

**DE NOVO CLASSIFICATION REQUEST FOR
WALLFLEX BILIARY RX FULLY COVERED STENT SYSTEM RMV**

REGULATORY INFORMATION

FDA identifies this generic type of device as:

Metallic Biliary Stent System for Benign Strictures: A metallic biliary stent system for benign strictures is a prescription device intended for the treatment of benign biliary strictures. The biliary stents are intended to be left indwelling for a limited amount of time and subsequently removed. The device consists of a metallic stent and a delivery system intended to place the biliary stent in the bile duct. This device type is not intended for use in the vasculature.

NEW REGULATION NUMBER: 21 CFR 876.5011

CLASSIFICATION: II

PRODUCT CODE: PNB

BACKGROUND

DEVICE NAME: WallFlex Biliary RX Fully Covered Stent System RMV

SUBMISSION NUMBER: DEN150040

DATE OF DE NOVO: August 28, 2015

CONTACT: BOSTON SCIENTIFIC CORPORATION
100 BOSTON SCIENTIFIC WAY
MARLBOROUGH, MA 01752

REQUESTER'S RECOMMENDED CLASSIFICATION: Class II

INDICATIONS FOR USE

The WallFlex Biliary RX Fully Covered Stent System RMV is indicated for indwell up to 12 months in the treatment of benign biliary strictures secondary to chronic pancreatitis.

LIMITATIONS

The sale, distribution, and use of the device are restricted to prescription use in accordance with 21 CFR §801.109.

Contraindications:

- The WallFlex Biliary RX Fully Covered Stent should not be placed in strictures that cannot be dilated enough to pass the delivery system, in a perforated duct, or in very small intrahepatic ducts.
- The WallFlex Biliary RX Fully Covered Stent System RMV should not be used in patients for whom endoscopic techniques are contraindicated.

Warnings:

The safety and effectiveness of the stent has not been established for indwell periods exceeding 12 months.

The WallFlex Biliary RX Fully Covered Stent System RMV is for single-use only.

The safety and effectiveness of the WallFlex Biliary RX Fully Covered Stent System RMV for use in the vascular system has not been established.

The safety and effectiveness of the WallFlex Biliary RX Fully Covered Stent System RMV has not been established in the treatment of benign biliary anastomotic strictures in liver transplant patients and benign biliary post abdominal surgery strictures.

Testing of overlapped stents has not been conducted.

The stent contains nickel, which may cause an allergic reaction in individuals with nickel sensitivity.

PLEASE REFER TO THE LABELING FOR A MORE COMPLETE LIST OF WARNINGS, PRECAUTIONS AND CONTRAINDICATIONS.

DEVICE DESCRIPTION

The WallFlex Biliary RX Fully Covered Stent System RMV consists of 2 components: the implantable fully covered self-expanding metallic biliary stent (FC-SEMBS) and the Rapid Exchange (RX) delivery device.

The FC-SEMBS is made out of Nitinol monofilament wire with a radiopaque platinum core, braided in a tubular mesh configuration. The stent has proximal and distal flares at each end to aid in preventing migration. The proximal flare also contains the biliary stent retrieval loop. The retrieval loop is used for removal during the initial placement procedure in the event of incorrect placement. The retrieval loop is also used for removal from the bile duct. See Figure 1 for a photograph of the FC-SEMBS.

The biliary stent is covered with a Permalume™ silicone covering along its entire length except for 2 mm on the retrieval loop end.

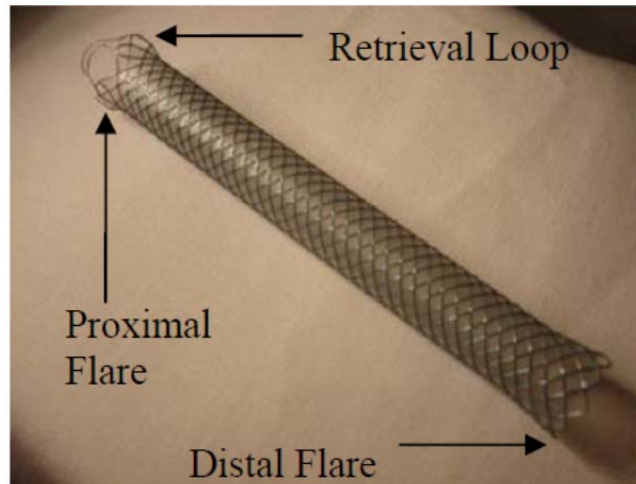


Figure 1 – FC-SEMBS

The following models of biliary stent (diameter and length) are part of this system.

Table 1 – Device Model Numbers

UPN	Description	Delivery System Working Length (cm)	Stent Diameter (mm)	Stent Length (mm)
M00570340	WallFlex Biliary Stent RX Fully Covered System RMV	194	8	60
M00570350	WallFlex Biliary Stent RX Fully Covered System RMV	194	8	80
M00570360	WallFlex Biliary Stent RX Fully Covered System RMV	194	10	40
M00570370	WallFlex Biliary Stent RX Fully Covered System RMV	194	10	60
M00670380	WallFlex Biliary Stent RX Fully Covered System RMV	194	10	80

The RX delivery device (see Figure 2) is a coaxial tube design. The exterior tube is used to constrain the biliary stent before deployment and re-constrain the biliary stent, if biliary stent repositioning is necessary, after partial deployment. The exterior tube has a clear section so that the constrained stent is visible. A yellow transition zone on the inner tube of the delivery system is visible between the stent and the blue outer sheath. There are four radiopaque (RO) markers to aid in the deployment of the stent while using fluoroscopy.

