SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Replacement Heart Valve
Device Trade Name:	Perceval Sutureless Heart Valve
Device Procode:	LWR
Applicant's Name and Address:	Sorin Group Canada Inc. 5005 North Fraser Way Burnaby, British Columbia V5J 5M1 Canada
Date(s) of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P150011
Date of FDA Notice of Approval:	January 8, 2016

II. INDICATIONS FOR USE

The Perceval bioprosthesis is indicated for the replacement of diseased, damaged, or malfunctioning native or prosthetic aortic valves.

III. CONTRAINDICATIONS

1. Aneurysmal dilation or dissection of the ascending aortic wall;
2. Known hypersensitivity to nickel or cobalt alloys;
3. Anatomical characteristics outside the specification given in Table 1.

Table 1. Patient anatomical characteristics

REF	**SIZE**	**AORTIC ANNULUS DIAMETER [A]** (mm)	**SINOTUBULAR JUNCTION DIAMETER [≤1.3 A]** (mm)
PVS21	S	19-21	≤24.7-27.3
PVS23	M	21-23	≤27.3-29.9
PVS25	L	23-25	≤29.9-32.5
PVS27	XL	25-27	≤32.5-35.1

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Perceval Sutureless Heart Valve labeling.

V. DEVICE DESCRIPTION

The Perceval Sutureless Heart Valve (Perceval Valve) is a bioprosthetic valve (Figure 1) designed to replace a diseased native or a malfunctioning prosthetic aortic valve via open heart surgery. The Perceval prosthesis consists of a tissue component made from bovine pericardium and a self-expandable Nitinol stent. The self-expanding stent frame along with a dedicated delivery system which allows physicians to position and anchor the valve suturelessly.

The stent has two cylindrical ring segments on the proximal (inflow ring) and distal (outflow ring) sides, and a double set of elements to connect the two rings. The first set comprises 3 straight elements (columns) to support the valve. The second set comprises 6 sinusoidal elements radially protruding from the cylindrical section to provide prosthetic anchorage to the aortic root in the sinus of Valsalva.

The inflow ring of the prosthesis has an external pericardial sealing collar encouraging adaptation to the aortic annulus. In correspondence with each valve sinus, this ring has three eyelets through which guide threads are passed to aid prosthesis positioning.

The Pericardial tissue component is stabilized by glutaraldehyde and consists of a pericardial tissue valve and a pericardial sealing collar. The tissue valve is produced from two sheets of bovine pericardium. The first sheet takes the form of the three valve leaflets, assembled in order to allow only one-way blood flow. The second sheet is the anchorage element between leaflets and stent. The tissue valve is set into the metal stent by overstitching the pericardium to the inflow ring around the full circumference and to the three columns.

The stent frame and threads used to assemble the bioprosthesis are coated with Carbofilm^{TM}, to create a thin and homogeneous layer of biocompatible high density turbostratic carbon.

The Perceval heart valve is supplied un-mounted. Prior to implantation, the physician loads the valve onto the Dual Holder by reducing the valve size using the polycarbonate Dual Collapser (Figure 1).

The Dual Holder is available for sternal approaches and includes a rigid shaft with an end section that houses the valve prosthesis during delivery. The holder is composed of PTFE, Delrin, Ultem, and stainless steel. The Dual MICS Holder is also available for minimally invasive procedures and is identical to the Dual Holder but is approximately 3 cm longer. The Dual Holder and Dual Collapsers each come in two sizes (S/M and L/XL) to cover the range of implant sizes.

After implantation, the physician uses the Post-dilation catheter to dilate the valve in-situ (Figure 1).

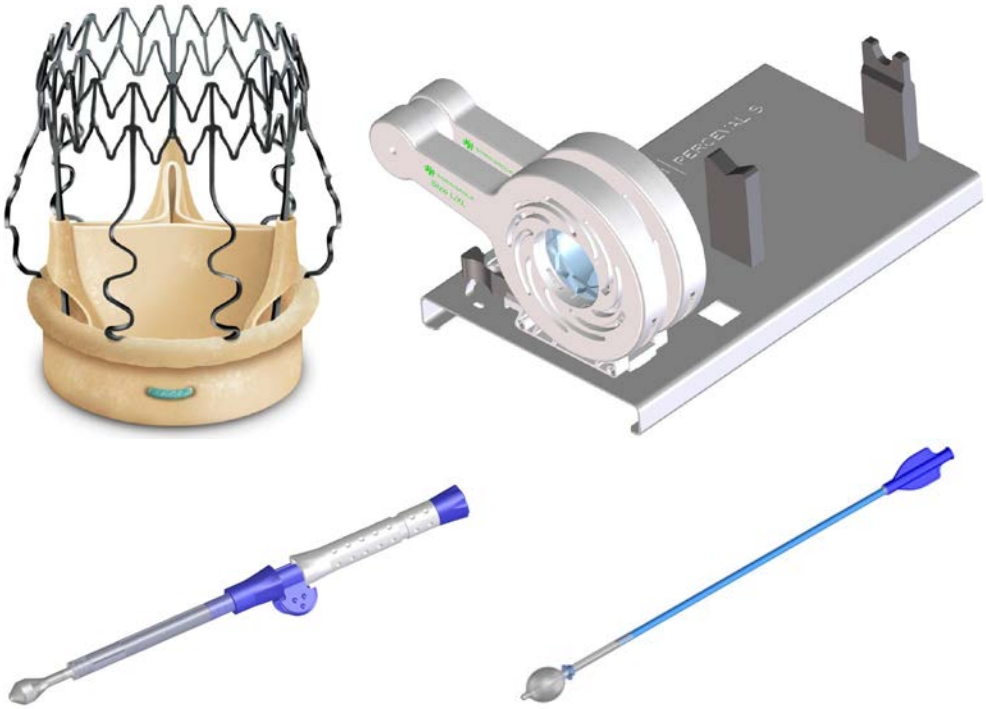

Figure 1. Top Left: Perceval Sutureless Heart Valve, Top Right: Perceval Dual Collapser, Bottom Left: Perceval Dual Holder, Bottom Right: Perceval Post-dilation Catheter.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the correction of diseased and malfunctioning heart valves: drug therapy, annuloplasty, valvuloplasty (with or without the use of implantable materials). If patients require replacement of his or her native or previously implanted prosthetic valve, the alternatives include other commercially available mechanical valves or bioprosthetic valves, or a homograft. 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 lifestyle.

VII. MARKETING HISTORY

The Perceval Sutureless Heart Valve is currently marketed in more than 40 countries worldwide including: Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Israel, Italy, Poland, Portugal, Russia, Saudi Arabia, Slovenia, Spain, Sweden, Switzerland, The Netherlands, Turkey, United Kingdom.

