SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name:	Pulmonary valve, prosthesis, percutaneously delivered
Device Trade Name:	Edwards SAPIEN 3 Transcatheter Pulmonary Valve System with Alterra Adaptive Prestent
Device Procode:	NPV
Applicant Name and Address:	Edwards Lifesciences LLC One Edwards Way Irvine, CA 92614
Date of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P200015/S011
Date of FDA Notice of Approval:	December 16, 2021

The original PMA (P200015) of the Edwards SAPIEN 3 Transcatheter Pulmonary Valve System, which included the Edwards SAPIEN 3 Transcatheter Heart Valve System and Edwards Commander Delivery System was approved on August 31, 2020. The device was indicated for use in the management of pediatric and adult patients who have a clinical indication for intervention on a dysfunctional right ventricular outflow tract (RVOT) conduit or surgical bioprosthetic valve in the pulmonic position with ≥ moderate regurgitation and/or a mean RVOT gradient of ≥ 35 mmHg. The SSED to support this indication is available on the following FDA website and is incorporated by reference herein:

https://www.accessdata.fda.gov/cdrh_docs/pdf20/P200015B.pdf

The current supplement was submitted to introduce the Edwards Alterra Adaptive Prestent System and Edwards Pulmonic Delivery System and to expand the indications for use to include pediatric and adult patients with severe pulmonary regurgitation (PR) who have a dysfunctional native or surgically-repaired RVOT and are clinically indicated for pulmonary valve replacement.

II. INDICATIONS FOR USE

The Edwards SAPIEN 3 Transcatheter Pulmonary Valve System with Alterra Adaptive Prestent is indicated for use in the management of pediatric and adult patients with severe pulmonary regurgitation as measured by echocardiography who have a native or surgically-

repaired right ventricular outflow tract and are clinically indicated for pulmonary valve replacement.

III. CONTRAINDICATIONS

The Edwards SAPIEN 3 Transcatheter Pulmonary Valve System with Alterra Adaptive Prestent is contraindicated in patients who cannot tolerate an anticoagulation/antiplatelet regimen or who have active bacterial endocarditis or other active infections.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Edwards SAPIEN 3 Transcatheter Pulmonary Valve System with Alterra Adaptive Prestent labeling.

V. DEVICE DESCRIPTION

The Edwards SAPIEN 3 Transcatheter Pulmonary Valve System with Alterra Adaptive Prestent consists of the 29-mm Edwards SAPIEN 3 Transcatheter Heart Valve (THV), the Edwards Alterra Adaptive Prestent System, the Edwards Commander Delivery System, the Edwards Pulmonic Delivery System, the Edwards Crimper, and the Qualcrimp Crimping Accessory. During use, the Edwards Alterra Adaptive Present is first positioned within the patient's RVOT, serving as a docking adaptor for the Edwards SAPIEN 3 THV, which is subsequently deployed within the Edwards Alterra Adaptive Prestent.

Edwards SAPIEN 3 THV

The Edwards SAPIEN 3 THV, as shown in Figure 1, comprises a balloon-expandable, radiopaque, cobalt-chromium (MP35N) frame, a trileaflet bovine pericardial tissue valve, a polyethylene terephthalate (PET) internal fabric skirt, and a PET external sealing skirt for reduction of paravalvular leakage (PVL). The leaflets are treated according to the Edwards ThermaFix process. Although the Edwards SAPIEN 3 THV is available in multiple sizes, only the 29- mm valve is included in the scope of this PMA application. The Edwards SAPIEN 3 THV can be deployed using either the Edwards Commander Delivery System or the Edwards Pulmonic Delivery System.

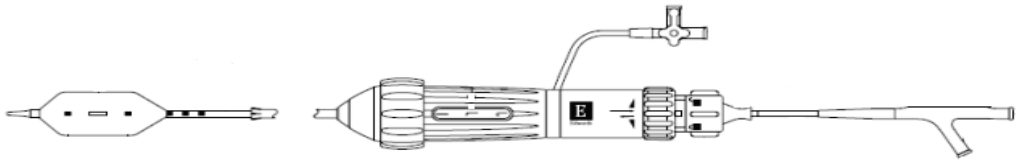
Figure 1: Edwards SAPIEN 3 Transcatheter Heart Valve

Edwards Commander Delivery System

The Edwards Commander Delivery System, as shown in Figure 2, includes a handle that

provides a flex wheel for articulation of the flex catheter, a tapered tip at the distal end, a balloon catheter for deployment of the THV, and radiopaque markers. A Loader component is used to aid insertion of the delivery system into the sheath.

Figure 2: Edwards Commander Delivery System



Edwards Pulmonic Delivery System

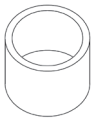
The Edwards Pulmonic Delivery System, as shown in Figure 3, consists of an inline sheath, a balloon catheter for deployment of the Edwards SAPIEN 3 THV, an outer shaft to cover the THV during insertion and tracking to the intended deployment location, and a tapered tip at the distal end to facilitate crossing of right heart structures. A 28F Dilator is used to predilate the vessel prior to insertion of the delivery system, if necessary.

Figure 3: Edwards Pulmonic Delivery System

Qualcrimp Crimping Accessory

The Qualcrimp Crimping Accessory, as shown in Figure 4, is a non-patient contacting device that is placed around the THV to protect the leaflets during the crimping process. It is manufactured of tubular polyester polyurethane foam and laminated cylindrically on both the inner and outer surfaces with a polyether urethane material.

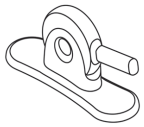
Figure 4: Qualcrimp Crimping Accessory



Edwards Crimper

The Edwards Crimper, as shown in Figure 5, is composed of various molded plastic components and is used to compress the SAPIEN 3 THV to a controlled aperture. The aperture is created by rotating the handle until it abuts the Crimp Stopper, a component used to ensure the THV is crimped correctly.

Figure 5: Edwards Crimper



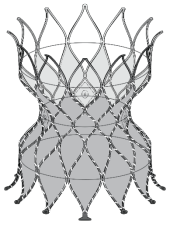
Edwards Alterra Adaptive Prestent System

The Edwards Alterra Adaptive Prestent System includes the Edwards Alterra Adaptive Prestent and Edwards Alterra Delivery System, as shown in Figure 6.

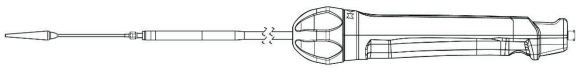
The Edwards Alterra Adaptive Prestent is used as a docking adaptor for the 29-mm SAPIEN 3 THV. It comprises a self-expanding, radiopaque, nitinol frame assembly, and PET fabric covering.

The Edwards Alterra Delivery System includes a handle which consists of a wheel that allows for deployment, two primary shafts with a flush port to flush the delivery system, and a long compliant tapered tip at the distal end to facilitate tracking through the vasculature.

Figure 6: Edwards Alterra Adaptive Prestent System



(a) Edwards Alterra Adaptive Prestent



(b) Edwards Alterra Delivery System

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the correction of severe PR in patients with a native or surgically-repaired RVOT, including surgical placement of a right ventricle-pulmonary artery (RV-PA) conduit or a prosthetic valve and implantation of another transcatheter pulmonary valve. 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 SAPIEN 3 Transcatheter Pulmonary Valve System with Alterra Adaptive Prestent has not been marketed in the United States or any foreign country.

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:

- Death
- Allergic reaction to anesthesia, contrast media, antithrombotic therapy, device materials
- Anemia
- Angina
- Aortic root distortion
- Atelectasis
- Arrhythmia
- Arteriovenous (AV) fistula
- Blood loss requiring transfusion
- Cardiovascular or vascular injury, such as perforation or damage (dissection) of vessels, myocardium or valvular structures including rupture of the RVOT that may require intervention
- Cardiac arrest
- Cardiac failure
- Cardiogenic shock
- Chest pain/discomfort
- Conduction system injury
- Coronary flow obstruction/transvalvular flow disturbance
- Deep vein thrombosis
- Device acute migration or malposition
- Device dysfunction (regurgitation and/or stenosis)
- Device embolization
- Device thrombosis
- Dislodgement of previously implanted devices (i.e., pacing lead)
- Dyspnea
- Electrolyte imbalance
- Embolic event: air, calcific material, thrombus, device fragments
- Embolic event: device fragments
- Endocarditis
- Exercise intolerance or weakness
- Fever
- Hematoma or ecchymosis
- Hemolysis/hemolytic anemia
- Hypertension or hypotension
- Infection including incisional site infection, septicemia and endocarditis
- Inflammation
- Injury to tricuspid valve
- Mechanical failure of delivery system, and/or accessories
- Myocardial infarction
- Pain
- Pericardial effusion/cardiac tamponade

- Pleural effusion
- Pneumothorax
- Pulmonary edema
- Radiation injury
- Renal insufficiency or renal failure
- Respiratory insufficiency or respiratory failure
- Stroke/transient ischemic attack
- Syncope
- Systemic or peripheral ischemia
- Systemic or peripheral nerve injury

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

IX. SUMMARY OF PRECLINICAL STUDIES

A summary of previously reported preclinical studies on the Edwards SAPIEN 3 THV System with the Edwards Commander Delivery System can be found in the SSED for PMA P140031 (https://www.accessdata.fda.gov/cdrh_docs/pdf14/P140031B.pdf) for the aortic valve replacement indication and in the SSED for PMA P200015 (https://fda.report/PMA/P200015/20/P200015B.pdf) for the pulmonic valve replacement indication. The following additional preclinical studies were performed to support the Edwards Alterra Adaptive Prestent System and Edwards Pulmonic Delivery System.

