SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name:	Prosthesis, Mitral Valve, Percutaneously Delivered
Device Trade Name:	Edwards SAPIEN 3 and SAPIEN 3 Ultra Transcatheter Heart Valve System
Device Procode:	NPU
Applicant Name and Address:	Edwards Lifesciences LLC One Edwards Way Irvine, CA 92614
Date of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P140031/S125
Date of FDA Notice of Approval:	May 13, 2021

The original PMA (P140031) for the Edwards SAPIEN 3 Transcatheter Heart Valve (THV) System was approved on June 17, 2015, with an indication for patients deemed to be at high or greater risk for surgical aortic valve replacement (SAVR). The indication was later expanded in PMA Supplement P140031/S010 on August 18, 2016, to include patients deemed to be at intermediate risk for SAVR. The indication was further expanded in PMA Supplement P140031/S028 on June 5, 2017, to include patients with a failing (stenosed, insufficient, or combined) surgical bioprosthetic aortic or mitral valve who are deemed to be at high or greater risk for redo SAVR. In PMA Supplement P140031/S085, which was approved on August 16, 2019, the indication of the SAPIEN 3 and SAPIEN 3 Ultra THV System was expanded to include patients deemed to be at low risk for SAVR. More recently, in PMA Supplement P140031/S112, which was approved on September 9, 2020, the indication of the SAPIEN 3 and SAPIEN 3 Ultra THV System was expanded to include patients with a failing (stenosed, insufficient, or combined) transcatheter bioprosthetic aortic valve who are deemed to be at high or greater risk for redo SAVR.

The SSEDs to support the above indications are available on the following FDA websites and are incorporated by reference herein:

https://www.accessdata.fda.gov/cdrh_docs/pdf14/P140031b.pdf
https://www.accessdata.fda.gov/cdrh_docs/pdf14/P140031S010b.pdf
https://www.accessdata.fda.gov/cdrh_docs/pdf14/P140031S028b.pdf
https://www.accessdata.fda.gov/cdrh_docs/pdf14/P140031S085B.pdf
https://www.accessdata.fda.gov/cdrh_docs/pdf14/P140031S112B.pdf

The current Panel Track PMA Supplement is to expand the indication of the Edwards SAPIEN 3 and SAPIEN 3 Ultra THV System to include patients with a failing native mitral valve with an annuloplasty ring (i.e., valve-in-ring) who are deemed to be at high or greater risk for open surgical therapy.

II. INDICATIONS FOR USE

The Edwards SAPIEN 3 and SAPIEN 3 Ultra THV System is indicated for patients with symptomatic heart disease due to failing (stenosed, insufficient, or combined) of a surgical or transcatheter bioprosthetic aortic valve, a surgical bioprosthetic mitral valve, or a native mitral valve with an annuloplasty ring who are judged by a heart team, including a cardiac surgeon, to be at high or greater risk for open surgical therapy (i.e., predicted risk of surgical mortality ≥ 8% at 30 days, based on the Society of Thoracic Surgeons (STS) risk score and other clinical co-morbidities unmeasured by the STS risk calculator).

III. CONTRAINDICATIONS

The Edwards SAPIEN 3 and SAPIEN 3 Ultra THV System are contraindicated in patients who cannot tolerate an anticoagulation/antiplatelet regimen, who have active bacterial endocarditis or other active infections, or who has significant annuloplasty ring dehiscence.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Edwards SAPIEN 3 and SAPIEN 3 Ultra THV System labeling.

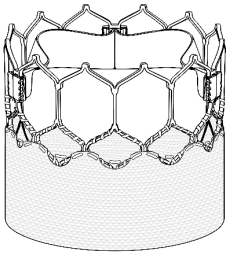
V. DEVICE DESCRIPTION

The Edwards SAPIEN 3 THV (model 9600TFX, 20, 23, 26, and 29 mm), as shown in Figure 1, is comprised of 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 regurgitation. The leaflets are treated according to the Carpentier-Edwards ThermaFix process. Note that the 20 mm SAPIEN 3 THV is not included in the scope of this application due to its size being too small for the mitral position.

Figure 1: SAPIEN 3 Transcatheter Heart Valve

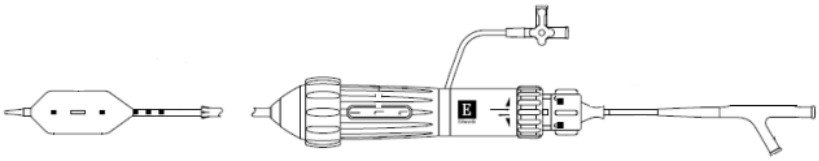
The Edwards SAPIEN 3 Ultra THV (model 9750TFX, 20, 23, and 26 mm), as shown in Figure 2, is a design iteration of the SAPIEN 3 THV, with a knitted outer skirt featuring a velour texture on one side. Note that the 20 mm SAPIEN 3 Ultra THV is not included in the scope of this application due to its size being too small for the mitral position.

Figure 2: SAPIEN 3 Ultra Transcatheter Heart Valve



The Edwards Commander Delivery System (models 9600LDS20, 9750CM20, 9600LDS23, 9750CM23, 9600LDS26, 9750CM26, and 9600LDS29), as shown in Figure 3, includes a handle that provides a flex wheel for articulation of the flex catheter, a tapered tip at the distal end of the delivery system, a balloon catheter for deployment of the THV, and radiopaque markers. It is used when a long access route is planned. The Commander Delivery System uses the Edwards eSheath Introducer Set (models 914ES and 916ES), which is an off-the-shelf device cleared in 510(k) K200258, to establish vascular access.

Figure 3: Edwards Commander Delivery System



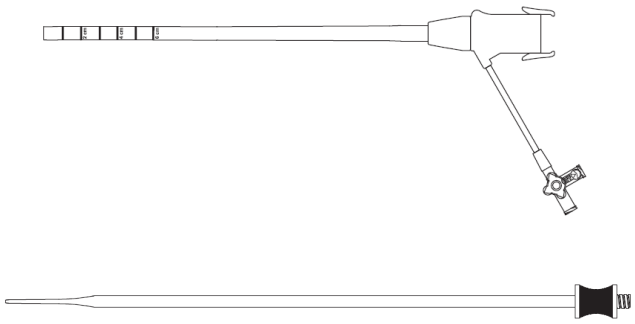
The Edwards Certitude Delivery System (models 9630TA20, 9600SDS20, 9630TA23, 9600SDS23, 9630TA26, 9600SDS26, 9630TA29, and 9600SDS29), as shown in Figure 4, includes a handle with a flex wheel for articulation of the balloon catheter and extension tubing. It is used when a short access route is planned.

