NIRxcell™

CoCr Coronary Stent on RX System

(NIRxcell Stent System)

INSTRUCTIONS FOR USE

Cordis®
A Cardinal Health company

Medinol Engineered

Rx ONLY
STERILE. Sterilized with ethylene oxide gas

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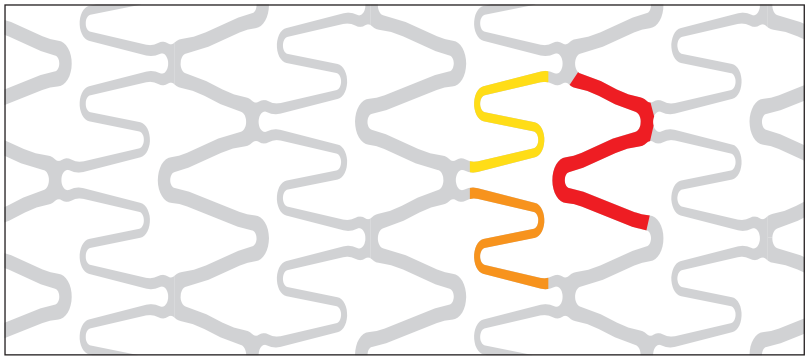
1 DEVICE DESCRIPTION

NIRxcell™ Stent System includes a balloon-expandable intracoronary L-605 Cobalt Chromium (CoCr) NIRxcell stent, premounted on a rapid exchange balloon catheter (the Delivery System).

The NIRxcell stent implant is identical to the stent previously approved under the brand name Presillion™ plus Stent System.

The NIRxcell stent is cut from panels of flat sheets of L-605 cobalt chromium alloy. First the pattern is cut from panels of flat sheet; then the stents are folded into cylinders and welded. The NIRxcell™ stent geometry is made up of alternating wide and narrow struts to enable the stent to be flexible in the unexpanded configuration and support the vessel, while conforming to its curvature, in the expanded configuration.

FIGURE 1: STENT DESIGN



At the distal end of the catheter is a delivery balloon. The balloon is designed to expand to a controlled diameter and length when inflated. The balloon delivery catheter has two platinum iridium radiopaque marker bands defining the length and location of the mounted stent.

The usable length of the delivery system is 140cm with a proximal shaft profile of 2.1F (0.69mm). For systems with a stent lenght of 8-28mm the distal shaft profile is 2.7F (0.9mm). For systems with a stent lenght of 33mm the distal shaft profile is 2.9F (0.97mm). The catheter has a distal port (hole) approximately 30cm from the distal tip that accesses the guidewire lumen. The guidewire lumen begins at the distal port and terminates at the distal tip. The catheter also has two (2) markers on the proximal catheter shaft that indicate, approximately, the exit of the balloon catheter tip from the guiding catheter (brachial: 93cm; femoral: 103cm).

TABLE 1: NIRxcell™ STENT SYSTEM SPECIFICATIONS

STENT INNER DIAMETER (mm)	STENT LENGTH (mm)	MINIMUM GUIDING CATHETER COMPATIBILITY (ID)	STENT NOMINAL PRESSURE (atm)	RATED BURST PRESSURE-RBP (atm)	STENT FREE AREA (%)
2.50	8, 12, 15, 17, 20	5F (0.056¨)	12	18	89.2
2.75, 3.00	8, 12, 15, 17, 20, 24, 28, 33	5F (0.056¨)	12	18	86.9
3.50, 4.00	8, 12, 15, 17, 20, 24, 28, 33	5F (0.056¨)	12	18	86.5

TABLE 2: NIRxcell™ STENT SYSTEM CROSSING PROFILES

SYSTEM LABELED DIAMETER (mm)	SYSTEM LABELED LENGTH (mm)	CROSSING PROFILE (AVERAGE)
2.5	8, 12, 15, 17, 20	0.96
2.75	8, 12, 15, 17, 20, 24, 28, 33	1.05
3.0	8, 12, 15, 17, 20, 24, 28, 33	1.05
3.5	8, 12, 15, 17, 20, 24, 28, 33	1.11
4.0	8, 12, 15, 17, 20, 24, 28, 33	1.14

2 INDICATIONS FOR USE

NIRxcell Stent System is indicated for improving coronary luminal diameter in patients with symptomatic ischemic heart disease associated with stenotic lesions in de novo native coronary arteries (length ⩽ 30mm) with a reference vessel diameter of 2.50mm to 4.00mm.

