SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Aortic valve, prosthesis, percutaneously delivered
Device Trade Name:	Trilogy Transcatheter Heart Valve System
Device Procode:	NPT
Applicant's Name and Address:	JenaValve Technology, Inc. 4 Cromwell Irvine, CA 92618
Date(s) of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P250024
Date of FDA Notice of Approval:	March 17, 2026
Breakthrough Device:	Granted breakthrough device status on December 20, 2019, because the device can provide for more effective treatment of an irreversibly debilitating disease; as well as represents a breakthrough technology and is in the best interest of patients.

II. INDICATIONS FOR USE

The Trilogy Transcatheter Heart Valve System is indicated for the treatment of symptomatic, severe native tricuspid aortic valve regurgitation (not due to acute endocarditis, rheumatic heart disease, or acute aortic dissection) in patients who are judged by a Heart Team, including a cardiac surgeon, to be at high or greater risk for surgical aortic valve replacement (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 Trilogy Transcatheter Heart Valve System is contraindicated in patients who cannot tolerate an anticoagulation/antiplatelet regimen, have known hypersensitivity to nitinol alloy (nickel and titanium) or contrast agents that cannot be managed with premedication, or who have active bacterial endocarditis or other active infection.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Trilogy Transcatheter Heart Valve System labeling.

V. DEVICE DESCRIPTION

The Trilogy Transcatheter Heart Valve System consists of the Transcatheter Heart Valve (THV), Introducer Sheath, Delivery Catheter, and Loading Tools.

The Trilogy THV, as shown in Figure 1, is made of a self-expanding nitinol frame with three porcine pericardial leaflets sewn on using polyester sutures. The THV design includes a flared Sealing Ring that extends from the inflow in the left ventricular outflow track (LVOT) to the annular basal plane. The frame has three (3) Locators that contain radiopaque tantalum markers covered by pericardial tissue. The Locators clip onto the native leaflets such that when the THV is deployed, the native leaflets are captured between the Locators and the stent frame body. The frame features large open Intermediate Strut cells. THV commissural alignment centers the Intermediate Strut cells within the coronary cusps, which is intended to preserve future access to coronary ostia. The THV is available in three sizes: 23 mm, 25 mm, and 27 mm.

Figure 1: Trilogy THV

The Trilogy Delivery System is comprised of the Trilogy Delivery Catheter, an introducer sheath and dilator, and loading tools. The Trilogy Delivery Catheter, as shown in Figure 2, is used to position and deploy the Trilogy THV into the native aortic valve and comprises three main shafts: the Guidewire Shaft, the Torque Tube and the Deflecting Catheter. The Delivery Catheter has an outer diameter of 20 Fr, a working length of approximately 126 cm, and is designed to be used over a 0.035” guidewire and to pass through the Introducer Sheath.

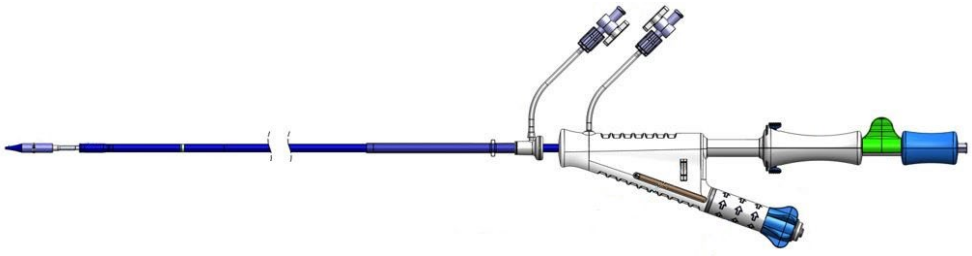


Figure 2: Trilogy Delivery Catheter

The Trilogy Introducer Sheath is a 22 Fr outer diameter (OD) Sheath, as shown in Figure 3. It is made of a PTFE-lined, stainless-steel braid-reinforced, multi-durometer Pebax jacket with a distal platinum-iridium marker band. The Sheath has a working length of 85 cm and is pre-shaped. The pre-shaped Sheath is intended to conform to the shape of the aortic arch when the Dilator is removed and before the Delivery Catheter is transferred. The OD of the distal end has a hydrophilic coating. The Sheath protects the THV and patient anatomy during Delivery Catheter advancement into the ascending aorta.

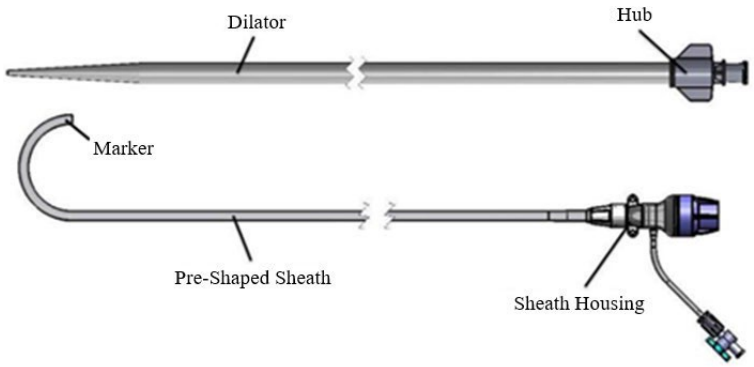


Figure 3: Trilogy Introducer Sheath with Dilator

The Trilogy Loading Tools, as shown in Figure 4, are used to load the Trilogy THV onto the Delivery Catheter.

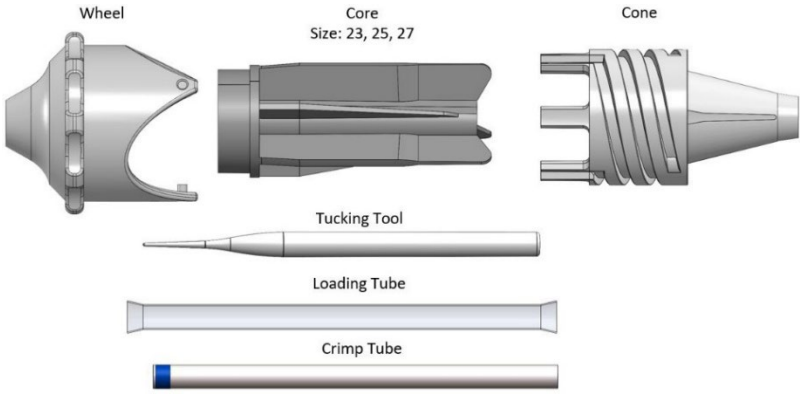


Figure 4: Trilogy Loading Tools

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are limited treatment options for patients with symptomatic, severe native tricuspid aortic valve regurgitation (AR) who are deemed to be at high or greater risk for surgical aortic valve replacement (SAVR). When surgery is not offered, patients are often treated conservatively with 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 Trilogy Transcatheter Heart Valve System is commercially available in Austria, Denmark, France, Germany, Hong Kong, Ireland, Italy, Netherlands, Switzerland, and the United Kingdom. It has not been withdrawn from marketing for any reason related to its safety or effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

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

- Death
- Allergic reaction to anesthesia, contrast media, antithrombotic therapy, device materials
- Anemia
- Angina
- Aortic root distortion
- Atelectasis
- Arrhythmia
- Arteriovenous (AV) fistula
- Blood loss requiring transfusion
- Cardiovascular or vascular injury, such as perforation or damage (dissection) of vessels, myocardium or valvular structures that may require intervention
- Cardiac arrest
- Cardiac failure
- Cardiogenic shock
- Chest pain/discomfort
- Conduction system injury
- Coronary flow obstruction/transvalvular flow disturbance
- Deep vein thrombosis
- Device acute migration or malposition
- Device dysfunction (regurgitation and/or stenosis)
- Device embolization
- Device thrombosis
- Dislodgement of previously implanted devices (i.e., pacing lead)

- Dyspnea
- Electrolyte imbalance
- Embolic event: air, calcific material, thrombus, device fragments
- Endocarditis
- Exercise intolerance or weakness
- Fever
- Hematoma or ecchymosis
- Hemolysis/hemolytic anemia
- Hypertension or hypotension
- Infection including incisional site infection, septicemia and endocarditis
- Inflammation
- Mechanical failure of delivery system, and/or accessories
- Myocardial infarction
- Pain
- Pericardial effusion/cardiac tamponade
- Pleural effusion
- Pneumothorax
- Pulmonary edema
- Radiation injury
- Renal insufficiency or renal failure
- Reoperation
- Respiratory insufficiency or respiratory failure
- Stroke/transient ischemic attack
- Syncope
- Systemic or peripheral ischemia
- Systemic or peripheral nerve injury

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

IX. SUMMARY OF NON-CLINICAL STUDIES

A. Laboratory Studies

Nonclinical laboratory studies on the Trilogy Transcatheter Heart Valve System were performed in accordance with but not limited to: ISO 5840-1:2021, *Cardiovascular implants – Cardiac valve prostheses – Part 1: General Requirements*, and ISO 5840-3:2021, *Cardiovascular implants – Cardiac valve prostheses – Part 3: Heart valve substitutes implanted by transcatheter techniques*, along with relevant FDA guidance documents.

1. Biocompatibility

   Biocompatibility assessments were completed on the Trilogy Transcatheter Heart Valve System in accordance with ISO 10993-1, *Biological Evaluation of Medical Devices - Part 1: Evaluation and testing within a risk management process*, and the FDA Guidance for

Industry and Food and Drug Administration Staff, *Use of International Standard ISO 10993-1, Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process*. The required testing for each component was determined based on the nature and duration of body contact per ISO 10993-1. The test articles consisted of patient-contacting device components after exposure to all manufacturing processes, including sterilization. The biocompatibility test results for the Trilogy THV, Trilogy Delivery Catheter, Introducer Sheath and Dilator, and Loading Tools are summarized in the tables below.

Table 1: Summary of Biocompatibility Testing – Trilogy THV

Biological Effect Per ISO 10993-1	Test Method	Results
Cytotoxicity	MEM Elution Cytotoxicity	Non-cytotoxic
Sensitization	Guinea Pig Maximization	Non-sensitizing
Irritation	Intracutaneous Reactivity (Rabbit)	Non-irritant
Acute Systemic Toxicity	Acute Systemic Toxicity Test in Mice	Non-toxic
Hemocompatibility	In vitro hemolysis (indirect contact)	Non-hemolytic
	In vitro hemolysis (direct contact)	Non-hemolytic
	Complement activation test	No risk to activate complement
	Partial Thromboplastin Time (PTT)	Non-coagulant
	In vivo thrombogenicity with domestic sheep	No evidence of clinically significant thrombus or thromboembolism after implantation for up to 20-weeks
Material Mediated Pyrogenicity	USP Material Rabbit Mediated Pyrogen Study	Non-pyrogenic
Genotoxicity	Ames Assay – plate incorporation	Non-mutagenic
	Chromosomal aberration assay	Non-mutagenic

Biological Effect Per ISO 10993-1	Test Method	Results
Physiochemical*	Chemical characterization of volatile organic compounds, semivolatile organic compounds, nonvolatile organic compounds, and elements followed by toxicological risk assessment	Exposure estimates, safety margins, and the likelihood of extractable chemicals from the implant producing unacceptable carcinogenic or non-carcinogenic health risks in the adult patient population under the proposed conditions and duration of clinical use (long term; >30 days) were acceptable.
*The Trilogy loading tools were also considered in the physiochemical assessment via simulated use with the device prior to extraction.		

Table 2: Summary of Biocompatibility Testing – Trilogy Delivery Catheter, Introducer Sheath and Dilator

Biological Effect Per ISO 10993-1	Test Method	Results
Cytotoxicity	MEM Elution Cytotoxicity	Non-cytotoxic
Sensitization	Guinea Pig Maximization	Non-sensitizing
Irritation	Intracutaneous Reactivity (Rabbit)	Non-irritant
Acute Systemic Toxicity	Acute Systemic Toxicity Test in Mice	Non-toxic
Hemocompatibility	In vitro hemolysis (indirect contact)	Non-hemolytic
	In vitro hemolysis (direct contact)	Non-hemolytic
	Complement activation test	No risk to activate complement
	Partial Thromboplastin Time (PTT)	Non-coagulant
	In vivo thrombogenicity in domestic sheep	No evidence of clinically significant thrombus or thromboembolism after procedure
Material Mediated Pyrogenicity	USP Material Rabbit Mediated Pyrogen Study	Non-pyrogenic

Table 3: Summary of Biocompatibility Testing – Loading Tools		
Biological Effect Per ISO 10993-1	**Test Method**	**Results**
Cytotoxicity	MEM Elution Cytotoxicity	Non-cytotoxic
Sensitization	Guinea Pig Maximization	Non-sensitizing
Irritation	Intracutaneous Reactivity (Rabbit)	Non-irritant
Acute Systemic Toxicity	Acute Systemic Toxicity Test in Mice	Non-toxic
Hemolysis	ASTM Extract Method	Non-hemolytic

2. Bench Testing

A summary of the bench testing results is summarized in **Table 4** and **Table 5**.

