SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name: Replacement Heart Valve

Device Trade Name: Trifecta™ Valve: aortic sizes 19, 21, 23, 25, 27, and 29mm

Applicant's Name and Address: St. Jude Medical
177 County Rd B East
St. Paul, MN 55117

Date of Panel Recommendation: none

Premarket Approval Application (PMA) Number: P100029

Date of Notice of Approval: April 20, 2011

Expedited: not applicable

II. INDICATIONS FOR USE

The Trifecta Valve is indicated as a replacement for a diseased, damaged, or malfunctioning native or prosthetic aortic heart valve.

III. CONTRAINDICATIONS

None known.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions are provided in the device labeling for the Trifecta Valve.

V. DEVICE DESCRIPTION

The Trifecta Valve is a tri-leaflet stented pericardial valve designed for supra-annular placement in the aortic position. The valve is fabricated using a polyester-covered titanium stent. The stent, excluding the sewing cuff, is next covered with porcine pericardial tissue. This covering provides protection from mechanical wear by allowing only tissue-to-tissue contact during valve function. A silicone insert within the polyester sewing cuff is slightly contoured to conform to the shape of the native annulus.

The valve leaflets are made from bovine pericardium. The porcine and bovine pericardium are preserved and cross-linked in glutaraldehyde. Glutaraldehyde, formaldehyde, and ethanol are used in the valve sterilization process. The Trifecta Valve is processed using Linx™ anticalcification technology.

Non-clinical testing has demonstrated that the Trifecta Valve is MR Conditional.

The Trifecta Valve is available for aortic annulus sizes 19mm, 21mm, 23mm, 25mm, 27mm and 29mm.

The Trifecta Valve is supplied sterile and non-pyrogenic.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

The alternative treatments to the Trifecta Valve include drug therapy or surgical treatments such as annuloplasty or valvuloplasty (with or without the use of implantable materials). If a patient requires replacement of their native or previously implanted prosthetic valve, the alternatives include other commercially available mechanical valves, homografts, or bioprosthetic valves. The choice of replacement valve depends on an assessment of patient factors which include age, preoperative condition, anatomy, and the patient's ability to tolerate long-term anticoagulant therapy. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyles.

VII. MARKETING HISTORY

Commercial distribution of the Trifecta Valve outside the U.S. began in 2010, and the valve is currently available in the following countries: Austria, Belgium, Bulgaria, Canada, Cyprus, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Latvia, Liechtenstein, Luxembourg, Malta, Netherlands, Portugal, Romania, Slovenia, Spain, Switzerland, Sweden, and the United Kingdom.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Adverse events potentially associated with the use of bioprosthetic heart valves (in alphabetical order) include:

- angina
- cardiac arrhythmias
- endocarditis
- heart failure
- hemolysis
- hemolytic anemia
- hemorrhage
- leak, transvalvular or perivalvular
- myocardial infarction
- nonstructural dysfunction (entrapment by pannus or suture, inappropriate sizing or positioning, or other)
- prosthesis regurgitation
- stroke
- structural deterioration (calcification, leaflet tear, perforation, or other)
- thromboembolism
- valve thrombosis

It is possible that these complications could lead to:

- reoperation
- explantation
- permanent disability
- death

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

IX. SUMMARIES OF PRECLINICAL STUDIES

A. Laboratory Studies

A.1 Biocompatibility

Based on the results of the biocompatibility testing performed, the materials used in the Trifecta Valve were determined to be biocompatible, non-mutagenic, and non-toxic.

Non-Biological Components

The non-biological components of the Trifecta Valve consist of polyester fabric (knitted and spun), polyester/PTFE surgical sutures, a titanium alloy stent, and a silicone ring within the sewing cuff. These materials have a long history of use in cardiovascular implantation devices.

Biocompatibility testing of the non-biological components including the polyester fabric, polyester /PTFE suture, and the titanium stent were performed in accordance with the requirements detailed in International Standards Organization 10993-1 and United States Food and Drug Administration General Program Memorandum G95-1. The tests performed, the test objective and test results are provided in Table 1. Carcinogenicity, chronic and reproductive toxicity testing were not conducted since the chemical residual profile of the valve did not indicate that these long-term chronic studies were necessary.

