

SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Transcatheter Patent Ductus Arteriosus (PDA) Occlusion Device

Device Trade Name: Nit-Occlud® PDA

Device Procode: MAE

Applicant's Name and Address: pfm medical ag
Wankelstrasse 60
Cologne, 50996
Germany
ERN: 9617465

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P120009

Date of FDA Notice of Approval: August 16, 2013

Expedited: Not applicable

II. INDICATIONS FOR USE

The Nit-Occlud® PDA is a permanently implanted prosthesis indicated for percutaneous, transcatheter closure of small to moderate size patent ductus arteriosus with a minimum angiographic diameter less than 4 mm.

III. CONTRAINDICATIONS

- Endocarditis, endarteritis or active infection at the time of the implantation
- Patients with a body weight < 5 kg
- Pulmonary hypertension (calculated PVR greater than 5 Wood Units)
- Thrombus in a blood vessel through which access to the PDA must be obtained
- Thrombus in the vicinity of the implantation site.

IV. WARNINGS AND PRECAUTIONS

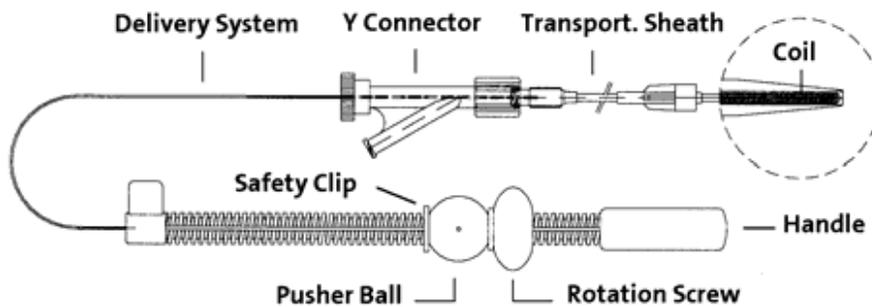
The warnings and precautions can be found in the Nit-Occlud® PDA labeling.

V. DEVICE DESCRIPTION

Nit-Occlud® PDA is a system for transcatheter occlusion of Patent Ductus Arteriosus (PDA) with spiral coils. The system consists of the following parts:

- Nit-Occlud® Spiral Coil with disposable handle

Figure 1. Nit-Occlud® Spiral Coil

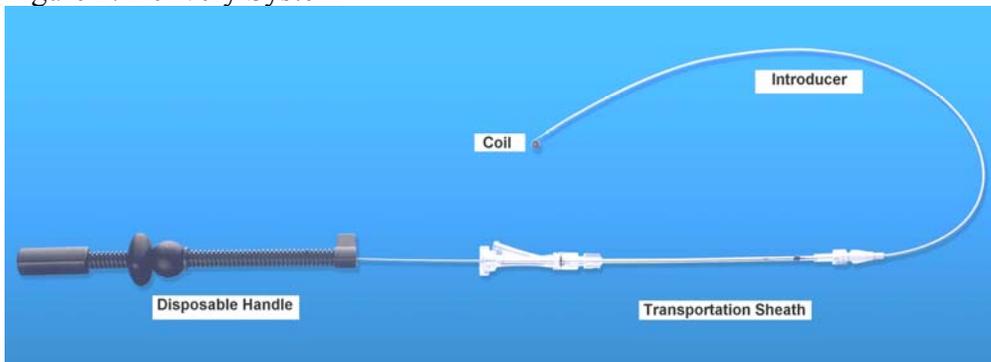


The spiral coil is mounted in a straightened fashion on a delivery system including a disposable handle to which it is connected by means of a patented detachment mechanism.

The Nit-Occlud® PDA is available as Flexible and Medium Type. The flexible coils do not have a core wire, while the medium coils have core wires that are 0.1mm in diameter tapered to 0.25mm flat.

The flexible and medium types are pre-loaded into the transportation sheath. For insertion the transportation sheath must be connected to the implantation catheter.

Figure 2. Delivery System



The Nit-Occlud® PDA has a cone in cone configuration which results from the fact that the proximal windings of the coil are wound the reverse direction (see Fig.3).

Figure 3. Coil Configuration

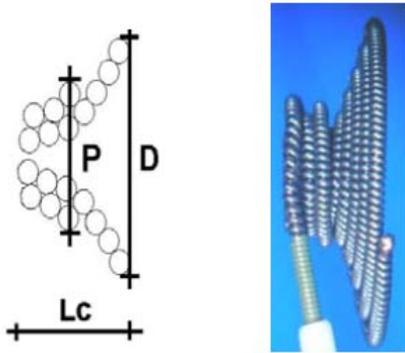


Fig.: Nit-Occlud® Coil
(D=Distal diameter, P=Proximal diameter, Lc=Length configured).

The following types and sizes are available:

Table 1: Nit-Occlud® PDA Sizes

Description	Catalog #
Nit-Occlud® PDA, 4 x 4 mm, Flexible, Sheath 4F x 85 cm	145044
Nit-Occlud® PDA, 5 x 4 mm, Flexible, Sheath 4F x 85 cm	145054
Nit-Occlud® PDA, 6 x 5 mm, Flexible, Sheath 4F x 85 cm	145065
Nit-Occlud® PDA, 7 x 6 mm, Medium, Sheath 5F x 85 cm	145076
Nit-Occlud® PDA, 9 x 6 mm, Medium, Sheath 5F x 85 cm	145096
Nit-Occlud® PDA, 11 x 6 mm, Medium, Sheath 5F x 85 cm	145116

Table 2: Nit-Occlud® Device by D1 and D2

PDA Dimensions		Recommended Device	
D1	D2	Size (DxP)	Type
1 mm	Up to 3 mm	4x4	Flex
1 mm	4 mm	5x4	Flex
1 mm	5 mm or greater	6x5	Flex
2 mm	Up to 5 mm	6x5	Flex
2 mm	6-7 mm	7x6	Medium
2 mm	8 mm or greater	9x6	Medium
3 mm	Up to 7 mm	7x6	Medium
3 mm	8-9 mm	9x6	Medium
3 mm	9 mm or greater	9x6 / 11x6	Medium
4 or 5 mm	9 mm or greater	11x6	Medium
D1 = Narrowest diameter; D2 = Aortic Ampulla diameter			

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the correction of a PDA:

- Surgical ligation/division
- Medication to help close the PDA or treat symptoms of the PDA
- Interventional use of the Amplatzer Duct Occluder (St. Jude Medical -formerly AGA Medical Corp.- Golden Valley MN)

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 Nit-Occlud® PDA has had CE Mark Approval since 2001 and has been in commercial distribution primarily in Europe and Latin American countries as well as Asia, Eastern Europe and the Middle East.

