Summary of Safety and Effectiveness Data
On-X® Prosthetic Heart Valve, Models ONXM and ONXMC

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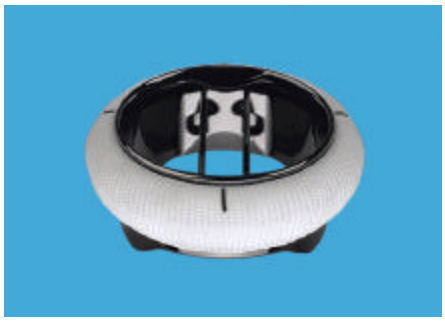


Figure 1 – On-X® Prosthetic Heart Valve

1. GENERAL INFORMATION

Device Generic Name:	Replacement Heart Valve
Device Trade Name:	On-X® Prosthetic Heart Valve Model: ONXM, sizes 25, 27/29 and 31/33 mm ONXMC size 25/33
Applicant's Name and Address:	Medical Carbon Research Institute, LLC (MCRI™) 8200 Cameron Road, A-196 Austin, Texas 78754
PMA Application Number:	P000037/S1

Date of Notice of Approval to the Applicant: March 6, 2002

2. INDICATIONS FOR USE

The On-X® Prosthetic Heart Valve is indicated for the replacement of diseased, damaged, or malfunctioning native or prosthetic heart valves in the mitral position.

3. DEVICE DESCRIPTION

The On-X® Prosthetic Heart Valve (Figure 1) is a bileaflet mechanical heart valve, which consists of an orifice housing two leaflets. The orifice inflow area has a flared inlet designed to reduce flow turbulence, and the outflow rim consists of leaflet guards designed to protect the leaflets while in the closed position. The leaflets rotate around tabs located within the inner circumference of the orifice ring. In the closed position, the each leaflet forms a nominal angle of 40º relative to the plane of the orifice. In the open position, the plane of

each leaflet forms a nominal angle of 90° relative to the plane of the orifice. The leaflets have a travel arc of 50° to the closed position.

The orifice is composed of graphite substrate coated with On-X® Carbon, a pure unalloyed form of pyrolytic carbon. The leaflets consist of On-X® Carbon deposited on a graphite substrate, which is impregnated with 10 weight% tungsten to provide radiopacity.

The sewing cuff is constructed of polytetrafluoroethylene (PTFE) fabric mounted on the orifice using titanium retaining rings and 5-0 suture material. This form of sewing cuff attachment to the orifice allows for rotation of the sewing cuff *in situ* during implantation. Orientation reference marks are provided on the sewing ring for valve orientation.

The On-X® Prosthetic Heart Valve is available in mitral sizes 25, 27/29, 31/31 and 25/33 mm. The valve is designed for intra-annular implantation.

4. CONTRAINDICATIONS

The On-X® Prosthetic Heart Valve is contraindicated for patients unable to tolerate anticoagulation therapy.

5. WARNINGS AND PRECAUTIONS

5.1 Warnings

FOR SINGLE USE ONLY.

DO NOT use the On-X® Prosthetic Heart Valve if:

- the prosthesis has been dropped, damaged, or mishandled in any way;
- the tamper evident seal is broken;
- the serial number tag does not match the container label;
- the expiration date has elapsed.

DO NOT resterilize any On-X® Prosthetic Heart Valve:

- once it is removed from its plastic container;
- more than 3 times - resterilization of a valve which has passed the sterility expiration date is permitted, up to this limit, only if the valve has remained in the original unopened container and undamaged;
- with any method other than steam sterilization, with the identified resterilization parameters. Note: Gamma radiation is known to damage the sewing ring.

DO NOT pass a catheter, surgical instrument, or transvenous pacing lead through the prosthesis as this may cause valvular insufficiency, leaflet damage, leaflet dislodgment, and/or catheter/instrument/lead entrapment.

5.2 Precautions

Handle the prosthesis with only MCRI™ On-X® Prosthetic Heart Valve Instruments, particularly during selection of the valve size; other sizers may result in improper valve selection.

Avoid damaging the prosthesis through the application of excessive force to the valve orifice or leaflets.