There are two RO markers on the inner tube of the delivery system identifying the ends of the constrained biliary stent. Between these RO markers is an additional RO marker that indicates at what point re-constraint is no longer possible. The fourth RO marker at the leading end of the exterior tube indicates how far the biliary stent has been deployed. There is one visual marker on the interior tube between the handles to aid in the deployment of the biliary stent. The visual marker indicates the point at which re-constraint is no longer

possible. The interior tube has a single central lumen to accommodate a 0.035 inch (0.86 mm) guidewire.

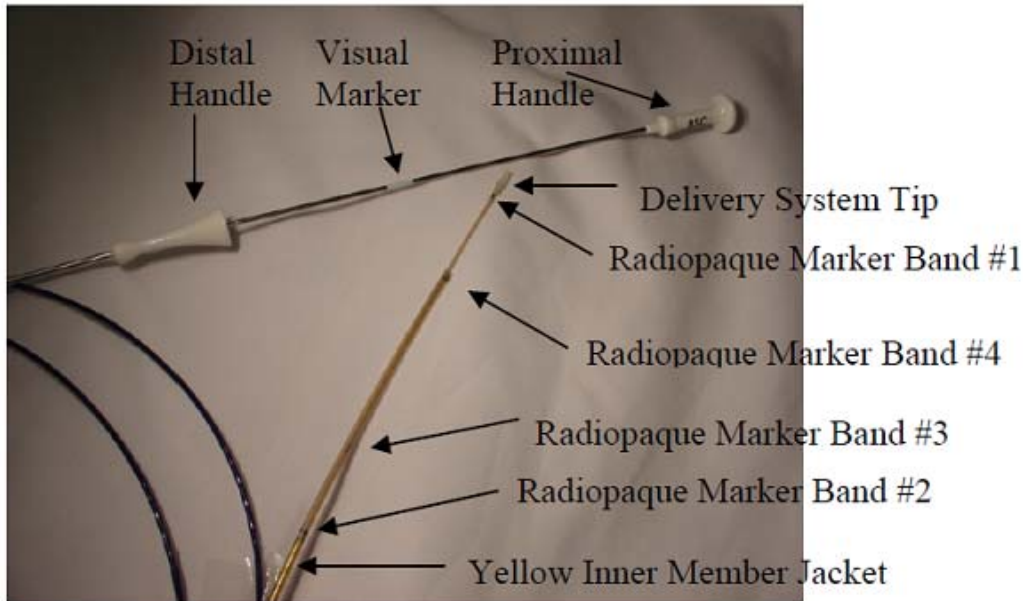


Figure 2 – RX Delivery Device

A schematic drawing (Figure 3) of the WallFlex Biliary RX Fully Covered Stent System RMV provides additional details for the primary design features.

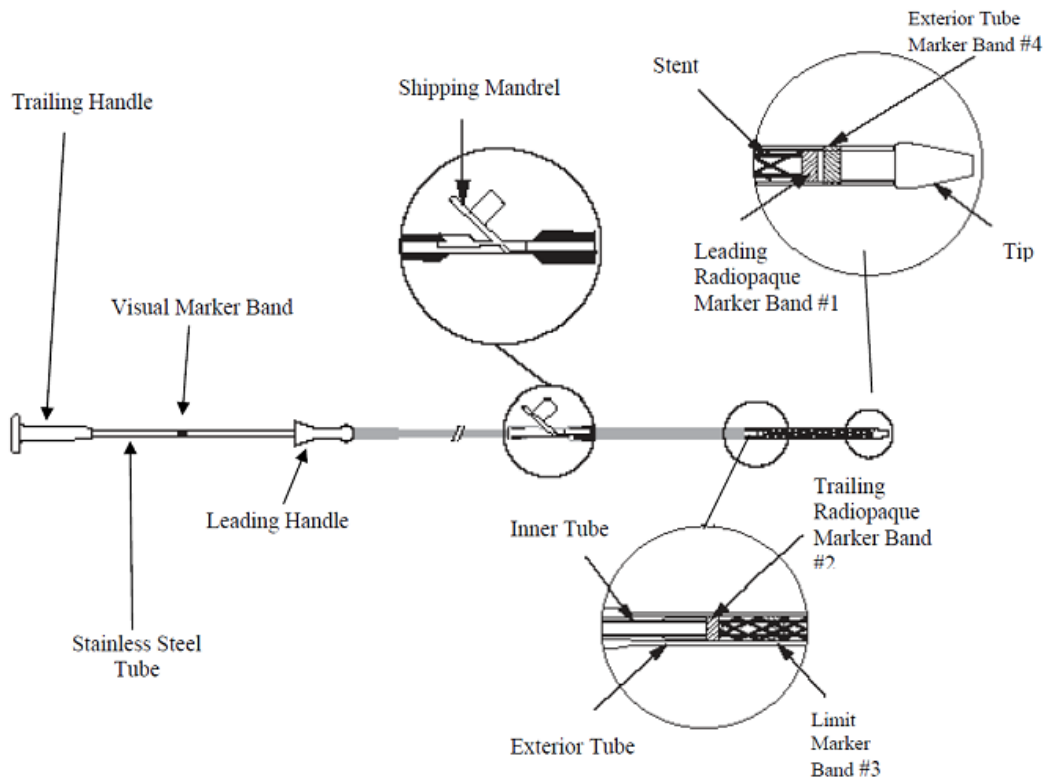


Figure 3 – Schematic of the WallFlex Biliary RX Fully Covered Stent System RMV

SUMMARY OF NONCLINICAL/BENCH STUDIES

As noted below in Table 2, the WallFlex Biliary RX Fully Covered Stent System RMV is identical in biliary stent design and delivery system to the WallFlex Biliary RX Covered stent and delivery system that was previously cleared for marketing (K083627) for a different intended use. Notations of non-clinical information that were relied upon and/or leveraged from prior marketing submissions to support the *de novo* request are summarized in Table 2.