The Perceval Sutureless Heart Valve has never been withdrawn from marketing for any reason related to its safety or effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

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

- arrhythmias
- cardiac tamponade
- conduction system disturbances (e.g., atrioventricular node block, left-bundle branch block, asystole)
- death
- dislodgement or migration
- endocarditis
- heart failure (acute cardiac failure)
- hemolysis
- hemolytic anemia
- hemorrhage (bleeding)
- infection other than endocarditis
- myocardial infarction
- nonstructural valve dysfunction (e.g., entrapment by pannus or suture, inappropriate sizing or positioning, etc.)
- pericardial effusion
- paravalvular and transvalvular leakage
- prosthesis thrombosis
- stroke or any related neurologic disorders
- structural valve deterioration (SVD) (e.g., regurgitation, stenosis, leaflet tear or perforation, etc.)
- thromboembolism
- tissue dehiscence
- stenosis
- stent distortion due to thoracic compression (i.e., cardiopulmonary resuscitation) or trauma.

It is possible that these adverse events could lead to:

- reoperation
- explantation
- permanent disability
- permanent pacemaker implantation
- death

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

IX. SUMMARY OF PRECLINICAL STUDIES

A. Laboratory Studies

In vitro testing was performed for the Perceval valve in accordance with the ISO 5840:2005 standard "Cardiovascular Implants - Cardiac Valve Prostheses."

1. Hydrodynamic Performance

In vitro hydrodynamic performance studies were completed on Perceval valve in accordance with the ISO 5840 standard "Cardiovascular Implants – Cardiac Valve Prosthesis."

Valves were evaluated after deployment in circular and non-circular annuli. Testing included steady flow pressure drop, steady backflow leakage, pulsatile flow pressure drop, pulsatile flow regurgitation, flow visualization and the verification of the Bernoulli relationship. For test articles deployed in circular annulus, commercially available aortic valve replacements were used as controls, while for articles deployed in irregular shape nominal deployed Perceval valves. For test articles deployed in circular annulus, commercially available aortic valve replacements were used as controls, while for articles deployed in irregular shape nominal deployed Perceval valves were used as controls. The characterization was conducted using both low compliant and high compliant chambers. A matrix of the tests performed and corresponding results are provided in Table 2.

Table 2. Hydrodynamic Performance Testing Summary

Test	**Purpose/ Objective**	**Test/ Reference articles**	**Results**
Steady Forward Flow Pressure Drop	To determine the pressure drop at various steady forward flow rates	Nominal: Test: Size S, M, L and XL Reference: Size 21, 23, 25 and 27 Irregular: Test: Size S and XL Reference: Nominal Perceval size S and XL	Perceval prostheses have small pressure drops and high EOAs and performance indexes when compared to the reference valves.
Steady Backflow Leakage	To determine the leakage rate at various steady back flow pressures	Nominal: Test: Size S, M, L and XL Reference: Size 23, 25, 27 and 29 Irregular: Test: Size L and XL Reference: Nominal Perceval size L and XL	Perceval prostheses offer satisfactory performance in terms of its competency to prevent significant transvalvular aortic backflow during the diastolic phase.
Pulsatile Flow Pressure Drop	To determine pressure drop and effective orifice area performance under pulsatile flow conditions.	Nominal: Test: Size S, M, L and XL Reference: Size 21, 23, 25, 27 and 29 Irregular: Test: Size S and XL	The Perceval valve offers satisfactory hydrodynamics with a larger effective orifice area than those required by the ISO 5840:2005 acceptance criteria for aortic valves, and similar pressure drop to the reference valves.

Test	Purpose/ Objective	Test/ Reference articles	Results
		Reference: Nominal Perceval size S and XL	
Pulsatile Flow Regurgitation	To determine regurgitation performance under pulsatile flow conditions.	Nominal: Test: Size S, M, L and XL Reference: Size 23, 25, 27 and 29 Irregular: Test: Size L and XL Reference: Nominal Perceval size L and XL	The Perceval valve offers satisfactory hydrodynamics with regurgitant fractions that were lower than those required by the ISO 5840:2005 acceptance criteria for aortic valves.
Flow Visualization	To qualitatively investigate flow characteristics in the vicinity of the valve	Test: Size S in low and high compliant chamber	The Perceval valve offers satisfactory aortic flow patterns throughout the entire cardiac cycle. Single broad jet covering the complete flow cross-section was observed. No flow stasis during valve opening and no regurgitation during the diastolic phase were observed.
Verification of the Bernoulli Relationship		Test: Size S, M, L and XL	Pressure drop results for the Perceval valve demonstrated correlation with the Bernoulli relationship

2. Structural Performance

In-vitro structural performance studies were conducted on Perceval valve in accordance with the ISO 5840 standard "*Cardiovascular Implants – Cardiac Valve Prosthesis.*" Commercially available aortic valve replacements and self-expandable stents were used as controls. A matrix of tests performed and corresponding results are provided in Table 3.

Table 3. Structural Performance of the Perceval Valve

Test	Purpose/ Objective	Test/ Reference articles	Results
Accelerated Wear	To assess long-term performance of the valve though accelerated wear	Nominal: Test: Size S, M, L and XL Reference: Size 21, 23, 25 and 27 Irregular: Test: Size S, L and XL Reference: Nominal Perceval	All valves survived durability testing to 200 million cycles in accelerated wear testers without structural damage and/or functional impairment. After testing to 200 million cycles, all valves met the minimum EOA and Total Regurgitation Fraction requirements of ISO 5840:2005.

Test	Purpose/ Objective	Test/ Reference articles	Results
		size S, L and XL	
Dynamic Failure Mode	To obtain information about the failure modes affecting the durability of the valve.	Test: Size S, M, L and XL	All of the failures for the test valves occurred at pressures well beyond what would be experienced *in vivo*.
Stent corrosion resistance	To characterize the corrosion resistance of the valve stent in accordance with ASTM F2129, ISO 16429 and ISO 10993-15	Test: Perceval stents size S, M, L and XL Reference: commercially available self-expandable stents	All test results have shown the good corrosion resistance and electrochemical stability of the Perceval stent.
Stent fatigue testing	To determine stent fatigue resistance to 600 million cycles	Perceval stents size S, M, L and XL	No frame cracks or fractures observed at completion of 600 million cycles both in air and saline solution
Strain analysis (FEA)	To characterize the mechanical behavior of the stent during collapsing, deployment and operation	Modeling based on *in vitro* and clinical data of size S, M, L and XL Perceval stents	Results indicate that the worst-case size L and XL Perceval stents should not fracture for 600 million cycles, even under the unlikely simultaneous combination of all the worst case conditions.