Figure 4: Edwards Certitude Delivery System

The Edwards Certitude Introducer Sheath (models 9600IS18 and 9600IS21), as shown in Figure 5, is intended to be used with the Certitude Delivery System. It has a radiopaque marker for visualization of the sheath tip and non-radiopaque depth markings on the distal

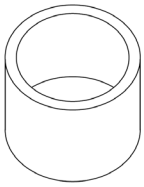
end. The proximal end of the introducer sheath includes a flush tube and three hemostasis valves.

Figure 5: Edwards Certitude Introducer Sheath



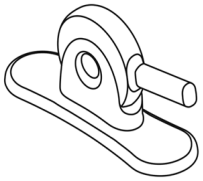
The Qualcrimp crimping accessory, as shown in Figure 6, is a non-patient contacting device that is placed around the THV to protect the leaflets during the crimping process. It is manufactured of tubular polyester polyurethane foam and laminated cylindrically on both the inner and outer surfaces with a polyether urethane material.

Figure 6: Qualcrimp Crimping Accessory



The Edwards Crimper (model 9600CR), as shown in Figure 7, is comprised of various molded plastic components which compress the valve to a controlled aperture. The aperture is created by rotating the handle until it abuts the crimp stopper. The Edwards Crimper is used with a Crimp Stopper to correctly crimp the THV.

Figure 7: Edwards Crimper



VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are other alternatives for patients with a failing native mitral valve with an annuloplasty ring, including reoperative surgical repair and replacement of the mitral valve for patients deemed surgical candidates, and palliative medical 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 SAPIEN 3 and SAPIEN 3 Ultra System has not been marketed in the United States or any foreign country for the mitral "valve-in-ring" indication.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

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

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

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

For the specific adverse events that occurred in the dataset used to support the PMA application, please see Section X.

IX. SUMMARY OF PRECLINICAL STUDIES

A summary of previously reported preclinical studies can be found in the SSEDs for the original PMA P140031 and PMA Supplement P140031/S028.

X. SUMMARY OF PRIMARY CLINICAL DATA

The applicant performed an analysis of the real-world off-label use data captured in the STS/American College of Cardiology (ACC) Transcatheter Valve Therapy (TVT) Registry and the investigational use data from the "valve-in-ring" cohort of the Mitral Implantation of Transcatheter Valves (MITRAL) study, which was a sponsor-investigator IDE (G140136), to establish a reasonable assurance of the safety and effectiveness of the Edwards SAPIEN 3 THV System in patients receiving mitral "valve-in-ring "treatment. The pooled data from these two sources were the basis of the PMA approval decision. A summary of the clinical data is presented below.

Note that the clinical dataset did not include the SAPIEN 3 Ultra THV System. However, the

results obtained on the Edwards SAPIEN 3 THV System are considered applicable to the Edwards SAPIEN 3 Ultra THV System based on prior demonstration of device comparability in PMA Supplement P140031/S074, which was the premarket application for the Edwards SAPIEN 3 Ultra THV System.

A. Study Design

A database extract from the TVT Registry was performed of all eligible patients in the registry on May 29, 2020, with a treatment cutoff date of May 28, 2019. This yielded 206 patients (SAPIEN 3 THV only) treated at 90 participating hospitals, which was pooled with 30 additional patients treated at 11 participating hospitals between February 2016 and October 2017 under the MITRAL study. While a formal poolability analysis was not conducted, the two datasets were deemed poolable because both included patients with comparable baseline characteristics, functional status, and clinical comorbidities, with similar risk for open surgical therapy. These 236 patients constituted the clinical dataset used to support this application.

1. Clinical Inclusion and Exclusion Criteria

   The database extract from the TVT Registry included all patients with a prior mitral annuloplasty ring who received a commercially available Edwards SAPIEN 3 THV. The baseline characteristics of these patients show a morbid population at high surgical risk with no other good options, as evidenced by an STS score of 9.4 ± 6.4 and 81% of the patients being in New York Heart Association (NYHA) class of III/IV.

   Enrollment in the "valve-in-ring" cohort of the MITRAL study was limited to patients who met the following inclusion criteria:

   - Patient has a failing surgical ring in the mitral position with at least moderate to severe mitral regurgitation or severe stenosis (echocardiographically derived mitral valve area [MVA] of $\leq$1.5 cm^2). Qualifying echocardiogram must be within 90 days of the date of the procedure.
   - Patient is symptomatic from mitral valve disease, as demonstrated by reported NYHA Functional Class II or greater, or symptoms during stress test, or severe hemolytic anemia requiring blood transfusions and no other cause of hemolytic anemia is found after extensive work-up.
   - The patient is at least 22 years old.
   - The heart team agrees (and verified in the case review process) that valve implantation will likely benefit the patient.
   - The heart team agrees that medical factors preclude operation, based on a conclusion that the probability of death or serious, irreversible morbidity exceeds the probability of meaningful improvement. Specifically, the STS score is ≥15% or the probability of death or serious, irreversible morbidity is ≥ 50%. The surgeons' consult notes shall specify the medical or anatomic factors leading to that conclusion and include a printout of the calculation of the STS score to additionally identify the risks in the patient. At least one of the cardiac surgeon

assessors must have physically evaluated the patient. All patients must be approved by the Patient Selection and Procedure Management Steering Committee (at least 2 member votes, one must be from a cardiac surgeon).
- The study patient has been informed of the nature of the study, agrees to its provisions and has provided written informed consent as approved by the Institutional Review Board (IRB) of the respective clinical site.
- The study patient agrees to comply with all required post-procedure follow-up visits including annual visits through 5 years and analysis close date visits, which will be conducted as a phone follow-up.

