SUMMARY OF SAFETY AND PROBABLE BENEFIT (SSPB)

I. GENERAL INFORMATION

Device Generic Name: Coronary Covered Stent

Device Trade Name: PK Papyrus Covered Coronary Stent System

Device Procode: NIV

Applicant's Name and Address: BIOTRONIK, Inc.
6024 Jean Road
Lake Oswego, OR 97035

Date(s) of Panel Recommendation: None

Humanitarian Device Exemption (HDE) Number: H170004

Humanitarian Use Device (HUD) Designation Number: HUD # 15-0343

Date of HUD Designation: November 30, 2015

Date of Notice of Approval to Applicant: September 14, 2018

II. INDICATIONS FOR USE

The PK Papyrus Covered Coronary Stent System is indicated for the treatment of acute perforations of native coronary arteries and coronary artery bypass grafts in vessels 2.5 to 5.0 mm in diameter.

The indication for use statement has been modified from that granted for the HUD designation. The HUD designation was for "permanent intraluminal placement in the coronary arteries to treat acute coronary artery perforations (CAP)." It was modified for the HDE approval to specify the types of vessels and vessel sizes appropriate for treatment with the subject device.

III. CONTRAINDICATIONS

- Patients in whom antiplatelet agents or anticoagulation therapy is contraindicated.
- Patients with a known allergy or hypersensitivity to amorphous silicon carbide or any other compound of the system (siloxane-based polyurethane, L-605 cobalt chromium alloy including tungsten and nickel).
- Lesions that cannot be reached or treated with the system.
- Lesions with threatened or abrupt closure during attempted pre-dilation prior to stent implantation.
- Risk of treatment-related occlusion of vital coronary artery side branches.

- Uncorrected bleeding disorders.
- Allergy to contrast media.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the PK Papyrus Covered Coronary Stent System labeling.

V. DEVICE DESCRIPTION

The PK Papyrus Covered Coronary Stent System (PK Papyrus) is a balloon-expandable covered stent, pre-mounted on a fast-exchange delivery system (see **Figure 1**). The covered stent is intended to be a permanent implant.

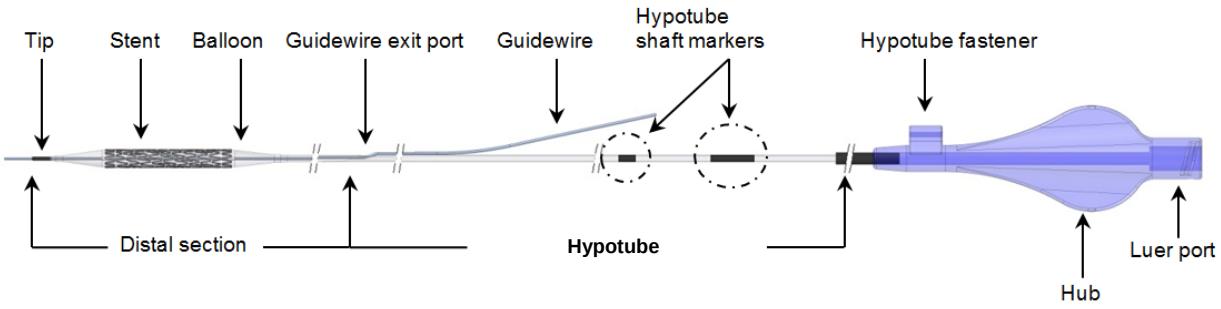

Figure 1: PK Papyrus Covered Coronary Stent System

The stent is laser-cut from a tube of L605 cobalt chromium alloy (CoCr) and is completely coated with amorphous hydrogen rich silicon carbide (a-SiC:H) referred to as proBIO. The abluminal side of the stent body is covered with a polymeric electrospun cover made of siloxane-based polyurethane. The stent body is available in three stent configurations: small (Ø = 2.5 – 3.0 mm), medium (Ø = 3.5 – 4.0 mm), and large (Ø = 4.5 – 5.0 mm). A matrix of the available sizes is provided in **Table 1**.

Table 1: Matrix of Available Sizes for PK Papyrus

Stent Design	Nominal Stent Inner Diameter (ND) [mm]	Nominal Stent Length [mm]		
		15	20	26
Small	2.5	✓	✓	
	3.0	✓	✓	✓
Medium	3.5	✓	✓	✓
	4.0	✓	✓	✓
Large	4.5	✓	✓	✓
	5.0	✓	✓	✓

The delivery system is a fast-exchange percutaneous transluminal coronary angioplasty (PTCA) catheter with a working length of 140 cm. To facilitate fluoroscopic visualization and positioning, the stent is centered between two radiopaque markers. The proximal shaft of the stent system is a hypotube. It has a single Luer port for connecting an inflation/deflation device to inflate/deflate the balloon. The catheter has a silicone-

based hydrophobic coating on the outer surface of the proximal shaft and a hydrophilic coating on the outer surface of the distal shaft. The stent system is compatible with guidewires of 0.014" (0.36 mm) diameter and guiding catheters with an inner diameter of ≥ 0.056" (1.42 mm).

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Alternatives for the correction of coronary artery perforations include:

- Prolonged balloon inflation at the site of contrast extravasation
- Reversal of anticoagulation
- Bare metal stent implantation
- Emergency cardiothoracic surgery

VII. MARKETING HISTORY

PK Papyrus has been marketed outside of the United States since November 2013. A list of countries where PK Papyrus is distributed is provided in **Table 2**. The device has not been withdrawn from marketing for any reason relating to safety and effectiveness.