The following additional structural performance studies were completed with acceptable results: Nitinol raw tube characterization, Nitinol as-processed characterization, fatigue life assessment, stent residual stress evaluation.

3. Design Specific Performance Studies

The following design-specific *in vitro* performance studies of Perceval were completed with acceptable results: stent radial strength, valve migration force, stent column deflection, and radiopacity.

4. MRI Compatibility

Testing of this device in magnetic fields of 1.5 and 3.0 Tesla showed that the device is MR Conditional. Perceval can be scanned safely under the following conditions:

- Static magnetic field of 1.5 Tesla or 3 Tesla
- Spatial gradient field of 2500 Gauss/cm or less.
- Maximum whole-body-averaged specific absorption rate (SAR) of 4 W/kg in the First Level Controlled Mode for the MR system for 15 minutes of scanning.

5. Accessory Performance Testing

The following tests were performed with the Perceval Dual Holder and MICS Dual Holder and showed acceptable results: dimensional verification, visual inspection, simulated use, and bond strength.

The following tests were performed for the Perceval Post-dilation Catheter and MICS Post-dilation Catheter and showed acceptable results: dimensional verification, simulated use, balloon characterization, bond strength, and balloon compliance.

The following tests were performed for the Perceval Dual Collapser and showed acceptable results: dimensional verification, visual inspection, and simulated use.

6. Biocompatibility

The biological safety assessment of the Perceval valve and its accessories was conducted in accordance with the requirements of the ISO 10993 standard series "Biological Evaluation of Medical Devices." Based on the results of the biocompatibility testing performed, the Perceval valve was determined to be biocompatible, non-mutagenic, and non-toxic. A summary of the testing conducted on the prosthetic valve and its accessories (i.e., the Dual Collapser, valve sizer kit, Dual Holder, and Post-Dilation Catheter for standard surgery and MICS) is provided in Table 4 and Table 5**,** respectively. Chemical characterization was performed in lieu of carcinogenicity testing and the characterization evaluations demonstrated that residuals did not require long-term studies.

Table 4. Summary of Biocompatibility Testing for the Perceval Valve Prosthesis

Test	**Objectives**	**Results**
Cytotoxicity	Assessment of test device toxicity on specific in vitro cell culture	Non-cytotoxic
Irritation (ISO Rabbit Intracutaneous Reactivity)	Evaluation of local irritation or toxic effects of leachable chemicals extracted from the test article following intra-cutaneous injection in rabbits	Non-irritant

Test	Objectives	Results
Sensitization (ISO Guinea Pig Maximization Test)	Determination of the potential for contact sensitization by extracts of test device	No evidence of sensitization
Acute Systemic Toxicity (ISO Mouse Systemic Injection)	Evaluation of acute systemic toxicity of leachable chemicals extracted from the test article following a single intravenous injection in mice	Non-toxic
Pyrogen Test (USP Rabbit Pyrogenicity)	Assessment of the potential febrile response from material mediated reaction occurring after intravenous injection of the test article in rabbits	Non-pyrogenic
LAL test	Determination of the presence of bacterial endotoxin	Free of bacterial endotoxin
Hemocompatibility	Assessment of the in vitro effects of the test article or its extract on blood properties, including hemolytic potential and alterations of the coagulation response	No alterations in blood properties
Genotoxicity (Ames test)	Evaluation of the potential of the test article to induce DNA reverse mutations in five strains of *Salmonella typhimurium* in the presence and absence of metabolic activation system	Non-mutagenic
Mouse Lymphoma Test	Detection of mutations at the thymidine kinase locus caused by DNA base pair changes, frame shift and small deletions, after exposure to the test article extract	Non-mutagenic
Implantation test (ISO Rabbit Subcutaneous and Intramuscular)	Evaluation of the test article local and systemic effects on living tissue throughout chronic implantation in rabbit	No signs of toxicity

Table 5. Summary of Biocompatibility Testing for Perceval Accessories (Dual Holder, Post-Dilation Catheter, Dual Collapser, and sizer kit)

Test	Objectives	Results
Cytotoxicity	Assessment of test device toxicity on specific in vitro cell culture for the accessories.	Non-cytotoxic
Intracutaneous reactivity (ISO Rabbit Intracutaneous Reactivity)	Evaluation of local irritation or toxic effects of leachable chemicals extracted from the test article following intra-cutaneous injection in rabbits	Non-irritant
Sensitization (ISO Guinea Pig Maximization Test)	Determination of the potential for contact sensitization by extracts of test device	No evidence of sensitization

Test	Objectives	Results
Acute Systemic Toxicity (ISO Mouse Systemic Injection)	Evaluation of acute systemic toxicity of leachable chemicals extracted from the test article following a single intravenous injection in mice	Non-toxic
Pyrogen Test (USP Rabbit Pyrogenicity)	Assessment of the potential febrile response from material mediated reaction occurring after intravenous injection of the test article in rabbits	Non-pyrogenic
LAL test	Determination of the presence of bacterial endotoxin	Free of bacterial endotoxin
Hemocompatibility	Assessment of the in vitro effects of the test article or its extract on blood properties, including hemolytic potential and alterations of the coagulation response	No alterations in blood properties

[1]Testing of the Dual Collapser was limited to cytotoxicity, sensitization, intracutaneous reactivity based on the limited contact with the patient.
[2]Testing of the sizer kit was limited to cytotoxicity, sensitization, irritation, systemic toxicity, and material mediated pyrogenicity based on the level of patient contact.

B. Animal Studies

One GLP chronic *in vivo* study in sheep and two non-GLP *in vivo* studies (acute swine and chronic sheep) were conducted to assess procedural feasibility, sutureless anchoring, healing and inflammatory responses to the implant, hemodynamic performance and valve-related pathology. The studies were completed accordance with the requirements of ISO 5840:2005 - *Cardiovascular Implants – Cardiac Valve Prostheses*.

During the GLP chronic study a total of 12 Perceval valves were implanted in aortic position of juvenile sheep for a 20 weeks evaluation period and compared to four commercially available bioprosthetic heart valve used as control valves. The study included the evaluation of procedural handling and implant characteristics, animal survival, hemodynamic performance, hematology, valve pathology and mineralization.

The Perceval valve demonstrated acceptable handling and anchoring to the implant site, normal tissue healing response and no thrombogenicity, satisfactory hemodynamic performance and lower mineralization propensity compared to the control valve.