Avoid contacting the carbon surfaces of the valve with gloved fingers or any metallic or abrasive instruments as they may cause damage to the valve surface not seen with the unaided eye that may lead to accelerated valve structural deterioration, leaflet escape, or serve as a nidus for thrombus formation.

6. ALTERNATIVE PRACTICES AND PROCEDURES

Alternative forms of treatment other than the On-X Prosthetic Heart Valve include medical therapy with drugs or surgical treatments such as annuloplasty or valvuloplasty with or without the use of implantable materials (i.e., sutures and/or annuloplasty rings). When the patient requires replacement of his/her native or previously placed prosthetic valve, the option of choosing a mechanical or biological valve exists. The choice of replacement valve depends upon factors that include the patient's age, preoperative conditions, cardiac anatomy, and ability to tolerate anticoagulation therapy.

7. MARKETING HISTORY

The On-X® Prosthetic Heart Valve is distributed in Argentina, Austria, Brazil, Canada, Chile, China, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, India, Indonesia, Iran, Italy, Jordan, South Korea, Norway, Pakistan, Philippines, Portugal, Romania, Slovakia, South Africa, Spain, Sweden, Syria, Taiwan R.O.C., Tunisia, Turkey, Vietnam, and the United Kingdom.

The On-X® Prosthetic Heart Valve has not been withdrawn from the market in any country for any reason.

8. ADVERSE EVENTS

A total of 229 mitral On-X® Prosthetic Heart Valves were implanted in 229 patients at 16 centers. The mean follow-up was 1.8 years (range of 0 to 4.5 years) with a total of 417.9 patient-years.

A total of 18 deaths occurred during the study and 3 of these were characterized as valve-related. The causes of the valve-related deaths were early uncontrolled bleeding (1 patient) and late, sudden, unexplained death (2 patients).

8.1 Observed Adverse Events

Adverse events were reported in the clinical study as shown in the following table.

Table 1: Mitral Observed Adverse Event Rates[1]

All patients implanted, N = 229, Cumulative follow-up = 417.9 patient-years

Complication	Early Events		Late Events[2]		Freedom from Event[3], % [SE]	
	n	% (n/N)[4]	n	%/pt-yr	1Year Postoperative (n=134)	3 Year Postoperative (n=44)
Mortality (all)	9	3.9%	9	2.2%	95.4%[1.4]	89.2%[2.7]
Mortality (valve-related)	1	0.4%	2	0.5%	99.5%[0.5]	97.2%[1.7]
Endocarditis	0	0.0%	3	0.7%	99.0%[0.7]	99.0%[0.7]
Explant	1	0.4%	3	0.7%	98.0%[1.0]	98.0%[1.0]
Hemolysis[5]	0	0.0%	0	0.0%	100.0%[0]	100.0%[0]
Hemorrhage[6] (all)	4	1.8%	6	1.4%	96.4%[1.3]	94.4%[2.0]
Hemorrhage (major)	4	1.8%	2	0.5%	97.0%[1.2]	97.0%[1.2]
Perivalvular Leak (all)	2	0.9%	3	0.7%	98.0%[1.0]	97.1%[1.2]
Perivalvular Leak (major)	1	0.4%	1	0.2%	99.4%[0.6]	99.4%[0.6]
Nonstructural Valve Dysfunction	0	0.0%	1	0.2%	100.0%[0]	99.1%[0.9]
Reoperation (valve-related)	3	1.3%	5	1.2%	97.0%[1.2]	97.0%[1.2]
Structural Valve Dysfunction	0	0.0%	0	0.0%	100.0%[0]	100.0%[0]
Thromboembolism	2	0.9%	7	1.7%	97.0%[1.2]	96.3%[1.4]
Thrombosis	0	0.0%	0	0.0%	100.0%[0]	100.0%[0]

Notes:

1. Data does not include results from double valve replacement.
2. Late events calculated as linearized rates based on total patient-years.
3. Freedom from event was calculated based on the method of Kaplan-Meier. SE = Standard Error.
4. n = number of patients in each category; N = total number of study patients.
5. Blood studies conducted at a core laboratory established that the valve creates a low level of fully compensated hemolysis typified by an increase in SLDH with a mean within normal range, a decrease in haptoglobin to below normal in 65% MVR patients at 1-year, and all other analytes within normal range.
6. The anticoagulant agents used were reported. The target International Normalized Ratio was 3.0 to 4.5.