Table 1: List of Countries where PK Papyrus is Distributed

Argentina	Croatia	Iran	Palestine	South Africa
Australia	Curacao	Israel	Panama	Spain
Austria	Czech Republic	Italy	Paraguay	Sri Lanka
Bahrain	Denmark	Kuwait	Poland	Sweden
Bangladesh	Finland	Latvia	Portugal	Switzerland
Belgium	France	Lebanon	Romania	Thailand
Brazil	Germany	Macedonia	Saudi Arabia	Turkey
Bulgaria	Greece	Malaysia	Serbia	United Arab
Canada	Hong Kong	Malta	Singapore	Emirate
Chile	Hungary	Netherlands	Slovakia	United Kingdom
Colombia	India	New Zealand	Slovenia	Venezuela
Costa Rica	Indonesia	Oman		Yemen

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

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

- Cardiac events: myocardial infarction or ischemia, abrupt closure of the treated artery or side branch; restenosis of the treated artery; cardiogenic shock; angina; dissection, perforation or other coronary artery or aortic injury; residual perforation; pericardial effusion; cardiac tamponade; aneurysm formation; emergency cardiac surgery
- Arrhythmic events: ventricular tachycardia, ventricular fibrillation, atrial fibrillation, bradycardia

- Stent system events: failure to deliver the stent to the intended site, stent dislodgement from the delivery system, stent misplacement, stent deformation, stent embolization, stent thrombosis or occlusion, stent fracture, stent migration, stent loss, inadequate apposition or deformation of the stent, inflation or deflation difficulties, rupture of the delivery system balloon, stent system withdrawal difficulties, embolization of catheter material
- Respiratory events: acute pulmonary edema, congestive heart failure, respiratory insufficiency or failure
- Vascular events: hypotension/hypertension; pseudoaneurysm; arteriovenous fistula; retroperitoneal hematoma; vessel dissection, perforation, rupture or other injury; restenosis; thrombosis or occlusion; compromise of side branch patency; occlusion of side branches; vasospasm; peripheral ischemia; embolization of air, thrombotic, atherosclerotic or catheter material
- Neurologic events: stroke, TIA, femoral nerve injury, peripheral nerve injury
- Bleeding events: access site bleeding or hemorrhage, access site hematoma
- Local or systemic infection
- Allergic reactions to contrast media, antiplatelet agents, anticoagulants, amorphous silicon carbide or any other stent system compound (e.g., siloxane-based polyurethane and L-605 cobalt chromium alloy including tungsten and nickel)
- Death

The non-US PK Papyrus post-market clinical survey provided the analysis of serious adverse events, which are described in the summary of clinical studies in Section X.

IX. SUMMARY OF NON-CLINICAL STUDIES

A. Laboratory Studies

The objectives of the laboratory studies were to assess the functional characteristics of PK Papyrus.

a. *In Vitro* Bench Testing

Testing was conducted according to the guidelines provided in *FDA Guidance for Industry and FDA Staff – Non-clinical Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems* (April 18, 2010).

Additionally, testing followed updated guidelines provided in *Select Updates for Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems* – (Updated BMS guidance, August 18, 2015).

Table 3 summarizes the bench testing performed on the PK Papyrus. The test results are supportive of the device safety and probable benefit.

Table 2: Non-Clinical Engineering Tests of Stent and Delivery System

Test	Test Purpose	Acceptance Criteria	Results
Stent Dimensional and Functional Testing			
Identification of stent materials	To identify and list all materials used in the construction of the stent body, including the a-SiC:H coating and the stent cover.	The test passed if all materials could be identified.	Pass
Identification of packaging materials	To identify the design and all materials used for the packaging design.	The test passed if all materials could be identified.	Pass
Surface characterization	Characterization of the stent surface and a-SiC:H coating.	Characterization study only.	Elemental components of the coating and stent were detected. Coating was confirmed to be uniform.
Accelerated durability testing stent overlapped/Coating durability/Fretting corrosion assessment	To evaluate the aspects of the long-term integrity of the stent and any coating under cyclic radial loading conditions in overlapping and statically bent configuration and the susceptibility of the metallic components of the stent to fretting corrosion in a simulated physiological environment.	The test passed if no failure due to fatigue or coating damages was seen.	Pass

Corrosion resistance – Galvanic, Pitting, Crevice	To determine the susceptibility of the metallic components of the stent to Galvanic, Pitting, and Crevice Corrosion in a simulated physiological environment.	The test passed if the stent was resistant to corrosion when subjected to physiological conditions at the implantation site.
		• Galvanic Corrosion – The theoretical calculated corrosion rate in penetration < 0.001 mm/year.
		• Pitting and Crevice Corrosion:
		  • Range of stable passivity >200 mV
		  • Breakdown potential >300 mV vs. Saturated Calomel Electrode (SCE).
			Pass