Table 4: Summary of Design Performance Testing – Trilogy THV		
Test	**Purpose**	**Results**
THV Foreshortening	To evaluate the relationship of the THV length and diameter between catheter-loaded and deployed conditions.	Met design requirements and acceptance criteria
THV Corrosion and Nickel Ion release	To verify the corrosion resistance of the THV and determine the nickel ion release rate.	Met design requirements and acceptance criteria
Galvanic Corrosion	To determine the susceptibility of the metallic components of the THV stent to corrosion in a simulated physiological environment.	Met design requirements and acceptance criteria
Chronic Outward Force (CoF), Radial Resistive Force (RRF), and Migration Resistance	To determine the valve has acceptable CoF and RRF to ensure migration resistance and delivery system compatibility.	Met design requirements and acceptance criteria
Accelerated Wear Testing	To assess long-term valve performance through accelerated wear testing.	Met minimum prespecified hydrodynamic performance specifications through 150M cycles, which did not meet the 200M-cycle requirement in ISO 5840-1:2023
Dynamic Failure Mode Analysis	Characterize potential failure modes affecting valve durability.	Demonstrated a gradual degradation failure mode

Test	Purpose	Results
Finite Element Analysis	To determine mechanical strain during valve loading, deployment and cyclic loading. Results used to assess the fatigue life of the device.	No fracture of valve structural components predicted within a minimum of 600 million cycles under clinically representative challenging conditions.
Fatigue Resistance	To demonstrate the fatigue resistance of the THV stent to 600 million cycles.	No fractures observed following 600 million cycles of fatigue testing.
Magnetic Resonance Imaging (MRI) Compatibility	To evaluate MRI safety and compatibility of the Trilogy THV and ensure that the Trilogy THV is not affected by scanning at 1.5 Tesla and 3.0 Tesla field strengths.	Trilogy THV can be labeled "MR Conditional."
Hydrodynamic Assessment	To determine the hydrodynamic performance of the valve in terms of effective orifice area and regurgitation under aortic cardiac conditions.	Met prespecified minimum hydrodynamic performance for each condition.
Tissue Characterization	Characterize shrinkage temperature to confirm the effectiveness of glutaraldehyde crosslinking.	Met design requirements and acceptance criteria
	Characterize tissue properties via uniaxial tensile testing, ball burst testing, and histological staining.	Characterization Only

Table 5: Summary of Design Performance Testing – Trilogy Delivery System

Test	Purpose	Results
Visual inspection	To verify the Trilogy Delivery System is free of visible defects or damage.	Met design requirements and acceptance criteria.
Dimensional inspection	To ensure the prespecified dimensions of the Trilogy Delivery System are met.	Met design requirements and acceptance criteria.
Flushing	To ensure inner lumens of the Trilogy Delivery System can be flushed with standard syringes.	Met design requirements and acceptance criteria.
Hydrophilic Coating Integrity and Particulate Characterization	To evaluate and characterize particulate counts via light obscuration and hydrophilic coating integrity of the Introducer Sheath after a simulated use procedure.	Met design requirements and acceptance criteria.
Leakage	To ensure the Trilogy Delivery System maintains hemostasis.	Met design requirements and acceptance criteria.

Test	Purpose	Results
Bond Strength	Verification that the bonds and tubing of the Trilogy Delivery System remain intact when subjected to prespecified tensile testing and/or simulated use.	Met design requirements and acceptance criteria.
Simulated Use	To verify the functionality of the Trilogy THV System, including loading, tracking, deployment, and retrieval in a simulated clinical setting.	Met design requirements and acceptance criteria.
Corrosion Testing	To verify the corrosion resistance of the Delivery Catheter.	Met design requirements and acceptance criteria.

B. Animal Studies

The Trilogy Transcatheter Heart Valve System underwent Good Laboratory Practice-compliant preclinical *in vivo* evaluations in an ovine model as summarized in **Table 6**.

Table 6: Summary of Animal Studies

Acute GLP Animal Study	
Test Purpose / Requirement	An acute animal study was performed to evaluate the *in vivo* safety and performance of the Delivery System
Device Tested	Size 25- & 27-mm THV, Trilogy Delivery System
Animal Model & Sample Size	Sheep, N = 5
Test Method	Implants performed by study physician under beating heart conditions. Physician evaluation of access, introduction, visualization, delivery, deployment, and system removal.
Study Duration	Acute
Results	All five animals survived transfemoral implantation.
Conclusions	All devices were delivered and implanted as intended. All devices were well seated. No adverse events or test device-related complications occurred during any procedure and all animals remained hemodynamically stable throughout the procedure. The results of the acute animal study demonstrated the safety and performance of the subject Trilogy Heart Valve System in an *in vivo* (ovine) model.
90-Day GLP Aortic Implant Study	
Test Purpose / Requirement	A 90-day chronic animal study was performed to evaluate the safety and performance of the Trilogy THV in an *in vivo* model
Device Tested	Size 25-mm THV, Trilogy Delivery System*
Animal Model & Sample Size	Sheep, N = 7
Test Method	Implants performed by study physician under beating heart conditions, under brachiocephalic delivery. Device implant

	characteristics and ease of use were evaluated at the time of the procedure by the implanting physician.
Study Duration	90 days
Results	Six animals survived to a minimum of 90 days. One death occurred prior to the planned implant duration due to complications related to the sheep anatomy.
Conclusions	All devices were delivered and implanted as intended. All devices were well seated, stable, and stents were intact with no strut fracture. For the six surviving animals, there were no clinically significant injuries to adjacent anatomic structures or other clinically significant device-related events under histological assessment. The results of the 90-Day study demonstrated the safety and performance of the subject Trilogy Heart Valve in an *in vivo* (ovine) model.
Long-term GLP Aortic Implant Study	
Test Purpose/ Requirement	Evaluation of the safety and performance of the THV under long term *in vivo* conditions.
Device Tested & Sample Size	Size 25-mm THV[#] Control and Test: Trilogy Delivery System*
Animal Model & Sample Size	Sheep, N=12
Test Method	Implants performed by study physician under beating heart conditions using left subclavian delivery. Device implant characteristics and ease of use were evaluated at the time of the procedure by the implanting physician.
Study Duration	20 weeks
Results	Seven animals survived as planned (137-138 days). Five deaths occurred prior to the planned implant duration due to complications unrelated to the device.
Conclusions	All devices were delivered and implanted as intended. All devices were well seated, stable, and stents were intact with no strut fracture. No clinically significant injuries to adjacent anatomic structures or other clinically significant device-related events under gross and histological assessment. Host/tissue interface results were characteristic of implanted transcatheter aortic valves. Echocardiographic evaluations demonstrated low gradients to study completion.

*The 90-day and long-term implant studies used earlier delivery system iterations. These studies were considered representative of the final device as the delivery system modifications were minor and the primary purpose of the 90-day and long-term implant studies was to understand the longer-term function of the implant.

[#]n=9 devices used proprietary tissue processing (representative of final device) and n=3 devices used contractor tissue processing. Host/tissue interface results were comparable among groups.

C. Sterilization

The Trilogy THV is sterilized by terminal liquid sterilization (TLS) in buffered 0.5% glutaraldehyde solution. The validated TLS process has demonstrated a Sterility Assurance Level (SAL) of 10^{-6}, following ISO 14160:2020, *Sterilization of health care products -- Liquid chemical sterilizing agents for single-use medical devices utilizing animal tissues and their derivatives.*

The Trilogy Delivery Catheter, Introducer Sheath, and Loading Tools are sterilized by ethylene oxide (EO). The EO sterilization processes have demonstrated Sterility Assurance Levels (SAL) of 10^{-6} in accordance with ISO 11135-1:2014+A1:2018*, Sterilization of health care products – Ethylene oxide – Requirements for development, validation and routine control of a sterilization process for medical devices.*

D. Packaging and Shelf-life

The Trilogy THV is stored in a jar filled with buffered glutaraldehyde solution tightly sealed with a lid and silicone disc/seal to form the primary sterile barrier. The jar is contained within a shelf carton with foam pieces (secondary packaging).

The Trilogy Delivery System components (Trilogy Delivery Catheter, Trilogy Introducer Sheath, and Loading Tools) are packaged separately. Each component is packaged in a sealed Tyvek/Nylon pouch and shelf carton.

The packaging validation for the sterile components of the Trilogy THV System was conducted per ASTM D4332 *Standard Practice for Conditioning Containers, Packages, or Packaging Components for Testing*, ASTM D4169 *Standard Practice for Performance Testing of Shipping Containers and Systems*, ASTM F1980 *Standard Guide for Accelerated Aging of Sterile Barrier Systems and Medical Devices*, ASTM F2203 *Standard Test Method for Linear Measurement Using Precision Steel Rule*, ASTM F2096 *Standard Test Method for Detecting Gross Leaks in Packaging by Internal Pressurization (Bubble Test*), and ASTM F88/F88M *Standard Test Method for Seal Strength of Flexible Barrier Materials*. The packaging validation demonstrated that the packaging system was able to maintain a sterile barrier after exposure to environmental conditioning, distribution simulation, and aging.

The shelf life of the Trilogy THV is 16 months based on real-time aging of the THV and accelerated aging of the packaging. The shelf-life of all components of the Trilogy Delivery System is 1 year based on accelerated aging. Packaging integrity and product functional testing were conducted on aged samples to ensure that the components meet specifications throughout the stated shelf life.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study under IDE #G150035 (entitled the "ALIGN-AR" study) to establish a reasonable assurance of safety and effectiveness of transcatheter aortic valve replacement with the Trilogy Transcatheter Heart Valve System in patients with symptomatic, severe aortic regurgitation (not due to acute endocarditis, rheumatic heart disease, or acute aortic dissection) who are at a high or greater risk for surgical aortic valve replacement (SAVR). Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

The ALIGN-AR study was a prospective, multicenter, single-arm study. Patients were treated between July 10, 2018, and August 29, 2022. The database for this PMA reflected data collected through October 5, 2023, and included 180 patients. There were 20 investigational sites in the United States.

The ALIGN-AR study was a prospective, multicenter, single-arm study. The ALIGN-AR study utilized: a Case Review Board (CRB) to confirm subject suitability prior to enrollment; an independent Clinical Events Committee (CEC) to adjudicate safety events and protocol deviations; and an independent core laboratory to assess echocardiography data and computed tomography (CT) data.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the ALIGN-AR study was limited to patients who met the following inclusion criteria:

   – Adult subjects with severe AR (Grade ≥ 3) as assessed by echocardiography based on American Society of Echocardiography (ASE) guidelines using a multiparametric approach with:
     - Jet width ≥65% of LVOT
     - Vena contracta width of >6 mm
     - Holodiastolic flow reversal in proximal abdominal/descending aorta
     - Jet deceleration rate/pressure half time < 200 ms

     AND

     For Grade 3
     - Regurgitant volume 45-59 ml/beat
     - Regurgitant fraction 40-49%
     - Effective regurgitant orifice area (EROA) 0.2-0.29 cm^2

     OR

     For Grade 4
     - Regurgitant volume ≥ 60 ml/beat
     - Regurgitant fraction 50%
     - EROA ≥ 0.3 cm^2

- Patient symptomatic according to New York Heart Association (NYHA) functional class II or higher
- Patient with high risk for SAVR as documented by heart team and Heart Team agrees that patient can undergo SAVR for "bail out"/to address unfavorable circumstances if necessary
- Patient has suitable anatomy to accommodate the insertion and delivery of the Trilogy Transcatheter Heart Valve System
- Patient or the patient's legal representative has provided written informed consent
- Patient or the patient's legal representative agrees to comply with all required post-procedure follow-up visits

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

- Congenital uni- or bicuspid aortic valve morphology
- Previous prosthetic aortic valve (bioprosthesis or mechanical) implant
- Mitral regurgitation > moderate
- Clinically significant coronary artery disease (CAD) requiring revascularization within 30 days prior to index procedure, or planned CAD revascularization procedure within 12 months after index procedure
- Echocardiographic evidence of left ventricular thrombus
- Endocarditis within 180 days prior to the index procedure
- Hypertrophic cardiomyopathy with or without obstruction
- Severe pulmonary hypertension (systolic pulmonary artery pressure > 80 mmHg)
- Severe right ventricle (RV) dysfunction as assessed clinically and by echo
- Severely reduced left ventricular ejection fraction (LVEF <25%)
- Aortic annular perimeter-derived diameter of <21.0 mm or >28.6 mm or perimeter <66 mm or >90 mm (assessed by Multi-Detector CT (MDCT) measurement)
- Aortic annulus angulation >70° (assessed by MDCT measurement)
- Straight length of ascending aorta of <55 mm
- Significant disease of ascending aorta, including ascending aortic aneurysm (defined as maximal luminal diameter of 50 mm or greater) or atheroma (including if thick [>5 mm], protruding or ulcerated)
- Need for urgent or emergent TAVR procedure for any reason
- Cardiogenic shock or hemodynamic instability requiring inotropic support or ventricular assist device within 30 days prior to index procedure
- Myocardial infarction <30 days prior to index procedure
- Cerebrovascular event (transient ischemic attack (TIA), stroke) < 180 days prior to index procedure
- Severe renal insufficiency (GFR < 30 ml/min) at Screening, OR renal disease requiring renal replacement therapy within 180 days prior to index procedure
- Blood dyscrasias as defined: leukopenia (WBC < 3000/mm^3), or thrombocytopenia (platelets < 90,000/µl) or anemia (Men: Hgb < 8.1 g/dl; Women: Hgb < 7.4 g/dl)
- Active peptic ulcer or upper gastrointestinal bleeding < 90 days prior to index procedure

- Known hypersensitivity or contraindication to aspirin, heparin, ticlopidine or clopidogrel, nitinol, tantalum or allergy to contrast agents that cannot be premedicated
- Contraindication to intraoperative transesophageal echocardiography and/or MDCT scan
- Estimated life-expectancy of < 24 months
- Patient is enrolled in another investigational medical device or drug study which has not completed the required primary endpoint follow-up. (Note: Patients involved in a long-term surveillance phase of another study are eligible for enrollment in this study)
- Other medical, social, or psychological conditions that in the opinion of an Investigator precludes the patient from providing appropriate informed consent
- Severe dementia (resulting in either inability to provide informed consent for the trial/procedure, prevents independent lifestyle outside of a chronic care facility, or will fundamentally complicate rehabilitation from the procedure or compliance with follow-up assessments)
- Unable to comply with follow-up requirements

In addition to the exclusion criteria above, subjects were excluded from the CT sub-study if the following condition was present:

- Inability to have high-quality MDCT study for any reason performed (e.g., atrial fibrillation with rapid ventricular response)

2. Follow-up Schedule

All patients were scheduled to return for follow-up examinations at 30 days, 6 months, 12 months, and then annually through 5 years.

