# SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

## I. GENERAL INFORMATION

Device Generic Name: Stent, Coronary

Device Trade Name: COBRA PzF™ NanoCoated Coronary Stent System

Device Procode: MAF

Applicant's Name and Address: CeloNova BioSciences, Inc.
8023 Vantage Drive, Ste. 1500
San Antonio, TX 78230, USA

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P160014

Date of FDA Notice of Approval: 2/21/2017

## II. INDICATIONS FOR USE

The COBRA PzF NanoCoated Coronary Stent System is indicated for improving coronary luminal diameter in patients, including patients with diabetes mellitus, with symptomatic ischemic heart disease due to do novo lesions in native coronary arteries. The COBRA PzF NanoCoated Stent System is intended for use in patients eligible for percutaneous transluminal coronary angioplasty (PTCA) with a reference vessel diameter (RVD) of 2.5-4.0 mm and lesion length of ≤24 mm.

## III. CONTRAINDICATIONS

The COBRA PzF NanoCoated Coronary Stent System is contraindicated for use in patients with:

- known sensitivity to L605 cobalt-chromium alloy (including its major elemental constituents cobalt, chromium, tungsten, and/or nickel).
- contraindication to coronary artery stenting:
    - Patients with lesions that may prevent complete inflation of an angioplasty balloon, proper placement of the delivery device or stent deployment;
    - Patients are unable to receive recommended anti-platelet and/or anti-coagulant therapy.
- known severe reaction to contrast agents that cannot be adequately pre-medicated prior to the COBRA PzF NanoCoated Coronary Stent System placement procedure.

## IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the COBRA PzF NanoCoated Coronary Stent System labeling.

## V. DEVICE DESCRIPTION

The COBRA PzF NanoCoated Coronary Stent System (COBRA PzF Stent System) consists of two main components: a rapid-exchange delivery system and a balloon-expandable stent with a polymeric nanocoating. The COBRA PzF Stent System is shipped with the stent pre-mounted (in a crimped, unexpanded state) on the delivery system. It is a single-use system and is furnished sterile within the associated packaging.

There are three different variants of the stent design (designated "sA", "sB", and "sC") as shown in Table 1 below.

**Table 1**
**COBRA PzF Stent Design Variant Identification**

| Stent Diameter (mm) | Stent Lengths (mm) | Stent Design Variant | Crowns per Ring | Interconnect Pattern |
|---|---|---|---|---|
| 2.50 | 8, 12, 15, 18, 24, 30 | **sA** | 8 | 4-4-[2]-4-4 |
| 2.75 | 8, 12, 15, 18, 24, 30 | | | |
| 3.00 | 8, 12, 15, 18, 24, 30 | | | |
| 3.50 | 8, 12, 15, 18, 24, 30 | **sB** | 10 | 4-4-[2]-4-4 |
| 4.00 | 8, 12, 15, 18, 24, 30 | **sC** | 10 | 4-4-[4]-4-4 |

The delivery system is a rapid-exchange (RX) catheter with a working length of 135 cm and comprises:

- a single-arm Luer adapter at its proximal end;
- a flexible, low-profile (5Fr compatible) catheter with an inflation/deflation lumen running along its entire length and a guidewire lumen running from its distal tip to an RX entry/exit port at the transition between the proximal and distal portions of the catheter;
- a balloon mounted near the distal end of the catheter, providing a platform for securing, delivering, and deploying the stent.

The stent is delivered to the lesion site via the delivery system and then deployed (i.e., expanded) by pressurizing the balloon. Following stent deployment, the balloon is deflated and the entire delivery system is removed, with the stent remaining at the deployed site as a permanent vessel scaffolding implant.

The complete compliance chart for the COBRA PzF product matrix is shown in Table 2 below.

**Table 2**
**COBRA PzF Stent Compliance Chart**

| Inflation Pressure (atm) | Stent Diameters (mm) | | | | |
|---|---|---|---|---|---|
| | ***2.50*** | ***2.75*** | ***3.00*** | ***3.50*** | ***4.00*** |
| 10 (NOM) | 2.45 | 2.71 | 2.91 | 3.48 | 3.90 |
| 11 | 2.50 | 2.75 | 2.96 | 3.53 | 3.96 |
| 12 | 2.55 | 2.80 | 3.01 | 3.58 | 4.01 |
| 13 | 2.59 | 2.85 | 3.07 | 3.63 | 4.06 |
| 14 | 2.64 | 2.91 | 3.12 | 3.67 | 4.10 |
| 15 | 2.69 | 2.95 | 3.16 | 3.73 | 4.15 |
| 16 (RBP) | 2.74 | 3.00 | 3.21 | 3.78 | 4.20 |
| 17 | 2.78 | 3.05 | 3.26 | 3.83 | |
| 18 | 2.83 | 3.10 | 3.31 | 3.87 | |

NOM = Nominal Inflation Pressure; RBP = Rated Burst Pressure

Coating Description

- The COBRA PzF stent is coated with a proprietary polymeric polyphosphazene nano-coating produced by CeloNova BioSciences (branded Polyzene™-F or PzF) through an immersion process. The PzF coating is hydrophobic, with long molecular chains and high molecular weight.

## VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are other alternatives for the correction of coronary artery disease. These include lifestyle changes such as exercise, diet, and smoking cessation. Alternative treatment methods include medication, percutaneous coronary interventions (such as balloon angioplasty alone, bare metal stents, drug eluting stents, and coronary artery bypass surgery [CABG]). 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 COBRA PzF Stent System received CE Mark in December 2012. As of January 31, 2016, over 7,400 units have been distributed outside the United States. Table 3 contains a list of countries where the COBRA PzF Stent System is currently distributed. The device has not been withdrawn from market in any countries for any reason(s) related to the safety or effectiveness of the device.

**Table 3**
**Countries With COBRA PzF Stent System Distribution**

| | | |
|---|---|---|
| Austria | France | Germany |
| Croatia | Italy | Netherlands |
| Kuwait | Bosnia and Herzegovina | Switzerland |

| | | |
|---|---|---|
| Sweden | Serbia | Estonia |
| Latvia | Lithuania | Belgium |
| Czech Republic | Switzerland | Denmark |
| Finland | Norway | Saudi Arabia |

## 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 COBRA PzF Stent System.

- Abrupt closure
- Access site pain, hematoma, or hemorrhage
- Allergic/reactions (including to contrast media, stent materials or medication)
- Angina
- Aneurysm (Coronary)
- Arteriovenous fistula
- Arrhythmias, including ventricular tachycardia or fibrillation
- Bleeding
- Cardiac tamponade
- Cardiogenic shock
- Cardiomyopathy
- Death
- Dissection
- Emboli (including air, tissue, plaque, thrombus or device materials)
- Failure to deliver stent to intended site
- Heart failure
- Hematoma
- Hypotension and/or hypertension
- Infection, local and/ or systemic
- Ischemia, myocardial
- Myocardial infarction
- Pericardial effusion
- Pseudoaneurysm
- Pulmonary edema
- Renal insufficiency or failure
- Respiratory failure
- Restenosis of the stented segment
- Shock
- Stent fracture or deformation
- Stent migration

- Stent thrombosis
- Stroke or transient ischemic attack (TIA)
- Total vessel occlusion
- Vessel spasm
- Vessel injury (including dissection, perforation, rupture or trauma)

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

## IX. SUMMARY OF NONCLINICAL STUDIES

### A. Laboratory Studies

**A1. In vitro Bench Testing and Shelf Life**

Bench testing of the COBRA PzF Stent System was performed in accordance with the 2010 FDA bare metal stent (BMS) Guidance Document: *Non-Clinical Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems*, and all applicable ASTM and ISO standards. This testing is summarized in Table 4.