Test	Test Purpose	Acceptance Criteria	Results
Dimensional inspection – stent	To inspect and measure the stent body dimensions before placement onto delivery system.	The test passed if the stent met the design specifications for dimensions.	Pass
Foreshortening stent	To determine the foreshortening of the stent.	The test passed if the foreshortening of the stent was +5%/-10%.	Pass
Elastic recoil	To determine the amount of elastic recoil after deployment to determine the diameter of the stent in its deployed state.	The test passed if the elastic recoil was ≤ 9%.	Pass
Stent integrity	To determine the ability of the stent surface/coating to resist damage due to loading, tracking, and deployment.	The test passed if no failures due to baseline/simulated use testing and no cracks or ruptures in the metal stent body was seen.	Pass
Radial stiffness & radial strength, crush resistance	To determine the load/deformation characteristics of the stent while a radial load was applied.	Characterization study only.	The covered stent demonstrated sufficient radial stiffness to resist acute recoil and to keep the lumen open.
Mechanical properties of the stent raw materials and post processing	To determine the mechanical properties of the materials of the stent.	Mechanical properties of the raw materials must meet the following parameters: • Yield strength YS: 580 - 650 MPa • Tensile strength UTS: 1000 – 1250 MPa • Elongation at fracture at: 45%	Pass
Stress analysis/Fatigue analysis overlapped	To determine the stent durability due to worst case physiological loads and configuration by means of a Finite Element Analysis. Calculation of Safety Factor (SF).	Equivalent stress and strain levels and load history shall be documented. The test passed if the following specification was met: • SF > 1	Pass

Test	Test Purpose	Acceptance Criteria	Results
Acute particulate evaluation – particle count, visual inspection of stent and coating after expansion, and cover integrity	The purpose of this test is to determine the size and quantity of particles that could potentially be introduced into the bloodstream during delivery and deployment of the stent and retraction of the delivery system.	Characterization study only.	Particle release during tracking and dilatation was within the limits described in USP <788>.
Chronic particulate evaluation – chronic	To investigate the size and quantity of particles under cyclic radial loading conditions in overlapped and statically bent configuration representing an equivalent of 10 years of implantation life.	Characterization study only.	Particle release during the complete use, including simulated 1 year and 10 years of implantation, was within the limits described in USP <788>.
MRI safety and compatibility	To determine the effect of Magnetic Resonance on the position and temperature of the stent platform. Also to determine the extent of image artifact during MRI.	Displacement and Torque testing: MR-induced deflection force and torque should be less than the forces and torques to which the device would be subjected outside of the MR environment. Artifact testing and image analysis: This is a characterization test to identify the profile of the stent in an MRI screen and its image in relation to surrounding structures. Heating testing: The maximum heating allowed during a 15 min. scanning period shall conform to CEM43 which limits temperature rises to approx. 6°C. No tissue damage is expected at temperature rises below this limit.	Pass

Test	Test Purpose	Acceptance Criteria	Results
X-ray visibility	To determine the ability to visualize the stent system and/or stent using the imaging techniques specified in the IFU.	The test passed if the X-ray visibility of the stent system was comparable to commercially available control devices of similar size.	Pass
Delivery System Dimensional and Functional Testing			
Identification of delivery system materials	To identify and list all components and their respective materials used in the construction of the delivery system.	The test passed if all materials could be identified.	Pass
Dimensional and visual inspection of the final product	To inspect the physical and dimensional properties of the Stent System.	The test passed if the delivery system met the design specifications.	Pass
Crossing profile	To measure the crossing profile of the stent system.	The test passed if the distal part of the stent system could pass through a ring hole gauge with specified minimum and maximum diameters.	Pass
Trackability	To assess the tracking performance of the device.	The test passed if tracking performance was significantly better than comparable stent systems.	Pass
Simulated use (Delivery, deployment and retraction)	To evaluate the performance of the stent system and if the delivery system can reliably deliver the stent to the intended location.	The test passed if the delivery system delivers the stent to the intended location without damage to the stent.	Pass
Balloon rated burst pressure (RBP) testing	To determine the rated burst pressure (RBP) of the balloon when used with the stent.	The test passed if the following specification was met: • Lower 99.9% quantile at 95% confidence: for Ø 2.5 mm to 4.0 mm: ≥16 atm; for Ø 4.5 mm to 5.0 mm: ≥14 atm • No part of the specimen is to become detached • No fracture/damage of stent.	Pass

Test	Test Purpose	Acceptance Criteria	Results
Balloon fatigue[1]	To determine the ability of the balloon to withstand repeated inflation/ deflation cycles.	The test passed if the balloon resisted 10 cycles with 30s holding time at RBP for each cycle.	Pass
Balloon compliance	To determine the relationship between the stent diameter and the balloon inflation pressure and to verify that at all labeled pressure steps the diameter stated on the label is achieved.	The test passed if the following specification was met: • Statistically calculated min and max stent inner Ø of all tested balloon expandable stents at all labeled pressure steps: ±8% of calculated mean Ø • Radial compliance: 14% ± 8%.	Pass
Balloon inflation and deflation time	To determine the balloon inflation and deflation time.	The test passed if the deflation time from RBP was maximum 30s for sizes up to 4.0/40 and maximum 40s for sizes up to 5.0/40.	Pass
Tensile strength catheter/Tip pull test	To determine the bond strength of the joints and/or fixed connections of the PK Papyrus stent system, including its distal tip.	The test passed if the minimum force at break was greater than the specified lower limit for each catheter bond location (≥5 N for catheter body, (≥3 N for distal tip).	Pass
Flexibility	To evaluate the flexibility and resistance to kink of the stent system.	The test passed if the distal shaft (mounted over a guide wire) did not kink nor did its function become compromised, while passed through a 4mm radius curve.	Pass
Rotatability	To evaluate the transmission of rotational forces.	The device must transmit rotational movement. The balloon must still be inflatable to NP and deflatable after five-fold rotation of the proximal end of the device with distal end clamped.	Pass

[1] Additional balloon fatigue testing will be performed per the Approval Order.

