure 5: Model 11500A Sizes 19, 21, 23, and 25mm VFit Size Markings



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. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The Edwards Pericardial Aortic Bioprosthesis, Model 11000A, and the Edwards INSPIRIS RESILIA Aortic Valve, Model 11500A received CE Mark approval for European commercial distribution in the following countries: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Liechtenstein, Lithuania, Luxemburg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey, and the United Kingdom. The device has not been withdrawn from marketing for any reason related to its safety or 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
- Angina
- Annulus (damage, dissection, tear)
- Arterial dissection
- Aorta (damage, dissection, tear)
- Aortic Root damage
- Asystole and/or cardiac arrest
- Bleeding
    - Peri- or post-procedural
    - Anticoagulant related
    - Pericardial tamponade
    - Hematoma
    - Cerebrovascular
- Blood – Anemia
- Blood – Coagulopathy
- Blood – Hemolysis/Hemolytic Anemia
- Blood Pressure alteration (hypotension, hypertension)
- Cardiac – Arrhythmias/Conduction Disturbances
- Cardiogenic shock
- Coronary artery ostia occlusion

- Deep vein thrombosis (DV)
- Disseminated intravascular coagulation (DIC)
- Embolism
- Endocarditis
- Esophageal tear/rupture
- Hypoxemia
- Infection – local, wound or systemic
- Multi-system organ failure (MOF)
- Myocardial infarction
- Neurologic Events
    - Stroke (CVA)
    - Transient Ischemic Attack (TIA)
- Pericardial effusion
- Pleural effusion
- Pneumonia
- Prosthetic Insufficiency –Regurgitation/Stenosis
- Pulmonary edema
- Reduced exercise tolerance
- Renal failure, acute
- Renal insufficiency
- Respiratory failure
- Thrombocytopenia, heparin induced (HIT)
- Thrombocytopenia (Non-HIT)
- Thromboembolism
    - Arterial, venous, peripheral, central
- Transvalvular or Valvular Leaking
    - Valve dislodgement/instability
    - Valve – Nonstructural dysfunction
    - Paravalvular Leak
    - Leaflet impingement
    - Leaflet tissue damage (instruments /sutures)
    - Pannus
    - Prosthesis Mismatch (PPM) (due to inappropriate sizing)
    - Distortion at implant
- Valve – Structural dysfunction/deterioration
- Valve – Thrombosis
- Valve Wireform/Stent Fracture or Distortion

It is possible that these complications may lead to:

- Reoperation
- Explantation
- Permanent disability
- Death

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

IX. SUMMARY OF PRECLINICAL STUDIES

A. Laboratory Studies

1. Biocompatibility Studies

Biocompatibility evaluations were completed on the Edwards Pericardial Aortic Bioprosthesis, Model 11000A, and INSPIRIS RESILIA Aortic Valve, Model 11500A, 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 test results for the Edwards Pericardial Aortic Bioprosthesis, Model 11000A, and INSPIRIS RESILIA Aortic Valve, Model 11500A, are provided in **Table 1**. 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 Pericardial Aortic Bioprosthesis, Model 11000A, and Edwards INSPIRIS RESILIA Aortic Valve, Model 11500A

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	Pass
Irritation/Intracutaneous Toxicity	Rabbit Intracutaneous Reactivity	Pass
Systemic Toxicity	Mouse Systemic Injection	Pass
Systemic Toxicity	Rabbit Pyrogen, Material-Mediated Test	Pass
Genotoxicity	Gene Mutation, in vitro Ames Plate Incorporation Test	Pass
Genotoxicity	Chromosomal Aberration in vitro Chinese Hamster Ovary (CHO) Cells	Pass
Genotoxicity	Chromosomal Aberration in vivo Mouse Micronucleus Test	Pass
Implantation	Rabbit Intramuscular Implantation with Histology, 7-, 30- and 90-Day Implant Durations	Pass

Biological Effect per ISO 10993-1	Test Method	Results
Hemocompatibility	ASTM Blood Compatibility	Pass
Hemocompatibility	Complement Activation Test	Pass
90-Day Systemic Toxicity	Rats via Subcutaneous Implantation with Histology	Pass
26-Week Systemic Toxicity	Rats via Subcutaneous Implantation with Histology	Pass

2. Hydrodynamic Performance

In vitro hydrodynamic testing was conducted on the Edwards Pericardial Aortic Bioprosthesis, Model 11000A, and INSPIRIS RESILIA Aortic Valve, Model 11500A. Studies were conducted in accordance with EN ISO 5840:2009 Cardiovascular Implants-Cardiac Valve Prostheses. The tests are summarized in **Table 2** below.