Table 2 – Summary of Nonclinical Studies

<u>Test</u>	<u>Purpose</u>	<u>Methods</u>	<u>Acceptance Criteria</u>	<u>Results</u>
Sterilization, Cleaning, and Disinfection – Sterilization validation was provided for the WallFlex Biliary RX Partially Covered stent and delivery system that was previously cleared for marketing (K061231). The design and materials of this marketed device are nearly identical to those of the subject device, and therefore it is acceptable to adopt the current device into the sterilization process.				
Sterilization	Evaluate the sterility level of device components	ANSI/AAMI/ISO 11135:1994: Medical Devices – Validation and Routine Control of Ethylene Oxide Sterilization;	The sterility assurance level (SAL) shall be 10 ⁻⁶	Passed: Sterilization was re-assessed in 2015 to ensure compliance to most recent version of ANSI/AAMI/ISO 10993-7. Testing was conducted on the 10 X 120 mm fully covered stent, which was considered worst-case for all the covered WallFlex Biliary stents as it has the largest surface area and greatest amount of silicone covering.
Ethylene oxide sterilization residuals	Ensure acceptable level of ethylene oxide (EtOH) residuals	ANSI/AAMI/ISO 10993-7: Biological Evaluation of Medical Devices: Ethylene Oxide Sterilization Residuals	EtOH residual amounts are below the maximum amount allowed: For the stent, the average daily dose of EO to patient shall not exceed 0.1 mg/day. In addition, the maximum EO dose shall not exceed 20 mg in the first 24 hr; 60 mg in the first 30 days; 2.5 g in a lifetime. For the delivery catheter, the average daily dose shall not exceed 4 mg.	
Biocompatibility: All testing except that for nickel leaching and the toxicological risk assessment was provided for the WallFlex Biliary RX Partially Covered stent and delivery system that was previously cleared for marketing (K061231). This device is identical to the subject device with the exception that the stent has both covered and uncovered portions. This is acceptable as the surrogate stent represents the materials found in the current stent design.				

Cytotoxicity	Determine if polar and non-polar extract of the stent and delivery catheter elicit a cytotoxic response	ISO 10993-5 Biological Evaluation of Medical Devices: Tests for Cytotoxicity: <i>in vitro</i> ; MEM Elution method	-	Grade 0 (non-cytotoxic)
Irritation	Determine if polar and non-polar extracts of the stent and delivery catheter elicit a hypersensitive response	ISO 10993-10: Biological Evaluation of Medical Devices: Tests for Irritation and Sensitization: Rabbit Intracutaneous method	-	Based on histopathologic evaluations, the stent with delivery system is considered a non-irritant
Sensitization	Determine if polar and non-polar extracts of the stent and delivery catheter cause a hypersensitive response	ISO 10993-10: Biological Evaluation of Medical Devices: Tests for Irritation and Delayed Type Hypersensitivity: Guinea Pig Maximization Sensitization method	-	No signs of sensitization from polar and non-polar extracts
Acute Systemic Toxicity	Determine if polar and non-polar extracts of the stent cause adverse effects	ISO 10993-11: Biological Evaluation of Medical Devices: Tests for Systemic Toxicity: b(4)	-	No evidence of mortality or systemic toxicity from test material extracts
Genotoxicity	Determine if polar and non-polar extracts of stent are mutagenic	ISO 10993-3: Biological Evaluation of Medical Devices: Tests for Genotoxicity, Carcinogenicity, and Reproductive Toxicity: Bacterial Mutagenicity (Ames Assay) method	-	The stent is considered non-mutagenic in the Ames Bacterial mutagenicity assay

Implantation	Determine if surgically implanted sections of the stent cause a hypersensitive response	ISO 10993-6: Biological Evaluation of Medical Devices: Tests for Local Effects After Implantation: Rabbit 28-Day Duration Intramuscular Implant method	-	Based on histopathologic evaluations, the stent with delivery system is considered a non-irritant
Subchronic Toxicity	Determine if polar and non-polar extracts of the stent cause prolonged exposure adverse effects	ISO 10993-11: Biological Evaluation of Medical Devices: Tests for Systemic Toxicity: b(4) Study method	-	There were no signs of systemic toxicity due to leachable components
Nickel leaching	Determine if the stent can leach toxic levels of nickel	ASTM F2129: Standard Test Method for Conducting b(4) the Corrosion Susceptibility of Small Implant Devices	-	Based on the manufacturing methods, acceptable ASTM F2129 results, the available literature on nickel leaching in similar systems, and considering the stent is coated, there is sufficient evidence that the device will exhibit adequate resistance to corrosion and the nickel leach rates will be acceptable.

Toxicological risk assessment	Determine if polar and non-polar extracts of the stent pose a chronic systemic toxicity risk	A toxicological risk assessment of the fully covered stent was conducted per ISO 10993-18: Biological Evaluation of Medical Devices: Chemical Characterization of Materials, considering the tolerable intake of analytically identified leachables considering ISO 10993-17: Biological Evaluation of Medical Devices: Methods for the Establishment of Allowable Limits for Leachable Substances	-	Exposure to the stent is not likely to lead to systemic toxicity.
Bench Testing: All testing was provided for the WallFlex Biliary RX Covered stent and delivery system that was previously cleared for marketing (K083627) for a different intended use. This device is identical to the subject device. This is acceptable as the stent and delivery system are identical between the K083627 submission and this <i>de novo</i> request. MRI compatibility testing to support the current MRI safety labeling was previously reviewed (K112543) for the identical stents.				
Deployment Testing <ul style="list-style-type: none"> • Stent delivery accuracy • Trackability • Guidewire passage • Deployment and reconstraint force 	The delivery catheter should safely and reliably deliver the stent to the intended location without damage to the stent or the patient. This testing is used to validate the accuracy and repeatability of the delivery system.	b(4) b(4)) stents with the delivery system were evaluated through simulated use in a worst-case scenario model	The delivery catheter must safely and accurately deliver the stent to the intended anatomic location. No damage to the stent or simulated stricture model should occur.	Pass: Stent sizes tested represent the smallest and largest sizes available. Therefore, they can be used as surrogates to represent the spectrum of available stent sizes.