Preoperative and post-operative assessments included physical assessment, laboratory measurements, imaging tests, as well as health status questionnaires. Adverse events and complications were recorded at all visits.

3. Clinical Endpoints

Primary Safety Endpoint

With regards to safety, the primary safety endpoint was a composite of major adverse events at 30 days consisting of the following components:

- All-cause mortality
- All stroke
- Life threatening or major bleeding
- Acute kidney injury (AKI) Stage 2, 3 or dialysis
- Surgery/intervention related to the device (including coronary intervention)
- Major vascular complications

- Permanent pacemaker implantation
- Moderate or severe total aortic regurgitation

With regard to success/failure criteria, the hypothesis for the primary safety endpoint was defined as follows:

H_0: Pt $\geq$ 40.5%
H_1: Pt < 40.5%

where Pt is the proportion of patients with a composite safety endpoint event at 30 days and 40.5% was the pre-specified performance goal (PG), which was derived from past TAVR trials in aortic stenosis patients with high or greater surgical risk. The primary safety endpoint assessment was performed at a one-sided significance level of 0.025.

Primary Effectiveness Endpoint

With regards to effectiveness, the primary effectiveness endpoint was the incidence of all-cause mortality at 1 year. With regard to success/failure criteria, the primary effectiveness hypothesis was defined as follows:

H_0: $\pi \geq 25\%$
H_1: $\pi < 25\%$

where π was the proportion of patients with all-cause mortality at 1 year and 25% was the PG derived from reported mortality rates for patients with severe, symptomatic AR treated via conservative medical management, weighted by NYHA Classification (70% NYHA Class III/IV and 30% NYHA class I/II). The primary effectiveness endpoint assessment was performed at a one-sided significance level of 0.025.

Secondary Endpoint

The secondary effectiveness endpoint was the change in health status from baseline to 1-year, as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score. Only subjects who had KCCQ score measured at both baseline and 1-year were included in this analysis.

The secondary endpoint was to be tested only if both the primary safety and effectiveness hypotheses were successful. With regard to success/failure criteria, the hypothesis for the secondary endpoint was defined as:

H_0: $\mu_t \leq 10$ points
H_1: $\mu_t > 10$ points

where: μ_t was the mean change in KCCQ score from baseline to 1 year and 10 points was the pre-specified performance goal. The secondary endpoint was evaluated using a paired t-test with one-sided significance level of 0.025.

Descriptive Endpoints

Key descriptive endpoints included the following:

- KCCQ overall summary score
- NYHA functional class
- 6-minute walk test distance (6MWT) distance
- Proportion of patients with none-to-trace AR
- Echocardiographic parameters

B. Accountability of PMA Cohort

At the time of database lock, a total of 180 patients out of 346 patients enrolled for screening had the procedure started (Enrolled/Eligible Patient [EP] population) and 177 patients had the study valve implanted (Valve Implant [VI] Population). The primary analysis populations and patient disposition are summarized in **Table 7** and **Table 8**, respectively.

Table 7: Subject Accounting Summary (Primary Analysis Population)

Analysis Population	Definition	Number of Patients
Eligible Patient (EP)	All patients who had the procedure started.	180
Valve Implant (VI)	All patients who had a study valve implanted upon leaving the procedure room.	177*

*Two patients did not have a study valve successfully implanted because of valve embolization followed by surgical aortic valve replacement (n=1) and embolization followed by commercial THV implantation (n=1). A third patient did not receive a study valve implanted due to an aortic dissection that developed during the procedure but before the Trilogy THV was inserted into the body. This patient was treated with a commercial THV device.

Table 8: ALIGN-AR Patient Disposition Summary		
	30-Day	**1-Year**
Total Patients	180	180
Non-eligible†	4	15
Death	4	14
Withdrawal	0	0
Lost to follow-up	0	0
Exit for other reason	0	1
Eligible	176	165
Visit Completed	175	160
Missed visit‡	1	5
Follow-up Compliance*	99.4%	96.7%
† Includes all patients who exited the study prior to the end of the follow-up visit window and who have not had the visit. ‡ Data extract date has exceeded the end of the visit window, and the patients have not completed the visit. * Follow-up Compliance is calculated as follows: (Number with visit completed) / (Number eligible).		

C. Study Population Demographics and Baseline Characteristics

The demographics and baseline characteristics of the subjects, as shown in **Table 9**, present an elderly cohort of patients, with comorbidities consistent with the high operative risk of the population. The STS score (4.04 ± 3.37) is lower than anticipated for a high surgical risk population, but all patients were determined to be high risk by a cardiac surgeon, often based on factors not measured by the STS risk calculator. Factors considered by the heart team included hostile chest, frailty, right ventricular dysfunction, pulmonary hypertension, and need for concomitant procedures that elevated surgical risk as denoted by the heart team surgeon (e.g., coronary artery bypass grafting (CABG) or mitral valve intervention). Study enrollment ensured that the proportion of patients with NYHA III/IV was between 0.6 and 0.8 to align with the PG derivation assumption for the primary effectiveness endpoint.

Table 9: Patient Demographics and Baseline Characteristics – EP Population	
Description	**Summary Statistics* N=180**
Age (years)	75.5 ± 10.77 (180)
Sex	
Male	52.8% (95/180)
Female	47.2% (85/180)
Race	
American Indian or Alaska Native	0.6% (1/180)
Asian	7.2% (13/180)
Black or African American	10.6% (19/180)
White	72.8% (131/180)
Not available	8.9% (16/180)
BMI (kg/m^2)	25.10 ± 5.64 (179/180)
KCCQ Overall Summary Score	55.34 ± 27.06 (177/180)
NYHA Functional Class	
I	0
II	32.2% (58/180)
III	62.8% (113/180)
IV	5.0% (9/180)
STS Score (%)	
Mean ± SD	4.04 ± 3.37
Median	3.08
Q1, Q3	1.91, 4.92
Min, Max	0.59, 21.03
Comorbidities	
Atrial Fibrillation/Flutter	40.0% (72/180)
COPD	17.8% (32/180)
Diabetes: Any	14.4% (26/180)
Endocarditis	11.7% (21/180)
Peripheral vascular disease	11.7% (21/180)
Renal insufficiency	32.8% (59/180)
Stroke	10.6% (19/180)
Systemic hypertension	82.8% (149/180)
Left bundle branch block	8.3% (15/180)
Right bundle branch block	13.3% (24/180)
Procedure History	
Permanent pacemaker	16.7% (30/180)
Prosthetic Valve Implant	8.3% (15/180)
Previous CABG	11.1% (20/180)

Description	Summary Statistics* N=180
Previous PCI	20.6% (37/180)
Echocardiographic core lab assessment	
AR Severity**	
Severe	65.2% (116/178)
Moderate-Severe	32.0% (57/178)
Moderate	2.8% (5/178)
Vena Contracta of Central AR jet	0.67 ± 0.13 (177/180)
Aortic Valve Mean Gradient (mmHg)	8.66 ± 6.58 (176/180)
AR regurgitant fraction (by PISA)	55.3 ± 12.9 (124/180)
AR regurgitant volume (by PISA)	55.5 ± 17.2 (130/180)
LV End Diastolic Diameter (cm)	5.59 ± 0.84 (165/180)
LV End Systolic Diameter (cm)	3.96 ± 1.02 (165/180)
LV End Systolic Diameter Index (cm/m^2)	2.26 ± 0.66 (164/180)
LV End Diastolic Volume by Simpson (ml)	144.6 ± 56.7 (157/180)
LV End Systolic Volume by Simpson (ml)	70.6 ± 38.9 (157/180)
LV Ejection Fraction by Simpson (%)	53.8 ± 11.4 (157/180)
LV mass index (g/m^2)	180.1 ± 63.0 (164/180)
N = total number of patients; BMI = body mass index; KCCQ; Kansas City Cardiomyopathy Questionnaire; NYHA= New York Heart Association; STS = Society of Thoracic Surgeons (score); SD= Standard Deviation; Min = minimum; Max = maximum; COPD = Chronic Obstructive Pulmonary Disease; CABG = Coronary Artery Bypass Grafting; PCI = Percutaneous Coronary Intervention; AR= Aortic Regurgitation; PISA = Proximal Isovelocity Surface Area; LV = Left Ventricle *Categorical variables: % (n/N.); continuous variables: mean ± standard deviation (n) **AR severity was missing/not evaluable by echocardiogram in 2 subjects.	

D. Safety and Effectiveness Results

1. Primary Safety Endpoint

The primary safety endpoint results are presented in **Table 10** An event within the composite 30-day primary safety endpoint occurred in 48 (26.7%) subjects treated with the Trilogy THV. The 97.5% upper confidence interval (CI) was 34.1%, which was less than the pre-specified performance goal of 40.5%. Thus, the primary safety endpoint was met.

Table 10: Primary Safety Endpoint Results (EP Population)				
Event	**Summary Statistics* (N=180)**	**One-sided 97.5% Upper Confidence Interval ****	**Performance Goal**	**p-value**
Composite Endpoint Failures***	48 (26.7%)	34.1%	40.5%	<0.0001
* no. of patients with an event (%) ** One-sample binomial proportion test with normally approximated variance and a one-sided statistical significance level of alpha=0.025 *** The primary safety endpoint was a composite of major adverse events at 30 days consisting of: all-cause mortality, all stroke, life threatening or major bleeding, acute kidney injury (AKI) Stage 2, 3 or dialysis, surgery/intervention related to the device (including coronary intervention), major vascular complications, permanent pacemaker implantation, and moderate or severe total aortic regurgitation				

Each component of the composite safety endpoint is further described in **Table 11.** The most common event within 30-days was new permanent pacemaker implantation in 36/150 (24.0%) of subjects without prior pacemakers. A post-hoc multivariable analysis suggested the following factors were potentially associated with permanent pacemaker implantation: pre-existing right bundle branch block, prior history of congestive heart failure, annular perimeter ≥85mm, and severe baseline AR (as compared to moderate-severe AR). There were 4 deaths (2.2%) within 30 days. There was 1 subject with moderate or severe total aortic regurgitation within 30 days. This subject was described as having moderate AR by the core laboratory, and at 1 year, the AR was deemed mild in this subject.

Table 11: Primary Safety Composite Endpoint Components (EP Population)	
Primary Safety Composite Endpoint	**Summary Statistics* (N=180)**
Composite endpoint at 30 days post-procedure	**26.7% (48)**
All-cause mortality	2.2% (4)
All stroke	2.2% (4)
Life-threatening or major bleeding	4.4% (8)
Acute kidney injury (AKI) stage 2, 3 or dialysis	1.1% (2)
Major vascular complications	3.9% (7)
Surgery/intervention related to the device (including coronary intervention)	2.8% (5)
Permanent pacemaker implantation**	24.0% (36)
Moderate or severe total aortic regurgitation	0.6% (1)
*% (no. of patients with the event) **Subjects with prior pacemakers (n=30) were excluded	

2. Primary Effectiveness Endpoint

The primary effectiveness endpoint was 1-year mortality assessed in the VI population. In the 177 VI subjects, there were 11 subjects (6.2%) who expired at 1-year follow-up. The one-sided 97.5% upper CI was 11.5%, which is below the pre-specified PG of 25%, (P<0.0001) based on expected mortality rates for severe AR patients treated by medical management (**Table 12).** The Kaplan-Meier curve for overall all-cause mortality through 1 year is presented in **Figure 5.**

Table 12: Primary Effectiveness Endpoint Results (VI Population)

Primary Efficacy Variable	Summary Statistics* (N=177)	One-sided 97.5% Upper Confidence Interval**	Performance Goal	p-value
All-Cause Mortality	11 (6.2%)	11.5%	25%	<0.0001

* no. of patients with an event (%)
** Weighted PG analysis using z-test, with z derived as specified by Lu and Xu[1]