1. Handling and anchoring to implant site

The ease, repeatability and safety of the surgical procedure were confirmed. The deployment and anchoring of the sutureless Perceval bioprosthesis were demonstrated to be satisfactory since there was no evidence of dislodgement, migration or embolization of the valve either during the initial implantation or following 140 days of implantation. The low incidence of paravalvular leaks also confirms that adequate anatomic sizing and the design features of the Perceval allow the safe implantation of the valve within the aortic root as a replacement aortic valve.

2. Animal Survival

Of the 12 sheep implanted with Perceval valve during the GLP chronic study, 7 animals were explanted as per the study protocol 20 weeks after surgery; 2 intra-operative deaths occurred as technical failures; 1 animal was euthanized 77 days after surgery for ethical reasons secondary to endocarditis; 2 early animal deaths occurred 68 and 104 days after surgery and determined to be non-valve related based on the necropsy findings.

3. Hemodynamic Performance

The hemodynamic performance of the Perceval valve – as assessed by transvalvalular pressure gradient, EOA, regurgitation and leaflet motion – was comparable to the control valve and within the normal physiologic range.

4. Hematology and Clinical Chemistry

Hematology monitoring was performed at the following time-points throughout the scheduled follow-up: 0 (baseline), 7, 90 and 140 days. Although large variations were registered for almost all the parameters both in the test and control groups, the hematology results were within the normal range. No observable negative effect of the Perceval valve on blood chemistry was identified.

5. Valve-Related Pathology

Macroscopic findings demonstrated adequate biocompatibility and healing response of the Perceval prosthesis as aortic valve replacement in sheep. Histopathology results showed favorable tissue response to the implant with minimal pannus formation covering the inflow ring and the base of prosthetic cusps. Though there were focal sites of fibrin deposition as typically seen on the surface of porcine aortic valve and pericardial bioprostheses, no valve-related thrombosis was reported throughout the study.

6. Mineralization

Mineralization was analyzed by X-ray radiography, histopathology of prosthetic cusps and quantitative calcium determination by inductively coupled plasma atomic emission spectroscopy. Some local sites of dystrophic calcification in the cusp tissue were observed as typically reported for porcine and pericardial prostheses after 20 weeks implantation in juvenile sheep. Quantitative inorganic calcium and phosphorous analysis demonstrated a lower mineralization rate in the Perceval valve compared to the control valve.

C. Additional Studies

1. Sterilization

The Perceval valve bioprosthesis is sterilized by terminal liquid sterilization in glutaraldehyde sterilant solution. The sterilization process has been validated to assure a sterility assurance level (SAL) of 10^{-6}.

The Perceval Dual Holder, Dual MICS Holder, Post-Dilation Catheter, Post-Dilation MICS Catheter, and Dual Collapser are provided sterile and sterilized using Ethylene Oxide. The sterilization process has been validated to assure a sterility assurance level

(SAL) of 10^{-6}. Validation was performed to ensure that reusable accessories could be appropriately sterilized.

2. Shelf Life

The shelf life of the Perceval Valve, Dual Holder, Dual MICS Holder, Post-Dilation Catheter, Post-Dilation MICS Catheter, and Dual Collapser has been established at 3 years based on real time aging. Packaging and product integrity studies were conducted to ensure that the shelf life for each package and product is maintained for a minimum of three (3) years based on accelerated aging-studies.

Integrity of the finished device was evaluated after 3 years of real-time ageing. This evaluation included testing on: pericardial tissue (shrinkage temperature, biomechanical properties, collagen content, tissue microstructure); storage solution (pH value, residuals); valve (hydrodynamic performance, accelerated wear testing, corrosion, valve migration force and stent radial strength); and jar (microbiological barrier and leaching analysis). Acceptable results were observed for all tests with samples aged to 3-years.

Functionality and product integrity of the Dual Holder, Dual MICS Holder, Post-Dilation Catheter, Post-Dilation MICS Catheter, and Dual Collapser was demonstrated after three years accelerated aging and simulated distribution testing.

3. Package Integrity

The Perceval prosthesis is provided sterile in a polycarbonate jar. The Dual Holder, Dual MICS Holder, Post-Dilation Catheter, Post-Dilation MICS Catheter, and Dual Collapser are packaged in a blister and closed in double sealed Tyvek pouches. The packaging systems were evaluated via physical testing (peel testing) and microbial challenge testing and shown to maintain the sterile barriers following three year accelerated aging.

Package integrity studies were conducted after simulated shipping process (manual handling, vehicle stacking, vibration, and low pressure hazard) to ensure integrity of packaging. Testing included package integrity, and microbial challenge after real-time aging. The results demonstrate that the package integrity is maintained.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of heart valve replacement with the Perceval valve in the European CAVALIER study. The study was conducted in the following countries: France, Germany, Poland, Belgium, England, Netherlands, and Austria. Data from the CAVALIER clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

Patients were treated between February 23, 2010, and September 30, 2013. The database for this PMA reflected data collected through November 5, 2014, and included 658 patients. There were 26 investigational sites.

The study was a prospective, multi-center, non-randomized clinical study of the Perceval heart valve implanted in patients requiring native or prosthetic aortic valve replacement. 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.

The study used an independent Data Monitoring Committee (DMC). The purpose of the DMC was to review the progress of the trial. A Clinical Events Committee (CEC) was formed and the aim of the CEC was to independently review and adjudicate events. A core lab was used to independently evaluate echocardiogram data.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the CAVALIER study was limited to patients who met the following inclusion criteria:

1. Patients of age ≥ 65 years;
2. Patients with aortic valve stenosis or steno-insufficiency;
3. Patients in which a preoperative evaluation indicated the need for native or prosthetic aortic valve replacement with a biological prosthesis;
4. Patients willing to sign the informed consent; and
5. Patients willing to undergo all the medical follow-ups and echocardiography examinations and laboratory tests in the study protocol.

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

1. Patients involved in any other clinical study for drugs or devices;
2. Patients with a previously implanted Perceval prosthesis, within the clinical study, that required replacement;
3. Patients with previous implantation of valve prostheses or annuloplasty ring not being replaced by the study valve;
4. Patients that required simultaneous cardiac procedures, apart from septal myectomy and/or coronary bypass;

5. Patients who required double or multiple valve replacement or repair in whom the mitral, tricuspid, or pulmonic valve would be replaced with a non-Perceval valve or repaired;

6. Patients with aneurysmal dilation or dissection of the ascending aortic wall;

7. Patients needing non-elective intervention;

8. Patients with active endocarditis;

9. Patients with active myocarditis;

10. Patients with congenital bicuspid aortic valve;

11. Patients with aortic root enlargement, where the ratio between the diameter of the sino-tubular junction and the annulus diameter, assessed by TTE, is >1.3;

12. Patients with an aortic root height (measured from aortic annulus to sino-tubular junction) ≥ 21 mm for size S/21, ≥ 22.5 mm for size M/23, ≥ 24 mm for size L; and ≥ 25 mm for size XL/27;

13. Patient with myocardial infarction ≤ 90 days before the planned valve implant surgery;

14. Patients with known hypersensitivity to nickel alloys;

15. Patients with a documented history of substance (drug or alcohol) abuse;

16. Patients who were a prison inmate, institutionalized, or unable to give informed consent;

17. Patients with a major or progressive non-cardiac disease that, in the investigator's experience, results in a life expectancy of less than 12 months, or in whom the implant of the device would create an unacceptable risk to the patient;

18. Patients undergoing renal dialysis for chronic renal failure or suffering from hyperparathyroidism; or

19. Patients with an acute preoperative neurological deficit, myocardial infarction, or cardiac event that had not returned to baseline or stabilized ≥ 30 days prior to the planned valve implant surgery.