Argentina	Germany	Poland
Australia	Great Britain	Portugal
Austria	Greece	Romania
Belarus	Hungary	Russia
Bolivia	India	Saudi Arabia
Brazil	Iran	Serbia
Bulgaria	Israel	South Africa
Canada	Italy	Spain
China	Jordan	Sweden
Columbia	Kazakhstan	Switzerland
Czech Republic	Korea	Turkey
Denmark	Latvia	Ukraine
Ecuador	Malaysia	Venezuela
Egypt	Netherlands	
France	Oman	

Between 2001 and 2011 a total of 14,490 devices were sold. The device has never been withdrawn from Market for any safety or effectiveness issues.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

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

- Air embolism

- Allergic reaction to drug/contrast
- Apnea
- Arrhythmia requiring medical treatment or pacing
- Arteriovenous Fistula
- Bacterial Endocarditis
- Blood loss requiring transfusion
- Chest Pain
- Damage to the tricuspid or pulmonary valves
- Death
- Embolization of the occluder, requiring percutaneous or surgical intervention
- Endarteritis
- False aneurysm of the femoral artery
- Fever
- Headache/migraine
- Heart failure
- Hemolysis after implantation of the occluder
- Hypertension
- Hypotension or shock
- Infection
- Myocardial infarction
- Occluder fracture or damage
- Perforation of the heart or blood vessels
- Stenosis of the left pulmonary artery or descending thoracic aorta
- Stroke/TIA
- Thromboembolism (cerebral or pulmonary)
- Valvular Regurgitation
- Vessel damage at the site of groin puncture (loss of pulse, hematoma etc.).

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

IX. SUMMARY OF PRECLINICAL STUDIES

A. Laboratory Studies

A1. In vitro bench testing

Table 3 lists the bench testing conducted on the Nit-Occlud® PDA.

Table 3. Engineering Tests

TEST	PURPOSE/DESCRIPTION	ACCEPTANCE CRITERIA	RESULTS AVE ± SD (RANGE)	CONCLUSION
Tensile Strength Pin / Pusher Core Wire	The tensile strength of the pin / pusher core wire connection is measured.	F>40 N	125.32N ± 12.05 (102.4 – 147.0N)	PASS
Tensile Strength Pusher	The tensile strength of the pusher core	F>100N	125.10N ± 3.78	PASS

Core Wire	wire is measured.		(115.34–130.61N)	
System Release Force	The force on the delivery system when releasing the implant is measured.	$20N < F < 30N$	Flex.: $26.82N \pm 1.05$ (24.5 – 28.8N) Med.: $26.04N \pm 1.25$ (23.6 – 28.5N)	PASS
Repeated System Release Force (10X)	The reproducibility of the release force after repeated re-mounting of the implant is determined.	No deterioration of the release force. $20N < F_{aver.} < 30N$	1: $26.37N \pm 3.46$ (20.50-33.34N) 2: $25.59N \pm 2.60$ (22.63-29.58N) 3: $23.84N \pm 3.81$ (18.08-32.75N)	PASS
Coil Fixation (holding force)	The proximal coil fixation force is a proof test with the tensile testing machine applying 20N for 10 seconds on the delivery system to show that the implant is connected correctly to the delivery system.	20 N; $t=10s$ without detaching the implant from the delivery system	Flex.: $20.36N \pm 0.51$ (20.0-23.3N) Med.: $20.45N \pm 0.45$ (20.0-23.3N)	PASS
Distal Coil Fixation Force	The force necessary to pull the implant off the delivery system is determined in a tensile test. Meeting the specification prevents loss of the coil during intervention (e.g. during retraction of the implant into the catheter or pulling the device through the defect).	$>9 N$	$12.69N \pm 1.23$ (9.75 – 16.85N)	PASS
Pull through PDA model	The purpose of this test was to prove in a simulated use environment, that if the coil is inadvertently pulled through the defect in its configured/expanded state, it will not disconnect from the delivery system, it will still be possible to pull the implant back into the implantation catheter, and it will correctly (re-) configure when again released.	$<6N$	$5.11N \pm 0.69$ (3.2 N – 5.9 N)	PASS
Retraction Force into Sheath	The catheter retraction force is determined in a simulated use environment in order to ensure that during retraction the spiral may not detach from the delivery system.	$<6 N$	$4.39N \pm 1.65$ (3.27 – 5.87N)	PASS
System Friction Test – Pushability	This test determined the force needed to advance the implant through the implantation catheter. It should be possible to push the implant easily through the implantation catheter in order to avoid possible damage to the device and to facilitate the application of the device for the user.	$<6 N$	$1.26N \pm 0.06$ (1.0 – 1.5N)	PASS
Introducer/ Connector Bond Strength	This test was performed to determine if the overmolded connection between luer and catheter meets the specification thus avoiding breakage of the sheath at the hub or leakage of liquids at this junction of luer hub and tube.	$F > 10N$	4F: $18.24N \pm 3.54$ (14.19 N – 25.92N) 5F: $25.85N \pm 6.58$ (17.70 N – 41.75N)	PASS
Y-Connector / T. Sheath Bond Strength	The purpose of this test was to verify, that the tensile strength of the connection y-connector – transportation sheath meets the specification in order to ensure that the connection does not break during clinical use.	$F > 10N$	$189.64N \pm 67.7$ (46.14 – 255.72N)	PASS
Catheter / Y-Connector Bond Strength	The purpose of this test was to verify, that the tensile strength of the luer connection between y-connector and implantation catheter meets the	$F > 10N$	4F: $64.1N \pm 10.76$ (42.86 – 78.37N) 5F: $63.1N \pm 11.58$ (49.13 – 81.76N)	PASS