A. Laboratory Studies

Nonclinical laboratory studies on the Edwards Alterra Adaptive Prestent System and Edwards Pulmonic Delivery System were performed in accordance with ISO 5840-1:2015, *Cardiovascular implants – Cardiac valve prostheses – Part 1: General requirements* and ISO 5840-3:2013, *Cardiovascular implants – Cardiac valve prostheses – Part 3: Heart valve substitutes implanted by transcatheter techniques*.

1. Biocompatibility

Biocompatibility assessments were completed on the Edwards Alterra Adaptive Prestent System and Edwards Pulmonic Delivery System in accordance with ISO 10993-1:2018, *Biological Evaluation of Medical Devices Part 1: Evaluation and testing within a risk management process*, and the FDA Guidance for Industry and Food and Drug Administration Staff, *Use of International Standard ISO 10993-1, "Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process.*" The required testing for each component was determined based on the nature and duration of body contact per ISO 10993-1:2018. Test articles consisted of the patient-contacting device components after exposure to all manufacturing processes, including sterilization. The biocompatibility test results for the Edwards Alterra Adaptive Prestent System and Edwards Pulmonic Delivery System are summarized in Table 1 and Table 2, respectively.

Table 1: Summary of Alterra Adaptive Prestent System Biocompatibility Assessments

Biological Effect per ISO 10993-1	Test Method	Results
Alterra Adaptive Prestent		
Cytotoxicity	Medium eluate method using human fibroblast cells	Pass
Sensitization	Guinea pig maximization test	Pass
Irritation/intracutaneous reactivity	Rabbit intracutaneous reactivity test	Pass
Acute systemic toxicity	Mouse systemic injection test	Pass
Pyrogenicity	Materials mediated rabbit pyrogenicity	Pass
Genotoxicity	Ames test – plate incorporation	Pass
	Chromosomal aberration assay	Pass
Implantation	4-week rabbit intramuscular implantation test	Pass
	90-day systemic toxicity in rabbits via intramuscular implantation	Pass
Hemocompatibility	*In vitro* hemolysis (indirect)	Pass
	In vitro hemolysis (direct method)	Pass
	Complement activation	Pass
	In vivo thrombogenicity	Pass
Physicochemical	Chemical characterization and toxicological risk assessment	Pass
Alterra Delivery System		
Cytotoxicity	Medium eluate method using human fibroblast cells	Pass
Sensitization	Guinea pig maximization test	Pass
Irritation/intracutaneous reactivity	Rabbit intracutaneous reactivity test	Pass
Acute systemic toxicity	Mouse systemic injection test	Pass
Pyrogenicity	Materials mediated rabbit pyrogenicity	Pass
Hemocompatibility	*In vitro* hemolysis (indirect)	Pass
	In vitro hemolysis (direct method)	Pass
	Complement activation	Pass

Table 2: Summary of Pulmonic Delivery System Biocompatibility Assessments

Biological Effect per ISO 10993-1	Test Method	Results
Cytotoxicity	Medium eluate method using L-929 mouse fibroblast cells	Pass
Sensitization	Guinea pig maximization test	Pass
Irritation/intracutaneous reactivity	Rabbit intracutaneous reactivity test	Pass
Acute systemic toxicity	Mouse systemic injection test	Pass
Pyrogenicity	Materials mediated rabbit pyrogenicity	Pass
Hemocompatibility	*In vitro* hemolysis (indirect)	Pass
	In vitro hemolysis (direct method)	Pass
	Complement activation	Pass
	Thrombogenicity (Yorkshire Cross pig model)	Pass

2. Bench testing

Summaries of the bench testing results for the Edwards Alterra Adaptive Prestent System and Edwards Pulmonic Delivery System are provided in Table 3 and Table 4, respectively.

Table 3: Summary of Edwards Alterra Adaptive Prestent System Bench Testing

Test	Purpose	Results
Alterra Adaptive Prestent		
Frame characterization	To characterize properties of the material and finished frame.	For characterization only
Frame corrosion and nickel ion release	To assess the potential for pitting corrosion and for the leaching of nickel ions from the frame.	Pass
Durability and migration	To assess the durability, fretting resistance, and migration resistance of the Alterra Adaptive Prestent and 29-mm SAPIEN 3 THV when deployed together.	Pass
Marker visualization and skirt integrity	To assess the radiopaque markers sewn within the Alterra component.	Pass
Finite element analysis	To investigate the strain distribution in the Alterra Adaptive Prestent.	Pass
Radial pulsatile fatigue testing	To assess the fatigue resistance of the Alterra Adaptive Prestent under cyclic radial loading for up to 600 million cycles.	Pass

Test	Purpose	Results
Magnetic resonance imaging (MRI) compatibility	To evaluate the MRI compatibility of the Alterra Adaptive Prestent.	Pass
Alterra Delivery System		
Visual inspection	To verify the external surface of the effective length of the Alterra Delivery System is free from surface defects and extraneous matter.	Pass
Dimensional inspection	To verify the working or effective dimensions of the Alterra Delivery System are met.	Pass
Hemostasis	To ensure the Alterra Delivery System maintains hemostasis.	Pass
Tensile testing	To ensure the prespecified tensile strengths of the Alterra Delivery System are met.	Pass
Corrosion testing	To ensure the Alterra Delivery System is corrosion resistant per ISO 10555-1.	Pass
Simulated use	To simulate the use of the Alterra Delivery System with the Alterra Adaptive Prestent, including loading, tracking, and deployment in a clinical setting.	Pass
Edwards Alterra Adaptive Prestent System		
Design validation study	To confirm that the user needs are met for the Alterra Adaptive Prestent System.	Pass

Table 4: Summary of Edwards Pulmonic Delivery System Bench Testing

Test	Purpose	Results
Visual inspection	To verify the Pulmonic Delivery System is free from surface defects and extraneous matter.	Pass
Dimensional inspection	To ensure the working or effective dimensions of the Pulmonic Delivery System are met.	Pass
Hemostasis	To ensure the Pulmonic Delivery System maintains hemostasis.	Pass
Tensile testing	To ensure the prespecified tensile strengths of the Pulmonic Delivery System are met.	Pass
Simulated use	To simulate the use of the Pulmonic Delivery System with the Edwards	Pass

Test	Purpose	Results
	SAPIEN 3 THV, including loading, tracking, and deployment in a clinical setting.	
Design validation study	To confirm that the user needs are met for the Edwards Pulmonic Delivery System.	Pass

B. Animal Studies

The Edwards Alterra Adaptive Prestent System was evaluated in a Good Laboratory Practice (GLP)-compliant chronic study in a porcine model, as summarized in Table 5. The results of this study demonstrated that the Edwards Alterra Delivery System delivered and deployed the Edwards Alterra Adaptive Prestent as intended and the implant showed appropriate healing. An earlier chronic study evaluated the implantation of a SAPIEN 3 THV inside an Alterra Adaptive Prestent in a porcine model, which showed that the valves were well-seated and functional with no signs of migration, embolization, thrombus, or valve dysfunction after a minimum 90-day duration.

Table 5: Summary of Alterra Adaptive Prestent System Chronic Animal Study

Description	Details
Animal model/ sample size	Ten (10) pigs.
Test Article	Edwards Alterra Adaptive Prestent System.
Technique	Transcatheter implantation of the Edwards Alterra Adaptive Prestent through the femoral vein to the pulmonary position. Native pulmonic leaflets were blocked open and valve function was completely disabled.
Results	Four (4) early deaths occurred prior to the minimum 90-day implant duration due to complications unrelated to the device. Six (6) animals survived to a minimum of 90 days.
Conclusion	All devices were delivered and implanted as intended. No clinically significant injuries to the right heart structures including the tricuspid valve and chordae were observed. A single device apex embolized and was found embedded in a branch of the pulmonary artery at explant, although no clinically significant injury to this site was discovered.