2. Follow-up Schedule

All patients were scheduled for follow-up examinations at discharge or within 30 days post-procedure, between 3 and 6 months, 12 months, and annually thereafter to a minimum of five years post procedure.

Preoperatively, demographic and baseline data including NYHA functional classification were collected. Postoperatively, the objective parameters measured during the study included blood value, NYHA functional class and echocardiography data were collected at each follow-up. Adverse events and complications were recorded at the time of occurrence or site notification.

3. Clinical Endpoints

With regards to safety, the following criteria were evaluated:

1) the complication and survival rates for the Perceval valve are comparable to appropriate historical controls manifested as Objective Performance Criteria (OPCs), and to that reported in the literature for other stentless and stented bioprosthesis.

With regards to effectiveness, the following criteria were evaluated:

1) the hemodynamic performance of the Perceval valve is comparable to that reported in the literature for other bioprosthetic valves; and

2) clinically significant improvement in overall patient condition by comparison of preoperative and postoperative NYHA functional classification.

B. Accountability of PMA Cohort

At the time of database lock, of 815 patients enrolled in the PMA study, implant was attempted in a total of 658 patients and 599 patients were followed longer than 31 days post-procedure. A total of 157 patients were excluded before implant and 30 patients were classified as implant failures, received a non-study valve, and were not included in the main analysis. Study accountability is detailed in Table 6.

Table 6. Study Accountability

Visit interval	Possible N (100%)	Clinical visit or phone call n (%)	Clinical visit n (%)	Phone call n (%)	Missed n (%)
Preoperative	658 (100.0%)	658 (100.0%)	658 (100.0%)	-	-
Discharge (or 30 days)	615 (100.0%)	614 (99.8%)	614 (99.8%)	-	1 (0.2%)
3-6 Months	580 (100.0%)	541 (93.3%)	512 (88.3%)	29 (5.0%)	39 (6.7%)

Visit interval	Possible N (100%)	Clinical visit or phone call n (%)	Clinical visit n (%)	Phone call n (%)	Missed n (%)
12 Months	554 (100.0%)	537 (96.9%)	498 (89.9%)	39 (7.0%)	17 (3.1%)
2 Years	453 (100.0%)	435 (96.0%)	396 (87.4%)	39 (8.6%)	18 (4.0%)
3 Years	318 (100.0%)	308 (96.9%)	279 (87.7%)	29 (9.1%)	10 (3.1%)
4 Years	83 (100.0%)	83 (100.0%)	77 (92.8%)	6 (7.2%)	-

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for an aortic heart valve study (Table 7).

Table 7. CAVALIER Study Preoperative Patient Characteristics

Patients	658	%
Mean age ± SD (range)	78.3 ± 5.6 (61.6 ; 92.6)	
Age		
< 65	7	1.1%
65-69	41	6.2%
70-74	138	21.0%
75-79	209	31.8%
80-84	186	28.3%
85-89	70	10.6%
≥ 90	7	1.1%
Sex		
Female	424	64.4%
Male	234	35.6%
Mean BSA ± SD (range)	1.8 ± 0.2 (1.0 - 2.4)	
NYHA		
I	22	3.3%
II	198	30.1%
III	386	58.7%
IV	32	4.9%
Not available	20	3.0%
Mean EuroScore ± SD (range)	10.2 ± 7.8 (1.2 - 75.3)	
Mean STS Score ± SD (range)	7.2 ± 7.4 (0.8 - 50.0)	
Cardiac Rhythm[1]		
Sinus Atrial Fibrillation Paced Other	559 52 21 22	85.5% 8.0% 3.2% 3.4%
Previous Cardiovascular Intervention[2]		
None **Previous intervention**	531 (80.7%) 127 (19.3%)	

Valve replacement	10	1.5%
CABG surgery	13	2.0%
PCI[3]	78	11.9%
Valve repair with annuloplasty ring	1	0.2%
Pacemaker	33	5.0%
Other	10	1.5%

1. Missing data for 4 patients.
2. Patients may have more than one previous intervention.
3. PCI=Percutaneous Coronary Intervention (with or without stents)

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the implanted patient cohort of 628 patients over the course of 1,494.77 total patient-years and 1,444.44 late patient-years. The key safety outcomes and adverse event rates for aortic valve replacement for this study are presented in Table 8. The data are presented as percentages for early events, linearized late rates for late events, and "freedom from event" (actuarial analysis) at year 1, 2, 3, and 4 post-implant.