	specification in order to ensure that the connection does not break during clinical use.			
Radiopacity	This test was performed according to American Society for Testing and Materials (ASTM) F640 to verify that the radiopacity of the device results in an adequate fluoroscopic contrast/visibility during clinical use.	contrast >>0.1	contrast 42.6 ± 5.5	PASS
3 year Functional Shelf Life Testing	Bench-testing above was repeated on devices that were accelerated aged for an equivalent of 3 years shelf life to ensure device functionality and integrity at the end of the labeled shelf life. All tests used the same test methods and acceptance criteria as for the unaged samples.		PASS	PASS
F = Force N = Newtons T = time S = seconds Ave = Average SD = Standard Deviation				

Physio-Chemical Tests

- Corrosion Test - The electrochemical characterization of Nit-Occlud® PDA was performed using potentiodynamic methods according to ASTM F2129-08. The rest potential E_r of the implant as well as the breakdown potential E_b were determined. The test parameters were set appropriate to the standard. A total of 22 of the 30 implants tested showed no breakdown up to 1100mV, 6 had a breakdown potential of more than 600 mV, 2 implants had breakdown potentials between 600 mV and 300 mV. With an average breakdown potential of at least 990mV and no breakdown potentials observed below 300mV the device shows adequate corrosion resistance and fulfilled all preset acceptance criteria.
- Fatigue Testing - Evaluation of 84 angiogram sequences of 42 representative PDA patients from the US clinical trial showed that the coil implant can move as a whole with the tissue and vasculature, but that there is minimal structural deformation of the implant over the heart cycle, i.e. the elongation/compression forces and bending/torsional moments on the coil are essentially zero. Ingrowth of a Nit-Occlud® PDA within 6 – 12 weeks following implantation further immobilizes the device and the surrounding tissue. Fatigue resistance of the pfm medical Nit-Occlud® VSD occlusion device, which also consists of a nitinol coil with a very similar design as the Nit-Occlud® PDA, has been tested and is leveraged to support the fatigue resistance of the Nit-Occlud® PDA. The Nit-Occlud® VSD occlusion device was subjected to a fatigue test which mimics the oscillating deflection due to the heart's contractions in the septum, i.e. a cyclic deformation of about 1mm amplitude between the distal and proximal part of the device. After 400 million cycles, there were no fractures and the comparison of SEM pictures of the fatigued and non-fatigued VSD implants showed no change of the surface, e.g. cracks or beginning cracks. Long-term coil structural integrity of the Nit-Occlud® PDA is also supported by the evaluation of 45 follow-up

angiograms (time interval from implantation ranging from 0-75 months, mean 27m, median 20m) where no deformation or fracture was observed.

Abrasion Resistance/Particulate Test

Particulate testing was performed to determine the amount of particles generated and/or released from the device under anatomically relevant simulated use conditions. Baseline testing and a simulated use with a tortuous path model (developed in conjunction with the intended use of the Nit-Occlud® PDA) were performed. The investigation was performed with the device (implant and delivery system) and the accessories as manufactured. Particulate detection and analysis was performed according to USP 788 (Particulate Matter in Injections) and for all tests, the limits set forth by USP 788 for small-volume injections were not exceeded.

Magnetic Resonance (MR) Imaging Safety

The Nit-Occlud® PDA coil was determined to be MR-conditional according to the terminology specified in the ASTM International, Designation: F2503-05. Non-clinical testing demonstrated that the Nit-Occlud® PDA coil is MR conditional. A patient with this device can be scanned safely immediately after placement under the following conditions:

- Static magnetic field of 3 Tesla or less;
- Maximum spatial gradient magnetic field of 720 Gauss/cm or less; and
- The maximum whole-body averaged specific absorption rate (SAR) shall be limited to 2.0 W/kg (normal operating mode only) for 15 minutes of scanning.

MRI-Related Heating

- In non-clinical testing, the Nit-Occlud® PDA coil produced the following temperature rise during MRI performed for 15-min in the 3-Tesla (3-Tesla/128-MHz, Excite, HDx, Software 14X.M5, General Electric Healthcare, Milwaukee, WI) MR system: Highest temperature change +1.6°C.

Therefore, the MRI-related heating experiments for the Nit-Occlud® PDA coil at 3-Tesla using a transmit/receive RF body coil in an MR system reported whole body averaged SAR of 2.9 -W/kg (i.e., associated with a calorimetry measured whole body averaged value of 2.7-W/kg) indicated that the greatest amount of heating that occurred in association with these specific conditions was equal to or less than +1.6°C.

Artifact Information

- MR image quality may be compromised if the area of interest is in the exact same area or relatively close to the position of the Nit-Occlud® PDA coil. Therefore, optimization of MR imaging parameters to compensate for the presence of this device may be necessary.

A2. Biocompatibility

Based on extensive chemical investigations according to United States Pharmacopeia (USP 661) Physiochemical Tests – Plastics and ISO 10993-18 (Chemical Characterization of Materials) a biological safety evaluation was established focusing on the requirements of ISO 10993-1 as well as FDA General Program Memorandum #G95-1. According to the nature and duration of patient contact, for biological/toxicological testing performed, the Nit-Occlud® PDA system was divided into its two main components: The implant and the accessories, i.e. the implantation catheter, transportation sheath, delivery system, y-connector and the handle.