Tensile Strength Testing (bond integrity)	Evaluate if failure of bonds in the delivery catheter could lead to device failure and clinical complications	Bonded joints of the delivery catheters loaded with b(4) fully covered stents were tested to failure using a tensile tester b(4)	All bonded components of the delivery catheter should withstand forces that exceed those encountered during clinical use.	Pass
Stent Integrity	Evaluate if stent corrosion can cause or contribute to premature stent failure	Stents were exposed to simulated bile in an accelerated fashion to replicate an aging period of one year: <ul style="list-style-type: none"> b(4) 	Stents: <ul style="list-style-type: none"> No crevice or pitting corrosion No more than 2 weld breaks No significant weight loss Meet specification requirements for radial compression and expansion forces Wire must meet specification requirements for tensile properties Stent cover integrity must meet requirements for holes and delamination	Pass: Stents tested represent the worst-case scenario as they span the size range of the stents offered and are not all fully covered which allows potentially more degradation to occur.

<p>MRI Compatibility</p> <ul style="list-style-type: none"> • Displacement force • RF induced heating • Artifact testing 	<p>Determine the presence of magnetic field interactions, localized tissue heating, and image artifacts in association with the use of an MR system</p>	<p>Testing was conducted in accordance with ASTM F2052-02: Standard Test Method for Measurement of Magnetically Induced Displacement Force on Passive Implants in the Magnetic Resonance Environment, ASTM F2182-02a: Standard Test Method for Measurement of Radio Frequency Induced Heating Near Passive Implants During Magnetic Resonance Imaging, and ASTM F2119-01: Standard Test Method for Evaluation of MR Image Artifacts from Passive Implants</p>	<p>MRI compatibility labeling must be supported by testing. To be considered MRI conditional, displacement forces should not have the potential to damage the tissue where the device is placed and localized temperature increases should not damage tissues when patients are scanned as outlined in the labeling</p>	<p>Evaluated ^{b(4)} configurations as worst-case scenario configurations</p> <p>Mean deflection angle of 3°</p> <p>Worst case projected temperature rise of 5.5°C for a whole body average specific absorption rate (SAR) of 4 W/kg</p> <p>Artifacts appeared on the MR images as localized signal voids that extend ~10 mm from the stent wall perimeter and ~2 mm beyond each end of the length of the stent</p>
<p>Shelf Life: Package integrity testing was conducted for the Wallstent Enteral Stent (K000281). The packaging of the Wallstent Enteral Stent is identical to that of the WallFlex Biliary RX Fully Covered Stent System RMV. Functional performance testing to support a 2 year shelf life was conducted on the subject device of this <i>de novo</i>.</p>				
<p>Package integrity</p> <ul style="list-style-type: none"> • heat seal peel test • dye penetration 	<p>Evaluate the sterile packaging integrity to ensure that devices remain sterile throughout the shelf-life</p>	<p>ISTA 2A Partial Simulation Performance Tests for Packaged Products weighing 150 lbs followed by heat seal peel testing of packaging (Tray/Lid and Pouch) ^{b(4)}</p> <p>ISTA 2A Partial Simulation Performance Tests for Packaged Products weighing 150 lbs followed by dye penetration testing of packaging ^{b(4)}</p>	<p>Packaging must not be able to be compromised below a minimum pressure threshold.</p> <p>No channels, pinholes, or other barrier breaches allowed</p> <p>All samples must not have channels visible at 10X magnification</p>	<p>Pass</p>

<p>Deployment Testing</p> <ul style="list-style-type: none"> • Trackability • Guidewire passage • Deployment and reconstraint force • System withdrawal 	<p>The delivery catheter should safely and reliably deliver the stent to the intended location without damage to the stent or the patient. This testing is used to validate the accuracy and repeatability of the delivery system upon 25 month real time aging</p>	<p>Simulated use in a trackability model consisting of an endoscope working channel configured in a tortuous path (b(4))</p>	<p>The delivery catheter must safely and accurately deliver the stent to the intended anatomic location. No damage to the stent or simulated stricture model should occur. The stent should be able to be removed with the delivery catheter if the reconstraint point has not been exceeded.</p>	<p>Pass: Stent size tested represents the largest size available. This is acceptable for shelf life testing as we do not expect stent size to impact performance after aging.</p>
<p>Expansion/ Compression Force Testing</p>	<p>Excessive radial force could injure the surrounding tissue, while a radial force that is too low can result in incomplete apposition of the stent to the lumen. Compression force testing characterizes the ability of the stent to resist collapse under external loads upon 25 month real time aging</p>	<p>Expansion and compression forces were measured for (b(4)) each)</p>	<p>Expansion and compression forces must not be impacted by aging</p>	<p>Passed</p>