Table 1: Biocompatibility Tests and Results - Non-Biological Components

Test Performed	Objectives	Test Article	Results
Cytotoxicity (ISO MEM L929)	Evaluate cytotoxic effects of the test article on a mouse fibroblast monolayer.	Stent Stent Covering Suture Sewing cuff	**Passed** Non-cytotoxic
Sensitization (LLNA or ISO Maximization)	Evaluate the chemically processed stent to determine if it causes a sensitization reaction	Stent Stent Covering	**Passed** No evidence of sensitization
Intracutaneous Reactivity (ISO Rabbit Intracutaneous Reactivity)	Evaluation of local dermal irritation or toxic effects of leachables extracted from the test article following intra-cutaneous injection in rabbits (ISO, USP) and mice (USP).	Stent Stent Covering	**Passed** Non-irritant
Acute Systemic Toxicity (ISO Mouse Systemic Injection)	Evaluation of acute systemic toxicity of leachables extracted from the test article following a single intravenous or intraperitoneal injection in mice or guinea pigs.	Stent Stent Covering	**Passed** Non=toxic
Pyrogen Test (USP Rabbit Pyrogen)	Determine if a febrile response occurs in New Zealand white rabbits either from a material mediated reaction or as a result of endotoxin or other possible pyrogens that may be present.	Stent	**Passed** Non-pyrogenic
Hemocompatibility (ASTM Direct Contact and NIH Direct Contact)	Determine if leachables extracted from the test article will cause a significant level of hemolysis in blood.	Stent Stent Covering Suture Sewing cuff	**Passed** Non-hemolytic
Genotoxicity (Ames)	Evaluation of the potential of the titanium stent to induce reverse mutations in four strains of Salmonella and one strain of Escherichia coli in the presence and absence of exogenous mammalian metabolic activation system (S9).	Stent	**Passed** Non-mutagenic
Implantation (ISO Rabbit Subcutaneous and Intramuscular)	Evaluation of a test article to local pathological effects on living tissue in rabbit (macro and histopathological examinations of implant tissue/muscle sites).	Stent Stent Covering	**Passed** Non-irritant

Biological Components

Glutaraldehyde-fixed porcine and bovine pericardial tissue is well established for use in bioprosthetic devices and each has a long history of safe usage in clinical applications. The tissues incorporated in the Trifecta Valve are liquid chemically processed in a similar fashion to other commercially available tissue valves incorporating animal tissues.

A thorough assessment of potential leachables from the Trifecta valves has been performed which includes a study of extractable residuals during rinsing. The results of the biocompatibility testing performed confirm that the extractable chemical residues from the Trifecta valves are similar in type and concentration as compared to a clinically approved (U.S.) control valve.

Valve Accessories and Packaging Components

The non-implantable valve accessories and packaging components (valve holders, valve sizer sets, jar, lid, and lid liner) were subjected to a number of biocompatibility tests as appropriate for these components. All results were found to be acceptable.

A.2 Hydrodynamic Performance

Hydrodynamic performance studies were completed on the Trifecta Valve in accordance with the *ISO 5840, Cardiovascular Implants-Cardiac Valve Prosthesis* (1996). Testing included steady flow pressure drop, steady backflow leakage, pulsatile flow pressure drop, pulsatile flow regurgitation, flow visualization, and verification of the Bernoulli relationship. Commercially available bioprosthetic heart valves were used as controls. Test results are summarized in Table 2.

Table 2: Hydrodynamic Performance Summary

Test Type	Sample Size	Control Size	Results
Steady Flow Pressure Drop	5 each size	1 valve, sizes 19, 25, and 29mm	Steady flow pressure drop is directly correlated to and consistent with pulsatile flow pressure drop results.
Steady Back Flow Leakage	5 each size	1 valve, sizes 19, 25, and 29mm	Valve closes completely and maintains complete coaptation under a back pressure of 200mmHg.
Pulsatile Flow Pressure Drop	5 each size	1 valve, sizes 19, 25, and 29mm	Meets the requirements in ISO 5840/FDIS: 5840 2005 (E), Cardiovascular Implants-Cardiac valve prosthesis.
Pulsatile Flow Regurgitation	5 each size	1 valve, sizes 19, 25, and 29mm	Valve maintains complete coaptation and meets requirements in ISO/FDIS: 5840 2005 (E), Cardiovascular implants-Cardiac valve prostheses
Flow Visualization	1 vale, size 19mm	NA	Results indicate the valve opens efficiently and symmetrically. The flow field produced by the Trifecta Valve is a centralized flow field and is evenly distributed over a wide region.
Bernoulli Relationship	1 each, sizes 19, 25 and 29mm	NA	The Bernoulli equation accurately projects true pressure gradient for the valve.