- Based on the tests in the Table 4, the Nit-Occlud® PDA is considered safe for its intended use:

Table 4. Implant Biocompatibility Testing

Test	Results, Justification
Cytotoxicity Study according to ISO 10993-5 with Extract	Non-cytotoxic
Maximization Sensitization Study according to ISO 10993-10	Saline and sesame oil extracts were not a sensitizer
Genotoxicity Study according to ISO 10993-3, Mouse Bone Marrow Micronucleus Study	Saline and sesame oil extracts are not mutagenic
Genotoxicity Study according to ISO 10993-3, In Vitro Chromosomal Aberration Study in Mammalian Cells	Saline and dimethyl sulfoxide extracts are not genotoxic
Genotoxicity Study according to ISO 10993-3, Bacterial Reverse Mutation	Saline and dimethyl sulfoxide extracts are not mutagenic
Hemocompatibility according to ISO 10993-4, ISO 10993 and ASTM Hemolysis	Non-hemolytic
Hemocompatibility according to ISO 10993-4, ISO C3a Complement Activation Test	Not an activator
Hemocompatibility according to ISO 10993-4, ISO SC5b-9 Complement Activation Test	Not an activator

- Based on the tests in Table 5, the implantation catheter, transportation sheath, delivery system, y-connector and the handle (termed “accessories”) are considered safe for the intended use of the device:

Table 5. Delivery System and Accessories Biocompatibility Testing

Test	Results, Justification
Cytotoxicity Study according to ISO 10993-5 with Extract on the handle	Non-cytotoxic
Cytotoxicity Study according to ISO 10993-5 with	Non-cytotoxic

Extract on the accessories (beside handle)	
Maximization Sensitization Study according to ISO 10993-10	Saline and sesame oil extracts were not a sensitizer
Intracutaneous Irritation Test by Intradermal Injection in the Rabbit according to ISO 10993-10	Saline and sesame oil extracts met study requirements
Acute Systemic Toxicity Study in the Mouse according to ISO 10993-11	Saline and sesame oil extracts met study requirements
Rabbit Pyrogen Study according to USP 34-NF 29	Non-pyrogenic
Hemocompatibility according to ISO 10993-4, ISO 10993 and ASTM Hemolysis	Non-hemolytic
Hemocompatibility according to ISO 10993-4, ISO C3a Complement Activation Test	Not an activator
Hemocompatibility according to ISO 10993-4, ISO SC5b-9 Complement Activation Test	Not an activator
Hemocompatibility according to ISO 10993-4, In vivo Thromboresistance Following Acute Implantation in the Jugular Vein of the Domestic Pig	Test articles showed sufficient thromboresistance In addition to this neither the clinical study nor post market surveillance identified any thromboembolic risk associated with the accessory

A pyrogen test on the accessories was performed in order to detect any substances causing a rise in body temperature in a rabbit model after intravenous injection of the accessories extract. The procedures corresponded to the requirements of USP 34 - NF29, Rabbit Pyrogen Study. The Nit-Occlud® PDA Accessories met the requirements of the USP 34 – NF 29 and are rated as non-pyrogenic as well as the Nit-Occlud® PDA Implant as worst case article which met the requirements of the USP 24 for the absence of pyrogens.

A3. Shelf Life

Samples of the Nit-Occlud® PDA system were subjected to accelerated aging and evaluated through functional testing to ensure adherence to the product specifications. The data collected to date supports a product shelf life of three (3) years for the Nit-Occlud® PDA.

A4. Sterilization

The Nit-Occlud® PDA is sterilized with ethylene oxide to achieve a sterility assurance level (SAL) of 10^{-6} . The sterilization plant is validated and operated in accordance to EN ISO 11135-1:2007 Sterilization of healthcare products – Ethylene Oxide – Part 1: Requirements for development, validation and routine control of sterilization process for medical devices. The Sterilization is validated and controlled per ISO 11135-2:2007 Medical Devices – Validation and Routine Control of Ethylene Oxide Sterilization. Sterilization residual limits meet the

requirements of ANSI/AAMI/ISO 10993-7:2008 (Biological evaluation of medical devices – Part 7: Ethylene Oxide sterilization residuals).

B. Animal Studies

The two animal studies conducted on the Nit-Occlud® PDA are described in Tables 6 and 7 below:

Table 6. PDA Occlusion in a chronic ovine model

Objective	To evaluate practicability and effectiveness of the device in occluding large PDAs (>6mm) in a lamb model of a chronic PDA.
Endpoint assessment	The Nit-Occlud® PDA was placed into nine neonatal lambs. At follow-up (Day 1, Day 4, and prior to euthanasia) all nine lambs had no audible murmur and seven of the nine lambs showed complete occlusion just prior to euthanasia. Average survival was 107 days (range 7-278 days).
Histology	Macroscopic examination of the ductal orifices post-mortem showed little if any protrusion of the outer rings of the coils into the lumen of the aorta or the pulmonary artery. Depending on the duration of implantation the coils were partially or completely covered by a thin, shiny tissue. Scanning electron microscopy (SEM) and Histology. Most of the coils were covered by a monolayer of cells resembling neointimal coverage, starting as early as 7 days after implantation. Comparing different intervals after implantation, the cellular coverage was more pronounced with longer intervals of implantation.
Adverse Events	No adverse events reported
GLP conformity	Study was performed in accordance with the GLP and the German Animal Protection Law and approved by the supervising state agency for animal experiments.

Table 7. Closure of Patent Foramen Ovale in an ovine model

Objectives	To assess the biocompatibility of the device for closure of patent foramen ovale in the ovine model (8 lambs at the age of 6 to 12 weeks)						
Endpoints	<ul style="list-style-type: none"> • Ingrowth of the coil into surrounding tissue • Calcification • Inflammatory infiltrates as shown by infiltration of lympho-plasmatocytes • Lympho-histiocytic reaction as a sign of foreign body reaction 						
Endpoint assessment	After a period of implantation of at least 47 days, devices were completely ingrown without any signs of thrombus formation or local inflammation. Few signs of calcification and moderate foreign body reaction were observed in single animals. The results suggest good biocompatibility of the Nitinol devices tested.						
Histology	Animal	Time of implantation	Ingrowth	Calcifications	Amorphous particles	Inflammatory infiltrates	Histiocytic reaction
	1	4 days	no	no	no	No	no
	2	47 days	complete	no	no	No	moderate
	3	47 days	complete	no	moderate	No	moderate
	4	47 days	complete	no	no	no	moderate
	5	72 days	complete	few	no	No	moderate
	6	72 days	complete	no	few	No	no
	7	113 days	complete	few	few	No	moderate

	8	113 days	complete	no	no	No	no
Adverse events	No adverse events reported						
GLP conformity	Study was not conducted in accordance with GLP, but with the guidelines of the German Animal Protection Law and approved by the supervising state agency for animal experiments						

X. SUMMARY OF PRIMARY CLINICAL STUDY(IES)

Patients were treated between November 2002 and October 2007. The database for this PMA reflected data collected through October 2008 and included 357 patients. There were 15 investigational sites.