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

- Heart Team assessment of operability (the heart team considers the patient is a surgical candidate).
- Evidence of an acute myocardial infarction ≤ 1 month (30 days) before the intended treatment [defined as: Q wave myocardial infarction (MI), or non-Q wave (MI) with total creatine kinase (CK) elevation of CK-MB ≥ twice normal in the presence of MB elevation and/or troponin level elevation (World Health Organization definition)].
- Complex untreated coronary artery disease:
    - Unprotected left main coronary artery
    - Syntax score > 32 (in the absence of prior revascularization)
- Any therapeutic invasive cardiac procedure resulting in a permanent implant that is performed within 30 days of the index procedure (unless part of planned strategy for treatment of concomitant coronary artery disease). Implantation of a permanent pacemaker is not excluded.
- Any patient with a balloon mitral valvuloplasty (BMV) within 30 days of the procedure (unless BMV is a bridge to procedure after a qualifying echocardiogram).
- Patients with planned concomitant surgical or transcatheter ablation for atrial fibrillation.
- Leukopenia (white blood cell < 3000 cell/mL), acute anemia (hemoglobin < 9 g/dL), thrombocytopenia (platelet < 50,000 cell/mL).
- Hypertrophic obstructive cardiomyopathy (HOCM).
- Hemodynamic or respiratory instability requiring inotropic support, mechanical ventilation or mechanical heart assistance within 30 days of screening evaluation.
- Need for emergency surgery for any reason.
- Severe ventricular dysfunction with left ventricular ejection fraction (LVEF) < 20%.
- Echocardiographic evidence of intracardiac mass, thrombus or vegetation.
- Active upper gastrointestinal bleeding within 3 months (90 days) prior to procedure.
- A known contraindication or hypersensitivity to all anticoagulation regimens, or inability to be anticoagulated for the study procedure.

- Surgical ring with a true mean internal diameter ≤18 mm or ≥ 29 mm or an area < 275 mm^2 or > 740 mm^2 as measured by computerized tomography (CT) scan.
- Clinically (by neurologist) or neuroimaging confirmed stroke or transient ischemic attack (TIA) within 6 months (180 days) of the procedure.
- Estimated life expectancy < 24 months (730 days) due to carcinomas, chronic liver disease, chronic renal disease or chronic end stage pulmonary disease.
- Expectation that patient will not improve despite treatment of mitral stenosis.
- Active bacterial endocarditis within 6 months (180 days) of procedure.

2. Follow-up Schedule

All patients entered into the TVT Registry were followed post-implantation according to their local standards of care. The TVT Registry collects follow-up data at 30 days and 1 year. All patients enrolled in the MITRAL study were scheduled for follow-up examinations at discharge, 30 days, 6 months, 1 year, and annually thereafter to a minimum of 5 years post-procedure.

Preoperative and post-operative assessments included physical assessment and patient interview, laboratory measurements, imaging tests, and health status/quality of life (QoL) questionnaire. Adverse events and complications were recorded at all visits.

3. Clinical Endpoints

The endpoints analyzed in this application included: death, stroke/TIA, valve reinterventions, key site reported adverse events, valve performance based on echocardiographic data, NYHA classification, and the Kansas City Cardiomyopathy Questionnaire (KCCQ) score. The analyses focused on the 30-day and 1-year time points and were carried out descriptively.

B. Accountability of PMA Cohorts

At the time of database extract, 205 of the 236 patients were eligible for the 30-day visit and 178 (86.8%) completed the visit within the 30-day follow-up window, defined as the period between 21 days post-procedure and 75 days post-procedure. At 1 year, 152 patients were eligible for the 1-year visit and 103 (67.8%) completed the visit within the follow-up window, defined as the period between 305 days post-procedure and 425 days post-procedure. A detailed summary of the patient accountability at 30 days and 1 year is shown in Table 1.

Table 1. Patient Visit Accountability

	30-day Visit	1-year Visit
Total patients	236	236
Non-eligible	31	84
Death	24	54
Withdrawal	3	5

	30-day Visit	1-year Visit
Lost to follow-up	4	13
Visit not yet due	0	12
Eligible	205	152
Follow-up visit completed	86.8% (178)	67.8% (103)
Missed visit	13.2% (27)	32.2% (49)

The "Attempted Implant (AI)" population consisted of all patients in the dataset. The "Valve Implant (VI)" population consisted of those patients for whom the valve implant procedure had started and a "No" was indicated for both "procedure aborted" and "conversion to open heart surgery" in the case report form of the TVT Registry (no patients in the MITRAL study had an aborted procedure). The numbers of patients in these two analysis populations are shown in Table 2.

Table 2: Analysis Populations

Analysis Population	Number of Patients
Attempted implant population	236
Valve implant population	232

C. Study Population Demographics and Baseline Characteristics

The demographics and baseline characteristics of the patients, as shown in Table 3, represent an elderly, multimorbid cohort of patients, consistent with the high operative risk of the populations.

Table 3: Patient Demographics and Baseline Characteristics (AI Population)

Demographics and Baseline Characteristics	Summary Statistics*		
	TVT Registry (N = 206)	MITRAL Study (N = 30)	Overall (N = 236)
Age - years	72.1 ± 10.3 (206)	71.7 ± 8.9 (30)	72.1 ± 10.1 (236)
Male sex	47.6% (98/206)	63.3% (19/30)	49.6% (117/236)
Society of Thoracic Surgeons (STS) score	9.4 ± 6.4 (196)	8.7 ± 4.7 (30)	9.3 ± 6.2 (226)
New York Heart Association (NYHA) class			
I/II	18.7% (38/203)	23.3% (7/30)	19.3% (45/233)
III/IV	81.3% (165/203)	76.7% (23/30)	80.7% (188/233)
Previous myocardial infarction	30.2% (62/205)	22.2% (6/27)	29.3% (68/232)