Flexural Rigidity	Evaluate rigidity of stents to ensure stent integrity upon 25 month real time aging	Flexural rigidity b(4)	Stents must not become rigid after aging	Pass
Covering Material Integrity	Evaluate covering material for compromised surfaces upon 25 month real time aging	Covering b(4) were evaluated with the unaided eye after deploying and restraining the stent b(4)	Maximum of 6 diamonds (openings in the stent mesh) containing compromised coating integrity	Pass
Weld Integrity	Evaluate integrity of stent welded wires upon 25 month real time aging	Examined b(4) r broken wire weld joints after stent is deployed and restrained b(4)	No more than two broken wire weld joints observed	Pass
Tensile Strength Testing (bond integrity)	Evaluate if failure of delivery catheter could lead to device failure and clinical complications upon 25 month real time aging	Bonded joints were tested to failure using a tensile tester for delivery catheters with the b(4)	All bonded components of the delivery catheter should withstand forces that exceed those encountered during clinical use after aging.	Pass

SUMMARY OF CLINICAL INFORMATION

A prospective, nonrandomized clinical study (clinicaltrials.gov Identifier: NCT01014390) was conducted to determine the effectiveness and safety of WallFlex Biliary Fully Covered Stent System in the treatment of benign biliary stricture secondary to chronic pancreatitis (CP), post-liver transplant (OLT), and post-abdominal surgery (CCY).

Only the CP cohort consisting of 127 subjects was evaluated for the *de novo* request. Neither the *de novo* request nor the labeling include indications for the OLT and CCY patient populations with the exception of a Warning included within the labeling that states the following:

Warning: The safety and effectiveness of the WallFlex Biliary RX Fully Covered Stent System RMV has not been established in the treatment of benign biliary anastomotic strictures in liver transplant patients and benign biliary post abdominal surgery strictures.

Objective of the study

To assess the safety and performance of temporary placement of the WallFlex Biliary RX Fully Covered Stent as a treatment of biliary obstruction resulting from benign bile duct strictures.

Methods

The study was a large prospective multinational study utilizing 13 centers in 11 countries outside of the US (OUS). The results of this study were published in the journal *Gastroenterology* (Deviere, Nageshwar Reddy et al. 2014).

Primary Endpoint:

Stent removability, defined as ability to remove the stent endoscopically without serious stent removal related adverse events as assessed from the time of stent removal to 1 month post-stent removal. Per-protocol stent removal occurred at 11 ± 1 month for CP patients.

Secondary Endpoints:

1. Stricture resolution during stent indwell, defined by lack of stent-related re-interventions
2. Stricture resolution after stent removal, defined by lack of stricture related re-intervention
3. Occurrence and severity of adverse events related to the stent and/or the procedure
4. Ability to deploy the stent in satisfactory position across the stricture (technical success at placement)
5. Length of stent placement procedure, length of stent removal procedure and methods of removal (to include video recording if available)
6. Biliary obstructive symptom assessment at all visits
7. Liver Function Tests (LFT's) at baseline, at month 1 post-stent placement, at stent removal and at months 6, 12 and 24 post-stent removal

Inclusion Criteria:

- Age 18 or older

- Willing and able to comply with the study procedures and provide written informed consent to participate in the study
- Chronic pancreatitis or prior liver transplantation or prior other abdominal surgery (to include cholecystectomy)
- Indicated for endoscopic retrograde cholangiopancreatography (ERCP) procedure with stent placement for:
 - Symptomatic bile duct stricture (i.e. obstructive jaundice, persistent cholestasis, acute cholangitis) confirmed by cholangiogram and/or
 - Bile duct stricture confirmed by cholangiogram and/or
 - Exchange of prior plastic stent(s) for management of benign stricture

Exclusion Criteria:

- General:
 - Placement of the stent in strictures that cannot be dilated enough to pass the delivery system
 - Placement of the stent in a perforated duct
 - Placement of the stent in very small intrahepatic ducts
 - Patients for whom endoscopic techniques are contraindicated
 - Biliary stricture of malignant etiology
 - Biliary stricture of benign etiology other than chronic pancreatitis or liver transplant anastomosis or other abdominal surgery
 - Stricture within 2 cm of duct bifurcation
 - Symptomatic duodenal stenosis (with gastric stasis)
 - Prior biliary self-expanding metal stent
 - Suspected stricture ischemia based on imaging of hepatic artery occlusion or endoscopic evidence of biliary cast syndrome
 - Known bile duct fistula
 - Known sensitivity to any components of the stent or delivery system
 - Participation in another investigational study within 90 days prior to consent or during the study
- Additional Exclusion Criteria Specific to Chronic Pancreatitis Patients:
 - Developing obstructive biliary symptoms associated with an attack of acute pancreatitis
- Additional Exclusion Criteria Specific to Post-Abdominal Surgery Patients:
 - History of hepatectomy
 - History of liver transplant
- Additional Exclusion Criteria Specific to Liver Transplant Patients:
 - Live donor transplantation

Results

Chronic Pancreatitis Study Cohort Information

Patients:

One hundred and twenty-seven (127) patients with a benign biliary stricture secondary to chronic pancreatitis with either ongoing biliary obstructive symptoms or being managed for biliary obstructive symptoms were enrolled.

Demographics:

The mean age was 52.5 years (sd 10.3 years) and 104 (82%) of the 127 enrolled were male. The median time since CP diagnosis was 28 months. At baseline median total bilirubin level was 0.6 mg/dl (range 0.1-22.0 mg/dl) and median alkaline phosphatase level was 201 IU/l (range 27-2371 IU/l).

The benign biliary stricture location was mostly distal, notably 115 (90.6%) were in the distal common bile duct (CBD), 2 (1.6%) in the mid CBD, 8 (6.3%) in the proximal CBD, and 2 (1.6%) were papillary. The majority of patients had received a prior sphincterotomy (124; 97.6%) and had previously received endotherapy using plastic biliary stents (105; 82.7%). The gallbladder was in situ in 101 (79.5%) of patients.