The Sentinel Study was conducted in the US under IDE # G010278 to establish a reasonable assurance of safety and effectiveness of the Nit-Occlud® PDA for the treatment of patent ductus arteriosus of diameter < 4 mm. Data from this clinical study (including continued access patients) were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

The Sentinel Study is a prospective, multi-center, single-arm study. The primary effectiveness endpoints were echocardiographic and clinical closure rates at 12 months. The primary safety endpoint was the serious adverse event rate at 12 months.

The endpoint rates were compared to an Objective Performance Criteria. The study paradigm (primary effectiveness and safety endpoints) was recommended by a 1997 Circulatory System Devices Advisory Panel to FDA for the assessment of PDA closure. The OPC was specified in the Panel's report [2].

An independent Core Echocardiography Laboratory reviewed and validated a subset of echo videotapes or CD's for the 12 month follow-up echocardiograms. A Data Safety Monitoring Board (DSMB) reviewed and adjudicated all adverse events.

A1. Clinical Inclusion and Exclusion Criteria

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

Primary Inclusion Criteria:

1. PDA with 4 mm or smaller minimum diameter by color Doppler
2. Patient weight ≥ 5 Kg, Age 6 months to 21 years (Patients older than 21 years may have device implanted and be included in a study registry.)
3. Previous treatment by surgery or Nit-Occlud® device with residual PDA noted at least 6 months after the procedure

Secondary Inclusion Criterion:

Angiographic minimum PDA diameter (D1) less than 4 mm. (Patients with angiographic diameters larger than 4 mm and smaller or equal to 5 mm were eligible for Nit-Occlud® device implantation but were included in a separate study registry.)

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

1. Associated cardiac anomalies requiring surgery
2. Known bleeding or blood clotting disorders
3. Ongoing febrile illness
4. Pregnancy
5. Pulmonary hypertension/increased pulmonary vascular resistance (>5 Wood Units)
6. Known hypersensitivity to contrast medium

A2. Follow-up Schedule

Clinical follow-up, including medical history, physical examination, and complete echocardiogram, were required after device implant at hospital discharge, 6 months, and 12 months.

Table 8. Patient Follow-up Plan

Visits	Pre-Diagnostics	Intervention	Post Procedural Care / Discharge	FU 1	FU 2
<i>Period</i>		0	$>+1$ day	6 months	12 months
In/Exclusion criteria	X				
Informed consent	X				
Admission	X				
Medical history	X			X	X
Physical examination including auscultation of murmur	X		X	X	X
Echocardiographic examination of the heart and the great vessels including color Doppler	X		X	X	X

with imaging of the PDA shunt, measuring the width of the color flow stream					
Routine post catheterization care and observation			X		
Coil implantation		X			
Intra-interventional data		X			
Follow Up Visits			X	X	X
Final visit	X	X	X	X	X
Adverse Events		X	X	X	X

Adverse events and complications were recorded at all visits.

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

A3. Clinical Endpoints

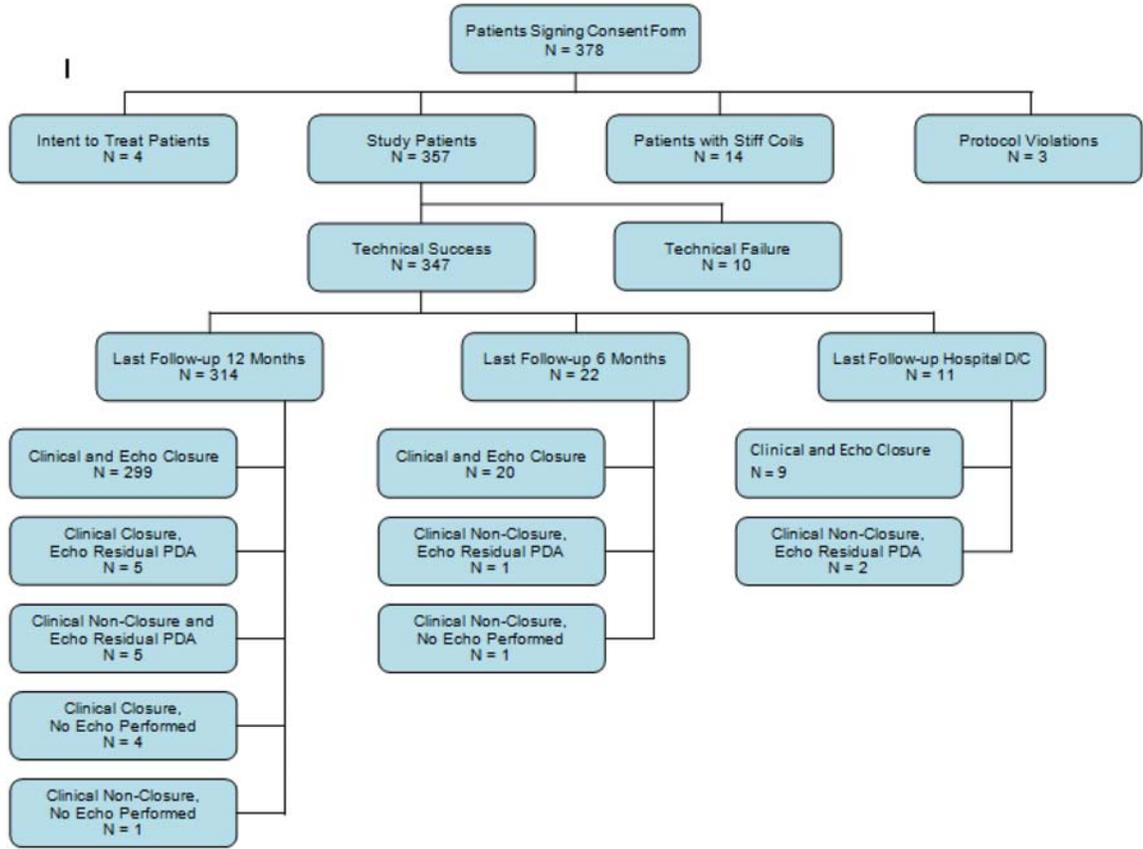
The primary effectiveness endpoints were echocardiographic and clinical closure rates at 12 months. Echocardiographic closure was defined as absence of detectable residual PDA flow by color Doppler echocardiographic examination. Clinical closure was defined as absence of a heart murmur and/or complete echocardiographic closure. Failures of clinical closure had a residual PDA by echocardiogram as well as a heart murmur audible by stethoscope examination.