Demographics and Baseline Characteristics	Summary Statistics*		
	TVT Registry (N = 206)	MITRAL Study (N = 30)	Overall (N = 236)
Stroke	15.0% (31/206)	13.8% (4/29)	14.9% (35/235)
Transient Ischemic Attack	8.8% (18/205)	7.1% (2/28)	8.6% (20/233)
Diabetes	31.1% (64/206)	30.0% (9/30)	30.9% (73/236)
Hypertension	88.3% (182/206)	90.0% (27/30)	88.6% (209/236)
Previous intervention			
Coronary artery bypass grafting (CABG)	46.1% (95/206)	63.3% (19/30)	48.3% (114/236)
Percutaneous coronary Intervention (PCI)	25.2% (52/206)	31.0% (9/29)	26.0% (61/235)
Atrial fibrillation/flutter	66.0% (136/206)	70.0% (21/30)	66.5% (157/236)
Permanent pacemaker	23.3% (48/206)	36.7% (11/30)	25.0% (59/236)
Porcelain aorta	1.9% (4/206)	0.0% (0/30)	1.7% (4/236)
Previous implantable cardioverter defibrillator (ICD)	23.3% (48/206)	23.3% (7/30)	23.3% (55/236)
Echocardiographic findings (Valve Implant Population)			
Mitral valve area (cm^2)	1.9 ± 0.9 (115)	2.7 ± 0.8 (30)	2.1 ± 0.9 (145)
Mitral valve mean gradient (mmHg)	8.0 ± 4.6 (171)	7.5 ± 4.8 (30)	7.9 ± 4.6 (201)
Left ventricular ejection fraction (LVEF)	47.0 ± 14.5 (201)	46.3 ± 14.0 (30)	46.9 ± 14.4% (231)
≥ Moderate mitral regurgitation	80.1% (161/201)	66.7% (20/30)	78.4% (181/231)
Annuloplasty ring type			
Partial ring	16.5% (34/206)	26.7% (8/30)	17.8% (42/236)
Circumferential ring	83.5% (172/206)	73.3% (22/30)	82.2% (194/236)

*Continuous measures - Mean ± SD (Total no.); Categorical measures – % (no./Total no.)

D. Safety and Effectiveness Results

1. Safety Endpoints

The Kaplan-Meier estimates of site-reported adverse events through 1 year are presented in Table 4. The Kaplan-Meier curves for all-cause mortality and cardiovascular mortality are shown in Figure 8. The all-cause mortality rate was 10.9% at 30 days and 28.6% at 1 year, including a cardiovascular mortality rate of 5.6% at 30 days and 9.5% at 1 year. Other relatively more frequent adverse events included new requirement for dialysis (6.8% at both

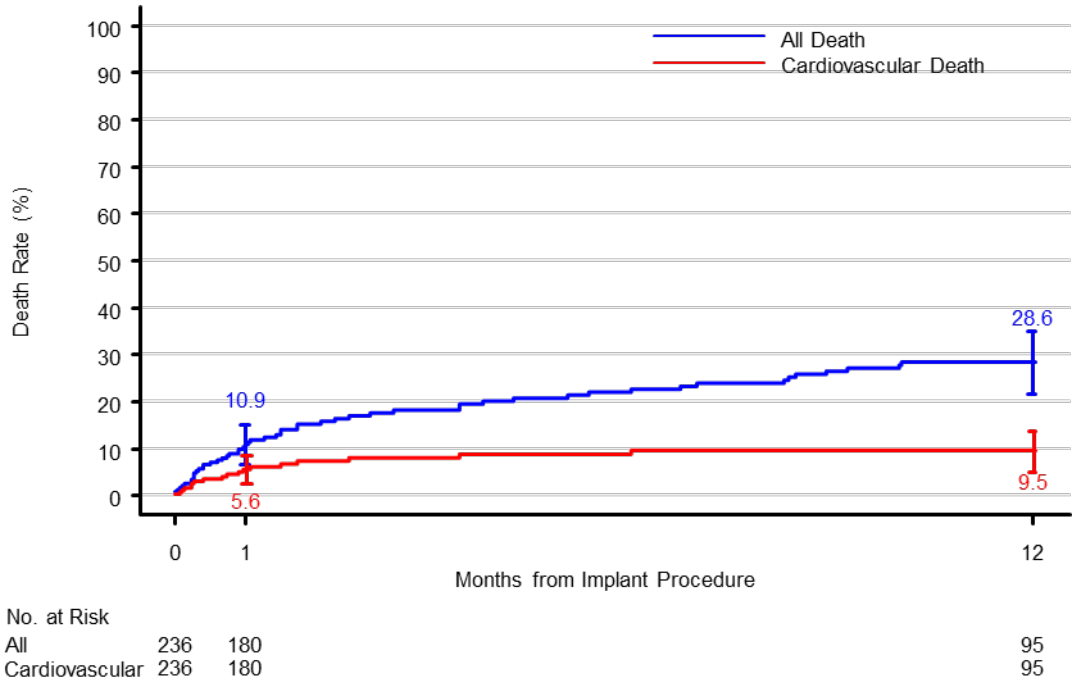
30 days and 1 year), left ventricular outflow tract (LVOT) obstruction (6.6% at 30 days and 7.2% at 1 year), readmission due to heart failure (6.2% at 30 days and 22.4% at 1 year), and non-cardiac readmission (8.9% at 30 days and 32.6% at 1 year).

Table 4: Site Reported Adverse Events (AI Population)

Adverse Event	Kaplan-Meier Rate*	
	30 Days (N = 236)	1 Year (N = 236)
All-cause death	10.9% (24, 24)	28.6% (53, 53)
Cardiovascular death	5.6% (12, 12)	9.5% (18, 18)
All strokes	1.3% (3, 3)	1.3% (3, 3)
Ischemic stroke	0.9% (2, 2)	0.9% (2, 2)
Hemorrhagic stroke	0.4% (1, 1)	0.4% (1, 1)
Transient ischemic attack	0.4% (1, 1)	1.4% (2, 2)
Major vascular complication	2.2% (5, 5)	2.2% (5, 5)
Life threatening/Major bleeding	1.4% (3, 3)	4.8% (8, 7)
Myocardial infarction	0.8% (2, 2)	1.5% (4, 3)
New onset atrial fibrillation	2.9% (6, 6)	6.6% (11, 11)
Conduction/native pacer disturbance requiring pacer	0.9% (2, 2)	3.0% (5, 5)
New requirement for dialysis	6.8% (15, 15)	6.8% (15, 15)
Mitral valve reintervention	4.7% (12, 10)	11.4% (22, 19)
Device thrombosis	1.0% (2, 2)	1.0% (2, 2)
Device embolization	0.8% (2, 2)	0.8% (2, 2)
Device migration	0.5% (1, 1)	0.5% (1, 1)
LVOT obstruction	6.6% (15, 15)	7.2% (16, 16)
Other device related event	4.9% (12, 11)	5.7% (13, 12)
Endocarditis	0.0% (0, 0)	0.8% (1, 1)
Readmission – heart failure	6.2% (13, 12)	22.4% (48, 34)
Readmission – cardiac	3.1% (6, 6)	14.5% (33, 22)
Readmission – non-cardiac	8.9% (18, 18)	32.6% (62, 49)
Unplanned other cardiac surgery or intervention	10.1% (23, 23)	11.7% (25, 25)