Table 8. Observed Adverse Event Rates

Adverse event	**Early events[1]**		**Late events[2]**		**Freedom From Event [95% CI][3]**			
	N	**%**	**N**	**%/pt-yr**	**1 year**	**2 years**	**3 years**	**4 years**
All mortality	23	3.7	74	5.1	91.7 [88.6 – 93.9]	88.7 [86.1 – 91.3]	83.2 [79.9 – 86.5]	77.4 [72.5 – 82.4]
Valve-related and valve- and procedure-related death	8	1.3	24	1.8	97.2 [95.9 – 98.5]	96.2 [94.6 – 97.8]	94.4 [92.4– 96.5]	89.5 [85.1– 93.8]
Valve reintervention	5	0.8	14	1.0	98.0 [96.9 – 99.1]	97.4 [96.1– 98.7]	97.1 [95.7 – 98.5]	95.2 [92.3 – 98.2]
Explant[4]	5	0.8	13	0.9	98.0 [96.9 – 99.1]	97.4 [96.1– 98.7]	97.1 [95.7 – 98.5]	95.2 [92.3 – 98.2]
All bleeding	28	4.5	37	2.6	87.5 [84.8 – 90.1]	86.6 [83.9 – 89.4]	85.2 [82.2 – 88.2]	84.1 [80.5 – 87.7]
Major bleeding	22	3.5	28	1.9	89.1 [86.6– 91.6]	88.5 [85.9 – 91.0]	87.6 [84.9 – 90.3]	86.5 [83.1 – 89.9]
Major anticoagulation-related bleeding	11	1.8	16	1.1	94.6 [92.8 – 96.5]	94.3 [92.4 – 96.1]	93.7 [91.6 – 95.7]	92.6 [89.6 – 95.5]
Thromboembolism[5]	27	4.3	29	2.0	94.3 [92.4 – 96.1]	92.8 [90.7 – 94.9]	91.7 [89.3 – 94.0]	89.4 [86.0 – 92.9]
Stroke	14	2.2	12	0.8	96.7 [95.3 – 98.1]	95.9 [94.3 – 97.5]	95.1 [93.2 – 96.9]	94.1 [91.4 – 96.7]
Endocarditis	1	0.2	17	1.2	98.5 [97.5– 99.5]	97.7 [96.4 – 98.9]	97.4 [96.0 – 98.8]	93.7 [89.2 – 98.1]
Valve thrombosis	0	0	0	0	100 [100 - 100]	100 [100 - 100]	100 [100 - 100]	100 [100 - 100]
Structural valve deterioration[6]	0	0	9	0.6	100 [100 - 100]	99.8 [99.4 – 100]	99.8 [99.4 – 100]	95.5 [91.0 – 100]

Adverse event	Early events[1]		Late events[2]		Freedom From Event [95% CI][3]			
	N	%	N	%/pt-yr	1 year	2 years	3 years	4 years
Nonstructural valve dysfunction[7]	7	1.1	10	0.7	97.9 [96.7 – 99.0]	97.5 [96.2 – 98.7]	97.5 [96.2 – 98.7]	93.4 [88.7 – 98.0]
All paravalvular leak	4	0.6	5	0.3	98.9 [98.0 – 99.7]	98.6 [97.7 – 99.6]	98.6 [97.7 – 99.6]	97.2 [95.0 – 99.5]
Major paravalvular leak	2	0.3	3	0.2	99.3 [98.7 – 99.9]	99.1 [98.4 – 99.9]	99.1 [98.4 – 99.9]	98.2 [96.1 – 100]
All hemolysis	4	0.6	5	0.3	98.6 [97.7 – 99.6]	98.4 [97.3 – 99.5]	98.4 [97.3 – 99.5]	98.4 [97.3 – 99.5]
Adverse events leading to pulse generator implant[8]	46	7.3	29	2.0	84.8 [81.9 – 87.6]	83.9 [81.0 – 86.9]	83.3 [80.3 – 86.4]	81.6 [77.1 – 86.1]

1. Early valve-related events include postoperative events occurring 1-30 days post implant. Early events rates are calculated as the percentage of events on total number of patients (628 evaluable patients).
2. Late postoperative events (> 30 days). Linearized late rates calculated using 1444.44 late patient-years.
3. Freedom from first event (early or late) rates were calculated using the Kaplan-Meier method. In brackets the 95% lower and upper limits are reported.
4. There was 1 additional explant which was perioperative on Day 0.
5. There was 1 additional thromboembolic event which was a perioperative transient ischemic attack on Day 0.
6. The Kaplan-Meier rates are calculated considering only the 7 cases out of 9, adjudicated by the CEC as SVD.
7. Includes paravalvular leak. Also includes 2 cases of late tricuspid regurgitation reported as nonstructural valve dysfunction (NSVD) but reclassified as non-NSVD by the CEC.
8. There were 27 additional adverse events leading to pulse generator implant which were perioperative on Day 0.

The results of the CAVALIER study were compared to the OPC per ISO 5840 requirements and detailed in Table 9. The study valve successfully met the OPC requirements.

Table 9. Linearized Hazard Rates (%/late patient-years) based on CEC adjudicated valve-related events and follow-up greater than 30 days after surgery). Total patients, N= 628.

Adverse event	Linearized Hazard Rates for >30 days post-op (All patients = 599) (1,444.44 late patient-years; mean = 829.7 days; max = 1624 days)			
	Number of patients	Number of events	one-sided 95% CI [Poisson distribution]	2 x OPC[1]
Bleeding	20	22	2.1%	2.8
Major Bleeding	15	16	1.6%	1.8
Thromboembolism	19	21	2.1%	5
Non structural valve dysfunction PVL	3	3	0.5%	2.4
Major PVL	2	2	0.4%	1.2
Endocarditis	15	16	1.6%	2.4
Valve thrombosis	0	0	-	0.4

[1] FDA Objective Performance Criteria

Table 10 presents the results of the Clinical Event Committee (CEC) adjudication for the 102 new or worsened cardiac conduction disturbances and other adverse events, occurring in 100 patients, leading to pulse generator implantation in the CAVALIER

study. One (1) patient had 2 different early arrhythmia events and a second patient had 2 late events.

Table 10. CEC-Adjudicated Cardiac Conduction Disturbances and Other Adverse Events Leading to Pulse Generator Implantation in CAVALIER Study [1, 2]

Adverse Event Leading to Pulse Generator Implant	Perioperative [Day 0]	Early [1-30 Days]	Late [> 30 Days]	Overall
Device-Related				
Cardiac Arrhythmia	1	2	0	3
3rd Degree AV Block	1	0	0	1
Bradycardia	0	1	0	1
Other Arrhythmias	0	1	0	1
Total	1	2	0	3
Device- and Procedure-Related				
Cardiac Arrhythmia	25	36	1	62
3rd Degree AV Block	24	25	0	49
2nd Degree AV Block	0	2	0	2
1st Degree AV Block	0	1	0	1
Atrial Fibrillation	1	2	0	3
Left Bundle Branch Block	0	2	1	3
Right Bundle Branch Block	0	1	0	1
Bradycardia	0	1	0	1
Other Arrhythmias	0	2	0	2
Total	25	36	1	62
Procedure-Related				
Cardiac Arrhythmia	1	4	0	5
3rd Degree AV Block	0	1	0	1
Atrial Fibrillation	0	2	0	2
Ventricular Fibrillation	1	0	0	1
Asystole	0	1	0	1
Heart Failure [3]	0	1	0	1
Total	1	5	0	6
Unrelated to Device or Procedure				
Cardiac Arrhythmia	0	3	24	27
3rd Degree AV Block	0	0	11	11
2nd Degree AV Block	0	1	3	4
Atrial Fibrillation	0	1	4	5
Left Bundle Branch Block	0	0	1	1
Bradycardia	0	0	2	2
Asystole	0	1	1	2
Other Arrhythmias	0	0	2	2
Heart Failure	0	0	2	2
Myocardial Infarction	0	0	1	1

Total	0	3	27	30
TOTAL	27	46	28	101

1. N = 628 implanted
2. Table presents 102 events in 100 patients, with 1 patient having 2 different early arrhythmia events and a second patient having 2 late events.
3. The event worsening of heart failure was not adjudicated by the CEC.