C. Sterilization

The Edwards Alterra Adaptive Prestent System is sterilized using electron beam (e-beam) radiation in accordance with ISO 11137-1:2006, *Sterilization of health care products - Radiation - Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices*, and ISO 11137-2:2013, *Sterilization of health*

care products - Radiation - Part 2: Establishing the sterilization dose, which demonstrated a sterility assurance level (SAL) of 10^{-6} under a minimum dose of 25 kGy.

The Edwards SAPIEN 3 Pulmonic Delivery System is sterilized using ethylene oxide (EO) gas per ISO 11135:2014, *Sterilization of health-care products - Ethylene oxide - Requirements for the development, validation and routine control of a sterilization process for medical devices*, ISO 11737-1:2018, *Sterilization of health care products - Microbiological methods - Part 1: Determination of a population of microorganisms on products*, and ISO 10993-7:2008, *Biological evaluation of medical devices - Part 7: Ethylene oxide sterilization residuals*, which demonstrated an SAL of 10^{-6} under 100% EO sterilization.

D. Packaging and Shelf Life

The Edwards Alterra Adaptive Prestent System components are packaged together. The Edwards Alterra Adaptive Prestent is supplied preloaded within the Edwards Alterra Delivery System, which is secured in a tray/retainer. The secured device is sealed within a Tyvek/Nylon pouch and placed in a solid bleach sulfate (SBS) shelf box. The shelf box is housed in a corrugated shipper for transport. The shelf life of all components of the Edwards Alterra Adaptive Prestent System is 2 years as demonstrated by packaging integrity and product functional testing on aged samples.

The Edwards Pulmonic Delivery System is secured in a polyethylene terephthalate glycol (PETG) tray, along with a Dilator, a 2-piece Crimp Stopper, and a Qualcrimp Crimping Accessory. A PETG retainer is then placed over the tray, and the tray is placed within a Tyvek/Nylon sealed pouch. The pouched system is placed in an SBS shelf carton, which is then placed in a corrugated shipper box for transport. The shelf life of all components of the Edwards Pulmonic Delivery System is 1 year as demonstrated by packaging integrity and product functional testing on aged samples.

X. SUMMARY OF CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of the safety and effectiveness of transcatheter pulmonary valve replacement (TPVR) with the Edwards SAPIEN 3 Transcatheter Pulmonary Valve System with Alterra Adaptive Prestent under IDE G170053 (entitled the "Alterra Clinical Study"). The data from this study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

The Alterra Clinical Study was a prospective, single-arm, multicenter study. It consisted of two cohorts, namely, the main cohort and the pulmonic delivery system (PDS) registry cohort. The main cohort comprised patients implanted with the Edwards Commander Delivery System, the enrollment of which took place between August 2017 and September 2019 at 11 investigational sites in the U.S. The main purpose of the PDS registry cohort was to evaluate the use of the Edwards Pulmonic Delivery System, which was developed later in the clinical study. The enrollment of the PDS registry cohort occurred between January 2020

and August 2020 at 13 investigational sites. The database for this PMA application reflected data collected through June 2, 2021.

The Alterra Clinical Study used an independent Data Safety Monitoring Board (DSMB) that was instructed to notify the applicant of any safety or compliance issues and a Clinical Events Committee (CEC) that was responsible for adjudicating endpoint-related events reported during the study. An independent echocardiographic core laboratory was used for standardized assessment of echocardiograms.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the Alterra Clinical Study was limited to patients who met the following inclusion criteria:

   - The candidate/candidate's legal guardian has been informed of the nature of the study, agrees to its provisions and has provided written informed consent.
   - Weight is ≥ 20 kg (44 lbs).
   - RVOT/pulmonary valve (PV) with moderate or greater PR by transthoracic echocardiogram (TTE).
   - RVOT/PV proximal and distal landing zone diameter ≥ 27 mm and ≤ 38 mm, and minimum of 35 mm from contractile tissue to lowest pulmonary artery takeoff.

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

   - Active infection requiring current antibiotic therapy (if temporary illness, patient may be a candidate 2 weeks after discontinuation of antibiotics).
   - History of or active endocarditis (active treatment with antibiotics) within the past 180 days.
   - Leukopenia (white blood cell < 2000 cells/µL), anemia (hemoglobin (Hgb) < 7 g/dL), thrombocytopenia (platelets < 50,000 cells/µL) or any known blood clotting disorder.
   - Inappropriate anatomy for introduction and delivery of Alterra or the SAPIEN 3.
   - Need for concomitant atrial septal defect or ventricular septal defect closure or other concomitant interventional procedures other than pulmonary artery or branch pulmonary artery stenting or angioplasty.
   - Interventional/surgical procedures within 30 days prior to the Alterra or valve implant procedure.
   - Any planned surgical, percutaneous coronary or peripheral procedure to be performed within the 30-day follow-up from the Alterra or valve implant procedure.
   - History of or current intravenous drug use.
   - Major or progressive non-cardiac disease resulting in a life expectancy of less than one year.
   - Known hypersensitivity to aspirin or heparin and cannot be treated with other antiplatelet and/or antithrombotic medications.

- Known hypersensitivity to nitinol, cobalt-chromium, nickel or contrast media that cannot be adequately pre-medicated.
- Currently participating in an investigational drug or another device study. [Note: Trials requiring extended follow-up for products that were investigational, but have since become commercially available, are not considered investigational devices.]
- Positive urine or serum pregnancy test in female patients of child-bearing potential.
- Renal insufficiency (creatinine > 3.0 mg/dL) and/or renal replacement therapy.

2. Follow-up Schedule

Follow-up time points included discharge, 30 days, 6 months, and annually through 5 years post procedure. Preoperative and post-operative assessments included physical assessment and medical history, laboratory measurements, imaging tests, and health surveys. Adverse events and complications were recorded at all visits.

3. Clinical Endpoints

The primary endpoint for the main cohort was THV dysfunction at 6 months defined as a non-hierarchical composite of:

- RVOT/PV reintervention
- Moderate or greater total PR via TTE
- Mean RVOT gradient ≥ 35 mmHg via TTE

A performance goal of 25% was pre-specified for the primary endpoint of the main cohort. The hypothesis for the primary endpoint was as follows:

$$H_0: \pi_{Alterra} \geq 25\%$$
$$H_A: \pi_{Alterra} < 25\%$$

where π_{Alterra} represented the composite event rate at 6 months. If the upper limit of the two-sided 95% confidence interval for the composite event was less than 25%, the performance goal would be met. The hypothesis was tested at a one-sided significance level of 0.025.

The primary endpoint for the PDS registry cohort was acute PDS success, defined as a non-hierarchical composite of:

- Single THV implanted in the desired location.
- Right ventricular (RV)-pulmonary artery (PA) peak-to-peak gradient < 35 mmHg post-THV implantation.
- Less than moderate total PR by discharge TTE (or earliest evaluable TTE).
- Free of SAPIEN 3/Alterra explant at 24 hours post-implantation.

The primary endpoint for the PDS registry cohort was analyzed descriptively.

Other outcome measures for the main cohort included:

- Technical success at exit from the procedure room, defined as a composite of:
  - Alive, and
  - Successful access, delivery, and retrieval of the Alterra Delivery System, and
  - Successful access, delivery, and retrieval of the SAPIEN 3 delivery system, and
  - Single Alterra deployed in the desired location, and
  - Single THV implanted in the desired location within the Alterra (staged procedures allowed), and
  - No need for additional unplanned or emergency surgery or intervention related to the device or access procedure.
- Device success at 30 days and 6 months, defined as a composite of:
  - Alive, and
  - Original intended device(s) in place, and
  - No additional surgical or interventional procedures related to access or the device since completion of the original procedure (i.e., exit from the procedure room), and
  - Intended performance of the device:
    - Structural performance: no migration, embolization, fracture, detachment, hemolysis, thrombosis (including reduced leaflet mobility if detected) or endocarditis, and
    - Hemodynamic performance: net pulmonary valve peak gradient < 35 mmHg and transvalvular PR ≤ mild, and
    - Absence of para-device complications (paravalvular regurgitation > mild, need for a permanent pacemaker, erosion, new pulmonary embolism).
- Procedure success at 30 days, defined as a composite of:
  - Device success, and
  - No device or procedure related serious adverse events (SAEs) from the following list:
    - Life threatening bleed; major vascular or access site complications requiring unplanned reintervention or surgery; stage 2 or 3 acute kidney injury (AKI) (including new dialysis); severe heart failure or hypotension requiring intravenous inotrope, ultrafiltration or mechanical circulatory support; prolonged intubation > 48 hours.
- THV hemodynamic function.
- New York Heart Association (NYHA) Functional Class.
- Characterization of right ventricular remodeling.

