The Trilogy® Transcatheter Heart Valve System

Trilogy® Transcatheter Heart Valve
Trilogy® Delivery Catheter
Trilogy® Introducer Sheath
Trilogy® Loading Tools

TRILOGY-THV (sizes S, M, L), TRILOGY-DC (sizes S, M, L), TRILOGY-LT (sizes S, M, L), TRILOGY-INT

Instructions for Use

CAUTION: Federal (USA) law restricts these devices to sale by or on the order of a physician. Implantation of the transcatheter heart valve should be performed only by physicians who have received JenaValve Technology Inc. training

STERILE The Trilogy® Transcatheter Heart Valve System is supplied sterile and is for single use only. Do not reuse or resterilize.

Please verify you have the latest version of the IFU prior to using the device by visiting: www.eifu.jenavalve.com.
Read all instructions carefully. Failure to properly follow the instructions, warnings and precautions may lead to serious consequences or injury to the patient.

BIO The Trilogy® Transcatheter Heart Valve contains tissue of animal origin.

1.0 Device Description

The Trilogy® Transcatheter Heart Valve System consists of the Trilogy® Transcatheter Heart Valve (THV), Trilogy® Delivery Catheter, Trilogy® Loading Tools, and Trilogy® Introducer Sheath (**Table 1**). The terms 'prosthetic aortic valve', 'THV', 'transcatheter aortic valve', and 'bioprosthesis' are used throughout this document to refer to the Trilogy® THV.

Table 1: Trilogy® Transcatheter Heart Valve System Model Numbers[1]

Product Name	Size 23mm System	Size 25mm System	Size 27mm System
Trilogy® THV	TRILOGY-THV-S	TRILOGY-THV-M	TRILOGY-THV-L
Trilogy® Delivery Catheter	TRILOGY-DC-S	TRILOGY-DC-M	TRILOGY-DC-L
Trilogy® Loading Tools	TRILOGY-LT-S	TRILOGY-LT-M	TRILOGY-LT-L
Trilogy® Introducer Sheath	TRILOGY-INT		

[1]One complete system includes one (1) of each same-sized device listed in Table 1.

1.1 Trilogy® Transcatheter Heart Valve (THV)

The Trilogy® THV (**Figure 1**) is comprised of a trileaflet porcine pericardial valve attached to a self- expanding, radiopaque nitinol stent using polyester sutures. Three (3) covered Locators having additional radiopaque tantalum markers and the Sealing Ring serve to engage with the native valve Leaflets and annulus and anatomically fix the valve in place. The Trilogy® THV is loaded into the Trilogy® Delivery Catheter using the Trilogy® Loading Tools at the time of the procedure; the Sealing Ring (inflow) and Eyelets (outflow) are constrained by the Trilogy® Delivery Catheter until release.

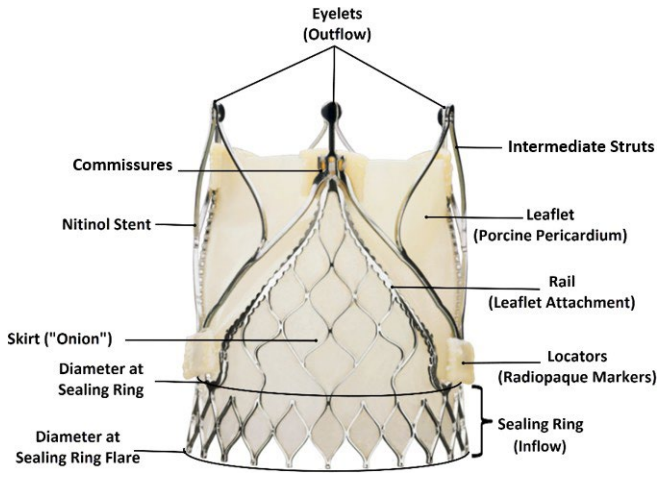


Figure 1: Trilogy® THV

1.1.1 Patient Anatomical Criteria

The transcatheter aortic valve is available for treatment of patients with aortic annulus diameters ranging from 21mm to 28.6mm, as shown in **Table 2**.

Table 2: Patient anatomical specifications. THV Sizing Chart Based on Annulus Perimeter and Annulus Perimeter Derived Diameter[1]

Valve Size	TRILOGY-THV-S	TRILOGY-THV-M	TRILOGY-THV-L
Indicated Annulus Diameter	21-24.2mm	24.2-26.4mm	26.4-28.6mm
Indicated Annulus Perimeter	66-76mm	76-83mm	83-90mm

[1]As determined on multidetector computed tomography (MDCT) scan. Patient anatomical factors and imaging quality should be considered during THV size selection. Note: Risks associated with under sizing and oversizing should be considered.

1.2 Trilogy® Delivery Catheter (DC)

The Trilogy® DC (**Figure 2** through **Figure 4**) delivers the THV transfemorally through the Trilogy® Introducer Sheath (INT) (**Figure 5**). Preparation of the Trilogy® DC for THV loading is detailed in Sections 10.2 and 10.3 and use of the Trilogy® INT and Trilogy® DC is detailed in Section 10.5.

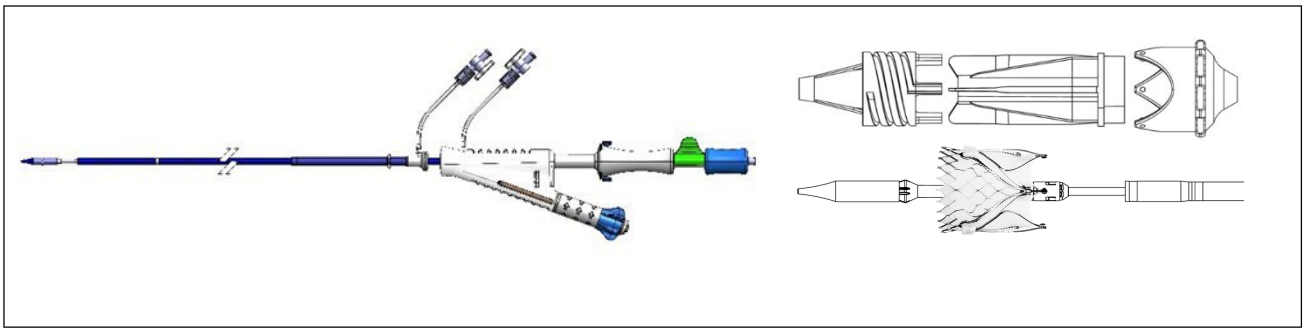


Figure 2: Trilogy® Delivery Catheter (Left) and THV Loading Process (Right)

The Trilogy® DC features distal components (**Figure 3**) which are controlled by the Trilogy® DC handle (**Figure 4**).

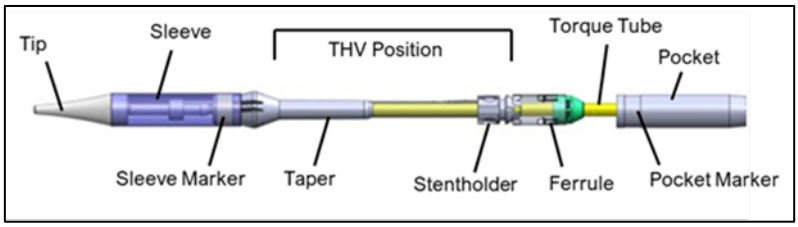


Figure 3: Trilogy® Delivery Catheter, Distal Components

The Trilogy® DC features a flushable handle and transition tube (**Figure 4**). The handle facilitates Trilogy® THV delivery and deployment through three mechanisms: a Deflector (rotation of the knob deflects the THV within the ascending aorta to center the THV Locators (**Figure 1**) above the native aortic cusps prior to deployment), a Controller (to position/advance the Trilogy® THV into the native aortic cusps by gripping the buttons and simultaneously rotating or advancing the Controller), and a Deployer (to deploy the Trilogy® THV from the Trilogy® DC).

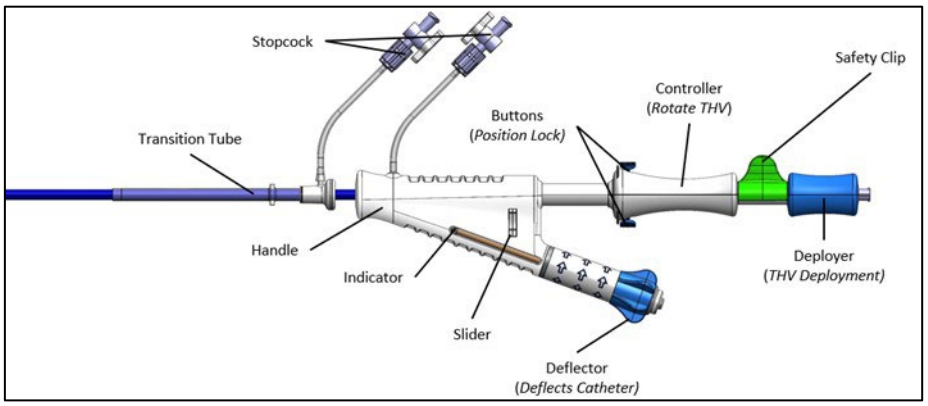


Figure 4: Trilogy® Delivery Catheter Handle

1.3 Trilogy® Loading Tools (LT)

The Trilogy® THV is loaded into the Trilogy® DC utilizing the Trilogy® LT (**Figure 5**). Preparation and use of the Trilogy® LT are detailed in Sections 10.2 and 10.3. One end of the Core, the Cone, and Wheel are used initially to place the THV Eyelets (**Figure 1**) into the Stentholder of the Trilogy® DC. The Trilogy® THV and Trilogy® DC subassembly is then removed from the Trilogy® LT and the Tucking Tool is used to tuck the THV Leaflets (**Figure 1**) into proper formation. The Core halves are opened, the Trilogy® THV/DC subassembly is placed into the Core and the Core is closed around the subassembly. The Wheel and Cone are reassembled around the Core and the Wheel is rotated to extrude the THV Sealing Ring (**Figure 1**) from the Cone into the DC Sleeve (**Figure 3**). The Trilogy® LT are then removed from the subassembly and the Loading Tube and crimp tube are used to crimp the Trilogy® THV to prepare for introduction into the Transition Tube of the Trilogy® DC (**Figure 4**).

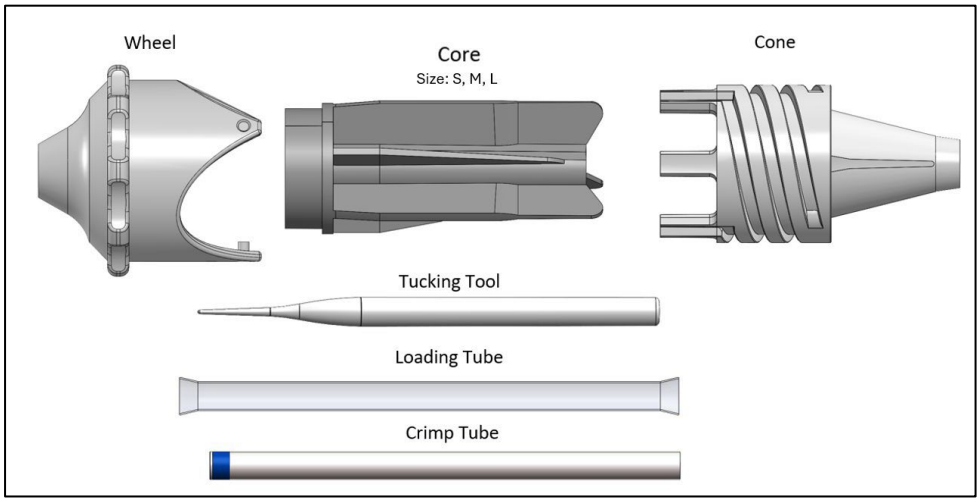


Figure 5: Trilogy® Loading Tools

1.4 Trilogy® Introducer Sheath (INT)

The Trilogy® INT (**Figure 6**) is comprised of a dilator and a 20Fr introducer sheath (22Fr outer profile), with a hydrophilic coated pre-shaped distal end and a proximal housing with a hemostatic seal. The Dilator accommodates all TAVR guidewires with a diameter up to 0.035". The Dilator is inserted into the Trilogy® INT, the system is flushed and then inserted into the ascending aorta, upon which the Dilator is removed, and the Trilogy® DC is inserted into the Trilogy® INT. The Trilogy® INT is sterilized by ethylene oxide gas for single use only.