3 CONTRAINDICATIONS

Coronary artery stenting is generally contraindicated in the following patient types:

- Patients for whom antiplatelet and/or anticoagulation therapy is contraindicated
- Patients judged to have a lesion which prevents complete inflation of an angioplasty balloon or proper placement of the stent or delivery system

4 WARNINGS

- Since the use of this device carries the associated risks of thrombosis, vascular complications, and/or bleeding events, judicious selection of patients is necessary.
- Persons allergic to L-605 cobalt chromium alloy may suffer an allergic response to this implant.

5 PRECAUTIONS

See also section 8.1 *Individualization of Treatment*.

- Do not use with Ethiodol or Lipiodol contrast media*.
- Do not expose the delivery system to organic solvents such as alcohol or detergents.
- Only physicians who have received appropriate training should perform implantation of the stent.
- Stent placement should be performed only at hospitals where emergency coronary artery bypass graft surgery can be readily performed.
- Subsequent restenosis may require repeat dilatation of the arterial segment containing the stent. The long-term outcome following repeat dilatation of endothelialized coronary stents is not well characterized.
- When multiple stents are required, stent materials should be of similar composition. Placing multiple stents of different materials in contact with each other may increase the potential for corrosion.
- The device should be manipulated while under high-quality fluoroscopic observation.
- Do not advance or retract the catheter unless the balloon is fully deflated. If resistance is met during manipulation, determine the cause of resistance under fluoroscopy before proceeding.
- Do not try to straighten a kinked hypotube. Straightening a kinked metal shaft may result in breakage of the shaft.

5.1 USE IN SPECIAL POPULATIONS

The safety and effectiveness of NIRxcell™ Stent System has not been established in the following patient populations:

- Patients with presence of definite or probable intra-luminal thrombus
- Patients with coronary artery reference vessel diameter < 2.5mm or > 4.0mm
- Patients with lesions longer than 30 mm
- Patients with unprotected lesions located in the left main coronary artery
- Patients with tortuous vessels that may impair stent placement in the region of the obstruction or proximal to the lesion
- Patients with moderate or severe lesion calcification
- Patients with poor flow in the target vessel
- Patients with multi-vessel disease
- Patients with in-stent restenosis
- Patients with chronic total occlusions
- Patients with ostial lesions
- Patients with bifurcation lesions
- Patients with longer than 12 months follow-up

The safety and effectiveness of using mechanical atherectomy devices (directional atherectomy catheters, rotational atherectomy catheters) or laser angioplasty catheters, in conjunction with the NIRxcell Stent System, have not been established.

* Ethiodol and Lipiodol are trademarks of Guebet S.A

5.2 STENT AND DELIVERY SYSTEM HANDLING – PRECAUTIONS

- **For single use only**. Do not re-sterilize or reuse.
- Note the product "Use By" date.
- Do not remove the stent from its stent delivery system as removal may damage the stent and/or lead to stent embolization. NIRxcell Stent System is intended to perform as a system. The NIRxcell stent is not designed to be manually re-crimped onto another delivery device.
- Do not use the stent delivery system in conjunction with any other stents.
- Take special care not to handle or in any way disrupt the stent on the balloon. This is most important during removal of the catheter from the packaging, placement over the guidewire, and advancement through the large-bore rotating hemostatic valve and guiding catheter hub.
- Do not manipulate the stent. Manipulation, e.g. rolling the mounted stent with your fingers, may loosen the stent from the delivery system balloon and cause dislodgment.
- Take care when inserting the delivery system into the hemostatic valve in order to avoid kinking.
- Use only the appropriate balloon inflation media. Do not use air or any gaseous medium to inflate the balloon.
- When back loading the catheter on the guidewire, provide adequate support to shaft segments.