**Table 4**
**In vitro Bench Testing of COBRA PzF Stent System**

| Test | Test Purpose | Results |
|---|---|---|
| **Stent Dimensional and Functional Testing** | | |
| Polyzene-F Coating Characterization | To ensure the thickness and integrity of the polymeric nano-coating are adequate | Pass |
| Material Composition | To identify and list all materials used in the construction of the stent and coating. | Pass |
| Mechanical Properties | To characterize the raw material and post-processed material mechanical properties | Post-processed materials met specifications |
| Fretting Corrosion | To ensure acceptable resistance to fretting corrosion after experiencing at least 400 million cycles (10-year real-time equivalent) of physiologic loading | Pass |

| Test | Test Purpose | Results |
|---|---|---|
| Pitting and Crevice Corrosion | To ensure the corrosion resistance of the COBRA PzF stent is sufficient such that pitting or crevice corrosion would be unlikely to occur after experiencing at least 400 million cycles (10-year real-time equivalent) of physiologic loading | Pass |
| Galvanic Corrosion | To determine the susceptibility of the metallic components of the stent to galvanic corrosion when implanted and overlapped with a stainless steel stent | Pass |
| Dimensional Verification | To inspect and measure the stent body dimensions while expanded and crimped. | Pass |
| Percent Surface Area | To determine the surface coverage (stent-artery ratio) of the stent in the vessel. The calculation has been performed for all stent sizes. | Pass |
| Foreshortening | To determine the foreshortening of the stent. | Pass |
| Recoil | To determine the amount of elastic recoil (percent recoil) after deployment to determine the diameter of the stent in its deployed state. | Pass |
| Stent Integrity | To determine the ability of the stent surface/coating to resist damage and defects | Pass |
| Radial Stiffness and Radial Strength | To determine the load/deformation characteristics of the stent during application of a radial load. | Radial Stiffness: For Characterization Only<br>Radial Strength: Pass |
| Stress/Strain Analysis | To ensure the strain during manufacturing and deployment steps does not exceed the ultimate strain of the stent material | Pass |

| Test | Test Purpose | Results |
|---|---|---|
| Fatigue Analysis | To determine the factor of safety for long-term durability of the stent under simulated physiologic pulsatile loading | Pass |
| Accelerated Durability Testing | To ensure integrity and functionality of the COBRA PzF Stent while overlapped after experiencing the 10 year real-time equivalent of physiologic loading. | Pass |
| Acute Particulate Evaluation (Baseline and Overlapping) | To ensure the size and quantity of particles that could be potentially introduced into the bloodstream during delivery, deployment and retraction are acceptable | Pass |
| Chronic Particulate Evaluation | To ensure the size and quantity of particles under cyclic radial loading conditions in an overlapped configuration representing an equivalent of 10 years of implantation life are acceptable. | Pass |
| Magnetic Resonance Imaging (MRI) Safety and Compatibility | To determine the effect of Magnetic Resonance on the position (translation or torque) and temperature of the COBRA PzF Stent, and to determine the extent of image artifact during MRI. | Pass |
| Radiopacity (X-Ray Visibility) | To ensure clinically acceptable radiographic visibility during delivery, deployment, and post-implantation. | Pass |
| Coating Durability | To ensure the durability of the PzF coating | Pass |
| Longitudinal Deformation | To ensure the COBRA PzF Stent displays adequate longitudinal deformation resistance | Pass |
| **Delivery System Dimensional and Functional Testing** | | |
| Dimensional Verification | To ensure the working length, guidewire lumen inner diameter, proximal shaft outer diameter, and distal shaft outer diameter meet specifications | Pass |
| Crossing Profile | To ensure the crossing profile of the COBRA PzF Stent System meets specifications | Pass |

| Test | Test Purpose | Results |
|---|---|---|
| Dimensional Verification: Luer | To verify compliance with ISO 594 and to confirm compatibility with 6% taper threaded medical fittings | Pass |
| Delivery, Deployment, and Retraction (Simulated Use) | To ensure the delivery system can be advanced and retracted without adversely affecting stent position on the balloon or the ability to deploy | Pass |
| Balloon Rated Burst Pressure (RBP) | To ensure the rated burst pressure (RBP) of the balloon meets specifications | Pass |
| Balloon Fatigue | To ensure the balloon can withstand repeated inflation/deflation cycles | Pass |
| Balloon Compliance | To ensure the relationship between the stent diameter and the balloon inflation pressure stays within specifications | Pass |
| Balloon Inflation and Deflation Time | To ensure the balloon inflation and deflation time meet specifications | Pass |
| Catheter Bond Strength | To ensure the bond strength of the luer bond, catheter bonds, and proximal balloon bond are sufficient for clinical use | Pass |
| Tip Pull Tensile Strength | To ensure the bond connecting the distal tip to the delivery system has sufficient tensile strength | Pass |
| Flexibility and Kink | To ensure the delivery system has sufficient flexibility and kink resistance | Pass |
| Torque Strength | To ensure the delivery system continues to meet tensile and burst acceptance criteria after experiencing at least 1 full tip-to-tip twist | Pass |
| Coating Integrity and Functionality | To characterize the hydrophilic coating before and after simulated use and to ensure frictional drag on the catheter meets specifications when pulled while under clamping force | Integrity: Characterization Only<br>Functionality: Pass |

| Test | Test Purpose | Results |
|---|---|---|
| Particulate Evaluation – Delivery System | To investigate the size and quantity of particles that could potentially be introduced into the blood stream during delivery, deployment and retraction | Particulate results were characterized and determined to be at an acceptable |
| Stent Securement for Unsheathed Stents | To ensure the force that will dislodge the stent from the delivery system meets specifications | Pass |

**A2. Biocompatibility Studies**

Biocompatibility was performed on the COBRA PzF Stent System in accordance with ISO-10993-1:2009 *Biological Evaluation of Medical Devices – Part 1: Evaluation and Testing*. All testing was performed according to good laboratory practice (GLP) and performed by a third party using finished devices or surrogate test articles fully representative of the device and production process including sterilization. Testing concluded that the COBRA PzF Stent System meets the requirements of ISO 10993-1:2009. A summary is provided in Table 5, below.