8.2 Potential Adverse Events

Adverse events potentially associated with the use of prosthetic heart valves (in alphabetical order) include, but are not limited to:

- angina
- cardiac arrhythmia
- endocarditis
- heart failure
- hemolysis
- hemolytic anemia
- hemorrhage
- myocardial infarction
- prosthesis leaflet entrapment (impingement)
- prosthesis nonstructural dysfunction
- prosthesis pannus
- prosthesis perivalvular leak
- prosthesis regurgitation
- prosthesis structural dysfunction
- prosthesis thrombosis
- stroke
- thromboembolism

It is possible that these complications could lead to:

- reoperation
- explantation
- permanent disability
- death

9. SUMMARY OF NONCLINICAL STUDIES

All testing of the On-X® Prosthetic Heart Valve was conducted in accordance with the applicable sections of the GLP regulation (21 CFR58).

MCRI™ certified that the On-X® Prosthetic Heart Valve complies with the following international regulatory and/or voluntary standards:

1. ISO 10993 Parts 1-12 as applicable (Also prEN30993) for biocompatibility
2. ISO 5840 (Also prEN12006-1) Cardiac Implants - Cardiac Valve Prostheses
3. EN554 and EN556 Sterility
4. EN ISO 9001 Quality Systems, EN 46001 Medical Device Quality Systems

9.1 IN VITRO STUDIES

9.1.1 Hydrodynamics and Flow Visualization

Hydrodynamic studies of the On-X® Prosthetic Heart Valve were conducted according to section VI.A.2.a of the Draft Replacement Heart Valve Guidance Document, October 14, 1994. Commercially available valves were used as controls. Table 3 provides a summary of hydrodynamic tests.

Table 3 – Hydrodynamic Performance Testing and Results

Test	Sample Size: Control	Sample Size: On-X® Prosthetic Heart Valve	Results
Steady forward flow pressure gradient	1 each 19, 21, 23, 25, 27, 29 mm	3 each 19, 21, 23, 25 mm	At 30 LPM, On-X® gradients were substantially lower size for size than the controls.
Steady backflow leakage	1 each 19, 21, 23, 25, 27, 29 mm and a reference nozzle	3 each 19, 21, 23, 25 mm	At 180 mmHg, On-X® leakage was higher by design compared to equivalent geometric size controls and lower than the reference nozzle.
Pulsatile flow pressure gradients	1 each 19, 21, 23, 25, 27, 29 mm	3 each 19, 21, 23, 25 mm	Under all conditions, On-X® gradients were lower than the equivalent control valve.
Pulsatile flow regurgitation	1 each 19, 21, 23, 25, 27, 29 mm	3 each 19, 21, 23, 25 mm	Equivalent geometric size valves had equivalent total regurgitation. On-X® closure volume was lower, but leakage volume was higher.
Verification of Bernoulli equation	Not applicable (N/A)	1 each 19, 23, 25 mm	The Bernoulli equation accurately projects true pressure gradient for the valve.
Flow visualization: Laser Doppler anemometry	1 of 25 mm	1 of 25 mm	Similar flow patterns exist, but On-X® has lower peak velocities and shear stresses. No adverse flow patterns.
Flow visualization: Backflow leakage jets	N/A	1 of 25 mm	Four major leakage jets emanate from the four pivots similar to all bileaflet valves.
Flow visualization: Hinge flow	5X model 25 mm control and second control	5X model 25 mm	No areas of stasis at any time in the cycle for On-X®, no vortex formation for On-X® or control, prominent vortexes for second control.

9.1.2 Durability and Lifetime Analysis

Structural performance of the On-X® Prosthetic Heart Valve was studied in accordance with the Draft Replacement Heart Valve Guidance Document. Commercially available valves were used as controls where applicable. Table 4 summarizes these tests.