5.3 STENT PLACEMENT – PRECAUTIONS

- Do not prepare or pre-inflate the stent delivery system prior to placement of the stent across the lesion. Use the balloon purging technique described in Section 10 Operator's Manual.
- Implanting a stent may lead to a dissection of the vessel distal and/or proximal to the stented portion and may cause acute closure of the vessel, requiring additional intervention (CABG, further dilatation, placement of additional stents, or other).
- When treating multiple lesions, the distal lesion should be stented first, followed by stenting of the proximal lesion. Stenting in this order obviates the need to cross the proximal stent in placement of the distal stent and reduces the chances for dislodgment.
- Do not expand the stent if it is not properly positioned in the vessel.
- Placement of the stent has the potential to compromise side branch patency.
- Use of pressures higher than what is specified on the product label may result in a ruptured balloon, with possible intimal damage and dissection.
- Should any resistance be felt at any time during either lesion access or removal of the stent delivery system pre-stent implantation, the system should be removed per instructions in section 5.4 Stent/System Removal - Precautions.
- Stent retrieval methods (use of additional wires, snares, and/or forceps) may result in additional trauma to the coronary vasculature and/or the vascular access site. Complications may include bleeding, hematoma, pseudoaneurysm, or vessel perforation.
- Guiding catheters used must have lumen sizes that are suitable to accommodate the introduction of the 2.7F Stent Delivery System for 8mm-28mm stent lengths, or 2.9F for 33mm stent length. Refer to table 1 for recommended guiding catheter.

5.4 STENT/SYSTEM REMOVAL – PRECAUTIONS

Should **unusual** resistance be felt at **any time** during either lesion access or removal of the stent delivery system pre-stent implantation, the entire system must be removed as a single unit.

When removing the delivery system as a single unit, proceed as follows:

1. **DO NOT** retract the delivery system into the guiding catheter.
2. Position the proximal balloon marker distal to the tip of the guiding catheter.
3. Advance the guidewire into the coronary anatomy as far distally as safely possible.
4. Tighten the rotating hemostatic valve to secure the stent delivery system to the guiding catheter.
5. Remove the guiding catheter and stent delivery system as a **single unit**.

Failure to follow these steps and/or the application of excessive force to the stent delivery system can potentially result in loss or damage to the stent and/or stent delivery system components.

5.5 POST IMPLANT - PRECAUTIONS

Great care must be exercised when crossing a newly deployed stent with other devices, such as another stent delivery system, an intravascular ultrasound (IVUS) catheter, a coronary guidewire, or balloon catheter, to avoid disrupting the stent geometry.

MR Conditional

5.5.1 MRI INFORMATION

Non-clinical testing has demonstrated the NIRxcell™ stent, in single and overlapped configurations of up to 73mm of length, is MR Conditional. It can be scanned safely, immediately after placement, under the following conditions:

- Static magnetic field of 1.5 or 3 Tesla.
- Maximum spatial gradient magnetic field of 1100 Gauss/cm or less.
- Maximum whole body averaged specific absorption rate (SAR) of 2.0 W/kg or less with the MR system operating in the Normal Operating Mode for 15 minutes of scanning (per pulse sequence).

ADDITIONAL MRI HEATING INFORMATION

Stent heating was derived by using the measured non-clinical, in vitro temperature rises in a GE Excite 3 Tesla scanner and in a Siemens Magnetom 1.5 Tesla coil in combination with the whole body averaged specific absorption rates (SARs) in the ASTM phantom. At overlapped lengths of up to 73mm, the NIRxcell stent produced a nonclinical maximum local temperature rise of 2.5ºC scaled to a maximum whole body averaged SAR of 2.0 W/kg (normal operating mode) for one sequence of 15 minutes. These calculations do not take into consideration the cooling effects of blood flow.

IMAGE ARTIFACT INFORMATION

The calculated image artifact extends approximately 4.7mm from the perimeter of the device diameter and 1mm beyond each end of the length of the stent when scanned in non-clinical testing using a Spin Echo sequence. With a Gradient Echo sequence, the calculated image artifact extends 7.4mm beyond the perimeter of the diameter and 3mm beyond each end of the length, with both sequences partially shielding the lumen; measurements performed in a 3.0 Tesla Magnetom Trio, Siemens Medical Solutions, software version Numaris/4, syngo MR 2004A 4VA25A, actively shielded MR system.

MEDICAL REGISTRATION

It is recommended that patients register the conditions under which the implant can be scanned safely with the MedicAlert Foundation (www.medicalert.org) or equivalent organization.

6 ADVERSE EVENTS

6.1 OBSERVED ADVERSE EVENTS

The principal adverse event experience with the PIONIR stent (identical to the NIRxcell™ stent) is derived from the PIONIR study. This study was a comparison of the PIONIR stent to a performance goal (PG) derived from literature on other approved coronary stents.