Patient Disposition:

The intent-to-treat (ITT) patient cohort includes all 127 enrolled patients. The per-protocol (PP) patient cohort has 118 patients. Nine (9) patients were excluded from the PP cohort due to death due to unrelated causes (7), transition to palliative care in setting of pancreatic cancer (1) and withdrawal of consent (1).

Stent removability, stricture resolution and rates of SAEs were assessed for the ITT cohort (127) and PP cohort (118).

Stricture recurrence after stent removal or complete distal migration was assessed on 94 patients who reached stricture resolution.

Clinical indwell performance and removal success were assessed as post-hoc analyses in the ITT and PP cohorts.

Stent Placement:

Five WallFlex stent sizes (diameter x length) were available and stent selection was as follows: 8 x 60 mm (4; 3.1%), 8 x 80 mm (0; 0%), 10 x 40 mm (78; 61.4%), 10 x 60 mm (43; 33.9%), and 10 x 80 mm (2; 1.6%). The stent was successfully placed in 100% (127/127) of patients. Mean procedure duration was 26.6 min (sd 21.0 min).

Stent Migration

Stent migration in the course of the study was reported in 19 of 127 patients. The migration was proximal – in the direction of the liver – in 7 cases (37%), was partial distal – in the direction of the duodenum but still inside of the common bile duct – in 7 cases (37%), and was complete distal – completely out of the common bile duct – in 5 cases (26%). The 19 migrations were observed a median of 318 days (range 60-1140 days) after stent placement.

Stent Removability

Stent removability is defined as the ability to remove the stent endoscopically without serious stent removal related adverse events as assessed from the time of stent removal to one (1) month post-stent removal. Stent removability was successful in 72.4% (92/127) ITT patients and 78.0% (92/118) PP patients. A summary of the subjects classified as failures is given below:

- Seven (7) deaths due to unrelated causes (ITT only)

- One (1) transition to palliative care in setting of pancreatic cancer (ITT only)
- One (1) withdrew consent (ITT only)
- Thirteen (13) early endoscopic removal
- Four (4) loss to follow-up
- One (1) surgery for progression of CP
- Three (3) stent removal related SAEs
- Three (3) spontaneous stent migration without restenting
- Two (2) spontaneous stent passage with immediate restenting

Removal Success

Removal success is defined as either scheduled endoscopic stent removal with no removal-related serious adverse events (SAEs), or spontaneous stent passage without the need for immediate restenting. Removal success was achieved in 84.3% (107/127) ITT patients and 90.7% (107/118) PP patients after stent indwell ranging from 8 to 613 days. Forceps/graspers and/or a snare were used in all but one case in which a stent-in-stent technique was used for endoscopic removal of the WallFlex stents.

A summary of the subjects classified as failures is given below:

- Four (4) patients experienced removal-related serious adverse events including three (3) cases of cholangitis and one (1) case of abdominal pain.
- Stent removal was not indicated in nine patients (9) due to death (7), transition to palliative care in setting of pancreatic cancer (1) and withdrawal of consent (1) (ITT only).
- Attempts were not made in five (5) patients due to loss to follow up (4) and surgery for CP progression (1).
- Two (2) patients experienced complete distal stent migration that required immediate restenting.

NOTE: Stent-in-Stent removal as a technique for removal of biliary self-expanding metal stents was described in peer-reviewed publications (Tan, Lillemoe et al. 2012, Menon 2013, Tringali, Blero et al. 2014). In total, the three references report on 7 cases. The authors concluded that the stent-in-stent technique is effective when difficulties are encountered during self-expanding metal stent removal due to stent migration or hyperplastic stent ingrowth or overgrowth.

Stent Functionality During Stent Indwell

Stent functionality during stent indwell is defined as lack of required reintervention during intended indwell or spontaneous stent passage without the need for immediate restenting within 6 days. Stent functionality during stent indwell was obtained in 77.2% (98/127) ITT patients and in 83.1% (98/118) PP patients.

A summary of the subjects classified as failures is given below:

- Seven (7) deaths due to unrelated causes (ITT only)
- One (1) transition to palliative care in setting of pancreatic cancer (ITT only)
- One (1) withdrew consent (ITT only)
- Thirteen (13) early endoscopic removal
- Four (4) loss to follow-up

- Two (2) spontaneous stent passage with immediate restenting
- One (1) surgery for progression of CP

Stricture Resolution

Stricture resolution is defined by the lack of stricture-related re-intervention. At the end of indwell, stricture resolution without the need for restenting was achieved in 74.0% (94/127) ITT patients and in 79.7% (94/118) PP patients.

A summary of the subjects classified as failures is given below:

- Nine (9) not indicated for removal due to death (7), transition to palliative care in setting of pancreatic cancer (1) and withdrawal of consent (1) (ITT only)
- Nine (9) immediate restenting after scheduled removal
- Eight (8) immediate restenting after early removal
- Four (4) loss to follow-up
- Two (2) spontaneous stent passage with immediate restenting
- One (1) surgery for progression of CP

Stricture Recurrence

Stricture recurrence is defined by the need for stricture related re-intervention post-stent removal. Over a median follow-up period of 19.0 months (range 0.9–29.7 months) after stent removal, 85.1% (80/94) ITT patients and 85.1% (80/94) PP patients with stricture resolution at time of removal did not experience stricture recurrence.

A summary of the subjects classified as failures is given below:

- Ten (10) patients had strictures re-occur
- Four (4) patients were lost to follow-up

Liver Function Tests

Bilirubin levels and alkaline phosphate levels were measured at visits from baseline to 24 months post-removal. Reported are the mean \pm standard deviation (number of patients) bilirubin level in mg/dL and alkaline phosphatase level in U/L.