Table 4 – Structural Performance Testing and Results

Test	Sample Size: Control	Sample Size: On-X® Prosthetic Heart Valve	Results
Fracture mechanics of materials	N/A	On-X® Carbon on graphite On-X® Carbon solid	K_{IC} = 2.46 MPa-$m^{1/2}$, ΔK_{th} = 1.24 MPa-$m^{1/2}$, m = 40.2, log C = -14.6 K_{IC} = 1.67 MPa-$m^{1/2}$, ΔK_{th} = 1.11 MPa-$m^{1/2}$, m = 70.3, log C = -14.4 Worst-case properties used for fatigue life calculations.
Accelerated durability testing	2 of 23 mm, 1 each of 27 and 29 mm	5 each 19, 21, 23, 25, 27/29 mm	All valves survived cycling for 600 million cycles without failure or damage. The maximum wear depth was 26.7 microns (25 mm) as compared to the control wear depth of 3.1 microns. The worst-case total *in-vitro* wear at 15 years was less than half the minimum coating thickness (102 microns).
Dynamic impact factor	N/A	25 mm dynamic model and test valve	Impact factor of 2.0, predicted from FEA model, was confirmed by strain gage measurements during pulse duplicator testing at 200 mmHg peak systolic pressure.
Physiological stresses	N/A	Finite element model of 19, 21, 23, 25 mm	FEA results and impact factor combined to result in worst-case stress of 3040 psi used in fatigue lifetime calculations.
Fatigue life	N/A	19, 21, 23, 25 mm	Paris law calculations were made, for an assumed lifetime of 600 million cycles, to determine critical flaw size under worst-case conditions. Proof testing and other non-destructive tests were used to assure that critical flaws were not in final product. Based on the critical flaw size, the worst-case life calculation was well in excess of the human lifespan.
Static failure mode	N/A	3 each 19, 21, 23, 25 mm	Minimum static load to failure was 94 psi. Failure mode was spalled sockets and shattered leaflets.
Dynamic failure mode	1 of 27 mm	3 each 25 mm after wear test	Cycle to 30 psi without failure. Failure of valve by leaflet shatter at 72 psi for On-X®. Control failed by housing fracture at 67 psi.

Test	Sample Size: Control	Sample Size: On-X® Prosthetic Heart Valve	Results
Cavitation potential	2 of 27 mm 3 of 29 mm	3 each 25 mm	The dp/dt at threshold was higher for the On-X® than the control.
Sewing ring integrity Tear out	1 of size 29 mm	3 - 25 mm mitral	Suture breaks before tear out, tear out at 10.5 lbs for control
Sewing ring integrity Push off	N/A	25, 27/29, 31/31 mitral	Minimum push off force 111 N, over 7 time physiologic force
Load deflection tests Bind Escape	N/A	3 each 25 mm	Minimum to bind – 20N without sewing ring, 28N with sewing ring Minimum to escape – 110N.
Valve sounds Clinical study	3 29mm mitral	7 mitral – 2 25 mm, 5 27/29 mm	No differences in perceived sounds were found between valves.

9.2 ANIMAL STUDIES

Preclinical animal studies were conducted using the standard adult sheep model at the University of Minnesota with implants occurring between October and December 1995. Eight sheep were implanted with 25 mm On-X® Prosthetic Heart Valves. Two sheep were implanted with the control valves. One animal was found to have a large atrial septal defect and was sacrificed on the operating table. All other animals survived the 20 week minimum implant duration. Serial postoperative blood samples showed no difference between valves and no negative experimental device effect. Hemodynamic parameters measured for each device were normal and there were no surgical handling difficulties for the test valve. Pathology studies demonstrated that the interior surfaces of the housing, the hinge region, and the leaflets were free of thrombus and pannus. However, a single thrombus was observed in one explanted valve at the interface of the sewing cuff and the outflow region of the valve housing. Postmortem examination of the major organs was normal in all animals, except for foreign material in the renal artery of one control valve sheep. The control valve from this animal displayed chipping and pitting in the pivot regions upon microscopic examination believed to have occurred *in situ,* and possibly explaining the renal artery observation. All other valves had normal surfaces under microscopy after implant.