Test	Test Purpose	Acceptance Criteria	Results
Adhesive strength of catheter coating (Coating Integrity)	To evaluate the adhesive strength of the surface coating on the proximal outer shaft of Catheters.	The test passed if there was no visible indication of delamination.	Pass
Coating integrity	To evaluate the ability of catheters (delivery systems, balloon catheters) with coating to resist damage due to loading, tracking, deployment and delivery system withdrawal.	The test passed if: • Prior simulated use (Baseline): coating on the catheter was homogeneous and without any drop formation. • Post simulated use: No visible indication of delamination under 10-40 times microscopic magnification.	Pass
Stent dislodgement by forward/reverse motion	To determine whether the stent will dislodge from the delivery system after conditioning by passing the device through a simulated coronary arterial model.	No stent or cover dislodgement, crimped stent and cover has to remain between the X-ray markers.	Pass
Stent retention force	To determine the force that will dislodge the stent from the unstressed stent system and after conditioning.	The test passed if the retention force was • Unstressed: ≥ 1.5 N for 2.5 - 3.0 mm stent diameters and ≥ 2.5 N for 3.5 – 5.0 mm stent diameters • After conditioning: ≥1.0 N No displacement of the cover from the stent.	Pass
Cover Dimensional and Functional Testing			
Dimensional / Mass inspection polymer cover	To determine the cover mass and thickness and to evaluate for cover imbalance.	The test passed if distance cover end to stent end had ranges between 1 and 2.5 times the strut width. Cover mass is 3 – 8.67 mg, depending on stent size.	Pass
Hydrolytic stability	To characterize the *in-vitro* hydrolytic stability of the polymer cover.	Characterization study only.	The stent cover showed resistance to accelerated hydrolytic degradation.

Test	Test Purpose	Acceptance Criteria	Results
Oxidative stability	To evaluate stability of the polymer cover via oxidative methods.	The ElastEon 2 AS membrane must be superior to the Pellethane 2363-80A membrane (positive control) and similar or better than the Pellethane 2363-55D membrane (negative control) regarding weight loss and molecular weight change.	Pass
Toxicological evaluation of cover degradation	To determine systemic toxicity risks related to possible cover degradation.	The requirements were met if the simultaneous implantation of 2 of the largest PK Papyrus stents (highest cover mass) was evaluated as biologically safe related to possible cover degradation.	Pass
Baseline stent cover integrity (t=0)	To determine the ability of the stent cover to resist damage after expansion to nominal diameter and overexpansion.	The test passed if there is no relevant damage, detachment or dislodgement of the cover.	Pass
Permeability test of cover	To evaluate the cover for permeability/blood leaking performance.	The maximum initial blood leak volume is 10 ml within the first 10 minutes after implantation of the stent. Maximum allowed permeability 10 min and later after implantation is 0.25 ml/min/cm^2.	Pass
Durability test of the cover	To evaluate the fatigue strength of the stent cover.	The test passed if all test specimens withstand a pulsatile load of 120 ± 40 mmHg at a simulated heart rate of 70 bpm for at least 48 hours (no stent cover damage).	Pass

b. Biocompatibility

As per ISO 10993-1:2009, Biological Evaluation of Medical Devices, the stent system was evaluated for biocompatibility, as summarized in **Table 4**. Tests were conducted separately on sterilized products to support the biocompatibility of the delivery system and the stent. The delivery system was categorized as an externally communicating device with limited contact duration (<24 hours) with vascular tissue and circulating blood. The stent was categorized as an implant device with permanent contact

(>30 days) with vascular tissue and circulating blood. The results from the biocompatibility evaluation support the overall conclusion that PK Papyrus is biocompatible.

Table 4: Biocompatibility Testing

Test Performed	Test Method	Stent	Delivery System	Results
Cytotoxicity	ISO MEM Elution Cytotoxicity	✓	✓	Non-cytotoxic
Sensitization	ISO Maximization Sensitization (Guinea Pig Maximization Test, (GPMT))	✓	✓	Non-sensitizing
Irritation/Intracutaneous Reactivity	ISO Intracutaneous Reactivity	✓	✓	Non-irritating
Acute Systemic Toxicity	ISO Acute Systemic Toxicity (4 Extracts)	✓	✓	Non-toxic
Pyrogenicity	ISO Material Mediated Rabbit Pyrogen Test	✓	✓	Non-pyrogenic
Subchronic/Chronic Systemic Toxicity/Implantation	Implantation 90 days (combined with subchronic/chronic systemic toxicity)	✓	N/A	Non-toxic
Genotoxicity	• Ames test	✓	✓	Non-mutagenic
	• Mouse Lymphoma Assay	✓	✓	
	• Mouse Micronucleus Assay	✓	N/A	
Hemocompatibility	ASTM *In vitro* Hemolysis (indirect and direct contact)	✓	✓	Non-hemolytic
	Complement activation assay	✓	✓	Non-activator
	In vivo Thrombogenicity[2]	✓	✓	Non-thrombogenic

c. Sterilization

PK Papyrus is sterilized with ethylene oxide (EO) gas to a sterility assurance level (SAL) of $1x10^{-6}$ in compliance with ISO 11135-1:2007 – Sterilization of health care products -- Ethylene oxide -- Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices. The product has also been shown to meet the endotoxin limit of 20 EU/device in USP <85> and FDA 2012 Guidance for Pyrogen/Endotoxin testing.

d. Packaging and Product Shelf Life

Packaging verification testing was performed to demonstrate that the design of the PK Papyrus packaging can withstand the hazards of the distribution environment and that the sterility of the device is maintained throughout the labeled shelf life. Two-year shelf life was verified by conducting performance testing on samples that have undergone

[2] This endpoint was evaluated as part of the animal studies, as out lined in Section IX. B

accelerated aging representing 24 months.