Table 2: Model 11000A and 11500A Hydrodynamic Testing and Results

Test	Purpose/ Objective	Test and reference articles	Results
Flow Visualization	To qualitatively assess the flow characteristics of the valve.	Test: Model 11000A size 19mm Reference: Carpentier-Edwards PERIMOUNT Magna Ease size 19 mm	Model 11000A offers acceptable aortic flow patterns throughout the entire cardiac cycle. No retrograde jets or valvular incompetence was observed. These results are applicable to Model 115000A.
Bernoulli Coefficient	Use pressure drop testing to confirm the Bernoulli coefficient for Model 11000A is consistent with the theoretical coefficient.	Test: Model 11000A sizes 19mm, 25mm, and 29mm Reference: PERIMOUNT Magna Ease sizes 19mm, 25mm, and 29mm	Pressure drop testing for Model 11000A test valves show no statistically significant differences from the Carpentier-Edwards PERIMOUNT Magna Ease reference valves that previously demonstrated correlation with the Bernoulli relationship. These data justify using a Bernoulli coefficient of four with Model 11000A. These results are applicable to Model 115000A.
Steady	To determine	Test: Model	Model 11000A and Model 11500A

Test	Purpose/ Objective	Test and reference articles	Results
Forward Flow Test	pressure drop at various steady forward flow rates.	11000A sizes 19mm- 29mm and Model 11500A sizes 19mm-29mm Reference: PERIMOUNT Magna Ease size 19mm- 29mm	offer acceptable hydrodynamics with pressure gradients and 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: Model 11000A sizes 19mm- 29mm and Model 11500A sizes 19mm-29mm Reference: PERIMOUNT Magna Ease size 19mm- 29mm	Model 11000A and Model 11500A offer 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: Model 11000A sizes 19mm- 29mm and Model 11500A sizes 19mm-29mm Reference: PERIMOUNT Magna Ease size 19mm- 29mm	Model 11000A and Model 11500A offer acceptable hydrodynamics and meet the effective orifice area required by ISO 5840:2009/ISO 5840-2:2015, with results that are comparable to the reference valves.
Pulsatile Flow Regurgitation	To determine regurgitation performance under pulsatile flow conditions.	Test: Model 11000A sizes 19mm- 29mm and Model 11500A sizes 19mm-29mm Reference: PERIMOUNT Magna Ease size 19mm- 29mm	Model 11000A and Model 11500A offer acceptable hydrodynamics with regurgitant fractions that meet ISO 5840:2009/ISO 5840-2:2015, with results that are comparable to the reference valves.

3. Structural Performance

The structural performance of the Edwards Pericardial Aortic Bioprosthesis, Model 11000A, and INSPIRIS RESILIA Aortic Valve, Model 11500A, was evaluated per the testing listed in **Table 3**. Studies were conducted in accordance with ISO 5840:2009 Cardiovascular Implants-Cardiac Valve Prostheses.

Table 3: Model 11000A and 11500A Structural Performance Evaluation

Test	Purpose/ Objective	Test and reference articles	Results
Accelerated Wear Testing	To assess long-term performance of Model 11000A and Model 11500A valve through accelerated wear.	Test: Model 11000A sizes 19, 25, and 29mm, 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 5840:2009. The results are applicable to Model 11500A.
Dynamic Failure Mode	To obtain information about the failure modes affecting the durability of the valve.[1]	Test: Model 11000A sizes 19, 25, and 29mm, 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*. The results are applicable to Model 11500A.
Stent Deflection	To determine the relationship between peak pressure difference and stent post deflection of the study valve.	Test: Model 11000A sizes 19mm- 29mm and Model 11500A sizes 19mm- 29mm Reference: PERIMOUNT Magna Ease size 19mm- 29mm	Testing demonstrated no statistical difference between Model 11000A/Model 11500A and PERIMOUNT Magna Ease which has previously shown acceptable stent fatigue results.
Sewing Ring Integrity	To determine the force required to separate the sewing ring from the stent subassembly of the study valve.	Test: Model 11000A size 19mm and Model 11500A size 19mm	Test results demonstrated that the sewing ring integrity of Model 11000A and Model 11500A is acceptable.
Suture	To evaluate the	Test: Model	Test results demonstrated that the

