SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Prosthesis, Mitral Valve, Percutaneously Delivered
Device Trade Name:	Edwards SAPIEN 3, SAPIEN 3 Ultra, and SAPIEN 3 Ultra RESILIA Transcatheter Heart Valve Systems
Device Procode:	NPU
Applicant's Name and Address:	Edwards Lifesciences LLC One Edwards Way Irvine, CA 92614
Date(s) of Panel Recommendation:	None

Premarket Approval Application (PMA) Number: P140031/S162

Date of FDA Notice of Approval: May 23, 2024

The original PMA of the Edwards SAPIEN 3 Transcatheter Heart Valve (THV) System, P140031, was approved on June 17, 2015, with an indication for relief of aortic stenosis in patients with symptomatic heart disease due to severe native calcific aortic stenosis who are judged by a heart team, including a cardiac surgeon, to be at high or greater risk for open surgical therapy. Subsequent indication expansions include the following:

- P140031/S010 (approved August 18, 2016) - The indication was expanded to include patients deemed to be at intermediate risk for surgical aortic valve replacement (SAVR).
- P140031/S028 (approved June 5, 2017) - The indication was expanded to include patients with a failing (stenosed, insufficient, or combined) surgical bioprosthetic aortic or mitral valve (i.e., Valve-in-Valve) who are deemed to be at high or greater risk for open surgery.
- P140031/S085 (approved August 16, 2019) - The indication was expanded to include patients deemed to be at low risk for SAVR for the relief of aortic stenosis in patients with symptomatic heart disease due to severe native calcific stenosis.
- P140031/S112 (approved September 9, 2020) - The indication was expanded to include patients with a failing (stenosed, insufficient, or combined) transcatheter bioprosthetic aortic valve (i.e. THV-in-THV) who are deemed to be at high or greater risk for redo SAVR.
- P140031/S125 (approved May 13, 2021) - The indication was expanded to include patients with a failing native mitral valve with an annuloplasty ring (i.e., THV-in-Ring) who are deemed to be at high or greater risk for open surgery.

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

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
https://www.accessdata.fda.gov/cdrh_docs/pdf14/P140031S125B.pdf

The current supplement expands the indication of the Edwards SAPIEN 3, SAPIEN 3 Ultra THV, and SAPIEN 3 Ultra RESILIA THV Systems to include patients with a failing surgical bioprosthetic mitral valve who are at intermediate risk for open surgical therapy (i.e., THV-in-surgical valve).

II. INDICATIONS FOR USE

1) The Edwards SAPIEN 3, SAPIEN 3 Ultra, and SAPIEN 3 Ultra RESILIA Transcatheter Heart Valve system is indicated for relief of aortic stenosis in patients with symptomatic heart disease due to severe native calcific aortic stenosis who are judged by a Heart Team, including a cardiac surgeon, to be appropriate for the transcatheter heart valve replacement therapy.

2) The Edwards SAPIEN 3, SAPIEN 3 Ultra, and SAPIEN 3 Ultra RESILIA Transcatheter Heart Valve system is indicated for patients with symptomatic heart disease due to a failing (stenosed, insufficient, or combined) surgical or transcatheter bioprosthetic aortic 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).

3) The Edwards SAPIEN 3, SAPIEN 3 Ultra, and SAPIEN 3 Ultra RESILIA Transcatheter Heart Valve system is indicated for patients with symptomatic heart disease due to a failing (stenosed, insufficient, or combined) surgical bioprosthetic mitral valve who are judged by a heart team, including a cardiac surgeon, to be at intermediate or greater risk for open surgical therapy (i.e., predicted risk of surgical mortality ≥ 4% 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, SAPIEN 3 Ultra, and SAPIEN 3 Ultra RESILIA THV Systems are contraindicated in patients who cannot tolerate an anticoagulation/antiplatelet regimen, who have active bacterial endocarditis or other active infections, or who have significant annuloplasty ring dehiscence.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Edwards SAPIEN 3, SAPIEN 3 Ultra, and

SAPIEN 3 Ultra RESILIA THV System labeling.

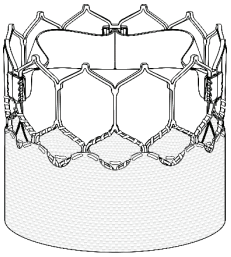
V. DEVICE DESCRIPTION

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.

Figure 1: SAPIEN 3 Transcatheter Heart Valve

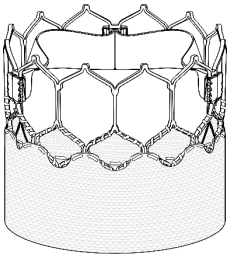
The Edwards SAPIEN 3 Ultra THV (model 9750TFX, 20, 23, and 26 mm), as shown in Figure 2, is a design iteration of the SAPIEN 3 THV, with a knitted outer skirt featuring a velour texture on one side.

Figure 2: SAPIEN 3 Ultra Transcatheter Heart Valve



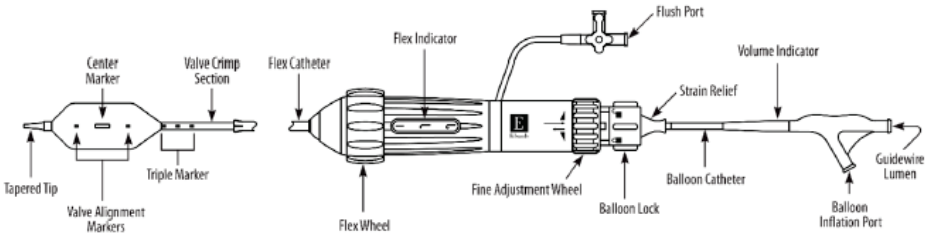
The Edwards SAPIEN 3 Ultra RESILIA THV (model 9755RSL, 20, 23, 26, and 29 mm), as shown in Figure 3, is a design iteration of the SAPIEN 3 Ultra THV, with RESILIA bovine pericardial tissue leaflets.

Figure 3: SAPIEN 3 Ultra RESILIA Transcatheter Heart Valve



The Edwards Commander Delivery System (models 9600LDS20, 9750CM20, 9600LDS23, 9750CM23, 9600LDS26, 9750CM26, 9600LDS29, and 9750CM29), as shown in Figure 4, 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) or Edwards eSheath+ Introducer Set (models 914ES) and 916ESP), which are off-the-shelf devices cleared in 510(k) K200258, to establish vascular access.

Figure 4: Edwards Commander Delivery System

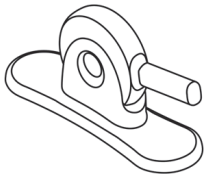


The Qualcrimp crimping accessory, as shown in Figure 5, is a non-patient contacting device that is placed around the THV to protect the leaflets during the crimping process. It is manufactured of tubular polyester polyurethane foam and laminated cylindrically on both the inner and outer surfaces with a polyether urethane material.

Figure 5: Qualcrimp Crimping Accessory

The Edwards Crimper (model 9600CR), as shown in Figure 6, 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 6: Edwards Crimper



VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are other alternatives for patients with a failing bioprosthetic mitral valve who are at intermediate surgical risk including percutaneous balloon valvuloplasty for temporary relief of stenosis, surgical replacement of the degenerated device, 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, SAPIEN 3 Ultra, and SAPIEN 3 Ultra RESILIA THV System have not been marketed in the United States or any foreign country for the intermediate risk mitral valve-in-valve indication.

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
- 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 or brachial plexus injury
- Restenosis
- Pulmonary edema
- Pleural effusion
- Bleeding

- Anemia
- Abnormal lab values (including electrolyte imbalance)
- Hypertension or hypotension
- Allergic reaction to anesthesia, contrast media, or device materials
- Hematoma
- Syncope
- Pain or changes at the access site
- Exercise intolerance or weakness
- Inflammation
- Angina
- Heart murmur
- Fever
- Cardiac arrest
- Cardiogenic shock
- Emergency cardiac surgery
- Cardiac failure or low cardiac output
- Coronary flow obstruction/transvalvular flow disturbance
- Device thrombosis requiring intervention
- Valve thrombosis
- Device embolization
- Device migration or malposition requiring intervention
- 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, please see Section X below.

IX. SUMMARY OF NON-CLINICAL STUDIES

A summary of previously reported non-clinical studies can be found in the SSEDs for the original PMA P140031, PMA Supplement P140031/S028, PMA Supplement P140031/S074, and PMA Supplement P140031/S141.

X. SUMMARY OF PRIMARY CLINICAL STUDY(IES)

The applicant performed an analysis of the real-world off-label use data captured in the Society of Thoracic Surgeons (STS)/American College of Cardiology (ACC) Transcatheter Valve Therapy (TVT) Registry and the investigational use data collected under the PARTNER 3 Mitral Valve-in-Valve (P3 MVIV) study (IDE G150278) to establish a reasonable assurance of the safety and effectiveness of the Edwards SAPIEN 3 and Edwards SAPIEN 3 Ultra THV Systems in intermediate-risk patients receiving mitral Valve-in-Valve treatment. The data from these two sources was the basis of the PMA approval decision. A summary of the clinical data is presented below.