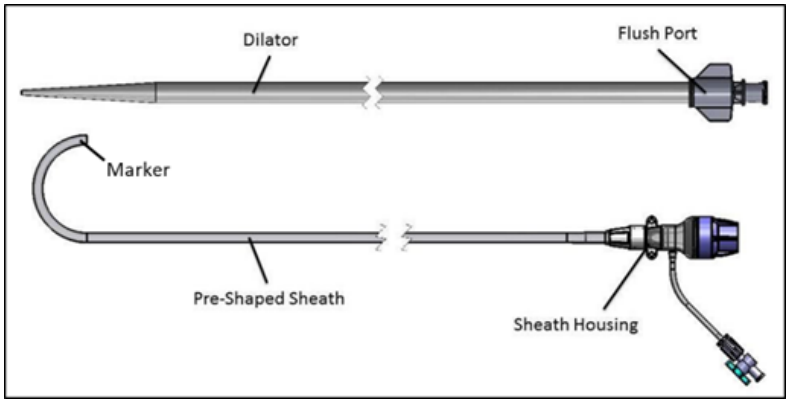


Figure 6: Trilogy® INT: Dilator (top); Pre-Shaped Introducer Sheath (bottom)

2.0 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).

3.0 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.

4.0 Warnings and Precautions

Carefully read all warnings, precautions, and instructions for use for all components of the system before use. Failure to read and follow all instructions or failure to observe all stated warnings could cause serious patient injury or death.

4.1 Warnings

4.1.1 General

- The Trilogy® THV is only to be used with the Trilogy® INT, Trilogy® DC and Trilogy® LT. Use of other devices may damage the THV and/or result in patient injury.
- This procedure should only be performed by physicians **experienced in transcatheter aortic valve replacement (TAVR) procedures and trained** in the use of the Trilogy® Transcatheter Heart Valve System, and where emergency cardiac surgery (surgical aortic valve replacement) may be promptly performed. Only physicians

who have successfully completed the JenaValve Professional Education training program are authorized to use the Trilogy Heart Valve System.

- The procedure must be conducted under fluoroscopic guidance. Some fluoroscopically guided procedures are associated with a risk of radiation injury to the skin. These injuries may be painful, disfiguring, and long-lasting.
- Ensure the guidewire is in proper location in the ventricle throughout the procedure to mitigate risk of ventricular wall perforation. Improper management of the guidewire, allowing it to move forward into the left ventricle, may lead to ventricular injury requiring intervention.
- Systemic anticoagulation with heparin should be administered and adjusted as needed throughout the procedure per hospital and physician preference. Activated clotting time (ACT) > 250 seconds is recommended to be maintained prior to Introducer Sheath insertion through completion of the procedure. Failure to maintain proper ACT levels may lead to patient harm or death.
- If heparin is contraindicated, an alternative anticoagulant should be considered and administered as per institutional policy.
- The THV must be sized appropriately to fit the patient's anatomy. Proper device sizing is the responsibility of the treating physician. Refer to **Table 2** for the THV sizing chart. Failure to implant a device within the sizing matrix could lead to adverse effects such as those listed in Section 6.0 of this manual.
- **DO NOT** bend or kink the Introducer Sheath. Doing so may damage the Delivery Catheter and the THV during or after the loading process.
- **DO NOT** mix the sizes of the THV, Delivery Catheter, or Loading Tools. Use of mixed size configurations of THV, Delivery Catheter, and Loading Tools may result in implantation difficulties such as premature/failure to release the THV from the Delivery Catheter, THV damage, or patient injury requiring intervention.
- **DO NOT** use the Trilogy® THV System components if:
    - the Use-By date has elapsed
    - the packaging or any of its components are not sterile or have been unintentionally opened before use
    - the product has been dropped, damaged, or mishandled.
- **DO NOT** use the Trilogy® INT with any pre-implant balloon valvuloplasty catheter.

4.1.2 Trilogy® THV

- **DO NOT** use the THV if:
    - the serial number tag is missing or does not match the container label
    - the container or seal is damaged, cracked, or leaking
    - the temperature indicator is out of range
    - the THV is not fully covered in solution after opening the package
- Incorrect sizing of the THV with the patient's native aortic valve may lead to paravalvular leak, migration, annular injury, embolization, and/or unsuccessful implant.
- Accelerated deterioration of the THV may occur in patients with an altered calcium metabolism.

4.2 Precautions

4.2.1 General

- **DO NOT** expose the THV to solutions other than the storage, sterile rinse, and sterile chilling solutions.
- **DO NOT** add any other substance or drug to the THV storage, sterile rinse, or sterile chilling solutions.
- Always keep the THV tissue moist with rinsing or immersion.
- Long-term clinical durability has not been established for the Trilogy transcatheter heart valve. Engineering testing has demonstrated an *in vitro* valve durability equivalent to 3.5 years, which did not meet the 5 years recommended by the relevant international standard. Regular medical follow-up, including assessment of valve function, is advised.
- The safety and effectiveness of the THV has not been evaluated in the following patient populations:
    - Patients with percutaneous Ventricular Assist Devices (pVAD) or Left Ventricular Assist Devices (LVAD)
    - Pediatric patients

- Patients who are pregnant or breastfeeding.

- The safety and effectiveness of the THV has not been evaluated in patient populations presenting with the following:
  - Blood dyscrasias as defined: leukopenia (WBC < 3000/mm³), thrombocytopenia (platelets < 90,000/µl) or anemia (Men: Hgb < 8.1 g/dl; Women: Hgb < 7.4 g/dl).
  - Congenital/functional unicuspid, bicuspid or quadricuspid native aortic valve morphology.
  - Previous prosthetic aortic valve (bioprosthesis or mechanical) implant.
  - Echocardiographic evidence of current left heart thrombus.
  - Hypertrophic cardiomyopathy with or without obstruction.
  - Severe pulmonary hypertension (systolic PA pressure > 80 mmHg) or severe RV dysfunction as assessed clinically and by echo
  - Very severely reduced left ventricular ejection fraction (LVEF < 25%).
  - Significant disease of ascending aorta, including ascending aortic aneurysm (defined as maximal luminal diameter of 50 mm or greater) or significant protruding or ulcerated atheroma.
  - Aortic annular diameter of less than 21 mm or more than 28.6 mm (assessed by multidetector computed tomography (MDCT) measurement).
  - Access vessel characteristics that would preclude safe placement of the JenaValve 20Fr introducer sheath, such as severe obstructive calcification, severe tortuosity, or vessel diameter <7mm.
  - severe renal insufficiency (GFR < 30 mL/min) or renal disease requiring renal replacement therapy (e.g., dialysis)

4.2.2 Prior to Use

- Removal of the Delivery Catheter and Introducer Sheath from the respective packaging should be performed carefully to prevent damage or kinking.
- The Trilogy® THV System is designed for single patient use only. Do not reuse, reprocess or resterilize any component of this product. Reusing, reprocessing or resterilizing this product may compromise its initial integrity which could result in patient injury, illness, or death.
- The THV and the glutaraldehyde storage solutions are STERILE. The exterior of the THV container is NONSTERILE and must NOT be placed in the sterile field.
- Exposure to glutaraldehyde may cause irritation of the skin, eyes, nose, and throat. Avoid prolonged or repeated exposure to the vapors and use adequate ventilation. If skin contact occurs, immediately flush the affected area with water. In the event of eye contact, flush with water and seek immediate medical attention.

4.2.3 During Use

- Adequate rinsing of the THV with sterile cold saline prior to use as described in this manual is mandatory before implantation. No other solutions, drugs, or chemicals (including antibiotics) should be added to the storage or rinsing solutions, as irreparable damage to the THV Leaflets, which may not be apparent under visual inspection, may occur.
- The use of this device requires administration of intravascular contrast. Patients with pre-existing renal insufficiency may have an increased risk of renal failure post-operatively (e.g., patients with Stage 4 or 5 chronic kidney disease). Care should be taken to limit the amount of contrast media used during the procedure.
- Introducer Sheath and Delivery Catheter advancement should be performed under fluoroscopic guidance. Do not use excessive force to advance or withdraw the Introducer Sheath or Delivery Catheter when resistance is encountered. Vessel or device damage may occur. Care should be taken in areas of stenosis, intravascular thrombosis, or in calcified and/or tortuous vessels.
- Pre-dilatation of the native aortic annulus using balloon aortic valvuloplasty (BAV) is performed at physician discretion.
- Ensure guidewire access and positioning is maintained at all times. Do not remove the guidewire while the Delivery Catheter and Introducer Sheath are inserted in the patient.

- Inaccurate placement, inadequate Locator to Leaflet fixation and/or incomplete sealing of the THV within the annulus may result in increased risk of paravalvular leakage, migration, or inadvertent coronary occlusion. Incorrect deployment or migration of the THV may require intervention.
- Once deployment has occurred, repositioning of the THV (e.g., using a snare) is not recommended. Repositioning of a deployed THV may cause patient injury and/or require emergent surgery.
- **DO NOT** attempt to retrieve or recapture the prosthetic aortic valve if the sealing ring has been deployed. If the sealing ring has been deployed, the THV must be released from the catheter before the catheter can be withdrawn with the Introducer Sheath.
- Take care during manipulation of catheters, wires, and sheaths within the aorta. Excessive manipulation may dislodge fragments of atheroma or calcification which can cause embolization.
- Clinical long-term durability for the Trilogy® THV has not been established. Regular medical follow-up is advised to evaluate THV performance as per standard of care for similar bio-prosthetic valves.
- Post-procedure, administer appropriate antibiotic prophylaxis as needed for patients at risk of prosthetic valve infection or endocarditis.
- Post-procedure, administer anticoagulation and/or antiplatelet therapy per physician judgment.

4.3 Magnetic Resonance Imaging (MRI)

MRI may be used on the implanted THV only under specific conditions. See Section 7.4 for more information.

5.0 Potential Adverse Events

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

6.0 Patient Information and Follow Up

6.1 Patient Selection

Patient selection should be performed by the multidisciplinary heart team. Specific factors that need to be considered include the following:

- 18 years of age or older
- NYHA Functional Class II or higher
- Suitable anatomy to accommodate the insertion and delivery of the Trilogy® delivery system [femoral access size of 7.0 mm diameter or higher, straight length of ascending aorta of ≥ 55mm, aortic annulus angle ≤ 70° (measured in 3-cusp co-planar view) and acceptable calcification as identified per appropriate imaging modality (e.g., echo, multi-slice CT, MRI)]
- Absence of significant disease of the ascending aorta, including ascending aortic aneurysm (defined as maximal luminal diameter of 50 mm or greater) or atheroma (especially if thick [> 5mm], protruding or ulcerated)
- Aortic annulus diameter from ≥ 21 mm up to ≤ 28.6 mm by MDCT or TEE

All patients should be made aware of the benefits and risks of TAVR, and alternative treatment options available.