B. Animal Studies

The objective of the animal study was to evaluate the biological safety profile of PK Papyrus. Animal studies were conducted in hybrid farm swine (28 days) and Yucatan miniature swine (180 days). Stent implantations were performed in a maximum of 2 coronary arteries per animal. After pre-stent angiography was obtained, the test and control stents were introduced into the coronary arteries (RCA, LAD, or LCX) and deployed to achive a target balloon to artery ratio of 1.20:1, estimated visually by the interventionalist. Post-stent angiograms were performed to document stent deployment and apposition.

At 28 days or 180 days following stent placement each treated vessel was qualitatively evaluated by angiography for evidence of lumen narrowing, presence of dissection, presence of aneurysms, presence of thrombosis, TIMI flow, closure of side branches, and stent migration. After final angiography, animals were euthanized and subjected to a comprehensive necropsy, defined as gross examination of the heart and the external aspect of stented vessels, the thoracic and abdominal cavities and their contents. Stented vessels were excised and processed for histology. Vascular tissue responses were assessed using quantitative coronary angiography (QCA), histomorphometry, and histopathology, and included the following endpoints:

- Marginal vessel (proximal and distal) mean lumen diameter
- Mean lumen diameter of the treated region
- Minimal lumen diameter [MLD] of the target region
- Reference vessel diameter
- Diameter stenosis [1 – (MLD/RVD) x 100%]
- Balloon to artery ratio [balloon/pre-stent mean lumen diameter]
- Late lumen loss [MLD post-stent- MLD final]
- Late loss index [(MLD post-stent - MLD final) / MLD post-stent]
- Internal Elastic Lamina and External Elastic Lamina (IEL & EEL) area
- Luminal area (area bound by the luminal border)
- Medial area (EEL area– IEL area)
- Intimal area (IEL area – luminal area)
- Area stenosis ({1 – (luminal area/IEL area)} x 100)
- Mean intimal thickness (distance between the IEL and the luminal border)
- Inflammation
- Endothelialization

Notable outcomes from the animal study are provided in **Table 5**. In the 28-day study, PK Papyrus behaved comparably to the control device. In the chronic 180-day study, significant stenosis was observed in both the PK Papyrus-stented vessels and the vessels treated with the control device, although stenosis was significantly higher in the PK

Papyrus group. On histopathologic evaluation of the stented porcine coronary arteries, there was a statistically significant difference in the mean inflammation score between the PK Papyrus group and the control group at 180 days (1.79±1.20 vs. 0.45±0.64, respectively). This difference was associated with a higher injury score in the arteries treated with PK Papyrus as compared to the control device.

Table 5 Pre-Clinical Results from 28-Day and 180-Day Studies

Parameter	28-day study		180-day study	
	Subject Device (n=9)	**Control Device (n=9)**	**Subject Device (n=7)**	**Control Device (n=7)**
Late Loss Index Median (25% - 75% Percentiles)	0.47 (0.38 – 0.56)	0.57 (0.47 – 0.70)	0.30 (0.27 – 0.41)	0.33 (0.27 – 0.44)
Area Stenosis (%) Mean ± SD	70.5 ± 8.6	73.3 ± 12.2	61.9 ± 15.9*	47.5 ± 6.3
Inflammation Score Mean ± SD	0.70 ± 0.76	1.04 ± 0.83	1.79 ± 1.20**	0.45 ± 0.64

*significantly different vs. Abbott GraftMaster (p=0.045); ** significantly different vs. Abbott GraftMaster (p=0.023)

X. SUMMARY OF CLINICAL INFORMATION

A. Study Design

The clinical information collected to support the safety and probable benefit of PK Papyrus was obtained from use of the device outside of the United States. BIOTRONIK has been collecting voluntary clinical use data for PK Papyrus through a post-market survey since the product entered the global market in 2013. The objective of the ongoing survey is to evaluate the technical success and safety of PK Papyrus in treating coronary perforations. All complaint data received through April 27, 2017 for PK Papyrus were considered in the clinical analysis.

B. Overview of Results

As of April 27, 2017, BIOTRONIK has received voluntary survey responses or complaints for 121 patients treated since June 11, 2013, comprising 153 PK Papyrus. Coronary artery perforation was cited by the physician as the indication for 80 of these patients treated in 16 European and Asian nations, with a total of 100 PK Papyrus being used in the treatment of a coronary artery perforation (some patients received more than one PK Papyrus). At least one PK Papyrus was successfully implanted in 76 of the 80 patients.

The in-patient data for the 80 coronary artery perforation patients was based on surveys only (69), complaints only (6), or both (5), and on follow-up visits with physicians as appropriate. Of the 80 patients treated for coronary perforation, BIOTRONIK received

post-hospital discharge follow-up surveys on 22 cases (duration 8 to 832 days post-PK Papyrus implantation).

C. Study Population Demographics

Demographic information was limited to patient age ranges (**Table 6**) due to national data collection and privacy laws effective in the countries where the data were collected.

Table 3: Patient Age Ranges

Age (n = 80)	Number (%)
Under 40	0 (0.0%)
40 to 49	1 (1.3%)
50 to 59	4 (5.0%)
60 to 69	22 (27.5%)
70 to 79	27(33.8%)
80 to 89	18(22.5%)
Over 90	2 (2.5%)
Answer not provided	6 (7.5%)

D. Safety and Probable Benefit Results

Information regarding Ellis Classification for perforation, procedural characteristics, device and procedure success, and complications was collected (**Table 7** to **Table 12**).