The clinical data set did not include the SAPIEN 3 Ultra RESILIA THV System. However, the results obtained on the Edwards SAPIEN 3 and SAPIEN 3 Ultra THV Systems are considered applicable to the Edwards SAPIEN 3 Ultra RESILIA THV System based on prior demonstration of device comparability in PMA Supplement P140031/S141, which was the premarket application for the Edwards SAPIEN 3 Ultra RESILIA THV System.

A. Study Design

A database extract from the TVT Registry was performed on January 27, 2023, with a treatment cutoff date of November 27, 2021, yielding 452 patients. In addition, 50 patients from the P3 MVIV study at 12 participating hospitals treated between June 2018 and August 2021 were pooled with the TVT registry patients, resulting in a total of 502 patients. These 502 patients constituted the clinical data set 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 bioprosthetic valve who received a commercially available Edwards SAPIEN 3 or Edwards SAPIEN 3 Ultra THV and were at intermediate surgical risk.

   Enrollment in the P3 MVIV study was limited to subjects who met the following inclusion criteria:

   - Patient has a failing surgically implanted bioprosthetic valve in the mitral position demonstrating ≥ moderate stenosis and/or ≥ moderate insufficiency.
   - The patient's surgical bioprosthetic valve has a true internal diameter of 16.5 mm to 28.5 mm.
   - NYHA Functional Class of II or greater.
   - Heart Team agrees the patient is intermediate risk (i.e., Society of Thoracic Surgeons [STS] score of ≥3 and < 8). The Heart Team evaluation includes risk calculators such as the STS, as well as overall clinical status and comorbidities not fully addressed by the STS risk score (verified during the case review process).
   - 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.

Subjects were not permitted to enroll in the P3 MVIV study if they met any of the following exclusion criteria:

- Index valve had mild paravalvular regurgitation or greater where the surgical bioprosthesis was not securely fixed in the native annulus or was not structurally intact as determined by transesophageal echocardiography (TEE).
- Surgical or transcatheter aortic valve placed so that extension into left ventricular outflow tract (LVOT) that may impinge on the mitral implant.
- Known residual mean gradient >10 mmHg at the end of the index procedure for implantation of the original surgical valve.
- Severe right ventricle (RV) dysfunction.
- Anatomical characteristics that would preclude safe access to the apex (transapical).
- Severe regurgitation or stenosis of any other valve.
- Severe lung disease (FEV1 < 50% predicted) or currently on home oxygen
- Severe pulmonary hypertension (e.g., PA systolic pressure ≥ 2/3 systemic pressure)
- Anatomical characteristics that would increase risk of LVOT obstruction (e.g., aortomitral angle, LVOT size, etc.).
- Evidence of an acute myocardial infarction ≤ 1 month (30 days) before enrollment.
- Any therapeutic invasive cardiac procedure resulting in a permanent implant that was performed within 30 days prior to the index procedure.
- Patients with planned concomitant surgical or transcatheter ablation for atrial fibrillation.
- Leukopenia (white blood count < 3000 cell/mL), anemia (hemoglobin < 9 g/dL), thrombocytopenia (blood platelet count < 50,000 cell/mL), history of bleeding diathesis or coagulopathy, or hypercoagulable states.
- Untreated clinically significant coronary artery disease requiring revascularization.
- Hemodynamic or respiratory instability requiring inotropic support, mechanical ventilation, or mechanical heart assistance within 30 days of enrollment.
- Emergency intervention/surgical procedures within one month (30 days) prior to the procedure.
- Any planned surgical, percutaneous coronary, or peripheral procedure that was performed within the 30-day follow-up from the procedure.
- Hypertrophic cardiomyopathy with obstruction (HOCM).
- Left ventricular ejection fraction (LVEF) < 30%.
- Cardiac imaging evidence of intracardiac mass, thrombus, or vegetation.
- Inability to tolerate or condition precluding treatment with antithrombotic/anticoagulation therapy during or after the valve implant procedure.

- Absolute contraindications or allergy to iodinated contrast that could not be adequately treated with premedication.
- Stroke or transient ischemic attack within 90 days of enrollment.
- Symptomatic carotid or vertebral artery disease or successful treatment of carotid stenosis within 30 days of enrollment.
- Renal insufficiency (eGFR < 30 ml/min per the Cockcroft-Gault formula) and/or renal replacement therapy at the time of screening.
- Active bacterial endocarditis within 6 months (180 days) of the procedure.
- Patient refused blood products.
- Estimated life expectancy < 24 months.
- Currently participation in an investigational drug or another device study.
- Positive urine or serum pregnancy test in female subjects of childbearing potential.

2. Follow-up Schedule

All patients enrolled in the TVT Registry were followed post-implantation according to their local standards of care. The TVT Registry collected follow-up data at 30 days and 1 year.

All patients enrolled in the P3 MVIV study are scheduled for follow-up examinations at discharge, 30 days, 6 months, 1 year, and annually thereafter through 10 years post-procedure. Preoperative and post-operative evaluations included physical assessments, laboratory measurements, imaging tests, patient interviews, and health status/quality of life (QoL) assessments. Adverse events and complications were recorded at all visits.

3. Clinical Endpoints

The analysis included two co-primary endpoints that were analyzed sequentially.

1. A composite of death and stroke at 30 days compared to a performance goal with the following hypothesis:

   H_0: $DS_{30D} \geq 10.4\%$
   H_A: $DS_{30D} < 10.4\%$

   Where DS_{30D} was the combined death and stroke risk at 30 days and 10.4% was a performance goal derived from the modeled combined risk of 30-day death and stroke risks for redo-surgery in an intermediate risk population, as derived from the STS Adult Cardiac Surgery Risk Calculator, plus a clinical margin to incorporate data uncertainty.

2. The rate of death at 1 year compared to a performance goal with the following

hypothesis:

H_0: $D_{1Y} \geq 19.6\%$
H_A: $D_{1Y} < 19.6\%$

Where D_{1Y} was the death rate at 1 year and 19.6% was a performance goal based on the risk of death in intermediate risk redo-surgical MVR, as modeled from the medical literature, plus a clinical margin.

For both co-primary endpoints, success would be defined by rejecting the null in favor of the alternative and would occur if the upper limit of the 95% confidence interval of the observed risks were less than corresponding performance goals.

B. Accountability of PMA Cohort

At the time of database extract, of the 502 patients in the pooled analysis of data from the P3 MVIV study and subjects entered into the TVT Registry, 483 patients were eligible for the 30-day visit and 425 (88.0%) completed the visit within the 30-day follow-up window, defined as the period between 23 days and 75 days post-procedure for the TVT Registry and between 30 days and 37 days for the P3 MVIV cohort. At 1 year, 439 patients were eligible for the 1-year visit and 308 (70.2%) completed the visit within the follow-up window, defined as the period between 305 days and 425 days post-procedure for the TVT Registry and between 365 days and 395 days for the P3 MVIV cohort. A detailed summary of the patient accountability at 30 days and 1 year is shown in Table 1.

Table 1. Patient Visit Accountability (AI Population)

	30-day Visit	1-year Visit
Total Patients	502	502
Non-eligible	19	63
Death	9	28
Lost to follow-up	10	35
Eligible	483	439
Follow-up visit completed	88.0% (425)	70.2% (308)
Missed visit	12.0% (58)	29.8% (131)

The "Attempted Implant" (AI) population consisted of all patients in the dataset from the TVT Registry and the P3 MVIV study. The "Valve Implant" (VI) population consisted of all patients in the analysis population who received and retained the intended valve during the index procedure in the P3 MVIV study and all subjects who had started the procedure and had 'No' for procedure aborted and 'No' for conversion to open heart surgery in the TVT Registry. The number of patients in these two analysis populations is shown in Table 2.

Table 2: Analysis Populations

Analysis Population	Number of Patients
Attempted implant population	502
Valve implant population	499

C. Study Population Demographics and Baseline Parameters

The demographics and baseline characteristics of the patients, as shown in Table 3, present an elderly cohort of patients, with comorbidities consistent with the intermediate operative risk of the population, a majority of whom were white.