**Table 5**
**Summary of Biocompatibility Test Results**

| Biological Endpoints | Test | Test Article[1] | Pass/Fail | Result |
|---|---|---|---|---|
| Cytotoxicity | MEM Elution L-929 Mouse Fibroblast Cells (ISO 10993-5) | Stent | Pass | Non-cytotoxic |
| | | Delivery System | Pass | Non-cytotoxic |
| | Direct Contact L-929 Mouse Fibroblast Cells (ISO 10993-5) | Stent | Pass | Non-cytotoxic |
| Sensitization | Guinea Pig Maximization Sensitization (ISO 10993-10) (polar and non-polar extracts) | Stent | Pass | No sensitization |
| | | Delivery System | Pass | No sensitization |
| Irritation or Intracutaneous Reactivity | ISO Intracutaneous reactivity (ISO 10993-10) (polar and non-polar extracts) | Stent | Pass | Pass |
| | | Delivery System | Pass | Pass |
| Acute Systemic Toxicity | Systemic Injection (ISO 10993-11) (polar and non-polar extracts) | Stent | Pass | Pass |
| | | Delivery System | Pass | Pass |

| Biological Endpoints | Test | Test Article[1] | Pass/Fail | Result |
|---|---|---|---|---|
| Material Mediated Pyrogenicity | Rabbit Pyrogen – Material mediated (ISO 10993-11) | Stent | Pass | Non-pyrogenic |
| | | Delivery System | Pass | Non-pyrogenic |
| Hemo-compatibility | Direct and indirect contact In vitro hemolysis test (ASTM method) (ISO 10993-4) | Stent | Pass | Non-hemolytic |
| | | Delivery System | Pass | Non-hemolytic |
| | Direct and indirect contact complement activation tests (C3a and SC5b-9) (ISO 10993-4) | Stent | Pass | Pass |
| | | Delivery System | Pass | Pass |
| Genotoxicity | Bacterial reverse mutation assay (4 Salmonella typhimurium and one Escherichia coli) (ISO 10993-3) | Stent | Pass | Non-mutagenic |
| | Mammalian cell in vitro assay (ISO 10993-3) (in vitro mouse lymphoma) | Stent | Pass | Non-mutagenic |
| | In vivo Mouse Micronucleus Assay (ISO 10993-3) (polar and non polar) | Stent | Pass | Non-mutagenic |
| Implantation | 1 week intramuscular implantation study in rabbits (ISO 10993-6) | Stent | Pass | Non-irritant |
| | 4 week intramuscular implantation study in rabbits (ISO 10993-6) | Stent | Pass | Non-irritant |

[1] Stent analogs were used for biocompatibility testing that were fabricated from the same materials and manufacturing process as actual COBRA PzF stents.

**A3. Sterilization**

The COBRA PzF Stent System is sterilized using ethylene oxide (EO) gas. Validation in accordance with ISO 11135:2007 *Sterilization of Health Care Products – Ethylene oxide – Part 1 and 2: Requirements for cycle development, validation and routine monitoring of a sterilization process for medical devices* demonstrated that the sterilization process meets a Sterility Assurance Level (SAL) of $10^{-6}$. Ethylene oxide residuals meet limits in accordance with ISO 10993-7:2008 *Biological evaluation of medical devices – Part 7: Ethylene oxide sterilization residuals*. In addition, the amount of bacterial endotoxins was verified to be within the specification limits.

**A4. Packaging and Shelf Life**

Packaging validation testing has been conducted in accordance with ISO 11607:2006 reflecting three (3) year shelf life. Samples of the COBRA PzF Stent System were subjected to accelerated aging and evaluated through functional testing to ensure the product continues to meet specifications.

### B. Animal Studies

The COBRA PzF Stent System was compared to Abbott Vascular Inc's MULTI-LINK VISION® Coronary Stent System (P020047, approved July 16, 2003) in a GLP study using a porcine model. A total of twenty-four animals were used in this study and received either single configuration stents implanted in two or three main coronary arteries, or overlapping stents placed in only two of the three main coronary arteries (two overlapping stents per artery). Stent size 3.0 x 15 mm was studied, with an angiographic, histomorphometric, and histopathologic evaluation at 5, 28, and 90 days. At histopathologic evaluation, the COBRA PzF Stent System demonstrated comparable safety and vascular compatibility compared to VISION in the non-injured porcine coronary artery.

## X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study (PzF SHIELD study) to establish a reasonable assurance of safety and effectiveness of percutaneous coronary intervention with the CeloNova PzF NanoCoated Coronary Stent System for improving coronary luminal diameter in patients, including patients with diabetes mellitus, with symptomatic ischemic heart disease, due to de novo lesions in native coronary arteries in the US, Germany, France, Latvia, Serbia, Spain, and Switzerland under IDE #G130190. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

### A. Study Design

Patients were enrolled between August 21, 2013 and February 18, 2015. The database for this PMA reflected data collected through January 8, 2016 and included 296 patients. There were 35 investigational sites.

The major design characteristics are outlined in Table 6 below.

**Table 6**
**PzF SHIELD Trial Design Characteristics**

| | |
|---|---|
| Study Title | COBRA PzF™ Coronary Stent System in Native Coronary Arteries for Early Healing, Thrombus Inhibition, Endothelialization, and Avoiding Long-Term Dual Anti-Platelet Therapy – The PzF SHIELD Trial |
| Study Type/Design | • Multi-center study (n=35), performed in United States, Germany, France, Latvia, Serbia, Spain and Switzerland<br>• Prospective<br>• Single arm<br>• Subjects treated with COBRA PzF Stent System |
| Number of Patients | Total 296 |
| Lesion Criteria | Single de novo lesion contained within a native coronary artery with |

| | |
|---|---|
| | reference vessel diameter between 2.5mm and 4.0mm and lesion length ≤24mm |
| Stent sizes (mm) | Stent Diameter — Stent Lengths<br>2.50mm — 8, 12, 15, 18, 24, 30mm<br>2.75mm — 8, 12, 15, 18, 24, 30mm<br>3.00mm — 8, 12, 15, 18, 24, 30mm<br>3.50mm — 8, 12, 15, 18, 24, 30mm<br>4.00mm — 8, 12, 15, 18, 24, 30mm |
| Anti-platelet therapy | Aspirin recommended indefinitely<br>Clopidogrel, Prasugrel, Ticagrelor or Ticlopidine for a minimum of 1 month post procedure |
| Primary Endpoint | The incidence of target vessel failure (TVF): cardiac death, target vessel myocardial infarction (MI) [Q wave or non-Q wave, ARC-definition], or clinically driven target vessel revascularization (TVR) by percutaneous or surgical methods within 270 days post-procedure. This rate is compared with a performance goal derived using a meta-analysis of literature articles reporting outcomes with bare metal coronary stents. |
| Follow-up | At: Discharge, 30, 180, 270, 360, 720, 1080, 1440 and 1800 days |
| Sponsor | CeloNova BioSciences Inc. |

The null hypothesis for this study stated that the COBRA PzF Stent System would have a primary endpoint rate of TVF at 9 months greater than or equal to 19.62%. The alternative hypothesis stated that the COBRA PzF Stent System would have a primary endpoint rate less than 19.62%.

Specifically:

$H_o$: $\pi_{COBRA\ PzF} \geq 19.62\%$

$H_A$: $\pi_{COBRA\ PzF} < 19.62\%$

where $\pi_{COBRA\ PzF}$ is the true primary endpoint rate for the COBRA PzF Stent System and the 19.62% is the meta-analytically derived performance goal for the primary endpoint rate. Rejection of the null hypothesis would signify that the performance goal had been met, and that the COBRA PzF Stent System's primary endpoint rate was less than 19.62%.

Oversight for the PzF SHIELD trial incuded an angiographic core laboratory, a clinical events committee (CEC), and a data safety monitoring board (DSMB).