Table 7 shows the Ellis Classification for Perforation and other anatomic and procedural elements.

Table 4: Coronary Perforation and Stent Characteristics

Variable	Category	Number (%)
Ellis Classification for Perforation* (n=80 patients)	Class I	8 (10.0%)
	Class II	12 (15.0%)
	Class Ill	40 (50.0%)
	Class IV	14 (17.5%)
	Answer not provided	6 (7.5%)
Implant location (n = 80 patients)	LAD	39 (48.8%)
	RCA	19 (23.8%)
	LCX	17 (21.3%)
	Bypass Graft	3 (3.8%)
	LMCA	2 (2.5%)
Reference vessel diameter (mm) (n = 60 patients)	mean ± SD	3.13 ± 0.64
Perforation length (mm) (n = 53 patients)	mean ± SD	6.21 ± 6.71
Number of PK Papyrus implanted per patient (n = 80 patients)	mean ± SD	1.11 ± 0.48
	Any attempt†	50 (62.5%)

Table 4: Coronary Perforation and Stent Characteristics

Variable	Category	Number (%)
Previous procedures performed in attempts to stop bleeding from perforation site prior to PK Papyrus implantation (n = 80 patients)	*Balloon*	46 (57.5%)
	Stenting	7 (8.8%)
	Coil	2 (2.5%)
	Use of a different covered stent	2 (2.5%)
	Protamine injection	1 (1.3%)

* Ellis Classification for Perforation Definitions: Class I (Extraluminal crater without extravasation), Class II (Pericardial or myocardial blush without contrast jet extravasation), Class Ill (Extravasation through frank (>1 mm) perforation), Class IV (Cavity Perforation into an anatomic cavity chamber, spilling coronary sinus, etc.).

† More than one prior attempt may be recorded per case.

Procedure success was evaluated on a patient-level basis. In the 80 perforation cases; PK Papyrus was successfully delivered in 95.0% (76) of cases, with 91.3% (73) of perforations successfully sealed (**Table 8**).

Table 5: Procedure Success

Procedure Success (patient-level evaluation)	Number (%)
PK Papyrus successfully delivered to perforation* (n = 80)	76 (95.0%)
Perforation sealed successfully† (n = 80)	73 (91.3%)

* Patient-level delivery success was defined as the successful delivery of at least one PK Papyrus to the target perforation, such that the stent was able to be positioned properly in the area of the perforation.

† Patient-level perforation sealing success was defined as successful sealing of a coronary perforation per operator assessment with use of one or more PK Papyrus as assessed after the procedure.

Immediate procedure outcome is defined as the patient status at the close of the procedure. Of the 80 patients who underwent attempted PK Papyrus implantation, 77 (96.3%) survived the procedure, with two deaths occurring in patients with Class IV perforations (**Table 9**). There was no information regarding procedural survival of one patient with a Class IV perforation. Reasons for unsuccessful delivery include one case in which PK Papyrus was dislodged when passing through a previously implanted stent, one case in which two PK Papyrus were attempted for use but could not pass a lesion, one case in which PK Papyrus could not reach the perforation, and one case in which PK Papyrus could not pass through a previously implanted stent. These four cases were all considered both unsuccessful in delivery and sealing. There was a total of three patients in whom PK Papyrus was successfully delivered to the site of perforation, but the perforation was not sealed by the stent(s); two of these patients died in the hospital (one during the procedure and one post-procedure), and one survived (perforation ultimately sealed with arterial post-dilatation).

Table 6: Immediate Procedural Patient Survival Stratified by Ellis Perforation Classification

Ellis Perforation Classification	Survival	Death	Answer not provided
Class I (n = 8)	8 (100.0%)	0 (0.0%)	0 (0.0%)
Class II (n = 12)	12 (100.0%)	0 (0.0%)	0 (0.0%)
Class III (n = 40)	40 (100.0%)	0 (0.0%)	0 (0.0%)
Class IV (n = 14)	11 (78.6%)	2 (14.3%)	1 (7.1%)
Class not provided (n = 6)	6 (100.0%)	0 (0.0%)	0 (0.0%)
Overall (n = 80)	**77 (96.3%)**	**2 (2.5%)**	**1 (1.3%)**

In-hospital complications are shown in **Table 10**.

Table 7: In-Hospital Complications

Category	Number of Complications	Number of Patients with Complication	Percentage of Patients (n = 80)
Death	8	8	10.0%
Timing			
Post-procedural death	6	6	7.5%
Procedural death	2	2	2.5%
Mode			
Sudden cardiac death	1	1	1.3%
Cardiac death	7	7	8.8%
Non-cardiac death	0	0	0.0%
Pericardiocentesis due to tamponade	7	7	8.8%
Other urgent cardiac surgery	0	0	0.0%
Post-procedural MI	0	0	0.0%
Overall Hospital Outcome Events Total	**15**	**14***	**17.5%**

* Patients may have had more than one category of complication; therefore, the number of unique patients with any complication is not the sum of the individual components.

Of the 8 in-hospital deaths, there were 2 procedural deaths (1 patient with successful and 1 patient with unsuccessful perforation sealing with PK Papyrus Stents). The patient with unsuccessful sealing (Class IV perforation) had persistent intrapericardial bleeding and developed electro-mechanical dissociation. Information on the cause of death was not available in the patient with successful perforation sealing (Class IV perforation, death assumed to be cardiac).