9.3 BIOCOMPATIBILITY

Biocompatibility tests were conducted according to ISO 10993 guidelines for the On-X® Carbon and polytetrafluoroethylene (PTFE) yarn materials. Yarn with an ink mark was tested, also. Biocompatibility testing was not conducted for the titanium (Ti6Al4V ELI) alloy because the material meets ASTM F136 Standard Specification for Wrought Titanium 6Al-4V ELI Alloy for Surgical Implant Applications and because of the long history of successful biomedical implant applications for this alloy. No significant reactions were observed in the tests performed. Results are presented in Table 5.

Table 5 – Biocompatibility Studies Results Summary

Test	Objective	Sample: Control	Sample: Test Article	Results
Cytotoxicity L-929 Membrane Elution	To determine the biological reactivity of a cell culture to an extract of the test article	Negative control: silicone rubber Positive control: natural rubber	On-X® Carbon	Non-cytotoxic
Hemolysis	To assess the hemolytic activity of the test article	Negative control: water for injection Positive control: 0.9% saline	On-X® Carbon	Non-hemolytic at 0% hemolysis
Physicochemical tests to USP	To determine physical and chemical properties of extracts	Negative control: water for injection Positive control: N/A	On-X® Carbon	Passed USP physicochemical tests for plastics
Ames mutagenicity test	To assess the mutagenic potential of the test article	Negative control: 0.9% NaCl Positive controls: 2-aminoanthracene, sodium azide, 2-nitrofluorene, 9-aminoacridene	On-X® Carbon	Non-mutagenic
Intracutaneous injection	To assess toxic effects of extracts of the test article	Negative control: 0.9% NaCl, cottonseed oil Positive control: N/A	On-X® Carbon	Negligible irritant
Systemic injection	To assess the systemic toxic effect of extracts of the test article	Negative control: 0.9% NaCl, cottonseed oil Positive control: N/A	On-X® Carbon	Negative, non-toxic
Rabbit pyrogen	To determine the presence of chemical pyrogens on finished components	Negative control: 0.9% NaCl Positive control: N/A	On-X® Carbon	Non-pyrogenic
Klingman sensitization	To evaluate the allergenic potential of test articles	Negative control: 0.9% NaCl, cottonseed oil Possitive control: dinitrochlorobenzene	On-X® Carbon	0% sensitization: Grade I reaction
Cytotoxicity L-929 Membrane Elution	To determine the biological reactivity of a cell culture to an extract of the test article	Negative control: MEM extractant Positive control: Known toxic material	PTFE yarn PTFE yarn with surgical marker	Non-cytotoxic

Test	Objective	Sample: Control	Sample: Test Article	Results
Hemolysis	To assess the hemolytic activity of the test article	Negative control: water for injection Positive control: 0.9% saline	PTFE yarn	Non-hemolytic
Intracutaneous injection	To assess toxic effects of extracts of the test article	Negative control: 0.9% NaCl, cottonseed oil Positive control: N/A	PTFE yarn	Negligible irritant
Systemic injection	To assess the systemic toxic effect of extracts of the test article	Negative control: 0.9% NaCl, cottonseed oil Positive control: N/A	PTFE yarn	Negative, non-toxic
Rabbit implantation (1 and 4 weeks)	To assess the effects of implantation of the test article	Negative control: USP strips Positive control: N/A	PTFE yarn	Macroscopic: non-significant Microscopic: slight irritant

9.4 MAGNETIC RESONANCE IMAGING (MRI) COMPATIBILITY

The On-X® Prosthetic Heart Valve has been shown to be MRI safe when tested using systems operating with shielded static magnetic field strengths of 1.5 Tesla or less. Note, however, that the effects of a time-varying magnetic field were not examined. The testing should not cause significant MRI image artifacts or distortion – should this occur, this phenomenon produces no harmful effects to the patient.

9.5 SHELF LIFE AND STERILITY

The On-X® Prosthetic Heart Valve is sterilized by standard moist heat (steam) methods. It carries a shelf life of 5 years from its date of sterilization. Packaging and sterility tests were provided that establish the integrity of the package materials and sterile barrier throughout their 5 year life, including challenges of simulated shipping, storage temperature, pressure and humidity variations, and sterility by vacuum dust drum.