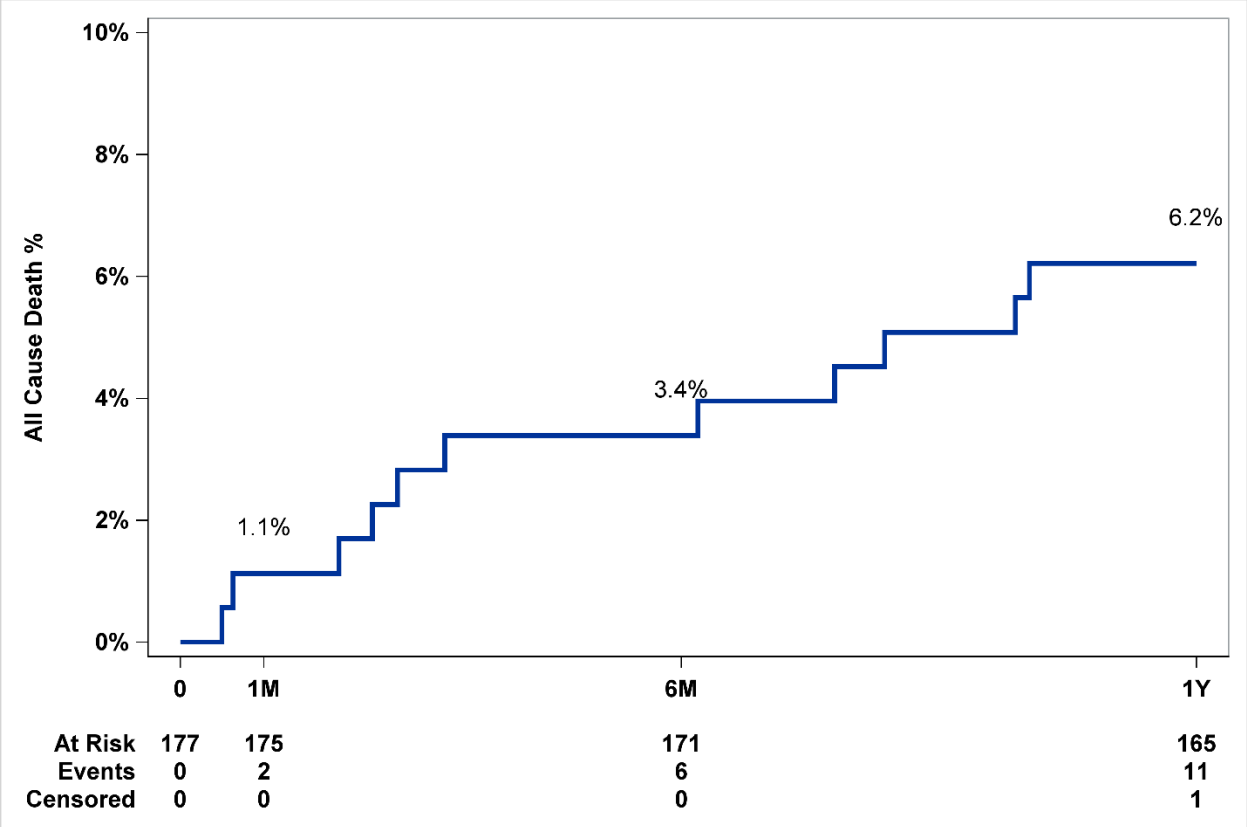


Figure 5: Kaplan-Meier Analysis of All-Cause Mortality through 1 Year (VI Population)

[1] Lu N, Li H, Xu Y-L. Use of Weighted Performance Goals in Prospective Single-Arm Clinical Studies Designed to Assess the Safety and Effectiveness of Medical Devices. *Statistics in Biopharmaceutical Research.* 2021;13(4):504-507.

3. Secondary Endpoint

The analysis of the pre-defined secondary endpoint in the trial was based on the VI subjects who completed a KCCQ assessment at baseline and at 1 year. As shown in **Table 13,** the mean improvement seen in the 141 patients that completed the KCCQ assessment both at baseline and 1-year follow-up was 20.6 ± 24.3 points, with a 97.5% lower CI of 15.9 points. These results show that the mean improvement of KCCQ per patient treated with the Trilogy THV is significantly greater than 10 points (P<0.0001), confirming that the pre-specified PG was met. The mean KCCQ overall summary score (KCCQ-OS) was 55.7 ± 26.9 at baseline and 77.6 ± 22.7 at 1-year for the entire VI population. Twenty-four (24) patients (15.8%) had a moderate improvement in KCCQ-OS (increase between 10 and < 20 points), and 41.4% had a large improvement (≥ 20-point increase). 10.5% of patients had a worse (> 5-point decrease from baseline) KCCQ-OS at 1-year.

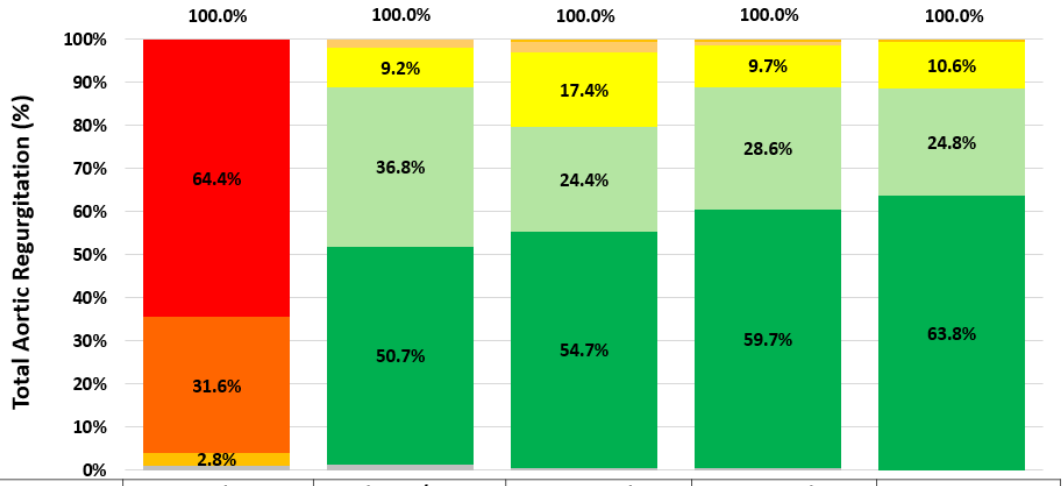
Table 13: Secondary Effectiveness Endpoint, KCCQ Improvement at 1-Year (VI Population)

Secondary Efficacy Variable	Summary Statistics* (N=177)	97.5% Confidence Interval**	Performance Goal	p-value
Change in KCCQ	20.6 ± 24.3 (141/177)	15.9 – 25.2	10-point KCCQ improvement	<0.0001

* mean ± standard deviation (no./total no.)
**Paired t-test with a one-sided nominal significance level of 0.025

4. Valve Hemodynamics

The AR severity for the VI population through 1 year is shown in **Figure 6**. At 1 month after implantation with the Trilogy THV, 0 subjects presented moderate-severe or severe AR and 136 subjects (79.1%) had none to trace AR. The AR reduction was maintained through 1 year, with 88.7% (125/141) of subjects having none to trace AR. One subject (0.7%; 1/141) had moderate AR with no subjects having greater than moderate AR.



Total Aortic Regurgitation	Baseline (N=177)	Discharge/10 Day (N=152)	1-Month (N=172)	6-Months (N=154)	1-Year (N=141)
Not Measured	2 (1.1%)	2 (1.3%)	1 (0.6%)	1 (0.6%)	0
None	0	77 (50.7%)	94 (54.7%)	92 (59.7%)	90 (63.8%)
Trace	0	56 (36.8%)	42 (24.4%)	44 (28.6%)	35 (24.8%)
Mild	0	14 (9.2%)	30 (17.4%)	15 (9.7%)	15 (10.6%)
Mild-Moderate	0	3 (2.0%)	4 (2.3%)	1 (0.6%)	0
Moderate	5 (2.8%)	0	1 (0.6%)	1 (0.6%)	1 (0.7%)
Mod-severe	56 (31.6%)	0	0	0	0
Severe	114 (64.4%)	0	0	0	0

Note: The number of subjects available at follow-up visits is lower than the total VI population (n=177) due to follow-up visits without echocardiographic evaluation, patients that missed visits and deaths.

Figure 6: Total Aortic Regurgitation through 1-Year (VI population)

Paravalvular leak (PVL) was measured post-implantation and is displayed in **Figure 7**. At 1 month, the majority of subjects had none or trace PVL (80.8%). PVL improved through 1-year, with 92.2% of subjects having none or trace PVL and no subjects having greater than mild PVL at the 1-year evaluation.

Paravalvular Aortic Regurgitation	Discharge/10 Day (N=151)	1-Month (N=172)	6-Months (N=154)	1-Year (N=141)
Not Measured	2 (1.3%)	1 (0.6%)	1 (0.6%)	0
None	79 (52.3%)	100 (58.1%)	113 (73.4%)	108 (76.6%)
Trace	53 (35.1%)	39 (22.7%)	31 (20.1%)	22 (15.6%)
Mild	15 (9.9%)	27 (15.7%)	8 (5.2%)	11 (7.8%)
Mild-Moderate	2 (1.3%)	4 (2.3%)	0	0
Moderate	0	1 (0.6%)	1 (0.6%)	0

Note: The number of subjects available at follow-up visits is lower than the total VI population (n=177) due to follow-up visits without echocardiographic evaluation, patients that missed visits and deaths.

Figure 7: Paravalvular Regurgitation/Leak through 1-Year (VI population)

Effective orifice area (EOA) and aortic mean gradient through 1 year are presented below in **Figure 8 .** EOA was 2.87 ± 0.56 cm^2 at 30 days and 2.78 ± 0.61 cm^2 at 1 year. Mean aortic valve pressure gradient was 8.59 ± 6.56 mmHg at baseline, which decreased to 3.88 ± 1.62 mmHg at 30 days and 4.25 ± 1.83 mmHg at 1 year.

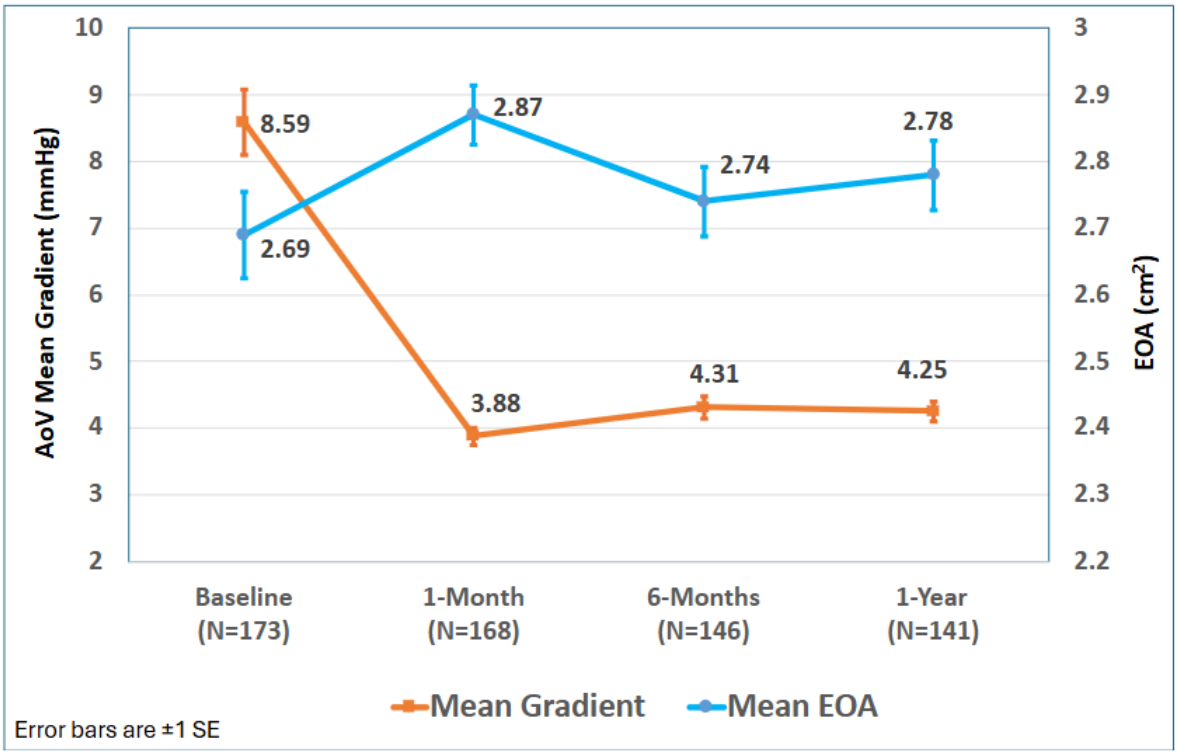


Figure 8: Mean EOA and Aortic Valve (AoV) Mean Gradient Through 1-Year (VI Population)

5. Left Ventricle (LV) Remodeling

Decreases in left ventricular LV end systolic volume (LVESV) and LV mass index were observed from screening through 1-year (**Figure 9** and **Figure 10**, respectively). Additional echocardiographic measurements are shown in **Table 14**.