TABLE 3: IN AND OUT OF HOSPITAL COMPLICATIONS THROUGH 360 DAYS
% (NUMBER/DENOMINATOR) [95% CONFIDENCE INTERVAL]

SAFETY MEASURES	IN HOSPITAL COMPLICATIONS	COMBINED IN AND OUT OF HOSPITAL COMPLICATIONS TO 30 DAYS	COMBINED IN AND OUT OF HOSPITAL COMPLICATIONS TO 180 DAYS	COMBINED IN AND OUT OF HOSPITAL COMPLICATIONS TO 270 DAYS	COMBINED IN AND OUT OF HOSPITAL COMPLICATIONS TO 360 DAYS
TVF[1] (CARDIAC DEATH, TARGET VESSEL MI, CLINICALLY DRIVEN TVR[2])	2.2% (6/278) [0.8%, 4.6%]	2.5% (7/277) [1.0%, 5.1%]	4.7% (13/277) [2.5%, 7.9%]	8.7% (24/276) [5.7%, 12.7%]	10.3 (28/273) [6.9%, 14.5%]
ALL DEATH	0.4% (1/278) [0.0%, 2.0%]	0.4% (1/277) [0.0%, 2.0%]	1.1% (3/277) [0.2%, 3.1%]	1.4% (4/276) [0.4%, 3.7%]	1.5% (4/273) [0.4%, 3.7%]
CARDIAC DEATH	0.4% (1/278) [0.0%, 2.0%]	0.4% (1/277) [0.0%, 2.0%]	0.7% (2/277) [0.1%, 2.6%]	1.1% (3/276) [0.2%, 3.1%]	1.1% (3/273) [0.2%, 3.2%]
NON CARDIAC DEATH	0.0% (0/278) [0.0%, 1.3%]	0.0% (0/277) [0.0%, 1.3%]	0.4% (1/277) [0.0%, 2.0%]	0.4% (1/276) [0.0%, 2.0%]	0.4% (1/273) [0.0%, 2.0%]
TARGET VESSEL MI	2.2% (6/278) [0.8%, 4.6%]	2.5% (7/277) [1.0%, 5.1%]	2.9% (8/277) [1.3%, 5.6%]	3.3% (9/276) [1.5%, 6.1%]	3.3% (9/273) [1.5%, 6.2%]
Q WAVE MI[3]	0.7% (2/278) [0.1%, 2.6%]	0.7% (2/277) [0.1%, 2.6%]	0.7% (2/277) [0.1%, 2.6%]	0.7% (2/276) [0.1%, 2.6%]	0.7% (2/273) [0.1%, 2.6%]
NON-Q WAVE MI[4]	1.4% (4/278) [0.4%, 3.6%]	1.8% (5/277) [0.6%, 4.2%]	2.2% (6/277) [0.8%, 4.7%]	2.5% (7/276) [1.0%, 5.2%]	2.6% (7/273) [1.0%, 5.2%]
CLINICALLY DRIVEN TVR	0.7% (2/278) [0.1%, 2.6%]	1.1% (3/277) [0.2%, 3.1%]	2.9% (8/277) [1.3%, 5.6%]	6.5% (18/276) [3.9%, 10.1%]	8.1% (22/273) [5.1%, 11.9%]
CLINICALLY DRIVEN TLR[5]	0.7% (2/278) [0.1%, 2.6%]	1.1% (3/277) [0.2%, 3.1%]	2.5% (7/277) [1.0%, 5.1%]	5.1% (14/276) [2.8%, 8.4%]	6.2% (17/273) [3.7%, 9.8%]
STENT THROMBOSIS[6] (DEFINITE, PROBABLE)	0.7% (2/278) [0.1%, 2.6%]	1.1% (3/277) [0.2%, 3.1%]	1.1% (3/277) [0.2%, 3.1%]	1.1% (3/276) [0.2%, 3.1%]	1.1% (3/273) [0.2%, 3.2%]
BLEEDING COMPLICATIONS[7]	0.0% (0/278) [0.0%, 1.3%]	0.7% (2/277) [0.1%, 2.6%]	0.7% (2/277) [0.1%, 2.6%]	1.1% (3/276) [0.2%, 3.1%]	1.1% (3/273) [0.2%, 3.2%]
VASCULAR COMPLICATIONS[8]	1.4% (4/278) [0.4%, 3.6%]	1.8% (5/277) [0.6%, 4.2%]	1.8% (5/277) [0.6%, 4.2%]	1.8% (5/276) [0.6%, 4.2%]	1.8% (5/273) [0.6%, 4.2%]