B. Accountability of the PMA Cohorts

At the time of database lock, a total of 85 patients were enrolled in the study, including 60 in

the main cohort and 25 in the PDS registry cohort.

There were 3 different analysis populations defined in the protocol: All Treated (AT), Attempted Implant (AI), and Valve Implant (VI), as summarized in Table 6.

Table 6: Analysis Populations

Analysis Population	Definition	Number of Patients	
		Main Cohort	PDS Registry
All Treated (AT)	All patients who signed informed consent, passed screening and for whom the procedure was begun (defined as the time of vascular access – incision or puncture).	60	25
Attempted Implant (AI)	All AT patients who had an attempted implant (the introducer sheath for vascular delivery of the Alterra Adaptive Prestent was inserted).	60	25
Valve Implant (VI)	All AI patients who received and retained a SAPIEN 3 THV upon leaving the catheterization laboratory/hybrid suite.	60	25

Study visit compliance is summarized in Table 7. One patient in the main cohort had not completed the 6-month visit at the time of the database lock.

Table 7: Study Visit Compliance

	Main Cohort (N = 60)		PDS Registry (N = 25)	
	30 Days	6 Months	30 Days	6 Months
Ineligible*	0	0	1	1
Eligible	60	60	24	24
Visit completed	60 (100.0%)	59 (98.3%)	24 (100%)	23 (95.8%)

*Ineligible patients included those who had died, withdrawn, lost to follow-up, or not reached the visit window.

C. Study Population Demographics and Baseline Characteristics

The demographics and baseline characteristics of the study population are typical for a transcatheter pulmonary valve study performed in the U.S., as shown in Table 8.

Table 8: Demographics and Baseline Characteristics (AT Population)

Demographics and Baseline Characteristics	Summary Statistics*	
	Main Cohort (N = 60)	PDS Registry (N = 25)
Age - years	29.5 ± 2.14 (60)	29.1 ± 3.45 (25)
<12 years (child)	1.7% (1/60)	0.0% (0/25)
12-21 years (adolescent)	48.3% (29/60)	44.0% (11/25)
>21 years (adult)	50.0% (30/60)	56.0% (14/25)
Male sex	56.7% (34/60)	56.0% (14/25)
Weight (kg)	73.1 ± 3.05 (60)	73.7 ± 4.44 (25)
New York Heart Association (NYHA) Class		
Class I	53.3% (32/60)	37.5% (9/24)
Class II	38.3% (23/60)	45.8% (11/24)
Class III	8.3% (5/60)	16.7% (4/24)
Class IV	0.0% (0/60)	0.0% (0/24)
NYHA Class grouped		
Class I/II	91.7% (55/60)	83.3% (20/24)
Class III/IV	8.3% (5/60)	16.7% (4/24)
Primary diagnosis		
Pulmonary atresia	5.0% (3/60)	4.0% (1/25)
Pulmonary valve stenosis	23.3% (14/60)	20.0% (5/25)
Tetralogy of Fallot	70.0% (42/60)	68.0% (17/25)
Other	1.7% (1/59)	8.0% (2/25)
Secondary diagnosis		
Atrial septal defect	18.3% (11/60)	12.0% (3/25)
Coarctation of the aorta	3.3% (2/60)	4.0% (1/25)
Ventricular septal defect	30.0% (18/60)	12.0% (3/25)
Other	21.7% (13/60)	20.0% (5/25)
Most recent RVOT/PV intervention or surgery		
Pericardial/transannular patch	65.0% (39/60)	60.0% (15/25)
Valvuloplasty alone	25.0% (15/60)	20.0% (5/25)
Other†	10.0% (6/60)	20.0% (5/25)

*Continuous measures - mean ± SD (total no.); categorical measures - % (no./total no.)
†Tetralogy of Fallot repairs, unspecified RVOT/PV procedures, or none.

The breakdowns of prior cardiac interventions by patient age in the AT population are shown in Table 9 for the main cohort and Table 10 for the PDS registry cohort.

Table 9: Prior Cardiac Interventions by Age Group (AT Population) - Main Cohort

Most Recent RVOT/PV Intervention or Surgery	Summary Statistics*		
	<12 Years (N = 1)	12-21 Years (N = 29)	≥22 Years (N = 30)
Pericardial/transannular patch	100.0% (1/1)	82.8% (24/29)	46.7% (14/30)
Valvuloplasty alone	0.0% (0/1)	17.2% (5/29)	33.3% (10/30)
Other	0.0% (0/1)	0.0% (0/29)	20.0% (6/30)
Tetralogy of Fallot repairs	0.0% (0/0)	0.0% (0/0)	66.7% (4/6)
Unspecified RVOT/PV procedure	0.0% (0/0)	0.0% (0/0)	16.7% (1/6)
None	0.0% (0/0)	0.0% (0/0)	16.7% (1/6)

*Event rate (no./total no.)

Table 10: Prior Cardiac Interventions by Age Group (AT Population) - PDS Registry

Most Recent RVOT/PV Intervention or Surgery	Summary Statistics*	
	12-21 Years (N = 11)	≥ 22 Years (N = 14)
Pericardial/transannular patch	72.7% (8/11)	50.0% (7/14)
Valvuloplasty alone	18.2% (2/11)	21.4% (3/14)
Other	9.1% (1/11)	28.6% (4/14)
Tetralogy of Fallot repairs	100.0% (1/1)	25.0% (1/4)
Unspecified RVOT/PV procedure	0.0% (0/1)	50.0% (2/4)
None	0.0% (0/1)	25.0% (1/4)

*Event rate (no./total no.)

D. Safety and Effectiveness Results

1. Primary Endpoint

The primary endpoint result for the main cohort is presented in Table 11. The rate of THV dysfunction at 6 months was 0% (two-sided 95% confidence interval: 0.0% to 6.1%). Since the upper limit of the two sided 95% confidence interval for the primary endpoint event rate was < 25%, the endpoint was met.

Table 11: Primary Endpoint Result - Main Cohort

Endpoint	Summary Statistics* (N = 60)	95% Confidence Interval†	Less Than Prespecified Performance Goal (25%)?
THV dysfunction‡	0.0% (0/59)	[0.0%, 6.1%]	Yes
RVOT/PV reintervention	0.0% (0/60)		
Moderate or greater pulmonary regurgitation	0.0% (0/59)		
Mean RVOT gradient ≥35 mmHg	0.0% (0/59)		

*Event rate (no./total no.)
†One patient did not have evaluable echocardiogram data.
‡Two-sided 95% confidence interval.

The primary endpoint result for the PDS registry cohort is presented in Table 12. Acute PDS success was achieved in 88.0% of the patients.

Table 12: Primary Endpoint Result - PDS Registry

Endpoint	Summary Statistics* (N = 25)
Acute PDS success	88.0% (22/25)
Single THV implanted in the desired location	100.0% (25/25)
RV-PA peak-to-peak gradient < 35 mmHg post implantation	100.0% (25/25)
Less than moderate PR by discharge TTE (or earliest evaluable TTE)	88.0% (22/25)
Free of explant at 24 hours post implantation	100.0% (25/25)

*Event rate (no./total no.)

2. Additional Outcome Measures

Technical Success

Technical success at exit from the procedure room was achieved in 96.7% of the patients in the main cohort, as summarized in Table 13.

Table 13: Technical Success Result - Main Cohort

Endpoint	Summary Statistics* (N = 60)
Technical Success	96.7% (58/60)
Alive	100.0% (60/60)
Successful access delivery and retrieval of the Alterra delivery system	100.0% (60/60)

Endpoint	Summary Statistics* (N = 60)
Successful access delivery and retrieval of the SAPIEN 3 delivery system	100.0% (60/60)
Single Alterra deployed in the desired location	100.0% (60/60)
Single SAPIEN 3 valve deployed to the desired location	96.7% (58/60)
No need for unplanned or emergency surgery or intervention related to the device or access procedure	100.0% (60/60)

*Event rate (no./total no.)

Device Success

The device success rate in the main cohort was 88.3% at 30 days and 76.3% at 6 months, as summarized in Table 14.