A.3 Structural Performance

Structural performance studies on the Trifecta Valve were conducted in accordance with the *ISO 5840, Cardiovascular Implants – Cardiac Valve Prosthesis (1996).* Testing included accelerated wear, dynamic failure mode, fatigue, stent creep, and sewing cuff integrity. The structural performance testing summary is provided in Table 3. The valve passed all of the tests performed. Commercially available bioprosthetic heart valves were used as controls.

Table 3: Structural Performance Summary

Test Type	Sample Size	Control Size	Results
Accelerated Wear	5 each, sizes 19, 25, and 29mm	1 valve, sizes 19, 25, and 29mm	Trifecta valves maintained their performance and did not demonstrate significant wear out to 200 million cycles. One valve showed a slight change in coaptation line, however the valve continued to function normally throughout duration of test.
Dynamic Failure Mode	6 valves, 19mm 5 each, sizes 21, 23, 25,27, and 29mm	1 valve, size 19mm 2 valves, size 21mm 3 valves size 25mm 1 valve, size 19mm 2 valves, size 33mm	The failure mode observed was excessive regurgitation due to leaflet tear at the commissure apex. For Trifecta valves which failed, the failures occurred between 460 million and 1020 million cycles. The control valves which failed, failed between 140 million and 210 million cycles.
Finite Element Analysis	All stent sizes included in analysis	NA	The largest stress observed was 269 MPa (42.9 ksi) for the size 23mm stent.
Stent Fatigue	30 stents, size 25mm	NA	No failures observed through 600 million cycles at 586 MPa (85 ksi).
Stent Creep	30 stents, size 25mm	NA	No sign of yielding or dynamic creep was observed through 600 million cycles at 586 MPa (85 ksi).
Sewing Cuff Integrity	3 each size stent	NA	All test samples exhibited cuff retention in excess of the minimum device specification.

B. Animal Studies

Chronic GLP animal studies were performed with the Trifecta Valve using both the adult and juvenile ovine model. The studies were completed following the requirements specified in the *ISO 5840, Cardiovascular Implants – Cardiac Valve Prosthesis (1996).*

A total of 6, size 19mm, Trifecta valves were implanted in the aortic position of adult female sheep between 1 to 3 years of age for a minimum of 90 days. A total of 6, size 25mm, Trifecta valves were implanted in the mitral position of juvenile sheep between 18 to 20 weeks of age for a minimum of 140 days.

Commercially available bioprosthetic heart valves with an anticalcification treatment were used as controls.

The study included an evaluation of handling and implant characteristics, animal survival, hemodynamic performance, valve pathology, hematology and mineralization. The Trifecta Valve demonstrated normal valve tissue response,

acceptable hemodynamic performance, good animal survival rates, and favorable mineralization rates.

B.1 Handling and Implant Characteristics

Handling and implantation characteristics of the Trifecta Valve were evaluated by the implanting surgeons and were considered comparable to the control valve.

B.2 Animal Survival

There was one early animal death at day 33 in the test group implanted in the adult sheep model (aortic position); however, cause of death was not attributed to valve performance.

There was one early death at day 21 in the test group implanted in the juvenile sheep model (mitral position); however, cause of death was not attributed to valve performance.

B.3 Hemodynamic Performance

At the time of explant, all animals were subjected to standard heart (direct) catheterization to obtain hemodynamic measurements. Hemodynamic parameters obtained on all animals were typically within the normal physiologic range.

B.4 Valve Pathology

Valve pathology included photographic analysis of the explanted valves. Gross observations of the mitral and aortic valves indicated a similar pathology for both the Trifecta valves and the control valves. In general, the valves were well seated in the annulus. The base of leaflets and sewing cuffs were covered with minimal white translucent-shining tissue (pannus). There were minimal fibrinous deposits on the commissures and margins.

The degree of host tissue reaction to the valve appeared to be similar in all groups. There was minimal diffuse pannus growth on the base of the leaflets and sewing cuff, and minimal focal fibrinoid thrombosis on the valve margin and commissures.

B.5 Hematology

The overall blood chemistries appeared normal when compared to juvenile ovine reference values (Nemi C. Jain *Veterinary Hematology* - Fourth Edition).[2] There were no observable negative effects of the test valves on any serial blood parameters.