2. Effectiveness Results

Effectiveness of the Perceval heart valve was evaluated by NYHA functional class and echocardiographic assessment of the hemodynamic performance of the study valve.

The differences between the NYHA class at 12 months and the baseline were calculated. The data are presented in Table 11. In total, 77.5% of patients (362 over 467) showed a decrease of NYHA equal of at least one class, whereas 19.7% of patients remained stable over the time. Only 2.8% of patients showed a worsened clinical status.

Reduction in mean gradients and increase in EOA were observed at one year follow-up.

Table 11. Effectiveness Outcome, NYHA Functional Classification

	NYHA class change at 12 months vs. baseline													
	NYHA improved						**NYHA Stable**		**NYHA worsened**					
NYHA class at baseline	**-3**		**-2**		**-1**		**No change**		**+1**		**+2**		**+3**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
NYHA I (N = 15)	-	-	-	-	-	-	8	53.3	7	46.7	-	-	-	-
NYHA II (N = 160)	-	-	-	-	97	60.6	57	35.6	6	3.8	-	-	-	-
NYHA III (N = 277)	-	-	152	54.9	98	35.4	27	9.7	-	-	-	-	-	-
NYHA IV (N = 15)	8	53.3	7	46.7	-	-	-	-	-	-	-	-	-	-
Total (N = 467)	8	1.7	159	34.0	195	41.8	92	19.7	13	2.8	-	-	-	-

In Table 12 all of the main non-regurgitation hemodynamic data obtained at the 1 year follow-up echocardiographic exams are presented. Reduction in mean gradients and increase in EOA compared to pre-implant were observed at 1 year follow-up.

Table 12. Effectiveness Outcome at 1 Year Follow-up Visit: Hemodynamic Results

Hemodynamic parameter	**All sizes**	**S/21 mm**	**M/23 mm**	**L/25 mm**	**XL/27 mm**
Mean Gradient [mmHg]	N[1] = 362	n = 46	n = 156	n = 143	n = 17
Mean ± SD	9.1 ± 5.0	10.1 ± 4.2	9.4 ± 5.5	8.5 ± 4.6	9.7 ± 4.7
EOA [cm^2]	N[1]= 300	n=31	n=131	n=123	n=15
Mean ± SD	1.5 ± 0.4	1.3 ± 0.3	1.5 ± 0.4	1.5 ± 0.4	1.6± 0.4

[1] N = number of subjects with available hemodynamic parameter.

Valvular regurgitation data obtained at the echocardiographic exams at 1 year through 3 years follow-up are presented in Tables 13-15.

Table 13. Postoperative valvular regurgitation by valve size at 1 year in the CAVALIER Study[1]

Size	21 mm	23 mm	25 mm	27 mm
Severity				
None	12 (24.5%)	99 (51.3%)	73 (43.2%)	10 (45.5%)
Trace	13 (26.5%)	34 (17.6%)	46 (27.2%)	2 (9.1%)
Mild	20 (40.8%)	46 (23.8%)	43 (25.4%)	5 (22.7%)
Moderate	2 (4.1%)	5 (2.6%)	4 (2.4%)	0 (0%)
Severe	1 (2.0%)	1 (0.5%)	1 (0.6%)	0 (0%)
Not Evaluable	1 (2.0%)	8 (4.1%)	2 (1.2%)	5 (22.7%)
Total Number	49	193	169	22
Location				
None	12 (24.5%)	99 (51.3%)	73 (43.2%)	10 (45.5%)
Central	29 (59.2%)	70 (36.3%)	68 (40.2%)	5 (22.7%)
Paravalvular	3 (6.1%)	6 (3.1%)	9 (5.3%)	1 (4.5%)
Both	3 (6.1%)	10 (5.2%)	7 (4.1%)	0 (0%)
Not Evaluable	2 (4.1%)	8 (4.1%)	12 (7.1%)	6 (27.3%)
Total Number	49	193	169	22

1. N = 628 implanted. 433 patients with available regurgitation data at 1 year post-implant. Data updated to July 2, 2015.

Table 14. Postoperative valvular regurgitation by valve size at 2 years in the CAVALIER Study[1]

Size	21 mm	23 mm	25 mm	27 mm
Severity				
None	5 (12.2%)	54 (33.3%)	48 (34.5%)	5 (55.6%)
Trace	10 (24.4%)	36 (22.2%)	30 (21.6%)	1 (11.1%)
Mild	16 (39.0%)	48 (29.6%)	45 (32.4%)	3 (33.3%)
Moderate	5 (12.2%)	14 (8.6%)	8 (5.8%)	0 (0%)
Severe	1 (2.4%)	2 (1.2%)	0 (0%)	0 (0%)
Not Evaluable	4 (9.8%)	8 (4.9%)	8 (5.8%)	0 (0%)
Total Number	41	162	139	9
Location				
None	5 (12.2%)	54 (33.3%)	48 (34.5%)	5 (55.6%)
Central	32 (78.0%)	79 (48.8%)	65 (46.8%)	4 (44.4%)
Paravalvular	0 (0%)	7 (4.3%)	7 (5.0%)	0 (0%)
Both	2 (4.9%)	12 (7.4%)	8 (5.8%)	0 (0%)
Not Evaluable	2 (4.9%)	10 (6.2%)	11 (7.9%)	0 (0%)
Total Number	41	162	139	9

1. N = 628 implanted. 433 patients with available regurgitation data at 1 year post-implant. Data updated to July 2, 2015.

Table 15. Postoperative valvular regurgitation by valve size at 3 years in the CAVALIER Study[1]

Size	21 mm	23 mm	25 mm	27 mm
Severity				
None	4 (12.9%)	24 (21.1%)	28 (23.5%)	-
Trace	7 (22.6%)	33 (28.9%)	21 (17.6%)	-

Mild	13 (41.9%)	37 (32.5%)	45 (37.8%)	-
Moderate	5 (16.1%)	13 (11.4%)	9 (7.6%)	-
Severe	1 (3.2%)	0 (0%)	1 (0.8%)	-
Not Evaluable	1 (3.2%)	7 (6.1%)	15 (12.6%)	-
Total Number	31	114	119	0
Location				
None	4 (12.9%)	24 (21.1%)	28 (23.5%)	-
Central	22 (71.0%)	68 (59.6%)	58 (48.7%)	-
Paravalvular	0 (0%)	4 (3.5%)	9 (7.6%)	-
Both	4 (12.9%)	12 (10.5%)	12 (10.1%)	-
Not Evaluable	1 (3.2%)	6 (5.3%)	12 (10.1%)	-
Total Number	31	114	119	0

1. N = 628 implanted. 433 patients with available regurgitation data at 1 year post-implant. Data updated to July 2, 2015.