Test	Purpose/ Objective	Test and reference articles	Results
Retention	sewing ring suture retention strength of the study valve.	11000A size 19mm and Model 11500A size 19mm	sewing ring integrity of Model 11000A and Model 11500A is acceptable.
Corrosion Resistance	To characterize the corrosion resistance of metallic components in accordance with ASTM F2129.	Test: Model 11000A size 19mm-29mm and Model 11500A size 29mm	Test results show high corrosion resistance of the cobalt chromium stiffener band/wireform.
Tissue Ultimate Tensile Strength	To determine the tensile strength of processed tissue.	Test: RESILIA tissue leaflets Reference: Tissue processed with Edwards ThermaFix process	Test results demonstrate the ultimate tensile strength of the RESILIA tissue is not inferior to the reference tissue.
Tissue Stress Relaxation	To determine the relaxation properties of processed tissue.	Test: RESILIA tissue leaflets Reference: Tissue processed with Edwards ThermaFix process	Test results demonstrate the stress relaxation of the RESILIA tissue is not inferior to the reference tissue.
Tissue Shrinkage Temperature	To determine the shrinkage temperature of the RESILIA tissue.	Test: RESILIA tissue leaflets Reference: Tissue processed with Edwards ThermaFix process	Test results demonstrate the shrink temperature of the RESILIA tissue is equivalent to the reference tissue.

4. Animal Studies

The performance of the Edwards Pericardial Aortic Bioprosthesis, Model 11000A, was evaluated in the aortic position in the young adult ovine model. A total of 9 test articles (Model 11000A) and 8 control articles (4 each of Carpentier-Edwards PERIMOUNT Magna Ease Pericardial Aortic Bioprosthesis Models 3300TFX and 3300) 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 11000A aortic valve was biocompatible in the ovine model, had normal healing, was durable, and had similar performance to the control valves, models 3300TFX and 3300, when implanted in adult sheep for 20 weeks. Implant characteristics, calcification, thrombus, and vegetations were similar among the three groups. The valves were all hemocompatible, as there was no clinically significant hemolysis or valve related thromboemboli observed among the test and control groups.

The performance of the INSPIRIS RESILIA Aortic Valve, Model 11500A, was evaluated in the aortic position in the young adult ovine model. A total of 10 test articles (Model 11500A) and 4 control articles (Model 3300TFX) were implanted in the aortic position for a total of 120 days. A transcatheter valve, Edwards SAPIEN XT, Model 9300TFX, was deployed and implanted in a valve-in-valve position on day 90. 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 11500A aortic valve was biocompatible in the ovine model, had normal healing, was durable, and had similar performance to the control valve, Carpentier-Edwards PERIMOUNT Magna Ease Pericardial Aortic Bioprosthesis, Model 3300TFX. Specific areas of evaluation after implant of both the INSPIRIS RESILIA Aortic Valves and SAPIEN XT transcatheter valves included healing characteristics, hemolysis, thromboembolic complications, structural deterioration and calcification as compared to the control valves. Implant characteristics, calcification, thrombus, and vegetations were similar among the two groups. The valves were all hemocompatible, as there was no clinically significant hemolysis or valve related thromboemboli observed among the test and control groups. All surviving test and control animals in the 120-day cohort were clinically normal (appeared healthy) prior to explant.

B. Additional Studies

1. Sterilization

The Edwards Pericardial Aortic Bioprosthesis, Model 11000A, and the INSPIRIS RESILIA Aortic Valve, Model 11500A, are terminally sterilized by ethylene oxide. After sterilization, the devices are held in quarantine until sterility is verified per process specifications. Ethylene oxide process sterilization has demonstrated Sterility Assurance Levels (SAL) of better than 10^{-6} in validation studies.

2. Package Integrity and Shelf Life

The packaging for the Edwards Pericardial Aortic Bioprosthesis, Model 11000A, and INSPIRIS RESILIA Aortic Valve, Model 11500A, consists of a

double barrier tray package sealed with a Tyvek lid. The double tray package is in a foil pouch which is in a carton that includes the Instructions for Use. A temperature indicator is displayed through a window on the side panel of the carton to identify products exposed to transient temperature extremes.

The shelf life of the Edwards Pericardial Aortic Bioprosthesis and INSPIRIS RESILIA Aortic Valve is two years as demonstrated by package and functional product integrity testing on aged valves and packaging.

3. MRI Compatibility

Non-clinical testing has demonstrated that the Edwards Pericardial Aortic Bioprosthesis, Model 11000A, and INSPIRIS RESILIA Aortic Valve, Model 11500A, are MR Conditional. A patient with the Edwards Pericardial Aortic Bioprosthesis, Model 11000A, or INSPIRIS RESILIA Aortic Valve, Model 11500A, can be scanned safely under the following conditions:

- Static magnetic field of 1.5 Tesla or 3 Tesla only.
- Maximum spatial gradient magnetic field of 3,000 gauss/cm (30 T/m) or less.
- Maximum MR system-reported, whole-body averaged specific absorption rate (SAR) of 2.0 W/kg in Normal Operating Mode.