*Kaplan-Meier rate - % (no. of events, no. of patients with the event)

Figure 8: Mortality through 1 Year (AI Population)



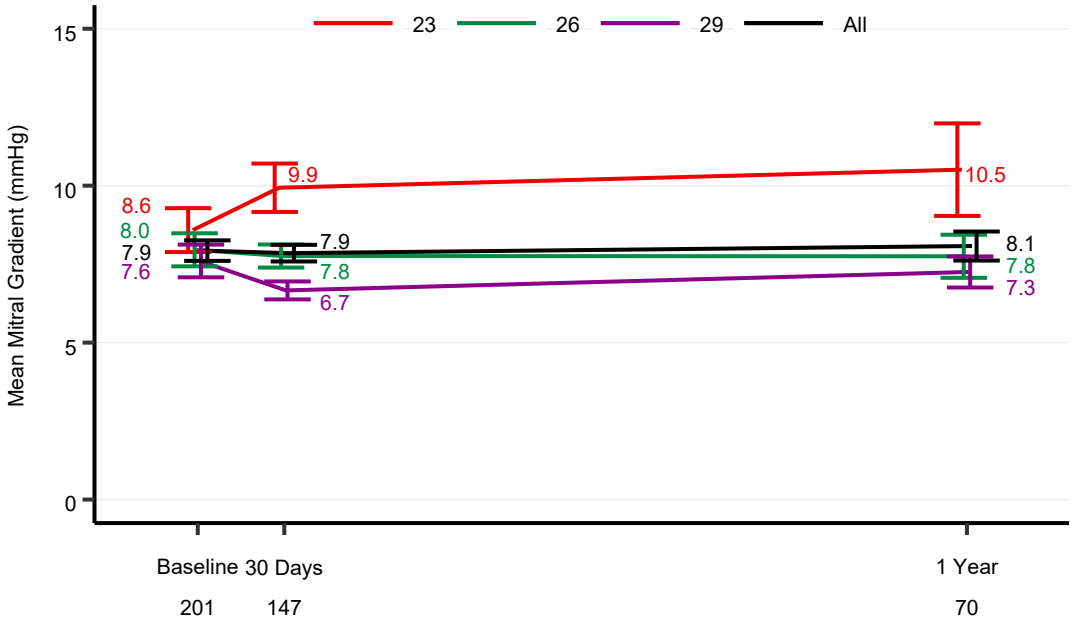
Note: The 95% confidence intervals were calculated without multiplicity adjustment. The adjusted confidence intervals could be wider than presented here. As such, confidence intervals are provided to illustrate the variability only and should not be used to draw any statistical conclusion.

2. Effectiveness Endpoints

Valve Performance

The echocardiographic valve performance results are shown in Figures 9-11. The mean mitral gradient was 7.9 mmHg at baseline, which was maintained at 30 days (7.9 mmHg) and through 1 year (8.1 mmHg). Moderate or greater total mitral regurgitation was observed in 78.4% of the patients at baseline, which decreased to 5.3% at 30 days and 5.5% at 1 year. The proportion of patients with moderate or greater paravalvular regurgitation was 3.3% at 30 days and 0.0% at 1 year.

Figure 9: Mean Mitral Gradient (VI Population)



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

Figure 10: Total Mitral Regurgitation (VI Population)