10. SUMMARY OF CLINICAL STUDIES

The On-X® Prosthetic Heart Valve clinical trials were designed to study the safety and effectiveness of the valve in mitral valve replacement. Patients requiring isolated mitral heart valve replacement were enrolled from September 12, 1996 to June 2001 at 8 European centers and 8 North American centers in a prospective, non-randomized study with retrospective controls.

The cohort included 229 patients (86 men, 143 women), aged from 21 to 78 years (mean of 59.4 years). The cumulative follow-up was 417.9 patient-years with a mean follow-up of 1.8 years (SD = 1.3 years, range = 0 to 4.5 years). Tables 2 and 3 present preoperative and

operative patient demographics. Figure 2 shows the number of patients implanted versus duration of follow-up. Table 4 presents implant information by valve size, including the number of patients implanted and the number of patient-years.

The safety endpoints captured in the studies were complications; blood analyses were used to confirm the absence or presence of certain complications. The safety results are provided above in Table 1. Effectiveness endpoints were New York Heart Association (NYHA) classification and echocardiographic assessments. NYHA and blood data were obtained pre-operatively, intra-operatively, and post-operatively at 3 to 6 months, at one year, and annually thereafter. Hemodynamic data were obtained at discharge and at one year. Tables 5 and 6 present these effectiveness results.

Table 2: Preoperative Patient Demographics
All patients implanted, N = 229, Cumulative follow-up = 417.9 patient-years

Patient Characteristic		n	% (n/N)[1]
Age at implant in years		59.2 ± 10.6	
Gender:	• Male	86	37.6%
	• Female	143	62.4%
NYHA Classification:	• I	5	2.2%
	• II	68	29.7%
	• III	134	58.5%
	• IV	18	7.9%
	• Unknown	4	1.7%
Valve Lesion:	• Stenosis	29	12.7%
	• Insufficiency	111	48.5%
	• Mixed	87	38.0%
	• Other	2	0.9%

Notes:
1. n = number of patients in each category; N = total number of study patients.

Table 3: Operative Patient Demographics

All patients implanted, N = 229, Cumulative follow-up = 417.9 patient-years

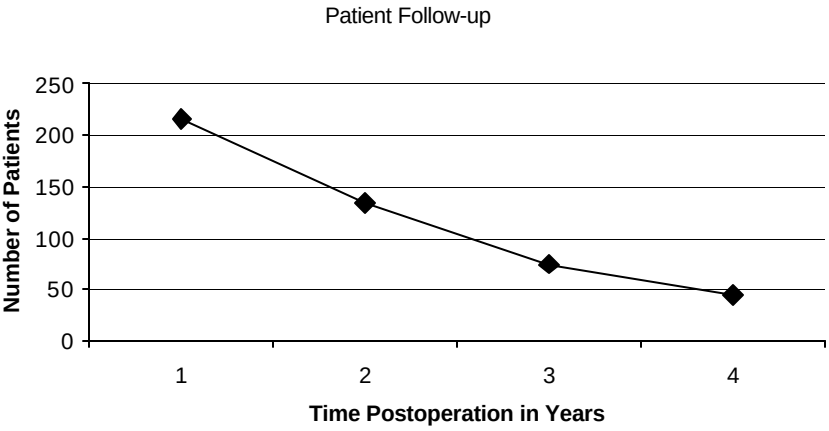
Variable	Category[1]	N	% (n/N)[2]
Etiology[3]	Calcific	36	15.7%
	Degenerative	62	27.1%
	Rheumatic	86	37.6%
	Congenital	4	1.8%
	Endocarditis	16	7.0%
	Prosthetic Valve Dysfunction	6	2.6%
	Other	38	16.6%
Concomitant Procedures[3]	None	130	56.8%
	Coronary Artery Bypass Graft	44	19.2%
	Tricuspid Repair	22	9.6%
	Closure of Atrial Appendage	12	5.2%
	Mitral Repair	12	5.2%
	Maze Procedure	12	5.2%
	Septal Defect Closure	8	3.5%
	Ventricular Aneurysm Repair	3	1.3%
	Muscularization	2	0.9%
	Tricuspid Replacement	1	0.4%
	Explant of Annuloplasty Ring	1	0.4%
Pre-existing Conditions[3]	Atrial Arrhythmias	137	59.3%
	Pulmonary Hypertension	108	46.8%
	Systemic Hypertension	88	38.1%
	Hyperlipidemia	88	38.1%
	Congestive Heart Failure	80	34.6%
	Other	77	33.3%
	Coronary Artery Disease	67	29.0%
	Cigarette Smoker	64	27.7%
	Left Ventricular Dysfunction	47	20.4%
	Cerebrovascular Accident	43	18.6%
	Diabetes Mellitus	40	17.3%
	Angina	38	16.4%
	Myocardial Infarction	30	13.0%
	Hyperthyriodism	27	11.7%
	Chronic Obstructive Pulmonary Disease	25	10.8%
	Endocarditis	18	7.8%
	Gastroinestinal Ulcer	18	7.8%
	Chronic Kidney Failure	13	5.6%
	Carotid Art ery Disease	12	5.2%
	Coronary Artery Bypass Graft	10	4.4%
	Cancer	10	4.4%
	Previous Mitral Valve Replacement	9	3.9%
	Cardiomyopathy	8	3.5%
	Pacemaker Implant	6	2.6%
Valve Size	25 mm	33	14.4%
	27/29 mm	131	57.2%
	31/33 mm	65	28.4%