Table 14: Device Success Result - Main Cohort

Endpoint	Summary Statistics*	
	30 Days (N = 60)	6 Months (N = 59)
Device Success	88.3% (53/60)	76.3% (45/59)
Alive	100.0% (60/60)	100% (59/59)
No device explant	100.0% (60/60)	100% (59/59)
No additional surgical or interventional procedures related to access or the device since completion of the original procedure	100.0% (60/60)	100% (59/59)
Intended performance of the device†	88.3% (53/60)	76.3% (45/59)
Structural performance‡	90.0% (54/60)	76.3% (45/59)
Hemodynamic performance	100.0% (60/60)	100% (59/59)
Absence of para-device complications	98.3% (59/60)	100% (59/59)

*Event rate (no./total no.)

†Intended performance of the device is defined as a composite of: (1) structural performance - no migration, embolization, fracture, thrombosis (including reduced leaflet mobility if detected) or endocarditis; (2) hemodynamic performance - net pulmonary valve peak gradient ≤ 35mmHg and transvalvular PR ≤ mild; and (3) Absence of para-device complications – pulmonary valve regurgitation > mild, need for a permanent pacemaker, or new pulmonary embolism.

‡The structural performance events included 4 Alterra Prestent fracture events, 1 SAPIEN 3 THV thrombosis event, 1 Alterra Prestent thrombosis event, and 1 Alterra Prestent migration event at 30 days and an additional 8 Alterra Prestent fracture events at 6 months. Multiple events occurred on one patient are counted as one.

Procedural Success

Procedural success was met in 88.3% of patients in the main cohort at 30 days, as summarized in Table 15.

Table 15: Procedural Success Result - Main Cohort

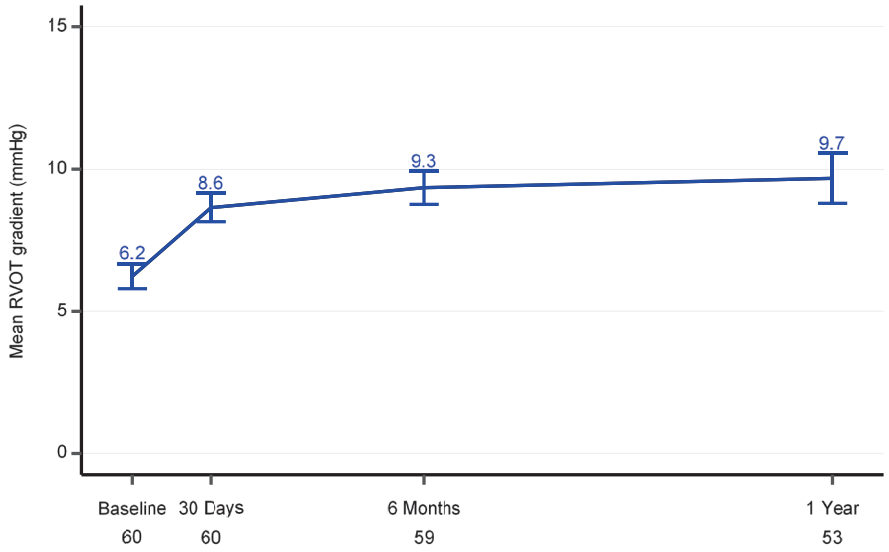
Endpoint	Summary Statistics* (N = 60)
Procedure Success	88.3% (53/60)
Device success	88.3% (53/60)
No device or procedure related SAEs†	100.0% (60/60)

*Event rate (no./total no.)
†SAEs: life threatening bleed; major vascular or access site complications requiring unplanned reintervention or surgery; stage 2 or 3 acute kidney injury (including new dialysis); severe heart failure or hypotension requiring intravenous inotrope, ultrafiltration or mechanical circulatory support; prolonged intubation > 48 hours.

THV Hemodynamic Function

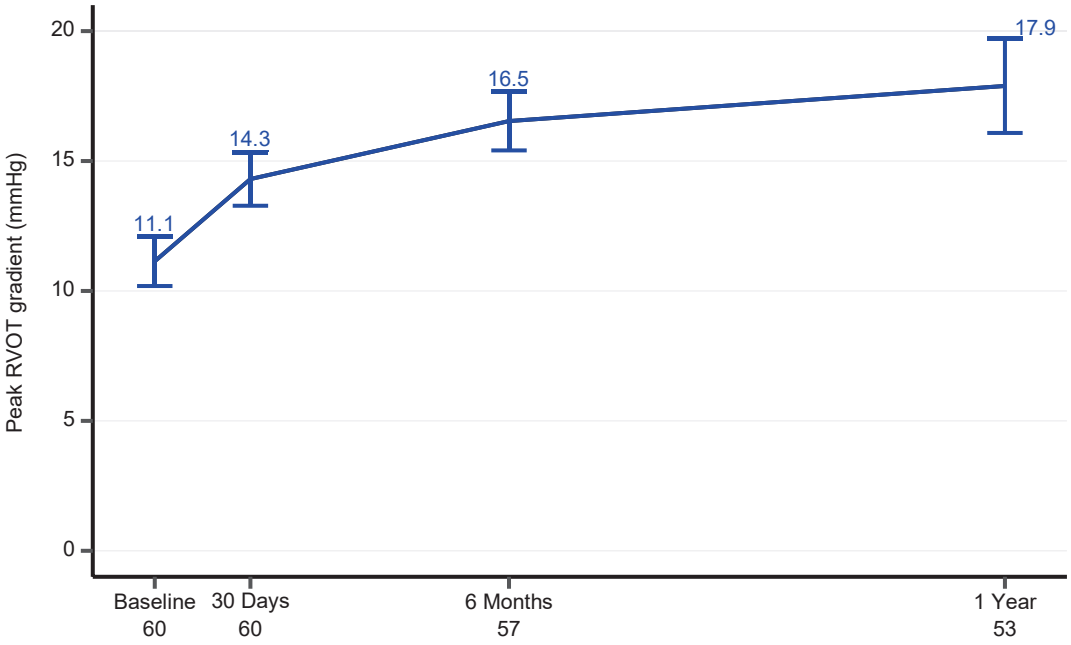
The mean RVOT gradient, peak RVOT gradient, total PR, and paravalvular regurgitation results through 1 year for the main cohort are shown in Figure 7 through Figure 10, respectively. The mean and peak RVOT gradients remained largely stable through 1 year post implant (9.7 mmHg and 17.9 mmHg, respectively, at 1 year). The proportion of patients with total PR ≥ moderate decreased from 100% to 9.6% at 1 year. The proportion of patients with paravalvular regurgitation ≥ moderate was 1.7% at 30 days and 0% at both 6 months and 1 year.

Figure 7: Mean RVOT Gradient (VI Population) - Main Cohort



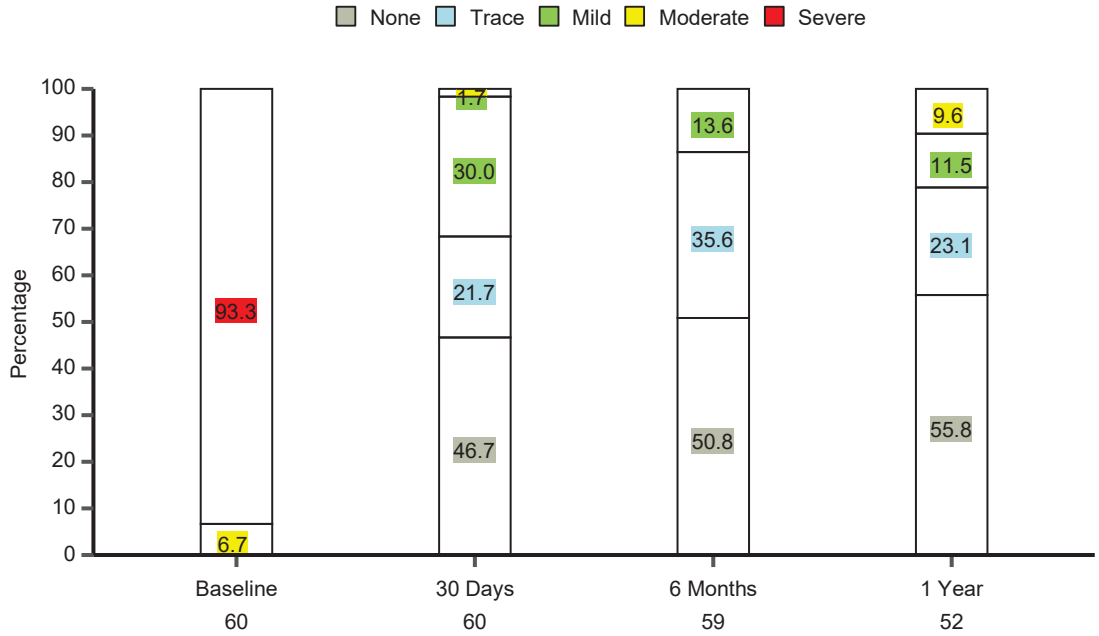
Note: Line plot with mean and standard error. The total number of patients at each visit time point only counted the patients with evaluable values.