The blood chemistries and hematological profiles were similar to the control valves.

B.6 Mineralization

Mineralization was evaluated by X-ray radiographs of whole valves, histopathological analysis of leaflet sections and quantitative analysis using inductively coupled plasma atomic emission spectroscopy (ICP).

A correlation between pathological observations (gross pathology, X-ray, and histology) of the explanted valve and leaflets and the chemical confirmation of calcium was noted. Only minimal calcium content was measured in the Trifecta leaflet tissue and was comparable to the control valves via ICP analysis.

One of the two control valves in the mitral position was severely calcified based upon gross pathology, X-ray, and histology.

C. Additional Studies

C.1 Sterilization

The Trifecta Valve is sterilized with a multi-component liquid chemical sterilant. Microbial screening studies were conducted with a variety of organisms exposed to the sterilant in a simulated manufacturing sterilization process. The D-values derived from the screening studies showed *Bacillus atraphaeus* to be the most resistant microbial organism to this sterilization process.

The D-value obtained from the *B. atraphaeus* microbial survival study was used to calculate the minimum sterilization time required to meet a minimum Sterility Assurance Level (SAL) of 10^{-6}.

C.2 Magnetic Resonance Imaging (MRI) Compatibility

Non-clinical testing has demonstrated that the Trifecta Valve is MR conditional. It can be scanned safely under the following conditions:

- Static magnetic field of 3 Tesla or less
- Spatial gradient of 525 Gauss/cm or less
- Maximum whole-body-averaged specific absorption rate (SAR) of 2.0-W/kg for 15 minutes of scanning.

C.3 Shelf Life

The shelf life for the Trifecta Valve was validated to ensure that both the package integrity and the product integrity were maintained for 2 years.

C.4 Package Integrity

The packaging used for the Trifecta Valve has been shown to maintain sterility for the 2-year product shelf-life. Structural integrity of the package was evaluated after exposure to thermal shock cycling, vibration, drop conditioning and accelerated aging to 2 years. Performance evaluation of the package included vacuum leakage testing, temperature indicator testing and microbial challenge after real-time aging to two years. The results demonstrate that the package integrity is acceptable for a 2-year shelf life.

C.5 Product Integrity

Integrity of the finished devices was evaluated after real-time aging to 2 years. The evaluation included shrinkage temperature, collagen content (i.e., hydroxyproline content), tissue microstructure, biomechanical properties, storage solution

concentration, storage solution pH, effectiveness of the physician's rinse, and hydrodynamic testing. The results demonstrate that the product integrity of the Trifecta Valve is acceptable for a 2-year shelf life.

X. SUMMARY OF PRIMARY CLINICAL STUDY

A. Study Design

The clinical study that formed the basis for FDA's finding that the Trifecta Valve is safe and effective for its intended use was a prospective, non-randomized, observational study without concurrent or matched controls. Adverse event (AE) rates as compared to a set of Objective Performance Criteria (OPC) and to literature-based control data were used for the design and analysis of this study. New York Heart Association (NYHA) functional classification status and hemodynamic performance of the valve by echocardiography were evaluated using a comparison to literature-based control data.

A.1 Clinical Inclusion and Exclusion Criteria

Clinical inclusion criteria for the Trifecta Valve clinical study included the following:

- Patient requires aortic valve replacement (Note: Patients undergoing concomitant procedures, e.g., coronary artery bypass grafting, or valve repair, are eligible for this study).
- Patient is legal age in host country
- Patient (or legal guardian) has given written informed consent for participation prior to surgery.
- Patient is willing to undergo all study procedures and adhere to data collection and follow-up requirements.

Clinical exclusion criteria for the Trifecta Valve Clinical Study included the following:

- Patient is pregnant or nursing (women of child bearing potential must have a documented negative pregnancy test within one week prior to surgery).
- Patient already has a prosthetic valve(s) at a site other than the aortic valve.
- Patient requires concomitant replacement of the tricuspid, pulmonary, or mitral valve.
- Patient has an inability or is unwilling to return for the required follow-up visits.
- Patient has active endocarditis (patients with previous endocarditis must have two documented negative blood culture results prior to enrollment).
- Patient has had an acute preoperative neurological event defined as: patient has not returned to baseline or has not stabilized 30 days prior to the planned valve implantation surgery.
- Patient is undergoing renal dialysis.
- Patient has a documented history of substance abuse within one year of enrollment, or is currently a prison inmate.
- Patient is currently participating in the study of an investigational drug or device, or the patient was previously participating in an investigational drug study and has not completed a 30-day wash out period.
- Preoperative evaluation indicates other significant cardiovascular abnormalities such as aortic dissection or ventricular aneurysm.
- Patient has a life expectancy less than two years.