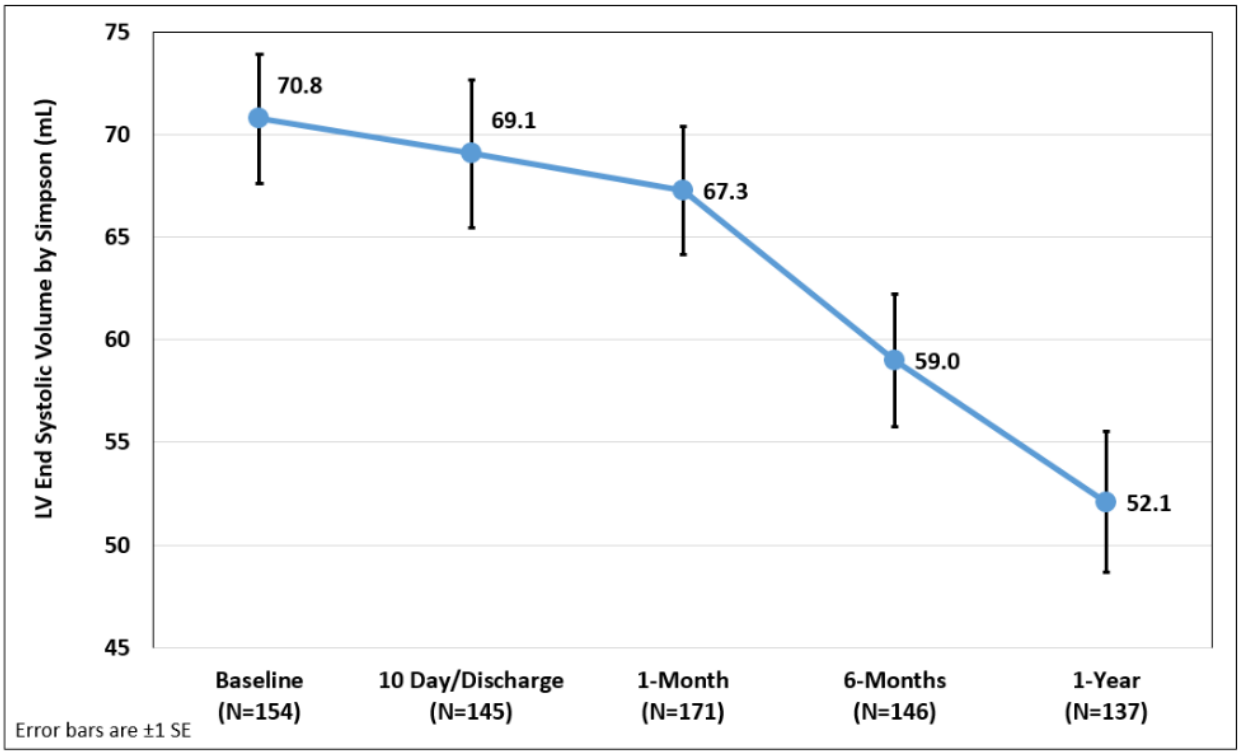


Figure 9: Mean LVESV and Standard Error Through 1 Year (VI Population)

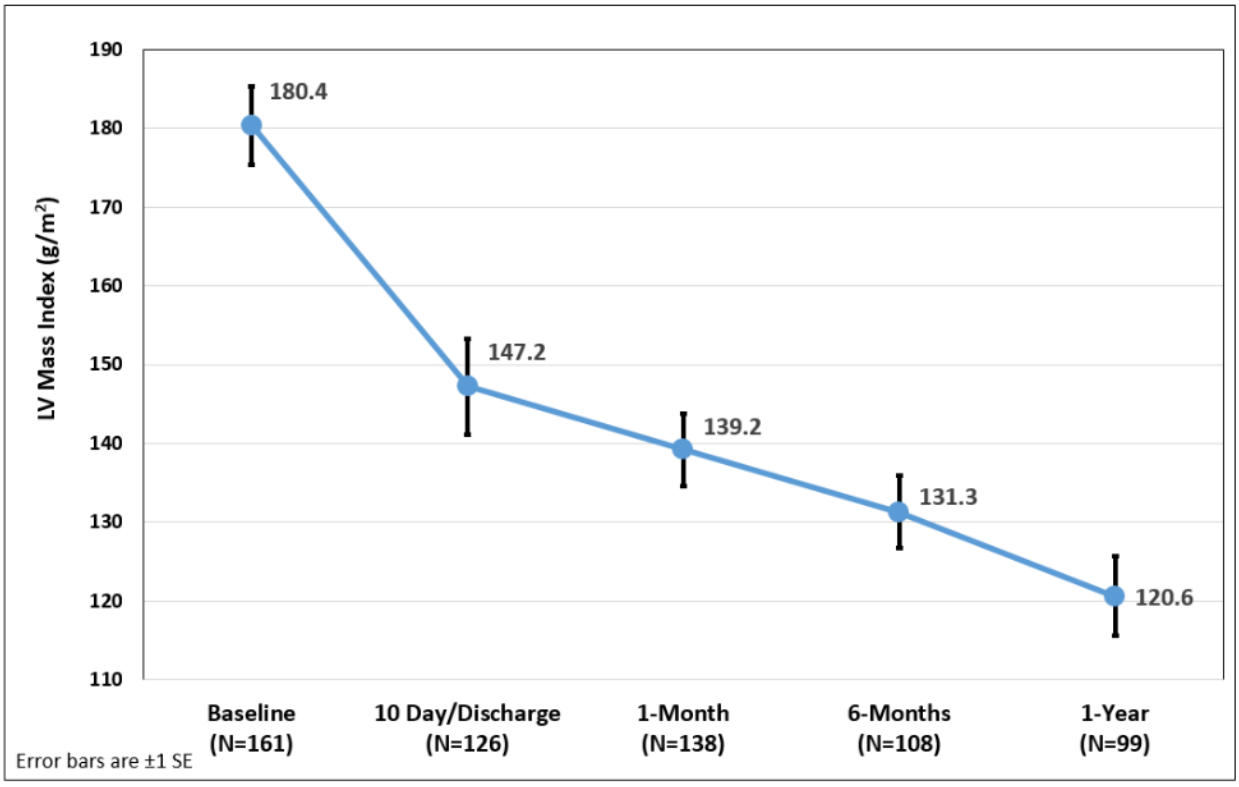


Figure 10: Mean LV Mass Index and Standard Error Through 1 Year (VI Population)

Table 14: Left Ventricular Remodeling (VI Population)				
Description	**Screening**	**1-Month**	**6-Month**	**1-Year**
LV End Systolic Volume** (mL)	70.8 ± 39.1 (154)	67.3 ± 41.0 (171)	59.0 ± 39.2 (146)	52.1 ± 40.1 (137)
LV End Diastolic Volume** (mL)	144.8 ± 56.7 (154)	132.6 ± 83.1 (171)	115.9 ± 50.3 (146)	109.9 ± 50.1 (137)
LV End Systolic Diameter (cm)	4.0 ± 1.0 (162)	3.7 ± 1.0 (170)	3.5 ± 0.9 (149)	3.4 ± 0.9 (138)
LV End Diastolic Diameter (cm)	5.6 ± 0.8 (162)	5.0 ± 0.9 (172)	4.8 ± 0.8 (149)	4.8 ± 0.8 (138)
LV Mass (g)	323.9 ± 123.6 (162)	254.3 ± 109.0 (139)	235.1 ± 95.4 (108)	219.5 ± 101.4 (99)
LV Mass Index (g/m^2)	180.4 ± 63.2 (161)	139.2 ± 54.7 (138)	131.3 ± 48.2 (108)	120.6 ± 50.5 (99)
LV: left ventricular continuous variables: mean ± standard deviation (no.) ** calculated by Simpson's method				

6. Additional Functional Assessments

Using the 6-minute walk test (6MWT), the mean distance walked was 807.5 ± 434.1 feet at baseline and 901.3 ± 546.9 feet at 1-year for the VI population. The mean change from baseline in total distance walked per subject was 78.4 ± 471.3 feet. The NYHA functional class of patients at baseline through 1-year is presented in **Figure 11**. At 1-year post-procedure, 8.6% of patients were NYHA class III or IV compared to 67.2% at baseline.

NYHA Classification	Baseline (N=177)	10 Day/Discharge (N=175)	1-Month (N=170)	6-Months (N=152)	1-Year (N=151)
Class I	0	40 (22.9%)	91 (53.5%)	83 (54.6%)	90 (59.6%)
Class II	58 (32.8%)	84 (48.0%)	62 (36.5%)	57 (37.5%)	48 (31.8%)
Class III	111 (62.7%)	51 (29.1%)	17 (10.0%)	11 (7.2%)	13 (8.6%)
Class IV	8 (4.5%)	0	0	1 (0.7%)	0

Figure 7: NYHA Classification through 1-Year (VI Population)

7. Procedural Information and Technical Success

The procedural information for the EP population is presented in **Table 15.** Overall, the mean procedure time was 71.4 ± 24.3 min, the mean fluoroscopy time was 25.5 ± 10.2 min, and the mean hospital stay duration was 2.2 ± 2.4 days. General anesthesia was used for the majority of procedures with 8.9% of patients receiving conscious sedation. The most commonly implanted valve size was 27 mm (57.2% of subjects). Three subjects did not receive a Trilogy THV. Two patients had ectopic Trilogy implantation and were successfully implanted with a second Trilogy THV in the correct position.

Table 15: Procedural Characteristics (EP Population)

Characteristics	Summary Statistics* N=180
Sedation Method	
General Anesthesia	164 (91.1%)
Conscious Sedation	16 (8.9%)
Femoral Access Site	
Right	138 (76.7%)
Left	42 (23.3%)
Access Technique Used	
Cut-down	3 (1.7%)
Puncture	177 (98.3%)

Characteristics	Summary Statistics* N=180
Pre-implant BAV performed prior to insertion of study sheath	
Yes	5 (2.8%)
No	175 (97.2%)
All 3 locators engaged within the cusps	177 (98.3%)
Post-implant BAV performed after Trilogy implantation	
Yes	7 (3.9%)
No	167 (92.8%)
Missing	6 (3.8%)
Average Procedure Time (min)	71.4 ± 24.3
Average Fluoroscopy Time	25.5 ± 10.2
Valve Size Used	
23 mm	41 (22.8%)
25 mm	36 (20.0%)
27 mm	103 (57.2%)
Number of Trilogy THVs Implanted	177 (98.3%)
0	3 (1.7%)
1	175 (97.2%)
2	2 (1.1%)
Average Hospital Duration (days)	2.2 ± 2.4
*continuous variables: mean ± standard deviation; categorical variables: no. (%)	

Technical success at time of exit from the operating room (OR), hybrid room, or catheterization laboratory was defined as absence of procedural mortality; successful access, delivery and retrieval of transcatheter delivery system; deployment and correct positioning of a single intended THV; and freedom from re-intervention related to the device or access procedure. Technical success was achieved in 171 of the 180 subjects (95.0%) for whom implantation of the THV was attempted as shown in **Table 16**. Two patients did not have a Trilogy THV successfully implanted because of valve embolization followed by surgical aortic valve replacement (n=1) and embolization followed by commercial THV implantation (n=1). A third patient did not receive a Trilogy THV due to an aortic dissection that developed during the procedure but before the Trilogy THV was inserted into the body. This patient was treated with a commercial THV device.

Table 16: Technical Success at Time of Exit from OR, Hybrid Room or Catheterization laboratory (EP Population)	
Technical Success	**Summary Statistics* (N=180)**
Technical Success at time of exit from OR, hybrid room or catheterization laboratory	**171 (95.0%)**
Successful access, delivery, and retrieval of Trilogy Introducer Sheath	179 (99.4%)
Successful access, delivery, and retrieval of Trilogy Delivery System	179 (99.4%)
Successful deployment and positioning of first intended Trilogy THV	175 (97.2%)
Freedom from emergency surgery/re-intervention on Trilogy THV	176 (97.8%)
Patient exited hybrid/Operating Room alive	180 (100.0%)
Access intervention	4 (2.2%)
OR: operating room; THV: transcatheter heart valve *categorical variables: no. (%)	

8. Subgroup Analyses

A pre-specified subgroup analysis was performed on the primary safety and effectiveness endpoints of the ALIGN-AR trial based on sex (male vs. female). The study population was evenly balanced by sex (52.5% male, 47.5% female). All-cause mortality at 1-year stratified by sex is shown in **Table 17** below and was comparable between male and females.

Table 17: All-Cause Mortality at 1-year by Sex (VI Population)			
Enrollment Subgroup	**N**	**Event Rate (n)**	**Event Rate (%)**
Male	93/177 (52.5%)	6	6.5%
Female	84/177 (47.5%)	5	6.0%

The 30-day composite safety endpoint event rates (overall and individual events) stratified by sex are provided in **Table 18.** The rate of composite endpoint failure was numerically higher in males (30.5%; 29/95) than females (22.4%; 19/85).