Figure 8: Peak RVOT Gradient (VI Population) - Main Cohort



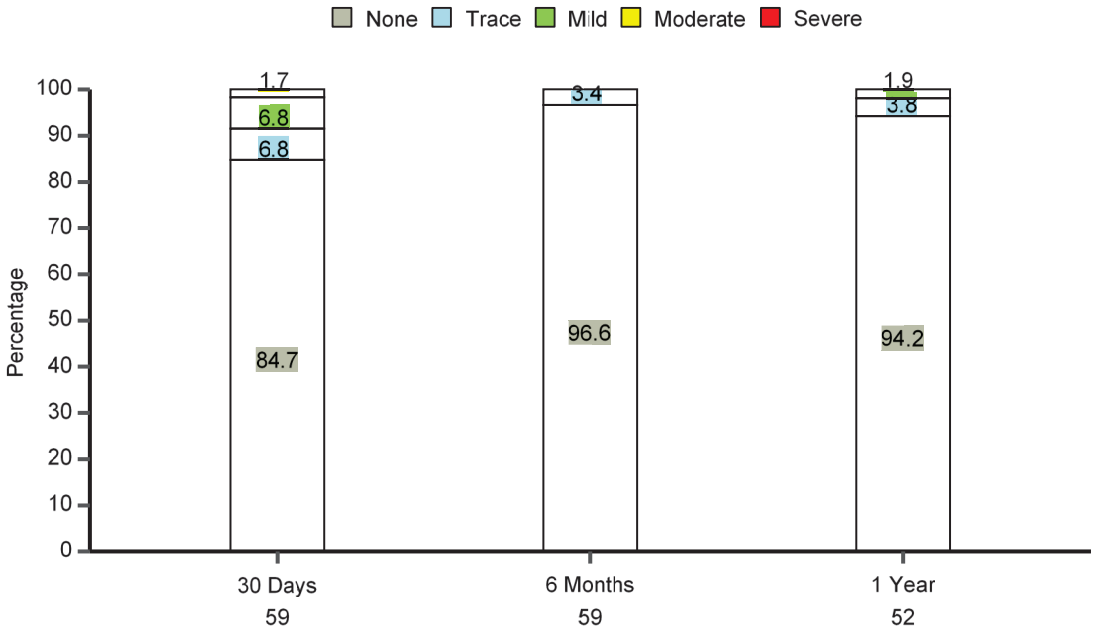
Note: Line plot with mean and standard error. The total number of patients at each visit time point only counted the patients with evaluable values.

Figure 9: Total Pulmonary Regurgitation (VI Population) - Main Cohort



Note: The total number of patients at each visit time point only counted the patients with evaluable values.

Figure 10: Paravalvular Regurgitation (VI Population) - Main Cohort

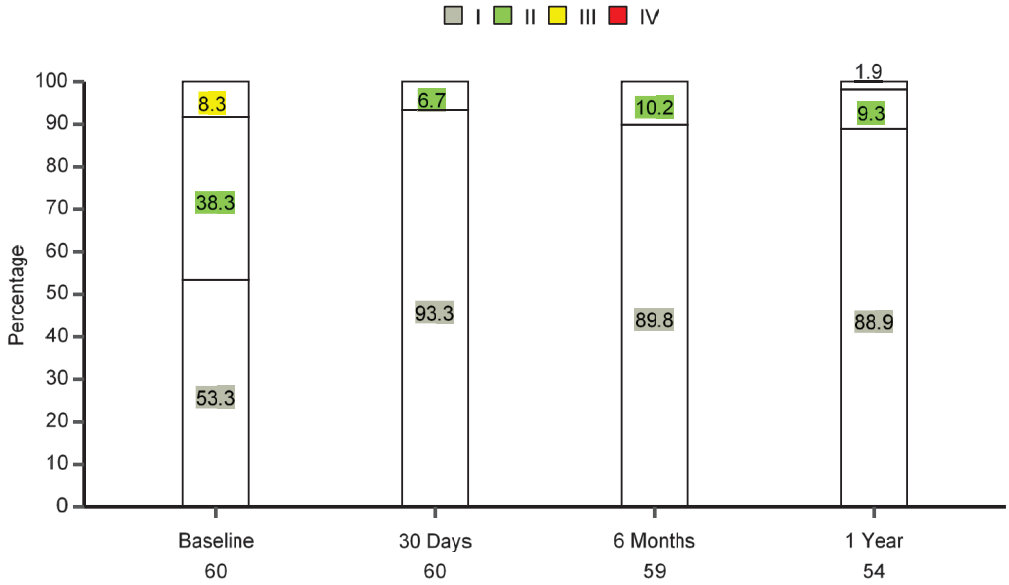


Note: The total number of patients at each visit time point only counted the patients with evaluable values.

NYHA Functional Class

The NYHA classifications by visit are presented for the main cohort in Figure 11. At baseline, 91.7% of patients in the main cohort were in NYHA Class I/II, which increased to 100% at 30 days and 6 months and 98.1% at 1 year.

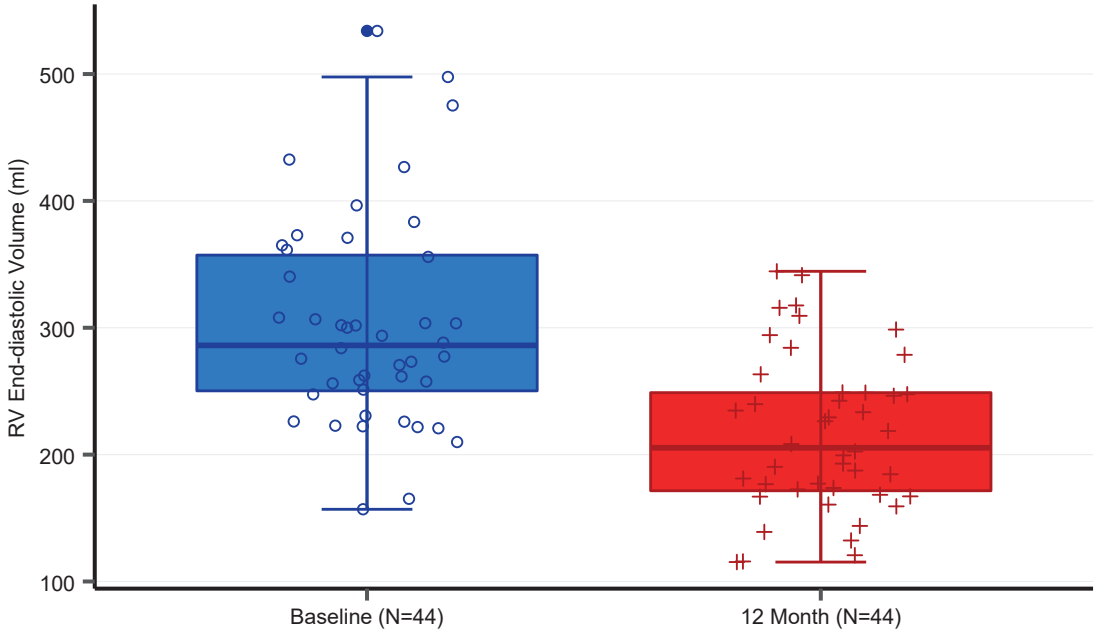
Figure 11: NYHA Class by Visit (VI Population) - Main Cohort