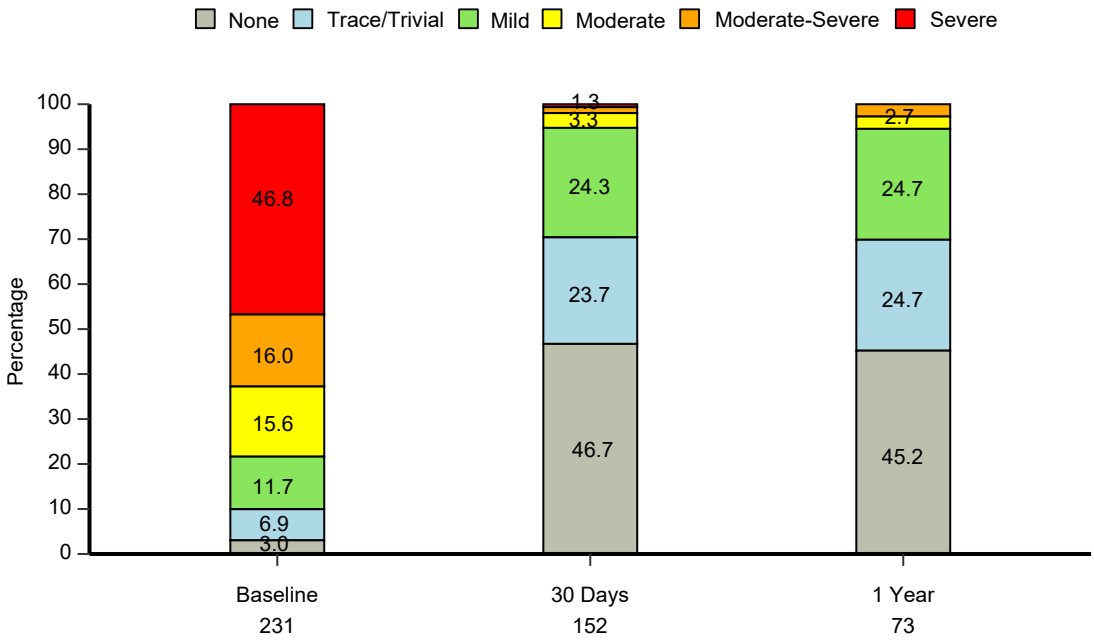
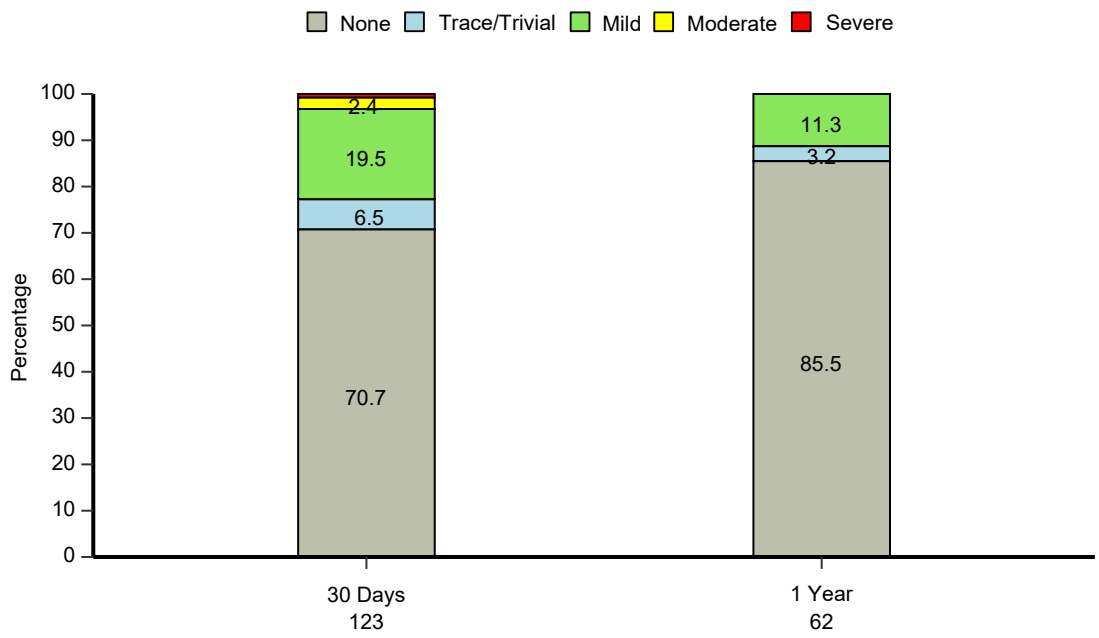


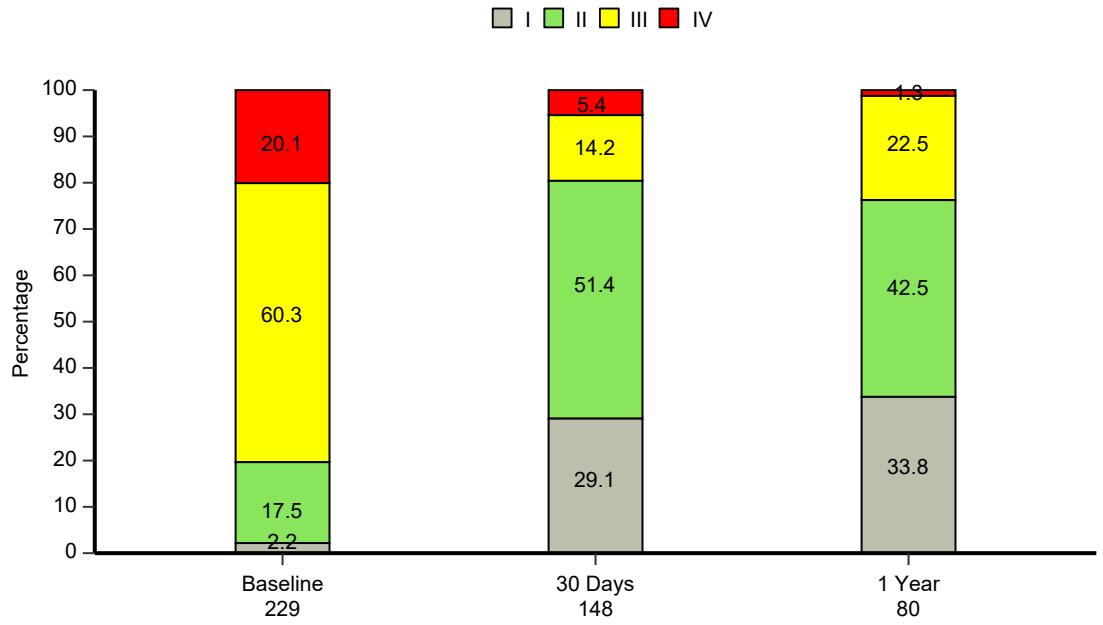
Figure 11: Paravalvular Regurgitation (VI Population)



NYHA Functional Class

The NYHA functional class distributions by visit are presented in Figure 12. At baseline, 80.4% of patients were in NYHA III/IV. At 1 year, the majority (76.3%) of patients were in NYHA I/II.

Figure 12: NYHA Class by Visit (VI Population)



Length of Stay

The mean index hospitalization stay was 7.4 days, which included an average of 2.8 days in the intensive care unit (ICU), as summarized in Table 5.

Table 5: Index Hospitalization (AI Population)