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

Demographics and Baseline Characteristics	Summary Statistics* (N = 502)
Age - years	71.7 ± 10.10 (502)
Gender	
Male	43.2% (217/502)
Female	56.8% (285/502)
Hispanic or Latino Ethnicity	6.7% (33/494)
Race	
White	82.3% (413/502)
Black/African American	9.6% (48/502)
Asian	1.8% (9/502)
American Indian/Alaskan Native	0.8% (4/502)
Native Hawaiian/Pacific Islander	0.2% (1/502)
Multiple	0.8% (4/502)
Unknown	3.2% (16/502)
Other	1.4% (7/502)
Society of Thoracic Surgeons (STS) score	5.0 ± 2.21 (479)
New York Heart Association (NYHA) class	
I/II	29.2% (143/490)
III/IV	70.8% (347/490)
Previous intervention	
Coronary artery bypass grafting (CABG)	26.3% (132/502)

Demographics and Baseline Characteristics	Summary Statistics* (N = 502)
Percutaneous coronary intervention (PCI)	13.7% (69/502)
Cerebrovascular accident (CVA)	16.3% (82/502)
Peripheral vascular disease	12.2% (61/502)
Atrial fibrillation/flutter	63.9% (321/502)
Permanent pacemaker	23.7% (119/502)
Hostile chest	12.5% (63/502)
Echocardiographic findings	
Mitral valve area (cm^2)	1.3 ± 0.73 (358)
Mitral valve mean gradient (mmHg)	12.5 ± 5.80 (478)
Left ventricular ejection fraction (LVEF), %	56.6 ± 10.82 (492)
≥ Moderate mitral regurgitation	53.5% (264/493)
≥ Moderate aortic regurgitation	8.3% (41/494)
≥ Moderate tricuspid regurgitation	42.0% (210/500)

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

D. Safety and Effectiveness Results

1. Co-Primary Endpoints

The co-primary endpoints are presented in Table 4 and in Kaplan-Meier curves in Figures 7 and 8. The composite rate of death and stroke at 30 days was 2.5% which was less than the prespecified performance goal of 10.4%. Thus the first co-primary endpoint was met. The rate of death at 1 year was 6.9% which was less than the prespecified performance goal of 19.6%. Thus, the second co-primary endpoint was also met.

Table 4: Co-Primary Endpoints (Pooled Cohort)
Attempted Implant Population (N=502)

Co-Primary Endpoints	Summary Statistics	95% Confidence Interval	Performance Goal	Pass/Fail*
All-cause death or all stroke at 30 days	2.5% (13, 12), 442	[1.41, 4.32]	10.4%	Pass
All-cause death at 1 year	6.9% (28, 28), 260	[4.81, 9.90]	19.6%	Pass

Co-Primary Endpoints	Summary Statistics	95% Confidence Interval	Performance Goal	Pass/Fail*
Kaplan-Meier estimate - % (no. of events, no. of subjects with the event), no. at risk. 95% CI is calculated based on normal distribution with KM estimated mean rate and Greenwood formula calculated standard error. *Tests are performed sequentially. Test for 1 year death is performed only if the composite endpoint of all-cause death or all stroke at 30 days has passed performance goal.				

Figure 7: All-Cause Death or All Stroke at 30 Days (AI Population)

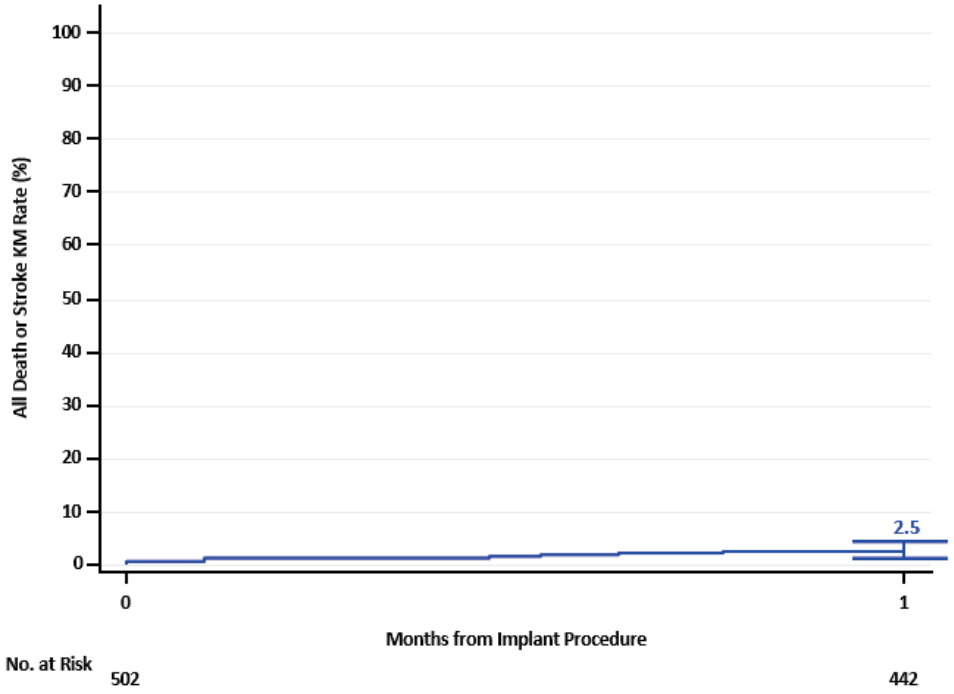
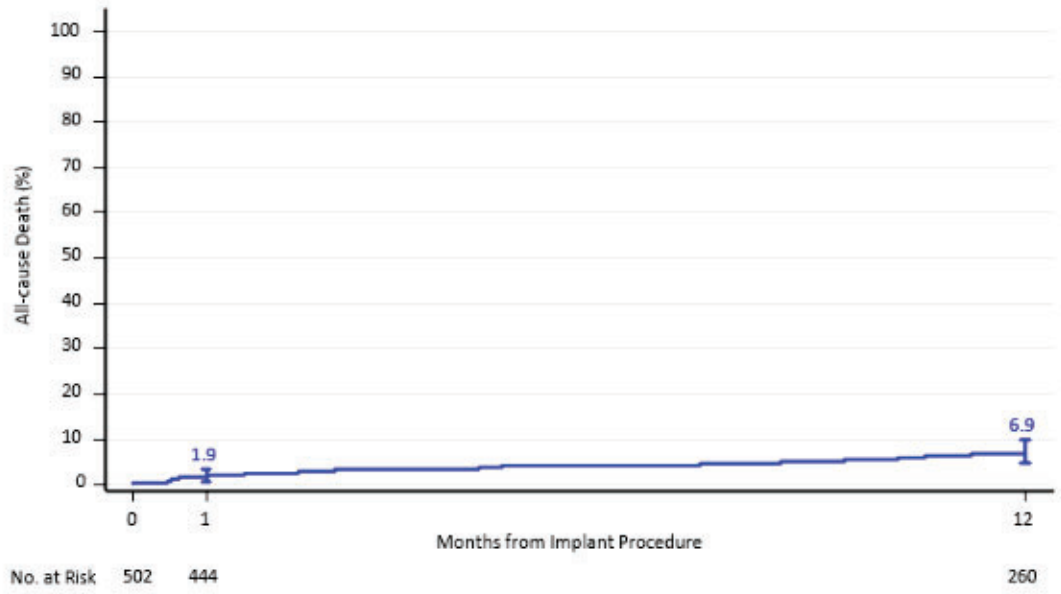


Figure 8: All-Cause Death through 1 year (AI Population)



Missing Data

As noted above, study compliance was 88% at 30 days and 70.2% at 1 year as of the original data cutoff date. During the course of FDA review, the sponsor was asked to provide updated analyses as of January 2024 and twenty-two additional patients had completed 1-year follow-up visits. The updated co-primary endpoints with the twenty-two additional patients are presented in the table below.

Table 5. Co-primary Endpoints (January 2024)
Attempted Implant Population (N=502)

Co-Primary Endpoints	Summary Statistics	95% Confidence Interval	Performance Goal	Pass/Fail*
All-cause death or all stroke at 30 days	2.5% (13, 12), 448	[1.41, 4.32]	10.4%	Pass
All-cause death at 1 year	7.2% (30, 30), 278	[5.07, 10.16]	19.6%	Pass
Kaplan-Meier estimate - % (no. of events, no. of subjects with the event), no. at risk. 95% CI is calculated based on normal distribution with KM estimated mean rate and Greenwood formula calculated standard error. *Tests are performed sequentially. Test for 1 year death is performed only if the				

Co-Primary Endpoints	Summary Statistics	95% Confidence Interval	Performance Goal	Pass/Fail*
composite endpoint of all-cause death or all stroke at 30 day has passed performance goal.				

In order to determine the impact of missing data on study outcomes, the sponsor performed a tipping point analysis by imputing the number of events in subjects with missing data across multiple scenarios ranging from worst-case to best-case scenarios. To exceed the performance threshold for death, deaths at 1 year among the 195 patients with missing data at 1 year would have had to occur in 52 or more patients (26.7 percent), which would correspond to a risk in subjects with missing data that is 3.7 times the risk of death observed in those without missing data (7.2%). The tipping point analysis demonstrated that it is highly unlikely that the primary endpoints would have failed under a reasonable scenario if the data for these subjects were available. Therefore, the sensitivity analyses to address missing data issues are supportive of the primary analysis findings.

2. Adverse Events

The Kaplan-Meier estimates of adverse events through 1 year are presented in Table 4; adverse events from the P3 MVIV study are CEC adjudicated, the adverse events from the TVT Registry are site-reported. The all-cause death rate was 1.9% at 30 days and 6.9% at 1 year. The cardiac death rate was 0.6% at 30 days and 2.5% at 1 year. Other notable adverse events included major vascular complication (1.6% at 30 days and 1.9% at 1 year), life-threatening or major bleeding (1.5% at 30 days and 3.7% at 1 year), cardiac readmission (2.1% at 30 days and 11.1% at 1 year), and readmission due to heart failure (1.1% at 30 days and 5.7% at 1 year).