1. Clinical Inclusion and Exclusion Criteria

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

   *General Inclusion Criteria*

1. Patient ≥ 18 years old.
2. Eligible for percutaneous coronary intervention (PCI).

3. Patient understands the nature of the procedure and provides written informed consent **prior** to the catheterization procedure.
4. Patient is willing to comply with specified follow-up evaluation and can be contacted by telephone.
5. Acceptable candidate for coronary artery bypass graft (CABG) surgery.
6. Stable angina pectoris (Canadian Cardiovascular Society (CCS) I, II, III, IV) or unstable angina pectoris (Braunwald Class I, II, III, B-C) or a positive functional ischemia study (e.g., ETT, SPECT, Stress echocardiography or Cardiac CT).
7. Male or non-pregnant female patient (Note: females of child bearing potential must have a negative pregnancy test prior to enrollment in the study).

*Angiographic Inclusion Criteria*

1. Patient indicated for elective stenting of a single stenotic lesion in a native coronary artery.
2. Reference vessel ≥ 2.5 mm and ≤ 4.0 mm in diameter by visual estimate.
3. Target lesion ≤ 24 mm in length by visual estimate (the intention should be to cover the whole lesion with one stent of adequate length).
4. Protected left main lesion with >50% stenosis.
5. Target lesion stenosis ≥ 70% and < 100% by visual estimate.
6. Target lesion stenosis <70% who meet physiological criteria for revascularization (i.e. positive FFR).

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

*General Exclusion Criteria*

1. Currently enrolled in another investigational device or drug trial that has not completed the primary endpoint or that clinically interferes with the current study endpoints.
2. Previously enrolled in another stent trial within the prior two (2) years.
3. ANY planned elective surgery or percutaneous intervention within the subsequent three (3) months.
4. A previous coronary interventional procedure of any kind within 30 days prior to the procedure.
5. The patient requires staged procedure of either the target or any non-target vessel within nine (9) months post-procedure.
6. The target lesion requires treatment with a device other than PTCA prior to stent placement (such as, but not limited to, directional coronary atherectomy, excimer laser, rotational atherectomy, etc.).
7. Previous drug eluting stent (DES) deployment anywhere in the target vessel.
8. Any previous stent placement within 15 mm (proximal or distal) of the target lesion.
9. Co-morbid condition(s) that could limit the patient's ability to participate in the trial or to comply with follow-up requirements, or impact the scientific integrity of the trial.
10. Concurrent medical condition with a life expectancy of less than 12 months.

11. Documented left ventricular ejection fraction (LVEF) < 30% within 12 months prior to enrollment.
12. Patients with diagnosis of MI within 72 hours (i.e. CK-MB must be returned to normal prior to enrollment) or suspected acute MI at time of enrollment.
13. Previous brachytherapy in the target vessel.
14. History of cerebrovascular accident or transient ischemic attack in the last six (6) months.
15. Leukopenia (leukocytes < $3.5 \times 10^9$ / liter).
16. Neutropenia (Absolute Neutrophil Count < $1000/mm^3$) ≤ 3 days prior to enrollment.
17. Thrombocytopenia (platelets < $100{,}000/mm^3$) pre-procedure.
18. Active peptic ulcer or active GI bleeding.
19. History of bleeding diathesis or coagulopathy or inability to accept blood transfusions.
20. Known hypersensitivity or contraindication to aspirin, heparin or bivalirudin, clopidogrel or ticlopidine, cobalt, nickel, L-605 Cobalt chromium alloy or sensitivity to contrast media, which cannot be adequately pre-medicated.
21. Serum creatinine level > 2.0 mg/dl within 7 days prior to index procedure.
22. Patients unable to tolerate dual anti-platelets therapy (DAPT) for one (1) month post procedure.

*Angiographic Exclusion Criteria*

1. Unprotected left main coronary artery disease (obstruction greater than 50% in the left main coronary artery that is not protected by at least one non-obstructed bypass graft to the left anterior descending (LAD) or Circumflex artery or a branch thereof).
2. Target vessel with any lesions with greater than 50% diameter stenosis outside of a range of 5 mm proximal and distal to the target lesion based on visual estimate or on-line quantitative coronary angiography (QCA).
3. Target lesion (or vessel) exhibiting an intraluminal thrombus (occupying > 50% of the true lumen diameter) at any time.
4. Lesion location that is aorto-ostial or within 5 mm of the origin of the LAD or left circumflex (LCX).
5. Target lesion with side branches > 2.0mm in diameter.
6. Target vessel is excessively tortuous (two bends > 90˚ to reach the target lesion).
7. Target lesion is severely calcified.
8. TIMI flow 0 or 1.
9. Target lesion is in a bypass graft.

2. Follow-up Schedule

All patients were scheduled to return for follow-up examinations at 30 days and 9 months (270 days) post-procedure.

Post-procedure, the objective parameters measured during the study are presented in Table 7 below. Adverse events and complications were recorded at all visits.

**Table 7**
**Summary of Study Procedures from Screening through End of Follow-up**

| Study requirement | Screening | | | Post | | | | |
|---|---|---|---|---|---|---|---|---|
| | ≤7 Days prior to procedure | 24 Hours prior to procedure | Procedure | Hospital discharge | 30 Days (+/-7days) | 180 Days (+/- 30days) | 270 Days (+/-30days | 360, 720, 1080, 1440 and 1800 Days (+/- 30 days) |
| Patient Inclusion/ Exclusion | X | | | | | | | |
| Informed consent | X | | | | | | | |
| Medical history | X | | | | | | | |
| Clinical assessment[1] & physical exam | X | | | X | X | | X | |
| Telephone assessment | | | | | | X | | X |
| Coagulation (INR, APTT) | | X | | | | | | |
| Pregnancy test | X[2] | | | | | | | |
| Cardiac enzymes | | X[3] | | X[4] | | | | |
| CBC and metabolic panel | | X | | X[5] | | | | |
| 12-lead ECG | | X[6] | | X[7] | | | X | |
| Coronary angiography | | | X | | | | X[8] | |
| OCT[9] | | | X | | | | X | |
| Procedure Parameters (procedure time; fluoroscopy time) | | | X | | | | | |
| ACT | | | X[10] | | | | | |
| Stenting | | | X | | | | | |
| Relevant concomitant | | X | X | X | X | X | X | X |
| Record of adverse events[11] | X | X | X | X | X | X | X | X |

1. A clinical assessment is defined as the standard of care provided to patients per facility/ institution policy.
2. For females of childbearing potential.
3. Pre-procedure cardiac enzymes: CK-MB performed within 24 hours prior to the procedure may be used as the baseline cardiac enzymes provided there have been no signs or symptoms of myocardial ischemia between the time of cardiac enzymes test and the time of arterial access.
4. Post-procedure cardiac enzymes: Blood to measure cardiac enzymes (CK-MB) must be drawn prior to hospital discharge. Blood specimens must be collected at 6-12 hours post procedure, and 18-24 hours post procedure or at the time of discharge but no earlier than 16 hours post-procedure. If observing an increase above upper limit, additional specimens should be drawn every 8±4 hours for 24 hours or until peak value ascertained. Post-procedure troponin: Blood to measure troponin may be drawn prior to hospital discharge per hospital standards but does not replace the protocol requirement for CKMB.
5. To be performed within 24 hours post-procedure.