Notes:

1. Ordered by frequency of occurrence, except for valve size.
2. n = number of patients in each category; N = total number of study patients.
3. May be more than one per patient.

Figure 2: Patient Follow-up Over Time

All patients implanted, N = 229, Cumulative follow-up = 417.9 patient-years



Patients Followed, N_f	Discharge	1Year Postoperative	2 Year Postoperative	3 Year Postoperative
	216	134	74	44

Table 4: Number of Patients Implanted and Number of Patient-years by Valve Size

All patients implanted, N = 229, Cumulative follow-up = 417.9 patient-years

	Numbers by Valve size					
		25 mm	27/29 mm	31/33 mm		Total
Number of Patients Implanted		33	131	65		229
Number of Patient-years		60.2	239.1	118.6		417.9

Table 5: Effectiveness Outcomes, Functional New York Heart (NYHA) Classification[1]

All patients implanted, N = 229, Cumulative follow-up = 417.9 patient-years

NYHA Class	Preoperative Assessment (N_d = 229)		Postoperative Assessments					
			1 Year (10-14 Months) (N_f = 134, N_d = 127)[2]		2 Year (22-26 Months) (N_f = 74, N_d = 69)		3 Year (34-38 Months) (N_f = 44, N_d = 42)	
	n[3]	% (n/N_d)	N	% (n/N_d)	n	% (n/N_d)	N	% (n/N_d)
I	5	2.2	85	66.9	35	50.7	14	33.3
II	68	29.7	29	22.8	24	34.8	22	52.4
III	134	58.5	5	3.9	5	7.2	6	14.3
IV	18	7.9	0	0	1	1.4	0	0
Undetermined[4]	4	1.7	8	6.3	4	5.8	0	0
Missing[5]	0	N/A	7	N/A	5	N/A	2	N/A

Notes:

1. Data does not include results from double valve replacement.
2. N_f = number of patients followed (reproduced from Figure 2); N_d = number of patients for which NYHA data were collected.
3. n = number of patients in each category.
4. Undetermined means data were collected but Class could not be determined during exam
5. Missing refers to the difference between the number of patients followed, N_f, and the number of patients for which NYHA data were collected, N_d.