3. Subgroup Analyses

Gender was evaluated for potential association with outcomes. Among the attempted implant (N=658), there were 424 females (64.4%) and 234 males (35.6%) patients in the CAVALIER study cohort. Analyses were performed on the 628 patients who were successfully implanted (females = 404; males = 224). The results do not include the 30 patients who were classified as failure to implant. The CAVALIER study was not designed nor powered to study safety and effectiveness differences between sexes, so this analysis is considered exploratory without definitive conclusions.

Safety endpoints stratified by gender are listed in Table 16.

Effectiveness endpoints were compared for both males and females. The two groups exhibited a significant improvement in NYHA classification at 12-months. However, there was a potential observed difference in the 12 month NYHA distribution between males and females (Table 17).

Table 16. Early Mortality and Survival Comparisons by Gender

Parameter	Total (N=628)	Female (N=404)	Male (N=224)
Early (≤30 day) mortality	3.5%	3.2%	4.0%
All mortality	77.43 (72.47 - 82.39)	76.39 (69.65 – 83.13)	78.93 (71.81 – 86.04)
Cardiac-related death	88.32 (84.19 - 92.45)	88.86 (83.6 – 94.11)	87.45 (80.91 - 94.0)
Valve-related death	89.45 (85.07 - 93.83)	89.32 (83.48 - 95.17)	89.60 (83.18 - 96.03)

Table 17. Comparison of 12 Month NYHA Functional Classification by Gender

Postoperative NYHA (12 months)	All (N=476)		Female (N=303)		Male (N=173)	
	N	%	N	%	N	%

Postoperative NYHA (12 months)	All (N=476)		Female (N=303)		Male (N=173)	
CLASS I	271	56.9%	155	51.2%	116	67.1%
CLASS II	171	35.9%	131	43.2%	40	23.1%
CLASS III	34	7.1%	17	5.6%	17	9.8%
CLASS IV	-	-	-	-	-	-

Although the study population included a greater proportion of female patients, the comparisons of safety and effectiveness data by gender support the conclusion that the results of the overall study can be applied equally well to males and females. Patients of both genders demonstrated acceptable hemodynamic outcomes and significant improvement in functional status.

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 pivotal clinical study included 26 investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XI. 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 Device panel, an 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 pre-clinical studies performed on the Perceval Sutureless Heart Valve for hydrodynamic performance, and structural performance demonstrate that this device is suitable for long term implant.

In-vivo animal studies in sheep demonstrate that the Perceval Sutureless Heart Valve is safe for aortic valve replacement.

The results of the CAVALIER trial demonstrate that the linearized late adverse event rates for valvular thrombosis, valve-related thromboembolism, all and major perivalvular leak, and endocarditis are significantly lower than the established

standard of twice the FDA Objective Performance Criterion (OPC). Comparisons of the early, linearized late, and actuarial rates for the 11 standard safety endpoints in the CAVALIER study to the corresponding data in the literature-based control articles for the study do not raise clinical concerns about the safety of the Perceval valve.

The rate for all-cause pulse generator implant following aortic valve replacement (AVR) with the Perceval valve in the CAVALIER study is higher than the 3.1-11.8% rate range for all-cause permanent cardiac pacemaker implant after surgical AVR noted in the published literature. Thus implant of the Perceval valve likely has a higher risk of permanent cardiac pacemaker implant than does surgical AVR with a sutured prosthetic valve.

B. Effectiveness Conclusions

The assessment of effectiveness was based on the evaluation of NYHA functional classification data and echocardiographic hemodynamic data.

The CAVALIER study results demonstrate improvement in NYHA class for the majority of patients throughout the study period. At the 1-year, 2-year, and 3-year follow-up time-points 75.1% or greater of the implanted patients with available data had improved by 1 to 3 classes and at the 4-year follow-up time-point 72.6% of the patients had improved by 1 to 3 classes. The data further show that at the 1-year, 2-year, and 3-year follow-up time-points 92.9% or greater of the patients were in Class I and Class II, and at the 4-year follow-up time-point 86.3% of the patients were in Class I and Class II.

The CAVALIER study peak gradient, mean gradient, and effective orifice area (EOA) hemodynamic data are overall similar to the corresponding data in the literature-based control articles for the study and indicate acceptable hemodynamic performance of the Perceval valve.

In the CAVALIER study there were higher percentages of patients with mild regurgitation than the percentages of patients with no or trace regurgitation. Most of the mild regurgitation was central and did not progress over the duration of the study. The predominance of central regurgitation likely reflects the conformability of the Perceval valve stent which is designed to help prevent perivalvular leak.

C. Benefit-Risk Conclusions

The probable benefits of the Perceval Sutureless Heart Valve include improved aortic valve hemodynamic performance, improved NYHA functional classification as compared to baseline, and reduction in pump time and cross-clamp time. Approximately 75% of patients implanted with the Perceval valve experienced improvement in their functional clinical status. The device design allows implantation through smaller incisions in comparison to typical surgical prosthetic aortic valves that are sutured in place.

The risks of the Perceval Sutureless Heart Valve include complications such as valvular thrombosis, thromboembolism, paravalvular leak, endocarditis, structural valve deterioration, nonstructural dysfunction, reoperation, explant, and death. However, these risks are similar to those observed with other surgical prosthetic aortic valves.

The data presented from the CAVALIER trial indicate relatively high percentages of patients with mild regurgitation and the likelihood that implant of the Perceval valve has a higher risk of permanent pacemaker implant than does surgical AVR with a sutured prosthetic valve. However, most of the mild regurgitation did not progress in severity. Additionally, the probable benefits of receiving the Perceval valve to restore aortic valve function outweigh the risks of requiring a permanent pacemaker.

In conclusion, given the available information above, the data support that for replacement of diseased, damaged, or malfunctioning native or prosthetic aortic valves, the probable benefits of implanting the Perceval Sutureless Heart Valve outweigh the risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. Preclinical and clinical studies provided in the PMA application demonstrate reasonable assurance that the Perceval Sutureless Heart Valve is safe and effective for replacement of diseased, damaged, or malfunctioning native or prosthetic aortic valves.

XIII. CDRH DECISION

CDRH issued an approval order on January 8, 2016.

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

XIV. 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.