The primary safety endpoint was the serious adverse event rate at 12 months. Serious adverse events were defined as events that were life-threatening, required surgery to correct, resulted in hospitalization or prolonged hospital stay, caused long-term disability, or resulted in genetic damage or birth defect. These included but were not limited to death, cerebral or pulmonary embolism, bacterial endocarditis, device embolization requiring surgery, and persistent cardiac arrhythmia requiring a pacemaker.

B. Accountability of PMA Cohort

At the time of database lock, of 378 patients enrolled in the PMA study, 94.4% (357) patients are available for analysis. At 12 month- study completion, 83.1% (314) subjects were available.

Figure 4. Patient Study Flow Diagram



C. Study Population Demographics and Baseline Parameters

The mean age of the study patients was 4.26 years, mean weight was 18.1 Kg. A total of 68.1 % (243) of enrolled patients were female and 31.9% (114) were male. Tables 9-12 describe the characteristics and baseline parameters of patients in the study:

Table 9. Patient Age

Age (Years)	N (%)
< 2	126 (36.3%)
2 - 6	138 (39.8%)
6 - 12	62 (17.9%)

> 12 years old	20 (5.8%)
----------------	-----------

Table 10. Patient Weight

Weight (Kg)	N (%) Tech Success
< 10 Kg	76 (21.9%)
10 - 25	213 (61.4%)
25 - 50	41 (11.8%)
> 50 Kg	17 (4.9%)

Table 11. Patient Body-Mass Index

BMI (kg/m ²)	N (%) Tech Success
< 15.2	88 (25.4%)
15.2-16.5	89 (25.7%)
16.5-18.0	82 (23.6%)
> 18.0	87 (25.1%)

Table 12. Baseline Congenital Heart Disease

Other CHD	Occurrences
Atrial Septal Defect	10
Ventricular Septal Defect	15
Stenosis	10
Patent Foramen Ovale	5
Other	8

Note: Some patients had more than one Other Congenital Heart Disease

Previous Cardiac Procedures: n = 6 (1.7%)

- Atrioventricular Septal Defect repair

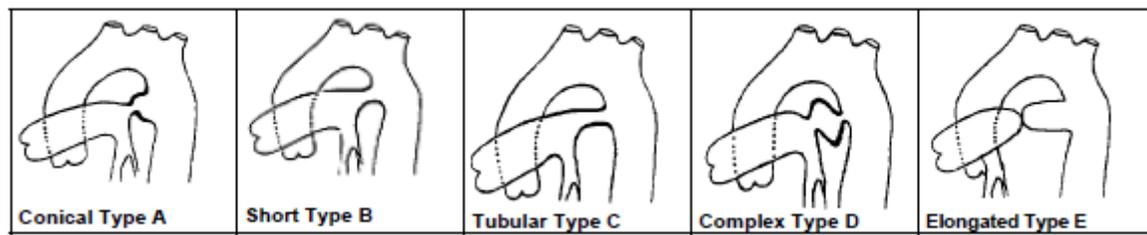
- PDA ligation & PA Band, PA Band tightening
- Balloon pulmonary valvuloplasty (n=2)
- PDA ligation (n=2)

Baseline physical examinations were performed on all patients. A systolic murmur was reported in 336 patients (96.8%). Eleven patients had no audible murmurs. Baseline echocardiograms and color Doppler examinations were performed on all patients. A PDA with minimum diameter of the color flow stream less than 4.0 mm was noted in all patients.

Angiographic Classification

In addition to hemodynamic and these dimensional characteristics, PDA were classified according to their configuration on the lateral angiogram using the Krichenko nomenclature illustrated below [1]:

Figure 5. Angiographic Classification of PDA on Lateral Aortogram



D. Safety and Effectiveness Results

D1. Safety and Effectiveness Results

The principal safety and effectiveness results are shown in Table 13.

- The 12 month clinical closure rate was 98.1% and the lower bound of the exact one-sided 95% confidence interval was 96.7%. Since this lower bound is greater than the established objective performance criteria of 95%, the objective performance criterion is considered to have been met.
- The 12-month echocardiographic closure rate was 96.8% and the lower bound of the exact one-sided 95% confidence interval was 95%. Since this lower bound is greater than the established objective performance criteria of 85%, the objective performance criterion is considered to have been met.
- The 12-month serious adverse event rate was 0% and the upper bound of the exact one-sided 95% confidence interval was 0.95%. Since this upper bound is less than the established objective performance criteria of 1%, the objective performance criterion is considered to have been met.