A.2 Follow-up Schedule

Preoperative demographic and baseline data including NYHA functional classification were collected. Postoperative data, including blood and echocardiography data were collected at discharge, 6 months, one year, and annually thereafter. All echos were sent to the Echocardiography Core Laboratory for interpretation. Postoperative NYHA functional classifications were collected at 6 months, one year, and annually thereafter. Adverse event data were collected at the time of occurrence or site notification using definitions from Edmunds *et al.*, 1996.[1]

A.3 Clinical Endpoint

The clinical endpoints for the study were to confirm the clinical safety and effectiveness of the Trifecta Valve by establishing the following:

- Adverse Event (AE) rates (early, linearized late, and Kaplan-Meier)
- New York Heart Association (NYHA) functional classification status
- Hemodynamic performance of the valve by echocardiography

B. Accountability of PMA Cohort

At the time of database freeze, one thousand and twenty-two (1022) subjects were implanted with the Trifecta Valve in the aortic position at a total of 31 investigational sites between June 2007 and November 2009. Data are being presented on the one thousand fourteen (1014) subjects who met eligibility criteria.

The number of subjects who were eligible as well as the number and percentage of subjects who had follow-up at each visit interval are presented in Table 4.

Table 4: Number of Subjects at Each Interval
All Subjects, N=1014

Interval	Eligible Subjects n	Follow-up %[1] (n_1)	Censored[2] Subjects N_1
Preoperative	1014	100% (1014)	16
Discharge	998	100% (998)	72
6 Month	926	97.8% (906)	277
1 Year	649	97.7% (634)	548
2 Year	101	98.0% (99)	101
Overall	**3688**	**99.0% (3651)**	**1014**

[1] %=(n_1/n)*100
[2] N_1 Censoring can be due to pending visit, explant, death or lost to follow-up

C. Study Population Demographics and Baseline Parameters

C.1 Description of Subjects

Between June 2007 and November 2009, one thousand and twenty-two (1022) subjects were implanted with the Trifecta Valve in the aortic position at 31 investigational sites: 18 sites in the United States, 7 sites in Canada, and 6 sites in Europe. Data are being presented on the one thousand fourteen (1014) subjects who met eligibility criteria.

Table 5 presents the mean age at implant and preoperative NYHA. The mean age at implant was 72.5 years (standard deviation (SD) 9.0 years, range 32 to 95 years), and 64.1% of subjects were male. Preoperatively, 49.3% of subjects were NYHA functional classification III/IV.

Table 6 presents the number of eligible subjects meeting all inclusion/exclusion criteria, cumulative and late patient-years, and mean follow-up. The cumulative follow-up was 924.18 patient-years with a mean follow-up of 0.91 years (SD 0.49 years, range 0-2.38 years).

Table 5: Preoperative Subject Demographics
All subjects included in data analysis, N=1014

Variable	N=1014
Age at Implant (years)	72.5 ± 9.0 (32,95)
Preoperative NYHA	
Class I	6.6% (67)
Class II	44.1% (447)
Class III	43.9% (445)
Class IV	5.4% (55)

Table 6: Eligible Subjects, Cumulative and Late Patient-Years, and Mean Follow-up
All subjects included in data analysis, N=1014

Implant Duration	Number of subjects	Total Patient-years	Mean	SD	Minimum	Maximum
Cumulative Patient-years	1014	924.18	0.91	0.49	0.00	2.38
Late Patient-years*	955	844.31	0.88	0.45	0.01	2.30

*Late patient-years are calculated from 31 days post-implant to the last follow-up visit (or contact), or adverse event.

D. Safety and Effectiveness Results

D.1 Safety Results

Table 7 provides the early adverse event rates, linearized late adverse event rates, and 1-year and 2-year Kaplan-Meier analysis results.