Table 6: Site Reported Adverse Events (AI Population)

Adverse Event	Kaplan-Meier Rate†	
	30 Days (N = 502)	1 Year (N = 502)
Death or Stroke	2.5% (13, 12)	8.8% (38, 36)
All-cause death	1.9% (9, 9)	6.9% (28, 28)
All stroke	0.8% (4, 4)	2.2% (10, 9)
Cardiac Death	0.6% (3, 3)	2.5% (10, 10)
Mitral valve reintervention	0.0% (0, 0)	0.8% (4, 3)
Major vascular complication	1.6% (8, 8)	1.9% (10, 9)
Life threatening/Major bleeding*	1.5% (7, 7)	3.7% (17, 15)
Life threatening bleeding*	0.2% (1, 1)	1.3% (7, 5)
Major bleeding*	1.3% (6, 6)	2.4% (10, 10)
Myocardial infarction	0.4% (2, 2)	1.2% (5, 5)
New onset atrial fibrillation**	0.8% (3, 3)	2.7% (8, 8)
New permanent pacemaker**	0.8% (3, 3)	1.9% (6, 6)

Adverse Event	Kaplan-Meier Rate†	
	30 Days (N = 502)	1 Year (N = 502)
Readmission – cardiac	2.1% (10, 10)	11.1% (53, 43)
Heart failure	1.1% (5, 5)	5.7% (29, 22)
Non-heart failure	1.1% (5, 5)	6.1% (24, 23)

† Kaplan-Meier rate - % (no. of events, no. of patients with the event). Percentages are normalized by number of patients with data available at database lock.

* In the TVT Registry data in-hospital bleeding is not captured as life-threatening or major event, therefore rates only include bleeding reported after index hospitalization.

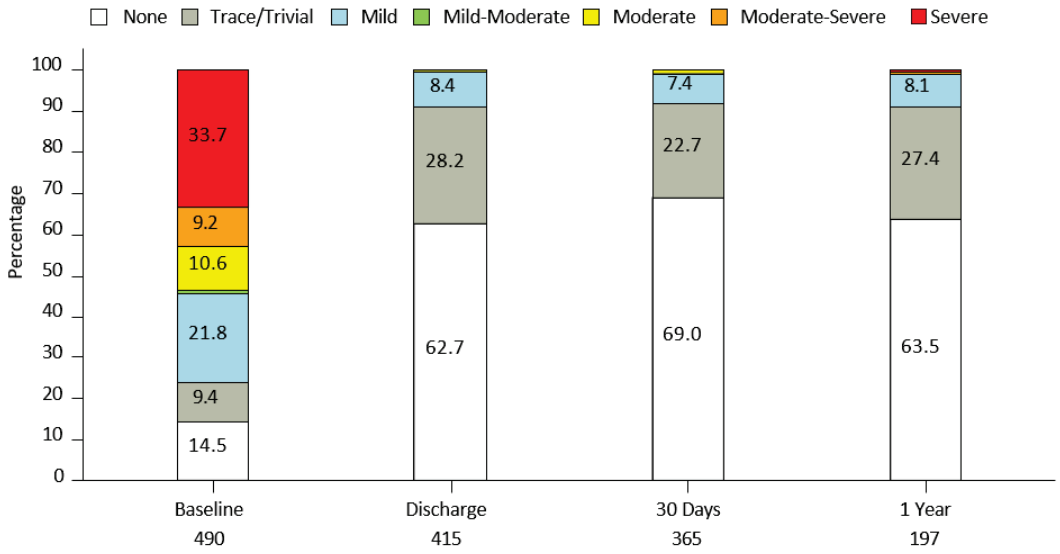
**Subjects with baseline condition are excluded.

3. Effectiveness Endpoints

Mitral Regurgitation

Mitral regurgitation is shown in Figure 9. Moderate or greater total mitral regurgitation was observed in 53.5% of the patients at baseline, which decreased to 0.8% at 30 days and 1.0% at 1 year.

Figure 9: Mitral Regurgitation (VI Population)

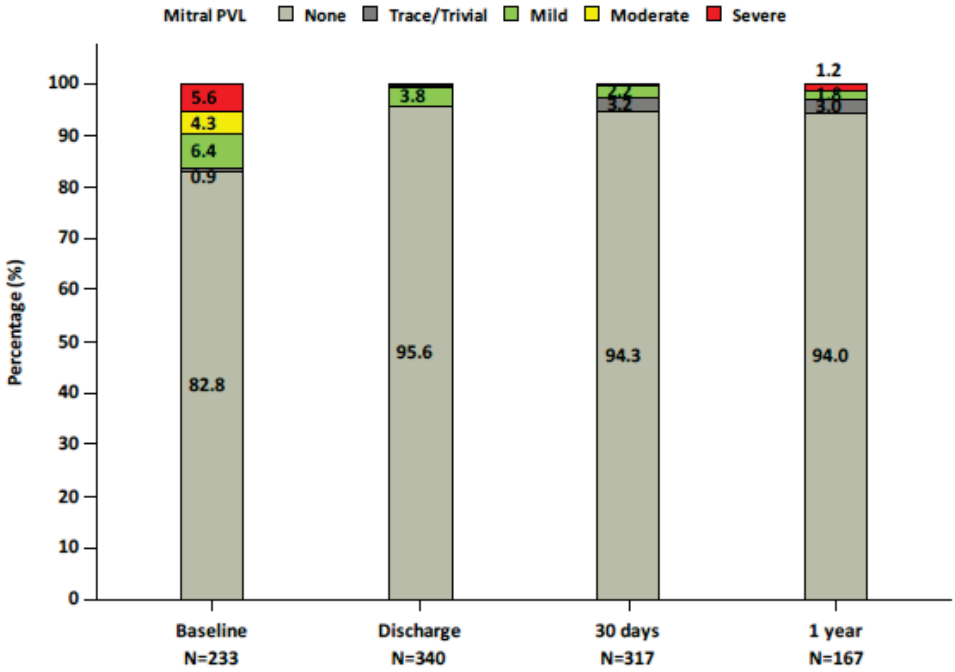


Note: The total number of subjects at each visit time point only counted the subjects with valid values.

Paravalvular Leak

Paravalvular leak (PVL) is shown in Figure 10. Moderate or greater PVL was observed in 9.9% of the patients at baseline, which decreased to 0.3% at 30 days and 1.2% at 1 year.

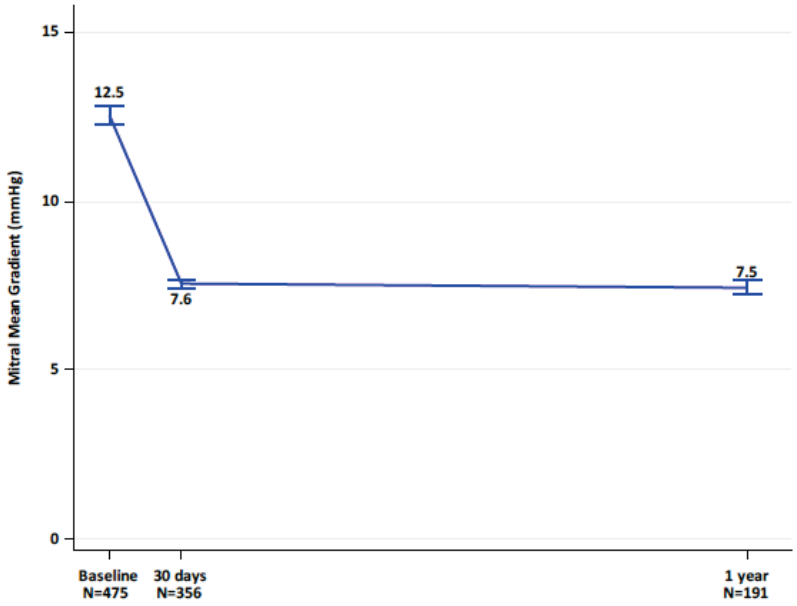
Figure 10: Paravalvular Leak (VI Population)



Mean Mitral Gradient

Mean mitral gradient is shown in Figure 11. At baseline, mean mitral gradient was 12.5 mmHg. The mean gradient decreased to 7.6 mmHg at 30 days and 7.5mmHg at 1 year.

Figure 11: Mean Mitral Gradient (VI Population)



Mitral Valve Area

At baseline, mean mitral valve area was 1.31cm^2. The mean mitral valve area increased to 1.72cm^2 at 30-days and 1.69cm^2 at 1 year.