Under the scan conditions defined above Model 11000A and Model 11500A are expected to produce a maximum *in vivo* temperature rise of less than 2.0°C at 1.5 T and less than 2.5°C at 3 T after 15 minutes of continuous scanning.

In non-clinical testing, the image artifact extends approximately 10 mm from the Model 11000A and Model 11500A valve when imaged with a spin echo pulse sequence and 17 mm from the device when imaged with a gradient echo pulse sequence and a 3 Tesla MRI system. The artifact obscures the device lumen.

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 Edwards Pericardial Aortic Bioprosthesis, Model 11000A, for patients who require replacement of their native or prosthetic aortic valve in the US and in the European Union under IDE # G120108. 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 January 2013 and February 2016. The database for this PMA reflected data collected through April 13, 2016, and included 694 patients. There were 27 investigational sites (25 US sites and 2 sites in the European Union).

The study was an open-label, prospective, non-randomized, multicenter clinical study for the Edwards Pericardial Aortic Bioprosthesis, Model 11000A. 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. All echocardiographic data were evaluated by an independent Echocardiographic Core Laboratory (ECL). The study also used an independent Data Monitoring Committee (DMC) that was instructed to notify Edwards Lifesciences of any safety or compliance issues and a Clinical Events Committee (CEC) that was responsible for adjudicating endpoint-related events reported during the trial per definitions established *a priori*.

The Edwards Pericardial Aortic Bioprosthesis, Model 11000A, which was assessed during the COMMENCE clinical study, and the Edwards RESILIA INSPIRIS Aortic Valve, Model 11500A, have identical designs with the exception of the expansion feature (Vfit) in Model 11500A. Therefore, the data from the COMMENCE clinical study was determined to be applicable to Model 11500A and additional clinical data was not required to support the safety and effectiveness of Model 11500A as a surgical replacement heart valve. Clinical data evaluating the Model 11500A sizes 19-25mm expansion feature (Vfit) in a valve-in-valve procedure are not currently available. This feature will be further evaluated in a post approval study as outlined in Section XIII.

1. Clinical Inclusion and Exclusion Criteria

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

1. Is 18 years of age or older
2. Provides written informed consent prior to trial procedures
3. Agrees to attend follow-up assessments for up to 5 years and is willing to comply with specified follow-up evaluations at clinical investigational sites that are participating in the COMMENCE trial and/or obtain the protocol-specified diagnostic tests at centers that are under the same IRB or the same healthcare system
4. Diagnosed with aortic or mitral valve disease requiring valve replacement based on preoperative evaluation
5. Scheduled to undergo planned aortic or mitral valve replacement with or without concomitant bypass surgery

6. Scheduled to undergo planned aortic valve replacement with or without resection and replacement of the ascending aorta from the sinotubular junction and without the need for circulatory arrest for hemi arch or arch replacement

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

1. Requires emergency surgery
2. Requires multiple valve replacement/repair (with the exception of mitral valve replacement with tricuspid valve repair)
3. Has prior valve surgery, which included implant of a bioprosthetic valve, mechanical valve, or annuloplasty ring that will remain *in situ*
4. Requires a surgical procedure outside of the cardiac area (e.g., vascular bypass)
5. Requires surgical replacement of the aortic root
6. Has active endocarditis/myocarditis or endocarditis/myocarditis within 3 months to the scheduled aortic or mitral valve replacement surgery
7. Has renal insufficiency as determined by creatinine (S-Cr) level $\geq$ 2.5 mg/dL or end-stage renal disease requiring chronic dialysis at screening visit
8. Has MRI or CT scan confirmed stroke, cerebrovascular accident (CVA) or transient ischemic attack (TIA) within 6 months (180 days) prior to planned valve surgery
9. Has acute myocardial infarction (MI) within 30 days prior to planned valve surgery
10. Has presence of non-cardiac disease limiting life expectancy to less than 12 months
11. Diagnosed with hypertrophic obstructive cardiomyopathy (HOCM)
12. Diagnosed with abnormal calcium metabolism and hyperparathyroidism
13. Exhibits left ventricular ejection fraction $\leq$ 20% as validated by diagnostic procedure prior to planned valve surgery
14. Echocardiographic evidence of an intra-cardiac mass, thrombus, or vegetation
15. Hemodynamic or respiratory instability requiring inotropic support, mechanical circulatory support, or mechanical ventilation within 30 days prior to planned valve surgery
16. Documented leukopenia (WBC < 3.5x $10^3/\mu L$), acute anemia (Hgb < 10.0 gm/dL or 6 mmol/L), thrombocytopenia (platelet count < $50x10^3/\mu L$) accompanied by history of bleeding diathesis or coagulopathy
17. Has prior organ transplant or is currently an organ transplant candidate
18. Current or recent participation (within 6 weeks prior to surgery) in another drug or device trial
19. Was previously implanted with the investigational device