Table 13. Principal Safety and Effectiveness Results

	OPC Rates	Nit-Occlud® Patients	Percent	95% Lower Bound	95% Upper Bound
Technical Success at Implantation	95% ²	347/357	97.2%	95.6%	
Clinical Closure at 12 Month Follow-up	95% ¹	308/314	98.1%	96.7%	
Echocardiographic Closure at 12 Month Follow-Up	85% ¹	299/309	96.8%	95.0%	
Mortality at 12 Months	0% ¹	0	0.0%		0.95%
Serious Adverse Events at 12 Months	1% ¹	0	0%		0.95%
Total Device and Procedure Related Adverse Events at 12 Months	6%	15/316*	4.7%		7.21%
		14/316**	4.4%		6.84%
Composite Success at 12 Months	80% ³	294/309	95.1%	93.0%	

¹ Objective Performance Criteria (OPC) specified by the 1997 Circulatory System Devices Advisory Panel report [2]
² Inferred from technical success rate of Gianturco coil technical success cited in the 1997 Circulatory System Devices Advisory Panel report [2]
³ Defined in IDE protocol but not defined by the 1997 Circulatory System Devices Advisory Panel report
* Numerator is number of events; denominator is number with 12 months follow-up + 2 with AE before 12 months
** Numerator is number of person; denominator is number with 12 months follow-up + 2 with AE before 12 months

Table 14 shows procedural and fluoroscopy times listed by device size and type.

Table 14. Procedure and Fluoroscopy Times by Nit-Occlud® Device

Catalog #	Device Size Distal x Proximal Diameter	Device Type	Number of Implants	Mean Procedure Duration [min.]	Median Procedure Duration [min.]	Mean Fluoroscopy Time [min.]	Median Fluoroscopy Time [min.]
145044	4 x 4 mm	Flex	38	68.6	66.0	17.2	14.0
145054	5 x 4 mm	Flex	27	77.8	72.0	19.6	17.0
145065	6 x 5 mm	Flex	57	91.5	82.0	19.8	18.5
145076	7 x 6 mm	Medium	110	83.3	73.5	17.0	15.0
145096	9 x 6 mm	Medium	97	92.0	79.0	18.8	16.0
145116	11 x 6 mm	Medium	26	93.0	85.0	25.5	23.5

Differing Technical Failure Rates were observed based on Angiographic Classification of the PDA on the lateral aortogram and are summarized in the Table 15 below.

Table 15: Technical Failure rate by Angiographic Classification (See Figure 5)

Classification	N(% of Total)	Technical Failure Rate	n/N (%)
Conical (A)	267 (74.8%)	4/267	(1.5%)
Short (B)	17 (4.8%)	3/17	(17.6%)
Tubular (C)	5 (1.4%)	1/5	(20%)
Complex (D)	18 (5.0%)	1/18	(11.1%)
Elongated (E)	50 (14.0%)	1/50	(2%)
TOTAL	357 (100%)	10/357	(2.8%)

Adverse effects that occurred in the PMA clinical study:

Study Adverse events were defined as follows:

Serious Adverse Events - Procedural or device related events which were life-threatening, required surgery to correct, resulted in hospitalization or prolonged hospital stay, caused long-term disability, or resulted in genetic damage or birth defect.

Major Adverse Events - Procedural or device related events which were not life-threatening, required interventional (catheter based) and /or medical treatment to correct up to one year follow-up evaluation but were resolved without surgical intervention.

Minor Adverse Events - Procedural or device related events which were not life-threatening, and were resolved without intervention or with a brief specific non-surgical intervention up to one year follow-up evaluation.

Observed adverse event experience with the Nit-Occlud® PDA is derived from the Sentinel study. Clinical events for this study are shown in Table 16 below.

Table 16. Adverse Events

DSMB Adjudication	Category	No of Events
Major Device Related	Device embolization	2
	Device Retrieval/Removal	2
	Obstruction of descending aorta	1
Minor Device Related	Possible Thrombus	1
Major Procedure Related	Decreased Pulse in Right Foot	1
	Reaction to anesthesia	2
Minor Procedure Related	Reaction to anesthesia	1
	Vascular access site complication	1
	Other Adverse Event	2
	Nausea	1

DSMB Adjudication	Category	No of Events
	Fever	1

D2. Subgroup Analyses

Gender Analysis

A post hoc evaluation of the Sentinel Study was conducted to identify possible sex-based differences in baseline characteristics and clinical outcomes. The Sentinel study was not designed nor powered to study safety and effectiveness differences between sexes, so this analysis is considered exploratory without definitive conclusions.

In the Sentinel study, 243/357 (68.1%) subjects were female and 114/357 (31.9%) were male. This is reflective of the imbalance of prevalence of persistent PDA in the patient population in the United States (i.e., the PDA population is greater in females compared to males).

With the inclusion of 68.1% female, the Sentinel study of the Nit-Occlud® PDA is representative of contemporary studies.

Table 17 shows baseline demographics and characteristics.

Table 17. Baseline demographics and characteristics by gender.

	Sex	n	min	median	mean	max	sd	sem	p value
Stats for age in years	F	212	0.52	3.30	4.37	19.59	3.90	0.27	0.27
	M	102	0.13	2.50	4.16	21.99	4.21	0.42	
Stats for weight in kg	F	212	5.2	14.45	18.26	65.5	12.44	0.85	0.54
	M	102	4.7	13.20	18.51	109.0	15.45	1.52	
Stats for bmi in kg/m ²	F	211	10.63	16.33	17.34	114.78	7.42	0.51	0.21
	M	102	7.34	16.92	17.29	32.20	3.70	0.37	
Stats for D1 in mm	F	212	0.5	1.9	1.95	3.9	0.74	0.05	0.09
	M	102	0.5	1.7	1.76	3.6	0.68	0.07	
Stats for Qp/Qs	F	211	0.81	1.3	1.42	3.4	0.42	0.029	0.20
	M	102	0.00	1.3	1.36	3.5	0.41	0.04	
F = Female M = Male N = Study Population Min = Minimum value Median = Middle value Mean = Average value Max = Maximum value					SD = Standard Deviation Sem = Standard Error p-value = kg = Kilograms bmi = Body mass index D1 = PDA at Narrowest Diameter Qp/Qs = Ratio of pulmonary flow (Qp) to Systemic flow (Qs)				

In the post-hoc analysis conducted, no statistically significant differences by gender were found in the outcomes or the five covariates (age, weight, body mass index, PDA diameter and pulmonary-systemic flow ratio [Qp/Qs]).