6.2 Post-Procedural Follow-Up

The long-term performance of the Trilogy® THV has not yet been established. All patients should be counseled that regular and consistent follow-up is imperative to ensure the ongoing safety and effectiveness of their TAVR treatment. Physicians should adhere to a follow-up schedule at 30 days and 1-year post-procedure, and yearly thereafter to assess patient health and performance of their prosthetic aortic valve or as is the standard of care for TAVI valves in the institution. Patients with specific clinical findings (e.g., paravalvular leakage, valve migration, endocarditis, conduction disorders or arrhythmias) should receive additional follow-up. Post-procedural anticoagulation therapy is recommended for 6 months per institutional procedure.

6.3 Patient Registration and Implant Card

JenaValve will provide a Device Identification Card in each THV package to be provided to the patient after implantation. The card contains the name and telephone number of the patient's physician as well as information that medical personnel would require in the event of an emergency (i.e., MRI Safety Information). The implant card must always be completed and provided to the patient with instructions for them to keep the card in their possession. The implant card includes the device serial number which is located on both the package and the identification tag attached to the Trilogy® THV.

6.4 MRI Safety Information

MRI Safety Information

The **Trilogy Transcatheter Heart Valve** is MR Conditional. A patient with the **Trilogy Transcatheter Heart Valve** may be safely scanned under the following conditions. Failure to follow these conditions may result in injury to the patient.

MR Conditional

Parameter	***Condition of Use/Information***
Nominal Values of Static Magnetic Field (T)	1.5-Tesla or 3.0-Tesla
Maximum Spatial Field Gradient (T/m and gauss/cm)	40-T/m (4,000-gauss/cm)
Type of RF Excitation	Circularly Polarized (CP) (i.e., Quadrature-Transmission)
Transmit RF Coil Information	There are no transmit RF coil restrictions. Accordingly, the following may be used: body transmit RF coil and all other RF coil combinations (i.e., body RF coil combined with any receive-only RF coil, transmit/receive head RF coil, transmit/receive knee RF coil, etc.)
Operating Mode of MR System	Normal Operating Mode
Maximum Whole Body Averaged SAR (W/kg)	2-W/kg (Normal Operating Mode)
Limits on Scan Duration	Whole body averaged SAR of 2-W/kg for 60 minutes of continuous RF exposure (i.e., per pulse sequence or back-to-back sequences/series without breaks)
MR Image Artifact	The presence of this implant produces an imaging artifact. Therefore, carefully select pulse sequence parameters if the implant is located in the area of interest.

7.0 How Supplied

7.1 THV

STERILE: The THV undergoes liquid chemical sterilization in a sealed jar with glutaraldehyde solution. Each jar is shipped in an enclosure containing a temperature indicator to detect exposure to extreme temperature. Ensure that the temperature indicator displays "OK" prior to opening the jar. Ensure that the serial number on the box, the jar, and the patient sticker match before opening the jar.

CAUTION: Handle the jar contents aseptically to prevent contamination.

7.2 Trilogy® Delivery Catheter (DC), Introducer Sheath (INT), and Loading Tools (LT)

STERILE: The Trilogy® DC, Trilogy® INT, and Trilogy® LT are supplied sterilized by ethylene oxide gas. These devices are sealed in Tyvek pouches and unit cartons.

8.0 Storage Conditions

These devices must be stored in a cool, dry place. Store the valve (THV) in the upright position. The THV must be stored between 2°C (36°F) and 25°C (77°F).

CAUTION: Do not use the THV if the temperature indicator is out of range (does not show "OK").

9.0 Directions for Use

9.1 Required Equipment and Materials

Table 3: Trilogy® Transcatheter Heart Valve System Model Numbers*

Product Name	**Size 23mm System**	**Size 25mm System**	**Size 27mm System**
Trilogy® THV	TRILOGY®-THV-S	TRILOGY®-THV-M	TRILOGY®-THV-L
Trilogy® Delivery Catheter	TRILOGY®-DC-S	TRILOGY®-DC-M	TRILOGY®-DC-L
Trilogy® Loading Tools	TRILOGY®-LT-S	TRILOGY®-LT-M	TRILOGY®-LT-L
Trilogy® Introducer Sheath	TRILOGY®-INT		

*One complete system includes one (1) of each same-sized device listed above.

The Trilogy® Transcatheter Heart Valve System consists of the Trilogy® Transcatheter Heart Valve (THV), Trilogy® Delivery Catheter, Trilogy® Loading Tools, and Trilogy® Introducer Sheath, (**Table 3**).

WARNING: The procedure must be conducted under fluoroscopic guidance. Some fluoroscopically guided procedures are associated with a risk of radiation injury to the skin. These injuries may be painful, disfiguring, and long-lasting

Additional equipment and materials:
Note: While comprehensive, this equipment list is not meant to cover all possible scenarios.

- Sterile table for THV, Delivery Catheter, Sheath System, and Loading Tool preparation
- Sterile THV rinsing basins (5), each with depth ≥ 5 cm and adequate capacity to accommodate 500 mL
- Pressurized Heparinized saline bag and sterile extension tubing
- Ambient temperature physiological sterile saline
- Cold (4 ± 2°C [39 ± 3°F]) physiological sterile saline
- 50 mL luer-lock syringe or larger
- 10 mL luer-lock syringe or smaller
- Sterile scissors

- Sterile blunt anatomical forceps
- Standard cardiac catheterization laboratory equipment
- Standard-length balloon valvuloplasty catheters, ≤4 cm x 18-26 mm diameters
- Tuohy-Borst Valve with Y-Connector
- Balloon inflation device
- Temporary pacemaker and lead
- Transesophageal or transthoracic echocardiography capabilities
- 0.035" (0.889 mm) x 260 cm length standard high-support guidewire
- 0.035" (0.889 mm) x ≥275 cm length high-support guidewire (e.g., Boston Scientific – SAFARI2™ Pre-Shaped TAVR/TAVI guidewire)
- Fluoroscopy equipment (appropriate for use in percutaneous coronary interventions)
- Contrast media
- Power injector, with syringe and high-pressure power injector tubing
- Hemostatic vessel introducer sheaths of various sizes
- Angiographic catheter with radiopaque graduated markers
- 2-port manifold with saline flush and pressure tubing or transducer
- Suture-mediated vessel closure systems (as applicable)

9.2 Inspection and Device Preparation

CAUTION: Once the THV is removed from its container, and the Delivery Catheter, Loading Tools, and Introducer Sheath, are removed from their respective packaging, perform all subsequent procedures in the sterile field.

9.2.1 Unpack the THV

CAUTION: DO NOT use the THV after the "Use-By" date, if there is evidence of damage to the packaging or jar, if the valve jar/lid or seal is damaged, if the THV is not completely covered in liquid, or if liquid has leaked from the jar.

CAUTION: Do not handle or manipulate the THV with sharp or pointed objects.

Step	Procedure
1	Before removing the bioprosthesis from the jar, carefully inspect the packaging for any evidence of damage that could compromise the sterility or integrity of the device (e.g., cracked jar or lid, leakage, broken or missing seals).
2	Ensure that the temperature indicator displays "OK" prior to opening the jar. **CAUTION:** Do not use the THV if the temperature indicator does not display "OK".
3	Ensure that the serial number on the box, the jar, and the patient sticker match before opening the jar. **CAUTION:** The THV and the glutaraldehyde storage solutions are STERILE. The outside of the THV container is NONSTERILE and must NOT be placed in the sterile field.
4	Open the jar using forceps, grasp the retainer ring and carefully transfer the THV to the first basin containing approximately 500 mL of cold (4 ± 2°C / 39 ± 3°F) physiologically sterile saline solution.
5	Remove the THV with its retainer ring from the basin and remove the THV from the ring by lightly pressing on the THV Eyelets.
6	Gently remove the serial number tag using sterile scissors and visually inspect the THV to ensure it is free from any damage. Verify that the serial number tag on the implant matches the serial number that is on the box and jar. Return the THV to the same basin with cold, physiologically sterile saline solution. **CAUTION:** DO NOT use THV if serial number on tag is not consistent with its packaging. Return any unused product to JenaValve for replacement in its original packaging.

9.2.2 Preparing the Introducer Sheath, Delivery Catheter, and Loading Tools

Step	Procedure
1	The Introducer Sheath, Delivery Catheter and the Loading Tools are individually packaged in sealed pouches. Verify all pouches are sealed and both Tyvek and clear surfaces are intact with no signs of damage. **CAUTION:** If the packaging is damaged or packaging seals are compromised, do not use the product.
2	Verify the correct model of Delivery Catheter and Loading Tool are selected for the THV size (**Table 1)**. **WARNING:** DO NOT mix THV, Delivery Catheter, or Loading Tool sizes. Use of mixed-size configurations may result in improper THV loading into the Delivery Catheter, implantation difficulties, premature THV release, failure to release the valve from the Delivery Catheter, THV damage, or injury to the patient.
3	Open the Loading Tool package, remove all components, and place on the sterile table. Inspect each for any damage. **CAUTION:** If the Loading Tools appear damaged, discard, and replace with a new set of Loading Tools.
4	Open the Trilogy® Introducer Sheath package and place the Introducer Sheath and Dilator onto the sterile table. Inspect the Introducer Sheath and Dilator to ensure the tips are circular and are free of sharp edges. If any Introducer Sheath components appear damaged, discard, and replace with a new system.
5	Holding the Introducer Sheath with its tip at least 45 degrees off the table off the table, flush all ports with sterile saline using the large syringe. This angulation during flushing is needed to ensure the removal of air in the housing. Visually inspect the clear Introducer Sheath housing for air pockets. If air is detected, re-flush the device. Note that the Introducer Sheath requires at least 60mL to fully flush. **CAUTION:** If leakage is detected at the proximal end of the Introducer Sheath Housing during flushing, discard and replace with a new Introducer Sheath.
6	Wet the Dilator and Introducer Sheath Housing inner diameter with sterile saline. Insert the Dilator tip into the Introducer Sheath Housing ensuring the Dilator tip has passed the sheath seal. Flush the Dilator port with sterile saline using the large syringe. Flush the Introducer with its tip at least 45 degrees off the table. Insert the

Step	Procedure
	Dilator until it is seated against the Sheath.
7	Open the Delivery Catheter package, place all items onto the sterile table. Place the Delivery Catheter flat on the preparation table and flush all ports using the large syringe until fluid exits the delivery catheter tip and pocket.
8	Functionally inspect the handle and Controller by depressing the Buttons and advancing/rotating the Controller to verify the locking feature between the Handles. Depress the Buttons and fully retract the Controller relative to the Handle to verify that the Slider engages. After the functional check, return the device Handle to the original configuration for loading. If the Delivery Catheter appears damaged or does not pass the functional test, discard, and replace with a new system. **CAUTION:** If leakage is detected at the handle during flushing, discard and replace with a new Delivery Catheter.

9.3 THV Rinsing and Catheter Loading Procedure

9.3.1 Rinse the THV

CAUTION: Adequate rinsing of the THV with sterile saline prior to use as described in this section is mandatory before implantation. No other solutions, drugs, or chemicals should be added to the storage or rinsing solutions, as irreparable damage to the THV Leaflets not apparent under visual inspection may occur.

CAUTION: Do not handle or manipulate the THV with sharp or pointed objects

Step	Procedure
1	Immerse and gently agitate the THV in the first basin of ambient temperature physiological sterile saline solution for at least 2 minutes.
2	Carefully remove the THV from the first basin and repeat the rinsing procedure in the second basin of ambient temperature physiological sterile saline solution for at least 2 minutes. Repeat this process again using the third basin of ambient temperature physiological sterile saline solution.
3	After completing the rinsing procedure, place the THV into a basin of cold (4 ± 2°C / 39 ± 3°F) physiological sterile saline solution for approximately 1 minute.
4	After approximately 1 minute, the THV is ready to be loaded into the Delivery Catheter. **CAUTION:** Keep THV hydrated in cold physiological sterile saline bath to prevent the Leaflet tissue from drying.