Of the 6 post-procedure in-hospital deaths, the coronary perforation was successfully sealed by PK Papyrus Stents in 5 cases and not successfully sealed in 1 case. Of the 5 patients with successful sealing (Class III perforation in 4 patients and unknown in 1

patient), 2 patients had cardiogenic shock, 1 patient had a cardiac arrest, and information was not provided in 2 cases (deaths assumed to be cardiac). The patient with unsuccessful perforation sealing (Class III perforation) underwent pericardial drainage but developed cardiopulmonary failure and died during dialysis. The mortality rate in patients with Class III perforations was 12.5% (5 out of 40).

In the surveys and complaint information received, there were no reported cases of post-procedural MI or other urgent cardiac surgery following implantation of PK Papyrus Stents. Seven patients (out of 80, 8.8%) were reported to have required pericardiocentesis due to pericardial tamponade following PK Papyrus implantation. Among 40 patients with Ellis Class III coronary artery perforations, pericardiocentesis due to tamponade was reported in 6 patients (15.0%).

Table 11 shows in-hospital complication events that had at least a possible relationship to the PK Papyrus.

Table 8: In-Hospital Device-Related Complications

Category	Number of Complications	Number of Patients with Complication	Percentage of Patients (n = 80)
Stent Dislodgement	9	6	7.5%
Dislodgement during retrieval	3	2	2.5%
Dislodgement in catheter extension	3	1	1.3%
Dislodgement during delivery	2	2	2.5%
Dislodgement during lesion or stent passage	1	1	1.3%
Stent Thrombosis	2	2	2.5%
Definite	1	1	1.3%
Probable	1	1	1.3%
Possible	0	0	0.0%
Overall Any In-Hospital Device-Related Complication Total	**11**	**8**	**10.0%**

Of the two PK Papyrus thrombosis cases, definite stent thrombosis was reported in a case where acute thrombosis was noted in the procedure notes. In the second stent thrombosis case, the patient died the day after implantation due to sudden cardiac arrest; therefore, the event is reported as a case of probable stent thrombosis per ARC definitions.

Post-hospital discharge follow-up surveys were received for 22 patients that received a PK Papyrus for coronary artery perforation. **Table 12** shows the Major Adverse Cardiac Events (MACE) that may have had at least a possible relationship to the procedure or the PK Papyrus.

Table 9: Follow-up MACE Complications

Complication Category	Number of Complications	Number of Patients	Percentage of Patients (n = 22)
All-cause death	1	1	4.5%
Sudden cardiac death	0	0	0.0%
Non-cardiac death	1	1	4.5%
Myocardial infarction	1	1	4.5%
Stent thrombosis	0	0	0.0%
Target lesion revascularization	1	1	4.5%
Target vessel non-target lesion revascularization	0	0	0.0%
Overall Follow-up MACE Complications Total	**3**	**3**	**13.6%**

One patient experienced a non-cardiac death due to cancer 630 days after PK Papyrus implantation. No complications were reported after discharge in 72.7% (16/22) of patients for which a follow-up survey was received. Three patients experienced clinical events that were determined to not meet the MACE categories and were unrelated to the procedure or the stent as assessed by the physician (one patient was hospitalized for pericarditis two weeks post-implant, one patient was hospitalized for cardiac decompensation with left bundle branch block and a repolarization disorder, and one patient experienced intermittent non-exertional chest pain).

Pediatric Extrapolation

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

XI. 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 45 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.

XII. SAFETY AND PROBABLE BENEFIT ANALYSIS

The biocompatibility and *in vivo* animal testing demonstrated that the performance characteristics of PK Papyrus provide reasonable assurance of safety for clinical use.

The *in vitro* engineering testing conducted on the stent and delivery system demonstrated that the performance characteristics met all product specifications and demonstrated that the device functions mechanically as intended. The test results obtained from the sterilization

testing demonstrated that the product can be adequately sterilized and is acceptable for clinical use. Shelf life testing has established acceptable performance for a labeled shelf life up to 24 months.

The PK Papyrus global clinical survey demonstrated the ongoing technical success, safety, and probable benefit of PK Papyrus as a potentially life-saving treatment for coronary artery perforations.

A. Probable Benefit Conclusions

Data to support the probable benefit of PK Papyrus were collected from 80 patients in 16 European and Asian countries in which PK Papyrus was used to treat coronary artery perforations. Of the 80 patients who underwent attempted PK Papyrus implantation, 77 (96.3%) survived the procedure. PK Papyrus was successfully delivered to the perforation site in 76 of 80 patients (95.0%), and the perforation was successfully sealed in 73 cases (91.3%). The magnitude of the probable benefit is high, because coronary artery perforation can be a life-threatening condition, and effective perforation sealing with the device can reduce the risk of morbidity and mortality. The high rates of successful stent delivery and implantation to the target coronary artery perforation site and successful perforation sealing meet an acceptable level of device performance.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and animal studies as well as data collected in a non-US post-market survey of device use to treat acute coronary artery perforations during percutaneous coronary intervention (PCI) procedures to support HDE approval as described above.