1. Target Vessel Failure – Cardiac death, target vessel myocardial infarction (Q Wave and non-Q-wave), or clinically driven target vessel revascularization (TVR) by percutaneous or surgical methods.
2. Target Vessel Revascularization–Any percutaneous intervention of surgical bypass of any segment of the target vessel.
3. Q wave MI (QWMI) - Requires one of the following criteria:
   - Chest pain or other acute symptoms consistent with myocardial ischemia and new pathological Q waves in two or more contiguous ECG leads as determined by an ECG core laboratory or independent review of the CEC, in the absence of timely cardiac enzyme data.
   - New pathologic Q waves in two or more contiguous ECG leads as determined by an ECG core laboratory or independent review of the CEC and elevation of cardiac enzymes. In the absence of ECG data the CEC may adjudicate Q wave MI based on the clinical scenario and appropriate cardiac enzyme data.
4. Non Q-Wave MI - Elevation of CK levels to > 2.0 times normal with elevated CK-MB in the absence of new pathological Q waves (WHO definition).
5. Target Lesion Revascularization – Any percutaneous intervention of the target lesion or bypass surgery of the target vessel performed for restenosis or other complication of the target lesion.
6. Stent Thrombosis (ARC)–Thrombus or closure within the stented vessel. Acute (0–24 hours post stent implantation), Subacute (>24 hours–30 days post stent implantation), or late (30 days – 1 year post stent implantation).
7. Bleeding complication – A procedure-related hemorrhagic event that requires a transfusion and/or surgical intervention.
8. Vascular complication– May include the following: Pseudoaneurysm, Arteriovenous fistula (AVF), Peripheral ischemia/nerve injury, Vascular event requiring transfusion or surgical repair.

6.2 POTENTIAL ADVERSE EVENTS

Adverse events (listed in alphabetical order) that may be associated with the implantation of a coronary stent in coronary arteries include, but are not limited to:

- Abrupt vessel closure
- Allergic reaction
- Aneurysm
- Arrhythmias
- Cardiac tamponade
- Coronary artery spasm
- Death
- Dissection
- Drug reactions to antiplatelet agents / anticoagulation agents / contrast media
- Emboli, distal (tissue, air or thrombotic emboli)
- Emergency CABG
- Failure to deliver the stent to the intended site
- Fever
- Fistulization
- Hemorrhage or hematoma
- Hypotension / Hypertension
- Infection and pain at the insertion site
- Myocardial infarction
- Myocardial ischemia
- Occlusion
- Perforation
- Prolonged angina
- Pseudoaneurysm
- Renal failure
- Repeat percutaneous intervention
- Restenosis of stented segment (greater than 50% obstruction)
- Rupture of native and bypass graft
- Stent compression
- Stent misplacement / migration / embolization
- Stroke
- Thrombosis (acute, sub-acute or late)
- Stable or Unstable angina
- Ventricular fibrillation
- Vessel spasm

7 CLINICAL DATA

All clinical data presented below is applicable to the NIRxcell™ stent system, as the stent is identical to the stent used in these studies (PIONIR stent). The NIRxcell is comprised of an identical stent to the Presillion and Presillion plus Stent Systems and a different delivery system.

Presillion and Presillion plus stent systems had been used in the PIONIR Study. The Presillion stent system had been used in the BLAST Study and the Belgium registry.

The PIONIR clinical study was the pivotal study conducted to demonstrate the safety and effectiveness of the Presillion and Presillion plus Stent Systems. As the Presillion™ plus Stent System represents minor modifications to the Presillion™ Stent System (the stent is identical in both systems), two additional clinical studies are applicable and considered supportive studies of the Presillion™ plus Stent System:

- The control arm from the BLAST study – a phase II, randomized, double blind clinical study of the Presillion Stent System in combination with Liposomal Alendronate, compared to the Presillion Stent System alone, in treatment of de novo stenotic lesions in native coronary arteries in a population undergoing PCI.
- The Belgian Registry – a single arm registry, evaluating the safety of Presillion Stent System in the treatment of de novo stenotic lesions in native coronary arteries.