Table 7: Observed Adverse Event Rates

All subjects analyzed: N=1014 Cumulative follow-up: 924.18 patient-years

Adverse Event	Early Events[1] %[2] (n)	Late Events[3] %/pt-yr[4] (n) [One-Sided Upper 95% CL]	Freedom From Event 1 Year[5] % [95% CI]	Freedom From Event 2Year[5] % [95% CI]
Thromboembolism	2.7% (27)	1.90% (16) [2.88%]	96.2% [94.7%,97.2%]	92.9% [88.5%,95.6%]
Valve Thrombosis	0.0% (0)	0.00% (0) [0.35%]	100.0% [100.0%,100.0%]	100.0% [100.0%,100.0%]
Major Bleed	8.0% (81)	2.61% (22) [3.72%]	90.4% [88.3%,92.2%]	86.0% [81.0%,89.8%]
Anticoagulant and/or Antiplatelet	1.4% (14)	1.90% (16) [2.88%]	96.8% [95.4%,97.8%]	93.7% [88.7%,96.5%]
Nonstructural Dysfunction	0.3% (3)	0.12% (1) [0.56%]	99.6% [98.9%,99.8%]	99.6% [98.9%,99.8%]
All Perivalvular Leak	0.1% (1)	0.00% (0) [0.35%]	99.9% [99.3%,100.0%]	99.9% [99.3%,100.0%]
Major Perivalvular Leak	0.0% (0)	0.00% (0) [0.35%]	100.0% [100.0%,100.0%]	100.0% [100.0%,100.0%]
Endocarditis	0.0% (0)	1.07% (9) [1.86%]	99.1% [98.1%,99.5%]	98.6% [97.1%,99.4%]
Clinically Significant Hemolysis	0.0% (0)	0.00% (0) [0.35%]	100.0% [100.0%,100.0%]	100.0% [100.0%,100.0%]
Structural Deterioration	0.0% (0)	0.12% (1) [0.56%]	99.9% [99.3%,100.0%]	99.9% [99.3%,100.0%]
Reoperation	0.1% (1)	0.59% (5) [1.25%]	99.4% [98.6%,99.7%]	99.4% [98.6%,99.7%]
Explant	0.1% (1)	0.59% (5) [1.25%]	99.4% [98.6%,99.7%]	99.4% [98.6%,99.7%]
Valve-Related Mortality	0.2% (2)	0.36% (3) [0.92%]	99.4% [98.6%,99.8%]	99.4% [98.6%,99.8%]

[1]Early events are those occurring on or before 30 days post-implant

[2]The early adverse event rate (%) is calculated as the number of early adverse events divided by the total number of subjects, times 100

[3]Late events are those occurring 31 days post-implant or thereafter

[4]Late adverse event rate (%/pt-yr) is calculated as the number of late events divided by the total late patient-years, times 100. The late adverse event rates were calculated based on 844.31 late patient-years

[5]Freedom from event estimates at 1 year and at 2 years from Kaplan-Meier analysis are calculated based on 12 months and 24 months, respectively (where 30.4 days = 1 month)

D.2 Effectiveness Results

Quantitative data were collected throughout the study (i.e., NYHA functional classification, echo parameters) to evaluate effectiveness. Table 8a presents subject NYHA classification preoperatively and at one year follow-up. Table 8b presents subject NYHA classification preoperatively and at two years follow up. Table 9 presents the hemodynamic follow-up results at one year follow-up.

Table 8a: Effectiveness Outcomes, NYHA Functional Classification: 1 Year Follow-up*
Subjects with both preoperative and 1 year NYHA measurements, N=606;
n_1=number per subgroup

NYHA Class	N=606			
	Preoperative		1 Year	
	n_1	% (n_1/N)	n_1	% (n_1/N)
I	34	5.6%	517	85.3%
II	275	45.4%	82	13.5%
III	273	45.0%	7	1.2%
IV	24	4.0%	0	0.0%
All	606	100.0%	606	100%

*Subjects with both preoperative and 1 year NYHA measurements available are included in table

Table 8b: Effectiveness Outcomes, NYHA Functional Classification: 2 Year Follow-up*
Subjects with both preoperative and 2 year NYHA measurements, N=97;
n_1=number per subgroup

NYHA Class	N=97			
	Preoperative		2 Year	
	n_1	% (n_1/N)	n_1	% (n_1/N)
I	8	8.2%	81	83.5%
II	45	46.4%	14	14.4%
III	36	37.1%	2	2.1%
IV	8	8.2%	0	0.0%
All	97	100.0%	97	100.0%

*Subjects with both preoperative and 2 year NYHA measurements available are included in table