Bilirubin: Baseline: 1.6 ± 3.1 (126), Indwell month 1: 0.6 ± 0.4 (109), Stent removal: 0.8 ± 1.3 (106), Post-removal month 6: 0.8 ± 1.2 (66), Post-removal month 12: 0.6 ± 0.3 (57), Post-removal month 24: 1.0 ± 2.1 (24)

Alkaline phosphatase: Baseline: 332 ± 363 (125), Indwell month 1: 166 ± 130 (113), Stent removal: 166 ± 198 (105), Post-removal month 6: 142 ± 151 (67), Post-removal month 12: 127 ± 139 (59), Post-removal month 24: 136 ± 115 (25)

Biliary Obstructive Symptoms

Biliary obstructive symptoms were right upper quadrant pain, fever, jaundice, itching, dark urine, pale stool, and nausea. The number of patients with any symptom was normalized by the number of patients for which visit data were available.

Baseline: 51.2% (65/127), Indwell month 1: 16.3% (20/123), Indwell month 3: 8.6% (10/116), Indwell month 6: 6.3% (7/112), Indwell month 9: 7.8% (8/102), Stent removal: 12.8% (14/109), Post-removal month 3: 7.0% (6/86), Post-removal month 6: 16.1% (14/87), Post-removal month 12: 9.7% (7/72), Post-removal month 24: 6.2% (2/33)

Summary of Clinical Findings

Stent removability was possible after stent indwell ranging from 8 to 613 days (<1 month to ~20 months). Key outcomes are summarized in Table 3 below for all patients and for the subset of patients with stent indwelling for the intended duration.

Table 3 – Summary of Key Clinical Outcomes

Metric	Intent-to-treat Patients (ITT)	Per Protocol Patients (PP)	PP Patients with Endoscopic Stent Removal as Scheduled
Stent functionality during stent indwell	77.2% (98/127)	83.1% (98/118)	100% (95/95)
Stent removability	72.4% (92/127)	78.0% (92/118)	96.8% (92/95)
Removal success	84.3% (107/127)	90.7% (107/118)	96.8% (92/95)
Stricture resolution	74.0% (94/127)	79.7% (94/118)	90.5% (86/95)
No stricture recurrence	85.1% (80/94)	85.1% (80/94)	87.2% (75/86)
SAEs (patients with at least one SAE)	36.2% (46/127)	36.4% (43/118)	29.5% (28/95)

Adverse Events

Serious adverse events (SAEs) that have the potential to be device/procedure related occurred in 27.6% (35/127) of patients during stent placement, indwell, removal or biliary reintervention. SAEs that have the potential to be device/procedure related occurred in 14.2% (18/127) of patients during the post stent removal follow-up period. In total, 36.2% (46/127) ITT patients and 36.4% (43/118) PP patients experienced 86 events as detailed below. There were no stent or stent removal related deaths; however, 7 patients died during the stent indwell period and an additional 3 patients died during the follow-up period due to non-device/procedure related causes. A summary of the potentially device/procedure related SAEs is provided in Tables 4-6.

Table 4 – Stent Placement, Stent Indwell, and Biliary Reintervention SAEs

SAE Term	Number of Events	Patient Incidence
Biliary leak	1	0.8% (1/127)
Gas embolism	1	0.8% (1/127)
Abdominal pain	12	5.5% (7/127)
Pancreatitis	14	10.2% (13/127)
Cholecystitis	3	2.4% (3/127)
Chest pain	1	0.8% (1/127)
Cholangitis	12	7.1% (9/127)
Cholelithiasis	1	0.8% (1/127)

Cholestasis	2	1.6% (2/127)
Peripancreatic abscess	1	0.8% (1/127)
Insufficient pancreatic drainage	1	0.8% (1/127)
Hepatic abscess	2	1.6% (2/127)
Peripancreatic cyst/pseudocyst	3	2.4% (3/127)
Sepsis	2	1.6% (2/127)
Bacterial infection	1	0.8% (1/127)

Table 5 – Stent Removal SAEs

SAE Term	Number of Events	Patient Incidence
Cholangitis	3	2.4% (3/127)
Abdominal pain	1	0.8% (1/127)

Table 6 – Post Stent Removal Follow-Up SAEs

SAE Term	Number of Events	Patient Incidence
Biliary leak	1	0.8% (1/127)
Abdominal pain	4	3.1% (4/127)
Pancreatitis	10	7.1% (9/127)
Cholangitis	8	4.7% (6/127)
Hepatic abscess	1	0.8% (1/127)
Peripancreatic pseudocyst	1	0.8% (1/127)

LABELING

The labeling comprises physician labeling that includes the device indications for use, a description of the device, warnings and precautions, clinical data on the device, and instructions for the safe and effective use of the device. The labeling satisfies the requirements of 21 CFR 801.109 Prescription devices.

The Instructions for Use address the known hazards and risks of the device for the intended use and incorporate safety statements to mitigate these risks. The labeling includes:

- Safety instructions intended to minimize the risk of improper placement of the stent
- A detailed summary of the clinical testing including device effectiveness, and device- and procedure-related adverse events
- Contraindications and warnings to ensure usage of the device for the intended patient population

- A shelf life
- Compatibility information for use in the magnetic resonance environment

RISKS TO HEALTH

Table 7 below identifies the risks to health that may be associated with use of a Metallic Biliary Stent System for Benign Strictures and the measures necessary to mitigate these risks.