Table 6: Effectiveness Outcomes, Hemodynamic Results[1]

All patients implanted, N = 229, Cumulative follow-up = 417.9 patient-years

Hemodynamic Parameter		Results by Valve Size					
		25 mm		27/29 mm		31/33 mm	
Early Postoperation (< 30 days), N_f[2] = 216							
Mean Gradient[3]		N_d = 31		N_d = 117		N_d = 59	
• Mean ± SD		4.3 ± 1.3		4.3 ± 1.6		4.5 ± 2.2	
• Min, max		1.7, 7.5		1.2, 10.0		1.0, 11.7	
EOA[5]		N_d = 25		N_d = 97		N_d = 53	
• Mean ± SD		2.4 ± 0.8		2.2 ± 0.6		2.2 ± 0.8	
• Min, max		0.9, 4.2		1.0, 4.3		0.8, 4.4	
Regurgitation[6]		N_d = 28		N_d = 104		N_d = 56	
		n	% (n/N_d)	N	% (n/N_d)	N	% (n/N_d)
• 0		20	71.4%	73	70.2%	40	71.4%
• 1-2+		4	14.3%	25	24.0%	16	28.6%
• 3+		0	0.0%	0	0.0%	0	0.0%
• 4+		0	0.0%	0	0.0%	0	0.0%
• Not available		4	14.3%	6	5.8%	0	0.0%
1 Year Postoperation, N_f = 134							
Mean Gradient		N_d = 18		N_d = 79		N_d = 30	
• Mean ± SD		3.7 ± 2.0		4.4 ± 1.8		4.0 ± 1.5	
• Min, max		1.7, 7.5		1.7, 10.0		2.0, 7.1	
EOA		N_d = 15		N_d = 70		N_d = 28	
• Mean ± SD		2.1 ± 0.6		2.1 ± 0.6		2.1 ± 0.6	
• Min, max		1.2, 3.1		0.9, 4.0		1.4, 4.3	
Regurgitation		N_d = 15		N_d = 66		N_d = 29	
		n	% (n/N_d)	n	% (n/N_d)	N	% (n/N_d)
• 0		11	73.3%	53	80.3%	23	79.3%
• 1-2+		3	20.0%	11	16.7%	6	20.7%
• 3+		1	6.7%	1	1.5%	0	0.0%
• 4+		0	0.0%	0	0.0%	0	0.0%
• Not available		0	0.0%	1	1.5%	0	0.0%

Notes:

1. Hemodynamic evaluations were performed using transthoracic echocardiography (TEE) and in some cases, transesophageal echocardiography (TEE). Data does not include results from double valve replacement.
2. N_f = number of patients followed (reproduced from Figure 2).
3. Mean gradient represents the pressure drop measured across the valve in mmHg.
4. N_d = number of patients for which hemodynamic data were collected.
5. EOA = effective orifice area measured in cm^2.
6. Regurgitation represents the valvular backflow of blood due to normal leakage and perivalvular leakage; 0 = none, 1+ = mild, 2+ = moderate, 3+ = moderate/severe, 4+ = severe.
7. n = number of patients in each category.

10.1 Description of Patients and Analysis for Gender Bias

In the mitral On-X® Prosthetic Heart Valve clinical trial the patients were 37.6 % male (86/229). The gender distribution is consistent with its incidence within the heart valve replacement population. No patient selection bias based on gender could be identified. An analysis of outcomes, including adverse event rates and NYHA changes, for gender differences showed no significant differences due to gender; thus, no gender bias was found.

11. CONCLUSIONS DRAWN FROM THE STUDIES

The results from pre-clinical laboratory studies performed on the On-X® Prosthetic Heart Valve for biocompatibility, hydrodynamic performance, and structural integrity demonstrate that this device is suitable for long-term implant.

The animal studies show that the On-X® Prosthetic Heart Valve is safe for valve replacement.

The clinical studies submitted in the PMA application provide scientific evidence that the On-X® Prosthetic Heart Valve is safe and effective for the replacement of native or prosthetic mitral valves.

12. PANEL RECOMMENDATIONS

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 application was not referred to the Circulatory Systems Device Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

13. FDA DECISION

FDA issued an approval order on March 6, 2002.

The applicant's manufacturing and control facilities were inspected on 10/12/00 (TX) and 11/21/00 (Germany), and the facilities were found to be in compliance with the Quality Systems Regulation (Part 820).

14. APPROVAL SPECIFICATIONS

Directions for use: See final labeling (Instructions for Use).

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the final labeling (Instructions for Use).

Post-approval Requirements and Restrictions: See Approval Order.