20. Pregnant (female subject of childbearing potential only), lactating or planning to become pregnant during the duration of participation in trial
21. Currently incarcerated or unable to give voluntary informed consent
22. Documented history of substance (drug or alcohol) abuse within the last 5 years prior to implant
23. Requires concomitant left ventricular assist device (LVAD) placement

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.

The key time-points are shown below in the tables summarizing safety and effectiveness.

3. Clinical Endpoints

With regards to safety, the following criteria were evaluated:

1. Rate of Structural Valve Deterioration (SVD) of the trial valve through the 1 year (post-operative discharge day 390) follow-up visit.
2. Adverse Event (AE) rates defined by the Objective Performance Criteria (OPC) reported in Table R.1 in EN ISO 5840:2009, Annex R.

With regards to effectiveness, the following criteria were evaluated:

1. New York Heart Association (NYHA) functional classification status
2. Hemodynamic performance evaluated by echocardiography

With regard to success/failure criteria, 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 694 patients enrolled in the PMA study, 99.3% (689) patients are available for analysis at the completion of the study, and 857.0 patient-years were collected (800.9 late patient-years). Five subjects were not successfully implanted with the study valve and were not included in the main analysis. Subject compliance is detailed in **Table 4**.

Table 4: Subject Compliance

Visit Interval	Eligible Subjects (N_1)	Follow-up Compliance %[1] (n)	Censored[2] (N_2)
Pre-operative	689	100.0% (689)	0
Discharge	682	100.0% (682)	7
1 Month	681	99.6% (678)	8
3 Month	668	97.2% (649)	21
1 Year	541	95.2% (515)	148
2 Year	254	94.5% (240)	435
3 Year	2	100.0% (2)	687

[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 5**.

Table 5: Preoperative Subject Demographics

Age at Implant	N: Mean ± SD (Min - Max)
Age (years)	689: 67.0 ± 11.6
Sex	**% (n/N)**
Female	28.2% (194/689)
Male	71.8% (495/689)
NYHA Classification	**% (n/N)**
Class I	24.1% (166 689)
Class II	49.6% (342/689)
Class III	24.4% (168/689)
Class IV	1.9% (13/689)
Risk Scores	N: Mean ± SD (Min - Max)
STS risk of mortality (%)[1]	526: 2.0 ± 1.8 (0.3 – 17.5)
EuroSCORE II (%)	672: 2.6 ± 2.9 (0.5 – 24.6)

[1]STS scores only calculated for subjects undergoing isolated aortic valve replacement (AVR) or AVR and coronary artery bypass grafting.

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the 689 patients that received the Edwards Pericardial Aortic Bioprosthesis over the course of 857 total patient-years. The key safety outcomes and adverse events for this study are presented below in **Table 6**. 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." Trial results demonstrated a 0.0% observed rate of SVD which is statistically less than 1% after 1 year of follow-up.

Table 6: Observed Adverse Event Rates

Adverse Event or Outcome	Early[1] (N=689) n, m (%)	Late[2] (LPY[3] = 800.9) n, m, (%/pt-yr)	Freedom-from Event at 1 Year (SE)[4]
All-cause mortality	8, 8 (1.2)	18, 18 (2.2)	0.976 (0.006)
Valve-related mortality	3, 3 (0.4)	6, 6 (0.7)	0.988 (0.004)
Reoperation	1, 1 (0.1)	2, 2 (0.2)	0.997 (0.002)
Explant	0, 0 (0.0)	2, 2 (0.2)	0.998 (0.002)
Thromboembolism	15, 15 (2.2)	14, 17 (2.1)	0.965 (0.007)
Valve thrombosis	0, 0 (0.0)	0, 0 (0.0)	1.000 (0.000)
All bleeding	6, 6 (0.9)	21, 21 (2.6)	0.960 (0.008)
Major bleeding	5, 5 (0.7)	11, 11 (1.4)	0.977 (0.006)
All paravalvular leak	2, 2 (0.3)	2, 2 (0.2)	0.994 (0.003)
Major paravalvular leak	1, 1 (0.1)	1, 1 (0.1)	0.997 (0.002)
Endocarditis	0, 0 (0.0)	5, 5 (0.6)	0.993 (0.004)
Hemolysis	0, 0 (0.0)	0, 0 (0.0)	1.000 (0.000)
Structural Valve Deterioration	0, 0 (0.0)	0, 0 (0.0)	1.000 (0.000)

[1] For 'Early Events' (events occurring thru post-implant day 30): 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.