Table 7. Mitral Valve Area (Pooled Cohort)
Valve Implant Population (N=499)

	Baseline	30-day visit	1-year visit
Mitral valve area (cm^2)	1.31 ± 0.039 (356) 1.08 (0.80, 1.68) [0.60, 2.30]	1.72 ± 0.052 (240) 1.54 (1.20, 2.00) [0.96, 2.71]	1.69 ± 0.075 (122) 1.50 (1.23, 1.88) [1.10, 2.30]

Continuous measures - Mean ± SE (Total no), median (Q1, Q3), [10%tile, 90%tile]. The total no. only counted the patients with valid values. The echo data from IDE cohort are from echo core lab and TVT echo data are site-reported.

Left Ventricular Ejection Fraction (LVEF)

At baseline, LVEF was 56.5%. LVEF was 55.4% at 30-days and 55.3% at 1 year.

Table 8. Left Ventricular Ejection Fraction (LVEF) (Pooled Cohort)
Valve Implant Population (N=499)

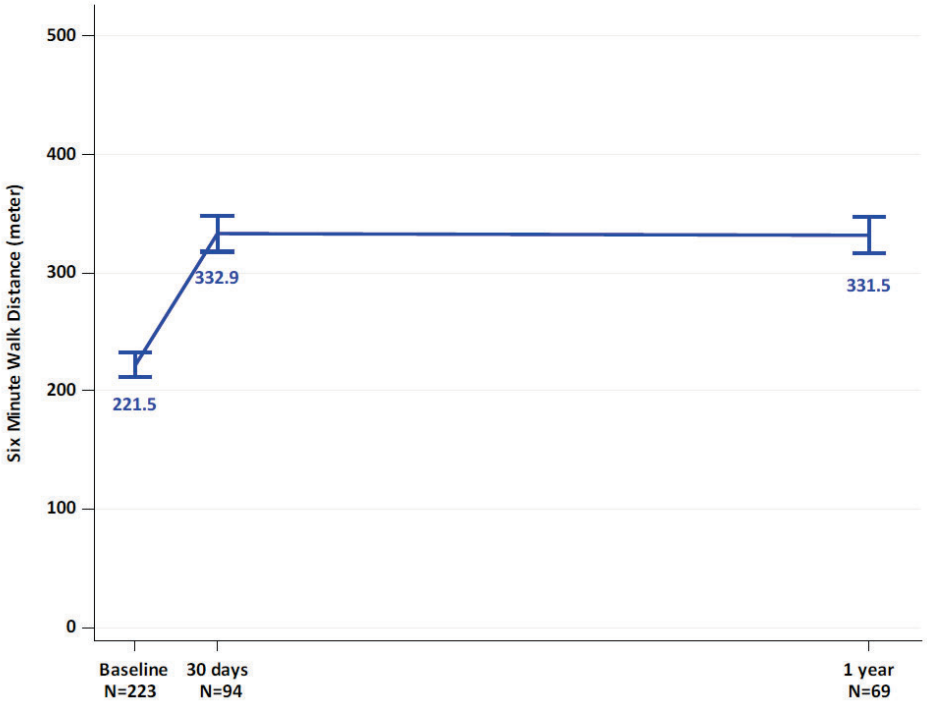
	Baseline	30-day visit	1-year visit
LVEF (%)	56.5 ± 0.49 (489) 59.0 (52.0, 63.0) [41.0, 68.0]	55.4 ± 0.58 (360) 57.0 (50.0, 63.0) [40.0, 68.5]	55.3 ± 0.80 (203) 57.0 (50.0, 63.0) [42.0, 68.0]

Continuous measures - Mean ± SE (Total no), median (Q1, Q3), [10%tile, 90%tile]. The total no. only counted the patients with valid values. The echo data from IDE cohort are from echo core lab and TVT echo data are site-reported.

Six-Minute Walk Test

At baseline, the six-minute walk test distance was 221.5 meters. The six-minute walk test distance increased to 332.9 meters at 30 days and 331.5 meters at 1 year.

Figure 12. Six-Minute Walk Test (Meter) (Pooled Cohort)
Valve Implant Population (N=499)

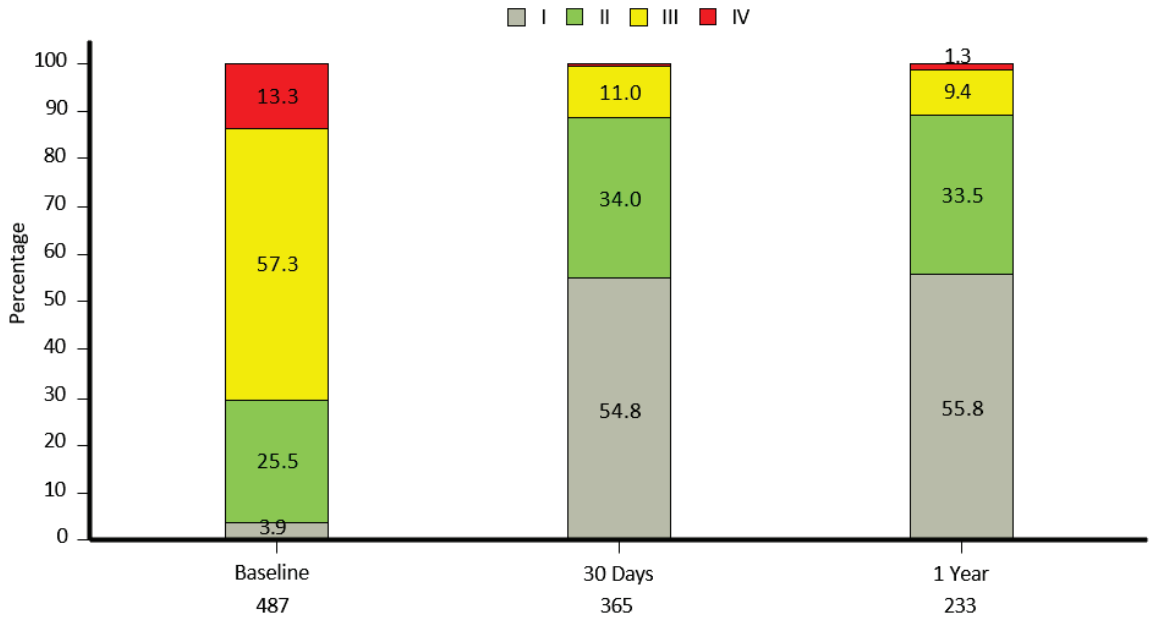


Note: The total number of patients at each visit time point only counted the patients with valid values.

NYHA Functional Class

The NYHA functional class distributions by visit are presented in Figure 13. At baseline, 70.6% of patients were in NYHA III/IV. At 1 year, the majority (89.3%) of patients were in NYHA I/II.

Figure 13: NYHA Class by Visit (VI Population)



Length of Stay

The mean index hospitalization stay was 2.4 days as summarized in Table 9.

Table 9: Index Hospitalization (AI Population)

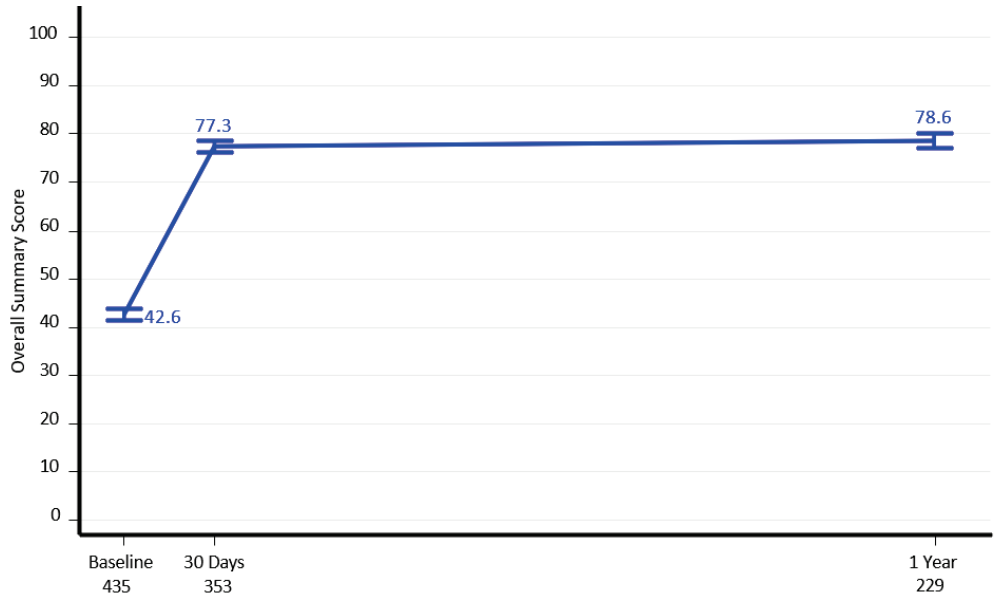
	Length of Stay (days)*
Index hospitalization duration	2.4 ± 0.11 (496)
In-hospital death	1.2% (6/502)
Discharge location	
Home	95.6% (474/496)
Skilled nursing facility	1.4% (7/496)
Extended care/TCU/rehab	2.4% (12/496)
Other acute care hospital	0.2% (1/496)
Other discharge location	0.4% (2/496)

*Continuous Measures - Mean ± SE (Total no.)