Table 7 – Identified Risks to Health and Mitigation Measures

Identified Risk	Mitigation Measure
Adverse tissue reaction	Biocompatibility Evaluation Labeling
Infection	Sterilization Validation Shelf Life Validation Labeling
Bile duct obstruction <ul style="list-style-type: none"> • Stent migration • Stent does not resolve obstruction • Stent cannot be placed • Expansion/compression forces • Foreshortening 	Clinical Performance Testing Non-clinical Performance Testing Shelf Life Validation Labeling
Trauma to bile ducts <ul style="list-style-type: none"> • During stent deployment • During removal • Due to stent migration • During stent indwell • Inability to safely remove stent • Expansion/compression forces 	Clinical Performance Testing Non-clinical Performance Testing Shelf Life Validation Labeling

SPECIAL CONTROLS:

In combination with the general controls of the FD&C Act, the Metallic Biliary Stent System for Benign Strictures is subject to the following special controls:

1. Clinical performance testing must demonstrate or provide the following:
 - a. The ability to safely place and subsequently remove the stent after the maximum labeled indwell period
 - b. All adverse event data including bile duct obstruction and trauma to the bile duct
 - c. The stent resolves strictures during the maximum labeled indwell period
 - d. Stricture resolution is maintained post-stent removal
2. Non-clinical performance testing must demonstrate that the device performs as intended under anticipated conditions of use. The following performance characteristics must be demonstrated:

- a. Corrosion testing to demonstrate that the stent maintains its integrity during indwell and does not release potentially toxic levels of leachables
 - b. Stent dimensional testing supports the intended use
 - c. Compression and expansion forces must be characterized
 - d. The delivery catheter must deliver the stent to the intended location and the stent must not be adversely impacted by the delivery catheter during deployment and catheter withdrawal.
 - e. The delivery system must withstand clinically anticipated forces.
 - f. Compatibility in a magnetic resonance environment.
3. All patient contacting components of the device must be demonstrated to be biocompatible.
 4. Performance data must demonstrate the sterility of the device components intended to be provided sterile.
 5. Shelf life testing must demonstrate that the device maintains its performance characteristics and that packaging maintains sterility for the duration of the labeled shelf life.
 6. Labeling for the device must include:
 - a. A detailed summary of the clinical testing including device effectiveness, and device- and procedure-related adverse events
 - b. Appropriate warning(s) to accurately ensure usage of the device for the intended patient population
 - c. Shelf life
 - d. Compatibility information for use in the magnetic resonance environment
 - e. Stent foreshortening information supported by dimensional testing

BENEFIT/RISK DETERMINATION

Summary of Benefits

Among a population of 127 patients with benign biliary strictures (BBS) related to CP, 94 (74%) patients had stricture resolution although 10 patients developed recurrent strictures. Stent removability was successful in 92/118 (78%) patients (PP population). In addition, 98/118 (83%) of the patients did not require reintervention during the intended indwell period or immediate restenting in the event of spontaneous stent passage.

At baseline, 51% of the ITT population patients complained of biliary obstructive symptoms which were right upper quadrant pain, fever, jaundice, itching, dark urine, pale stool, and nausea. This value was reduced to 16% after one month, 9% after 3 months, 6% after 6 months, 8% after 9 months, and 13% at stent removal. The value was maintained at 7% after 3 months post-stent removal, 16% after 6 months post-stent removal, 10% after 12 months post-stent removal, and 6% after 24 months post-stent removal.

Bilirubin levels and alkaline phosphate levels were measured at visits from baseline to 24 months post-removal. Reported are the mean \pm standard deviation (number of patients) bilirubin level in mg/dL and alkaline phosphatase level in U/L. The bilirubin and alkaline phosphatase levels decreased during the conduct of the study.

Bilirubin: Baseline: 1.6 ± 3.1 (126), Indwell month 1: 0.6 ± 0.4 (109), Stent removal: 0.8 ± 1.3 (106), Post-removal month 6: 0.8 ± 1.2 (66), Post-removal month 12: 0.6 ± 0.3 (57), Post-removal month 24: 1.0 ± 2.1 (24)

Alkaline phosphatase: Baseline: 332 ± 363 (125), Indwell month 1: 166 ± 130 (113), Stent removal: 166 ± 198 (105), Post-removal month 6: 142 ± 151 (67), Post-removal month 12: 127 ± 139 (59), Post-removal month 24: 136 ± 115 (25)

Summary of Risks

There were 57 SAEs among 35 (30%) patients related to stent placement, stent indwell or biliary intervention, 4 SAEs among 4 (3%) patients related to stent removal and 25 SAEs among 18 (14%) patients with post-stent removal follow-up SAEs.

Overall, there were 24 SAEs of pancreatitis among 20 (16%) and 20 SAEs among 12 (9%) of cholangitis.

Additional SAEs included biliary leaks, peripancreatic abscess, hepatic abscess and sepsis.

Study related SAEs are in accordance with those found in the literature. In a recent study of Covered self-expanding metallic stents (CSEMS) for the treatment of benign biliary strictures (BBS) of any etiology, stent migration (9.7%) was the most common complication, followed by stent occlusion (4.9%), cholangitis (4.1%), and pancreatitis (3.3%) (Saxena, Diehl et al. 2015). In another study, 11 serious adverse events occurred in 10 patients (29%), with cholangitis (n = 5) being most common (Walter, Laleman et al. 2015).

Patient Perspectives

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

Benefit/Risk Conclusion

Given the available information, the data support that when the WallFlex Biliary RX Fully Covered Stent System RMV is used as intended for the population identified in the labeling, the probable benefits outweigh the probable risks. The device provides clinical benefit and the risks can be mitigated by the use of general and the identified special controls.

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CONCLUSION

The *de novo* request for the WallFlex Biliary RX Fully Covered Stent System RMV is granted and the device is classified under the following:

Product Code: PNB

Device Type: Metallic Biliary Stent System for Benign Strictures

Class: Class II

Regulation: 21 CFR 876.5011