6. Pre-procedure 12-lead ECG: an ECG performed within 24 hours prior to the procedure may be used as the baseline ECG provided there have been no signs or symptoms of myocardial ischemia between the time of ECG and the time of arterial access.
7. Post-procedure 12-lead ECG: an ECG should be performed between 12 and 24 hours post-procedure.
8. Diagnostic Angiography at 270 days to be performed after clinical assessment only in patients participating in the angiographic subset.
9. Optimal coherence tomography (OCT) will be performed after the angiographic procedure at baseline and again at 270 days; only in OCT subset of patients.
10. Activated clotting time (ACT) monitoring should be done as per the respective institutions standard of care when heparin is used at the index procedure.
11. Adverse events should be captured after signature of the informed consent. During follow-up where a clinical contact is not required, if patient reports any adverse events or additional interventions that, in the opinion of the investigator, could potentially be related to the index procedure and/or COBRA PzF device, the patient shall undergo an office visit, whereupon an abbreviated physical examination, 12-lead ECG, and other appropriate testing deemed appropriate by the investigator shall be performed.

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

3. Medications

Pre-procedure, patients were required to receive ≥300 mg q.d. aspirin in patients who are aspirin-naïve, and 75-325 mg in patients on chronic aspirin therapy (per American Heart Association (AHA)/American College of Cardiology (ACC) PCI guidelines). Patients were also required be treated with a $P_2Y_{12}$ inhibitor prior to the procedure. Patients were required to receive dual antiplatelet therapy for a minimum of one (1) month post-procedure.

4. Clinical Endpoints

The PzF SHIELD primary endpoint was TVF at 9 months, defined as the composite of: cardiac death, target vessel myocardial infarction (MI) [Q wave or non-Q wave, ARC-definition], or clinically driven target vessel revascularization (TVR) by percutaneous or surgical methods within 270 days post-procedure. This rate was compared with a performance goal of 19.62% derived using a meta-analysis of literature articles reporting outcomes with bare metal coronary stents.

In-stent late lumen loss (LL) was a powered secondary endpoint for the PzF SHIELD trial. Specifically, the study assessed the ability of the COBRA PzF Stent System to meet a performance goal of LL <1.1 mm at 9 months.
Other secondary endpoints to examine the safety and effectiveness of the COBRA PzF Stent System are listed below.

- All Death at 30, 180, 270, 360, 720, 1080, 1440, and 1800 days
- Cardiac Death at 30, 180, 270, 360, 720, 1080, 1440, and 1800 days
- Major Adverse Cardiac Events (MACE) at 30, 180, 270, 360, 720, 1080, 1440, and 1800 days
- MI at 30, 180, 270, 360, 720, 1080, 1440, and 1800 days

- Composite endpoint of Cardiac Death and MI at 30, 180, 270, and 360 days
- Clinically driven target lesion revascularization (TLR) at 30, 180, 270, 360, 720, 1080, 1440, and 1800 days
- Stroke (ischemic and hemorrhagic) at 30, 180, 270 and 360 days
- Clinically driven TVR at 30, 180, 270, and 360 days
- TVF at 30, 180, and 360 days
- Acute Success at 30 days
    - Device Success: Defined as the attainment of < 30% final residual stenosis of the target lesion using only the COBRA PzF Stent System.
    - Lesion Success: Defined as the attainment of < 30% final residual stenosis of the target lesion using any percutaneous method.
    - Procedure Success: Attainment of < 30% residual stenosis of the target lesion and no in-hospital MACE.
- Bleeding or Vascular Complications at discharge
- Early Stent Thrombosis (ARC defined) at 30 days
- Late Stent Thrombosis at 180, 270, and 360 days
- Angiographic Endpoints (on first 90 evaluable patients) at 270 days (after clinical assessment)
    - In-stent late loss (LL) (powered Secondary Endpoint compared to performance goal)
    - In-segment percent diameter stenosis (%DS) (within the 5 mm margins proximal and distal to stent)
    - In-stent percent diameter stenosis (%DS)
    - In-segment late loss
    - In-segment binary restenosis (stenosis of > 50% of the reference vessel diameter)
    - In-stent binary restenosis
    - In-stent minimum lumen diameter (MLD)
    - In-segment MLD
    - Longitudinal stent deformation
    - Stent fracture
- Optical Coherence Tomography Endpoints (on 45 subjects) at 270 days (after clinical assessment)
    - in-stent neointimal thickness (NT)
    - Lumen area
    - Lumen volume
    - Stent area
    - Stent volume
    - Proportion of uncovered and/or malopposed struts

- Stent fracture

## B. Accountability of PMA Cohort

At the time of database lock for the 270-day primary endpoint, of 296 intention-to-treat (ITT) patients enrolled in the PMA study, 96.2% (287) patients were available for analysis.

**Table 8**
**Patient Accountability**

| | Subjects |
|---|---|
| Subjects enrolled (Intent-to-Treat analysis set) | 296 |
| Eligible for 270 days analysis | 287 |
| Death < 270 days | 4 |
| Withdrew consent | 2 |
| Visit performed before the eligible window | 3 |
| 270 day Clinical Follow-up | 96.2% (287/296) |

## C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a PCI study performed in the US.

Table 9 presents demographics and baseline clinical characteristics for the ITT analysis set (N=296). The ITT population was predominantly male (70.27%) with a history of hypertension (82.65%) and hyperlipidemia (80.61%). Approximately one-third of the ITT population was diabetic. Unstable angina was reported for 29.39% of subjects. Table 10 summarizes procedure characteristics.

**Table 9**
**Baseline Demographics and Medical History**

| Patient Characteristics | % of Number of Patients (N=296) |
|---|---|
| US Site | 56.08% (166/296) |
| Age (years) | 66.46±10.29 (296) |
| Male | 70.27% (208/296) |
| Hispanic or Latino | 8.16% ( 16/196) |
| Race | |
| American Indian or Alaskan | 0.00% (0/244) |
| Asian | 4.92% (12/244) |
| Black or African American | 6.97% (17/244) |
| Native Hawaiian or Pacific Islander | 0.00% (0/244) |
| White or Caucasian | 84.43% (206/244) |
| Other | 3.69% (9/244) |
| History of Coronary Artery Disease | 48.64% (143/294) |

| | |
|---|---|
| Prior Myocardial Infarction | 14.86% (44/296) |
| Previous Percutaneous Coronary Intervention | 30.41% (90/296) |
| Current Target Vessel involved | 11.11% (10/90) |
| History of Coronary Artery Bypass Graft Surgery | 5.07% (15/296) |
| Current Target Vessel involved | 13.33% (2/15) |
| Prior Stroke | 4.76% (14/294) |
| Peripheral Vascular Disease | 9.18% (27/294) |
| Diabetes Mellitus | 33.67% (99/294) |
| Most recent treatment of diabetes | |
| Insulin | 22.22% (22/99) |
| Oral AD | 78.79% (78/99) |
| Diet | 18.18% (18/99) |
| Hypertension | 82.65% (243/294) |
| Hyperlipidemia | 80.61% (237/294) |
| Chronic Renal Failure | 5.78% (17/294) |
| Atrial Fibrillation | 12.24% (36/294) |
| Heart Failure | 11.56% (34/294) |
| History of Smoking | 56.80% (167/294) |
| Prior smoker | 34.69% (102/294) |
| Current smoker | 22.11% (65/294) |
| Body Mass Index (BMI) | 29.46±5.32 (296) |
| Indication for Index Procedure | |
| Acute MI (>72 hours) | 2.36% (7/296) |
| Positive Functional Study without Angina | 13.51% (40/296) |
| Stable Angina | 54.73% (162/296) |
| Unstable Angina | 29.39% (87/296) |