Table 18: Primary Safety Composite Endpoint at 30 Days by Sex (EP Population)		
Event	**Summary Statistics* (N=180)**	
	Male (N=95)	**Female (N=85)**
Composite endpoint at 30 days post-procedure	**29 (30.5%)**	**19 (22.4%)**
All-cause mortality	2 (2.1%)	2 (2.4%)
All stroke	3 (3.2%)	1 (1.2%)
Life-threatening or major bleeding	5 (5.3%)	3 (3.5%)
AKI stage 2, 3, or dialysis	1 (1.1%)	1 (1.2%)
Major vascular complications	4 (4.2%)	3 (3.5%)
Surgery/intervention related to the device (including coronary intervention)	4 (4.2%)	1 (1.2%)
Permanent pacemaker implantation	21 (22.1%)	15 (17.6%)
Moderate or severe total aortic regurgitation	1 (1.1%)	0 (0.0%)
AKI: acute kidney injury *categorical variables: no. (%)		

All-cause mortality at 1-year and the 30-day composite safety endpoint event rates (overall and individual events) stratified by race are provided in **Table 19 and Table 20** respectively**.**

Table 19: All-Cause Mortality at 1-year by Race (VI Population)		
Race	**No. Events**	**No./Total No. Patients**
American Indian or Alaska Native	0	0/1
Asian	0	0/13
Black or African American	3	3/19
White	8	8/129
Not available	0	0/15

Table 20: Primary Safety Composite Endpoint at 30 Days by Race (EP Population)					
Event	**Summary Statistics***				
	American Indian or Alaska Native (N=1)	**Asian (N=13)**	**Black or African American (N=19)**	**White (N=131)**	**Not available (N=16)**
Composite endpoint at 30 days post-procedure	**0**	**5 (38.5%)**	**8 (42.1%)**	**33 (25.2%)**	**2 (12.5%)**
All-cause mortality	0	0	1 (5.3%)	3 (2.3%)	0
All stroke	0	0	1 (5.3%)	2 (1.5%)	1 (6.3%)
Life-threatening or major bleeding	0	2 (15.4%)	1 (5.3%)	4 (3.1%)	1 (6.3%)
AKI stage 2, 3, or dialysis	0	0	0	1 (0.8%)	1 (6.3%)
Major vascular complications	0	1 (7.7%)	1 (5.3%)	4 (3.1%)	1 (6.3%)
Surgery/intervention related to the device (including coronary intervention)	0	0	0	4 (3.1%)	1 (6.3%)
Permanent pacemaker implantation	0	3 (27.3%)	6 (42.9%)	26 (23.2%)	1 (8.3%)
Moderate or severe total aortic regurgitation	0	0	0	1 (0.8%)	0
AKI: acute kidney injury *categorical variables: no. (%)					

9. Adverse Events

An overview of the VARC-2 clinical events through 1-year are presented in **Table 21.**

Table 21: VARC-2 Clinical Events (VI Population)		
Event	**Summary Statistics* (N=177)**	
	30-Days	**1 Year**
All Cause death	2 (1.1%)	11 (6.2%)
Cardiac Death	1 (0.6%)	8 (4.5%)
Non-cardiac Death	1 (0.6%)	3 (1.7%)
Permanent Pacemaker Implantation**	34 (23.1%)	40 (27.2%)
AKI stage 2, 3 or dialysis	0	
Myocardial infarction	0	2 (1.1%)
Stroke	2 (1.1%)	8 (4.5%)
Disabling stroke	0	1 (0.6%)
Non disabling stroke	2 (1.1%)	7 (4.0%)

Event	Summary Statistics* (N=177)	
	30-Days	1 Year
All Bleeding	14 (7.9%)	18 (10.2%)
Major/Life threatening bleeding	7 (4.0%)	9 (5.1%)
Minor bleeding	8 (4.5%)	10 (5.6%)
Vascular complications	11 (6.2%)	11 (6.2%)
Major	5 (2.8%)	5 (2.8%)
Minor	6 (3.4%)	6 (3.4%)
Rehospitalization	2 (1.1%)	9 (5.1%)
Heart failure related	2 (1.1%)	8 (4.5%)
Index procedure related	0	0
TAVR valve related	0	1 (0.6%)
Valve intervention due to prosthetic valve thrombosis	0	0
Valve intervention due to endocarditis	0	1 (0.6%)
*categorical variables: no. (%) **Subjects with prior pacemakers (n=30) were excluded		

10. CT Sub-Study

A subset of patients was enrolled in a computed tomography (CT) sub-study to evaluate Hypoattenuation Leaflet Thrombosis (HALT) and reduced leaflet motion (RLM). The primary assessment of the CT sub-study was completed post-implant at baseline (approximately 30-90 days) and at approximately 1 year. A total of 29 patients were enrolled in the CT Sub-Study. Of these, 16 patients underwent the 1-month CT, and 8 patients underwent the 1-year CT. All patients with the 1-year CT also had the 1-month CT. Six (6/16) patients had HALT identified at 30-days (3 patients had <25% normal motion, 2 patients had 25 to 50% normal motion, and 1 patient had >75% normal motion). Five (5) of the 6 incidences of HALT involved the posterior leaflet and 1 involved the anterolateral leaflet. HALT was observed in 3/8 patients at 1-year: 1 patient did not have HALT at 30 days but had <25% normal motion at 1-year; 1 patient had HALT with >75% normal motion at 30 days that changed to 25-50% normal motion at 1 year; and 1 patient had unchanged findings comparing 30-day results to 1 year (HALT with <25% normal motion). No patient with HALT had a clinical event including stroke or death.

Pediatric Extrapolation

In this premarket application, existing clinical data was 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 ALIGN-AR Study involved 30 investigators of which none were full-time or part-time employees of the sponsor and 3 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: 0
- Significant payment of other sorts: 3
- Proprietary interest in the product tested held by the investigator: 0
- Significant equity interest held by investigator in sponsor of covered study: 0

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. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

As part of the review of the PMA application, FDA also considered the supplemental clinical information summarized below.

A. Study Design

The ALIGN-AR continued access program (CAP) study was a single-arm, prospective, multicenter study carried out under IDE G150035 after completing enrollment of the ALIGN-AR pivotal study cohort.

1. Clinical Inclusion and Exclusion Criteria
   The inclusion and exclusion criteria for the ALIGN-AR CAP cohort were the same as the ALIGN-AR main cohort.

2. Follow-up Schedule
   The follow-up schedule and pre- and post-procedure assessments were the same as the ALIGN-AR main cohort.

3. Clinical Endpoints
   The ALIGN-AR CAP cohort used the same primary safety and effectiveness endpoints as the ALIGN-AR study. No hypothesis testing was pre-specified for the CAP cohort; endpoints were analyzed with descriptive statistics only.

B. Accountability of CAP Cohort

The data presented represents the first 320 patients enrolled in the ALIGN-AR CAP cohort. Subjects were enrolled between December 13, 2022 and October 16, 2024. Five of the 320 patients did not receive the Trilogy valve; to be conservative all 320 patients regardless of procedure success have been included in all analyses. Patient accountability through 1 year is summarized in **Table 22** and **Table 23**.

Table 22: Subject Accounting Summary in the CAP Cohort

Description	ALIGN-AR CAP (N=320)
Screened	710
Eligible	320

Table 23: CAP Cohort Patient Disposition Summary

	30-Day	1-Year
Total Patients	320	320
Non-eligible†	3	31
Death	3	24
Withdrawal	0	4
Lost to follow-up	0	1
Exit for other reason	0	2
Eligible	317	289
Visit Completed	312	282
Missed visit‡	5	7
Follow-up Compliance*	98.4%	97.6%

† Includes all patients who exited the study prior to the end of the follow-up visit window and who have not had the visit.
‡ Data extract date has exceeded the end of the visit window, and the patients have not completed the visit.
* Follow-up Compliance is calculated as follows: (Number with visit completed) / (Number eligible).

C. Study Population Demographics and Baseline Characteristics

The demographics and baseline characteristics of the ALIGN-AR CAP study are summarized in **Table 24**. The CAP cohort demographic and baseline characteristics were consistent with the population enrolled in the main cohort.

Table 24 Study Population Demographics Baseline Measures in the CAP Cohort	
Description	**Summary Statistics* N=320**
Age (years)	77.3 ± 10.0 (320)
Sex	
Male	54.4% (174/320)
Female	45.6% (146/320)
Race	
American Indian or Alaska Native	0.0% (0/319)
Asian	4.4% (14/319)
Black or African American	6.3% (20/319)
White	80.3% (256/319)
Native Hawaiian or Pacific Islander	0.0% (0/319)
Not available	8.5% (27/319)
BMI (kg/m^2)	26.0 ± 5.4 (320)
KCCQ Overall Summary Score	22.5 ± 22.6 (274/320)
NYHA functional class	
I	0.0% (0/320)
II	42.2% (135/320)
III	54.4% (174/320)
IV	3.4% (11/320)
STS Score (%)	
Mean ± SD	3.71 ± 3.25
Median	2.87
Q1, Q3	1.78, 4.42
Min, Max	0.58, 28.10
Comorbidities	
Atrial Fibrillation/Flutter	38.4% (123/320)
COPD	15.9% (51/320)
Diabetes: Any	16.9% (54/320)
Endocarditis	2.5% (8/320)
Peripheral vascular disease	9.1% (29/320)
Renal insufficiency	28.1% (90/320)
Stroke	9.4% (30/320)
Systemic hypertension	79.1% (253/320)
Left bundle branch block	4.7% (15/318)
Right bundle branch block	10.1% (32/318)
Procedure History	
Permanent pacemaker	14.4% (46/320)
Prosthetic Valve Implant	3.4% (11/320)
Previous CABG	8.1% (26/320)
Previous PCI	18.4% (59/320)
Echocardiographic core lab assessment	
AR Severity	

Description	Summary Statistics* N=320
Severe	53.1% (169/318)
Moderate-Severe	46.2% (147/318)
Moderate	0.6% (2/318)
Vena Contracta of Central AR jet	0.69 ± 0.38 (222/320)
Aortic Valve Mean Gradient (mmHg)	6.93 ± 4.33 (314/320)
Aortic Regurgitation regurgitant fraction (by PISA)	51.7 ± 13.4 (164/320)
Aortic Regurgitation regurgitant volume (by PISA)	51.4 ± 17.3 (186/320)
LV End Diastolic Diameter (cm)	55.7 ± 8.0 (298/320)
LV End Systolic Diameter (cm)	39.5 ± 8.5 (298/320)
LV End Systolic Diameter Index (cm/m^2)	21.6 ± 5.0 (298/320)
LV End Diastolic Volume by Simpson (ml)	153.9 ± 54.6 (290/320)
LV End Systolic Volume by Simpson (ml)	70.4 ± 33.3(290/320)
LV Ejection Fraction by Simpson (%)	55.2 ± 9.3 (291/320)
LV mass index (g/m2)	137.4 ± 47.0 (257/320)
N = total number of patients; BMI = body mass index; KCCQ; Kansas City Cardiomyopathy Questionnaire; NYHA= New York Heart Association; STS = Society of Thoracic Surgeons (score); SD= Standard Deviation; Min = minimum; Max = maximum; COPD = Chronic Obstructive Pulmonary Disease; CABG = Coronary Artery Bypass Grafting; PCI = Percutaneous Coronary Intervention; AR= Aortic Regurgitation; PISA = Proximal Isovelocity Surface Area; LV = Left Ventricle *Categorical variables: % (n/N.); continuous variables: mean ± standard deviation (n)	

D. Safety and Effectiveness Results

1. Primary Safety Endpoint

The primary safety endpoint results are presented in **Table 25**. An event within the composite 30-day primary safety endpoint occurred in 85 (26.6%) subjects treated with the Trilogy THV. Similar to the main cohort outcomes, the most common event was new permanent pacemaker implantation in 64/274 (23.4%) in subjects without prior pacemaker. There were 3 deaths (0.9%) within 30 days. There were 2 subjects with moderate or severe total aortic regurgitation within 30 days.

Table 25 Primary Safety Composite Endpoint Breakdown in the CAP Cohort	
Primary Safety Composite Endpoint	**Summary Statistics* N=320**
Composite endpoint at 30 days post-procedure	**26.6% (85)**
All-cause mortality	0.9% (3)
All stroke	2.2% (7)
Life-threatening or major bleeding	2.5% (8)
Acute kidney injury (AKI) stage 2, 3 or dialysis	0.3% (1)
Major vascular complications	2.5% (8)
Surgery/intervention related to the device (including coronary intervention)	3.8% (12)
Permanent pacemaker implantation**	23.4% (64)
Moderate or severe total aortic regurgitation	0.7% (2)
*categorical variables: % (no.) **Subjects with prior pacemakers (n=46) were excluded	

2. Primary Effectiveness Endpoint

The primary effectiveness endpoint was all-cause mortality at 1-year. In the ALIGN-AR CAP cohort, there were 24 subjects (7.6%) who expired at 1-year follow-up as shown in **Table 26**. The Kaplan-Meier curve for overall all-cause mortality through 1 year is presented in **Figure 12.**

Table 26: Primary Efficacy Endpoint Results in the CAP Cohort		
Primary Efficacy Variable	**Summary Statistics (N=314)**	
	n	**%**
All-Cause Mortality	24	7.6