Table 9: Effectiveness Outcomes at 1 Year Follow-up Visit, Hemodynamic Results
All subjects included in data analysis, N=1014

Hemodynamic Parameter	19mm	21mm	23mm	25mm	27mm	29mm[1]
1 year postoperative	N[2]=68	N=160	N=198	N=136	N=40	N=15
Mean Gradient[4]	n[3]=66	n=160	n=197	n=135	n=40	n=15
Mean ± SD	10.7 ± 4.6	8.1 ± 3.5	7.2 ± 2.8	6.2 ± 2.7	4.8 ± 2.0	4.7 ± 1.6
Min, Max	3.3, 26.4	0.6, 23.7	1.0, 19.5	1.4, 20.3	0.5, 9.8	2.0, 7.1
EOA[5]	n=60	n=151	n=190	n=129	n=38	n=13
Mean ± SD	1.41 ± 0.24	1.63 ± 0.29	1.81 ± 0.30	2.02 ± 0.32	2.20 ± 0.20	2.35 ± 0.22
Min, Max	0.91, 2.19	0.87, 2.58	0.78, 2.77	1.15, 2.76	1.86, 2.82	2.02, 2.73
Regurgitation[6]	n=68	n=160	n=198	n=136	n=40	n=15
None	64.7% (44)	74.3% (119)	73.7% (146)	74.2% (101)	75.0% (30)	80.0% (12)
Trivial	25.0% (17)	22.5% (36)	23.2% (46)	19.1% (26)	22.5% (9)	20.0% (3)
Mild	2.9% (2)	1.8% (3)	0.5% (1)	3.6% (5)	0.0% (0)	0.0% (0)
Moderate	1.4% (1)	0.6% (1)	0.5% (1)	1.4% (2)	2.5% (1)	0.0% (0)
Severe	0.0% (0)	0.0% (0)	1.0% (2)	0.7% (1)	0.0% (0)	0.0% (0)
Unknown[7]	5.8% (4)	0.6% (1)	1.0% (2)	0.7% (1)	0.0% (0)	0.0% (0)

[1] Data for size 29 mm are based on follow-up cutoff date of 10/26/2010. All other data in table are based on follow-up cutoff date of 3/25/2010
[2] N = number of subjects with a completed echo per valve size
[3] n = number of subjects per valve size with available hemodynamic parameter
[4] Mean Gradient = pressure drop measured across the valve recorded in mmHg
[5] EOA = calculated effective orifice area measured in cm^2
[6] Aortic Regurgitation presented as 'Percentage (Count)'
[7] Unknown - Includes echos that did not contain the appropriate images to evaluate aortic regurgitation

D.3 Analysis for Sex Differences

Of the 1014 subjects implanted with the Trifecta Valve, 64.1% (n=650) were male and 35.9% (n=364) were female. This percentage of males is comparable to the results obtained from a 2008 STS database search for those patients undergoing aortic valve replacement with a biological prosthetic valve (62% male). Table 10 presents the gender distribution. Table 11 presents the baseline and operative information by gender.

Table 10: Gender Distribution

Gender	All Implants
Male	64.1% (650/1014)
Female	35.9% (364/1014)

Table 11: Baseline and Operative Information - by Gender
All subjects, N=1014

Variable	Male N= 650	Female N= 364	P-value
Age at implant	71.3 ± 9.1 (650)	74.5 ± 8.5 (364)	<.0001
Preoperative NYHA (III or IV)	46.6% (303/650)	54.1% (197/364)	0.0221
Small valve size (19mm or 21mm)	17.4% (113/650)	78.6% (286/364)	<.0001
Valve Dysfunction			
Regurgitation	6.9% (45/650)	4.4% (16/364)	0.1294
Stenosis	50.6% (329/650)	62.4% (227/364)	0.0004
Mixed	42.5% (276/650)	33.2% (121/364)	0.0040

To more carefully evaluate possible gender-based differences in outcome of treatment with the Trifecta Valve, several sex/gender-specific analyses were performed on safety and effectiveness endpoints. The results suggest that the general conclusions of the overall study regarding both safety and effectiveness can be generalized for males and females.