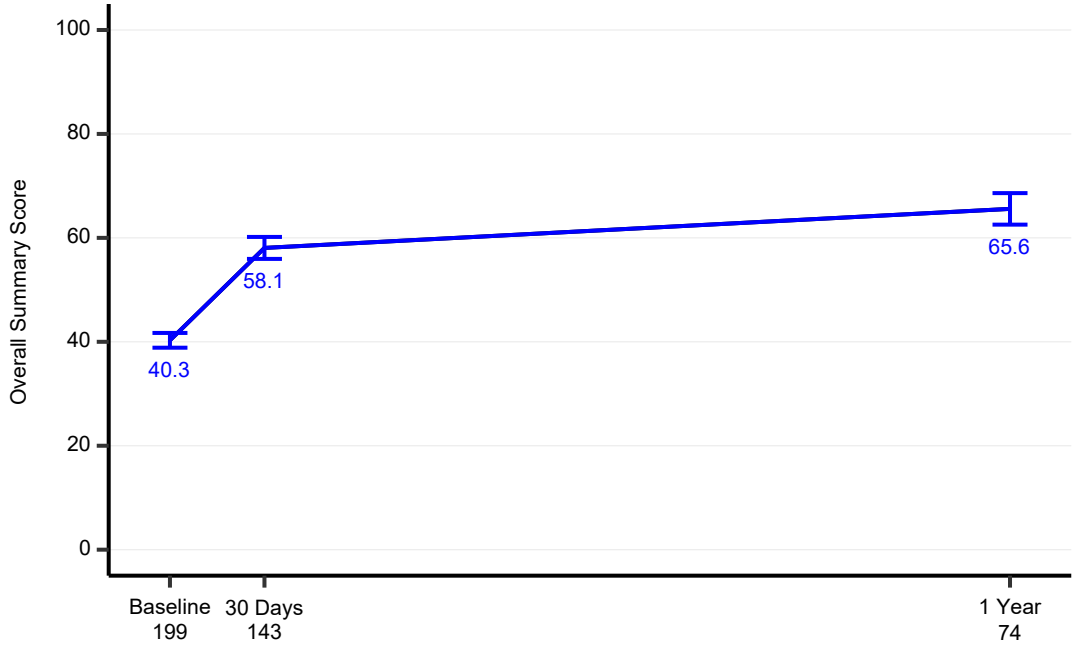
	Length of Stay (days)*
Index hospitalization duration	7.4 ± 0.55 (236)
Intensive care stay	2.8 ± 0.31 (233)

*Mean ± SE (Total no.)

QoL

The results for the KCCQ overall summary score are presented in Figure 13. The mean score increased from 40.3 at baseline to 58.1 and 65.6 at 30 days and 1 year, respectively.

Figure 13: KCCQ Overall Summary Score (VI Population)



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

3. Other Study Observations

Procedural Information

The procedural information is summarized in Table 6. General anesthesia was used in

the majority (97.9%) of patients. Conversion to open heart surgery occurred in two patients due to access related problem/injury and device embolization, respectively.

Table 6: Procedural Data Summary (AI Population)

Procedural Data	Summary Statistics* (N = 236)
Operator reason for procedure	
Inoperable/high risk	87.7% (207/236)
Intermediate risk	12.3% (29/236)
Implant approach	
Transseptal	81.8% (193/236)
Transapical	8.5% (20/236)
Femoral artery	8.9% (21/236)
Direct left atrium	0.4% (1/236)
Other	0.4% (1/236)
Valve size	
20 mm	0.4% (1/236)
23 mm	19.9% (47/236)
26 mm	44.5% (105/236)
29 mm	35.2% (83/236)
Type of anesthesia	
General anesthesia	97.9% (231/236)
Moderate sedation	2.1% (5/236)
Total procedure time (minute)	151.2 ± 82.9 (235)
Device implanted successfully	92.4% (218/236)
Procedure aborted	0.8% (2/236)
Access related	50.0% (1/2)
System issue	50.0% (1/2)
Conversion to open heart surgery	0.8% (2/236)
Access related problem/injury	50.0% (1/2)
Device embolization	50.0% (1/2)

*Continuous measures - mean ± SD (n); categorical measures - % (no./Total no.)

4. Subgroup analysis

The Kaplan-Meier curves for all-cause mortality and cardiovascular mortality are shown in

Figure 14 and Figure 15 for patients with a partial and circumferential annuloplasty ring, respectively. In patients with a partial annuloplasty ring, the 1-year all-cause and cardiovascular mortality rates were 25.1% and 10.9%, respectively, as compared to the corresponding rates of 29.4% and 9.2% for those with a circumferential annuloplasty ring.

Figure 14: Mortality Through 1 Year (Partial Ring Patients)

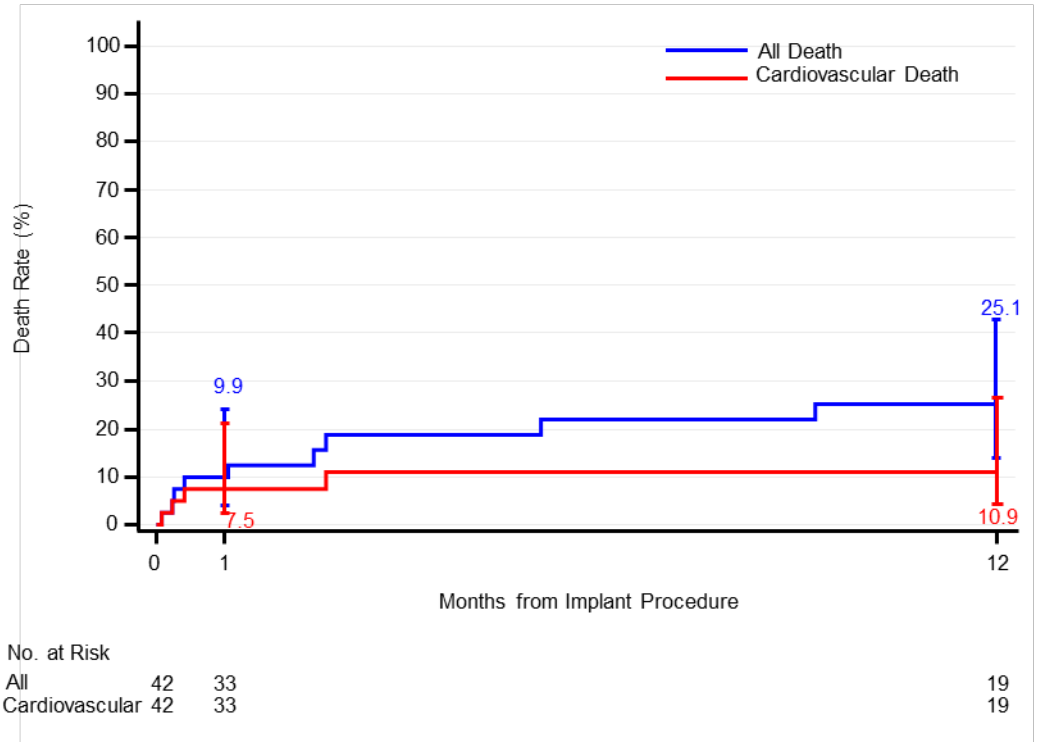
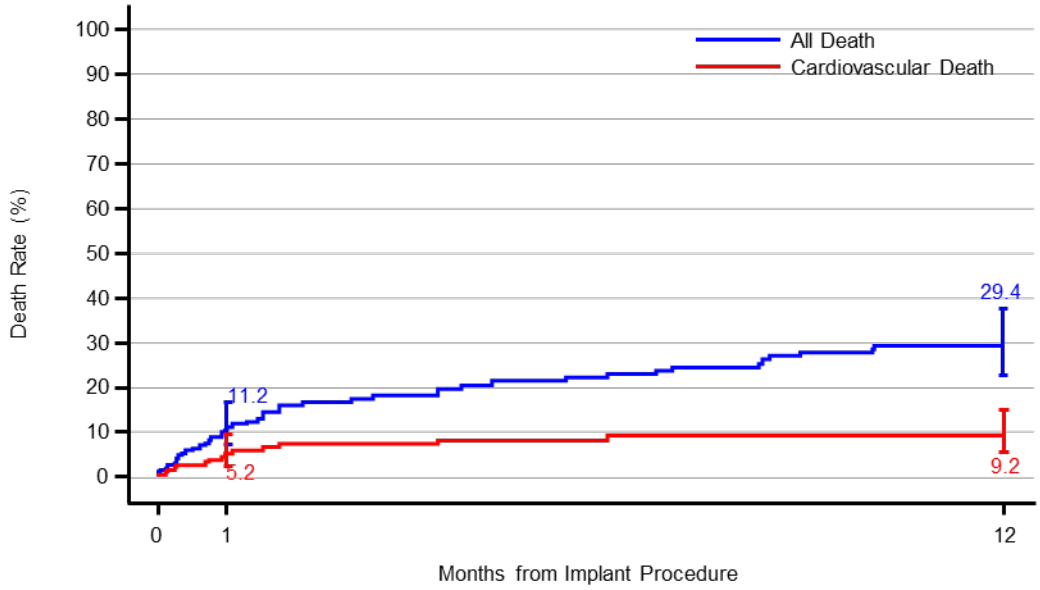