The results of the COMMENCE aortic arm were compared to the OPC as described in Table R.1 in EN ISO 5840:2009, Annex R.1. Thromboembolism, valve thrombosis, all and major paravalvular leak, and endocarditis met the statistical standard. The OPC criteria for all and major bleeding were not met;

however, none of the bleeding events were CEC-adjudicated as related to the trial device.

Table 7 : Linearized late rates compared to the OPC

Adverse Event or Outcome	Late[1] (LPY[2] = 800.9) n, m, (%/pt-yr)	95% UCL[3]	2X OPC[4]
Thromboembolism	14, 17 (2.1)	3.1	5.0
Valve thrombosis	0, 0 (0.0)	0.2	0.4
All bleeding	21, 21 (2.6)	3.7	2.8
Major bleeding	11, 11 (1.4)	2.2	1.8
All paravalvular leak	2, 2 (0.2)	0.7	2.4
Major paravalvular leak	1, 1 (0.1)	0.5	1.2
Endocarditis	5, 5 (0.6)	1.2	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 Criterial for tissue valves as described in Table R.1 of EN ISO 5840:2009, Annex R.1.

2. Effectiveness Results

The analysis of effectiveness was based on the 689 evaluable patients that received the Edwards Pericardial Aortic Bioprosthesis over the course of 857 total patient-years. Effectiveness of the Edwards Pericardial Aortic Bioprosthesis 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 8.**

Table 8: NYHA Functional Classification

NYHA Class	Baseline NYHA % (n / N[1])	1-Year NYHA[2] % (n / N[1])
Class I	24.0% (122 / 509)	80.7% (411 / 509)
Class II	49.7% (253 / 509)	17.3% (88 / 509)
Class III	24.4% (124 / 509)	1.6% (8 / 509)
Class IV	2.0% (10 / 509)	0.4% (2 / 509)

[1] N is the number of subjects who have both preoperative and 1 year NYHA data
[2] Improvement in NYHA observed demonstrated by a *p*-value < 0.0001 based on the test for marginal homogeneity after converting NYHA Class to numeric values (Class I = 1, Class II = 2, Class III = 3, Class IV = 4). Values of 0 were replaced with 0.5 to avoid sparseness of data.

Effective orifice area (EOA) and mean gradient at 1-year follow-up are presented in **Table 9**, and total aortic regurgitation at one year is shown in **Table 10**.

Table 9: 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])**
Mean Gradient (mmHg)	17.6 ±7.8 (16)	12.6 ±4.7 (97)	10.1 ±3.8 (158)	9.6 ± 5.2 (132)	8.2 ± 3.5 (69)
EOA (cm^2)	1.1 ± 0.2 (16)	1.3 ± 0.3 (97)	1.6 ± 0.4 (155)	1.8 ± 0.5 (131)	2.2 ± 0.6 (68)

[1]N represents the number of subjects with evaluable data for the specified valve size.

Table 10: Total Aortic Regurgitation at 1-Year

Total Regurgitation	**19 mm % (n/N[1])**	**21 mm % (n/N[1])**	**23 mm % (n/N[1])**	**25 mm % (n/N[1])**	**27 mm % (n/N[1])**
None (0)/Trivial (+1)	87.5% (14/16)	96.9% (94/97)	95.0% (151/159)	94.7% (124/131)	97.1% (66/68)
Mild (+2)	12.5% (2/16)	2.1% (2/97)	5.0% (8/159)	5.3% (7/131)	2.9% (2/68)
Moderate (+3)	0.0% (0/16)	1.0% (1/97)	0.0% (0/159)	0.0% (0/131)	0.0% (0/68)
Severe (+4)	0.0% (0/16)	0.0% (0/97)	0.0% (0/159)	0.0% (0/131)	0.0% (0/68)

[1]N represents the number of subjects with evaluable data for the specified valve size.

3. Subgroup Analysis

Gender was evaluated for potential association with outcomes. Among the 689 subjects enrolled, 71.8% were male and 28.2% were female.