Characterization of Right Ventricular Remodeling

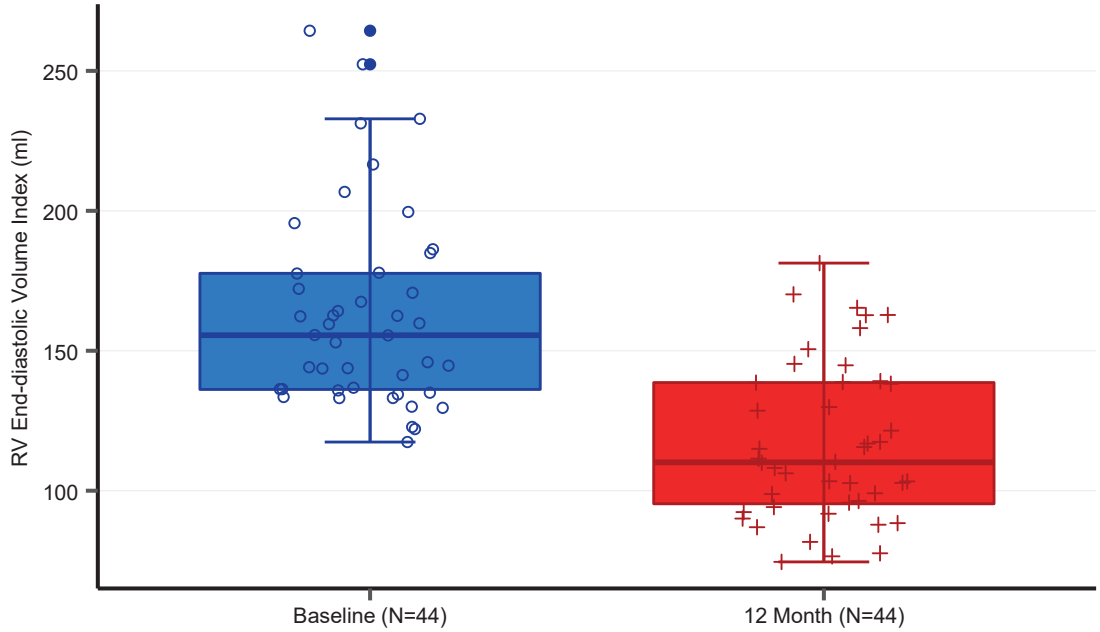
Right ventricular remodeling was characterized via magnetic resonance imaging (MRI) and computed tomography (CT) in the main cohort. Right ventricular end diastolic volume (RVEDV), RVEDV index, and main pulmonary artery regurgitant fraction at baseline and 1 year are presented in Figure 12 through Figure 14, respectively. The RVEDV decreased from 295.9 ml to 220.4 ml, with the corresponding RVEDV index decreasing from 162.7 ml/m^2 to 118.9 ml/m^2. The main pulmonary artery regurgitant fraction decreased from 47.4% to 4.1%.

Figure 12: Right Ventricular End Diastolic Volume (VI Population) - Main Cohort



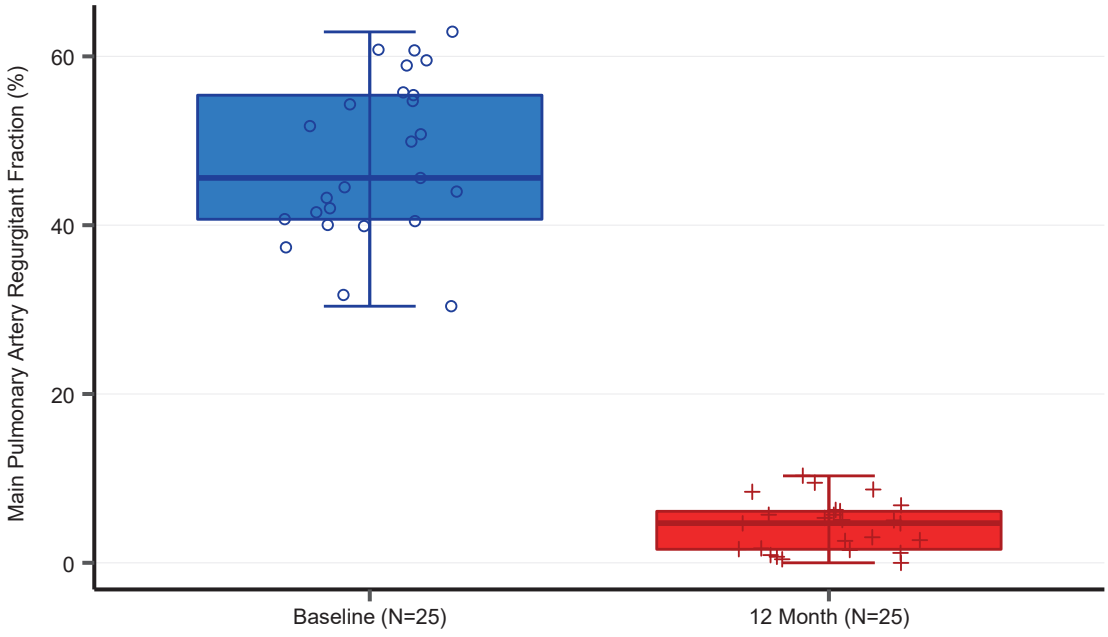
Note: The total number of patients at each visit time point only counted the patients with evaluable paired values.

Figure 13: Right Ventricular End Diastolic Volume Index (VI Population) - Main Cohort



Note: The total number of patients at each visit time point only counted the patients with evaluable paired values.

Figure 14: Main Pulmonary Artery Regurgitant Fraction (VI Population) - Main Cohort



Note: The total number of patients at each visit time point only counted the patients with evaluable paired values.

3. Adverse Events

Kaplan-Meier estimates of the CEC-adjudicated adverse events through 1 year for the main cohort and through 6 months for the PDS registry cohort are presented in Table 16 and Table 17, respectively.

Table 16: CEC-Adjudicated Adverse Events Through 1 Year (AT Population) - Main Cohort

Event	Summary Statistics*		
	30 Days (N = 60)	6 Months (N = 59)	1 Year (N = 49)
All-cause death	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)
Reintervention	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)
Arrhythmia	33.3% (21, 20)	33.3% (21, 20)	33.3% (21, 20)
Permanent pacemaker	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)
Acute kidney injury	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)
Bleeding	18.3% (12, 11)	21.7% (14, 13)	23.5% (16, 14)
Life threatening or disabling	0.0% (0, 0)	1.7% (1, 1)	3.5% (2, 2)
Major	1.7% (1, 1)	1.7% (1, 1)	1.7% (1, 1)
Minor	16.7% (11, 10)	18.4% (12, 11)	20.1% (13, 12)
Coronary artery compression	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)
Endocarditis	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)
Myocardial infarction	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)
Pulmonary embolism	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)
Stroke	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)
Transient ischemic attack	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)
Vascular injury or access site complication	5.0% (3, 3)	5.0% (3, 3)	6.8% (4, 4)
Major	0.0% (0, 0)	0.0% (0, 0)	1.8% (1,1)
Minor	5.0% (3, 3)	5.0% (3, 3)	5.0% (3, 3)

*Kaplan-Meier estimate (no. events, no. patients with event)

Table 17: CEC-Adjudicated Adverse Events Through 6 Months (AT Population) - PDS Registry

Event	Summary Statistics*	
	30 Days (N = 24)	6 Months (N = 24)
All-cause death	4.0% (1, 1)	4.0% (1, 1)
Cardiovascular	0.0% (0, 0)	0.0% (0, 0)
Non-Cardiovascular	4.0% (1, 1)	4.0% (1, 1)
Reintervention	0.0% (0, 0)	0.0% (0, 0)
Arrhythmia	48.0% (15, 12)	48.0% (15, 12)

Event	Summary Statistics*	
	30 Days (N = 24)	6 Months (N = 24)
Permanent pacemaker	0.0% (0, 0)	0.0% (0, 0)
Acute kidney injury	0.0% (0, 0)	0.0% (0, 0)
Bleeding	20.0% (6, 5)	20.0% (6, 5)
Life threatening or disabling	0.0% (0, 0)	0.0% (0, 0)
Major	0.0% (0, 0)	0.0% (0, 0)
Minor	20.0% (6, 5)	20.0% (6, 5)
Coronary artery compression	0.0% (0, 0)	0.0% (0, 0)
Endocarditis	0.0% (0, 0)	0.0% (0, 0)
Myocardial infarction	0.0% (0, 0)	0.0% (0, 0)
Pulmonary embolism	0.0% (0, 0)	0.0% (0, 0)
Stroke	0.0% (0, 0)	0.0% (0, 0)
Transient ischemic attack	0.0% (0, 0)	0.0% (0, 0)
Vascular injury or access site complication	8.0% (4, 2)	8.0% (4, 2)
Major	0.0% (0, 0)	0.0% (0, 0)
Minor	8.0% (4, 2)	8.0% (4, 2)

*Kaplan-Meier estimate (no. events, no. patients with event)

4. Other Study Observations

Procedural Information

Procedural data for the main cohort and PDS registry cohort are summarized in Table 18. Concomitant Alterra Adaptive Prestent and SAPIEN 3 THV procedures were performed on the majority of patients (98.3% for the main cohort and 100% for PDS registry cohort).