Safety Results by Sex: Kaplan-Meier analysis and Log-Rank tests were performed to compare each adverse event by gender. One year survival rates are provided in Table 12. Males had a significantly lower incidence of all cause mortality than females. However, when only valve-related deaths were considered the difference between genders was no longer significant. In addition, the observed difference for all cause mortality could be partially attributable to the fact that on average the women implanted in the study were 3 years older than the men. This observed higher rate of all cause mortality in women is consistent with what has been published in literature.[3] There were no significant differences between males and females for other adverse events such as embolism, major bleed, paravalvular leak, endocarditis, structural deterioration, or reoperation rates.

Effectiveness Results by Sex: The results from the Signed Rank test demonstrate significant improvement of NYHA from preoperative to 1 year for males and females. The Wilcoxon Rank-sum test was performed by gender for NYHA functional classification improvement from preoperative to one year. There is no significant difference in NYHA functional classification improvement between genders. Key hemodynamic performance at 1 year was evaluated for all subjects by gender across all valve sizes (29mm were all males). Data observed are equivalent by male and female for all sizes except for 21mm. However, the differences observed for size 21mm for peak gradient, mean gradient, and effective orifice area index are very small and not considered to be clinically significant.

Table 12: Kaplan-Meier Analysis Freedom From Adverse Event at 1 Year by Gender

Adverse Event	Female	Male	Log Rank p-value*
Thromboembolism	0.9594	0.9630	0.5070
Valve Thrombosis	1.0000	1.0000	--
Major Bleed	0.8990	0.9067	0.8271
All Perivalvular Leak	1.0000	0.9985	0.4541
Major Perivalvular Leak	1.0000	1.0000	--
Endocarditis	0.9850	0.9935	0.5292
Structural Deterioration	0.9970	1.0000	0.1702
Clinically Significant Hemolysis	1.0000	1.0000	--
Reoperation	0.9879	0.9967	0.1031
Mortality	0.9345	0.9707	0.0121
Mortality -Valve Related	0.9938	0.9969	0.5386

*p-value for the entire study experience is presented

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

In accordance with the provisions of section 515(c)(2) of the Act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory Systems Device panel, a FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Safety Conclusions

The results from the *in-vitro* pre-clinical studies performed for biocompatibility, hydrodynamic performance and structural performance demonstrate that the Trifecta Valve is safe and effective and, therefore, suitable for long-term implant.

The *in-vivo* animal studies in sheep demonstrate that the Trifecta Valve is safe for valve replacement.

The results of the Trifecta Valve clinical investigation demonstrate that the adverse event rates for the major safety variables were significantly lower than the established standard of twice the FDA's Objective Performance Criteria for a tissue valve, with the exception of Major Bleed. There was no clear indication that the major bleeding events were directly related to the Trifecta valve. Mortality, reoperation, and explant rates also support the safety of the valve.

B. Effectiveness Conclusions

The analysis of effectiveness was based on the change in NYHA functional classification between preoperative and one year for those subjects with available data at both intervals. Additionally, hemodynamic data change between discharge and one year, for those subjects with echocardiography data available at both intervals was assessed. Key effectiveness outcomes are presented in Table 8a, Table 8b, and Table 12.

There was a statistically significant improvement in NYHA functional classification, (p-value <0.0001) from the preoperative to one year visit.

More than 95% of subjects had none or trivial regurgitation at one year. Mean gradients at one year across all valve sizes were $\leq$ 10.7mmHg. A comparison of Trifecta hemodynamic data to current literature indicates better than or equal performance to other aortic stented tissue valves.

C. Overall Conclusion

The results of the clinical study presented in the PMA application demonstrate a reasonable assurance that the Trifecta Valve is a safe and effective replacement for a malfunctioning native or prosthetic aortic heart valve.

XIII. CDRH DECISION

FDA issued an approval order on April 20, 2011. The applicant's manufacturing facilities were inspected on February 3, 15, and 17, 2011 and were found to be in compliance with the Quality System Regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATION

Instructions 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: See approval order.

XV. REFERENCES

1. Edmunds LH, Clark RE, Cohn LH, Grunkemeier GL, Miller CM, Weisel RD. Guidelines for Reporting Morbidity and Mortality after Cardiac Valvular Operations. *Ann Thorac Surg* 1996;62:932-5.
2. Nemi C. Jain *Veterinary Hematology* - Fourth Edition
3. Brown J. Isolated aortic valve replacement in North America comprising 108,687 patients in 10 years: Changes in risks, valve types, and outcomes in the Society of Thoracic Surgeons National Database. *J thorac Cardiovasc Surg. 2009;137:82-90*