Analysis was performed on the 689 patients who were successfully implanted in order to assess potential differences between the sexes that may be relevant to the clinical evaluation of the Edwards Pericardial Aortic Bioprosthesis. The COMMENCE study was not designed nor powered to study safety and effectiveness differences between sexes, so this analysis is considered exploratory without definitive conclusions.

Freedom from thromboembolism, bleeding, paravalvular leak, endocarditis, death, and reoperation at 1 year were comparable between populations based on

log-rank testing comparing time to event (**Table 11**). No cases of valve thrombosis and structural valve deterioration were observed for either cohort.

Table 11: Female vs. Male Freedom from Safety Outcomes at 1-Year

Adverse Event or Outcome	Probability Event Free at 1 Year[1]		*p*-value[2]
	Female	Male	
Structural Valve Deterioration	100.0%	100.0%	---
Death	99.5%	96.9%	0.0605
Reoperation	99.5%	99.7%	0.5080
Thromboembolism	97.9%	95.9%	0.2338
Valve Thrombosis	100.0%	100.0%	---
All Bleeding	97.3%	95.5%	0.3855
Major Bleeding	99.0%	97.2%	0.2271
OPC All PVL	99.5%	99.4%	0.8838
OPC Major PVL	99.5%	99.8%	0.4962
Endocarditis	100.0%	99.0%	0.1988

[1] Probability event free based on Kaplan-Meier analysis; time to event truncated at 1 year (POD 365).
[2] *p*-values are based on log-rank test comparing time to event.

NYHA classification at 1 year was similar between males and females (**Table 12**) based on a Chi-Square test for categorical variables.

Table 12: Female vs. Male NYHA Classification at 1-Year

Post-operative NYHA	Female %(n/N[1])	Male %(n/N[1])	*p*-value[2]
Class I/II	96.7% (145/150)	98.6% (354/359)	0.1504
Class III/IV	3.3% (5/150)	1.4% (5/359)	

[1] N is the number of subjects with available data at the 1-year visit.
[2] *p*-values are based on Chi-Square tests for categorical variables.

EOA, mean gradient, and regurgitation severity at 1 year were also comparable between sexes based on mixed models for continuous variables and ordinal logistic regression for categorical variables with valve size and baseline Body Surface Area (BSA) as covariates (**Table 13**).

Table 13: Female vs. Male Hemodynamic Performance at 1-Year

Parameter	Female	Male	*p*-value[2]
EOA (cm^2)	N[1]: mean ± SD	N[1]: mean ± SD	0.2410
	136 (1.39 ± 0.38)	331: 1.77 ± 0.54	
Mean Gradient (mmHg)	N[1]: mean ± SD	N[1]: mean ± SD	0.9186
	82: 12.17 ± 5.78	162: 9.59 ± 3.59	
Total Regurgitation	% (n/N[1])	% (n/N[1])	0.3759
0 None/+1 Trivial	93.4% (128 / 137)	96.1% (321 / 334)	
+2 Mild	6.6% (9 / 137)	3.6% (12 / 334)	
+3 Moderate	0.0% (0 / 137)	0.3% (1 / 334)	
+4 Severe	0.0% (0 / 137)	0.0% (0 / 334)	

[1] N is the number of subjects with evaluable data at the 1-year visit.
[2] *p*-values are based on mixed models for continuous variables or ordinal logistic regression for categorical variables with valve size and baseline BSA as covariates.

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.

4. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

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 trial included 163 investigators (27 principal investigators.) Nine of the investigators had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) as 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: 7 investigators
- Proprietary interest in the product tested held by the investigator: None
- Significant equity interest held by investigator in sponsor of covered study: 2 investigators

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 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 Echocardiographic Core Lab assessments of echocardiography data, 97.9% of patients have no detectable or trivial aortic regurgitation at one year. 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 Edwards Pericardial Aortic Bioprosthesis, Model 11000A.

The Edwards Pericardial Aortic Bioprosthesis, Model 11000A, which was assessed during the COMMENCE clinical study, and the Edwards RESILIA INSPIRIS Aortic Valve, Model 11500A, have a very similar design. The effectiveness outcomes, which include NYHA classification and hemodynamics, of Model 11000A are representative of effectiveness outcomes of Model 11500A.

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 Pericardial Aortic Bioprosthesis, Model 11000A, and the Edwards RESILIA INSPIRIS valve, Model 11500A, for biocompatibility, hydrodynamic performance and structural performance demonstrate that this device is suitable for long-term implant.