7.1 PIONIR STUDY - PRESILLION™ AND PRESILLION™ *PLUS* STENT SYSTEMS

7.1.1 STUDY OVERVIEW

The PIONIR was a non-randomized, multi-center, prospective, single arm clinical study conducted in Germany, Sweden, Belgium and Israel.

The main objective of this study was to evaluate the safety and effectiveness of Presillion™/Presillion™ plus Stent Systems in the treatment of patients with symptomatic ischemic heart disease with single de novo stenotic lesions in native coronary arteries with length ≤ 30mm and a reference vessel diameter of 2.50mm to 4.00mm. The intention was to cover the index lesion with one stent of adequate length. For bailout procedures or in the event of a sub-optimal result, further stenting was employed, at investigator's discretion, using the Presillion™/Presillion™ plus Stent Systems, as required. Given the similarities between the Presillion and Presillion plus Stent Systems, either could be used in this study.

The primary endpoint was the incidence of target vessel failure (TVF - cardiac death, target vessel myocardial infarction (MI [Q wave or non-Q wave]), or clinically driven target vessel revascularization (TVR) by percutaneous or surgical methods) within 270 days of treatment with the Presillion™/Presillion™ plus Stent System. This rate was compared with a performance goal derived using a meta-analysis of literature articles reporting outcomes with approved bare metal coronary stents.

Secondary clinical endpoints included the following:

1. All Death at 30, 180, 270, and 360 days
2. Cardiac Death at 30, 180, 270, and 360 days
3. MI at 30, 180, 270, and 360 days
4. Clinically driven Target Lesion Revascularization (TLR) at 30, 180, 270, and 360 days
5. TVR at 30, 180, 270, and 360 days
6. Acute Success Rates
   a. Device Success: Attainment of < 50% final residual stenosis of the target lesion using only Presillion™ or Presillion™ plus Stent Systems
   b. Lesion Success: Attainment of < 50% final residual stenosis of the target lesion using any percutaneous method
   c. Procedure Success: Attainment of < 50% residual stenosis of the target lesion and no in-hospital death, MI, or TLR
7. Bleeding or Vascular Complications at hospital discharge
8. Stent Thrombosis at hospital discharge at 30, 180, 270, and 360 days

TABLE 4: SUMMARY OF THE PIONIR STUDY

STUDY TYPE	• Multi-center study (n=16), performed in Europe (Germany, Sweden and Belgium) and Israel. • Prospective single arm • Patients can be treated with the Presillion™ or Presillion™ plus Stent Systems, as available
NUMBER OF PATIENTS	278
LESION CRITERIA	Single de novo stenotic lesions in native coronary arteries (length ≤ 30 mm) with a reference vessel diameter of 2.50mm to 4.00mm
STENT SIZES (mm)	• Diameter 2.5; Lengths: 8, 12, 17, 20 • Diameters: 2.75, 3.0, 3,5, 4.0; Lengths: 8, 12, 17, 20, 24, 33
ANTI-PLATELET THERAPY	• Aspirin, indefinitely • Clopidogrel, Prasugrel, or Ticlopidine, for a minimum of 1 month post procedure
FOLLOW UP	At: discharge, 30 days, 180 days, 270 days, and 1 year
SPONSOR	Medinol Ltd.

7.1.2 PATIENT CHARACTERISTICS

The table below summarizes the characteristics of the patient cohort.

TABLE 5: PATIENT CHARACTERISTICS

	% OF NUMBER OF PATIENTS (N = 278)
AGE (YEARS)	65.5 ± 10.6
MALE	76.3%
CURRENT SMOKERS	23.7%
HYPERCHOLESTEROLEMIA	76.2%
HYPERTENSION	72.3%
PREVIOUS MI	27.8%
DIABETES	20.5%
DIET CONTROLLED	4.0%
ORAL HYPOGLYCEMICS	12.2%
INSULIN	4.3%

7.1.3 ADVERSE EVENTS

An independent Clinical Events Committee adjudicated all clinical endpoint events in this study.

7.1.4 EFFECTIVENESS AND SAFETY - RESULTS

The 270-day TVF rate was 8.7% and the upper bound of the exact one-sided 95% confidence interval was 12.7%. Since this upper bound is less than the established performance goal of 16.46%, the performance goal is considered to have been met.

The 270-day TLF rate was 7.6% (21/276). Lesion success[1] was achieved in 100.0% (281/281) of cases; device success[2] was achieved in 98.2% (276/281) of cases; and procedural success[3] was achieved in 97.8% (272/278) of cases.