9.3.2 Load the Retraction Taper

Step	Procedure
1	Advance the Deployer forward and rotate clockwise until it stops. Pull the Deployer back while applying a clockwise rotation, until positioned in the side slot, to retract the Sleeve over the Taper to prepare the Delivery Catheter for THV loading. **Note:** If the Sleeve is not over the Taper gently push the Sleeve over so that the Taper is inside of the Sleeve.
2	Visually inspect the Sleeve to ensure no damage occurred during retraction. **CAUTION:** Damage to the Sleeve could result in premature release of the THV prior to or during deployment.

9.3.3 Load the THV Eyelets

Step	Procedure
1	Assemble the Cone and Core by aligning the Core fins and inserting Core into the Cone, then place the THV Sealing Ring onto the Core platform. Align the 3 Wheel pins onto the Cone tracks, visually inspect the Wheel ID. If the THV Leaflets are blocking the ID, gently submerge the Cone/Core/Wheel-assembly,

Step	Procedure
	Wheel side down, into the cold physiological sterile saline bath and lift to allow the saline to flow out and open the Leaflets. **WARNING**: Failure to ensure the Cone ID is open prior to proceeding may result in damage to the THV Leaflets.
2	Insert the Delivery Catheter Tip into the Wheel opening and rotate the Wheel to partially crimp the THV while aligning the Eyelets and Intermediate Struts into the Stentholder recesses. After the Eyelets are seated within the Stentholder recesses and confirming that the three Intermediate Struts align with the three notches in the Ferrule, advance the Stentholder into the Ferrule until the Stentholder is engaged into the Ferrule tabs. **WARNING:** Failure to fully lock the Stentholder into the Ferrule may lead to premature deployment of the THV Eyelets, requiring intervention.
3	Carefully remove the Wheel from the Core and Cone, and then remove the Core from the Cone, without dislodging the THV.

9.3.4 Load the THV Sealing Ring

Step	Procedure
1	Use the Tucking Tool to carefully tuck the three THV Commissures into the interior of the valve, then tuck the THV Leaflets between the stent Rails and away from the three THV Commissures to ensure Leaflets do not protrude beyond the stent. Ensure that the THV Leaflets are folded in the same direction and that no THV Leaflets are overlapped.
2	Place THV with captured eyelets into a basin with cold physiological sterile saline for at least 1 minute.
3	Place the Delivery Catheter into the Core open halves aligning the recesses in the Core with the Torque Tube and proximal end of the Ferrule, then carefully close the Core halves together around the Delivery Catheter shaft. **CAUTION:** Ensure all three (3) THV Locators are correctly aligned in the Cone slots.
4	Align the Core fins with the THV Locators and insert the Core into the Cone. Verify that the THV Locators are aligned with and exit the Cone slots.
5	Slide Wheel from the proximal end of the Delivery Catheter to engage wheel with the Cone.
6	Securely grip the Cone, then rotate the Wheel until the THV Sealing Ring extrudes flush with the edge of the Cone. Verify that the extruded THV Sealing Ring has a circular shape. **CAUTION:** Ensure the THV Sealing Ring is over the Taper body, flush with the Cone, and the shape is circular. **WARNING:** Rotate the Wheel only. Rotation of the entire Loading Tool assembly while the THV is partially loaded may cause damage to the THV. If the THV Sealing Ring appears non-circular, the THV may be damaged. DO NOT proceed. Disassemble the Loading Tools, discard the THV and re-load a new THV.
7	Rotate the Deployer counterclockwise until a bump is felt, indicating the pin has left the side slot. Push the Sleeve over the Sealing Ring and rotate the Wheel to continue extrusion of the Sealing Ring from the Cone until the Sleeve cannot be advanced any further onto the Sealing Ring. This signifies sufficient Sleeve coverage over the THV.
8	Fully retract the Deployer and rotate the Deployer counterclockwise to lock it in place. Place the Safety Clip in between the Controller and Deployer. **WARNING:** Failure to place the Safety Clip into the Handle may result in premature THV deployment**.**
9	Push the Sleeve over the Sealing Ring one final time to ensure sufficient Sleeve coverage over the THV.
10	Rotate and disengage Wheel from the Cone and slide towards proximal end of the Delivery Catheter. Hold the Cone securely and gently retract the Core approximately 1-2 cm. Gently push the Sleeve through the Cone, then open and remove the Core. **CAUTION:** When removing the Loading Tools, be careful not to dislodge the THV from its loaded position within the Sealing Ring sleeve.
11	Once all Loading Tools have been removed, verify the THV Sealing Ring remains inside the Sleeve and no damage is observed on the Sleeve or THV Locators. **CAUTION:** If damage is observed, DO NOT proceed. Discard the THV and Delivery Catheter.
12	Verify that the Sleeve goes up to or covers the distal edge of the "U".

Step	Procedure
	CAUTION: If a Sleeve to "U" gap is visible, DO NOT proceed. Discard the THV and Delivery Catheter. Prepare a new THV and Delivery Catheter.
13	The THV Eyelets and Sealing Ring are now secured into the Delivery Catheter. If any Leaflet tissue is protruding from the stent, carefully tuck the tissue into the THV using the Tucking Tool.
14	Place secured THV into a basin with cold physiological sterile saline for at least 1 minute.
15	Insert the Delivery Catheter tip into the Loading Tube. Carefully advance the Loading Tube over the THV body to crimp the stent in a single, continuous motion, until the Loading Tube covers all Rail sutures. **CAUTION:** Do not apply excessive force to advance Loading Tube over the THV. Excessive force can deform the Locators, damaging the THV. If the THV is damaged, DO NOT proceed. Disassemble the Loading Tools and discard the THV and Delivery System. Prepare a new THV and Delivery System.
16	Immediately remove the Loading Tube and carefully advance the blue side of the Crimp Tube over the THV body until the Crimp Tube covers all Rail sutures.
17	Align one (1) THV Locator within the same plane as the Deflector by depressing the Buttons and rotating the Controller. This allows pre-orientation of the THV Locators to the anatomical position of the patient's native cusps.
18	Advance the Transition Tube from the Delivery Catheter shaft to the THV Locator covers (approximately 1-2 mm away). Remove the Crimp Tube and Wheel from the Delivery Catheter. Actuate the Buttons to unlock the Controller and advance the Handle forward to load the Ferrule into the pocket to complete the loading process.
19	Inspect the THV to verify its Sealing Ring remains captured within the Sleeve and that the three (3) Locators are evenly distributed around the Sleeve. Verify that no damage is observed on the Sleeve. **WARNING:** If the three (3) Locators are not evenly distributed around the Delivery Catheter tip or damage is observed on the Sleeve, DO NOT proceed. Discard the THV and Delivery Catheter. Prepare a new THV and Delivery Catheter.
20	Flush all ports of the Delivery Catheter with cold (4 ± 2°C / 39 ± 3°F) physiological saline using the large syringe to purge air within the Delivery Catheter • Start with the guidewire lumen, flush until saline passes through the Tip, then plug the Tip lumen and continue flushing to purge air from the THV. • Once air is purged from the THV, flush the Deflecting Catheter, then flush the Transition Tube using the small syringe. • Immerse the loaded THV in a basin with sterile, cold physiological saline until it will be implanted. **CAUTION:** To prevent possible Leaflet damage, do not leave the THV crimped in the Transition Tube in cold physiological sterile saline for more than 15 minutes.
21	Connect a hemostasis valve Y connector to the luer on the proximal end of the Delivery Catheter. Attach a heparinized saline continuous flush onto the Y connector (guidewire lumen) and verify that saline exits the Delivery Catheter tip prior to loading the device onto the guidewire.

9.4 Patient Preparation

Step	Procedure
1	Administer heparin according to hospital protocol and maintain ACT > 250 seconds from introducer sheath insertion to completion of procedure. **WARNING:** Failure to monitor ACT may lead to patient harm or death. **WARNING**: If heparin is contraindicated, an alternative anticoagulant should be considered and administered as per institutional policy.
2	Perform a supra-aortic angiogram with fluoroscopic visualization perpendicular to the aortic valve.
3	Place and test a temporary pacemaker wire according to hospital protocol.
4	Prepare the patient transfemoral access site percutaneously or using surgical cutdown (femoral exposure) according to hospital protocol. **Note:** Pre-dilation shall be performed as applicable prior placement of the Introducer Sheath. If pre-dilating the native aortic valve annulus is required, perform balloon valvuloplasty (BAV) per hospital protocol and according to the balloon manufacturer's instructions for use. Select a balloon that is 1-2 mm smaller than the diameter of the native aortic annulus as measured by CT. **CAUTION:** Pre-dilatation must not be performed through the Introducer Sheath. **WARNING:** Balloon over-inflation may cause patient injury, including annular rupture, requiring emergent intervention. **CAUTION:** The Introducer Sheath should be inserted only after the ACT > 250 seconds and the Delivery Catheter is loaded and ready for use. **CAUTION:** Close heparinization monitoring is required throughout the procedure. Minimizing the indwelling time of the Introducer Sheath once the Dilator is removed is recommended.
5	Insert the Introducer Sheath and Dilator over a ≥ 275 cm, 0.035" guidewire and into the femoral access site. Carefully advance the system through the aorta until the c-shaped marker at the distal end of the Introducer Sheath is just above the sinotubular junction (STJ). **Note:** Fluoroscopic view should be perpendicular to the aortic arch (LAO projection). **Note:** For prolonged Introducer Sheath placement, attach a hemostasis valve Y connector to the Dilator luer to minimize blood loss.
6	Remove the Dilator from the Introducer Sheath while maintaining guidewire positioning. **CAUTION:** Avoid excessive guidewire manipulation and keep the guidewire concentric within the Introducer Sheath housing to prevent damage and/or leakage at the Introducer Sheath hemostasis seal.

9.5 Implantation Procedure

9.5.1 Deliver the THV

Step	Procedure
1	Insert the Delivery Catheter and Transition Tube as a single unit into the Introducer Sheath Housing and advance until the Transition Tube stop is seated against the Introducer Sheath housing. **WARNING:** Ensure all three Locators are uniformly aligned to the Introducer Sheath hub prior to insertion. Improper alignment may cause damage to the THV Locators, potentially leading to patient injury and/or surgical intervention.
2	Carefully continue to advance the Delivery Catheter into the Introducer Sheath, ensuring that the Deflector is pointing towards the curvature of the patient's ascending aorta (patient's right).

Step	Procedure
	WARNING: After introduction of the Transition Tube into the Introducer Sheath housing, DO NOT retract the Delivery Catheter as this may damage the THV Locators, potentially leading to patient injury and/or surgical intervention.
3	Under fluoroscopic visualization and while maintaining strict guidewire position, continue to advance the Delivery Catheter until the radiopaque Delivery Catheter sleeve marker aligns with the radiopaque Introducer Sheath marker in the ascending aorta at the STJ
4	While holding the Delivery Catheter in place, retract the Introducer Sheath to expose the radiopaque THV Locators, and continue retracting the Introducer Sheath until the Tip is in the descending aorta (past the left subclavian artery).
5	Ensure the Deflector points towards the curvature of the patient's ascending aorta to ensure correct alignment with the patient anatomy.
6	Holding the Handle stationary, slowly rotate the Deflector to move the tip of the Delivery Catheter away from the outer curvature of the aorta to coaxially align the THV Locators with the native valve cusps. Adjust guidewire accordingly to assist in alignment of the THV Locators with the native valve cusps.