**Table 10**
**Procedure Characteristics**

| Procedure Details | ITT Population (N=296 Patients, N=300 Lesions) |
|---|---|
| Total procedure time (minutes) | |
| Mean ± SD (N) | 30.70 ± 15.68 (296) |
| Median | 27.50 |
| Range (Min, Max) | (5.00, 95.00) |
| Total Fluoroscopy time (minutes) | |
| Mean ± SD (N) | 10.80 ± 6.18 (296) |
| Median | 9.75 |
| Range (Min, Max) | (0.20,42.00) |
| Pre-Dilatation Details | |
| Pre-dilatation performed | 96.28% (285/296) |
| Balloons used | 100.00% (285/285) |
| One (1) balloon used | 96.49% (275/285) |

**Procedure Characteristics**

| Procedure Details | ITT Population (N=296 Patients, N=300 Lesions) |
|---|---|
| Two (2) balloons used | 2.81% (8/285) |
| Three (3) or more balloons used | 0.70% (2/285) |
| Total Pre-Dilatation Time (minutes) | |
| Mean ± SD (N) | 12.73 ± 2.70 (285) |
| Median | 12.45 |
| Range (Min, Max) | (7.28, 20.50) |
| Dissection Details | |
| Dissection occurred [PER] | 5.76% (17/295) |
| Grade A | 64.71% (11/17) |
| Grade B | 17.65% (3/17) |
| Grade C | 17.65% (3/17) |
| Grade D | 0.00% (0/17) |
| Grade E | 0.00% (0/17) |
| Grade F | 0.00% (0/17) |
| Post-Dilatation Details | |
| Post-dilatation performed | 48.31% (143/296) |
| Procedural Medications | |
| Aspirin (Pre-Procedure) | 94.93% (281/296) |
| P2Y12 Blocker | 98.65% (292/296) |
| Clopidogrel | 84.46% (250/296) |
| Ticagrelor | 7.43% (22/296) |
| Prasugrel | 6.42% (19/296) |
| Others | 0.34% (1/296) |
| Anticoagulant | 99.32% (294/296) |
| Heparin | 72.30% (214/296) |
| Bivalirudin | 27.03% (80/296) |
| Glycoprotein IIb/IIIa inhibitors | 6.08% (18/296) |
| Activated Clotting Time [ACT] Monitoring for Heparin (seconds) | |
| Mean ± SD (N) | 320.51 ± 98.25 (201) |
| Median | 300.00 |
| Range (Min, Max) | (93.00, 825.00) |

## D. Safety and Effectiveness Results

The principal safety and effectiveness results are shown below in Tables 11 and 12.

The primary endpoint of TVF to 270 days in the ITT population was met and is shown below in Table 11. The TVF rate at 270 days was 11.50% and the upper bound of the exact one-side 95% confidence interval (CI) of 15.07% was below the protocol specified

performance goal of 19.62%. Therefore, the null hypothesis was rejected and the study stent is considered to have met the performance goal.

**Table 11**
**Primary Endpoint: TVF to 270 days**

| Population | COBRA PzF Stent System | 95% CI | Upper Bound of 95% one-sided CI | Performance Goal |
|---|---|---|---|---|
| ITT (N=296) | 11.50% (33/287) | [8.05%, 15.77%] | 15.07% | 19.62% |
| Per-Protocol (N=295) | 11.54% (33/286) | [8.08%, 15.82%] | 15.12% | 19.62% |

The powered secondary endpoint of mean in-stent late lumen loss per patient at 270 days was 0.84 mm (±0.48) (in 113 evaluable patients) with an upper bound of the one-sided 97.5% CI of 0.93 mm. This value is below the established performance goal of <1.1 mm; therefore, the null hypothesis can be rejected and the study stent is considered to have met the performance goal.

Table 12 shows the results of all trial safety and effectiveness endpoints.

**Table 12**
**Principal Safety and Effectiveness Results (270 Days)**

| | COBRA PzF Stent System (N=296 patients, 300 lesions) | [95% CI] |
|---|---|---|
| TVF (COMPOSITE OF SAFETY AND EFFECTIVENESS) | 11.50% (33/287) | [8.05%, 15.77%] |
| SAFETY | | |
| Death (all cause) | 2.06% (6/291) | [0.76%, 4.43%] |
| Cardiac death | 0.35% (1/286) | [0.01%, 1.93%] |
| MI – CK-MB ≥ 3x ULN | 5.96% (17/285) | [3.51%, 9.38%] |
| Q-wave MI | 0.00% (0/285) | [0.00%, 1.29%] |
| Non Q-wave MI | 5.96% (17/285) | [3.51%, 9.38%] |
| MI – ARC definition | 7.02% (20/285) | [4.34%, 10.63%] |
| Composite endpoint of cardiac death and MI (historical definition) | 6.29% (18/286) | [3.77%, 9.76%] |
| Composite endpoint of cardiac death and MI (ARC definition) | 7.34% (21/286) | [4.60%, 11.01%] |
| MACE – (using MI definition of CK-MB ≥ 3x ULN) | 10.14% (29/286) | [6.90%, 14.24%] |
| Ischemic or hemorrhagic stroke | 0.35% (1/286) | [0.01%, 1.93%] |
| Late stent thrombosis (ARC defined) | 0.00% (0/285) | [0.00%, 1.29%] |
| | | |

| | | |
|---|---|---|
| EFFECTIVENESS | | |
| TLR | 5.61% (16/285) | [3.24%, 8.96%] |
| Clinically driven TLR | 4.56% (13/285) | [2.45%, 7.67%] |
| TVR | 7.34% (21/286) | [4.60%, 11.01%] |
| Clinically driven TVR | 5.94% (17/286) | [3.50%, 9.35%] |
| Secondary Endpoints at 30 Days | | |
| Early Stent Thrombosis (ARC defined) (SAFETY) | 0.00% (0/295) | [0.00%, 1.24%] |
| Acute Success Rates (EFFECTIVENESS) | | |
| Device Success[1] | 100.00% (291/291) | [98.74%, 100.00%] |
| Lesion Success[2] | 100% (292/292) | [98.74%, 100.00%] |
| Procedure Success[3] | 93.84% (274/292) | [90.43%, 96.31%] |

[1] Defined as the attainment of <30% final residual stenosis of the target lesion using only the COBRA PzF Stent System.
[2] Defined as the attainment of <30% final residual stenosis of the target lesion using any percutaneous method.
[3] Procedure Success is defined as the attainment of <30% residual stenosis of the target lesion and no in-hospital MACE.