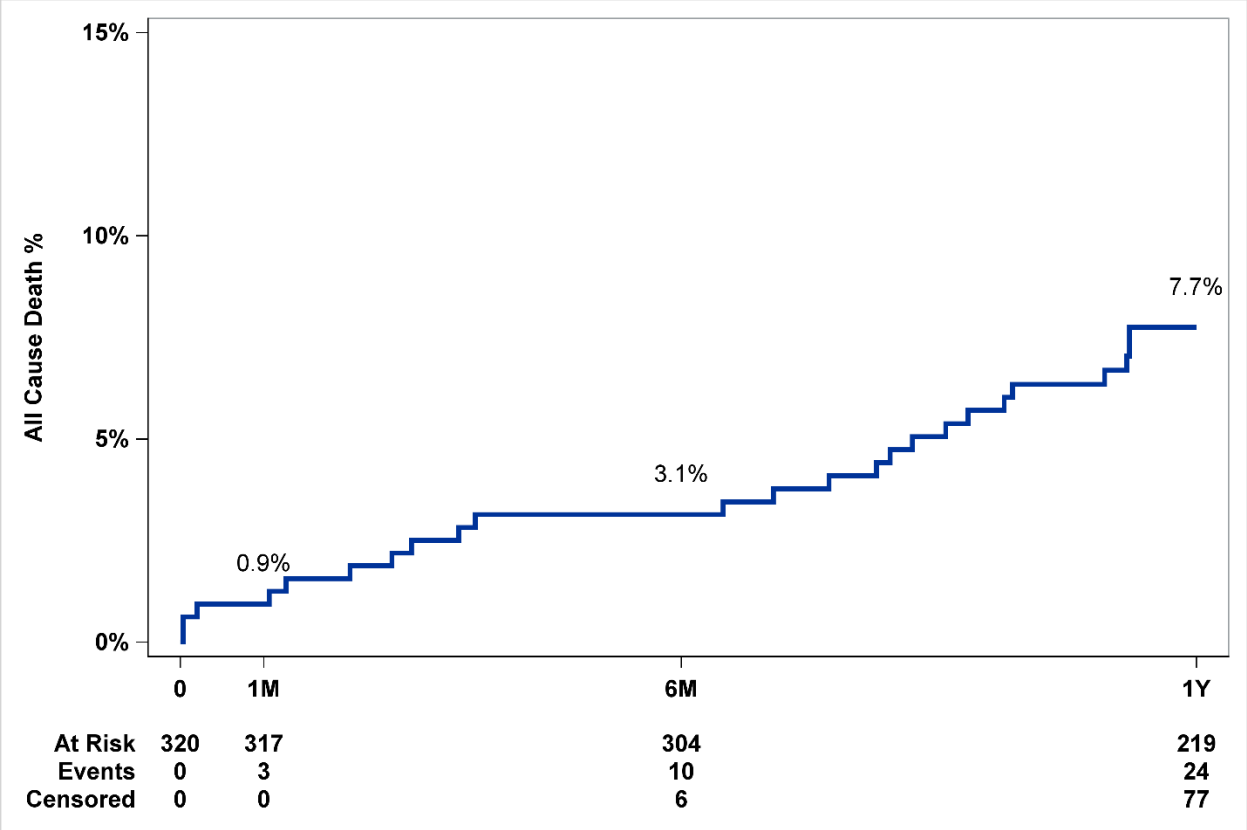


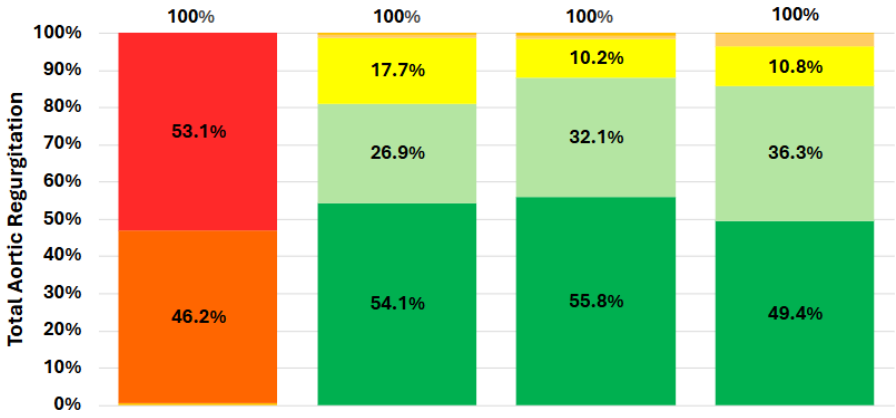
Figure 12: Kaplan-Meier Analysis of All-Cause Mortality through 1 Year CAP Cohort

3. Kansas City Cardiomyopathy Questionnaire (KCCQ)

   The KCCQ overall summary score increased from 60.3 ± 23.5 at baseline to 83.9 ± 17.0 at 1 year. The mean improvement seen in the 274 patients that completed the KCCQ assessment both at baseline and 1-year follow-up was 22.5 ± 22.6 points.

4. Valve Hemodynamics

   The AR severity for the CAP cohort through 1 year is shown in **Figure 13**. At 1 month after implantation with the Trilogy THV, 0 subjects presented moderate-severe or severe AR, and 247 subjects (80.9%) had none to trace AR. The AR reduction was maintained through 1 year, with 85.6% (215/251) of subjects having none to trace AR. One subject (0.4%; 1/251) had moderate AR with no subjects having greater than moderate AR.

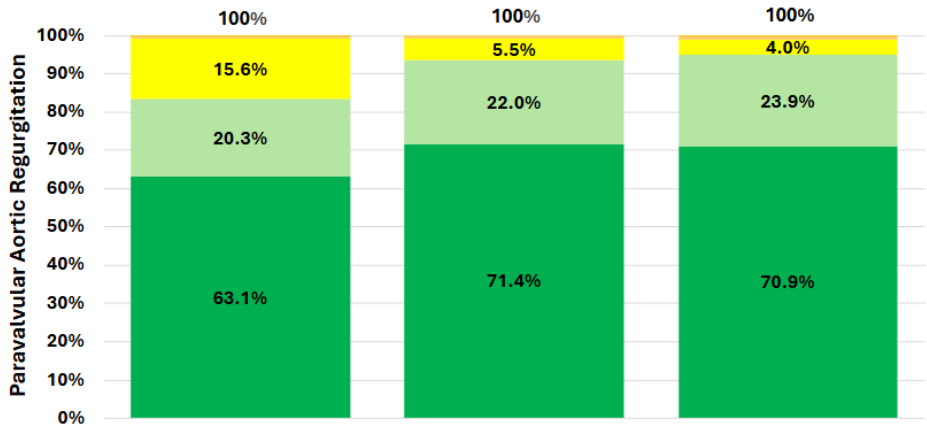


Total Aortic Regurgitation	Baseline (N=318)	1-Month (N=305)	6-Months (N=274)	1-Year (N=251)
None	0	165 (54.1%)	153 (55.8%)	124 (49.4%)
Trace	0	82 (26.9%)	88 (32.1%)	91 (36.3%)
Mild	0	54 (17.7%)	28 (10.2%)	27 (10.8%)
Mild-Moderate	0	2 (0.7%)	3 (1.1%)	8 (3.2%)
Moderate	2 (0.6%)	2 (0.7%)	2 (0.7%)	1 (0.4%)
Mod-severe	147 (46.2%)	0	0	0
Severe	169 (53.1%)	0	0	0

None Trace Mild Mild-Moderate Moderate Mod-severe Severe

Figure 13: Total Aortic Regurgitation through 1-Year in the CAP Cohort

Paravalvular leak (PVL) was measured post-implantation and is displayed in **Figure 14**. The majority of subjects (83.4%) had none or trace PVL at 1-month. PVL improved through 1-year, with 94.8% of subjects having none or trace PVL.



Paravalvular Aortic Regurgitation	1-Month (N=301)	6-Months (N=273)	1-Year (N=251)
None	190 (63.1%)	195 (71.4%)	178 (70.9%)
Trace	61 (20.3%)	60 (22.0%)	60 (23.9%)
Mild	47 (15.6%)	15 (5.5%)	10 (4.0%)
Mild-Moderate	2 (0.7%)	3 (1.1%)	2 (0.8%)
Moderate	1 (0.3%)	0	1 (0.4%)

None Trace Mild Mild-Moderate Moderate

Figure 14: Paravalvular Regurgitation/Leak through 1-Year in the CAP Cohort

EOA and aortic mean gradient through 1 year are presented below in **Figure 15** . EOA was 3.05 ± 0.69 cm^2 at 30 days and 2.80 ± 0.61 cm^2 at 1 year. Aortic valve mean gradient was 6.93 ± 4.33 mmHg at baseline, which decreased to 3.64 ± 1.85 mmHg at 30 days and 4.35 ± 1.83 mmHg at 1 year.

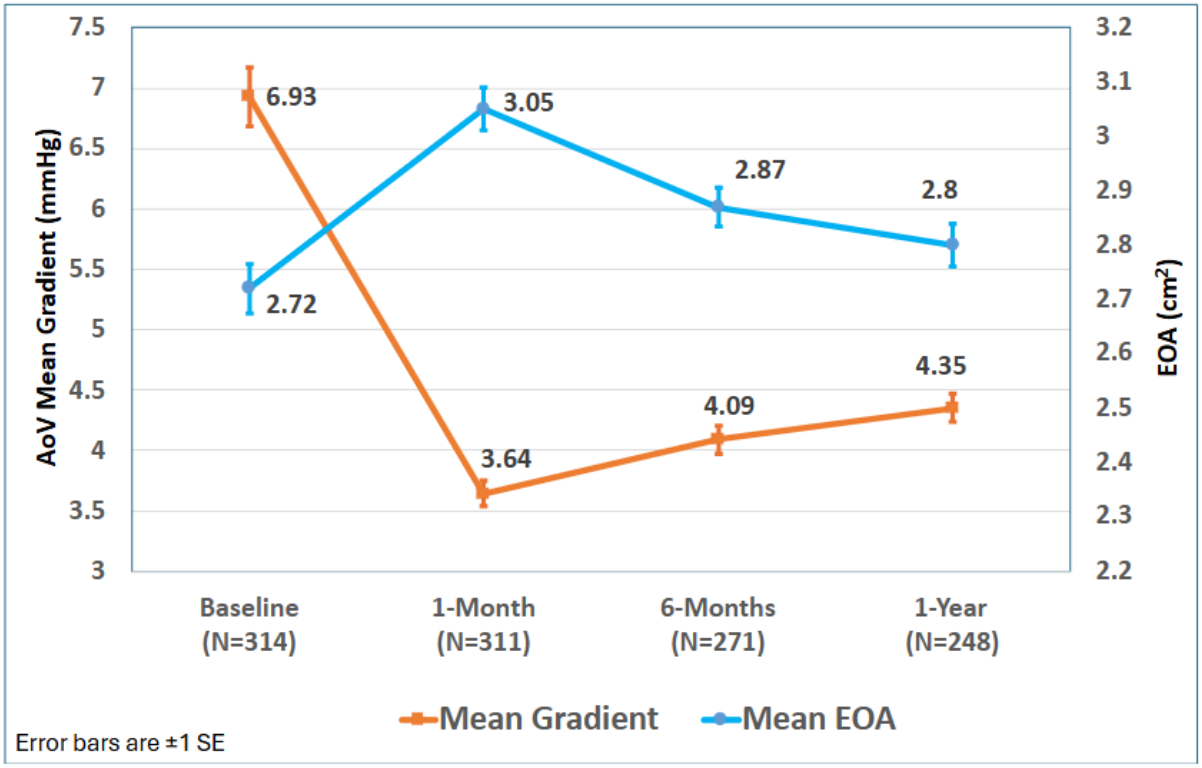


Figure 15: Mean EOA and Aortic Valve (AoV) Mean Gradient Through 1 Year in the CAP Cohort.

5. Left Ventricular Remodeling

Decreases in LV end systolic volume (LVESV) and LV mass index were observed from screening through 1-year (**Figure 16** and **Figure 17**, respectively). Additional echocardiographic measurements are shown in **Table 27**.