9.5.2 Position the THV

Step	Procedure
1	Prepare the THV for positioning by maintaining Handle position, actuating the Buttons, and advancing the Controller to lower the THV from the Pocket about 1 cm. Visualize the Locators under fluoroscopy using a C-arm sweep to confirm that the THV locators and Delivery Catheter position are maintained within the aortic lumen at the STJ, not in contact with the aortic wall. **WARNING:** Rotation of the THV Locators in the native cusps or in a constrained position against the aortic wall could result in premature release of the THV, potentially leading to THV embolization and/or need for surgical intervention.
2	While maintaining the Handle position, actuate the Buttons, and slowly rotate the Controller to position and align the THV Locators above the native valve cusps. Use the least amount of Controller rotation required to achieve alignment and do not exceed 360° Controller rotation. If the THV Locators do not respond with Controller rotation up to 360°, stop Controller rotation. Confirm under fluoroscopy that the THV is not constrained against the anatomy prior to repositioning the Delivery Catheter. To relieve the constraint, slowly rotate the Controller in the reverse direction back to a neutral position to remove stored torque within the system and manipulate Delivery Catheter and/or guidewire as needed. **WARNING:** Excessive rotation of the Controller >360° could result in premature release of the THV, potentially leading to patient injury and/or need for surgical intervention.
3	Carefully advance the Controller to lower the aligned THV locators into the native valve cusps.
4	Fluoroscopically confirm proper positioning of the Locators within the cusps. Ensure the THV Sealing Ring marker band is at the annular plane prior to proceeding with deployment. **NOTE:** If desired positioning is not achieved, maintain the Handle position, actuate the Buttons, retract the Controller so that the THV is above the native cusps, and repeat Steps 2 to 4 to reposition THV Locators into the native valve. Guidewire manipulation may be needed to achieve proper position.
5	Prior to deployment, retract the angiography catheter into the ascending aorta to avoid entrapment between the THV and the aortic wall. **WARNING:** Failure to retract the angiography catheter prior to THV deployment may lead to improper THV positioning and/or patient injury requiring intervention. **CAUTION**: Avoid excessive re-positioning and re-maneuvering of THV to avoid premature deployment.

9.5.3 Deploy the THV

Step	Procedure
1	Remove the safety clip and discard. Under fluoroscopic guidance and while maintaining the position of the Controller, rotate the Deployer clockwise and advance the Deployer until Deployer contacts Controller and stops. This will release (deploy) the THV Sealing Ring in the native aortic annulus followed by release of the THV

Step	Procedure
	Eyelets. **CAUTION:** Do not attempt to retrieve or recapture the prosthetic aortic valve once the Sealing Ring has been deployed. If the Sealing Ring has been deployed, the THV must be released from the Delivery Catheter before the Delivery Catheter can be withdrawn into the Introducer Sheath. **NOTE:** Use of fast pacing (120 to 160 bpm) may increase valve stability during deployment.
2	Release the Deployer to allow the Sleeve to automatically align with the taper for Delivery Catheter withdrawal. **CAUTION:** Do not rotate/advance the Deployer against resistance as this may damage the Deployer and lead to the inability to deploy the THV. **CAUTION:** After Eyelet release, do not pull the Deployer backward as this may damage the Sleeve, potentially leading to vascular damage or patient injury during system withdrawal.
3	Under fluoroscopic guidance, verify that the Ferrule and Pocket are not contacting the aortic wall. If the Delivery Catheter components are contacting the wall, then manipulate the system (advance or retract the Delivery Catheter and/or the guidewire). Hold the Handle stationary, actuate the Buttons, and slowly retract the Controller until the Slider clicks into place. This locks the Controller with the Handle to withdraw the Delivery Catheter tip from the implanted THV. **WARNING:** Failure to ensure that the Ferrule and Pocket are not contacting the aortic wall prior to retracting the Controller may lead to aortic damage or patient injury, necessitating intervention.
4	Maintain the Handle position and turn the Deflector counterclockwise to fully remove the deflection on the Delivery Catheter. Ensure the guidewire and Delivery Catheter are relaxed along the outer curvature of the aorta. **CAUTION:** Ensure that the guidewire and Delivery Catheter are not under tension and are centered in the aorta during system withdrawal. **WARNING:** Failure to maintain guidewire or Delivery Catheter position within the center of the aorta during Delivery Catheter withdrawal may lead to entanglement with the THV frame and/or may dislodge the THV.
5	Continue to slowly retract the Delivery Catheter into the Introducer Sheath in a straight segment of the descending aorta while maintaining guidewire position. **CAUTION:** Do not retract the Delivery Catheter if resistance is encountered at the Introducer Sheath Tip as this can damage the sleeve and/or Introducer Sheath and lead to vascular damage during system withdrawal. Instead, reposition the Introducer Sheath to ensure proper alignment with the Sleeve under fluoroscopy and slowly retract the Sleeve into the Introducer Sheath.
6	Retract the Delivery Catheter from the Introducer Sheath Housing until a white mark on the Delivery Catheter is visible and that the catheter Tip is within the sheath, then remove the Introducer Sheath and Delivery Catheter as a single unit from the patient. **CAUTION:** Once deployment has occurred, do not attempt to reposition the THV. Repositioning a deployed THV may cause aortic root damage, myocardial damage, vascular complications, prosthetic valve dysfunction, embolization, stroke, and/or require emergent surgery.
7	Fluoroscopically verify THV Locators/Leaflet fixation, function, and sealing within the native valve annulus. Aortic root angiography and/or transesophageal (TEE) or transthoracic echocardiography (TTE) may be performed according to hospital protocol to evaluate THV performance and coronary patency. **CAUTION:** Post-implant balloon dilatation of the THV has not been evaluated. If performed, THV size and patient anatomy must be considered when selecting the appropriate balloon size to ensure patient safety. The balloon size chosen for the dilatation should not exceed the diameter of the native aortic annulus. Refer to the specific

Step	Procedure
	balloon catheter manufacturer's labeling for proper instruction on the use of balloon catheter devices. Note: Post-dilatation must not be performed through the Trilogy® Introducer Sheath.
8	Remove all devices and close the access site per hospital protocol.

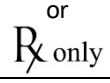
10.0 Explanted THVs and Device Disposal

An explanted THV should be placed in a container of 2% glutaraldehyde or 10% buffered formalin immediately after excision and returned to JenaValve. Refrigeration is not necessary. For further instructions and to request an Explant Kit, contact a JenaValve representative or Customer Service: **+1 866-588-8287** or **CustomerSupport.us@jenavalve.com** JenaValve product may be disposed of according to hospital protocol. There are no special risks related to the disposal of these devices.

11.0 Symbol Legend for Labeling

Symbol	Title of Symbol
REF	Catalog Number
SN	Serial Number
LOT	Batch Code
	Date of Manufacture
	Country of manufacture / Country of Origin
	Manufacturer
	Use-By Date
UDI	Unique device identifier
STERILE	Device is supplied sterile
STERILE EO	Sterilized Using Ethylene Oxide
STERILE LC	Sterilized Using Liquid Chemical Sterilants
	Single sterile barrier system with protective packaging inside
	Do Not Re-Use
	Do Not Resterilize
 www.eifu.jenavalve.com	Consult electronic Instructions for Use
CODE	Access Code to view or download related electronic Instructions for Use (eIFU) from the website
	Caution, See Instructions for Use

Symbol	Title of Symbol
	MR Conditional
	Temperature limitation: Store Between 2° and 25°C / 35.6° and 77°F

	Keep Away from Sunlight
	Keep Dry
	Quantity Per Box
	Device contains tissue of animal origin
	Do Not Use If Package or Seal Is Damaged
	Length
	Valve Diameter and System Size
	Medical Device
 or 	Prescription Device Only/ For prescription use only

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℞ only

The Trilogy® Transcatheter Heart Valve System

Trilogy® Transcatheter Heart Valve
Trilogy® Delivery Catheter
Trilogy® Introducer Sheath
Trilogy® Loading Tools

TRILOGY-THV (sizes S, M, L), TRILOGY-DC (sizes S, M, L), TRILOGY-LT (sizes S, M, L), TRILOGY-INT

Clinical Data

CAUTION: Federal (USA) law restricts these devices to sale by or on the order of a physician.
Implantation of the transcatheter heart valve should be performed only by physicians who have received JenaValve Technology Inc. training

STERILE: The valve is supplied sterilized with glutaraldehyde solution. The Delivery Catheter, Introducer Sheath and Loading tools are supplied sterilized with ethylene oxide gas.

1. 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.

1.1 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.

1.1.1 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)

1.1.2 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.

1.1.3 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

1.1.4 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 1** and **Table 2**, respectively.

Table 1: 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 2: 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).

1.2 Study Population Demographics and Baseline Characteristics

The demographics and baseline characteristics of the subjects, as shown in **Table 3**, 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 3: 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)

Description	Summary Statistics* N=180
Previous CABG	11.1% (20/180)
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.

1.3 Safety and Effectiveness Results

1.3.1 Primary Safety Endpoint

The primary safety endpoint results are presented in **Table 4** 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 4: 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 5.** 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 5: 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

1.3.2 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 6**). The Kaplan-Meier curve for overall all-cause mortality through 1 year is presented in **Figure 1.**

Table 6: 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]				

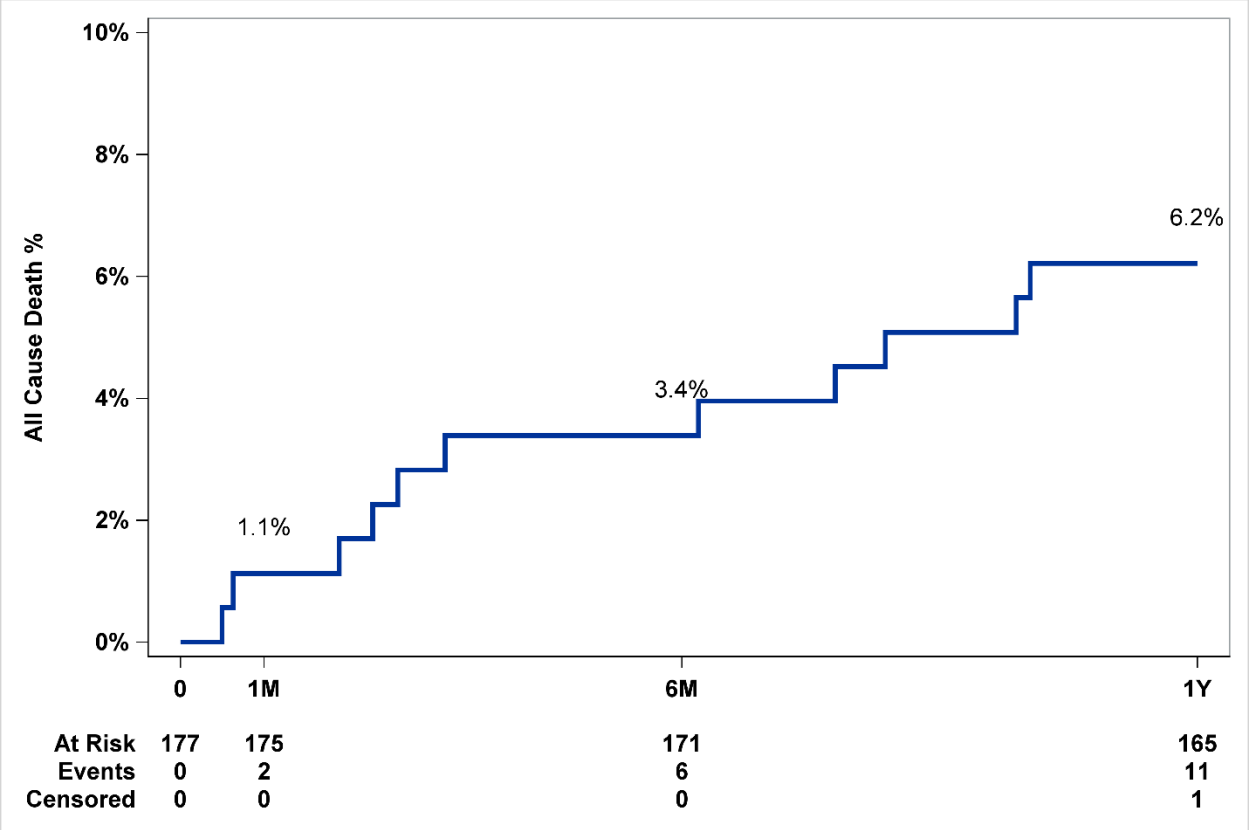


Figure 1: Kaplan-Meier Analysis of All-Cause Mortality through 1 Year (VI Population)

1.3.3 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 7,** 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

[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.

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 7: 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

1.3.4 Valve Hemodynamics

The AR severity for the VI population through 1 year is shown in **Figure 2**. 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

Not Measured ■ None ■ Trace ■ Mild ■ Mild-Moderate ■ Moderate ■ Mod-severe ■ Severe

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

Paravalvular leak (PVL) was measured post-implantation and is displayed in **Figure 3**. 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 3: Paravalvular Regurgitation/Leak through 1-Year (VI population)

Effective orifice area (EOA) and aortic mean gradient through 1 year are presented below in **Figure 4.** 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.

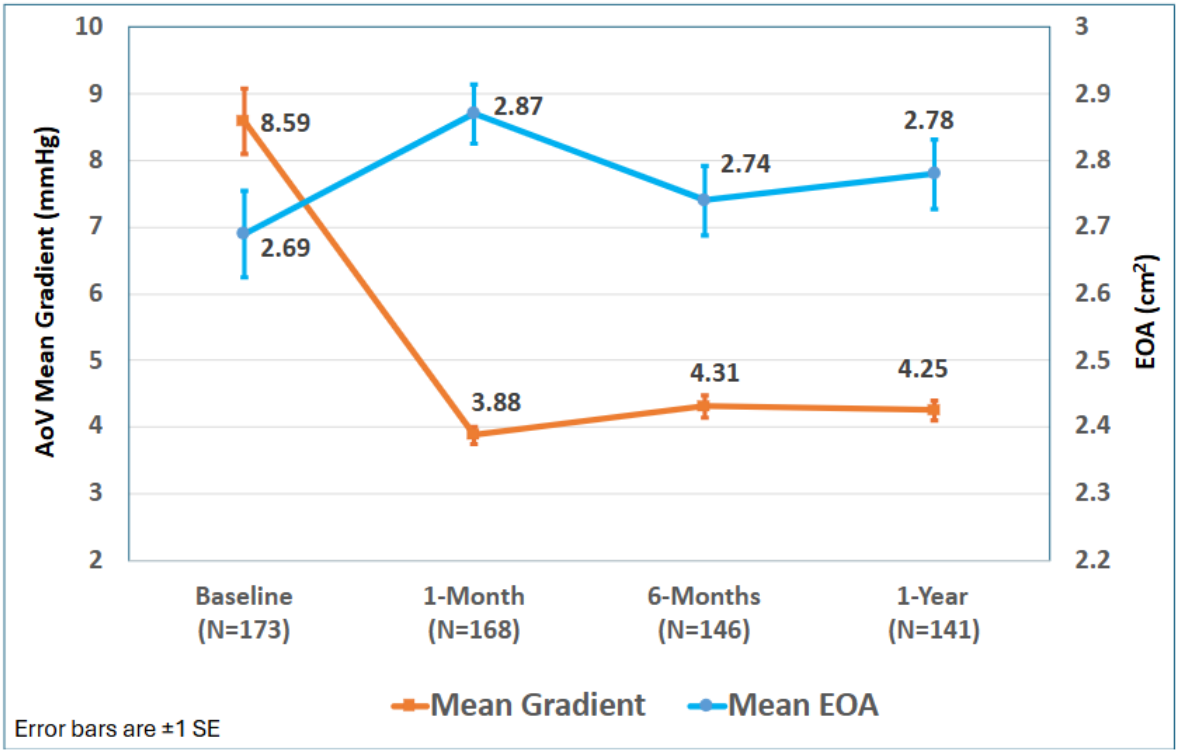


Figure 4: Mean EOA and Aortic Valve (AoV) Mean Gradient Through 1-Year (VI Population)

1.3.5 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 5** and **Figure 6**, respectively). Additional echocardiographic measurements are shown in **Table 8**.

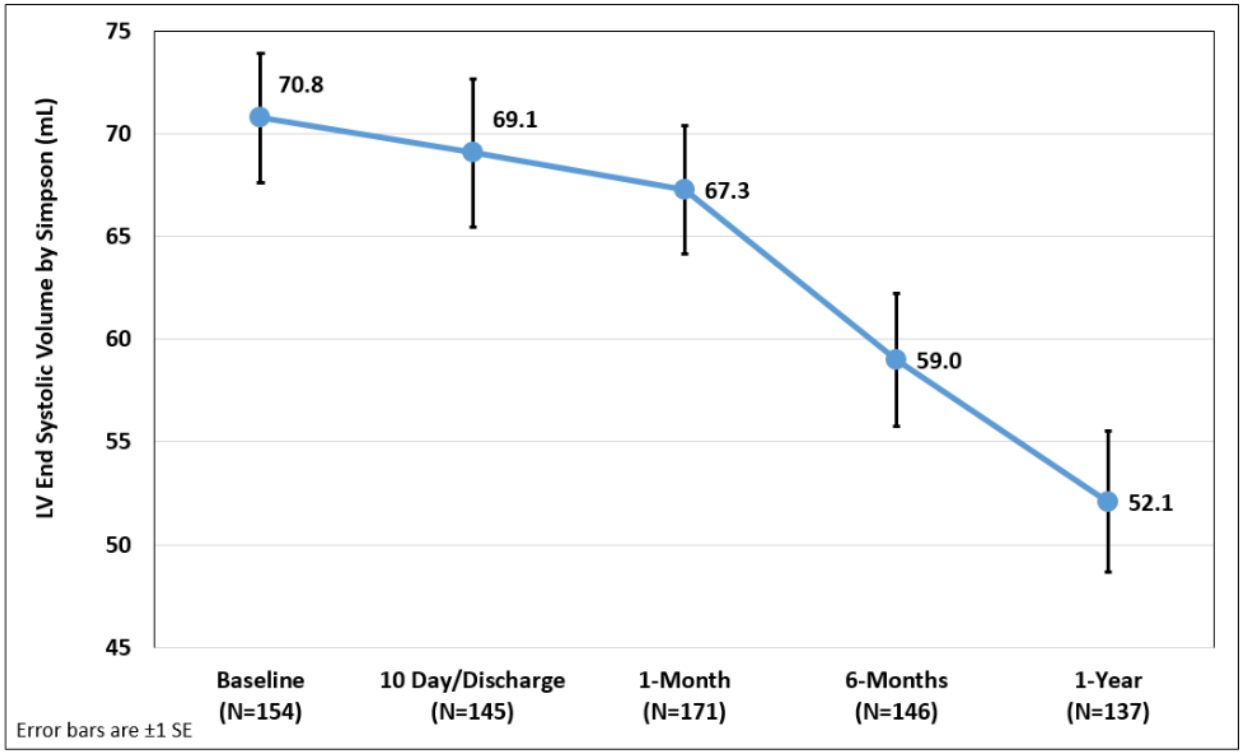


Figure 5: Mean LVESV and Standard Error Through 1 Year (VI Population)

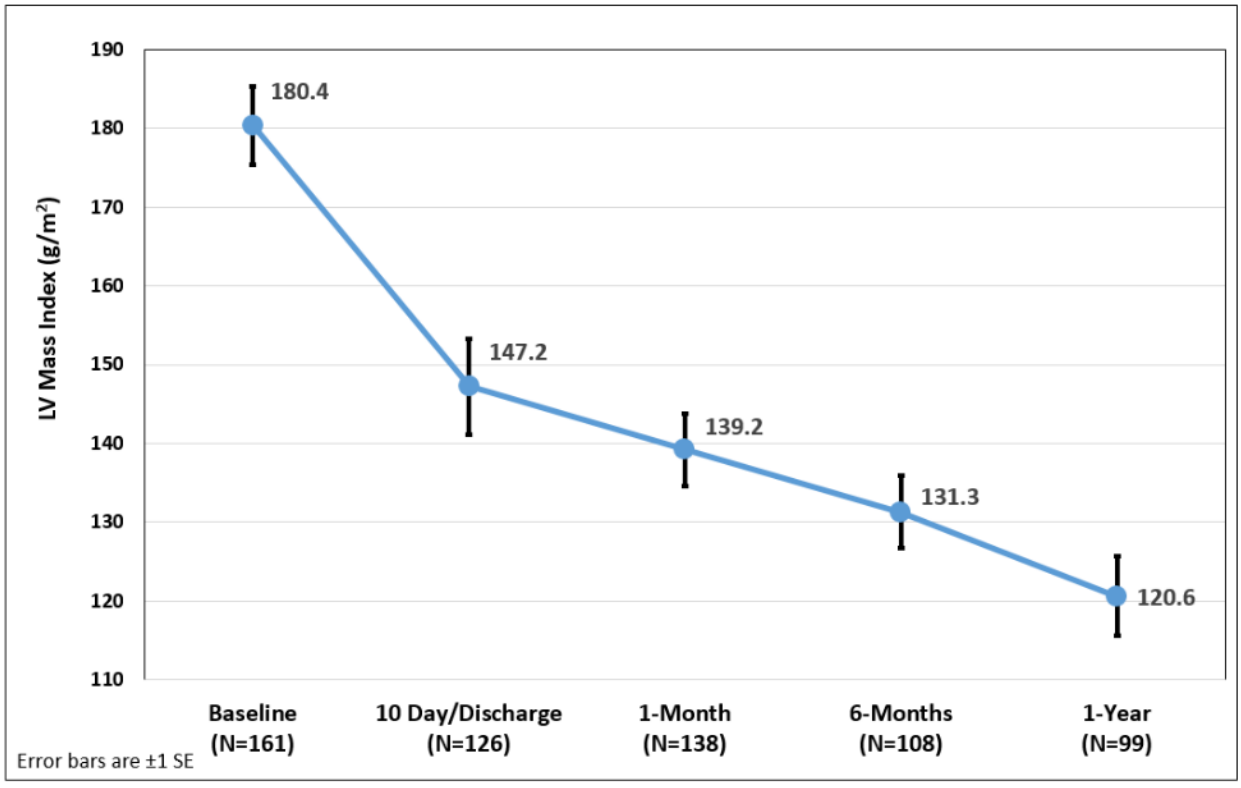
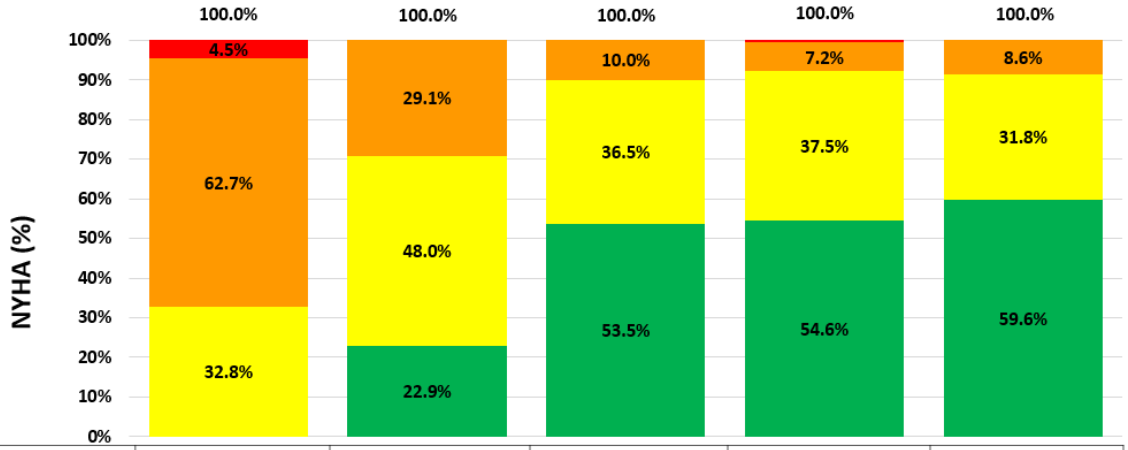


Figure 6: Mean LV Mass Index and Standard Error Through 1 Year (VI Population)

Table 8: 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				

1.3.6 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 7**. 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)

1.3.7 Procedural Information and Technical Success

The procedural information for the EP population is presented in **Table 9.** 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 9: 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%)
Pre-implant BAV performed prior to insertion of study sheath	
Yes	5 (2.8%)
No	175 (97.2%)

Table 9: Procedural Characteristics (EP Population)	
Characteristics	**Summary Statistics* N=180**
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 10**. 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 10: 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. (%)	

1.3.8 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 11** below and was comparable between male and females.

Table 11: 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 12.** The rate of composite endpoint failure was numerically higher in males (30.5%; 29/95) than females (22.4%; 19/85).

Table 12: 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%)

Event	Summary Statistics* (N=180)	
	Male (N=95)	Female (N=85)
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 13 and Table 14** respectively**.**

Table 13: 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 14: 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. (%)					

1.3.9 Adverse Events

An overview of the VARC-2 clinical events through 1-year are presented in **Table 15.**

Table 15: 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%)
All Bleeding	14 (7.9%)	18 (10.2%)
Major/Life threatening bleeding	7 (4.0%)	9 (5.1%)

Event	Summary Statistics* (N=177)	
	30-Days	1 Year
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		

1.3.10 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.

2. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

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

2.1 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.

2.2 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 16** and **Table 17**.

Table 16: Subject Accounting Summary in the CAP Cohort

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

Table 17: 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%

Table 17: CAP Cohort Patient Disposition Summary		
	30-Day	1-Year
† 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).		

2.3 Study Population Demographics and Baseline Characteristics

The demographics and baseline characteristics of the ALIGN-AR CAP study are summarized in **Table 18**. The CAP cohort demographic and baseline characteristics were consistent with the population enrolled in the main cohort.

Table 18: 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)

Table 18: Study Population Demographics Baseline Measures in the CAP Cohort	
Description	**Summary Statistics* N=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	
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)	

2.4 Safety and Effectiveness Results

2.4.1 Primary Safety Endpoint

The primary safety endpoint results are presented in **Table 19**. 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 19: 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	

2.4.2 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 20**. The Kaplan-Meier curve for overall all-cause mortality through 1 year is presented in **Figure 8.**

Table 20: Primary Efficacy Endpoint Results in the CAP Cohort		
Primary Efficacy Variable	**Summary Statistics (N=314)**	
	n	**%**
All-Cause Mortality	24	7.6

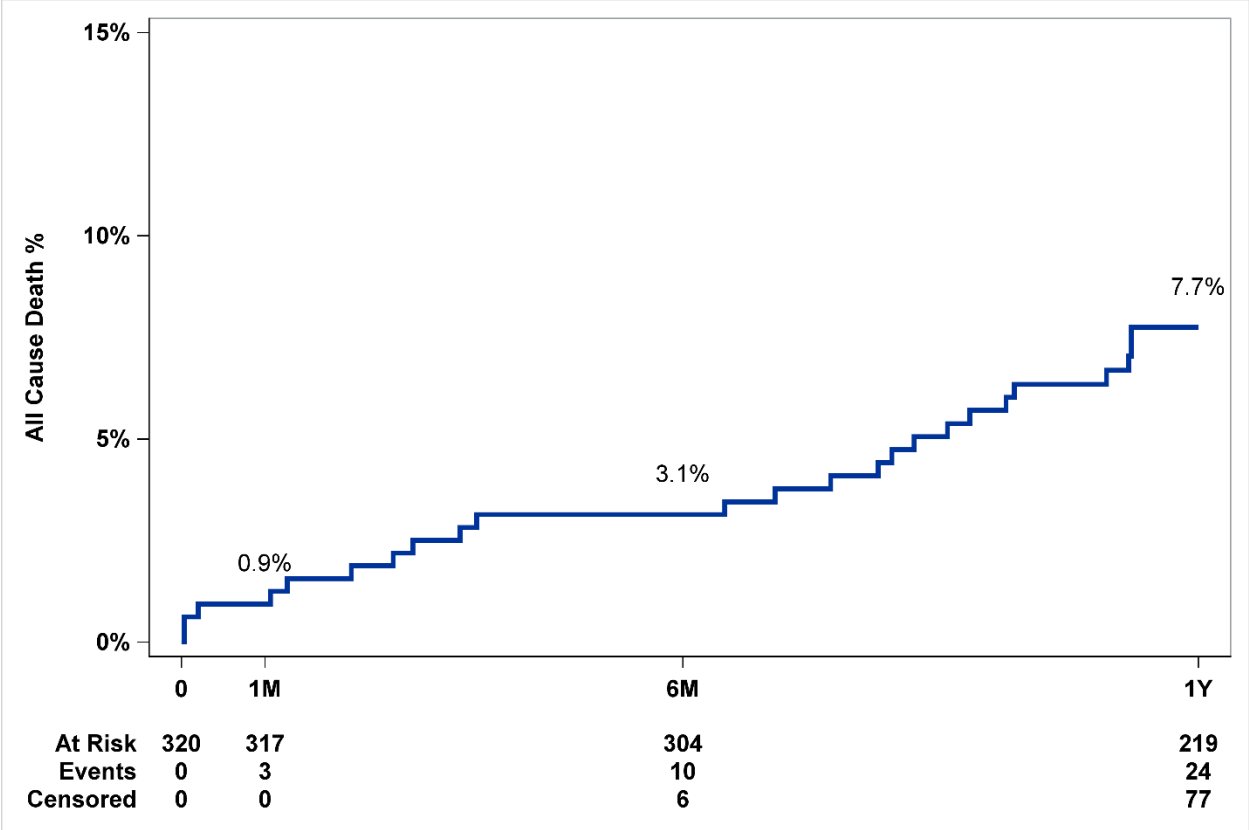


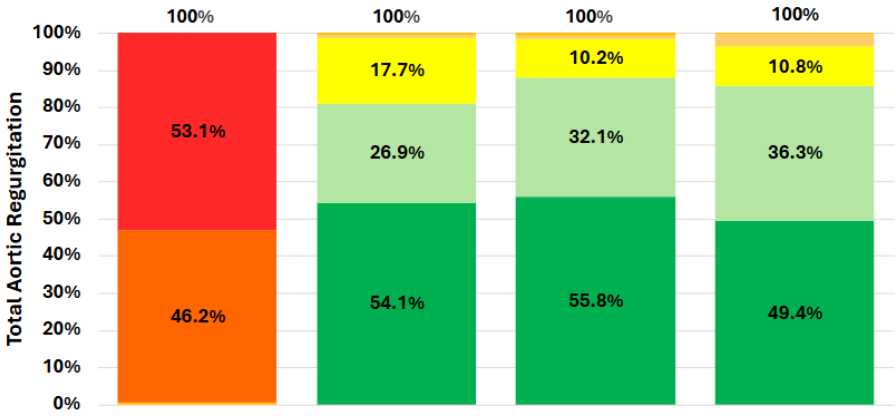
Figure 8: Kaplan-Meier Analysis of All-Cause Mortality through 1 Year CAP Cohort

2.4.3 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.

2.4.4 Valve Hemodynamics

The AR severity for the CAP cohort through 1 year is shown in **Figure 9**. 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.

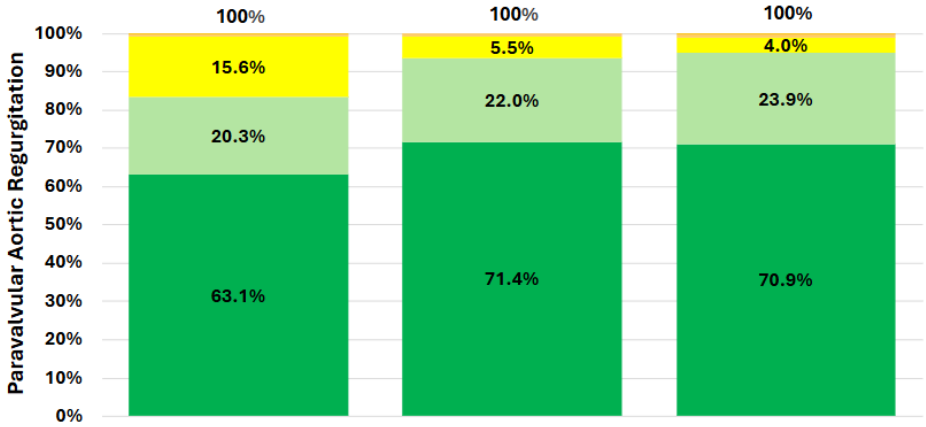


Total Aortic Regurgitation	Baseline (N=318)	1-Month (N=305)	6-Months (N=274)	1-Year (N=251)
None	0	165 (54.1%)	153 (55.8%)	124 (49.4%)
Trace	0	82 (26.9%)	88 (32.1%)	91 (36.3%)
Mild	0	54 (17.7%)	28 (10.2%)	27 (10.8%)
Mild-Moderate	0	2 (0.7%)	3 (1.1%)	8 (3.2%)
Moderate	2 (0.6%)	2 (0.7%)	2 (0.7%)	1 (0.4%)
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 9: Total Aortic Regurgitation through 1-Year in the CAP Cohort

Paravalvular leak (PVL) was measured post-implantation and is displayed in **Figure 10**. 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 10: Paravalvular Regurgitation/Leak through 1-Year in the CAP Cohort

EOA and aortic mean gradient through 1 year are presented below in **Figure 11**. 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.

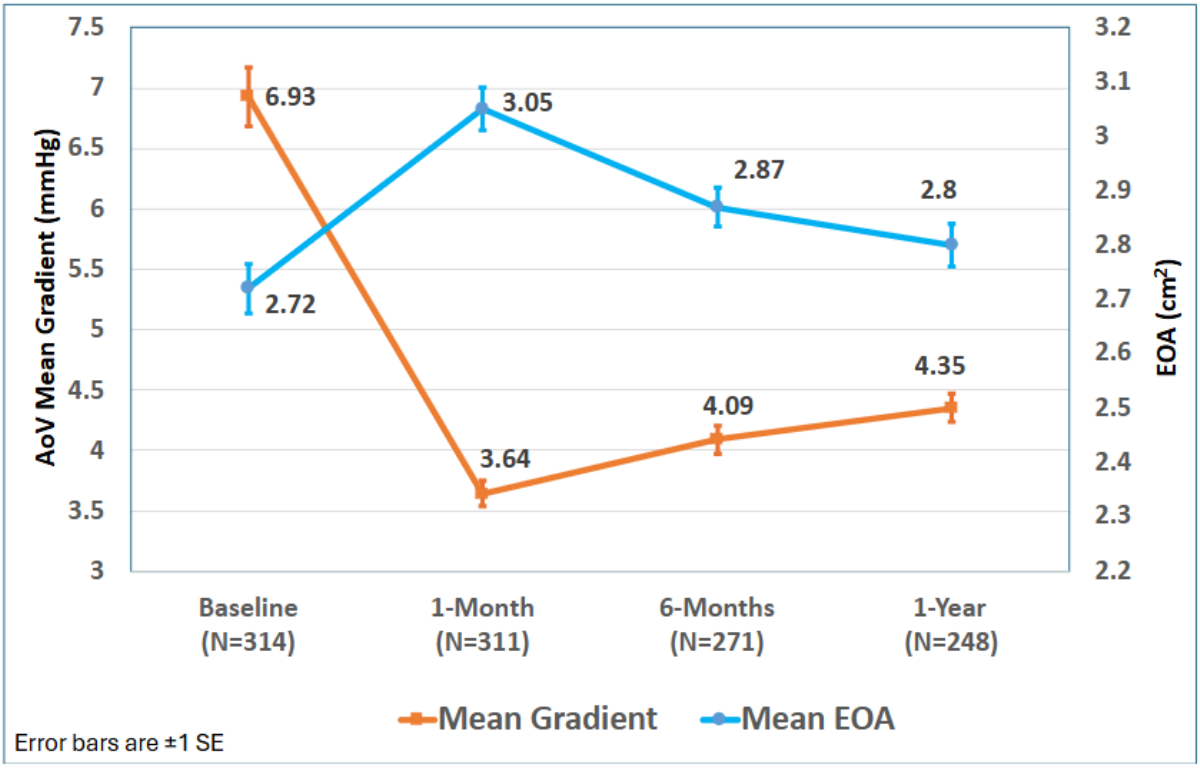


Figure 11: Mean EOA and Aortic Valve (AoV) Mean Gradient Through 1 Year in the CAP Cohort.

2.4.5 Left Ventricular Remodeling

Decreases in LV end systolic volume (LVESV) and LV mass index were observed from screening through 1-year (**Figure 12** and **Figure 13**, respectively). Additional echocardiographic measurements are shown in **Table 21**.

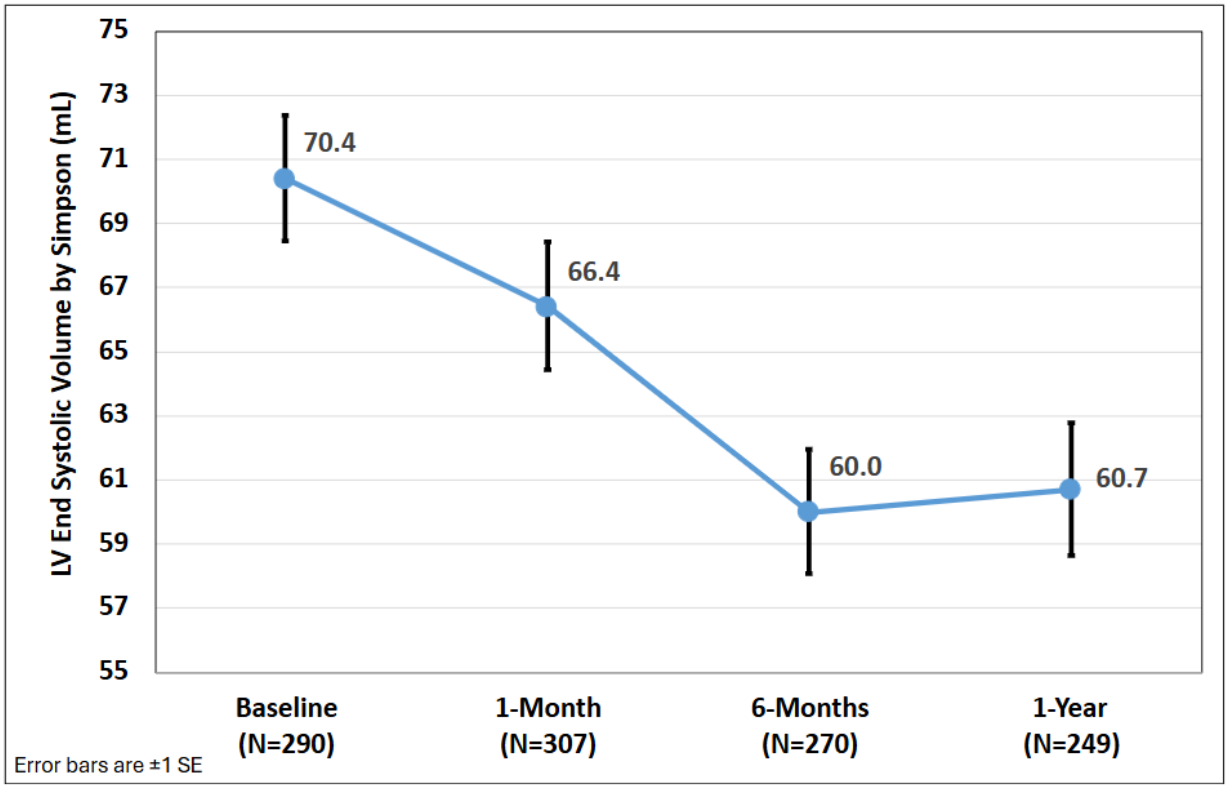


Figure 12: LVESV Through 1 Year in the CAP Cohort

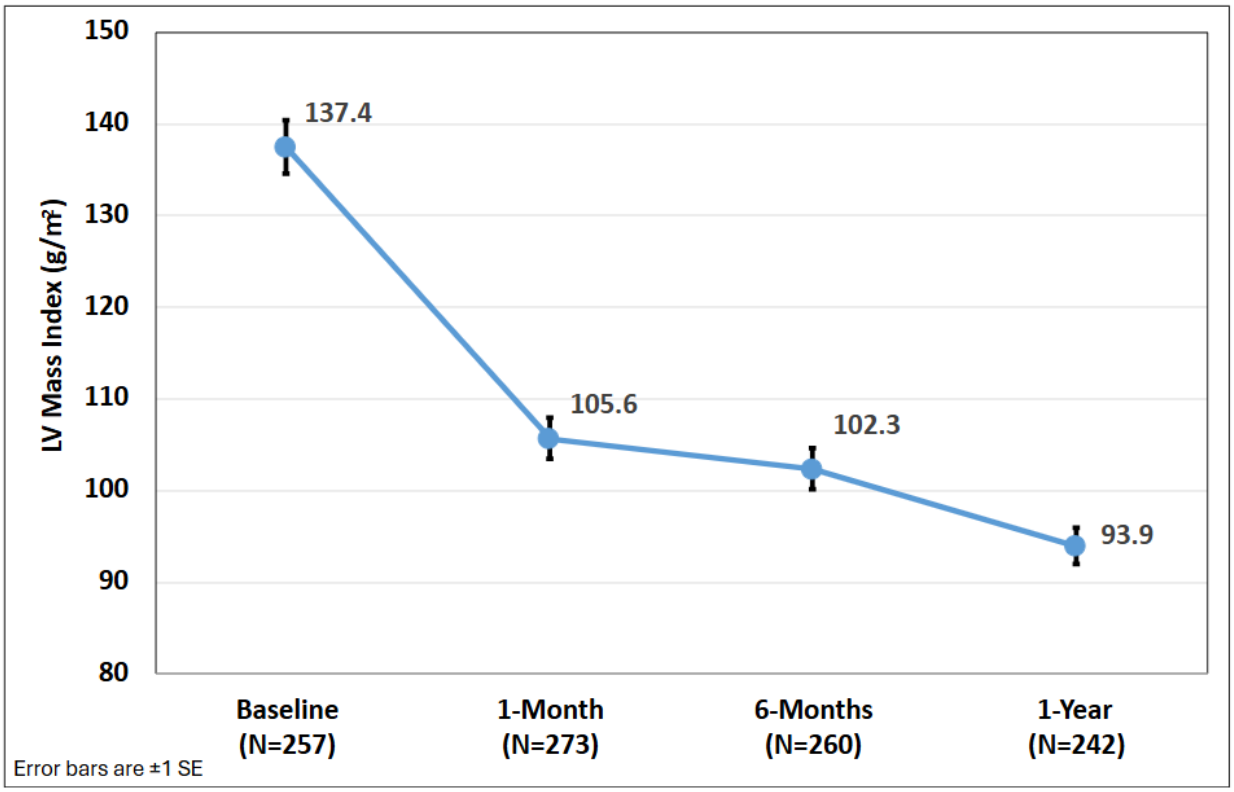
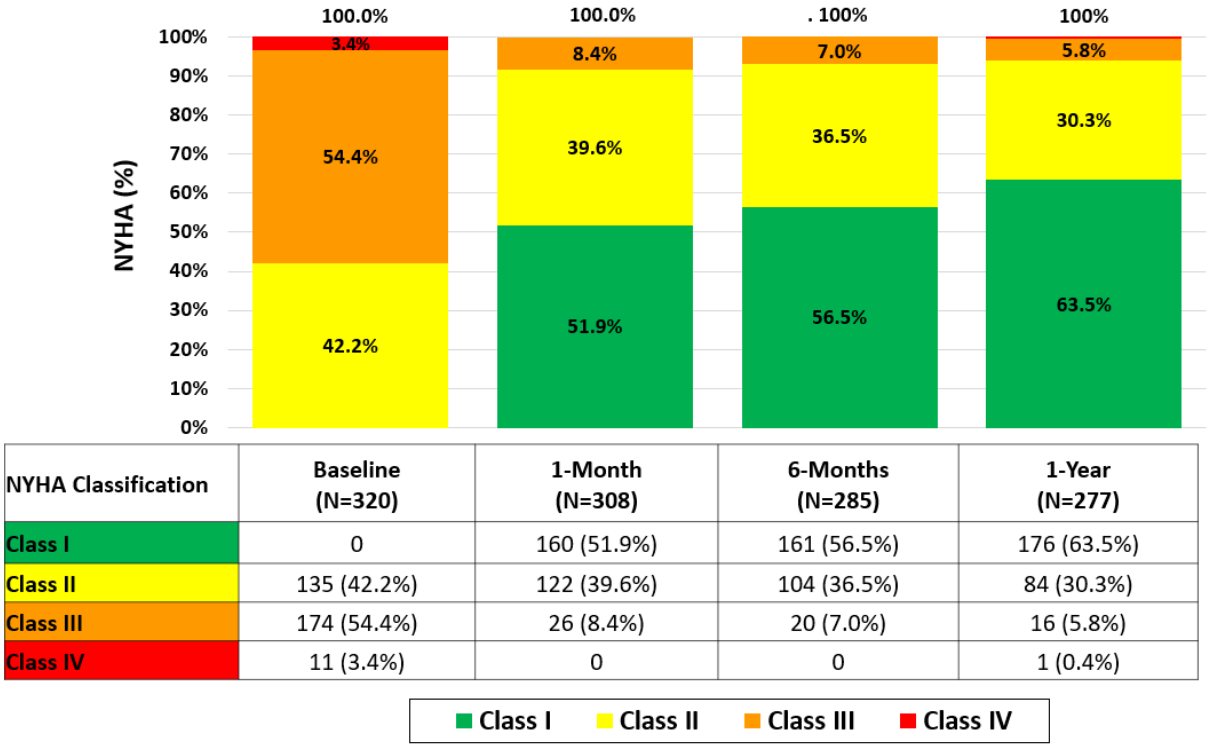


Figure 13: LV Mass Index Through 1 Year in the CAP Cohort

Table 21: 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				

2.4.6 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 14**. 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 14: NYHA Classification through 1-Year in the CAP Cohort

2.4.7 Adverse Events

An overview of the VARC-2 clinical events through 1-year for the CAP cohort are presented in **Table 22**.

Table 22: 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%)

Event	Summary Statistics*	
	30-Days (N=320)	1 Year[1] (N=314)
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.

3. References

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

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