**Adverse effects that occurred in the PMA clinical study:**

Adverse events presented in this section were observed in the PzF SHIELD trial and have been adjudicated by the Clinical Events Committee. Major clinical events of the PzF SHIELD study are presented in Table 13.

**Table 13**
**PzF SHIELD Major Clinical Events from Post-Procedure to 270-Day Follow Up**

| Event | PzF SHIELD Trial (N = 296) | | |
|---|---|---|---|
| Safety Measures | To 30 days [1] | To 180 days [2] | To 270 days [3] |
| All death | 0.34% (1/296) | 1.70% (5/294) | 2.06% (6/291) |
| Cardiac death | 0.34% (1/296) | 0.34% (1/292) | 0.35% (1/286) |
| MI (historical definition) | 5.76% (17/295) | 5.84% (17/291) | 5.96% (17/285) |
| Q-wave MI | 0.00% (0/295) | 0.00% (0/291) | 0.00% (0/285) |
| Non Q-wave MI | 5.76% (17/295) [4] | 5.84% (17/291) | 5.96% (17/285) |
| MI (ARC definition) | 6.10% (18/295) | 6.87% (20/291) | 7.02 % (20/285) |
| TLR | 0.00% (0/295) | 2.41% | 5.61% |

| | | | |
|---|---|---|---|
| | | (7/291) | (16/285) |
| Clinically driven TLR | 0.00% (0/295) | 2.41% (7/291) | 4.56% (13/285) |
| TVR | 0.68% (2/295) | 3.44% (10/291) | 7.34% (21/286) |
| Clinically driven TVR | 0.34% (1/295) | 3.09% (9/291) | 5.94% (17/286) |
| Cardiac death or MI (historical definition) | 6.08% (18/296) | 6.16% (18/292) | 6.29% (18/286) |
| Cardiac death or MI (ARC definition) | 6.42% (19/296) | 7.19% (21/292) | 7.34% (21/286) |
| MACE (historical definition) | 6.08% (18/296) | 7.88% (23/292) | 10.14% (29/286) |
| TVF | 6.42% (19/296) | 8.56% (25/292) | 11.50% (33/287) |
| Ischemic or hemorrhagic stroke | 0.00% (0/295) | 0.34% (1/292) | 0.35% (1/286) |
| Early stent thrombosis [ARC definition] (≤ 30days) | 0.00% (0/295) | N/A | N/A |
| Late stent thrombosis [ARC definition] (> 30 days) | N/A | 0.00% (0/291) | 0.00% (0/285) |

[1] Events defined for the period of 30 days post-procedure follow-up are reported for patients with at least 23 days of follow-up or with event to 30 days.
[2] Events defined for the period of 180 days post-procedure follow-up are reported for patients with at least 150 days of follow-up or with event to 180 days.
[3] Events defined for the period of 270 days post-procedure follow-up are reported for patients with at least 240 days of follow-up or with event to 270 days.
[4] 17/296 were periprocedural NQWMI (Historical definition- CKMB > 3x UNL)

Out of 318 stents deployed in the study, there was one (1) incidence of device malfunction (Stent Unable to Cross Lesion). This malfunction was not associated with an adverse effect.

Subgroup Analyses

The following preoperative characteristics were evaluated for potential association with outcomes: gender and diabetes.

**Gender**

The PzF SHIELD study was not powered to study safety or effectiveness of the COBRA PzF Stent System in gender-specific subgroups. However, a pre-specified analysis of primary and secondary endpoints by gender was performed. Analysis showed similar treatment effect between genders. This suggests that the overall conclusion of the trial regarding both safety and effectiveness can be generalized to males and females. Results are summarized in Table 14 below.

**Table 14**
**Summary of Gender Subgroup Analysis**

| Endpoints | Males (N = 208) | Females (N = 88) | p-value |
|---|---|---|---|
| **Primary Endpoints (270 days)** | | | |
| TVF [1] | 11.4% (23/202) | 11.8% (10/85) | 1.000 |
| Cardiac death | 0.5% (1/202) | 0.0% (0/85) | 1.000 |
| Target vessel myocardial infarction (MI) | 5.4% (11/202) | 7.1% (6/85) | 0.591 |
| Clinically TVR | 5.4% (11/202) | 7.1% (6/85) | 0.591 |
| **Secondary Endpoints (270 days)** | | | |
| All Causes Mortality | 2.0% (4/204) | 2.3% (2/87) | 1.000 |
| Cardiac Mortality | 0.5% (1/201) | 0.0% (0/85) | 1.000 |
| MI (historical definition) | 5.5% (11/200) | 7.1% (6/85) | 0.594 |
| Q-wave MI | 0.0% (0/200) | 0.0% (0/85) | -- |
| Non Q-wave MI | 5.5% (11/200) | 7.1% (6/85) | 0.594 |
| MI (ARC definition) | 6.5% (13/200) | 8.2% (7/85) | 0.616 |
| TLR | 5.5% (11/200) | 5.9% (5/85) | 1.000 |
| Clinically driven TLR | 4.5% (9/200) | 4.7% (4/85) | 1.000 |
| TVR | 6.5% (13/201) | 9.4% (8/85) | 0.457 |
| Clinically driven TVR | 5.5% (11/201) | 7.1% (6/85) | 0.593 |
| Composite endpoint of cardiac death and MI (historical definition) | 6.0% (12/201) | 7.1% (6/85) | 0.791 |
| Composite endpoint of cardiac death and MI (ARC definition) | 7.0% (14/201) | 8.2% (7/85) | 0.804 |
| MACE (historical definition) | 10.4% (21/201) | 9.4% (8/85) | 1.000 |
| Ischemic or hemorrhagic stroke | 0.5% (1/201) | 0.0% (0/85) | 1.000 |
| Early Stent Thrombosis [ARC definition] (≤ 30days) | 0.0% (0/207) | 0.0% (0/88) | -- |
| Late Stent Thrombosis [ARC definition] (> 30days) | 0.0% (0/200) | 0.0% (0/85) | -- |
| **Acute Success Rates** | | | |
| Device Success [2] | 100.0% (205/205) | 100.0% (87/87) | -- |
| Lesion Success [3] | 100.0% (205/205) | 100% (87/87) | -- |

[1] Events defined for the period of 270 days post-procedure follow up are reported for patients with at least 240 days of follow-up or with a composite primary endpoint to 270 days.
[2] Defined as the attainment of < 30% final residual stenosis of the target lesion using only the COBRA PzF NanoCoated Coronary Stent System.
[3] Defined as the attainment of < 30% final residual stenosis of the target lesion using any percutaneous method.

**Diabetes**

Patients with diabetes mellitus are at increased risk for cardiovascular morbidity and mortality and are generally associated with worse clinical outcomes when undergoing PCI compared with non-diabetics. In the PzF SHIELD trial, diabetic patients represented 33.7%

(99/294) of the trial population. Table 15 below shows the trial endpoint results in patients with and without diabetes.