Table 18: Procedural Data (AT Population)

Variable	Summary Statistics*	
	Main Cohort (N = 60)	PDS Registry (N = 25)
Procedure type		
Staged procedure	1.7% (1/60)	0.0% (0/25)
Prestent procedure sheath time (min)	61.0	N/A
SAPIEN 3 procedure sheath time (min)	23.0	N/A
Concomitant Alterra Adaptive Prestent + SAPIEN 3 THV procedure	98.3% (59/60)	100.0% (25/25)
Procedure sheath time (min)	66.8 ± 4.73 (59)	58.2 ± 8.42 (25)
Alterra Adaptive Prestent procedure complications	3.3% (2/60)	0.0% (0/25)

Variable	Summary Statistics*	
	Main Cohort (N = 60)	PDS Registry (N = 25)
SAPIEN 3 procedure complications	10.0% (6/60)	8.0% (2/25)
Total fluoroscopy time	37.2 ± 3.04 (60)	38.0 ± 4.88 (25)
Alterra Adaptive Prestent procedure post-dilatation performed	0.0% (0/60)	0.0% (0/25)
SAPIEN 3 procedure post-dilatation performed	11.7% (7/60)	0.0% (0/25)
Alterra Prestent implanted in the intended location at the time the patient left the procedure room	100.0% (60/60)	100.0% (25/25)
SAPIEN 3 THV implanted in the intended location at the time the patient left the procedure room	100.0% (60/60)	100.0% (25/25)
Single SAPIEN 3 THV implanted	96.7% (58/60)	100.0% (25/25)

*Continuous measures - Mean ± SD (total no.); categorical measures - % (no./total no.)

CT Core Laboratory Findings

The results of an imaging assessment by the CT Core Laboratory through 1 year for the main cohort and through 30 days for the PDS registry cohort are presented in Table 19 and Table 20, respectively. There were no device reinterventions associated with these findings.

Table 19: CT Core Laboratory Findings (VI Population) – Main Cohort

Finding	Summary Statistics*	
	30 Days (N = 60)	1 Year (N = 55)
Alterra Adaptive Prestent penetration†		
Minor penetration - into adjacent vasculature or cardiac structure without extravasation, pseudoaneurysm, or erosion	2.6% (1/39)	5.2% (1/19)
Major penetration - protrusion into surrounding tissue with blood pooling, or erosion, or pseudoaneurysm	0.0% (0/39)	0.0% (0/19)
Pedunculated mobile mass†	2.6% (1/39)	0.0% (0/19)
Alterra Adaptive Prestent fracture‡		
Fracture not requiring intervention	6.7% (4/60)	21.8% (12/55)
Fracture requiring intervention	0.0% (0/60)	0.0% (0/55)
SAPIEN 3 valve frame fracture‡	0.0% (0/60)	0.0% (0/55)

*Rate (no./total no.)
†Only included patients with evaluable images at visit time point.
‡Fracture was determined by either chest x-ray or fluoroscopy.

Table 20: CT Core Laboratory Findings (VI Population) – PDS Registry

Finding	Summary Statistics*
	30 Days (N = 25)
Alterra Adaptive Prestent penetration†	
Minor penetration - into adjacent vasculature or cardiac structure without extravasation, pseudoaneurysm, or erosion	8.7% (2/23)
Major penetration - protrusion into surrounding tissue with blood pooling, or erosion, or pseudoaneurysm	0.0% (0/23)
Pedunculated mobile mass†	4.3% (1/23)
Alterra Adaptive Prestent fracture‡	
Fracture not requiring intervention	20.0% (5/25)
Fracture requiring intervention	0.0% (0/25)
SAPIEN 3 valve frame fracture‡	0.0% (0/25)

*Rate (no./total no.)
†Only included patients with evaluable images at visit time point.
‡Fracture was determined by either chest x-ray or fluoroscopy.

5. 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 conduction clinical studies covered by the regulation. The Alterra Clinical Study involved 43 investigators of which none were full-time or part-time employees of the sponsor and 15 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: 15
- 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 Devices 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 THE PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

In the clinical study, 100% of the patients in the main cohort were free from THV dysfunction at 6 months post implant, with no RVOT/PV reintervention, moderate or greater total PR, or mean RVOT gradient ≥ 35 mmHg. The proportion of patients with severe PR decreased from 93.3% at baseline to 0% at 6 months. Positive changes in right ventricular function were seen post implant, as evidenced by the reduction in the mean right ventricular end diastolic volume (RVEDV: 295.9 to 220.4 ml; RVEDV index: 162.7 to 118.9 ml/m^2) and decrease in main pulmonary artery regurgitant fraction (47.4% to 4.1%) from baseline to 6 months.

In the main cohort, technical success was achieved in 96.7% of the patients at exit from the procedure room; device success was achieved in 88.3% of the patients at 30 days and 76.3% of the patients at 6 months; and procedural success was achieved in 88.3% of patients at 30 days. In the PDS registry cohort, acute device success was met in 88.0% of the patients.

All patients in the main cohort were NYHA functional class I/II (I: 89.8%; II: 10.2%) at 6 months compared to 91.7% (I: 53.3%; II: 38.3%) of patients at baseline, with more patients in class I post implant.

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 nonclinical laboratory (e.g., biocompatibility, hydrodynamic performance, durability, and structural integrity) and animal studies demonstrated that the Edwards Alterra Adaptive Prestent and Edwards SAPIEN 3 THV are suitable for long-term implant.

In the Alterra Clinical Study, there were no deaths at 6 months in the main cohort. The most frequent adverse event observed at 6 months in the main cohort was arrhythmia (33.3%), followed by bleeding (21.7%, including 18.4% minor bleeding), and minor vascular injury or access site complication (5.0%).

C. Benefit-Risk Determination

The probable benefits of TPVR with the Edwards SAPIEN 3 Transcatheter Pulmonary Valve System with Alterra Adaptive Prestent demonstrated in the Alterra Clinical Study include

improved RVOT/PV hemodynamics and patient functional status as measured by the NYHA classification at 6 months post implant. These improvements may delay the need for surgical replacement of the patient's dysfunctional RVOT/PV. For patients that require multiple reoperations over a lifetime, with incremental increases in risk of surgical morbidity and mortality with each reoperation, TPVR with the Edwards SAPIEN 3 Transcatheter Pulmonary Valve System with Edwards Alterra Adaptive Prestent may reduce the cumulative risks associated with such operations.

The probable risks of TPVR with the Edwards SAPIEN 3 Transcatheter Pulmonary Valve System with Alterra Adaptive Prestent include arrhythmia, bleeding, vascular injury or access site complications, and THV dysfunction.

1. Patient Perspectives

   This application did not include specific information on patient perspectives for TPVR with the Edwards SAPIEN 3 Transcatheter Pulmonary Valve System with Alterra Adaptive Prestent.

In conclusion, given the available information above, the data support that for patients with severe PR who have a native or surgically-repaired RVOT, the probable benefits of the Edwards SAPIEN 3 Transcatheter Pulmonary Valve System with Alterra Adaptive Prestent outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of the Edwards SAPIEN 3 Transcatheter Pulmonary Valve System with Alterra Adaptive Prestent for the management of pediatric and adult patients with severe PR who have a native or surgically-repaired right ventricular outflow tract and are clinically indicated for pulmonary valve replacement.

XIII. CDRH DECISION

CDRH issued an approval order on December 16, 2021. The final conditions of approval cited in the approval order are described below.

The applicant must conduct two post-approval studies:

1. **Continued Follow-up of the Alterra IDE Cohort**: This study will be conducted in accordance with the protocol, entitled, "Post-Approval Data Analysis Protocol: Continued Follow-up of IDE Cohorts", dated December 3, 2021. The study will consist of 119 patients enrolled in the IDE study (including the Continued Access Protocol investigation). The objective of the study is to characterize the clinical outcomes annually through 10 years post implant. The safety and effectiveness endpoints include RVOT/PV reintervention, THV hemodynamic function, and adverse events (including device frame fracture).

2. **Alterra New Enrollment Study:** This study will be conducted in accordance with the protocol, entitled, "Multicenter Post-Approval Study of Congenital Pulmonic Valve Dysfunction Studying the Edwards SAPIEN 3 Transcatheter Pulmonary Valve System with Alterra Adaptive Prestent", dated November 30, 2021. The study will enroll 150 patients at up to 25 sites in the U.S. The objective of the study is to characterize the real-world performance of the Edwards SAPIEN 3 Transcatheter Pulmonary Valve System with Edwards Alterra Adaptive Prestent through 10 years post implant. The safety and effectiveness endpoints include acute device success, THV dysfunction, echocardiographic assessments, NYHA functional class, and adverse events device (including device frame fracture).

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 final approved labeling (Instructions for Use).

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the final labeling (Instructions for Use).

Post-approval Requirements and Restrictions: See Approval Order.