Figure 15: Mortality Through 1 Year (Circumferential Ring Patients)



No. at Risk

All	194	147	76
Cardiovascular	194	147	76

5. Pediatric Extrapolation

In this premarket application, existing clinical data were 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 MITRAL study included 12 investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). 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)(2) of the Act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory System 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

The patients who underwent the mitral "valve-in-ring" procedures overall demonstrated clinically significant improvement in valve hemodynamics in regard to mitral regurgitation. The proportion of patients with moderate or greater total mitral regurgitation decreased from 78.4% at baseline to 5.5% at 1 year, and the mean mitral gradient was maintained from baseline (7.9 mmHg) to 1 year (8.1 mmHg).

The improvement in valve hemodynamics was further demonstrated with improvements in patients' functional status and quality of life. The majority (76.3%) of patients were in NYHA I/II at 1 year as compared to 19.7% at baseline. Similarly, clinically significant improvement was observed in the KCCQ overall summary score, which increased from 40.3 at baseline to 65.6 at 1 year on average.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory studies and clinical data collected in the TVT Registry and MITRAL study to support PMA approval as described above.

The Kaplan-Meier estimate of the all-cause mortality rate was 10.9% at 30 days (compared to a mean STS score of 9.3%) and 28.6% at 1 year, including a corresponding cardiovascular mortality rate of 5.6% and 9.5%. The Kaplan-Meier estimated rates of new requirement for dialysis, LVOT obstruction, and readmission due to heart failure were 6.8%, 6.6%, and 6.2% at 30 days and 6.8%, 7.2%, and 22.4% at 1 year, respectively.

C. Benefit-Risk Determination

The probable benefits of the mitral "valve-in-ring" treatment with the SAPIEN 3 THV include improved functional status as measured by the NYHA classification, and improved QoL as measured by the KCCQ score.

The probable risks of the mitral "valve-in-ring" treatment with the SAPIEN 3 THV include procedural and late complications such as death, new requirement for dialysis, LVOT obstruction, and readmission due to heart failure.

1. Patient Perspectives

   This submission did not include specific information on patient perspectives for the SAPIEN 3 THV. However, since patients without a surgical option can only receive palliative medical therapy and transcatheter mitral valve replacement with the Edwards SAPIEN 3 THV provides a less invasive option, FDA believes many patients and their physicians would prefer this option.

In conclusion, given the available information above, the data support that for patients with a failing native mitral valve with an annuloplasty ring who are at high or greater risk for open surgical therapy, the probable benefits of implanting an Edwards SAPIEN 3 THV outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of the SAPIEN 3 THV in treating patients with symptomatic heart disease due to failing of a native mitral valve with an annuloplasty ring who are judged by a heart team, including a cardiac surgeon, to be at high or greater risk for open surgical therapy. FDA has determined this conclusion is also applicable to the SAPIEN 3 Ultra THV.

XIII. CDRH DECISION

CDRH issued an approval order on May 13, 2021. The final conditions of approval cited in the approval order are described below.

The applicant must participate in and support continued surveillance of the SAPIEN 3 and SAPIEN 3 Ultra THV System used for the mitral "valve-in-ring" indication:

1. **SAPIEN 3 and SAPIEN 3 Ultra Mitral Valve-in-Ring Surveillance**: The applicant has agreed to work with the TVT Registry to ensure that FDA surveillance occurs for commercial uses of the Edwards SAPIEN 3 and SAPIEN 3 Ultra THV System for the mitral "valve-in-ring" indication. The surveillance is to continue to monitor the performance of the Edwards SAPIEN 3 and SAPIEN 3 Ultra THV System in the real-world setting. It will involve all consecutive patients treated within the first 5 years after the PMA approval that are entered into the TVT Registry. This surveillance will monitor the following: (1) device success (intra-procedure); (2) all-cause mortality, all stroke, life-threatening/major bleeding, new requirement for dialysis, peri-procedural myocardial infarction, and repeat procedure for valve-related dysfunction (surgical or interventional therapy) at 30 days and 12 months; and (3) neurological (non-stroke), vascular complications, and quality of life (KCCQ) outcomes at 30 days and 12 months.

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.