**Table 15**
**Summary of Diabetes Subgroup Analysis**

| Endpoints | Patients with Diabetes (N = 99) | Patients without Diabetes (N = 195) | p-value |
|---|---|---|---|
| **Primary Endpoints (270 days)** | | | |
| TVF[1] | 6.3% (6/96) | 13.8% (26/189) | 0.073 |
| Cardiac death | 1.0% (1/96) | 0.0% (0/189) | 0.337 |
| Target vessel MI | 2.1% (2/96) | 7.4% (14/189) | 0.099 |
| Clinically driven TVR | 4.2% (4/96) | 6.9% (13/189) | 0.437 |
| **Secondary Endpoints (270 days)** | | | |
| All-cause mortality | 3.1% (3/98) | 1.6% (3/191) | 0.411 |
| Cardiac mortality | 1.0% (1/96) | 0.0% (0/188) | 0.338 |
| MI (historical definition) | 2.1% (2/95) | 7.4% (14/188) | 0.099 |
| Q-wave MI | 0.0% (0/95) | 0.0% (0/188) | -- |
| Non Q-wave MI | 2.1% (2/95) | 7.4% (14/188) | 0.099 |
| MI (ARC definition) | 2.1% (2/95) | 9.0% (17/188) | 0.041 |
| TLR | 4.2% (4/95) | 6.4% (12/188) | 0.590 |
| Clinically driven TLR | 3.2% (3/95) | 5.3% (10/188) | 0.554 |
| TVR | 5.3% (5/95) | 8.5% (16/189) | 0.472 |
| Clinically driven TVR | 4.2% (4/95) | 6.9% (13/189) | 0.438 |
| Composite endpoint of cardiac death and MI (historical definition) | 3.1% (3/96) | 7.4% (14/188) | 0.190 |
| Composite endpoint of cardiac death and MI (ARC definition) | 3.1% (3/96) | 9.0% (17/188) | 0.085 |
| MACE (historical definition) | 5.2% (5/96) | 12.2% (23/188) | 0.090 |
| Ischemic or hemorrhagic stroke | 0.0% (0/95) | 0.5% (1/189) | 1.000 |
| Early Stent Thrombosis [ARC definition] (≤ 30days) | 0.0% (0/98) | 0.0% (0/195) | -- |
| Late stent thrombosis [ARC definition] (> 30days) | 0.0% (0/95) | 0.0% (0/188) | -- |
| **Acute Success Rates** | | | |
| Device Success [2] | 100.0% (98/98) | 100.0% (192/192) | -- |
| Lesion Success [3] | 100% (98/98) | 100% (192/192) | -- |

[1] Events defined for the period of 270 days post-procedure follow up are reported for patients with at least 240 days of follow-up or with a composite primary endpoint to 270 days.

[2] Defined as the attainment of < 30% final residual stenosis of the target lesion using only the COBRA PzF NanoCoated Coronary Stent System.
[3] Defined as the attainment of < 30% final residual stenosis of the target lesion using any percutaneous method.

### 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 244 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 System Devices 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

The safety and effectiveness information for the COBRA PzF Stent System was derived from non-clinical studies, including biocompatibility, *in vitro* engineering testing, *in vivo* animal testing, sterilization, and shelf life testing, and from the PzF SHIELD clinical study.

### A. Effectiveness Conclusions

The results of the PzF SHIELD study demonstrate that the primary endpoint of TVF and secondary endpoint of in-stent LL have met their performance goals. Device procedural success rates were high with a low incidence of stent malfunction.

### B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and/or animal studies as well as data collected in a clinical study conducted to support PMA approval as described above. These tests revealed the following information:

The biocompatibility and *in vivo* animal testing demonstrated that the *in vivo* performance of the product provides reasonable assurance of safety and acceptability for clinical use.

The *in vitro* engineering testing conducted on the stent and delivery system demonstrated that the performance characteristics met the product specifications and the coating characterization testing adequately described the important attributes of the PzF coating.

The sterilization testing demonstrated that the product can be adequately sterilized and is acceptable for clinical use. The shelf life testing demonstrated that the product can be labeled with a shelf life of three (3) years.

The results of the SHIELD study demonstrate the safety of the COBRA PzF Stent System through evaluation of the primary and secondary endpoints within 270 days of treatment. Safety endpoints evaluated included death, myocardial infarction, MACE, TVR, TLR and stent thrombosis rates.

## C. Benefit-Risk Determination

The probable benefits of the device are based on data collected in a clinical study conducted to support PMA approval as described above. The PzF SHIELD trial was an adequately designed prospective, single-arm trial with a performance goal (TVF at 9 months) based on a meta-analysis of bare metal stent performance from several prior well-executed trials involving bare metal stents. The pivotal PzF SHIELD study met its performance goal for the primary clinical endpoint of TVF and secondary endpoint of in-stent LL at 9 months. In addition, the performance of the COBRA PzF Stent System was in line with expectations given an acceptably low number of safety events, including stent thrombosis, and a technical success rate of 99.6% for stent delivery.

Additional factors that were considered in determining the probable risks and benefits of the COBRA PzF Stent System device included characterization of the disease, availability of alternative treatments, quality of the study design and conduct, robustness of analysis of study results, and risk mitigation. Coronary artery disease (CAD) can be accompanied by symptomatic chest pain or silent ischemia which affects patient's quality of life. CAD is treatable, but if left untreated, the condition can progress to further stenosis within the arteries, increased symptoms, and the need for revascularization. Available treatments for CAD include medical therapy, percutaneous coronary angiography (PCI) and coronary artery bypass graft (CABG) surgery. When treatment for coronary artery disease beyond medications and lifestyle changes is warranted, patients often choose stent deployment over surgical revascularization due to shorter recovery times and the less invasive nature of percutaneous coronary intervention. The risks associated with use of non-drug eluting stents are already well established, and in comparison to medical therapy, PCI

has been shown to reduce the incidence of angina. Patient tolerance of the stent device in the PzF SHIELD study was good and in line with expectations. The study did not exclude any typical patient subgroups that would be expected to benefit from treatment. The patients treated in the PzF SHIELD trial represent a standard PCI population, and the results can be applied to the general population of patients with coronary artery disease. Based on these trial results, the COBRA PzF Stent System provides an appropriate treatment option.

1. **Patient Perspectives**
   This submission did not include specific information on patient perspectives for this device.

In conclusion, given the available information above, the data support that for improving coronary luminal diameter in patients, including patients with diabetes mellitus, with de novo lesions ≤ 24 mm in length in native coronary arteries with a reference vessel diameter (RVD) of ≥2.5 to ≤4.0 mm, the probable benefits outweigh the probable 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.

## XIII. CDRH DECISION

CDRH issued an approval order on 2/21/2017. The final conditions of approval cited in the approval order are described below.

1. ODE Lead PMA Post-Approval Study – Continued Follow-up of PzF SHIELD IDE Cohort: The Office of Device Evaluation (ODE) will have the lead for this clinical study, which was initiated prior to device approval. The PzF SHIELD Trial is a multi-center prospective, single arm study of patients treated with the COBRA PzF NanoCoated Coronary Stent System.

The study objective is to characterize the safety and effectiveness of the COBRA PzF NanoCoated Coronary Stent System through 5 years post-index procedure. The primary endpoint is the incidence of target vessel failure (TVF): cardiac death, target vessel myocardial infarction (MI) [Q wave or non-Q wave], or clinically driven target vessel revascularization (TVR) by percutaneous or surgical methods.

You must collect and report to the Agency clinical outcomes through 5 years post-procedure on patients enrolled in the PzF SHIELD trial.

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.