Table 18 below shows safety and effectiveness results by gender.

Table 18. Safety and Effectiveness Results by Gender.

Frequency Row Percent	Sex	No	Yes	Total	Fisher p value	
Technical Success by Gender	Female	8 3.29	235 96.71	243	0.5121	
	Male	2 1.75	112 98.25	114		
	Total	10	347	357		
Clinical Closure at 12 months by Gender	Female	5 2.36	207 97.64	212	0.6679	
	Male	1 0.98	101 99.02	102		
	Total	6	308	314		
Echo Closure (no leak) at 12 months by Gender ¹	Female	8 3.83	201 96.17	209	0.5089	
	Male	2 2.00	98 98.00	100		
	Total	10	299	309		
Composite Success at 12 months by Gender ¹	Female	12 5.74	197 94.26	209	0.4012	
	Male	3 3.00	97 97.00	100		
	Total	15	294	309		
Number of Device & Procedure Adverse Events by Gender	Frequency Row Pct	0	1	2	Total	p-value
	Female	232 95.47	11 4.53	0 0.00	243	0.1497
	Male	111 97.37	2 1.75	1 0.88	114	
	Total	343	13	1	357	
¹ Frequency Missing = 5						

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 14 investigators of which none were full-time or part-time employees of the sponsor and two had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: none
- Significant payment of other sorts: two investigators
- Proprietary interest in the product tested held by the investigator: none
- Significant equity interest held by investigator in sponsor of covered study: none

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. 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)(2) 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 of the Nit-Occlud® PDA are based on the results obtained from: evaluation of biocompatibility; *in vitro* engineering testing; *in vivo* animal testing; sterilization information; shelf life testing; and clinical studies. These studies revealed the following:

A. Effectiveness Conclusions

The results of the Sentinel study demonstrated that the primary endpoint of clinical closure at 12 months was 98.1% and the lower bound of the exact one-sided 95% confidence interval was 96.7%. Since this lower bound is greater than the established objective performance criteria of 95%, the objective performance criterion is considered to have been met. In addition, the primary endpoint of echocardiographic closure at 12 months was 96.8% and the lower bound of the exact one-sided 95% confidence interval was 95%. Since this lower bound is greater than the established objective performance criteria of 85%, the objective performance criterion is considered to have been met.

B. Safety Conclusions

The biocompatibility testing and *in vivo* animal testing conducted on the Nit-Occlud® PDA demonstrate that the performance characteristics of the product provide reasonable assurance of safety and acceptability for clinical use.

The *in vitro* engineering testing conducted on the occluder and delivery system demonstrated that the performance characteristics met the product specifications. The test results obtained from the sterilization testing demonstrated that the product can be adequately sterilized and is acceptable for clinical use. The functional shelf life and package integrity testing demonstrated that the product can be labeled with a shelf life of 3 years.

The results of the Sentinel study demonstrated the safety of the Nit-Occlud® PDA through evaluation of the safety endpoint of serious adverse events (including but were not limited to death, cerebral or pulmonary embolism, bacterial endocarditis, device embolization requiring surgery, and persistent cardiac arrhythmia requiring a pacemaker) within 12 months of the treatment.

C. Benefit-Risk Conclusions

The probable benefits of the device are based on data collected in a clinical study conducted to support PMA approval as described above. The benefits of the Nit-Occlud® PDA include clinical and echocardiographic closure of PDA, curative closure for PDA and avoidance of an open surgical procedure.

The probable risks of the Nit-Occlud® PDA include procedure related risks such as device embolization, malposition, risk of anesthesia, access site complications, and thrombus, for which the total incidence is less than 5%.

In conclusion, given the available information above, the data support that for percutaneous, transcatheter closure of small to moderate size patent ductus arteriosus with a minimum angiographic diameter less than 4 mm, the probable benefits outweigh the probable risks.

D. Overall Conclusions

The clinical and preclinical testing conducted demonstrated that the Nit-Occlud® PDA provides a reasonable assurance of safety and effectiveness when used as indicated in accordance with the instructions for use.

XIII. CDRH DECISION

CDRH issued an approval order on August 16, 2013. The final conditions of approval cited in the approval order are described below.

The Nit-Occlud PDA Post-Approval Study: The study must be conducted as per agreed protocol received on July 25, 2013. The study will consist of a newly enrolled, prospective, single-arm, multi-center trial of patients treated with Nit-Occlud PDA, and followed for 5-years post-procedure.

The primary safety objective is to demonstrate that the 5-year serious adverse event rate for the device is no worse than the Objective Performance Criterion (OPC) of 1%.

The primary effectiveness objective is to demonstrate that the 5-year complete closure rate for the device is no worse than the OPC of 85%. The closure of the ductus arteriosus will be assessed by absence of residual flow at 5 years by transthoracic echocardiograph.

The secondary safety objective is to demonstrate that the rate of adverse events reported through 5 years post procedure is no worse than 6% (OPC rate of 3% plus an added 3% margin).

The secondary effectiveness is to demonstrate that echocardiographic closure at 12 and 36 months is no worse than an OPC of 85%.

A total of 215 patients will be enrolled to ensure 150 patients treated with the Nit-Occlud PDA per device labeling will be available at 5 years post-procedure. Clinical exams will be conducted at 2, 12, 24, 36, 48, and 60 months and an echocardiography will be conducted at 2, 12, 36, and 60 months.

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.

XV. REFERENCES

1. Krichenko A et al. Angiographic Classification of the Isolated, Persistently Patent Ductus Arteriosus and Implications for Percutaneous Catheter Occlusion. *Am J Cardiol* 1989; 63:877-880.)
2. Multiorganization Advisory Panel to FDA for Pediatric Cardiovascular Devices, Proposed Standards for Clinical Evaluation of Patent Ductus Arteriosus Occlusion Devices. *Cath Cardiovasc Interv* 2000;51:293-296).