The results from the COMMENCE clinical trial demonstrate a 0.0% observed rate of SVD which is statistically less than 1% after 1 year of follow-up. Furthermore, the

rates for all OPC-defined adverse events are lower than the established standard of twice the FDA's Objective Performance Criteria for a bioprosthetic valve, with the exception of all bleeding and major bleeding. In the COMMENCE study, the upper 95% confidence limit for the linearized rate for all bleeding was 3.7% and major bleeding was 2.2% which exceeds the FDA criterion of twice the OPC (all bleeding: 2.8% and major bleeding: 1.8%). However, detailed analysis of the major bleeding events showed no clear indication that the major bleeding events were directly related to Model 11000A valve. The safety outcomes of Model 11000A are representative of safety outcomes of Model 11500A.

C. Benefit-Risk Determination

Aortic valve disease is a progressive and potentially lethal condition. Diseased heart valves can be treated by medication or surgical replacement. Surgical alternatives include replacement with a commercially available prosthetic heart valve. The probable benefits of the Edwards Pericardial Aortic Bioprosthesis, Model 11000A, and the Edwards RESILIA INSPIRIS valve, Model 11500A, include improved aortic valve hemodynamic performance and improved NYHA functional classification compared to baseline values. The risks associated with the Edwards Pericardial Aortic Bioprosthesis, Model 11000A, and the Edwards RESILIA INSPRIS valve, Model 11500A, include complications such as valvular thrombosis, thromboembolism, paravalvular leak, endocarditis, structural valve deterioration, nonstructural dysfunction, reoperation, explant, and death. However, the risks are the same as those for other alternative aortic bioprosthetic valves.

1. Patient Perspectives

   This submission did not include specific information on patient perspectives for this device.

In conclusion, given the available information above, the data support that for the replacement of native or prosthetic aortic heart valves, the probable benefits of implanting the Edwards Pericardial Aortic Bioprosthesis, Model 11000A, and the Edwards RESILIA INSPRIS valve, Model 11500A 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 Pericardial Aortic Bioprosthesis, Model 11000A, and the Edwards RESILIA INSPRIS valve, Model 11500A, are safe and effective for replacement of native or prosthetic aortic heart valves.

XIII. CDRH DECISION

CDRH issued an approval order on June 29, 2017. The final conditions of approval cited in the approval order are described below.

1. *ODE Lead Post-Approval Study – Edwards Pericardial Aortic Bioprosthesis, Model 11000A, Continued Follow-Up:* This study will consist of all IDE patients who are currently enrolled and alive. The study objective is to characterize the safety and effectiveness of the Edwards Pericardial Aortic Bioprosthesis, Model 11000A. All IDE patients who are currently enrolled and alive will be followed to 5 years. In addition, all subjects enrolled at the top 3 enrolling sites (n=222) will be followed annually through 10 years post-procedure. For continued follow-up of patients, the safety and effectiveness endpoints are listed in the protocol as follows: The primary effectiveness endpoints include clinically acceptable hemodynamic performance confirmed by echocardiography, change in NYHA functional classification, and improvement in quality of life. The primary safety endpoint is the rate of implanted subjects that experience structural deterioration of the Model 11000A valve as determined by a Clinical Events Committee (CEC). Additional secondary safety endpoints include thromboembolism, valve thrombosis, all bleeding/major bleeding, endocarditis, all-cause mortality, valve-related mortality, valve-related reoperation, all paravalvular leak/major paravalvular leak, non-structural valve deterioration, explant, and hemolysis.

2. *OSB Lead PMA Post-Approval Study – Model 11500A Prospective PAS*: This prospective study will evaluate the safety of valve-in-valve (ViV) procedures within the INSPIRIS RESILIA aortic valve and the expansion feature during these procedures and at 30 days after the ViV procedure. This study will enroll 50 subjects implanted with the INSPIRIS RESILIA valve, experiencing aortic bioprosthetic valve failure and treated with implantation of a transcatheter aortic valve. These subjects will be enrolled in at least 10 centers with high transcatheter aortic valve replacement (TAVR) procedure volumes. Subjects will be followed through 3 months after the ViV procedure. The effectiveness endpoints are defined as the expansion of the area of the INSPIRIS RESILIA valve during the TAVR procedure, early post-procedure, and at 3 months using imaging. The INSPIRIS RESILIA valve area will be measured at all 3 time points using multi planar reconstruction chest CT scan or other modalities capable of measuring the valve area expansion with the same accuracy and precision. The same imaging technique should be use for all three measurements – pre-, early post-, and late post-procedure. The primary safety endpoint is device- and procedural-related adverse events through 30 days after the ViV procedure.

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.