The following table displays the principal effectiveness and safety results.

1. Lesion success - attainment of <50% final residual stenosis of the target lesion using only Presillion or Presillion plus Stent Systems.
2. Device success - attainment of <50% final residual stenosis of the target lesion using any percutaneous method.
3. Procedural success - attainment of <50% residual stenosis of the target lesion and no in-hospital death, MI or TLR.

TABLE 6: EFFECTIVENESS AND SAFETY RESULTS THROUGH 270 DAYS

	PRESILLION™ / PRESILLION™ PLUS (N = 278 PATIENTS N = 281 LESIONS)	[95% CI]
PRIMARY ENDPOINT		
TVF-FREE AT 270 DAYS	91.3%	[88.0%,94.6%]
EFFECTIVENESS MEASURES		
LESION SUCCESS	100.0% (281/281)	[98.7%,100.0%]
DEVICE SUCCESS	98.2% (276/281)	[95.9%,99.4%]
PROCEDURE SUCCESS	97.8% (272/278)	[95.4%,99.2%]
TVF-FREE AT 30 DAYS	97.5%	[95.6%,99.3%]
CLINICALLY DRIVEN TLR-FREE AT 30 DAYS	98.9%	[97.7%,100.0%]
CLINICALLY DRIVEN TVR-FREE AT 30 DAYS	98.9%	[97.7%,100.0%]
CLINICALLY DRIVEN TLR-FREE AT 270 DAYS	94.9%	[92.3%,97.5%]
CLINICALLY DRIVEN TVR-FREE AT 270 DAYS	93.5%	[90.5%,96.4%]
SAFETY MEASURES		
TVF TO 30 DAYS	2.5% (7/277)	[1.0%,5.1%]
ALL DEATH TO 30 DAYS	0.4% (1/277)	[0.0%,2.0%]
TARGET VESSEL MI TO 30 DAYS	2.5% (7/277)	[1.0%,5.1%]
TVF TO 270 DAYS	8.7% (24/276)	[5.7%,12.7%]
TLF TO 270 DAYS	7.6% (21/276)	[4.8%,11.4%]
ALL DEATH TO 270 DAYS	1.4% (4/276)	[0.4%,3.7%]
TARGET VESSEL MI TO 270 DAYS	3.3% (9/276)	[1.5%,6.1%]
STENT THROMBOSIS AT DISCHARGE	0.7% (2/278)	[0.1%, 2.6%]
STENT THROMBOSIS TO 270 DAYS (ARC DEFINITE/PROBABLE)[1]	1.1% (3/276)	[0.2%,3.1%]
ACUTE (0-1 DAYS)	0.4% (1/278)	
SUB ACUTE (2-30 DAYS)	0.7% (2/277)	
BLEEDING COMPLICATIONS AT DISCHARGE	0.0% (0/278)	[0.0%,1.3%]
VASCULAR COMPLICATIONS AT DISCHARGE	1.4% (4/278)	[0.4%,3.6%]

1. ARC defined Definite Stent Thrombosis - is considered either angiographic confirmed or pathologic confirmed

   Probable Stent Thrombosis - is considered to have occurred in the following cases:

   a. Any unexplained death within the first 30 days

   b. Irrespective of the time after the index procedure any myocardial infarction (MI) in the absence of any obvious cause which is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis

7.1.5 GENDER-BASED ANALYSIS OF THE PIONIR STUDY

BACKGROUND

Cardiovascular disease is the leading cause of death for both women and men in the U.S. and coronary artery disease is a major cause of morbidity and mortality in women. It is estimated that the prevalence of coronary artery disease in the United States is 9.1% (9,200,000) in males and 7.0% (8,400,000) in females for adults at least 20 years old according to the American Heart Association 2010 Update.[4] However, it is estimated that only 36% of annual PCIs are performed in women.[5] In PCI clinical trials, women represent only 25-35% of the enrolled populations, and there are relatively little gender-specific data. The disproportionate enrollment distribution in these trials may be partly attributable to gender differences in symptoms and pathophysiology,[6] which may lead to under-diagnosis and under-referral of female patients with CAD. Women tend to have worse clinical outcomes compared to men, most likely due to their higher baseline risk profile and more complex angiographic characteristics. [7, 8, 9]

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9. Vaina S, Voudris V, Morice M-C, de Bruyne B, