SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Aortic valve, prosthesis, percutaneously delivered
Device Trade Name:	Portico™ Transcatheter Aortic Valve Implantation System: Portico™ Transcatheter Aortic Heart Valve, FlexNav™ Delivery System, FlexNav™ Loading System
Device Product Code:	NPT
Applicant Name and Address:	Abbott One St. Jude Medical Drive St. Paul, MN 55117
Date of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P190023
Date of FDA Notice of Approval:	September 17, 2021

II. INDICATIONS FOR USE

The Portico Transcatheter Aortic Valve Implantation System is indicated for relief of aortic stenosis in patients with symptomatic heart disease due to severe native calcific aortic stenosis who are judged by a heart team, including a cardiac surgeon, to be at high or greater risk for open surgical therapy (i.e., predicted risk of surgical mortality ≥ 8% at 30 days, based on the Society of Thoracic Surgeons (STS) risk score and other clinical comorbidities unmeasured by the STS risk calculator).

III. CONTRAINDICATIONS

The valve is contraindicated for patients with inability to tolerate antiplatelet/ anticoagulant therapy, nitinol alloy (nickel and titanium), or who have active infections, including endocarditis.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Portico Transcatheter Aortic Valve Implantation System labeling.

V. DEVICE DESCRIPTION

The Portico Transcatheter Aortic Valve Implantation System (Portico System) is designed to be implanted in the native aortic heart valve without open heart surgery and without concomitant surgical removal of the failed native valve. The Portico System consists of 3 components: (1) Portico Transcatheter Aortic Heart Valve (Portico valve), (2) FlexNav Delivery System (DS), and (3) FlexNav Loading System (LS). Refer to **Table 1** for a list of model numbers for these components and their compatibility between the devices.

Table 1: Portico System Model Numbers and Device Compatibility

Portico Valve	FlexNav DS	FlexNav LS
PRT-23	FNAV-DS-SM	FNAV-LS-SM
PRT-25		
PRT-27	FNAV-DS-LG	FNAV-LS-LG
PRT-29		

A. Portico Valve

The Portico valve (**Figure 1**) is comprised of three main components: stent, cuff, and leaflets. The stent is made from nitinol, a nickel-titanium alloy that has self-expanding properties and is radiopaque. The cuff is made from porcine pericardium that is sutured to the stent frame. The cuff provides the sealing area for implantation. The leaflets are made from bovine pericardium and are sutured together into a tri-leaflet configuration on the stent frame.

The cuff and leaflet pericardial tissue is preserved and crosslinked in glutaraldehyde. Glutaraldehyde, formaldehyde and ethanol are used in the valve sterilization process. The valve's leaflets and cuff are processed using Linx™ anticalcification technology. The valve is supplied sterile and non-pyrogenic.

Figure 1: Portico Transcatheter Aortic Valve

The Portico valve is available in four different sizes (23 mm, 25 mm, 27 mm, and 29 mm) that are intended to treat patients with a native annulus size ranging from 19 - 27

mm, respectively. Refer to **Table 2,** for a detailed list of available sizes that are intended to treat patients with the anatomical measurements indicated below.

Table 2: Patient Anatomical Measurements				
Portico valve Size	**Model Number**	**Annulus Size Treated**	**Ascending Aorta Diameter**	**Minimum Vascular Access Diameter**
23 mm	PRT-23	19-21 mm	26-36 mm	≥ 5.0 mm
25 mm	PRT-25	21-23 mm	28-38 mm	≥ 5.0 mm
27 mm	PRT-27	23-25 mm	30-40 mm	≥ 5.5 mm
29 mm	PRT-29	25-27 mm	32-42 mm	≥ 5.5 mm

B. FlexNav Delivery System

The FlexNav Delivery System (DS) (**Figure 2**) consists of a handle, integrated sheath, stability layer, and outer/inner member. It facilitates Portico valve implantation using transfemoral, subclavian/axillary, or transaortic access methods. The FlexNav DS is an over-the-wire, 0.035" compatible system designed to facilitate gradual, controlled deployment of the Portico valve. The valve is deployed annulus end first from the distal end of the delivery system. If needed, the valve may be re-sheathed and repositioned up to two times, provided the valve has not been fully deployed.

Figure 2: FlexNav Delivery System

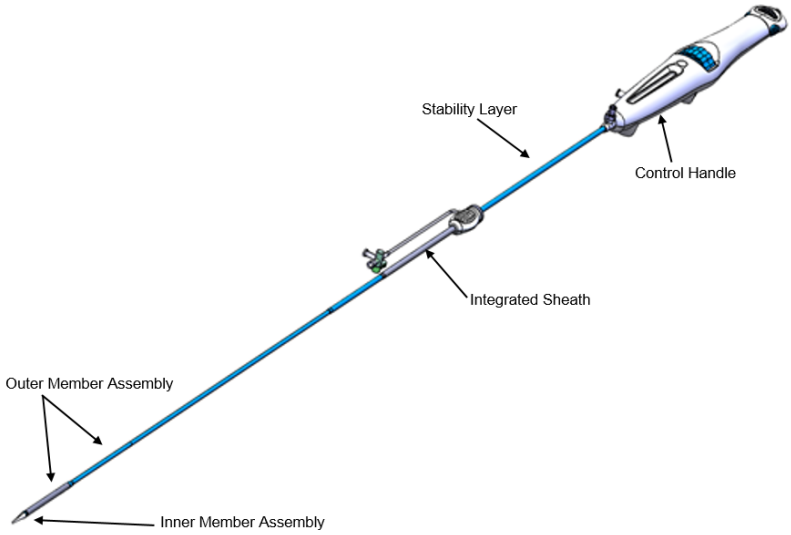


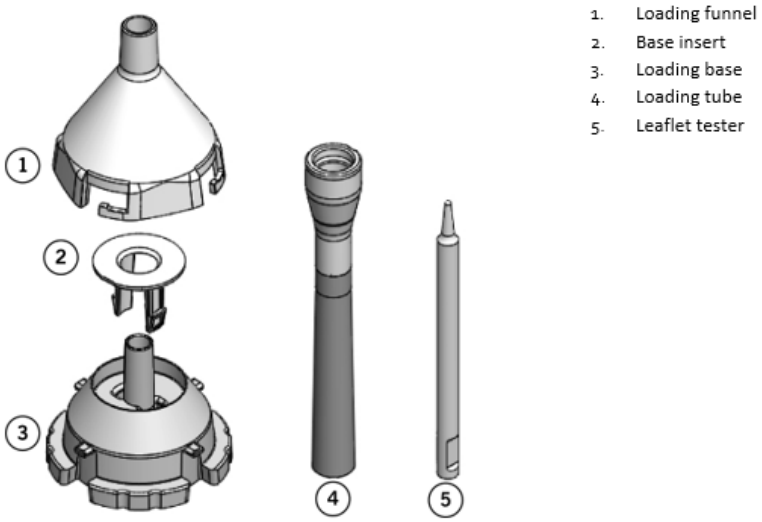
Table 3 lists FlexNav DS model numbers, specifications, and compatibility requirements.

Table 3: FlexNav Delivery System Specifications						
Delivery System Model Number	**Equivalent Integrated Sheath Diameter**	**Valve Capsule Outer Diameter**	**Integrated Sheath Working Length**	**Delivery System Working Length**	**Minimum Vessel Diameter Requirement**	**Compatible Guidewire**
FNAV-DS-SM	14F	6.0mm	30 cm	107 cm	≥ 5.0 mm	0.035" (0.89mm)
FNAV-DS-LG	15F	6.3mm	30 cm	107 cm	≥ 5.5 mm	0.035" (0.89mm)

C. FlexNav Loading System

The FlexNav Loading System (LS) (**Figure 3**) is an accessory used to facilitate valve preparation/loading onto the FlexNav DS. The LS includes a loading funnel, loading base, base insert, loading tube, and a leaflet tester.

Figure 3: FlexNav Loading System



VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for patients with severe symptomatic native aortic valve stenosis who are deemed to be high or greater risk for surgical aortic valve replacement, including treatment with other commercially available transcatheter aortic valve implantation (TAVI) devices, surgical aortic valve replacement (SAVR), temporary relief using a percutaneous technique called balloon aortic valvuloplasty (BAV), or medical therapy (no obstruction-relieving intervention). Each alternative has its own advantages and disadvantages. Patients should fully discuss these alternatives with their physician to select the best method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The Portico System is marketed in the following countries/geographies (**Table 4**).

Table 4: Countries/Geographies where the Portico System is Marketed		
Argentina	Hong Kong	Philippines
Algeria	Israel	Russia
Australia	Jordan	Saudi Arabia
Belarus	Kuwait	Singapore
Bolivia	Lebanon	South Korea
Brazil	Malaysia	Taiwan
Chile	Mexico	Thailand
Colombia	Macedonia	Tunisia
Costa Rica	Morocco	Turkey
Ecuador	New Zealand	UAE
Egypt	Paraguay	Ukraine
Europe	Peru	Vietnam

The Portico System has not been withdrawn from any market.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

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

- access site complications (e.g., pain, bleeding, infection, hematoma, pseudoaneurysm, etc.)
- acute coronary obstruction
- acute myocardial infarction
- allergic reaction to antiplatelet agents, contrast medium, or valve components
- aortic rupture
- ascending aorta trauma
- atrio-ventricular node block
- cardiac arrhythmias
- conduction system injury
- dissection
- embolism
- endocarditis
- heart failure
- hemodynamic compromise
- hemolysis
- hemolytic anemia
- hemorrhage
- hypotension or hypertension
- infection
- myocardial ischemia
- mitral valve insufficiency
- multi-organ failure
- non-structural dysfunction (i.e., entrapment by pannus, paravalvular leak, inappropriate sizing or positioning)
- pericardial effusion
- perforation of the myocardium, ventricle or a blood vessel

- pannus
- regurgitation
- renal insufficiency or renal failure
- respiratory failure
- sepsis
- stroke
- structural deterioration (i.e., calcification, leaflet tear)
- thrombosis
- tamponade
- valve embolization or migration
- vessel dissection or spasm
- transfusion
- conversion to open surgical procedure
- reoperation
- emergent balloon valvuloplasty
- emergent percutaneous coronary intervention (PCI)
- emergent surgery (i.e., coronary artery bypass, heart valve replacement)
- explantation
- permanent disability
- death
- permanent pacemaker implantation

For the specific adverse events that occurred in the clinical studies, please see **Sections X and XI** below.

IX. SUMMARY OF PRECLINICAL STUDIES

A. Laboratory Testing

A series of non-clinical laboratory studies were performed on the Portico System as recommended per ISO 5840, Cardiovascular implants – Cardiac valve prostheses: part 1-General requirements (2015), and part 3- Heart valve substitutes implanted by Transcatheter techniques (2013) along with relevant FDA Guidance Documents.

1. Biocompatibility

Biocompatibility and Toxicology evaluations were completed on the device components that makeup the Portico System in accordance with ISO 10993-1: Biological Evaluation of Medical Devices Part 1: Evaluation and Testing. A summary of the tests and results conducted on the Portico Valve, FlexNav DS, and FlexNav LS are provided in **Table 5 – Table 7** respectively. Test samples for the studies consisted of all patient-contacting portions of the device (direct and indirect) after all manufacturing processes, including sterilant exposure. All results were acceptable.

Table 5: Summary of the Portico Valve Biocompatibility Testing/Results

Biological Test	Test Method	Result
Cytotoxicity	MEM elution assay on L-929 mouse fibroblast cells; ISO 10993-5	**Pass** Non-cytotoxic

Table 5: Summary of the Portico Valve Biocompatibility Testing/Results		
Biological Test	**Test Method**	**Result**
Sensitization	ISO Guinea Pig Maximization Method; ISO 10993-10	**Pass** Non-sensitizing
Intracutaneous Reactivity (Rabbit)	ISO Intra-cutaneous Reactivity Test; ISO 10993-10	**Pass** Non-irritant
Acute Systemic Toxicity – (Mouse)	ISO Acute Systematic Injection Test; ISO 10993-11	**Pass** Non-toxic
Pyrogenicity	Materials Mediated Rabbit Pyrogen Test; ISO 10993-11	**Pass** Non-pyrogenic
Genotoxicity - AMES	Bacterial Mutagenicity (Ames); ISO 10993-3	**Pass** Non- Mutagenic
Genotoxicity – Mouse Lymphoma	In vitro mouse Lymphoma Assay; ISO 10993-3	**Pass** Non-Mutagenic
Hemocompatibility		
Hemolysis	ASTM Direct Contact; ISO 10993-4 ASTM Extract Method; ISO 10993-4	**Pass** Non-hemolytic
Partial Thromboplastin Time (PTT)	In vitro Hemocompatibility; ISO 10993-4	**Pass** Non-coagulant
Leukocyte and Platelet	In vitro Hemocompatibility; ISO 10993-4	**Pass** Hemocompatible
Complement Activation	C3a and SC5b-9 Assay; ISO 10993-4	**Pass** Non-activator
Chemical Characterization		
GC/MS Direct Inject	Gas Chromatography and Mass Spectrometry; ISO 10993-18	Acceptable based on toxicological risk assessment of identified leachable/extractable compounds
LC/MS	Liquid Chromatography-Mass Spectrometry; ISO 10993-18	Acceptable based on toxicological risk assessment of identified leachable/extractable compounds
ICP	Inductively Coupled Plasma; ISO 10993-18	Acceptable based on toxicological risk assessment of identified leachable/extractable compounds
FTIR	Fourier Transform Infrared Spectroscopy; ISO 10993-18	Confirmed Polymer identification
NVR	Non-volatile residual test; ISO 10993-18	**Pass**

Table 6: Summary of the FlexNav Delivery System Biocompatibility Testing/Results		
Biological Test	**Test Method**	**Result**
Cytotoxicity	MEM elution assay on L-929 mouse fibroblast cells; ISO 10993-5	**Pass** Non-cytotoxic
Sensitization	ISO Guinea Pig Maximization; ISO 10993-10	**Pass** Non-sensitizing
Irritation – Rabbit Intracutaneous Reactivity	ISO Intra-cutaneous Reactivity Test; ISO 10993-10	**Pass** Non-irritant
Acute Systemic Toxicity – (Mouse)	ISO Acute Systematic Injection Test; ISO 10993-11	**Pass** Non-toxic
Pyrogenicity	Materials Mediated Rabbit Pyrogen; ISO 10993-11	**Pass** Non-pyrogenic
Hemocompatibility		
Hemolysis	ASTM Direct Contact; ISO 10993-4 ASTM Extract Method ASTM Direct Contact; ISO 10993-4	**Pass** Non-hemolytic
Partial Thromboplastin Time (PTT)	In vitro Hemocompatibility; ISO 10993-4	**Pass** Non-coagulant
Leukocyte and Platelet	In vitro Hemocompatibility; ISO 10993-4	**Pass** Hemocompatible
Thrombogenicity	In vivo swine model; ISO 10993-4	**Pass** Non-thrombogenic
Complement Activation	C3a and SC5b-9 Assay; ISO 10993-4	**Pass** Non-activator
Chemical Characterization		
GC/MS Static and Dynamic headspace	Gas Chromatography and Mass Spectrometry; ISO 10993-18	**Pass** No leachable/ extractable of toxicological concern
ICP	Inductively Coupled Plasma; ISO 10993-18	**Pass** Acceptable based on toxicological risk assessment of identified leachable/extractable compounds
FTIR	Fourier Transform Infrared Spectroscopy; ISO 10993-18	Confirmed Polymer identification
NVR	Non-volatile residual test; ISO 10993-18	**Pass**

Table 7: Summary of the FlexNav™ Loading System Biocompatibility Testing/Results		
Biological Test	**Test Method**	**Result**
Cytotoxicity	Agarose Overlay method using mouse fibroblast cells (L-929); ISO 10993-5	**Pass** Non-cytotoxic
Heavy Metals	General polymers section of USP <661> physicochemical tests for plastics was followed. ISO 10993-18	**Pass**
FTIR	Fourier Transform Infrared Spectroscopy; ISO 10993-18	Confirmed Polymer identification
NVR	Non-volatile residual test; ISO 10993-18	**Pass** Acceptable levels of residuals

2. Bench Testing

Comprehensive preclinical bench testing and computational analysis was performed on the Portico System (i.e., Portico valve, FlexNav DS and FlexNav LS). All testing was conducted in accordance with national and international product standards (i.e., FDA guidance documents and ISO 5840-1, ISO 5840-3, and ISO 10555-1). Testing verified that all components of the Portico System were within design specifications and met its specified design performance requirements. The tests are summarized in **Table 8** and **Table 9.**

Table 8: Summary of Portico Valve In-Vitro Testing/Results			
Test	**Attribute**	**Test Description**	**Results**
Valve Testing: Hydrodynamic Assessment			
Hydrodynamic Assessment	Pressure Drop EOA Regurgitation	To determine the hydrodynamic performance of the Portico valve in terms of Pd, EOA, Regurgitation under normal cardiac conditions.	**Pass**
Variable Cardiac Conditions	Pressure Drop EOA Regurgitation	To determine the hydrodynamic performance of the Portico valve in terms of Pd, EOA, Regurgitation under variable cardiac conditions.	**Pass**
Steady Forward Flow	Pressure Drop	To determine the pressure drop at various steady forward flow rates.	**Pass**
Steady Backflow Leakage	Leakage	To determine the leakage rates at various steady forward flow rates.	
Bernoulli Relationship	Pressure drop measurement Doppler Velocity Measurement	To determine whether the Bernoulli relationship applies to clinical pressure drop measurements	**Pass**
Flow Visualization & Particular Image Velocimetry	Flow Characterization	To qualitatively investigate flow characteristics near the valve	**Pass**
Valve Testing: Migration			

Table 8: Summary of Portico Valve In-Vitro Testing/Results			
Test	**Attribute**	**Test Description**	**Results**
Chronic Outward Radial Force (COR) and Migration	Annulus & Aortic Chronic outward radial force	To determine the Portico stent is manufactured with acceptable COR to ensure migration resistance	**Pass**
Migration Resistance & Cadaver Calcified Annulus Pullout	Valve Migration Resistance	Verify the COR of the Portico valve is appropriate to assure valve migration resistance when exposed to simulated in-vitro conditions.	**Pass**
Valve: Post Dilatation Testing			
Balloon Valvuloplasty Post Dilatation	Pressure drop EOA Regurgitation Functional	Ensure post dilatation does not impact leaflet durability and functionality.	**Pass**
Valve Testing: Structural Performance			
Accelerated Wear Testing	Pressure drop EOA Regurgitation Functional	To assess long-term valve performance, 200 million cycles, through accelerated wear testing.	**Pass**
Dynamic Failure Mode Analysis	Pressure Drop EOA Regurgitation Visual	To obtain information about the failure mode affecting the durability of the valve.	**Pass**
Leaflet, Cuff, and stent Finite Element Analysis (FEA)	In Plane principle stress	FEA was used to characterize the structural behavior of the components of the Portico valve using computer analytics when subjected to anticipated in vivo operational conditions	**Pass**
Stent Testing			
Stent Fatigue Resistance	Freedom from fracture	Demonstrate the Portico stent has fatigue resistance to 600 million cycles.	**Pass**
Stent Corrosion	Nickel Leaching Corrosion Assessment Surface assessment	Evaluate the corrosion resistance of the Portico stent in accordance with ASTM F2129 and ISO 16429.	**Pass**
Stent length and Foreshortening	Valve Maximum Length Stent Foreshortening	To evaluate the relationship of the Portico stent length and diameter when crimped and deployed.	**Pass**
Magnetic Resonance Imaging	Displacement and Torque 1.5T RF Heating 3.0T RF Heating MR Artifacts Visual	To characterize the performance of the Portico valve in an MR field and determine the compatibility.	**Pass**

Table 9: Summary of FlexNav DS and FlexNav LS In Vitro Testing/Results		
Test	**Purpose/Objective**	**Results**
Delivery System Size Profile (Visual and Dimensional verification)	Verification that the manufacturing processes produce finish devices meeting design requirements for dimensions and the DS surface is free from defects.	**Pass**
Bond Strength	Verification that the bonds and tubing of the DS meet the strength specification when subjected to tensile testing.	**Pass**
Delivery System Kink Resistance	This test verifies the DS is resistant to kinks when subjected anatomical curvature expected in a clinical scenario.	**Pass**
Load and Re-sheath Forces	This test verifies when the Portico valve is loaded or re-sheathed into the FlexNav™ DS it meets the product force requirements.	**Pass**
Handle Function	Verification that the DS handle components (deployment lock button, deployment re-sheath wheel, macro slide release button and micro adjustment wheel) function as intended.	**Pass**
Radiopaque Feature and Delivery System Visibility	Verification that the DS and radiopaque features (tip and inner member marker band) are visible under fluoroscopy.	**Pass**
Deployment Accuracy	Verification that the DS can consistently deploy the Portico valve accurately.	**Pass**
Guidewire Compatibility	Verification that the DS is compatible to pass a 0.035" guidewire.	**Pass**
Hydrophilic effectiveness/Integrity	Verification that the integrity and effectiveness of the hydrophilic coating on the DS is maintained.	**Pass**

3. Sterilization

The Portico valve is sterilized using a multi-component liquid sterilant (MCS), a mixture of ethanol, glutaraldehyde, and formaldehyde. Following sterilization, the valves are aseptically transferred from the sterilization container to the final jar. The validated aseptic transfer MCS sterilization process has demonstrated a Sterility Assurance Levels (SAL) of 10^{-6}, following ISO 14160 requirements.

The FlexNav DS and LS are sterilized via Ethylene Oxide (EtO) in accordance with ISO 11135 - Sterilization of health-care products - Ethylene oxide - Requirements for the development, validation and routine control of a sterilization process for medical devices. The validated EtO sterilization process has demonstrated Sterility Assurance Levels (SAL) of 10^{-6}.

4. Packaging and Shelf Life

The device components which make up the Portico System are all packaged separately. The Portico valve is stored in a jar filled with sterile 0.5% formaldehyde storage solution which is tightly sealed with an integrated gasket lid to form the primary sterile barrier. The jar is contained within the inner packaging assembly which is contained within a shelf carton to complete the protective packaging system for the Portico valve. Non-clinical testing on Portico valves that were real time aged for three years following sterilization demonstrated the packaging integrity and valve performance are maintained following ISO 11607 (as applicable). Therefore, shelf life has been established at 3 years for the Portico valve.

The FlexNav DS is placed in a retainer tray to hold the DS in place. The retainer tray is covered with a formed cover lid and placed inside a pouch. The pouch is sealed to form the primary sterile barrier and is then placed in a shelf carton. The FlexNav LS is placed into a tray that is sealed with a Tyvek lid. Non-clinical testing of FlexNav DS/LS and related packaging, conducted on test articles accelerated aged for two years following sterilization, demonstrated that the FlexNav DS and LS performance and packaging integrity, in accordance with ISO 11607, are maintained. Therefore, shelf life has been established at 2 years for the FlexNav DS and LS.

B. Animal Studies

Four animal studies were performed in support of the safety and performance of the Portico System (i.e., Portico valve, FlexNav DS, and FlexNav LS) and according to ISO 5840 parts 1 & 3 product standard. One of the four studies was conducted to specifically evaluate the chronic in vivo safety and performance of the Portico valve in a domestic sheep model. The other three studies were conducted to evaluate the performance of FlexNav DS and the deployment/in vivo performance of the Portico valve using an acute in vivo porcine model. These studies are summarized in **Table 10**.

Table 10: Portico Valve and FlexNav DS and LS Overview of Acute and Chronic Animal Studies

Study Information	Chronic GLP Animal- Portico Valve Study	Acute GLP Animal - FlexNav DS Study	Acute GLP Animal - Subclavian Access Study	Acute non-GLP Animal - Transaortic Access Study
Device Evaluated	Portico valve	FlexNav DS (Small and Large Sizes) and Portico valve	Portico 18F DS and Portico valve	Portico 18F DS and Portico valve
Animal Model	Domestic Sheep	Domestic swine	Domestic swine	Domestic swine

Table 10: Portico Valve and FlexNav DS and LS Overview of Acute and Chronic Animal Studies				
Study Information	**Chronic GLP Animal- Portico Valve Study**	**Acute GLP Animal - FlexNav DS Study**	**Acute GLP Animal - Subclavian Access Study**	**Acute non-GLP Animal - Transaortic Access Study**
Methods	Implant the Portico valve (N=8) and control valves (N=3, commercially available surgical valves) into the native aortic valve in a domestic sheep model. An aortic band was placed around the aorta to simulate aortic stenosis.	Delivery performance of the FlexNav DS (N=6) was conducted using the transfemoral approach in a domestic swine model.	Delivery performance of the Portico DS (18F, N=7; 19F, N=6) was conducted using subclavian access in a domestic swine model.	Delivery performance of the Portico DS (N=2) was conducted using trans-aortic access in a domestic swine model.
Duration	Chronic 140 days	Acute (<24 hours)	Acute (<24 hours)	Acute (<24 hours)
Objective	• Evaluate the chronic in-vivo safety of the TAVI device with respect to the following items: ○ hemodynamic performance, ○ biostability, ○ calcification, ○ morbidity/ mortality, ○ valve migration, ○ pathological analysis.	• Evaluate the acute in-vivo safety of the FlexNav DS and Portico valve in terms of the following: ○ DS performance and valve deployment ○ In-vivo hemodynamic performance of the Portico valve ○ Pathological analysis	• Evaluate the acute in-vivo safety of the Portico DS deploying the Portico valve by subclavian access by the following endpoints: ○ DS performance and valve deployment ○ In-vivo hemodynamic performance of the Portico valve ○ Pathological analysis	• Evaluate the acute in-vivo safety of the Portico DS deploying the Portico valve by transaortic access by the following endpoints: ○ DS performance and valve deployment ○ In-vivo hemodynamic performance of the Portico valve ○ Pathological analysis.

Table 10: Portico Valve and FlexNav DS and LS Overview of Acute and Chronic Animal Studies				
Study Information	**Chronic GLP Animal- Portico Valve Study**	**Acute GLP Animal - FlexNav DS Study**	**Acute GLP Animal - Subclavian Access Study**	**Acute non-GLP Animal - Transaortic Access Study**
Results	The chronic animal study demonstrated the Portico valve performed as expected by meeting all study endpoints listed below: • The Portico valve demonstrated acceptable hemodynamic performance and migration resistance when compared to the control valve. • There were no significant variances between the Portico valve and control group with regards to clinical pathology parameters. • The overall morphologic findings of this study demonstrated a satisfactory tissue healing response and acceptable biocompatibility of the Portico valve.	The acute animal study demonstrated the FlexNav DS performed as expected by meeting all study endpoints listed below: • successfully deploying the Portico valve in all six animals • Acceptable device trackability, handling and functional performance of the DS, • Acceptable hemodynamic performance of the Portico valve, • Acceptable target organ pathology and no device related thrombus.	The acute animal study demonstrated the Portico DS performed as expected by meeting all study endpoints listed below: • successfully deploying the Portico valve in all animals • Acceptable device trackability, handling and functional performance of the DS, • Acceptable hemodynamic performance of the Portico valve, • Acceptable target organ pathology and no device related thrombus.	The acute animal study demonstrated the Portico DS performed as expected by meeting all study endpoints listed below: • successfully deploying the Portico valve in all animals • Acceptable device trackability, handling and functional performance of the DS, • Acceptable hemodynamic performance of the Portico valve, • Acceptable target organ pathology and no device related thrombus.
Conclusion	The Portico valve demonstrated acceptable hemodynamic performance with satisfactory healing response. The Portico valve was determined to be safe for clinical use.	The FlexNav DS demonstrated the delivery systems provides safe and effective deployment of the Portico valve within the aortic annulus and was determined to be safe for clinical use.	This acute study met the study endpoints and supports safe use of the Portico DS to deploy a valve using the subclavian access site.	This acute study met the study endpoints and supports safe use of the Portico DS to deploy a valve using the transaortic access site.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

The applicant performed a clinical study, the PORTICO randomized controlled trial (RCT), to establish a reasonable assurance of safety and effectiveness of transcatheter aortic valve implantation with the Portico Transcatheter Aortic Valve Implantation System in patients with symptomatic severe native aortic stenosis who are considered high or greater surgical risk in the United States and Australia under IDE # G120263.

The FlexNav Delivery System represents a design modification to the first-generation Portico Delivery System to improve the ease of use, reduce the occurrence of major vascular complications, and improve procedural safety outcomes observed in the RCT. The FlexNav Delivery System was evaluated in a non-randomized FlexNav DS Study arm added to the PORTICO study following completion of enrollment in the RCT cohort. The PORTICO FlexNav DS Study and a parallel study being conducted outside the U.S. (OUS) under a similar protocol, called the FlexNav EU CE Mark Study (NCT03724812), were combined to make two cohorts to supplement PORTICO RCT for the PMA approval decision: FlexNav PMA Analysis Cohort and FlexNav Global Cohort.

The FlexNav PMA Analysis Cohort was a prospective study group consisting of a subset of subjects from the PORTICO FlexNav DS Study and the FlexNav EU CE Mark Study. This cohort excludes roll-in subjects, continued access enrollees, and those enrolled after submission of the marketing application to FDA.

The Global FlexNav Cohort consists of all patients in the PORTICO FlexNav DS Study and the FlexNav EU CE Mark Study plus those enrolled after submission of the marketing application to FDA. The results of the Global FlexNav Cohort represent the totality of pre-market evidence on the FlexNav DS while the FlexNav PMA Analysis Cohort represents a subset of this evidence.

Table 11 captures the major characteristics of the primary RCT and supplemental studies. **Figure 4** illustrates the relationship of the FlexNav DS studies and the composition of the supplemental FlexNav cohorts.

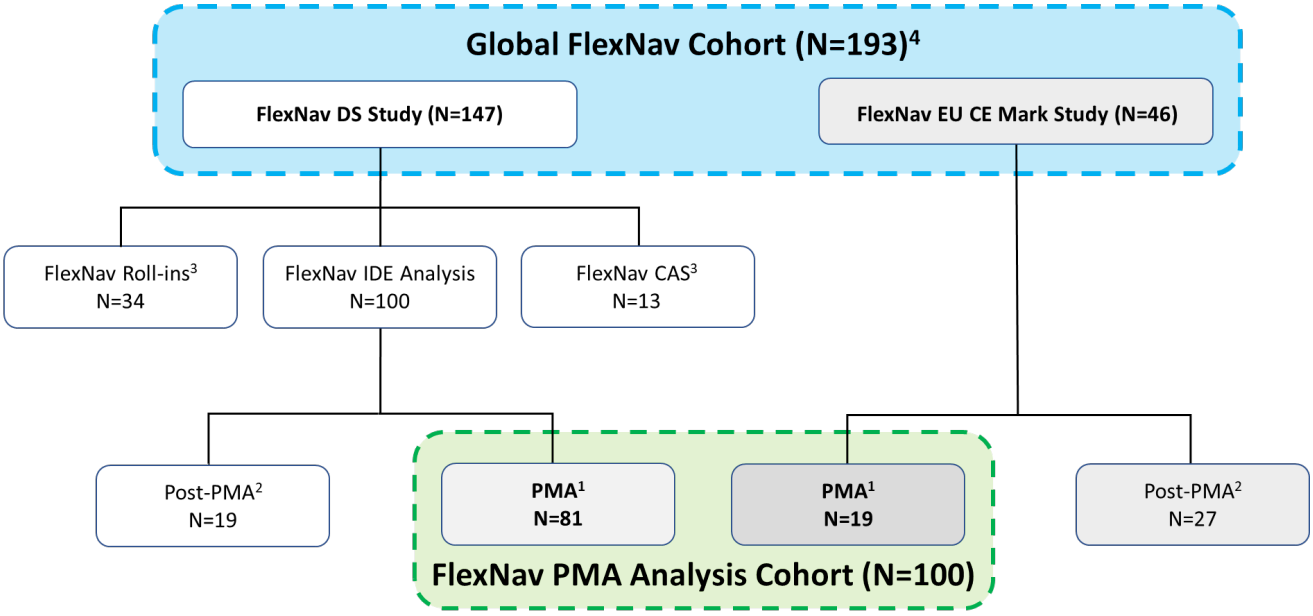
Table 11: Summary of Clinical Studies

Study/Cohort	N	Device	Geographies	Design and Endpoints
PORTICO RCT (ITT) • Portico Arm (n=381) • Control Arm (n=369)	750	Portico Valve vs. CAV Portico 1st Generation DS	US, AUS	Prospective Randomized (1:1) **Primary Safety:** Non-inferiority of a 5-component composite[2] at 30 days. **Primary Effectiveness:** Non-inferiority of a 2-component composite[3] at 1 year.
FlexNav PMA Analysis Cohort • PORTICO FlexNav DS Analysis Cohort (n=81) • FlexNav EU CE Mark Study (n=19)	100	Portico Valve FlexNav DS/LS	US, AUS, EU	Prospective Single Arm **Primary Safety:** Major vascular complication rate at 30 days.
Global FlexNav Cohort[1] • FlexNav Roll-ins (n=34) • PORTICO FlexNav DS Analysis	193	Portico Valve FlexNav DS/LS	US, AUS, EU	Observational Single Arm There were no prespecified primary endpoints for this aggregate Global

Cohort (n=100) • FlexNav Continued Access Study (n=13) • FlexNav EU CE Mark Study (n=46)				FlexNav cohort, however key PORTICO RCT and FlexNav Study endpoints were summarized descriptively.

[1] The Global FlexNav Cohort is inclusive of the patients in the FlexNav PMA Analysis Cohort, including 81 patients in the FlexNav IDE Analysis cohort and 19 patients in the FlexNav EU CE Mark Study
[2] The 5 components of the safety composite endpoint were all-cause mortality, disabling stroke, Acute Kidney Injury stage 3 requiring dialysis, life-threatening bleed requiring a transfusion and major vascular complications at 30 days.
[3] The 2 components of the effectiveness composite endpoint were all-cause mortality and disabling stroke at 1 year.
CAV = Commercially Available Valves, i.e. control group in RCT

Figure 4: Supplemental FlexNav Studies & Cohorts



1. Subjects enrolled prior to submission of marketing application to FDA were included in the FlexNav PMA Analysis Cohort
2. Subjects enrolled after submission of the marketing application to FDA were not included in the FlexNav PMA Analysis Cohort
3. FlexNav Roll-In and Continued Access Study (CAS) subjects were not included in the FlexNav IDE or PMA Analysis Cohorts
4. The Global FlexNav Cohort included all subjects from FlexNav DS Study and FlexNav EU CE Mark Study, including the FlexNav PMA Analysis Cohort.

A summary of the primary clinical study, PORTICO RCT, is presented below. Summaries of the supplemental clinical cohorts to evaluate the safety and performance of the FlexNav Delivery System design iteration (i.e., FlexNav PMA Analysis Cohort and Global FlexNav Cohort) are presented in **Section XI**. Data from the PORTICO RCT, in conjunction with supplemental data from the FlexNav PMA Analysis Cohort and Global FlexNav Cohort, were the basis for the PMA approval decision.

A. Study Design

Patients in the PORTICO RCT study were enrolled between May 30, 2014 and October 10, 2017. The database for this PMA reflected data collected through July 31, 2019 and included 750 randomized patients enrolled at 52 investigational sites in the United States and Australia.

The study was a prospective, multicenter, randomized controlled, open label non-inferiority trial designed to evaluate the safety and effectiveness of the Portico

Transcatheter Aortic Valve System for transcatheter aortic valve implantation (TAVI) via transfemoral, subclavian/axillary, or transaortic delivery for treatment of patients with symptomatic severe native aortic stenosis who are considered to be high or extreme surgical risk. All Portico valve implants in the PORTICO RCT were delivered with the Portico first-generation delivery system.

The control group was any FDA-approved and commercially available TAVI System for the treatment of severe symptomatic aortic stenosis in a high or extreme surgical risk patient population. The following commercially available TAVI Systems were used in the control group, referred to hereafter as "CAV" (Commercially Available Valves): SAPIEN, SAPIEN XT, SAPIEN 3, CoreValve, CoreValve Evolut R, and CoreValve Evolut PRO.

All patients were reviewed by an independent Subject Selection Committee (SSC) to confirm study eligibility and access route suitability. An independent Clinical Events Committee (CEC) adjudicated all primary endpoint clinical events according to Valve Academic Research Consortium (VARC)-2 criteria. Independent core laboratories assessed all echocardiographic and CT imaging data.

Patients were randomized in a 1:1 ratio to receive a Portico valve or CAV. Permuted block randomization was used and stratified by: (1) clinical investigational site, (2) surgical risk cohort (high vs extreme; as determined by the subject selection committee (SSC)), and (3) vascular access method (transfemoral or alternative access). Treatment assignment was not masked to the investigational site, implanting physician or study participant.

The analysis plan to demonstrate non-inferiority of the Portico Transcatheter Aortic Valve System compared to CAV in the safety and effectiveness endpoints was based on Kaplan-Meier estimates at the analysis timepoint and standard errors. Assuming 80% high risk and 20% extreme risk patients, and estimated event rates (in both Portico valve and CAV groups) of 30.81% for the primary safety endpoint at 30 days and 25.0% for the primary effectiveness endpoint at 1 year, 750 randomized patients were required to demonstrate non-inferiority with margins of 8.5% and 8.0% respectively.

A subset of consecutive randomized patients was enrolled in a computed tomography (CT) sub-study to investigate the prevalence of reduced leaflet motion (RLM). For these patients with interpretable 4D-CT, leaflet motion and Hypoattenuated Leaflet Thickening (HALT) were assessed by a CT core laboratory.

1. Clinical Inclusion and Exclusion Criteria

Inclusion Criteria

Enrollment in the PORTICO RCT was limited to patients who met the following inclusion criteria:

- Patients must have co-morbidities such that the surgeon and cardiologist Co-

Investigators concur that the predicted risk of operative mortality is ≥15% or a minimum STS score of 8%. A candidate who does not meet the STS score criteria of ≥ 8% can be included in the study if a peer review by at least two surgeons concludes and documents that the patient's predicted risk of operative mortality is ≥15%. The surgeon's assessment of operative comorbidities not captured by the STS score must be documented in the study case report form as well as in the patient medical record.

- Subject is 21 years of age or older at the time of consent.
- Subject has senile degenerative aortic valve stenosis with echocardiographically derived criteria: mean gradient >40 mmHg or jet velocity greater than 4.0 m/s or Doppler Velocity Index <0.25 and an initial aortic valve area (AVA) of ≤ 1.0 cm^2 (indexed EOA ≤ 0.6 cm^2/m^2). (Qualifying AVA baseline measurement must be within 60 days prior to informed consent).
- Subject has symptomatic aortic stenosis as demonstrated by NYHA Functional Classification of II, III, or IV.
- The subject has been informed of the nature of the study, agrees to its provisions and has provided written informed consent as approved by the Institutional Review Board (IRB) of the respective clinical site.
- The subject and the treating physician agree that the subject will return for all required post-procedure follow-up visits.
- Subject's aortic annulus is 19-27mm diameter as measured by CT conducted within 12 months prior to informed consent. Note: if CT is contraindicated and/or not possible to be obtained for certain patients, a 3D echo and non-contrast CT of chest and abdomen/pelvis may be accepted if approved by the subject selection committee.

For a subject to be considered an Extreme Risk candidate they must meet # 2, 3, 4, 5, 6, 7 of the above criteria, and:

- The subject, after formal consults by a cardiologist and two cardiovascular surgeons agree that medical factors preclude operation, based on a conclusion that the probability of death or serious, irreversible morbidity exceeds the probability of meaningful improvement. Specifically, the probability of death or serious, irreversible morbidity should exceed 50%. The surgeons' consult notes shall specify the medical or anatomic factors leading to that conclusion and include a printout of the calculation of the STS score to additionally identify the risks in these patients.

Exclusion Criteria

Patients were <u>not</u> permitted to enroll in the PORTICO study if they met any of the following exclusion criteria:

- Evidence of an acute myocardial infarction (defined as: ST Segment Elevation as evidenced on 12 Lead ECG) within 30 days prior to index procedure.
- Aortic valve is a congenital unicuspid or congenital bicuspid valve or is non-

calcified as verified by echocardiography.

- Mixed aortic valve disease (aortic stenosis and aortic regurgitation with predominant aortic regurgitation 3-4+).
- Any percutaneous coronary or peripheral interventional procedure performed within 30 days prior to index procedure.
- Pre-existing prosthetic heart valve or other implant in any valve position, prosthetic ring, severe circumferential mitral annular calcification (MAC) which is continuous with calcium in the LVOT, severe (greater than 3+) mitral insufficiency, or severe mitral stenosis with pulmonary compromise. Patients with pre-existing surgical bioprosthetic aortic heart valve should be considered for the Valve-in-Valve registry.
- Blood dyscrasias as defined: leukopenia (WBC<3000 mm^3), acute anemia (Hb < 9 g/dL), thrombocytopenia (platelet count <50,000 cells/mm^3).
- History of bleeding diathesis or coagulopathy.
- Cardiogenic shock manifested by low cardiac output, vasopressor dependence, or mechanical hemodynamic support.
- Untreated clinically significant coronary artery disease requiring revascularization.
- Hemodynamic instability requiring inotropic support or mechanical heart assistance.
- Need for emergency surgery for any reason.
- Hypertrophic cardiomyopathy with or without obstruction (HOCM).
- Severe ventricular dysfunction with LVEF <20% as measured by resting echocardiogram.
- Echocardiographic evidence of intracardiac mass, thrombus or vegetation.
- Active peptic ulcer or upper GI bleeding within 3 months prior to index procedure.
- A known hypersensitivity or contraindication to aspirin, heparin, ticlopidine (Ticlid), or clopidogrel (Plavix), or sensitivity to contrast media which cannot be adequately premedicated.
- Recent (within 6 months prior to index procedure date) cerebrovascular accident (CVA) or a transient ischemic attack (TIA).
- Renal insufficiency (creatinine > 3.0 mg/dL) and/or end stage renal disease requiring chronic dialysis.
- Life expectancy < 12 months from the time of informed consent due to non-cardiac co-morbid conditions.
- Significant aortic disease, including abdominal aortic or thoracic aneurysm defined as maximal luminal diameter 5cm or greater; marked tortuosity (hyperacute bend), aortic arch atheroma (especially if thick [> 5 mm], protruding or ulcerated) or narrowing (especially with calcification and surface irregularities) of the abdominal or thoracic aorta, severe “unfolding” and tortuosity of the thoracic aorta (applicable for transfemoral patients only).
- Native aortic annulus size < 19 mm or > 27 mm per the baseline diagnostic imaging.

- Aortic root angulation > 70° (applicable for transfemoral patients only).
- Currently participating in an investigational drug or device study.
- Active bacterial endocarditis within 6 months prior to the index procedure.
- Bulky calcified aortic valve leaflets in close proximity to coronary ostia.
- Non-calcified aortic annulus
- Iliofemoral vessel characteristics that would preclude safe placement of the introducer sheath such as severe obstructive calcification, or severe tortuosity (applicable for transfemoral patients only).

Additional Exclusion Criteria (Transcatheter Access-Related)

For selection of an appropriate alternative access delivery method, patients were screened using the following transaortic access specific exclusion criteria:

- Subject has pre-existing patent right internal mammary arterial (RIMA) graft that would preclude access.
- Subject has a hostile chest or other condition that complicates transaortic access.
- Subject has a porcelain aorta, defined as an extensive circumferential calcification of the ascending aorta that would complicate transaortic access.

Subclavian/Axillary Subject Cohort Specific Exclusion Criteria

- Subject's access vessel (subclavian/axillary) diameter will not allow for introduction of the applicable 18 Fr or 19 Fr delivery system.
- Subject's subclavian/axillary arteries have severe calcification and/or tortuosity.
- Subject's aortic root angulation is:
  - Left Subclavian/Left Axillary: >70°
  - Right Subclavian/Right Axillary: >30°
- Subject has a history of patent LIMA/RIMA graft that would preclude access

2. Follow-up Schedule

All patients were scheduled to return for follow-up examinations at discharge, 30 days, 6 months, 12 months, and then annually for 5 years post-procedure. For patients who were unable to attend an in-person follow-up visit at 12 months, a vital status phone call to determine survival and any new adverse events within 12 months was permitted. RCT patients who did not receive a study valve were followed for 12 months and then allowed to withdraw.

Preoperatively, patients were screened by a local Heart team to confirm they met study eligibility criteria including CT and echocardiographic imaging assessments to assess severity of aortic stenosis and confirm transcatheter vascular access route suitability. Baseline assessments included laboratory tests, quality of life surveys, functional and cognitive tests, and neurological assessments.

Postoperatively, the objective parameters measured during the study included New

York Heart Association (NYHA) functional classification, neurological assessments, transthoracic echocardiogram (TTE) evaluation and quality of life surveys. Adverse events and complications were recorded at all visits.

The key timepoints are shown below in the tables summarizing safety and effectiveness.

3. Clinical Endpoints

Primary Safety Endpoint:
The primary safety endpoint was a non-hierarchical composite of all-cause mortality, disabling stroke, life threatening bleeding requiring blood transfusion, acute kidney injury requiring dialysis, or major vascular complications at 30 days. The primary hypothesis was as follows:

$$H_0: \lambda_{test} \geq \lambda_{control} + \Delta_{p1}$$
$$H_a: \lambda_{test} < \lambda_{control} + \Delta_{p1}$$

where λ_{test} is the probability of a subject experiencing a primary safety endpoint event by 30 days in the Portico valve (test) group, $\lambda_{control}$ is the probability of a subject experiencing a primary safety endpoint event in the CAV (control) group, and Δ_{p1} is the non-inferiority margin for the primary safety endpoint pre-defined as 8.5%.

The hypothesis test was a non-inferiority test performed in the Intention-to-Treat (ITT) population by calculating a 95% one-sided upper confidence limit for the difference of (λ_{test} - $\lambda_{control}$), using Kaplan-Meier estimates for the event rates and standard errors. If the upper confidence limit for the difference was less than 8.5%, the Portico valve group was determined to be non-inferior to the CAV group. The endpoint was also analyzed for the As-Treated (AT) and Per Protocol (PP) populations.

Primary Effectiveness Endpoint:
The primary effectiveness endpoint was a composite of all-cause mortality or disabling stroke assessed at 1 year. The primary hypothesis was as follows:

$$H_o: p_{test} \geq p_{control} + \Delta_{p2}$$
$$H_a: p_{test} < p_{control} + \Delta_{p2}$$

where p_{test} is the probability of a subject experiencing a primary effectiveness endpoint event by 1 year in the Portico valve (test) group, $p_{control}$ is the probability of a subject experiencing a primary effectiveness endpoint event by 1 year in the CAV (control) group, and Δ_{p2} is the non-inferiority margin for the primary effectiveness endpoint pre-defined as 8.0%.

The hypothesis test was a non-inferiority test performed in the ITT population by calculating the 95% one-sided upper confidence limit for the difference of (p_{test} - $p_{control}$), using Kaplan-Meier estimates for the event rates and standard errors. If the

upper confidence limit for the difference was less than 8.0%, the Portico valve group was determined to be non-inferior to the CAV group. The endpoint was also analyzed for the AT and PP populations.

Secondary Endpoints:
Four pre-specified secondary endpoints were tested in a hierarchical testing scheme (as shown in **Table 12** below). Non-inferiority tests were performed in the ITT population for each secondary endpoint. To claim non-inferiority, both secondary endpoints tested per group must be within the pre-specified non-inferiority margins.

Table 12: Secondary Endpoints

Group	Secondary Endpoint	Alternative Hypothesis Test	Non-inferiority Margin
1	Severe aortic regurgitation (AR) at 1 year[1]	Ha: $\theta test_{,1} < \theta control_{,1} + 0.04$	4%
1	KCCQ Overall Score at 1 year[2]	Ha: $\theta test_{,2} > \theta control_{,2} - 10$	10 points
2	Moderate or severe aortic regurgitation at 1 year[1]	Ha: $\theta test_{,3} < \theta control_{,3} + 0.06$	6%
2	6-minute walk at 1 year[2]	Ha: $\theta test_{,4} > \theta control_{,4} - 36$	36m

[1] based on the Farrington-Manning method
[2] based on a two-sample t-test

Descriptive Endpoints:
Descriptive endpoints including acute device success, quality of life, NYHA functional classification, valve hemodynamics, and clinical outcomes were assessed at 30 days, 6 months, and 12 months post index procedure, unless otherwise specified. All descriptive endpoints were summarized using descriptive statistics.

- Acute device success defined as:
  - Absence of procedural mortality AND
  - Correct positioning of a single prosthetic heart valve into the proper anatomical location AND
  - Intended performance of the prosthetic heart valve (mean aortic valve gradient <20 mmHg or peak velocity <3 m/s, no moderate or severe prosthetic valve regurgitation) AND
  - Successful access was obtained as intended by group assignment
- Kansas City Cardiomyopathy Questionnaire (KCCQ) at 1 year
- Major vascular complications at 30 days
- NYHA functional classification at 30 days, 6 months, and 1 year
- Six-minute walk test at 30 days, 6 months, and 1 year
- Paravalvular Leak (PVL) at 30 days, 6 months, and 1 year
- Aortic insufficiency greater than trace at 30 days, 6 months, 1 year, and 2 years
- Reintervention to treat aortic insufficiency at 1 year and 2 years
- Permanent pacemaker insertion at 30 days
- Major bleeding at 30 days

- Acute kidney injury at 30 days
- Individual components of the primary effectiveness endpoint
    - All-cause mortality at 30 days, 6 months, 1 year and 2 years
    - Disabling stroke at 30 days, 6 months, 1year and 2 years
- Non-disabling Stroke and Transient Ischemic Attack (TIA) at 30 days, 6 months, 1 year, and 2 years
- Atrial fibrillation at 1 year and 2 years
- Quality of Life (QOL) from baseline to 30 days, 6 months and 1 year

B. Accountability of PORTICO RCT Cohort

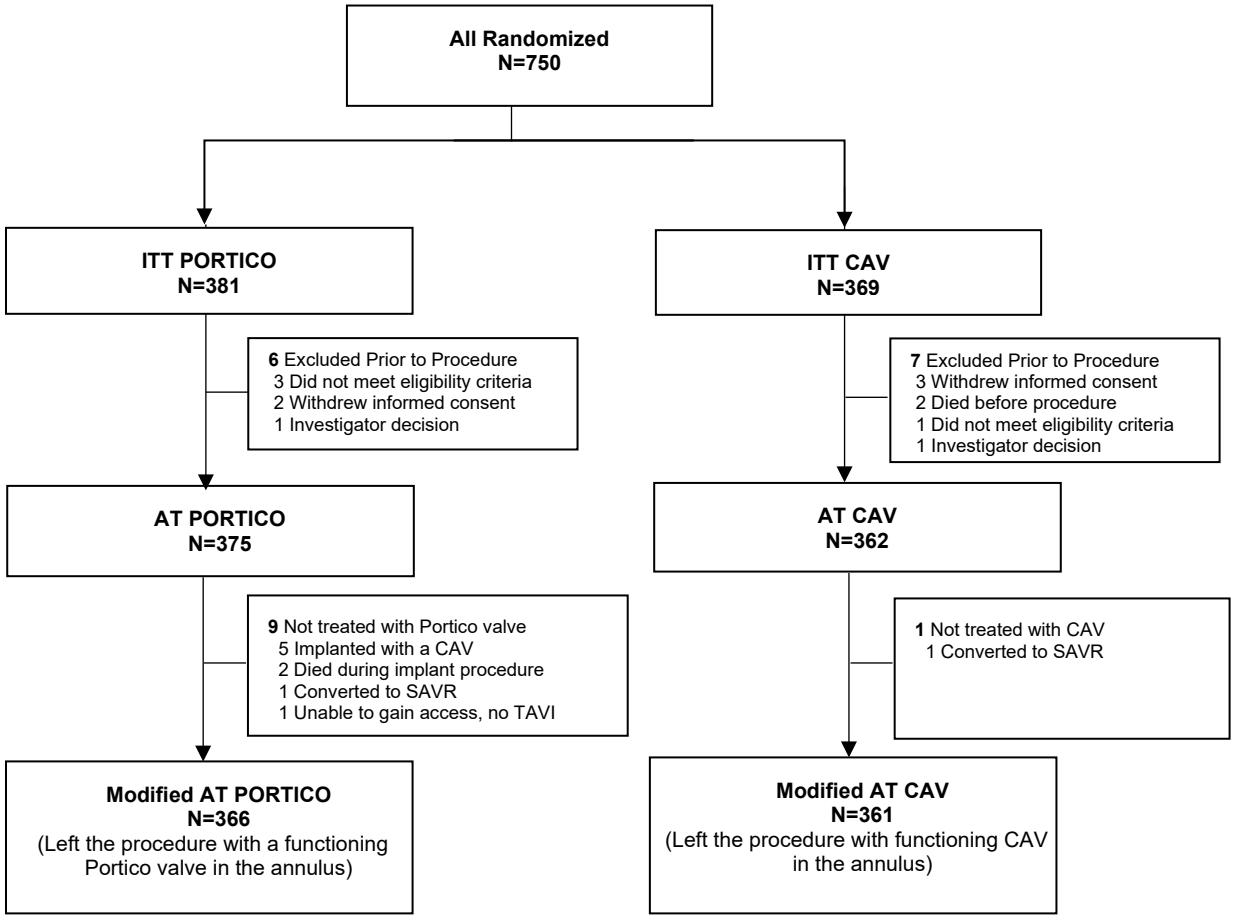
At the time of database lock, a total of 750 patients were randomized in the study, including 381 Portico valve patients and 369 CAV patients.

There were four different analysis populations defined in the protocol: Intention-to-treat (ITT), As-Treated (AT), Modified As-Treated (mod AT), and Per Protocol (PP), as summarized in **Table 13** and **Figure 5** below. The primary analysis was based on the ITT population, with the date of randomization considered Day 0.

Table 13: Summary of Analysis Populations and Patient Accountability

Analysis Populations	Definition	Cohort	
		Portico valve (N)	CAV (N)
Intention-to-Treat (ITT; *primary*)	All randomized patients, with the date of randomization considered Day 0	**381**	**369**
As-Treated (AT)	All randomized patients in whom treatment was initiated (defined as entering the procedure room), with date of the index procedure considered Day 0.	**375**	**362**
Per protocol (PP)	All randomized patients who were successfully treated with the assigned valve implant and had no deviation for inclusion/exclusion in the study, with date of the index procedure considered Day 0	**350**	**348**
Modified As-Treated (mod AT)	All randomized patients who were implanted with one or more valves per the assigned treatment (Portico valve or CAV) at the time of the index procedure. Patients that died during procedure, were converted to surgery or received a valve different than assigned were excluded. Date of the index procedure considered Day 0	**366**	**361**

Figure 5: Population Flowchart



Of the 750 randomized patients, 82.3% were alive and available for follow-up (i.e. not withdrawn) at the 12-month post-operative visit. The overall disposition of the patients and compliance for each follow-up visit is presented by group in **Table 14**.

Table 14: Overall Disposition and Study Compliance

Group	Visit Interval	Completed Visits	Expected Visits[1]	Missed Visits	Study Exits		Follow-up Compliance %
					Death	Withdrawal[2]	
Portico Valve (Intention-to-Treat)	Baseline	381	381	0	N/A	N/A	100.0%
	Procedure	375	375	0	0	6	100.0%
	Discharge	368	369	1	6	0	99.7%
	30 Days	346	356	10	13	1	97.2%
	6 Months	307	330	23	19	7	93.0%
	12 Months[3]	302	308	6	18	4	98.1%
CAV (Intention-to-Treat)	Baseline	369	369	N/A	N/A	N/A	100.0%
	Procedure	362	362	0	2	5	100.0%
	Discharge	360	360	0	2	0	100.0%
	30 Days	347	356	9	4	0	97.5%
	6 Months	314	334	20	19	3	94.0%

	12 Months[3]	301	309	8	18	7	97.4%

[1] Expected = Completed + Missed
[2] Withdrawals include subject withdrawals, investigator withdrawals and lost to follow-up.
[3] 12 Month visits include visits completed by phone.

C. Study Population Demographics and Baseline Parameters

The baseline demographics of the study population are typical for a TAVI study performed in the United States and are summarized in **Table 15**. The treatment cohorts were generally well balanced with respect to age, gender, baseline NYHA classification, and STS risk score.

Table 15: Study Population Demographics and Baseline Parameters (ITT population)

	Portico valve (N=381)	CAV (N=369)
Demographics		
Age, mean (SD), y	83.0 (7.6)	83.7 (7.0)
Female	198 (52.0%)	197 (53.4%)
NYHA functional class		
NYHA II	109 (28.6%)	100 (27.1%)
NYHA III	229 (60.1%)	234 (63.4%)
NYHA IV	43 (11.3%)	35 (9.5%)
STS PROM Score[1], %		
Mean (SD)	6.4 (3.4)	6.6 (3.4)
STS <4%	102 (26.8%)	88 (23.8%)
STS 4-7.9%	182 (47.8%)	173 (46.9%)
STS ≥8%	97 (25.5%)	108 (29.3%)
EuroSCORE II, %	6.8 (7.6)	6.6 (5.8)
Extreme risk	70 (18.4%)	63 (17.1%)
High risk	311 (81.6%)	306 (82.9%)
Comorbidities		
Hypertension	358 (94.0%)	331 (89.7%)
Diabetes mellitus	143 (37.5%)	142 (38.5%)
Oral controlled	73/143 (51.0%)	71/142 (50.0%)
Kidney disease	96 (25.2%)	94 (25.5%)
Atrial fibrillation	125 (32.8%)	145 (39.3%)
Permanent pacemaker	57 (15.0%)	63 (17.1%)
Pre-existing RBBB	56 (14.7%)	43 (11.7%)
Prior stroke	29 (7.6%)	49 (13.3%)
Prior transient ischemic attack	33 (8.7%)	25 (6.8%)
Carotid artery disease	93/380 (24.5%)	82 (22.2%)
Coronary artery disease	266 (69.8%)	256 (69.4%)
Prior coronary stenting	108 (28.3%)	107 (29.0%)
Prior bypass graft surgery	88 (23.1%)	76 (20.6%)

Table 15: Study Population Demographics and Baseline Parameters (ITT population)		
	Portico valve (N=381)	**CAV (N=369)**
Prior myocardial infarction	55 (14.4%)	43 (11.7%)
Peripheral vascular disease	72 (18.9%)	65 (17.6%)
Chronic lung disease	158 (41.5%)	148 (40.1%)
Hostile chest/Prohibitive chest deformity	11 (2.9%)	19 (5.1%)
Porcelain aorta	11 (2.9%)	10 (2.7%)
Severe liver disease	4 (1.0%)	3 (0.8%)
Pulmonary hypertension	131 (34.4%)	126 (34.1%)
Total frailty score (out of 4), mean (SD)	1.8 (0.9)	1.9 (0.8)
Katz index of activities of daily living, ≤4	40 (10.5%)	41 (11.1%)
Grip strength, <BMI and height-based cut-off	298/379 (78.6%)	302 (81.8%)
15-foot (5m) walk test ≥Height and sex-based cut-off	268/359 (74.7%)	256/342 (74.9%)
Albumin < 3.5g/dl	87/380 (22.9%)	93/366 (25.4%)
KCCQ-OS score, mean (SD)	55.0 (23.2) (375)	53.9 (23.7) (358)
EQ-5D Index score, mean (SD)	0.73 (0.19) (373)	0.74 (0.19) (359)
Six-minute walk distance, mean (SD), m	207.5 (116.5) (320)	208.9 (110.2) (306)
Echocardiographic parameters[2]		
Aortic valve area, mean (SD), cm^2	0.68 (0.17)	0.67 (0.16) (367)
Mean gradient, mean (SD), mm Hg	46.2 (11.2) (379)	45.9 (11.9) (368)
Ejection fraction, mean (SD), %	57.3 (11.5) (377)	57.4 (11.1) (367)
Mitral insufficiency (moderate/severe)	78/380 (20.5%)	83/367 (22.6%)
Tricuspid insufficiency (moderate/severe)	70/380 (18.4%)	67/367 (18.3%)

Data are presented as n (%), mean (SD), n/N (%) or mean (SD) (n).
KCCQ-OS= Kansas City Cardiomyopathy Questionnaire Overall Summary. NYHA= New York Heart Association. STS PROM= Society of Thoracic Surgeons predicted risk of mortality. EuroSCORE= European System for Cardiac Operative Risk Evaluation. EQ-5D= EuroQol- 5 Dimension. RBBB= Right Bundle Branch Block.
[1] Patients screened after November 15, 2018 were evaluated using risk models developed using STS data from 2011 to 2014 and validated using 2014 to 2016 data.
[2] Site-reported echo data

D. Safety and Effectiveness Results

1. Primary Safety Endpoint

The composite rate of all-cause mortality, disabling stroke, life threatening bleeding requiring blood transfusion, acute kidney injury requiring dialysis, or major vascular complications at 30 days for the Intention-to-Treat (ITT) and As-Treated (AT) populations are shown in **Table 16**.

The primary analysis was prespecified for the ITT population, for which Kaplan-Meier analysis shows the composite rate at 30 days was 13.8% in the Portico valve group and 9.6% in the CAV group. The 95% upper confidence limit of the difference was 8.1% for the ITT population, which falls within the pre-specified non-inferiority

margin of 8.5%, indicating the study's primary safety endpoint was met for the primary analysis population. A confirmatory analysis was also pre-specified using the AT population; however, the 95% upper confidence limit of the difference for the AT population was 8.9%, which was not within the pre-specified non-inferiority margin. Thus, non-inferiority of the Portico valve for the primary safety endpoint was not confirmed by the AT population.

Table 16: Primary Safety Endpoint Analysis (30 Days)

Analysis Set	Kaplan-Meier Estimate (SE) of Event Rate		Difference in event rate between groups	Upper limit of the one-sided 95% confidence interval of event rate difference[1]	P-value
	Portico valve	CAV			
Intention-to-Treat (N=750)	13.8% (1.8%) (N=381)	9.6% (1.5%) (N=369)	4.2%	8.1%	0.03
As-Treated (N=737)	14.4% (1.8%) (N=375)	9.4% (1.5%) (N=362)	5.0%	8.9%	0.07

[1] Kaplan-Meier method was used to estimate the event rate (SE). If the upper limit of the one-sided 95% confidence interval for the difference of event rate (Portico – CAV) is < 8.5%, then non-inferiority is demonstrated.
Note: Endpoint is measured from Day of Randomization for ITT and from Day of Procedure for AT.

Event rates for individual components of the composite primary safety endpoint for the ITT and AT analysis populations are shown in **Table 17**, along with 95% confidence intervals. Event rates for all-cause mortality and major vascular complications are numerically higher in the Portico group (ITT: 3.5% and 9.6%, respectively) than in the CAV group (ITT: 1.9% and 6.3%, respectively). Comparison of the component event rate differences between Portico and CAV groups across the ITT population, which included all randomized subjects with follow-up beginning at randomization, and the AT population, which included all treated subjects with follow-up beginning at the index procedure, identified that the individual component event rate differences were consistent across the two populations, except for all-cause mortality. In the AT population, there were 2 fewer patient deaths in the CAV group (occurred before index procedure) and 4 more patient deaths in the Portico group (occurred after 30 days from randomization but within 30 days of index procedure). As a result, the all-cause mortality rate difference increased 1.5% from the ITT to AT population (+1.6% vs. +3.1%, respectively) in favor of the CAV group.

Table 17: Components of Primary Safety Endpoint (30 Days)				
Component	**PORTICO RCT (Intention-to-Treat)**		**PORTICO RCT (As-Treated)**	
	Portico valve (N=381)	**CAV (N=369)**	**Portico valve (N=375)**	**CAV (N=362)**
All-Cause Mortality[1] [95% Confidence interval][2]	3.5% (13/375) [1.86%, 5.86%]	1.9% (7/364) [0.78%, 3.92%]	4.5% (17/374) [2.67%, 7.18%]	1.4% (5/362) [0.45%, 3.19%]
Disabling Stroke[1] [95% Confidence interval][2]	1.6% (6/375) [0.59%, 3.45%]	1.1% (4/364) [0.30%, 2.79%]	1.6% (6/374) [0.59%, 3.46%]	0.8% (3/362) [0.17%, 2.40%]
Life Threatening Bleeding Requiring Blood Transfusion[1] [95% Confidence interval][2]	4.5% (17/375) [2.66%, 7.16%]	3.6% (13/364) [1.92%, 6.03%]	4.8% (18/374) [2.88%, 7.50%]	3.6% (13/362) [1.93%, 6.06%]
Acute Kidney Injury Requiring Dialysis[1] [95% Confidence interval][2]	1.1% (4/375) [0.29%, 2.71%]	0.8% (3/364) [0.17%, 2.39%]	1.1% (4/374) [0.29%, 2.72%]	0.8% (3/362) [0.17%, 2.40%]
Major Vascular Complications[1] [95% Confidence interval][2]	9.6% (36/375)[3] [6.81%, 13.04%]	6.3% (23/364)[4] [4.05%, 9.33%]	9.6% (36/374) [6.83%, 13.08%]	6.6% (24/362) [4.29%, 9.70%]

[1] The proportion of patients who experienced each event was calculated. The numerator for the 30-day rate is the number of patients who experienced an event by 30 days (post randomization for ITT and post index procedure for AT). The denominator for each event type is the number of analysis patients excluding patients that have withdrawn before 30 days without an event.

[2] By Clopper-Pearson exact confidence interval.

[3] Of the 36 major vascular complications in the Portico ITT group, 19 (5.1%) occurred at an access site (3.2% TAVI, 1.9% non-TAVI access site), 16 (4.3%) did not occur at an access site, and 1 subject (0.3%) had multiple events (1 at the access site and 1 non-access site).

[4] Of the 23 major vascular complications in the CAV ITT group, 16 (4.4%) occurred at an access site (3.0% TAVI, 1.4% non-TAVI access site), 6 (1.6%) did not occur at an access site, and 1 subject (0.3%) had multiple events (1 at the access site and 1 non-access site).

2. Primary Effectiveness Endpoint

The composite rate of all-cause mortality or disabling stroke at 1 year for the Intention-to-Treat (ITT) and As-Treated (AT) populations are shown in **Table 18**.

The primary analysis was pre-specified for the ITT population, for which Kaplan-Meier analysis shows the composite rate was 14.9% in the Portico valve group and 13.4% in the CAV group. A confirmatory analysis was also pre-specified using the AT population. The 95% upper confidence limit for the difference was 5.7% in the ITT population and 6.2% in the AT population, which both fall within the pre-specified non-inferiority margin of 8.0%, indicating the study's primary effectiveness endpoint was met.

Table 18: Primary Effectiveness Endpoint Analysis (1 Year)					
Analysis Set	**Kaplan-Meier Estimate (SE) of Event Rate**		**Difference in event rate between groups**	**Upper limit of the one-sided 95% confidence interval of event rate difference[1]**	**P-value**
	Portico valve (N=381)	**CAV (N=369)**			
Intention-to-Treat (N=750)[2]	14.9% (1.8%) (N=381)	13.4% (1.8%) (N=369)	1.5%	5.7%	0.006
As-Treated (N=737)[3]	15.2% (1.9%) (N=375)	13.2% (1.8%) (N=362)	2.0%	6.2%	0.010

[1] Kaplan-Meier method was used to estimate the event rate (SE). If the upper limit of the one-sided 95% confidence interval for the difference of event rate (Portico – CAV) is < 8.0%, non-inferiority is demonstrated.
[2] Endpoint is measured from Day of Randomization
[3] Endpoint is measured from Day of Procedure

Event rates for individual components of the composite primary effectiveness endpoint for the ITT and AT analysis populations are shown in **Table 19** along with 95% confidence intervals. The individual component event rates of Portico and CAV groups were consistent across ITT and AT populations. While the mortality rate numerically favored the CAV group at 30-days and 1-year, the difference of all-cause mortality between Portico and CAV groups at 1-year was similar to the difference at 30 days (Table 17), suggesting the post-procedural mortality risk (beyond 30-days) is consistent between the Portico and CAV groups. Although the rate of disabling stroke at 30 days favored CAV (1.6% vs. 1.1%) (Table 17), the disabling stroke rate at 1 year numerically favored the Portico valve (1.6% vs. 2.9%).

Table 19: Components of Primary Effectiveness Endpoint (1 Year)				
Component	**PORTICO RCT (Intention-to-Treat)**		**PORTICO RCT (As-Treated)**	
	Portico valve (N=381)	**CAV (N=369)**	**Portico valve (N=375)**	**CAV (N=362)**
All-Cause Mortality[1] [95% Confidence interval][2]	14.4% (1.8%) [11.17%, 18.38%]	12.0% (1.7%) [9.05%, 15.85%]	14.7% (1.8%) [11.43%, 18.71%]	11.8% (1.7%) [8.86%, 15.63%]
Disabling Stroke[1] [95% Confidence interval][2]	1.6% (0.7%) [0.73%, 3.58%]	2.9% (0.9%) [1.56%%, 5.29%]	1.6% (0.7%) [0.73%, 3.54%]	2.6% (0.9%) [1.36%, 4.94%]

[1] Kaplan-Meier method was used to estimate the event rate (SE).
[2] The 95% confidence interval was estimated using KM method with Greenwood standard error.

3. Secondary Endpoints

The analysis of predefined secondary endpoints in the RCT was based on the ITT analysis population of 750 randomized patients that had available data at 1 year.

As shown in **Table 20**, the Portico valve group was found to be non-inferior to CAV within the pre-specified non-inferiority margins for proportion of severe aortic regurgitation and overall KCCQ score at 1 year. However, the Portico valve group

did not meet the non-inferiority criterion for proportion of moderate or severe aortic regurgitation at 1 year with respect to the CAV group. The remaining secondary endpoint (6-minute walk) in the hierarchy test was not tested.

Table 20: Non-Inferiority Testing of Secondary Endpoints (ITT population)

Secondary Endpoints at 1 year	Portico valve (N=381)	CAV (N=369)	Difference (Portico-CAV)	95% Upper or Lower Confidence Limit	P-value
Severe aortic regurgitation	0.4% (1/269)	0.0% (0/269)	0.4%	2.34%[1]	0.0012[5]
Kansas City Cardiomyopathy Questionnaire (KCCQ) Overall Score	75.4 (274)	75.9 (283)	-0.5	-3.50[2]	<0.0001[6]
Moderate or severe aortic regurgitation	7.8% (21/269)	1.5% (4/269)	6.3%	9.24%[3]	0.5714[5]
6-minute walk distance (m)	235.0 (227)	231.5 (225)	3.5	-15.36[4]	No test[6]

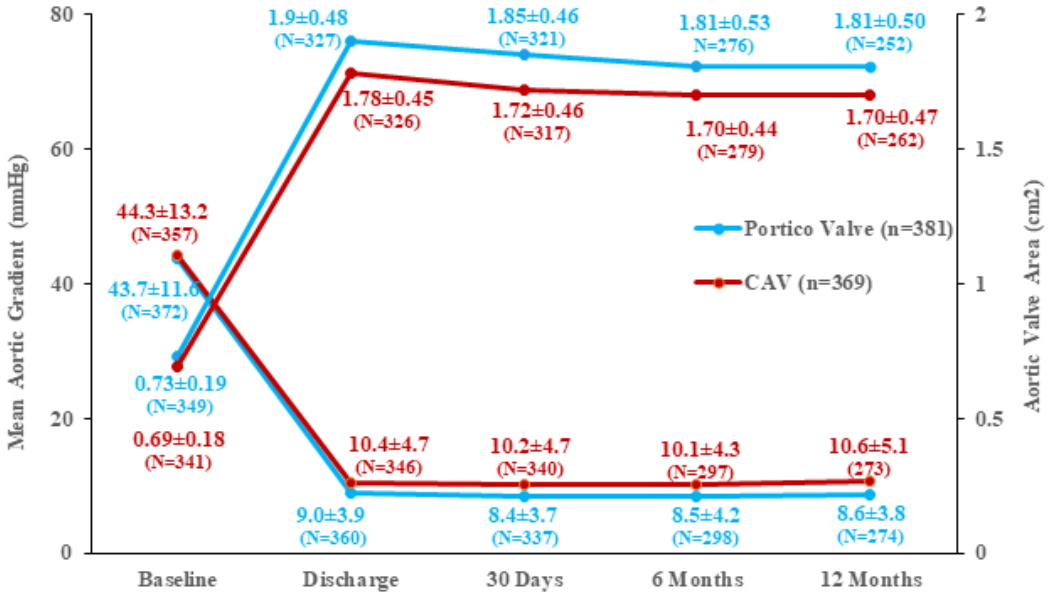
Note: all available data for randomized patients
[1] If the one-sided 95% upper confidence limit for the difference of proportions (Portico – CAV) is < 4%, then non-inferiority is demonstrated.
[2] If the one-sided 95% lower confidence limit for the difference of score (Portico – CAV) is > -10, then non-inferiority is demonstrated.
[3] If the one-sided 95% upper confidence limit for the difference of proportions (Portico – CAV is < 6%, then non-inferiority is demonstrated.
[4] If the one-sided 95% lower confidence limit for the difference of score (Portico – CAV) is > -36m, then non-inferiority is demonstrated.
[5] Farrington-Manning test
[6] Hypothesis testing was stopped after non-inferiority was not met for moderate or severe aortic regurgitation non-inferiority.

4. Additional Effectiveness Results

Valve Hemodynamics

Figure 6 presents mean aortic gradients and aortic valve areas at baseline through follow-up in the PORTICO RCT. Improvements in mean aortic gradients and valve areas from baseline to discharge were maintained through 30 days and through 1 year in both the Portico and CAV groups. The randomized Portico valve group reported numerically larger valve areas and smaller mean gradients compared to the randomized CAV group at 1 year.

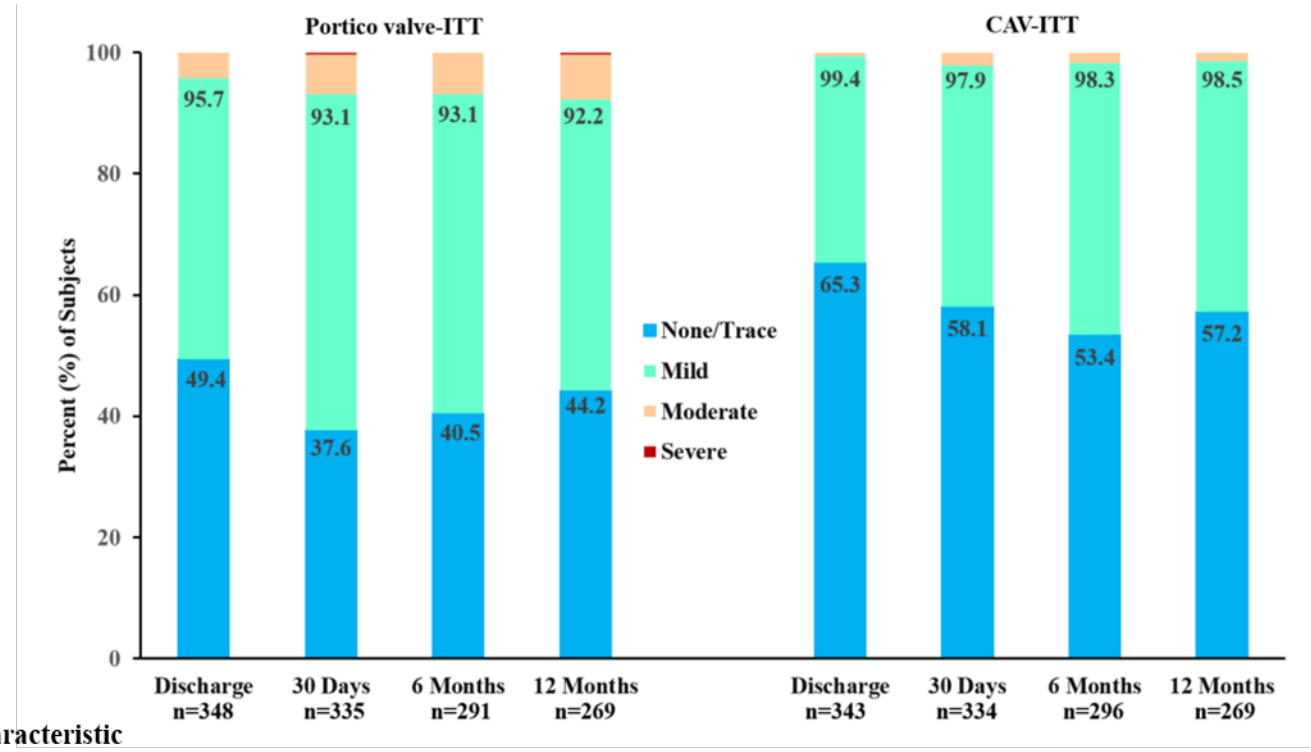
Figure 6: Valve Hemodynamics Through 1 Year (ITT population)



Total Aortic Regurgitation & Paravalvular Aortic Regurgitation

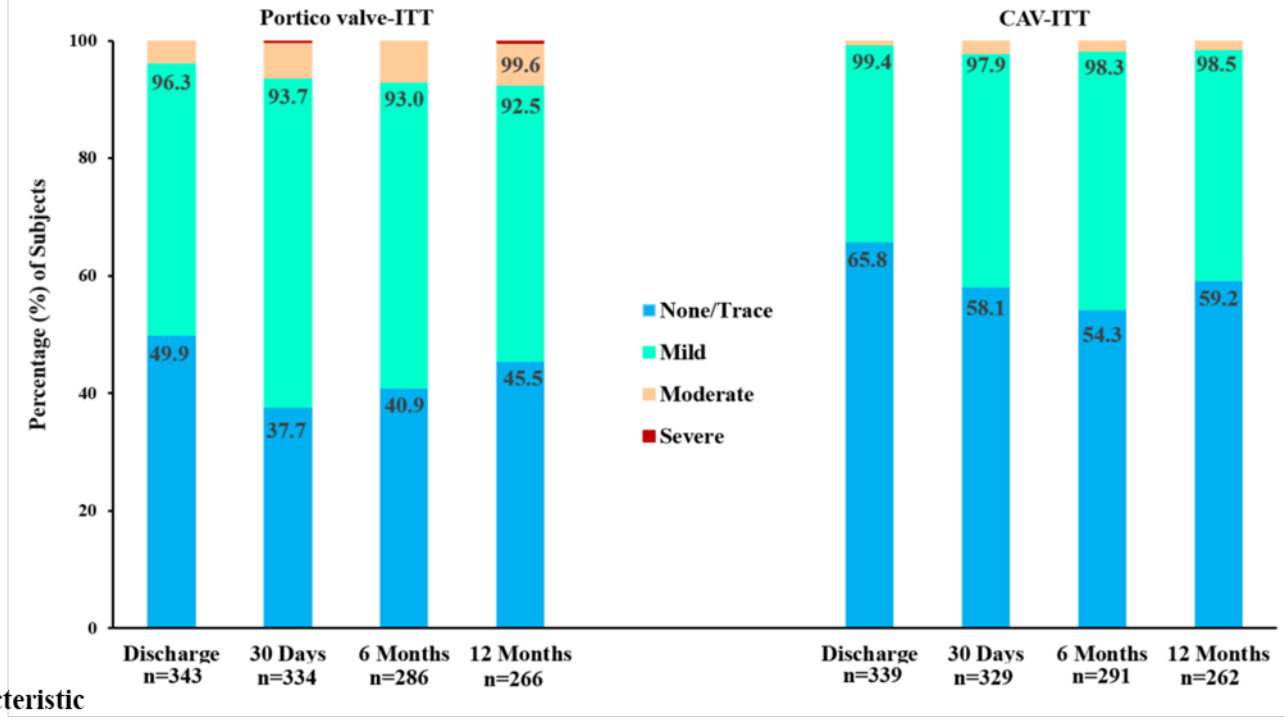
Figure 7 and **Figure 8** present core laboratory observed rates of total aortic regurgitation and paravalvular aortic regurgitation at discharge through follow-up in the PORTICO RCT, respectively. As determined in the secondary endpoint analysis, clinically significant total aortic regurgitation after 1 year was lower in the CAV group (1.5%) than in the Portico group (7.8%). In the Portico group, all reported moderate or severe total aortic regurgitation was attributable to paravalvular regurgitation. Patients treated with the Portico valve reported a three-times higher rate of clinically significant paravalvular regurgitation (6.3%) compared to the patients in the CAV group (2.1%) at 30 days, which persisted through 1 year (7.5% vs. 1.5%, respectively).

Figure 7: Total Aortic Regurgitation Through 1 Year (ITT population)



Characteristic								
None/Trace	49.4%	37.6%	40.5%	44.2%	65.3%	58.1%	53.4%	57.2%
Mild	46.3%	55.5%	52.6%	48.0%	34.1%	44.9%	44.9%	41.3%
Moderate	4.3%	6.6%	6.9%	7.4%	0.6%	1.7%	1.7%	1.5%
Severe	0.0%	0.3%	0.0%	0.4%	0.0%	0.0%	0.0%	0.0%

Figure 8: Paravalvular Aortic Regurgitation Through 1 Year (ITT population)



Characteristic								
None/Trace	49.9%	37.7%	40.9%	45.5%	65.8%	58.1%	54.3%	59.2%
Mild	46.4%	56.0%	52.1%	47.0%	33.6%	39.8%	44.0%	39.3%
Moderate	3.8%	6.0%	7.0%	7.1%	0.6%	2.1%	1.7%	1.5%
Severe	0.0%	0.3%	0.0%	0.4%	0.0%	0.0%	0.0%	0.0%

Reintervention to Treat Aortic Regurgitation

Table 21 presents the results for reintervention to treat aortic regurgitation (defined as moderate or greater paravalvular aortic regurgitation or transvalvular aortic insufficiency) among subjects after the TAVI procedure (N=732).

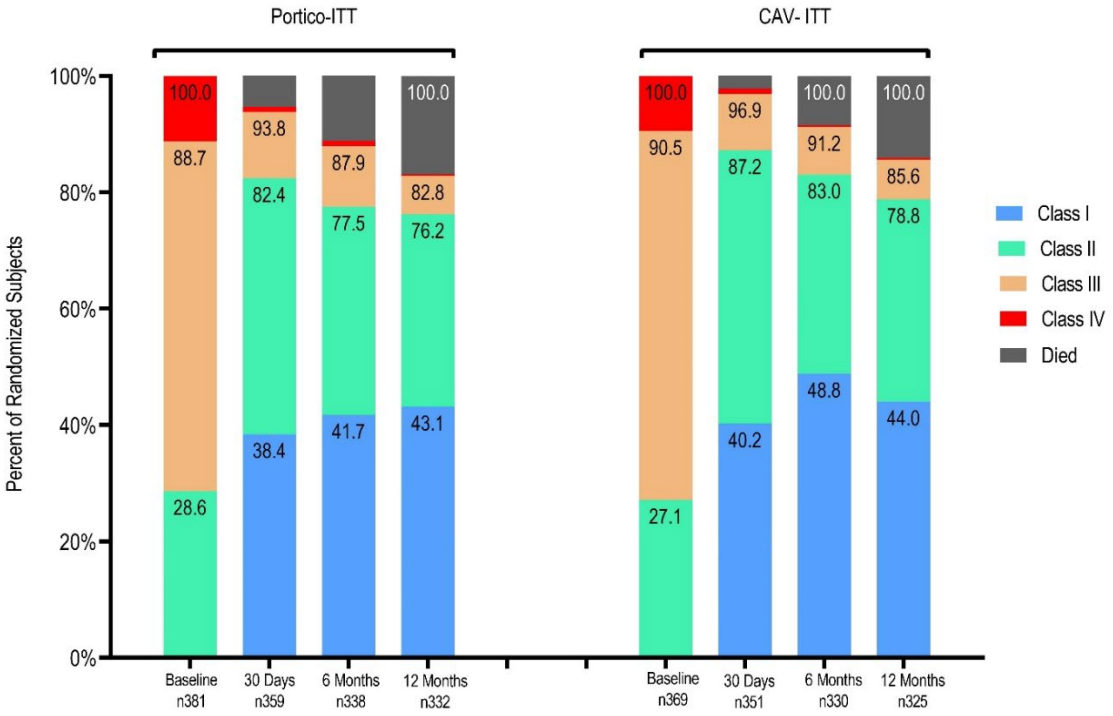
A total of 9 subjects (8 Portico, 1 CAV) required reintervention to treat moderate or greater paravalvular aortic regurgitation within 365 days post-index procedure; no subjects reported transvalvular aortic insufficiency. Of the 8 Portico subjects that required reintervention to treat aortic regurgitation, 7 underwent a TAV-in-TAV procedure with a commercially available valve and 1 was implanted with an Amplatzer Vascular Plug. The CAV subject that required reintervention to treat aortic regurgitation underwent a balloon aortic valvuloplasty procedure.

Table 21: Reintervention to Treat Aortic Regurgitation at 1 Year		
Characteristic	**Implanted Population**	
	Portico (N=371)	**CAV (N=361)**
Reintervention for Aortic Regurgitation	2.2% (8/371)	0.3% (1/361)

NYHA Functional Classification

Figure 9 presents NYHA functional class of patients at baseline through 1 year. The presentation of severe cardiac symptoms (NYHA class III or IV) was reduced from 71.4% at baseline to 8.4% at 1 year in Portico patients and from 72.9% at baseline to 8.3% at 1 year in CAV patients, which represents a similar improvement of clinically significant heart failure classification in both treatment groups.

Figure 9: New York Heart Association (NYHA) Functional Class Through 1 Year (ITT population)



Quality of Life

Table 22 summarizes self-reported quality of life over time as measured by KCCQ Overall Summary Score in the PORTICO RCT. KCCQ scores improved by approximately 20 points in both cohorts at 1 year.

Table 22: KCCQ Quality of Life Scores Through 1 Year (ITT population)		
Characteristic	**Portico valve (N=381)**	**CAV (N=369)**
KCCQ score at Baseline	54.99 ± 23.17 (375)	53.93 ± 23.71 (358)
KCCQ score at 30 days	69.59 ± 22.98 (335)	72.05 ± 22.22 (340)
KCCQ score at 6 months	73.49 ± 22.70 (297)	75.66 ± 21.16 (302)
KCCQ score at 1 year	75.43 ± 22.18 (274)	75.94 ± 20.48 (283)

5. Adverse Events

Table 23 presents VARC-2 defined endpoints in the PORTICO RCT at 30 days and 1 year.

Table 23: VARC-2 Clinical Events (ITT population)		
Outcomes	**Portico valve (N=381)**	**CAV (N=369)**
At 30 Days[1]		
All-cause mortality	13 (3.5%)	7 (1.9%)
Cardiovascular	12 (3.2%)	6 (1.6%)
Non-cardiovascular	1 (0.3%)	1 (0.3%)
All stroke	10 (2.7%)	9 (2.5%)
Disabling stroke	6 (1.6%)	4 (1.1%)
Non-disabling stroke	4 (1.1%)	5 (1.4%)
Transient ischemic attack	4 (1.1%)	1 (0.3%)
All Bleeding	40 (10.6%)	30 (8.2%)
Life threatening or disabling bleeding	22 (5.9%)	14 (3.8%)
Life threatening or disabling bleeding requiring transfusion	17 (4.5%)	13 (3.6%)
Major bleeding	19 (5.1%)	16 (4.4%)
Minor bleeding	33 (8.8%)	34 (9.3%)
Major vascular complications	36 (9.6%)	23 (6.3%)
Minor vascular complications	35 (9.3%)	32 (8.8%)
Acute kidney injury	22 (5.9%)	26 (7.1%)
Stage 1	10 (2.7%)	19 (5.2%)
Stage 2	5 (1.3%)	3 (0.8%)
Stage 3	7 (1.9%)	4 (1.1%)
Acute kidney injury requiring dialysis	4 (1.1%)	3 (0.8%)
Atrial fibrillation	15 (4.0%)	17 (4.7%)
New permanent pacemaker[3]	88 (27.7%)	35 (11.6%)
Valve intervention due to prosthetic valve thrombosis[4]	0 (0%)	0 (0%)
Valve intervention due to endocarditis[4]	0 (0%)	0 (0%)

At 1 Year[2]		
All-cause mortality	53 (14.3%)	43 (12.0%)
Cardiovascular	32 (8.8%)	28 (8.0%)
Non-cardiovascular	21 (6.0%)	15 (4.4%)
All stroke	16 (4.5%)	19 (5.4%)
Disabling stroke	6 (1.6%)	10 (2.9%)
Non-disabling stroke	10 (2.9%)	10 (2.9%)
Transient ischemic attack	7 (2.0%)	6 (1.8%)
Atrial fibrillation	27 (7.5%)	25 (7.0%)
New permanent pacemaker[3]	98 (31.1%)	41 (13.7%)
Myocardial infarction[4]	7 (1.8%)	6 (1.6%)
Endocarditis[4]	1 (0.3%)	1 (0.3%)
Valve intervention due to prosthetic valve thrombosis[4]	0 (0%)	0 (0%)
Valve intervention due to endocarditis[4]	0 (0%)	0 (0%)

Data are presented as n (binomial proportion %) at 30 days and as n (Kaplan-Meier probability %) at 1 year
[1] The numerator for the 30-day rate is the number of patients who experienced an event by 30 days post randomization. The denominator for each event type is the number of patients excluding patients that have withdrawn (e.g. due to subject preference or lost to follow-up) before 30 days without an event.
[2] Kaplan-Meier method was used to estimate the event rate at 1 year
[3] New pacemaker implant events were CEC adjudicated through 30 days and site reported at 1 year.
[4] Site reported, data not adjudicated by CEC. Data are presented as n (binomial proportion %).
NOTE: Event rates are from day of randomization for ITT analysis Population.

6. Other Results

Procedural Outcomes and Implant Characteristics

Table 24 shows the procedural outcomes and implant characteristics of the 737 PORTICO RCT patients that attended the index procedure (As-Treated population).

Table 24: Procedural Outcomes and Implant Characteristics (AT population)		
Outcome	**Portico valve (N=375)**	**CAV (N=362)**
Procedural outcomes (final disposition)		
Procedural success[1]	359 (95.7%)	356 (98.3%)
Procedural mortality	2 (0.5%)	0 (0%)
Conversion to open heart surgery	1 (0.3%)	1 (0.3%)
Need for second valve (TAV-in-TAV)	10 (2.7%)	5 (1.4%)
Unable to implant assigned valve type	2 (0.5%)	0 (0%)
Unable to gain vascular access, no TAVI implant	1 (0.3%)	0 (0%)
Implant characteristics		
Conscious sedation anesthesia	112 (29.9%)	116 (32.0%)
Implantation time[2], min	13.3 (13.8)	6.8 (13.7)
Pre-balloon valvuloplasty[3]	322/373 (86.3%)	200/361 (55.4%)

Resheathing performed	144 (38.4%)	NR
Post-implantation balloon valvuloplasty	186 (49.6%)	74 (20.4%)
Final TAVI Access route		
Transfemoral	347/371 (93.5%)	343/361 (95.0%)
Subclavian/Axillary	8/371 (2.2%)	5/361 (1.4%)
Transaortic	16/371 (4.3%)	12/361 (3.3%)
Transapical	0/371 (0%)	1/361 (0.3%)
Implanted prosthesis size[4]		
20 mm	..	7/361 (1.9%)
23 mm	14/371 (3.8%)	97/361 (26.9%)
25 mm	77/371 (20.8%)	..
26 mm	..	151/361 (41.8%)
27 mm	135/371 (36.4%)	..
29 mm	145/371 (39.1%)	87/361 (24.1%)
31 mm	..	7/361 (1.9%)
34 mm	..	12/361 (3.3%)

Data presented as n/N (%) or mean (SD)

[1] Procedural success is defined as: absence of procedural mortality and successful delivery of a single TAVI valve placed in the desired location

[2] Total implant time: Implant Start Time is defined as delivery system from first attempted valve inserted into the body; Implant End Time is defined as the time of last attempted valve fully deployed

[3] Denominator is number of patients with implant attempted

[4] Device size based on last implanted (functioning) valve; note that some device sizes are not available across all valve brands

Computed Tomography (CT) Sub-study

A subset of RCT patients were enrolled in a CT sub-study to investigate the prevalence of Hypoattenuated Leaflet Thickening (HALT) and reduced leaflet motion (RLM). Per protocol, a minimum of 200 consecutive RCT patients implanted with either a Portico valve or CAV with an adequate multi-slice 4D CT scan (or TEE, if the CT scan is medically or technically contraindicated) for leaflet mobility assessment at both 30 days and 6 months were required. The sub-study's primary outcome measure was the prevalence of RLM in all sub-study patients, defined as moderate or severely reduced motion or immobility of at least one valve leaflet.

There were 313 randomized patients (165 Portico valve and 148 CAV) with an interpretable 30-day CT/TEE, and 202 patients (111 Portico valve and 91 CAV) with a corresponding interpretable 6-month CT/TEE. Presence of HALT and RLM imaging findings are summarized in **Table 25** along with the associated mean aortic pressure gradients.

Table 25: Leaflet Mobility Findings and Mean Gradients

Findings	At 30 Days		At 6 Months	
	Portico valve (N=165)	CAV (N=148)	Portico valve (N=111)	CAV (N=91)
Oral Anticoagulant Use				

Proportion of patients on oral anticoagulants (OAC)* at the time of scan	13.3% (22/165)	12.8% (19/148)	9.9% (11/111)	19.8% (18/91)
HALT[1]				
Any Leaflets with Thickening (yes)	34.5% (57/165)	15.5% (23/148)	38.7% (43/11)	18.7% (17/91)
Mean Gradient (mmHg)	8.2 ± 2.5 (57)	12.9 ± 6.0 (23)	8.3 ± 3.9 (43)	11.0 ± 5.1 (17)
0 leaflet[2]	65.5% (108/165)	84.5% (125/148)	61.3% (68/111)	81.3% (74/91)
Mean Gradient (mmHg)	8.2 ± 3.5 (107)	9.7 ± 3.8 (124)	7.7 ± 3.2 (67)	9.9 ± 3.6 (73)
1 leaflet	27.3% (45/165)	10.1% (15/148)	27.0% (30/111)	9.9% (9/91)
Mean Gradient (mmHg)	8.0 ± 2.4 (45)	12.5 ± 6.1 (15)	8.3 ± 4.4 (30)	12.5 ± 6.2 (9)
2 leaflets	6.1% (10/165)	5.4% (8/148)	9.9% (11/111)	6.6% (6/91)
Mean gradient (mmHg)	9.5 ± 2.9 (10)	13.8 ± 6.2 (8)	8.3 ± 2.7 (11)	9.4 ± 3.5 (6)
3 leaflets	1.2% (2/165)	0%	1.8% (2/111)	2.2% (2/91)
Mean Gradient (mmHg)	6.2 ± 0.7 (2)	NA	8.5 ± 0.1 (2)	8.5 ± 1.9 (2)
Number of Leaflets with Reduced Motion (moderate or severe reduction in excursion, or immobile)				
0 leaflet[2]	74.5% (123/165)	93.2% (138/148)	79.3% (88/111)	89.0% (81/91)
1 leaflet	21.2% (35/165)	4.7% (7/148)	19.8% (22/111)	7.7% (7/91)
2 leaflets	4.2% (7/165)	2.0% (3/148)	0.9% (1/111)	3.3% (3/91)
3 leaflets	0% (0/165)	0% (0/148)	0% (0/111)	0% (0/91)
Degree of Leaflet Motion (5 categories)[3]				
Mobile- all leaflets	63.6% (105/165)	83.8% (124/148)	62.2% (69/111)	80.2% (73/91)
Mean Gradient (mmHg)	8.2 ± 3.5 (104)	9.7 ± 3.8 (123)	7.5 ± 3.0 (68)	9.9 ± 3.6 (72)
Mildly reduced in ≥1leaflet	10.9% (18/165)	9.5% (14/148)	17.1% (19/111)	8.8% (8/91)
Mean Gradient (mmHg)	8.6 ± 2.6 (18)	10.5 ± 4.9 (14)	7.6 ± 3.5 (19)	10.5 ± 4.8 (8)
Moderately reduced in ≥1leaflet	8.5% (14/165)	4.7% (7/148)	11.7% (13/111)	4.4% (4/91)
Mean Gradient (mmHg)	7.4 ± 1.9 (14)	15.2 ± 6.6 (7)	10.2 ± 5.2 (13)	9.6 ± 3.6 (4)
Severely reduced in ≥1leaflet	9.1% (15/165)	0.7% (1/148)	3.6% (4/111)	3.3% (3/91)
Mean Gradient (mmHg)	8.4 ± 2.7 (15)	21.4 (1)	8.9 ± 2.2 (4)	10.7 ± 4.3 (3)
Immobile in ≥1 leaflet	7.9% (13/165)	1.4% (2/148)	5.4% (6/111)	3.3% (3/91)
Mean Gradient (mmHg)	8.5 ± 2.8 (13)	16.7 ± 3.8 (2)	7.7 ± 3.8 (6)	14.5 ± 8.3 (3)

The analysis population included all patients enrolled in the CT sub-study that had an adequate CT for assessment of leaflet thickening or RLM 30 days.

* OACs include warfarin/coumadin, Heparin, or Enoxaparin/Levenox/Clexane, with or without anti-platelet therapy

[1] HALT is a dichotomous measure (Yes vs No), with the presence of any hypo-attenuation in a leaflet defined as HALT (yes).

[2] At 30 days, 11 patients had an adequate CT for assessment of 2 leaflets only. Both leaflets had no evidence of RLM, therefore these patients are included in the "no leaflet thickening" and "no RLM" category at 30 days

[3] Reduced Leaflet Motion Severity: Mildly reduced is <50% reduction in leaflet opening, Moderately reduced is 50-70% reduction in leaflet opening, Severely reduced is >70% reduction in leaflet opening; For patients with 2 leaflets with motion abnormalities, the degree of leaflet motion assigned is based on the most conservative reduced leaflet excursion assignment

Table 26 and **Table 27** present mean aortic gradient at 6 months for Portico valve and CAV patients by leaflet thickening and leaflet mobility status at 30 days follow-up, respectively.

Table 26: Mean Aortic Gradient at 6 Months Stratified by Any Leaflet Thickening at 30 Days

Findings	Summary Statistics			
	No Leaflet Thickening at 30 Days		Any Leaflet Thickening at 30 Days	
	Portico valve (N=108)	CAV (N=125)	Portico valve (N=57)	CAV (N=23)
Mean Gradient (mmHg) at 6 months	8.1 ± 3.8 (91)	9.8 ± 3.9 (108)	7.2 ± 2.4 (51)	10.2 ± 4.2 (23)

Data presented as mean ± SD (n patients).

The analysis population included all patients enrolled in the CT sub-study that had an adequate CT for assessment of presence of leaflet thickening or RLM at 30 days.

Note: At 30 days, 11 patients had an adequate CT for assessment of 2 leaflets only. Both leaflets had no evidence of RLM, therefore these patients are included in the "no leaflet thickening" category at 30 days

Table 27: Mean Aortic Gradient at 6 Months Stratified by Leaflet Mobility at 30 Days

Findings	Summary Statistics			
	No RLM at 30 Days		RLM at 30 Days	
	Portico valve (N=123)	CAV (N=138)	Portico valve (N=42)	CAV (N=10)
Mean Gradient (mmHg) at 6 months	8.0 ± 3.7 (105)	9.8 ± 4.0 (121)	7.1 ± 2.2 (37)	10.7 ± 3.5 (10)

Data presented as mean ± SD (n patients).

The analysis population included all patients enrolled in the CT sub-study that had an adequate CT for assessment of RLM at 30 days.

Note: At 30 days, 11 patients had an adequate CT for assessment of 2 leaflets only. Both leaflets had no evidence of RLM, therefore these patients are included in the "no leaflet thickening" and "no RLM" category at 30 days

Table 28 and **Table 29** summarize the rate of all-cause mortality, all stroke and transient ischemic attack (TIA) at 6 months from index procedure for Portico valve and CAV patients stratified by any leaflet thickening and leaflet mobility at 30 days follow-up, respectively.

Table 28: All-Cause Mortality, Stroke and TIA at 6 Months by Leaflet Thickening Status at 30 Days				
Outcomes at 6 Months	**Kaplan-Meier Rate**			
	No Leaflet Thickening at 30 Days		**Any Leaflet Thickening at 30 Days**	
	Portico valve (N=108)	**CAV (N=125)**	**Portico valve (N=57)**	**CAV (N=23)**
All-cause mortality	5.6% (6)	4.8% (6)	5.3% (3)	0.0% (0)
All stroke	1.9% (2)	3.2% (4)	1.8% (1)	4.3% (1)
TIA	1.9% (2)	0.8% (1)	1.8% (1)	4.3% (1)
Composite of mortality, stroke and TIA	8.4% (9)	7.3% (9)	8.8% (5)	4.3% (1)
Adverse events adjudicated by an independent Clinical Events Committee				

Table 29: All-Cause Mortality, Stroke and TIA at 6 Months by Leaflet Mobility Status at 30 Days				
Outcomes at 6 Months	**Kaplan-Meier Rate**			
	No RLM at 30 Days		**RLM at 30 Days**	
	Portico valve (N=123)	**CAV (N=138)**	**Portico valve (N=42)**	**CAV (N=10)**
All-cause mortality	5.7% (7)	4.4% (6)	4.8% (2)	0.0% (0)
All stroke	2.5% (3)	3.6% (5)	0.0% (0)	0.0% (0)
TIA	1.7% (2)	1.5% (2)	2.4% (1)	0.0% (0)
Composite of mortality, stroke and TIA	9.0% (11)	7.3% (10)	7.1% (3)	0.0% (0)
Adverse events adjudicated by an independent Clinical Events Committee				

The CT sub-study demonstrated that 34.5% and 38.7% of subjects receiving a Portico valve exhibited some degree of leaflet thickening at 30 days and 6 months, respectively, as compared to 15.5% and 18.7% of CAV subjects. In addition, 25.5% and 20.7% of Portico subjects experienced some degree of reduced leaflet mobility at 30-days and 6 months, respectively, as compared to 6.8% and 11.0% of CAV subjects. Regardless, mean aortic valve pressure gradients were clinically comparable in Portico valve and CAV subjects, independent of RLM and leaflet thickening. In addition, the data did not suggest that the presence of RLM or thickening result in worse mortality or neurological safety outcomes in Portico valve subjects. However, the CT sub-study was not designed to assess the severity of HALT, powered to compare the relative incidence of RLM between the treatment cohorts, or determine whether late clinical outcomes were affected by the presence of HALT or reduced leaflet mobility.

7. Subgroup Analyses

The protocol pre-specified subgroup analyses of the primary safety and effectiveness endpoints based on gender (male vs. female), surgical risk status (high vs. extreme risk) and access route (transfemoral vs. alternative). As shown in **Table 30** – **Table 32**, predefined subgroup analyses revealed no significant treatment by subgroup interaction effect on the primary safety and effectiveness endpoints.

Table 30: Analyses of Primary Safety and Effectiveness Endpoints by Gender (ITT population)				
Subgroup / Outcomes	**Primary Safety Endpoint (30 Days)**		**Primary Effectiveness Endpoint (1 Year)**	
	Portico valve (N=381)	**CAV (N=369)**	**Portico valve (N=381)**	**CAV (N=369)**
Male				
KM Estimate (SE) of Event Rate (%)	12.1% (2.4%) (N=183)	5.9% (1.8%) (N=172)	16.1% (2.7%) (N=183)	14.4% (2.7%) (N=172)
Female				
KM Estimate (SE) of Event Rate (%)	15.4% (2.6%) (N=198)	12.9% (2.4%) (N=197)	13.6% (2.5%) (N=198)	12.5% (2.4%) (N=197)
Treatment*Gender interaction p-value (Cox model)	0.248		0.995	
Note: Endpoint is measured from day of randomization for ITT				

Table 31: Analyses of Primary Safety and Effectiveness Endpoints by Surgical Risk (ITT population)				
Subgroup / Outcomes	**Primary Safety Endpoint (30 Days)**		**Primary Effectiveness Endpoint (1 Year)**	
	Portico valve (N=381)	**CAV (N=369)**	**Portico valve (N=381)**	**CAV (N=369)**
High Risk				
KM Estimate (SE) of Event Rate (%)	13.6% (2.0%) (N=311)	8.9% (1.6%) (N=306)	12.2% (1.9%) (N=311)	11.8% (1.9%) (N=306)
Extreme Risk				
KM Estimate (SE) of Event Rate (%)	14.6% (4.3%) (N=70)	12.9% (4.2%) (N=63)	27.2% (5.5%) (N=70)	21.0% (5.2%) (N=63)
Treatment*Risk interaction p-value (Cox model)	0.5401		0.5259	
Note: Endpoint is measured from day of randomization for ITT				

Table 32: Analyses of Primary Safety and Effectiveness Endpoints by Access Site (As-Treated population)				
Subgroup / Outcomes	**Primary Safety Endpoint (30 Days)**		**Primary Effectiveness Endpoint (1 Year)**	
	Portico valve (N=375)	**CAV (N=362)**	**Portico valve (N=375)**	**CAV (N=362)**
Transfemoral Access				
KM Estimate (SE) of Event Rate (%)	13.7% (1.8%) (N=351)	9.0% (1.5%) (N = 343)	14.2% (1.9%) (N=351)	12.2% (1.8%) (N=343)
Alternative Access				
KM Estimate (SE) of Event Rate (%)	25.0% (8.8%) (N=24)	15.8% (8.4%) (N=19)	30.0% (9.5%) (N=24)	31.6% (10.7%) (N=19)
Treatment*Access interaction p-value (Cox model)	0.9078		0.5621	
Note: Endpoint is measured from day of procedure for AT				

8. Pediatric Extrapolation

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

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The clinical study included 103 primary investigators of which none were full-time or part-time employees of the sponsor and 9 had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 1
- Significant payment of other sorts: 7
- Proprietary interest in the product tested held by the investigator: 0
- Significant equity interest held by investigator in sponsor of covered study: 2

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

A. Description of Supplemental Clinical Cohorts

FlexNav PMA Analysis Cohort

The FlexNav PMA Analysis Cohort was a prospective study group consisting of a subset of subjects from the PORTICO FlexNav DS Study and the FlexNav EU CE Mark Study – prospective, multicenter, single-arm investigational studies designed to characterize the safety of the FlexNav Delivery System in high or extreme surgical risk patients at 30 days after Portico valve implantation. Patients in the FlexNav PMA Analysis cohort were enrolled between November 7, 2018 and June 14, 2019 at 23 investigational sites in the United States, Australia, Italy, Demark, United Kingdom and Switzerland. The primary analyses of the FlexNav PMA Analysis cohort include 100 patients that underwent a Portico valve implant attempt with a FlexNav DS (FlexNav IDE Analysis cohort=81 and FlexNav EU CE Mark Study=19).

The primary safety endpoint was VARC-2 defined major vascular complication rate at 30 days post-index procedure. The primary safety endpoint rate at 30 days was descriptively compared with results of the PORTICO RCT AT population. Descriptive endpoints included a selection of endpoints from the PORTICO RCT that were assessed post index procedure and summarized using descriptive statistics.

Global FlexNav Cohort

The Global FlexNav Cohort was a retrospective, multicenter, single-arm analysis group that included patients at high or greater surgical risk undergoing an attempted Portico valve implant with the FlexNav Delivery System. Patients were enrolled between October 15, 2018 and February 10, 2020 in the Global FlexNav Cohort at 28 investigational sites in the United States, Australia, Italy, Denmark, United Kingdom and Switzerland. The Global FlexNav Cohort included 193 patients, comprised of 147 patients enrolled in the prospective, multicenter PORTICO IDE FlexNav DS Study arm and 46 patients enrolled in the prospective, multi-center FlexNav EU CE Mark Study.

The endpoints for the Global FlexNav Cohort were not prespecified; however, the Global FlexNav Cohort was assessed for key 30-day and 1-year endpoints of the PORTICO IDE study, with the date of the index procedure considered Day 0. Data from this cohort that contributed to the PMA approval decision are listed below:

- All-cause mortality at 30 days and 1 year from the index procedure
- Permanent pacemaker insertion at 30 days and 1 year from the index procedure
- Paravalvular Leak (PVL) at 30 days and 1 year

1. Clinical Inclusion and Exclusion Criteria of FlexNav Cohorts

   Patient selection criteria, assessments, key data collection, and adjudication were consistent across the PORTICO IDE FlexNav DS Study and the FlexNav EU CE Mark study to facilitate aggregate presentation of the FlexNav DS data.

Enrollment for both FlexNav PMA Analysis Cohort and FlexNav Global Cohort followed the same inclusion and exclusion criteria as described in Section X.A, with the following additional exclusion criteria for transaortic and subclavian/axillary access using the FlexNav Delivery System:

Transaortic access

- Subject has a distance between the annular plane and the aortic access site <7 cm (2.8")
- Subject has a distance between the annular plane and the separate introducer sheath distal tip <6 cm (2.4")

Subclavian/axillary access

- Subject's access vessel (subclavian/axillary) has a distance between the annular plane and the integrated sheath distal tip <17 cm (6.7")
- Subject's access vessel requires the delivery system to be advanced through a separate introducer sheath

2. Follow-up Schedule of FlexNav Cohorts

For both FlexNav cohorts, follow-up began at the date of the index procedure. Patients returned for follow-up examinations according to the schedule described in Section X.A, with the following exceptions: (i) a 6-month visit was not required for FlexNav CAP patients, and (ii) FlexNav EU CE Mark Study patients contributing to the FlexNav PMA Analysis cohort and Global FlexNav Cohort were followed for 1 year.

B. Accountability of FlexNav Cohorts

Table 33 presents the disposition and follow-up visit compliance of patients in the FlexNav PMA Analysis Cohort up to 30 days after the index procedure and in the Global FlexNav Cohort up to 1 year after the index procedure.

Of the 100 FlexNav PMA Analysis Cohort patients, all were alive and available for follow-up at the 30-day visit. Of the 193 patients enrolled in the Global FlexNav Cohort, 99.0% (191/193) were alive and available for follow-up at the 30-day visit and 93.3% (180/193) were alive and available for follow-up at the 12-month visit.

Table 33: Overall Disposition and Compliance in FlexNav Cohorts							
Group	**Visit Interval**	**Completed Visits**	**Expected Visits[1]**	**Missed Visits**	**Study Exits**		**Follow-up Compliance %**
					Death	**Withdrawal[2]**	
FlexNav PMA Analysis Cohort	Baseline	100	100	0	N/A	N/A	100.0%
	Procedure	100	100	0	0	0	100.0%
	Discharge	100	100	0	0	0	100.0%
	30 Days	99	100	1	0	0	99.0%
Global FlexNav Cohort	Baseline	193	193	0	N/A	N/A	100.0%
	Procedure	193	193	0	0	0	100.0%
	Discharge	193	193	0	0	0	100.0%
	30 Days	189	191	2	2	0	99.0%
	12 Months	179	180	1	8	3	99.4%

[1] Expected = Completed + Missed
[2] Withdrawals include Lost to Follow-up.

C. Demographics and Baseline Parameters of FlexNav Cohorts

The baseline demographics of patients enrolled in FlexNav PMA Analysis cohort and Global FlexNav Cohort are overall similar to those of the PORTICO RCT population, with a few differences. FlexNav DS cohorts exhibited lower frequency of NYHA Class IV, STS score ≥ 8%, and certain comorbidities in patients compared to PORTICO RCT cohorts. A sub-set of patient demographics highlighting key parameters, as well as similarities and differences from RCT, are presented in Table 34.

Table 34: Study Population Demographics and Baseline Parameters				
Characteristic	**PORTICO RCT (As-Treated)**		**FlexNav PMA Analysis Cohort (N=100)**	**Global FlexNav Cohort (N=193)**
	Portico valve (N=375)	**CAV (N=362)**		
Demographics				
Age, mean (SD), y	82.96 (7.6)	83.58 (7.02)	85.2 (5.7)	84.8 (5.7)
Female	193 (51.5%)	193 (53.3%)	60 (60.0%)	115 (59.6%)
NYHA II	108 (28.8%)	98 (27.1%)	35 (35.0%)	77 (39.9%)
NYHA III	225 (60.0%)	230 (63.5%)	61 (61.0%)	109 (56.5%)
NYHA IV	42 (11.2%)	34 (9.4%)	4 (4.0%)	7 (3.6%)
STS PROM Score[1], %, Mean (SD)	6.3 (3.4)	6.6 (3.4)	5.0 (2.4)	5.2 (2.8)
STS <4%	102 (27.2%)	87 (24.0%)	42 (42.0%)	84 (43.5%)
STS ≥8%	93 (24.8%)	103 (28.5%)	12 (12.0%)	31 (16.1%)
EuroSCORE II, %	6.6 (7.2)	6.7 (5.9)	4.8 (3.1)	4.6 (3.5)
Extreme risk	69 (18.4%)	61 (16.9%)	20 (20.0%)	41(21.2%)
High risk	306 (81.6%)	301 (83.1%)	80 (80.0%)	152 (78.8%)
Comorbidities				
Kidney disease	94 (25.1%)	93 (25.7%)	21 (21.0%)	37 (19.2%)

Table 34: Study Population Demographics and Baseline Parameters				
Characteristic	**PORTICO RCT (As-Treated)**		**FlexNav PMA Analysis Cohort (N=100)**	**Global FlexNav Cohort (N=193)**
	Portico valve (N=375)	**CAV (N=362)**		
Atrial fibrillation	122 (32.5%)	140 (38.7%)	29 (29.0%)	57 (29.5%)
Permanent pacemaker	55 (14.7%)	60 (16.6%)	11 (11.0%)	18 (9.3%)
Prior stroke	28 (7.5%)	49 (13.5%)	11 (11.0%)	15 (7.8%)
Coronary artery disease	261 (69.6%)	250 (69.1%)	60 (60.0%)	114 (59.1%)
Prior coronary stenting	106 (28.3%)	103 (28.5%)	25 (25.0%)	44 (22.8%)
Prior bypass graft surgery	86 (22.9%)	75 (20.7%)	14 (14.0%)	27 (14.0%)
Prior myocardial infarction	54 (14.4%)	40 (11.0%)	10 (10.0%)	20 (10.4%)
Peripheral vascular disease	18.7% (70/375)	18.0% (65/362)	14 (14.0%)	24 (12.4%)
Chronic lung disease	156 (41.6%)	144 (39.8%)	27 (27.0%)	52 (26.9%)
Porcelain aorta	11 (2.9%)	10 (2.8%)	0 (0%)	1 (0.5%)
Severe liver disease	4 (1.1%)	3 (0.8%)	0 (0%)	0 (0%)
Pulmonary hypertension	128 (34.1%)	124 (34.3%)	40 (40.0%)	60 (31.1%)
Total frailty score (out of 4), mean (SD)	1.8 (0.9)	1.9 (0.8)	1.7 (0.7)	1.7 (0.7)
Echocardiographic parameters[2]				
Aortic valve area, mean (SD), cm^2	0.69 (0.18)	0.67 (0.16)	0.68 (0.18)	0.69 (0.17)
Mean gradient, mean (SD), mmHg	46.2 (11.2)	46.1 (11.8)	45.1 (13.3)	44.1 (12.0)

Data are presented as n (%), mean (SD), n/N (%) or mean (SD) (n).
[1] Patients screened after November 15, 2018 were evaluated using risk models developed using STS data from 2011 to 2014 and validated using 2014 to 2016 data.
[2] Site-reported echo data

Although the FlexNav cohorts used the same enrollment criteria as the PORTICO RCT, the baseline demographics suggest potential differences between the study cohorts, which represents a limitation when comparing between the FlexNav cohorts and PORTICO RCT groups. To mitigate confounding and reduce the uncertainty in the descriptive comparisons of the FlexNav cohorts, post hoc propensity analyses of the primary safety endpoint composite and components, as well as clinically significant paravalvular regurgitation, were conducted and considered in the PMA approval decision. Overall, the post hoc propensity analyses indicated that patient population stratification did not have a significant, consistent effect on estimating the differences of the endpoints between the Global FlexNav and RCT CAV cohorts, which supported assessment of the FlexNav cohort data being presented in **Section XI.D**.

D. Safety and Effectiveness Results of FlexNav Cohorts

1. Primary Endpoint

Table 35 reports the major vascular complications for FlexNav PMA Analysis Cohort and Global FlexNav Cohort compared to PORTICO RCT groups.

Portico valve implantation with the FlexNav DS showed an observed rate of 7.0 % for major vascular complications at 30 days. The observed rate was numerically lower than the Portico valve group in the PORTICO RCT (9.6%) and similar to the CAV group (6.6%), owing to a reduction in access-related major vascular complications.

The Global FlexNav Cohort demonstrated a 5.7% major vascular complication rate at 30 days. The observed rate was numerically improved from the rates observed in the FlexNav PMA Analysis cohort (7.0%) and lower than the RCT CAV group (6.6%).

Table 35: Primary Endpoint – Major Vascular Complication (30 Days)

Primary Endpoint (pre-defined for PORTICO FlexNav DS Study arm)	**PORTICO RCT (As-Treated)**		**FlexNav PMA Analysis Cohort (N=100)**	**Global FlexNav Cohort (N=193)**
	Portico valve (N=375)	**CAV (N=362)**		
Major Vascular Complications	9.6% (36/375)	6.6% (24/362)	7.0% (7/100)	5.7% (11/193)
Access Site[a]	5.1% (19/375)	4.7% (17/362)	6.0% (6/100)	5.2% (10/193)
TAVI Delivery System Access Site	3.2% (12/375)	3.0% (11/362)	4.0% (4/100)	3.6% (7/193)
Non-TAVI Delivery System Access Site	1.9% (7/375)	1.7% (6/362)	2.0% (2/100)	1.6% (3/193)
Access-Related[b]	4.3% (16/375)	1.7% (6/362)	1.0% (1/100)	0.5% (1/193)
Multiple Events (1 Access Site and 1 Access-Related)	0.3% (1/375)	0.3% (1/362)	0.0% (0/100)	0.0% (0/193)

[a] Access site major vascular complication is defined as vascular injury at an arterial or venous access site used by a guidewire, vascular sheath or delivery catheter.
[b] Access-related major vascular complication is defined as vascular complication or injury that occurs along the arterial (usually) or venous pathway to the aortic root, or rupture of the aortic annulus or perforation of the left ventricle (LV).

Table 36 presents all-cause mortality at 30 days for Global FlexNav Cohort subjects that experienced a major vascular complication (n=11) and those that did not (n=182) compared to PORTICO RCT subjects, suggesting reduced rate and severity of major vascular complications with the FlexNav Delivery System.

Table 36: Impact of Major Vascular Complication on Mortality

All-Cause Mortality	**PORTICO RCT (As-Treated)**		**Global FlexNav Cohort (N=193)**
	Portico valve (N=375)	**CAV (N=362)**	
All Patients	4.5% (17/374)	1.4% (5/362)	1.0% (2/193)
With MVC at 30 days	19.4% (7/36)	8.3% (2/24)	9.1% (1/11)
No MVC at 30 days	2.9% (10/339)	0.9% (3/338)	0.5% (1/182)

2. PORTICO RCT Safety Endpoint – FlexNav Cohorts

Table 37 shows the primary safety composite results and the components (as defined for the PORTICO RCT) for FlexNav PMA Analysis Cohort and Global FlexNav Cohort compared to PORTICO RCT cohorts (AT population). Results for the composite

endpoint and individual components are consistent between the FlexNav PMA Analysis Cohort and Global FlexNav Cohort, which are comparable to the RCT CAV outcomes.

Table 37: Components of PORTICO RCT Primary Safety Endpoint (30 Days)

Primary Endpoint/Component	PORTICO RCT (As-Treated)		FlexNav PMA Analysis Cohort (N=100)[3]	Global FlexNav Cohort (N=193)[4]
	Portico valve (N=375)	CAV (N=362)		
Primary Safety Endpoint (30 days)				
Kaplan-Meier Estimate (SE) of Event Rate	14.4% (1.8%)	9.4% (1.5%)	8.0% (2.7%)	9.8% (2.1%)
Primary Safety Components (30 days)				
All-Cause Mortality[1] [95% Confidence interval][2]	4.5% (17/374) [2.7%, 7.2%]	1.4% (5/362) [0.45%, 3.2%]	0.0% (0/100) [0.0%, 3.6%]	1.0% (2/193) [0.13%, 3.7%]
Disabling Stroke[1] [95% Confidence interval][2]	1.6% (6/374) [0.59%, 3.5%]	0.8% (3/362) [0.17%, 2.4%]	0.0% (0/100) [0.0%, 3.6%]	2.1% (4/193) [0.57%, 5.2%]
Life Threatening Bleeding Requiring Blood Transfusion[1] [95% Confidence interval][2]	4.8% (18/374) [2.9%, 7.5%]	3.6% (13/362) [1.9%, 6.1%]	4.0% (4/100) [1.1%, 9.9%]	4.1% (8/193) [1.8%, 8.0%]
Acute Kidney Injury Requiring Dialysis[1] [95% Confidence interval][2]	1.1% (4/374) [0.29%, 2.7%]	0.8% (3/362) [0.17%, 2.4%]	0.0% (0/100) [0.0%, 3.6%]	0.0% (0/193) [0.0%, 1.9%]
Major Vascular Complications[1] [95% Confidence interval][2]	9.6% (36/374) [6.8%, 13.1%]	6.6% (24/362) [4.3%, 9.7%]	7.0% (7/100)[3] [2.9%, 13.9%]	5.7% (11/193)[3] [2.9%, 10.0%]

[1] The proportion of patients who experienced each event was calculated. The numerator for the 30-day rate is the number of patients who experienced an event by 30 days post index procedure. The denominator for each event type is the number of analysis patients excluding patients that have withdrawn before 30 days without an event.
[2] By Clopper-Pearson exact confidence interval.
[3] Of the 7 major vascular complications in the FlexNav PMA Analysis cohort, 6 (6.0%) occurred at an access site (4.0% TAVI and 2.0% non-TAVI access site), and 1 (1.0%) did not occur at an access site.
[4] Of the 11 major vascular complications in the Global FlexNav DS cohort, 10 (5.2%) occurred at an access site (3.6% TAVI 1.6% non-TAVI access site), and 1 (0.5%) did not occur at an access site.

3. PORTICO RCT Effectiveness Endpoint – Global FlexNav Cohort

Table 38 shows the primary 1-year effectiveness composite results and the components (as defined for the PORTICO RCT) for Global FlexNav Cohort. The rate of all-cause mortality at 1 year in the Global FlexNav Cohort was 4.7%, which is numerically lower than all-cause mortality occurring in RCT Portico group (14.7%) and RCT CAV group (11.8%).

Table 38: Components of PORTICO RCT Primary Effectiveness Endpoint (1 Year)			
Primary Endpoint/Component	**PORTICO RCT (As-Treated)**		**Global FlexNav Cohort (N=193)**
	Portico valve (N=375)	**CAV (N=362)**	
Primary Effectiveness Endpoint (1 Year)			
Kaplan-Meier Estimate (SE) of Event Rate[1]	15.2% (1.9%)	13.2% (1.8%)	5.7% (1.7%)
Primary Effectiveness Components (1 Year)			
All-Cause Mortality[1] [95% Confidence interval][2]	14.7% (1.8%) [11.43%, 18.71%]	11.8% (1.7%) [8.86%, 15.63%]	4.7% (1.5%) [2.47%, 8.84%]
Disabling Stroke[1] [95% Confidence interval][2]	1.6% (0.7%) [0.73%, 3.54%]	2.6% (0.9%) [1.36%, 4.94%]	2.1% (1.0%) [0.78%, 5.43%]
[1] Kaplan-Meier method was used to estimate the event rate (SE). [2] The 95% confidence interval was estimated using KM method with Greenwood standard error.			

4. Other Results

Technical device success using the FlexNav Delivery System was assessed in the Global FlexNav Cohort, which was defined as successful vascular access, delivery and deployment of the Portico valve; retrieval with the delivery system and correct positioning of a single valve in the proper anatomical location. The composite technical device success rate was 96.9%, as shown in **Table 39**.

Table 39: Technical Device Success in the Global FlexNav Cohort	
Component of Technical Success	**Global FlexNav Cohort (N=193)**
1. Successful vascular access, delivery and deployment of the Portico valve	100.0% (193/193)
2. Retrieval with the delivery system	100.0% (193/193)
3. Correct positioning of a single valve in the proper anatomical location	96.9% (187/193)
4. Technical device success	96.9% (187/193)

Table 40 presents the results for CEC adjudicated VARC-2 events at 30 days in the FlexNav PMA Analysis cohort. There were no deaths, disabling strokes, or acute kidney injury events requiring dialysis within 30 days.

Table 40: VARC-2 Clinical Events at 30 Days			
Outcomes	**PORTICO RCT (As-Treated)**		**FlexNav PMA Analysis cohort (N=100)**
	Portico valve (N=375)	**CAV (N=362)**	
All-cause mortality	17 (4.5%)	5 (1.4%)	0 (0%)
Cardiovascular	15 (4.0%)	4 (1.1%)	0 (0%)

Non-cardiovascular	2 (0.5%)	1 (0.3%)	0 (0%)
All stroke	11 (2.9%)	8 (2.2%)	3 (3.0%)
Disabling stroke	6 (1.6%)	3 (0.8%)	0 (0%)
Non-disabling stroke	5 (1.3%)	5 (1.4%)	3 (3.0%)
Transient ischemic attack	4 (1.1%)	1 (0.3%)	0 (0%)
All Bleeding	42 (11.2%)	30 (8.3%)	11 (11.0%)
Life threatening or disabling bleeding	24 (6.4%)	14 (3.9%)	4 (4.0%)
Life threatening or disabling bleeding requiring transfusion	18 (4.8%)	13 (3.6%)	4 (4.0%)
Major bleeding	20 (5.3%)	16 (4.4%)	7 (7.0%)
Minor bleeding	32 (8.5%)	33 (9.1%)	10 (10.0%)
Major vascular complications	36 (9.6%)	4 (6.6%)	7 (7.0%)
Minor vascular complications	35 (9.3%)	32 (8.8%)	10 (10.0%)
Acute kidney injury	21 (5.6%)	26 (7.2%)	1 (1.0%)
Stage 1	10 (2.7%)	19 (5.2%)	1 (1.0%)
Stage 2	4 (1.1%)	3 (0.8%)	0 (0%)
Stage 3	7 (1.9%)	4 (1.1%)	0 (0%)
Acute kidney injury requiring dialysis	4 (1.1%)	3 (0.8%)	0 (0%)
Atrial fibrillation	19 (5.1%)	19 (5.2%)	0 (0%)
New permanent pacemaker[2]	89/320 (27.8%)	35/302 (11.6%)	13/89 (14.6%)
Valve intervention due to prosthetic valve thrombosis[3]	0 (0%)	0 (0%)	0 (0%)
Valve intervention due to endocarditis[3]	0 (0%)	0 (0%)	0 (0%)

Data are presented as n (binomial proportion %) at 30 days
[1] The numerator for the 30-day rate is the number of patients who experienced an event by 30 days post procedure. The denominator for each event type is the number of patients excluding patients that have withdrawn (e.g. due to subject preference or lost to follow-up) before 30 days without an event.
[2]New pacemaker implant events were CEC adjudicated through 30 days and site reported at 1 year.
[3]Site reported, data not adjudicated by CEC.

Table 41 summarizes the paravalvular aortic regurgitation at 30 days and 1 year for the Global FlexNav Cohort and the PORTICO RCT patients with evaluable echocardiograms. The observed rate of clinically significant PVL (moderate or greater) in the Global FlexNav Cohort was 2.8% at 30 days and 0.6% at 1 year, with no subjects demonstrating severe PVL at either timepoint.

Table 41: Paravalvular Aortic Regurgitation Severity at 30 Days and 1 Year

PVL Severity	Paravalvular AR at 30 Days			Paravalvular AR at 1 Year		
	PORTICO RCT (Modified As-Treated)		Global FlexNav Cohort (N=178)	PORTICO RCT (Modified As-Treated)		Global FlexNav Cohort (N=160)
	Portico valve (N=329)	CAV (N=329)		Portico valve (N=262)	CAV (N=262)	
None/Trace	37.4% (123)	58.1% (191)	44.4% (79)	44.7% (117)	59.2% (155)	61.9% (99)

Mild	56.5% (186)	39.8% (131)	52.8% (94)	47.7% (125)	39.3% (103)	37.5% (60)
Moderate	5.8% (19)	2.1% (7)	2.8% (5)	7.3% (19)	1.5% (4)	0.6% (1)
Severe	0.3% (1)	0.0% (0)	0% (0)	0.4% (1)	0.0% (0)	0% (0)
Note: Results presented based on echocardiographic core laboratory assessment at 30 days and 1 year. AR = aortic regurgitation						

The rate of new permanent pacemaker implantation in the FlexNav PMA Analysis Cohort was 14.6% which was reduced from 28.1% in the PORTICO RCT and comparable to the RCT CAV observed rate of 11.6% (**Table 42**). New permanent pacemaker implantation rates in the Global FlexNav Cohort remained durable through 1-year follow-up, with 32 patients (18.4%) requiring new pacemaker implantation by 1 year.

Table 42: New Permanent Pacemaker Rates (30 Days)

New Permanent Pacemaker Implantation	PORTICO RCT (Modified As-Treated)		FlexNav Analysis Cohort (N=100)	Global FlexNav Cohort (N=175)
	Portico valve (N=366)	CAV (N=361)		
Naïve Subjects [a]	87 (28.1%)	35 (11.6%)	13 (14.6%)	27 (15.4%)
Subjects without pre-existing RBBB [b]	58 (21.9%)	25 (9.4%)	10 (12.5%)	15 (9.7%)

Data presented as: Number of Subjects (KM Event Rate, %)
[a] Subjects with a pre-existing pacemaker at baseline are excluded from the numerator and denominator
[b] Subjects with a pre-existing right bundle branch block (RBBB) and a pre-existing pacemaker at baseline are excluded from the numerator and dominator

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

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory Systems Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The primary effectiveness endpoint (composite of all-cause mortality or disabling stroke at 1 year) revealed event rates of 14.9% in the randomized Portico group and 13.4% in the randomized CAV group at 1 year for the predefined analysis population (ITT). The primary effectiveness endpoint event rates were within the predefined non-inferior margin of 8.0% for the ITT population as well as the AT population, indicating the study met its primary effectiveness endpoint. The rate of disabling stroke with the Portico valve at 1 year was 1.6%, which is typical for the given patient population and

was clinically comparable to the disabling stroke rate in the CAV group. Although all-cause mortality was observed to be numerically higher for the Portico group (14.4%) than the CAV (12.0%) at 1 year, the difference between mortality rates was predominantly due to deaths occurring within 30 days. Data collected using the FlexNav Delivery System had an observed rate of all-cause mortality at both 30-days and 1-year that more closely reflected observed rates of the RCT CAV population.

The secondary endpoint (hierarchical composite of severe aortic regurgitation and quality of life, and moderate or greater aortic regurgitation and 6-minute walk test) was not met for the PORTICO RCT due to exceeding the predefined non-inferiority margin for moderate or greater aortic regurgitation. The occurrence of moderate or greater aortic regurgitation was entirely attributed to paravalvular aortic regurgitation, with 1-year paravalvular regurgitation rates of 7.5% in the Portico group and 1.5% in the CAV group. However, this difference did not lead to a difference in mortality between the groups through 2 years. In addition, clinically significant paravalvular regurgitation with the Portico valve was markedly reduced when implanted with the FlexNav Delivery system, with a rate of 0.6% moderate or severe paravalvular regurgitation reported at 1 year in the Global FlexNav Cohort.

Analysis of functional endpoints demonstrated that the Portico valve was associated with numerically larger valve areas and lower mean gradients compared to CAV, as well as similar improvements from baseline to 1-year in NYHA functional classification and quality of life metrics compared to the CAV group. Moreover, the hemodynamic benefits and functional improvements observed for the Portico valve in the RCT were similarly observed in the supplemental FlexNav clinical cohorts.

Therefore, the PORTICO RCT demonstrated overall effectiveness of the Portico TAVI System and the supplemental FlexNav cohorts provided data that mitigated the concern of clinically significant aortic regurgitation.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and animal studies as well as data collected in clinical studies conducted to support PMA approval as described above. The results from the nonclinical laboratory studies performed on the Portico TAVI System (e.g., biocompatibility, hydrodynamic performance, durability, and structural integrity) demonstrated that this device is suitable for long-term implant.

The Kaplan-Meier estimate of the event rate of the primary safety endpoint (non-hierarchical composite of all-cause mortality, disabling stroke, life threatening bleeding requiring blood transfusion, acute kidney injury requiring dialysis or major vascular complications at 30 days) was 13.8% in the randomized Portico group and 9.6% in the randomized CAV group for the predefined primary analysis population (ITT). The Portico valve was found to be non-inferior to CAV in the ITT population, meeting a non-inferiority margin of 8.5%. The differences in the observed rate of individual components of the primary safety endpoint composite at 30 days for the RCT Portico group compared to the CAV group were as follows: all-cause mortality (1.6%),

disabling stroke (0.5%), life-threatening and major bleeding events (0.9%), acute kidney injury requiring dialysis (0.3%), or major vascular complications (3.3%).

Although non-inferiority was demonstrated in the ITT population, non-inferiority was not confirmed when the analysis was conducted using the AT population, resulting in an upper limit of the 95% confidence interval of the difference which exceeded the 8.5% non-inferiority margin. The discrepancy in the primary safety endpoint results between ITT and AT populations was largely due to a difference of six deaths between the AT population vs. the ITT population based on differences in the definitions of the 30-day follow-up windows for these populations. The RCT data further demonstrated that major vascular complications were more frequent with Portico valve implantation (9.6%) compared to CAV implantation (6.3%).

Evidence suggested that major vascular complications contributed to the higher all-cause mortality within 30 days in the RCT Portico group, which the applicant attributed, in part, to the first-generation Portico Delivery System that was used in the RCT. In response to this finding, the FlexNav Delivery System was introduced and safety outcomes were studied through supplemental FlexNav clinical cohorts. The supplemental data, which represent the final device design, demonstrated that the observed rate of major vascular complications at 30 days decreased from 9.6% in the randomized Portico group to 7.0% and 5.7% in the FlexNav PMA Analysis Cohort and Global FlexNav Cohort, respectively, which was clinically comparable to the rate observed in the CAV group of the RCT (6.3%). The rate of all-cause mortality in the Global FlexNav Cohort was 1.0%, which was clinically similar to the Kaplan-Meier rate of the CAV group of the RCT (1.4%; AT population).

The PORTICO RCT data revealed a 27.7% rate of new permanent pacemaker implantation within 30 days for the Portico group which was reduced to 15.4% in the Global FlexNav Cohort. While these rates for the Portico valve are relatively higher than 30-day new permanent pacemaker implantation rates for the CAV group of the RCT (11.6%), the incidence is not unreasonably high when considering other self-expanding valves.

The CT sub-study demonstrated that 34.5% and 38.7% of subjects receiving a Portico valve exhibited some degree of leaflet thickening at 30 days and 6 months, respectively, as compared to 15.5% and 18.7% of CAV subjects. In addition, 25.5% and 20.7% of Portico subjects experienced some degree of reduced leaflet mobility at 30-days and 6 months, respectively, as compared to 6.8% and 11.0% of CAV subjects. The long-term clinical sequelae of these imaging findings are presently unknown.

C. Benefit-Risk Determination

The probable benefits of the device are based on data collected in clinical studies conducted to support PMA approval, as described above. The probable benefits of the Portico Transcatheter Aortic Valve include improved valve hemodynamic performance, improved functional status as measured by NYHA classification and 6-minute walk test and improved quality of life at 1-year post-procedure (as measured by KCCQ).

The probable risks of the device are also based on data collected in clinical studies conducted to support PMA approval. The probable risks of the Portico Transcatheter Aortic Valve System include device and procedure-related complications including death, stroke, myocardial infarction, major vascular complications, life-threatening and major bleeding events, acute kidney injury, clinically significant paravalvular aortic regurgitation, and conduction disturbances requiring a new pacemaker.

1. Patient perspective

   This submission did not include specific information on patient perspectives for this device.

In conclusion, given the available information above, the data support that for patients with symptomatic severe native aortic stenosis who are at high or greater risk for open aortic valve replacement surgery, the probable benefits outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of the Portico Transcatheter Aortic Valve Implantation System with FlexNav Delivery System for the replacement of native aortic valves in patients with symptomatic severe native calcific aortic stenosis who are deemed to be at high or greater surgical risk, defined as predicted risk of surgical mortality ≥ 8% at 30 days based on the Society of Thoracic Surgeons (STS) risk score and other clinical comorbidities unmeasured by the STS risk calculator.

XIV. CDRH DECISION

CDRH issued an approval order on September 17, 2021. The final clinical conditions of approval cited in the approval order are described below.

The applicant must conduct one post-approval study as well as participate in and support continued surveillance as follows:

1. ***Continued Follow-Up of the* PORTICO IDE Study *Premarket Cohorts:*** This study should be conducted in accordance with protocol version L dated October 11, 2018. The study will consist of all living subjects who were enrolled in the PORTICO IDE randomized control trial (RCT) and FlexNav Delivery System (DS) Study, including randomized, FlexNav DS single-arm, roll-in, continued access, and nested registry cohorts. The objective of this PAS is to characterize the clinical outcomes annually through 5 years post-procedure. The safety and effectiveness endpoints include, but are not limited to: all-cause mortality, all-cause and disabling stroke, life-threatening and major bleeding events, stage 2 or 3 acute kidney injury, major vascular complications, paravalvular aortic regurgitation, myocardial infarction, re-operation for valve-related dysfunction, rehospitalization for valve-related symptoms or worsening congestive heart failure, new permanent pacemaker implantation, new-onset atrial fibrillation,

functional status as evaluated by New York Heart Association (NYHA), health status as evaluated by Kansas City Cardiomyopathy Questionnaire (KCCQ), and hemodynamic performance metrics by echocardiography.

2. ***Registry-Based Real-World Use Surveillance of the Portico Transcatheter Aortic Valve Implantation System for the "High Risk and above" Indication:*** The applicant has agreed to work with the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy (TVT) Registry to ensure that FDA surveillance occurs for the Portico Transcatheter Aortic Valve Implantation System used for the "high risk and above" indication over the next 2 years (enrollment period). The applicant has also agreed to link the data to Centers for Medicare and Medicaid Services (CMS) database for long-term surveillance of these patients through 5 years post implantation (follow-up period). This surveillance will monitor the following: (1) device success (intra-procedure); (2) all-cause mortality, all stroke, life-threatening/major bleeding, new requirement for dialysis, new pacemaker implant, peri-procedural myocardial infarction, and repeat procedure for valve-related dysfunction (surgical or interventional therapy) at 30 days and 12 months; (3) neurological (non-stroke), vascular complications, and quality of life (KCCQ) outcomes at 30 days and 12 months; and (4) all-cause mortality, all stroke, and repeat procedure for valve-related dysfunction (surgical or interventional therapy) annually at 2-5 year post implantation.

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

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.