Data on the risks associated with PK Papyrus were collected from 80 patients in 16 European and Asian countries in which PK Papyrus was used to treat coronary artery perforations. Serious adverse events were reported that could be related to the underlying coronary perforation, use of PK Papyrus, or both. Periprocedural death occurred in 2 patients (2.5%), and pericardiocentesis to treat pericardial tamponade was performed in 7 patients (8.8%). Of note, the need for pericardiocentesis could be attributable to the size of the hemorrhagic pericardial effusion that developed prior to implantation of PK Papyrus. There were no reported periprocedural MIs. Post-hospital discharge follow-up surveys were submitted for 22 patients. There were no late cardiac deaths; one patient (4.5%) had an MI, and 1 patient (4.5%) underwent target lesion revascularization. MIs can have long-term clinical impact, but successfully treated pericardial tamponade would not be expected to have long-term clinical sequalae.

Although comparisons of clinical outcomes between different datasets have substantial limitations, a meta-analysis conducted by Shimony et al. (Am J Cardiol 2009; 104: 1674-77) reported a pooled mortality rate of 21.2% (range 12.0% to 31.4%) and a pooled pericardiocentesis due to tamponade rate of 45.7% (range 34.9% to 57.5%) for patients with Ellis Class III coronary artery perforations.

The reported rates of serious adverse events associated with PK Papyrus and the implantation procedure appear to meet an acceptable level of device safety.

C. Probable Benefit-Risk Conclusions

The reported rates of serious adverse events associated with PK Papyrus and implantation procedure appear to meet an acceptable level of device safety. Additional factors to be considered in determining probable risks and benefits for PK Papyrus follow.

Implantation of PK Papyrus was associated with high rates of successful delivery to the coronary perforation site (95.0% of cases) and high rates of successful perforation sealing (91.3%). The rates of acute serious adverse events that could be related to the underlying coronary perforation, use of PK Papyrus, or both (death 2.5%, pericardiocentesis 8.8%, late MI 4.5%, and target lesion revascularization 4.5%) are acceptable when considering the benefits of device use, because coronary artery perforation is a life-threatening (albeit rare) complication associated with PCI procedures. Implantation of PK Papyrus can effectively seal the perforation and allow anterograde coronary flow to the myocardium. The magnitude of the probable benefit is high, because coronary artery perforation can be a life-threatening condition, and effective perforation sealing with the device can reduce the risk of morbidity and mortality. Following the achievement of an effective coronary artery perforation seal and normal anterograde coronary blood flow, PK Papyrus can provide life-long benefit.

Although there is a moderate degree of uncertainty regarding the magnitude of device-associated benefits, the totality of the clinical information provides a reasonable assurance of probable benefit.

Limitations in the robustness of the data quantity and quality with regard to the safety and probable benefit associated with PK Papyrus should be recognized and include: (1) a small number of treated subjects; (2) absence of a prespecified study protocol including prespecified study endpoints, enrollment criteria, protocolized treatments, and follow-up requirements; (3) the potential for selection bias because survey completion by operators was voluntary; (4) a single-arm dataset without a concurrent or a historical control group or a prespecified performance goal; (5) absence of blinded adjudication of events using prespecified event definitions; and (6) limited follow-up information on treated patients. Although there is a moderate degree of uncertainty regarding the magnitude of the rates and probability of harm from serious device-associated adverse events, the totality of the clinical information provides a reasonable assurance of device safety.

These limitations introduce a moderate level of uncertainty regarding effectiveness and the risk of harm from serious device-associated adverse events. Nevertheless, the totality of the clinical data supports device safety and probable benefit for the intended use.

The clinical data in support of the safety and probable benefit of PK Papyrus are generalizable to the population of patients with coronary artery perforations. Because coronary artery perforation can be life-threatening, it would be expected that patients with this condition would have a high risk tolerance.

The GRAFTMASTER RX is another available device that is used to treat coronary artery perforations (HDE number H000001). PK Papyrus has features distinct from the GRAFTMASTER RX, but the two devices were not directly compared in the clinical trial.

In conclusion, given the available information above, the data support that for the treatment of acute coronary artery perforations, the probable benefits outweigh the probable risks.

1. Patient Perspectives

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

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and probable benefit of this device when used in accordance with the indications for use. PK Papyrus implantation can effectively seal a coronary artery perforation and allow anterograde coronary flow to the myocardium. Although there is a moderate degree of uncertainty regarding the magnitude of device-associated benefits and the rates and probability of harm from serious device-associated adverse events (see above discussion regarding the limitation on the quantity and quality of the clinical data), the totality of the clinical information provides a reasonable assurance of safety and probable benefit.

Therefore, it is reasonable to conclude that the probable benefit to health from using the device for the target population outweighs the risk of illness or injury, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment when used as indicated in accordance with the directions for use.

XIII. PANEL RECOMMENDATION

This HDE was not referred to the FDA Circulatory System Devices Panel for review and recommendation because the information in the HDE did not raise any unanticipated safety concerns. Therefore, it was determined that this application need not be submitted to the advisory panel.

XIV. CDRH DECISION

CDRH has determined that, based on the data submitted in the HDE, the PK Papyrus Covered Coronary Stent System will not expose patients to an unreasonable or significant risk of illness or injury and the probable benefit to health from using the device outweighs the risks of illness or injury. CDRH issued an approval order on September 14, 2018. The final conditions of approval cited in the approval order are described below.

The applicant has agreed to collect clinical data through voluntary post-market surveillance

(i.e., Device Registration and Follow-up Forms) and report these clinical data to FDA every 6 months. The sponsor has also agreed to conduct additional balloon fatigue testing.

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

XV. APPROVAL SPECIFICATIONS

Directions for use: See the device labeling.

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

Post-approval Requirements and Restrictions: See approval order.