Quality of Life

The results for the KCCQ overall summary score are presented in Figure 14. The mean score increased from 42.6 at baseline to 77.3 and 78.6 at 30 days and 1 year, respectively.

Figure 14: 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.

4. Subgroup Analyses

The following baseline characteristics were evaluated for potential association with safety and effectiveness outcomes: gender, race and ethnicity. The study was not specifically powered for gender, race and ethnicity subgroups. Although race and ethnic groups were under-represented when compared with their representation in the U.S. census population, the results for subgroup analyses of the primary endpoints were consistent with those of the primary analysis.

Table 10: Co-Primary Endpoints by Gender

Attempted Implant Population (N=502)

	Male (N=217)		Female (N=285)	
Co-Primary Endpoints	**Summary Statistics**	**95% Confidence Interval**	**Summary Statistics**	**95% Confidence Interval**

All-cause death or all stroke at 30 days	1.9% (4, 4), 191	[0.72, 5.01]	2.9% (9, 8), 251	[1.46, 5.71]
All-cause death at 1 year	9.2% (16, 16), 114	[5.74, 14.67]	5.1% (12, 12), 146	[2.92, 8.90]
Kaplan-Meier estimate - % (no. of events, no. of subjects with the event), no. at risk. 95% CI is calculated based on normal distribution with KM estimated mean rate and Greenwood formula calculated standard error.				

Table 11: Co-Primary Endpoints by Race

Attempted Implant Population (N=502)

	Summary Statistics							
Co-Primary Endpoints	**White (N=413)**	**Black/ African American (N=48)**	**Asian (N=9)**	**American Indian/ Alaskan Native (N=4)**	**Native Hawaiian/ Pacific Islander* (N=1)**	**Multiple (N=4)**	**Unknown (N=16)**	**Other (N=7)**
All-cause death or all stroke at 30 days	(12,11), 364	(1,1), 41	(0,0), 9	(0,0), 2	(0,0), 0*	(0,0), 4	(0,0), 15	(0,0), 7
All-cause death at 1 year	(24,24), 212	(2,2), 21	(0,0), 5	(0,0), 2	(0,0), 0*	(0,0), 4	(2,2), 9	(0,0), 7
* The patient exited the study on Day 29. (no. of events, no. of subjects with the event), no. at risk.								

Table 12: Co-Primary Endpoints by Ethnicity

Attempted Implant Population (N=502)

	Hispanic (N=33)		Non-Hispanic (N=461)	
Co-Primary Endpoints	**Summary Statistics**	**95% Confidence Interval**	**Summary Statistics**	**95% Confidence Interval**
All-cause death or all stroke at	3.0% (1, 1), 31	[0.43, 19.63]	2.5% (12, 11), 405	[1.37, 4.41]

30 days				
All-cause death at 1 year	14.7% (4, 4), 18	[5.73, 34.71]	6.4% (24, 24), 240	[4.34, 9.49]
Kaplan-Meier estimate - % (no. of events, no. of subjects with the event), no. at risk. 95% CI is calculated based on normal distribution with KM estimated mean rate and Greenwood formula calculated standard error.				

Table 13: Site Reported Adverse Events by Gender

Attempted Implant Population (N=502)

	Kaplan-Meier Estimate			
	Male (N=217)		Female (N=285)	
	30 Days	1 Year	30 Days	1 Year
Death or stroke	1.9% (4, 4), 191	10.9% (19, 19), 112	2.9% (9, 8), 251	7.2% (19, 17), 142
All-cause death	1.4% (3, 3), 192	9.2% (16, 16), 114	2.2% (6, 6), 252	5.1% (12, 12), 146
All stroke	0.5% (1, 1), 191	1.7% (3, 3), 112	1.1% (3, 3), 251	2.5% (7, 6), 142
Cardiac death	0.0% (0, 0), 192	3.0% (5, 5), 114	1.1% (3, 3), 252	2.1% (5, 5), 146
Mitral valve reintervention	0.0% (0, 0), 192	0.6% (1, 1), 113	0.0% (0, 0), 252	0.9% (3, 2), 146
Major vascular complication	1.9% (4, 4), 189	1.9% (4, 4), 113	1.4% (4, 4), 250	1.9% (6, 5), 145
Life threatening/major bleeding*	1.5% (3, 3), 189	2.7% (5, 5), 112	1.5% (4, 4), 249	4.4% (12, 10), 143
Life threatening bleeding*	0.0% (0, 0), 192	0.6% (1, 1), 114	0.4% (1, 1), 252	1.8% (6, 4), 145
Major bleeding*	1.5% (3, 3), 189	2.1% (4, 4), 112	1.1% (3, 3), 249	2.6% (6, 6), 144
Myocardial infarction	0.0% (0, 0), 192	1.9% (3, 3), 112	0.7% (2, 2), 251	0.7% (2, 2), 146
New onset atrial fibrillation†	0.0% (0, 0), 145	1.0% (1, 1), 82	1.4% (3, 3), 198	4.0% (7, 7), 108
New permanent pacemaker†	1.3% (2, 2), 142	3.0% (4, 4), 87	0.5% (1, 1), 197	1.1% (2, 2), 115
Readmission – cardiac	1.0% (2, 2), 190	11.1% (20, 18), 104	3.0% (8, 8), 245	11.1% (33, 25), 132
Heart failure	1.0% (2, 2), 190	6.1% (12, 10), 110	1.1% (3, 3), 250	5.4% (17, 12), 141
Non-heart failure	0.0% (0, 0), 192	5.1% (8, 8), 108	1.9% (5, 5), 247	6.8% (16, 15), 136
Kaplan-Meier estimate - % (no. of events, no. of subjects with the event), no. at risk. *In TVTR data, in-hospital bleeding is not captured as life-threatening or major, therefore rates only include bleeding reported after index hospitalization. †Subjects with baseline condition are excluded.				

Table 14: Site Reported Adverse Events by Race – 30 Days

Attempted Implant Population (N=502)

	Summary Statistics			
	White (N=413)	**Black/African American (N=48)**	**Asian (N=9)**	**American Indian/Alaskan Native (N=4)**
Death or stroke	(12, 11), 364	(1, 1), 41	(0, 0), 9	(0, 0), 2
All-cause death	(8, 8), 366	(1, 1), 41	(0, 0), 9	(0, 0), 2
All stroke	(4, 4), 364	(0, 0), 41	(0, 0), 9	(0, 0), 2
Cardiac death	(3, 3), 366	(0, 0), 41	(0, 0), 9	(0, 0), 2
Mitral valve reintervention	(0, 0), 366	(0, 0), 41	(0, 0), 9	(0, 0), 2
Major vascular complication	(8, 8), 361	(0, 0), 41	(0, 0), 9	(0, 0), 2
Life threatening/major bleeding†	(5, 5), 362	(2, 2), 39	(0, 0), 9	(0, 0), 2
Life threatening bleeding†	(1, 1), 366	(0, 0), 41	(0, 0), 9	(0, 0), 2
Major bleeding†	(4, 4), 362	(2, 2), 39	(0, 0), 9	(0, 0), 2
Myocardial infarction	(2, 2), 365	(0, 0), 41	(0, 0), 9	(0, 0), 2
New onset atrial fibrillation‡	(3, 3), 278	(0, 0), 35	(0, 0), 6	(0, 0), 2
New permanent pacemaker‡	(3, 3), 273	(0, 0), 34	(0, 0), 8	(0, 0), 1
Readmission – cardiac	(6, 6), 361	(1, 1), 40	(0, 0), 9	(1, 1), 1
Heart failure	(2, 2), 365	(1, 1), 40	(0, 0), 9	(1, 1), 1
Non-heart failure	(4, 4), 362	(0, 0), 41	(0, 0), 9	(0, 0), 2

(no. of events, no. of subjects with the event), no. at risk.
* The patient exited the study on Day 29.
†In TVTR data, in-hospital bleeding is not captured as life-threatening or major, therefore rates only include bleeding reported after index hospitalization.
‡Subjects with baseline condition are excluded.

Table 15: Site Reported Adverse Events by Race – 30 Days (continued)

Attempted Implant Population (N=502)

	Summary Statistics			
	Native Hawaiian/ Pacific Islander (N=1)	**Multiple (N=4)**	**Unknown (N=16)**	**Other (N=7)**
Death or stroke	(0, 0), 0*	(0, 0), 4	(0, 0), 15	(0, 0), 7
All-cause death	(0, 0), 0*	(0, 0), 4	(0, 0), 15	(0, 0), 7

All stroke	(0, 0), 0*	(0, 0), 4	(0, 0), 15	(0, 0), 7
Cardiac death	(0, 0), 0*	(0, 0), 4	(0, 0), 15	(0, 0), 7
Mitral valve reintervention	(0, 0), 0*	(0, 0), 4	(0, 0), 15	(0, 0), 7
Major vascular complication	(0, 0), 0*	(0, 0), 4	(0, 0), 15	(0, 0), 7
Life threatening/major bleeding†	(0, 0), 0*	(0, 0), 4	(0, 0), 15	(0, 0), 7
Life threatening bleeding†	(0, 0), 0*	(0, 0), 4	(0, 0), 15	(0, 0), 7
Major bleeding†	(0, 0), 0*	(0, 0), 4	(0, 0), 15	(0, 0), 7
Myocardial infarction	(0, 0), 0*	(0, 0), 4	(0, 0), 15	(0, 0), 7
New onset atrial fibrillation‡	(0, 0), 0*	(0, 0), 3	(0, 0), 13	(0, 0), 6
New permanent pacemaker‡	(0, 0), 0*	(0, 0), 3	(0, 0), 13	(0, 0), 7
Readmission – cardiac	(0, 0), 0*	(0, 0), 4	(1, 1), 14	(1, 1), 6
Heart failure	(0, 0), 0*	(0, 0), 4	(1, 1), 14	(0, 0), 7
Non-heart failure	(0, 0), 0*	(0, 0), 4	(0, 0), 15	(1, 1), 6

(no. of events, no. of subjects with the event), no. at risk.
* The patient exited the study on Day 29.
†In TVTR data, in-hospital bleeding is not captured as life-threatening or major, therefore rates only include bleeding reported after index hospitalization.
‡Subjects with baseline condition are excluded.

Table 16: Site Reported Adverse Events by Ethnicity

Attempted Implant Population (N=502)

	Kaplan-Meier Estimate			
	Hispanic (N=33)		Non-Hispanic (N=461)	
	30 Days	1 Year	30 Days	1 Year
Death or stroke	3.0% (1, 1), 31	14.7% (4, 4), 18	2.5% (12, 11), 405	8.5% (34, 32), 234
All-cause death	3.0% (1, 1), 31	14.7% (4, 4), 18	1.8% (8, 8), 407	6.4% (24, 24), 240
All stroke	0.0% (0, 0), 31	0.0% (0, 0), 18	0.9% (4, 4), 405	2.4% (10, 9), 234
Cardiac death	3.0% (1, 1), 31	6.9% (2, 2), 18	0.4% (2, 2), 407	2.2% (8, 8), 240
Mitral valve reintervention	0.0% (0, 0), 31	0.0% (0, 0), 18	0.0% (0, 0), 407	0.8% (4, 3), 239
Major vascular complication	3.0% (1, 1), 31	3.0% (1, 1), 18	1.5% (7, 7), 402	1.8% (9, 8), 238
Life threatening/major bleeding*	0.0% (0, 0), 31	0.0% (0, 0), 18	1.6% (7, 7), 401	4.0% (17, 15), 235
Life threatening bleeding*	0.0% (0, 0), 31	0.0% (0, 0), 18	1.6% (1, 1), 407	1.4% (7, 5), 239
Major bleeding*	0.0% (0, 0), 31	0.0% (0, 0), 18	1.4% (6, 6), 401	2.6% (10, 10), 236

Myocardial infarction	0.0% (0, 0), 31	4.3% (1, 1), 17	0.5% (2, 2), 406	1.0% (4, 4), 239
New onset atrial fibrillation†	4.3% (1, 1), 21	4.3% (1, 1), 14	0.6% (2, 2), 316	2.7% (7, 7), 174
New permanent pacemaker†	0.0% (0, 0), 20	0.0% (0, 0), 14	0.9% (3, 3), 314	2.1% (6, 6), 186
Readmission – cardiac	3.1% (1, 1), 30	7.0% (2, 2), 17	1.8% (8, 8), 400	11.3% (50, 40), 218
Heart failure	0.0% (0, 0), 31	4.0% (1, 1), 17	1.2% (5, 5), 403	5.9% (28, 21), 232
Non-heart failure	3.1% (1, 1), 30	3.1% (1, 1), 18	0.7% (3, 3), 404	6.1% (22, 21), 225

Kaplan-Meier estimate - % (no. of events, no. of subjects with the event), no. at risk.
*In TVTR data, in-hospital bleeding is not captured as life-threatening or major, therefore rates only include bleeding reported after index hospitalization.
†Subjects with baseline condition are excluded.

Table 17: Mitral Regurgitation by Gender

Valve Implant Population (N=499)

	Summary Statistics					
	Male (N=217)			**Female (N=282)**		
	Baseline	**30-day Visit**	**1-year Visit**	**Baseline**	**30-day Visit**	**1-year Visit**
Mitral regurgitation						
None	14.2% (30/212)	71.0% (115/162)	67.0% (61/91)	14.7% (41/278)	67.5% (137/203)	60.4% (64/106)
Trace/Trivial	9.9% (21/212)	23.5% (38/162)	27.5% (25/91)	9.0% (25/278)	22.2% (45/203)	27.4% (29/106)
Mild	19.8% (42/212)	5.6% (9/162)	3.3% (3/91)	23.4% (65/278)	8.9% (18/203)	12.3% (13/106)
Mild-Moderate	0.5% (1/212)	0.0% (0/162)	0.0% (0/91)	1.1% (3/278)	0.0% (0/203)	0.0% (0/106)
Moderate	11.8% (25/212)	0.0% (0/162)	0.0% (0/91)	9.7% (27/278)	1.5% (3/203)	0.0% (0/106)
Moderate-Severe	9.9% (21/212)	0.0% (0/162)	1.1% (1/91)	8.6% (24/278)	0.0% (0/203)	0.0% (0/106)
Severe	34.0% (72/212)	0.0% (0/162)	1.1% (1/91)	33.5% (93/278)	0.0% (0/203)	0.0% (0/106)
Grouped mitral regurgitation						
<Moderate	44.3% (94/212)	100.0% (162/162)	97.8% (89/91)	48.2% (134/278)	98.5% (200/203)	100.0% (106/106)
≥Moderate	55.7% (118/212)	0.0% (0/162)	2.2% (2/91)	51.8% (144/278)	1.5% (3/203)	0.0% (0/106)

Continuous measures - Mean ± SE (Total no), median (Q1, Q3), [10%tile, 90%tile]. The total no. only counted the patients with valid values.

Table 18: Mitral Regurgitation by Race

Valve Implant Population (N=499)

	Summary Statistics							
	White (N=410)	**Black/ African American (N=48)**	**Asian (N=9)**	**American Indian/ Alaskan Native (N=4)**	**Native Hawaiian/ Pacific Islander* (N=1)**	**Multiple (N=4)**	**Unknown (N=16)**	**Other (N=7)**
Baseline								
Mitral regurgitation								
None	55	9	0	2	0	1	2	2
Trace/Trivial	39	2	0	0	0	0	4	1
Mild	88	13	3	0	0	1	2	0
Mild-Moderate	4	0	0	0	0	0	0	0
Moderate	43	5	1	1	0	1	1	0
Moderate-Severe	31	6	1	1	0	0	3	3
Severe	143	13	3	0	1	0	4	1
Grouped mitral regurgitation								
<Moderate	186	24	3	2	0	2	8	3
≥Moderate	217	24	5	2	1	1	8	4
30-day Visit								
Mitral regurgitation								
None	211	27	2	0	0	2	8	2
Trace/Trivial	67	4	3	1	0	2	2	4
Mild	20	4	1	0	0	0	1	1
Mild-Moderate	0	0	0	0	0	0	0	0
Moderate	3	0	0	0	0	0	0	0
Moderate-Severe	0	0	0	0	0	0	0	0
Severe	0	0	0	0	0	0	0	0
Grouped mitral regurgitation								

<Moderate	298	35	6	1	0	4	11	7
≥Moderate	3	0	0	0	0	0	0	0
1-year Visit								
Mitral regurgitation								
None	109	5	2	0	0	1	4	4
Trace/Trivial	44	4	2	0	0	0	1	3
Mild	13	3	0	0	0	0	0	0
Mild-Moderate	0	0	0	0	0	0	0	0
Moderate	0	0	0	0	0	0	0	0
Moderate-Severe	1	0	0	0	0	0	0	0
Severe	1	0	0	0	0	0	0	0
Grouped mitral regurgitation								
<Moderate	166	12	4	0	0	1	5	7
≥Moderate	2	0	0	0	0	0	0	0
The total no. only counted the patients with valid values. *The patient exited the study on Day 29.								

Table 19: Mitral Regurgitation by Ethnicity

Valve Implant Population (N=499)

	Summary Statistics					
	Hispanic (N=32)			Non-Hispanic (N=459)		
	Baseline	30-day Visit	1-year Visit	Baseline	30-day Visit	1-year Visit
Mitral regurgitation						
None	12.5% (4/32)	79.2% (19/24)	70.0% (7/10)	14.7% (66/450)	68.0% (229/337)	63.0% (116/184)
Trace/Trivial	12.5% (4/32)	16.7% (4/24)	20.0% (2/10)	9.3% (42/450)	23.4% (79/337)	28.3% (52/184)
Mild	15.6% (5/32)	4.2% (1/24)	10.0% (1/10)	22.0% (99/450)	7.7% (26/337)	7.6% (14/184)
Mild-Moderate	3.1% (1/32)	0.0% (0/24)	0.0% (0/10)	0.7% (3/450)	0.0% (0/337)	0.0% (0/184)
Moderate	6.3% (2/32)	0.0% (0/24)	0.0% (0/10)	11.1% (50/450)	0.9% (3/337)	0.0% (0/184)
Moderate-Severe	3.1% (1/32)	0.0% (0/24)	0.0% (0/10)	9.8% (44/450)	0.0% (0/337)	0.5% (1/184)

Severe	46.9% (15/32)	0.0% (0/24)	0.0% (0/10)	32.4% (146/450)	0.0% (0/337)	0.5% (1/184)
Grouped mitral regurgitation						
<Moderate	43.8% (14/32)	100.0% (24/24)	100.0% (10/10)	46.7% (210/450)	99.1% (334/337)	98.9% (182/184)
≥Moderate	56.3% (18/32)	0.0% (0/24)	0.0% (0/10)	53.3% (240/450)	0.9% (3/337)	1.1% (2/184)
Continuous measures - Mean ± SE (Total no), median (Q1, Q3), [10%tile, 90%tile]. The total no. only counted the patients with valid values.						

5. Other Study Observations

Procedural Information

The procedural information is summarized in Table 20. General anesthesia was used in the majority (96.8%) of patients. Conversion to open heart surgery occurred in two patients, one due to ventricular rupture and the other due to unknown cause.

Table 20: Procedural Data Summary (AI Population)

Procedural Data	Summary Statistics* (n=502)
Primary procedure indication	
Mitral stenosis	60.6% (114/188)
Mitral regurgitation	34.0% (64/188)
Both regurgitation and stenosis	5.3% (10/188)
Access site	
Transseptal	100.0% (502/502)
Valve type	
SAPIEN 3	83.7% (420/502)
SAPIEN 3 Ultra	16.3% (82/502)
Valve size	
20 mm	0.2% (1/502)
23 mm	4.8% (24/502)
26 mm	42.0% (211/502)
29 mm	53.0% (266/502)
Type of anesthesia	
General anesthesia	96.8% (486/502)

Deep sedation/analgesia	0.2% (1/502)
Moderate sedation/analgesia	3.0% (15/502)
Total procedure time (minute)	99.0 ± 2.31 (502)
Device implanted successfully	98.6% (495/502)
Procedure aborted	0.0% (0/452)
Conversion to open heart surgery	0.4% (2/452)
Ventricular rupture	1
Other	1
Subjects with more than one valve implanted during procedure	0.8% (4/502)

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

6. Pediatric Extrapolation

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

XI. 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 P3 MVIV Study involved 75 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.

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

In accordance with the provisions of section 515(c)(2) of the Act as amended by the

Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory 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.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The patients with a failing bioprosthetic mitral valve who are at intermediate surgical risk that underwent the mitral valve-in-valve procedures overall demonstrated clinically significant improvements in valve hemodynamics in regard to improvement in mitral regurgitation (MR) and mean mitral gradient. Moderate or greater total mitral regurgitation was observed in 53.5% of the patients at baseline, which decreased to 0.8% at 30 days and 1.0% at 1 year. Moderate or greater PVL was observed in 9.9% of the patients at baseline, which decreased to 0.3% at 30 days and 1.2% at 1 year. Mitral valve mean gradient decreased from 12.5 mmHg at baseline to 7.6 mmHg at 30 days and 7.5 mmHg at 1 year.

The improvements in valve hemodynamics were further demonstrated with improvements in patients' functional status and quality of life. The majority (89.3%) of patients were in NYHA Class I/II at 1 year as compared to 29.4% at baseline. Similarly, clinically significant improvement was observed in the mean KCCQ overall summary score, which increased from 42.6 points at baseline to 78.6 points 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 P3 MVIV study to support PMA approval as described above.

The study supporting this marketing application had two co-primary endpoints including all-cause death or all stroke at 30 days and all-cause death at 1 year which were both met. The Kaplan-Meier estimate for all-cause death or all stroke was 2.5% at 30 days which is less than the prespecified performance goal of 10.4%. The Kaplan-Meier estimate for all-cause death was 6.9% at 1 year which is less than the prespecified performance goal of 19.6%. The cardiac death rate was 0.6% at 30 days and 2.5% at 1 year. Other notable adverse events included major vascular complication (1.6% at 30 days and 1.9% at 1 year), life-threatening or major bleeding (1.5% at 30 days and 3.7% at 1 year), cardiac readmission (2.1% at 30 days and 11.1% at 1 year), and readmission due to heart failure (1.1% at 30 days and 5.7% at 1 year).

C. Benefit-Risk Determination

The probable benefits of the mitral valve-in-valve treatment with the SAPIEN 3

THV platform include improved functional status as measured by the NYHA classification, and improved QoL as measured by the KCCQ.

The probable risks of the mitral valve-in-valve treatment with the SAPIEN 3 THV platform include procedural and late complications such as death, stroke, myocardial infarction, major vascular complications, and conduction disturbance that may require a permanent pacemaker.

1. Patient Perspective
   This submission did not include specific information on patient perspectives for this device. However, since transcatheter valve replacement with an Edwards SAPIEN 3, SAPIEN 3 Ultra, or SAPIEN 3 Ultra RESILIA THV provides a less invasive alternative to surgical valve replacement, FDA believes many patients and their physicians would prefer the transcatheter valve replacement therapy as an alternative.

In conclusion, given the available information above, the data support that for patients with a failing bioprosthetic mitral valve who are at intermediate risk for open surgical therapy, the probable benefits of implanting an Edwards SAPIEN 3, SAPIEN 3 Ultra, or SAPIEN 3 Ultra RESILIA THV 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, SAPIEN 3 Ultra THV, and SAPIEN 3 Ultra RESILIA in treating patients with symptomatic heart disease due to a failing bioprosthetic mitral valve who are judged by a heart team, including a cardiac surgeon, to be at intermediate risk for open surgical therapy.

XIV. CDRH DECISION

CDRH issued the original approval order on May 23, 2024. A correction letter was issued on October 25, 2024, with the final conditions of approval cited in the approval order, as described below.

The applicant must participate in and support continued surveillance of the SAPIEN 3, SAPIEN 3 Ultra and SAPIEN 3 Ultra RESILIA THV System used for the mitral Valve-in-Valve treatment:

1. **Continued Follow-up of the SAPIEN 3 Transcatheter Heart Valve Implantation in Intermediate Risk Patients with a Failing Mitral Bioprosthetic Valve Premarket Cohort.** This study will be conducted in accordance with the protocol under the IDE (G150278). The study will consist of all living patients who were enrolled under the IDE. The objective of this post-approval study is to characterize the clinical outcomes annually through 10 years post-procedure. The study will report on all-cause mortality, all stroke, myocardial

infarction, valve reintervention, prosthetic valve endocarditis, prosthetic valve thrombosis, structural valve deterioration (SVD), New York Heart Association (NYHA) classification, Kansas City Cardiomyopathy Questionnaire (KCCQ) score, hemodynamic performance metrics by Doppler echocardiography and adverse events.

2. **Edwards SAPIEN 3, SAPIEN 3 Ultra, and SAPIEN 3 Ultra RESILIA Mitral Valve-in-Valve Intermediate Risk Indication Real-World Use Surveillance**: The applicant has agreed to work with the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy (TVT) Registry to ensure that FDA surveillance occurs for the SAPIEN 3, SAPIEN 3 Ultra, and SAPIEN 3 Ultra RESILIA Transcatheter Heart Valve Systems for the replacement of a failing surgical bioprosthetic mitral valve for the "intermediate-risk" indication over the next 3 years or a total of 1,000 consecutively treated patients, whichever is greater. Data collection will continue for underrepresented racial and ethnic groups (Black/African American, Asian, American Indian/Alaskan Native, Native Hawaiian/Pacific Islander, and Hispanic or Latino ethnicity) until each group has enrolled the following minimum number of patients:

   - 150 Hispanic
   - 150 Black/African American
   - 100 Asian
   - 50 American Indian/Alaskan Native
   - 25 Native Hawaiian/Pacific Islander

   Data will be collected through 1 year as part of the TVT Registry. You have also agreed to link the data to Centers for Medicare and Medicaid Services (CMS) database for long-term surveillance of these patients through 10 years post implantation.

   This surveillance will monitor the following: (1) device implanted successfully; (2) all-cause mortality, all stroke, life threatening/major bleeding, new requirement for dialysis, myocardial infarction, mitral valve reintervention, TIA, and vascular complications at 30 days and 12 months; (3) 6-minute walk distance, KCCQ, and change in NYHA functional class at 30 days and 12 months; (4) mitral valve hemodynamics at 30 days and 12 months; (5) all-cause mortality, all stroke, and mitral valve reintervention at 2-10 years post implantation.

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

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.