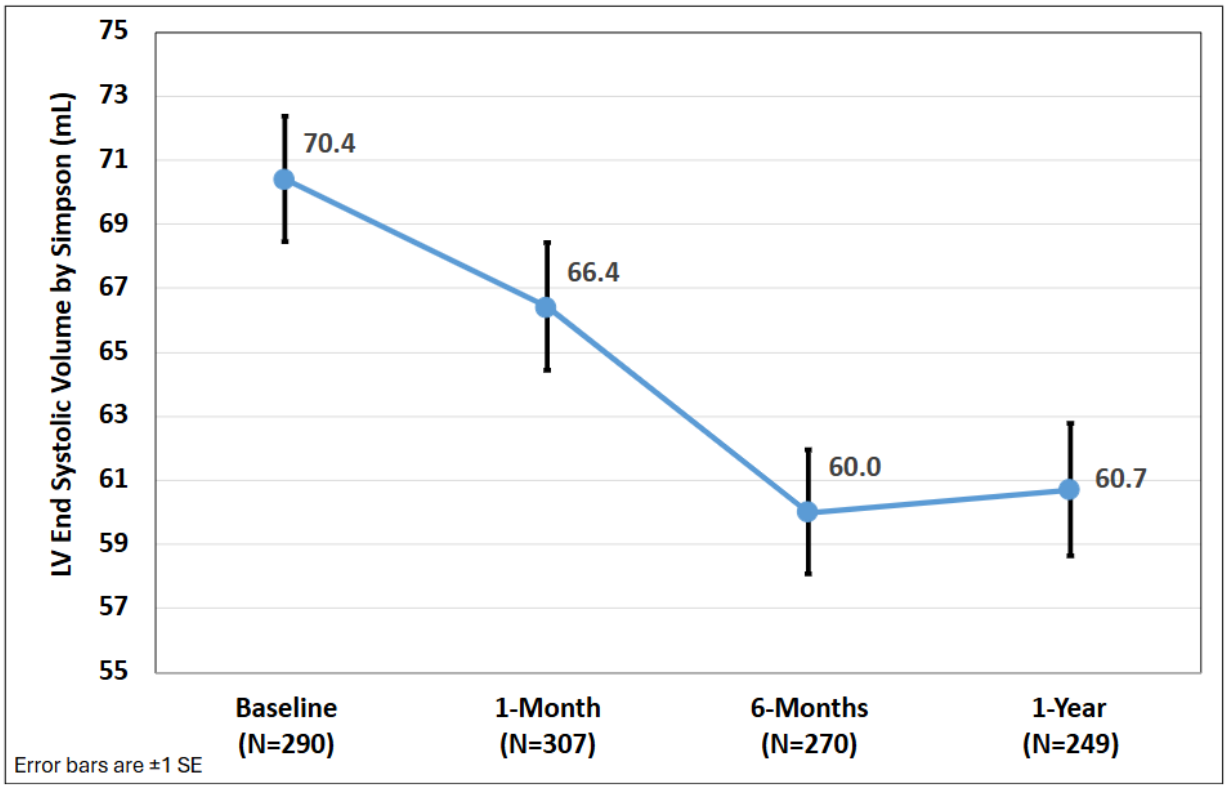


Figure 16: LVESV Through 1 Year in the CAP Cohort

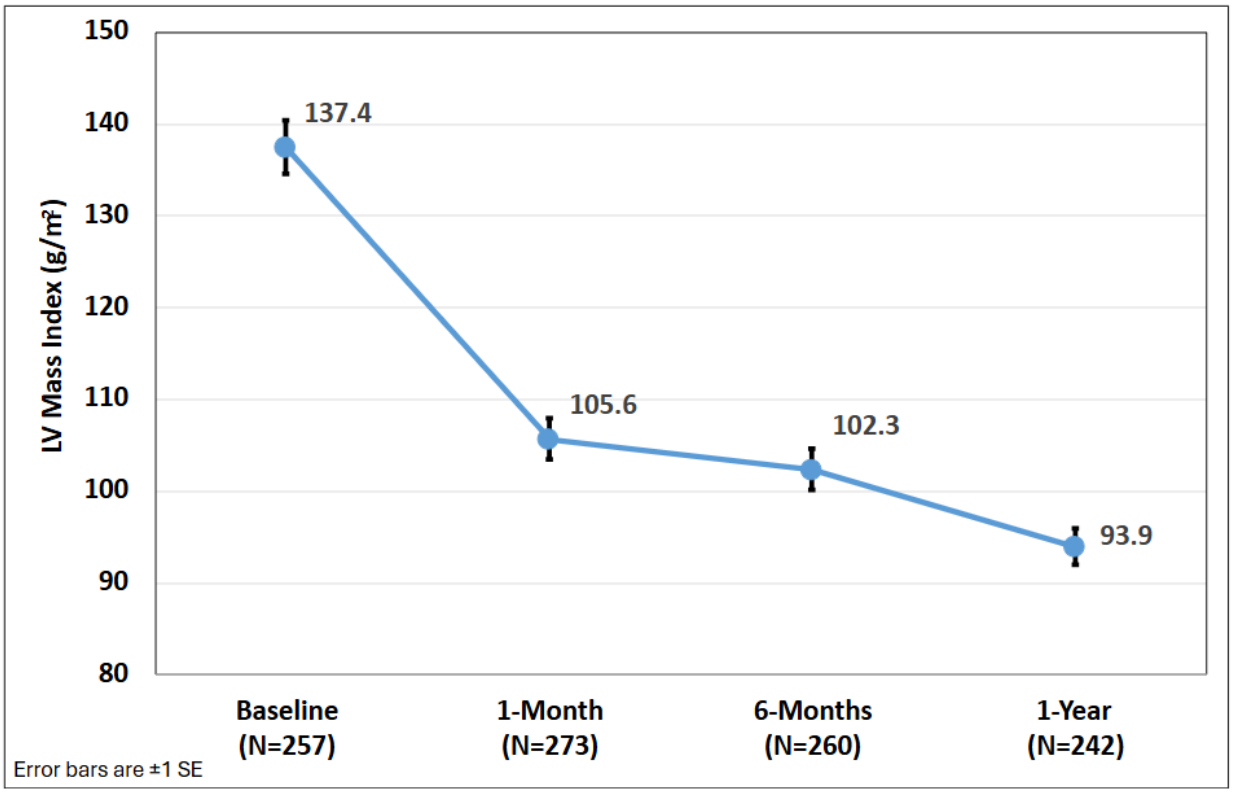


Figure 17: LV Mass Index Through 1 Year in the CAP Cohort

Table 27 Left Ventricular Remodeling in the CAP Cohort				
Description	**Screening**	**1-Month**	**6-Month**	**1-Year**
LV End Systolic Volume** (mL)	70.4 ± 33.3 (290)	66.4 ± 34.9 (307)	60.0 ± 31.8 (270)	60.7 ± 32.9 (249)
LV End Diastolic Volume** (mL)	153.9 ± 54.6 (290)	129.1 ± 46.8 (307)	119.8 ± 44.5 (270)	123.2 ± 47.7 (249)
LV End Systolic Diameter (cm)	3.95 ± 0.85 (298)	3.77 ± 0.81 (301)	3.57 ± 0.84 (272)	3.44 ± 0.80 (244)
LV End Diastolic Diameter (cm)	5.57 ± 0.80 (298)	5.00 ± 0.78 (301)	4.87 ± 0.80 (273)	4.78 ± 0.75 (244)
LV Mass (g)	253.2 ± 92.5 (257)	195.8 ± 74.7 (273)	189.8 ± 71.9 (260)	174.6 ± 63.0 (242)
LV Mass Index (g/m^2)	137.4 ± 47.0 (257)	105.6 ± 36.8 (273)	102.3 ± 35.7 (260)	93.9 ± 30.8 (242)
LV: left ventricular continuous variables: mean ± standard deviation (no.) ** calculated by Simpson's method				

6. Additional Functional Metrics

Using the 6-minute walk test (6MWT), the mean distance walked was 896.3 ± 397.9 feet at baseline and 976.3 ± 495.0 feet at 1-year for the CAP cohort. The mean change from baseline in total distance walked per subject was 42.2 ± 496.4 feet. The NYHA functional class of patients at baseline through 1-year is presented in **Figure 18**. At 1-year post-procedure, 6.2% of patients were NYHA class III or IV compared to 57.8% at baseline.

NYHA Classification	Baseline (N=320)	1-Month (N=308)	6-Months (N=285)	1-Year (N=277)
Class I	0	160 (51.9%)	161 (56.5%)	176 (63.5%)
Class II	135 (42.2%)	122 (39.6%)	104 (36.5%)	84 (30.3%)
Class III	174 (54.4%)	26 (8.4%)	20 (7.0%)	16 (5.8%)
Class IV	11 (3.4%)	0	0	1 (0.4%)

Figure 18: NYHA Classification through 1-Year in the CAP Cohort

7. Adverse Events

An overview of the VARC-2 clinical events through 1-year for the CAP cohort are presented in **Table 28**.

Table 28: VARC-2 Clinical Events in the CAP Cohort

Event	Summary Statistics*	
	30-Days (N=320)	**1 Year[1] (N=314)**
All Cause death	3 (0.9%)	24 (7.6%)
Cardiac Death	3 (0.9%)	16 (5.1%)
Non-cardiac Death	0 (0.0%)	8 (2.5%)
Permanent Pacemaker Implantation**	64 (23.4%)	72 (26.8%)
AKI Stage 2, 3 or dialysis	1 (0.3%)	
Myocardial infarction	1 (0.3%)	2 (0.6%)
Stroke	7 (2.2%)	15 (4.8%)
Disabling stroke	2 (0.6%)	4 (1.3%)
Non disabling stroke	5 (1.6%)	11 (3.5%)
All Bleeding	12 (3.8%)	14 (4.5%)
Major/Life threatening bleeding	8 (2.5%)	10 (3.2%)
Minor bleeding	4 (1.3%)	4 (1.3%)
Vascular complications	19 (5.9%)	19 (6.1%)
Major	8 (2.5%)	8 (2.5%)
Minor	11 (3.4%)	11 (3.5%)
Rehospitalization	6 (1.9%)	21 (6.7%)
Heart failure related	2 (0.6%)	15 (4.8%)
Index procedure related	4 (1.3%)	4 (1.3%)
TAVR valve related	0	3 (1.0%)
Valve intervention due to prosthetic valve thrombosis	0	1 (0.3%)
Valve intervention due to endocarditis	0	0

*Categorical variables: no. (%)

**Subjects with prior pacemakers (n=46) were excluded

[1] A subject is included in the 1-year denominator if they either experienced any adverse event within 365 days of the procedure or had at least 305 days of follow-up; otherwise the denominator is set to missing and they are excluded. 6 out of 320 subjects had no adverse events and <305 days of follow-up due to either withdrawal or lost-to-follow-up, giving a denominator of 314 at 1-year. The percentage calculation is based on the total number of patients per category of event.

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

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory 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.

XIV. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The primary effectiveness endpoint of all-cause mortality at 1-year was 6.2% in the ALIGN-AR subjects treated with the Trilogy THV (VI population). The upper bound of the one-sided 97.5% confidence interval was 11.5%, which was significantly lower than the pre-specified performance goal (PG) of 25%, indicating the study met its primary effectiveness endpoint. The mean change from baseline in KCCQ-OS at 1-year post-procedure was 20.6 points with a 2-sided 95% CI lower bound of 15.9, which was higher than the pre-specified performance goal (mean improvement of 10 points); therefore, the key secondary endpoint was met. The patients overall demonstrated improvements in valve hemodynamics including aortic regurgitation (AR). At baseline, 64.6% of subjects had severe AR, 31.6% had moderate-severe AR, and 2.8% had moderate AR while at 1-year 88.7% (125/141) of subjects had none to trace AR. Only one subject (0.7%; 1/141) had moderate AR and no subjects having greater than moderate AR at 1-year. The percentage of patients with a ≥1 NYHA class improvement from baseline to 1-year was 82.8%, indicating an improvement in functional status. These results were confirmed in the ALIGN-AR CAP cohort.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory studies and clinical data collected in the ALIGN-AR study to support PMA approval as described above. The results from the nonclinical studies performed on the Trilogy THV System (e.g., biocompatibility, hydrodynamic performance, and structural integrity) demonstrated that this device is suitable for implant. Engineering testing demonstrated a limited valve durability equivalent to 3.5 years, which did not meet the 5 years recommended by the relevant international standard.

The composite event rate of all-cause mortality, all stroke, life threatening or major bleeding, AKI Stage 2, 3 or dialysis, surgery/intervention related to the device (including coronary intervention), major vascular complications, permanent pacemaker implantation and moderate or severe total aortic regurgitation at 30 days was 26.7% (i.e., the primary safety endpoint). The upper bound of the one-sided 97.5% confidence interval was 34.1%, which was significantly lower than the pre-determined performance goal (PG) of 40.5%. As such, the pivotal study met the pre-specified primary endpoint. Notably, the rate of new

permanent pacemaker implantation was 24.0% within 30 days. The safety results from the primary analysis cohort were confirmed by the ALIGN-AR CAP cohort.

C. Benefit-Risk Determination

The probable benefits of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. They include improved hemodynamics and improved health and functional statuses as measured by KCCQ and NYHA functional class, respectively.

The probable risks of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. They include death, stroke, conduction disturbances requiring a new pacemaker, life-threatening bleeding, myocardial infarction, and major vascular complications.

The probable risks and benefits for the Trilogy Transcatheter Heart Valve system also considered that engineering testing demonstrated a limited valve durability equivalent to 3.5 years. However, the intended patient population for the Trilogy Transcatheter Heart Valve system is patients who are high or greater risk for surgical aortic valve replacement and thus have limited treatment options. Additionally, patients who experience structural valve deterioration may have the option of future valve-in-valve therapy with a transcatheter heart valve. The probable benefits of providing treatment to a patient population with limited treatment options outweigh the probable risks of limited valve durability in engineering testing. Long-term durability has not been established in a clinical setting for the Trilogy transcatheter heart valve.

1. Patient Perspective
   Patient perspectives considered during the review included patient reported outcomes as measured by KCCQ.

In conclusion, given the available information above, the data support that for patients with symptomatic, severe native tricuspid aortic valve regurgitation (not due to acute endocarditis, rheumatic heart disease, or acute aortic dissection) who are judged by a Heart Team, including a cardiac surgeon, to be at high or greater risk for surgical aortic valve replacement, the probable benefits outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use.

XV. CDRH DECISION

CDRH issued an approval order on March 17, 2026. The final clinical conditions of approval cited in the approval order are described below.

The applicant must conduct two post-approval studies:

1. **Continued Follow-up of the Premarket Cohort:** The study will consist of all living patients who were enrolled under the IDE, including the Continued Access Protocol investigation. The objective of this study is to characterize the clinical outcomes annually through 10 years. The follow-up data will be collected per the study protocol through 5 years post-procedure, including, but not limited to, adverse events, all-cause mortality, aortic valve reintervention, heart failure hospitalizations, echocardiographic parameters, Kansas City Cardiomyopathy Questionnaire (KCCQ) score, New York Heart Association (NYHA) functional classification, and 6-Minute Walk Test (6MWT) distance. Bioprosthetic valve failure, assessed using established echocardiographic criteria, will be reported with a minimum of 80% completeness rate each year through 5 years. The follow-up data (including all-cause mortality, all stroke, aortic valve reintervention, and heart failure hospitalizations) from year 6 through year 10 post-procedure will be obtained through linking the IDE data with the Centers for Medicare and Medicaid Services (CMS) claims and encounter data.

2. **Registry-Based Real-World Use Surveillance**: The surveillance will be carried out to assess the real-world performance of the Trilogy Transcatheter Heart Valve System and the clinical outcomes of the device in patient populations under-enrolled in the pivotal trial. It will involve all consecutive patients treated within the first 2 years following device approval or a total of 2,000 consecutively treated patients, whichever is greater, who are entered into the Society of Thoracic Surgeons (STS)/American College of Cardiology (ACC) Transcatheter Valve Therapy (TVT) Registry (enrollment period). Data collection will continue for under-enrolled racial and ethnic groups until each group has enrolled a minimum number of patients as specified: Black/African American, 100; Asian, 100, American Indian/Alaskan Native, 25, Native Hawaiian/Pacific Islander, 25; and Hispanic or Latino ethnicity, 100. All patients will be followed through 10 years post-procedure (follow-up duration). The clinical data through one (1) year will be collected through the TVT Registry. The follow-up data (including all-cause mortality, all stroke, aortic valve reintervention, and heart failure hospitalizations) from year 2 through year 10 post-procedure will be obtained through linking the TVT Registry data with the Centers for Medicare and Medicaid Services (CMS) claims and encounter data.

The applicant's manufacturing facility was inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820), which was in effect at the time of the inspection. As of February 2, 2026, the revised part 820, referred to as the Quality Management System Regulation (QMSR), is effective.

XVI. 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.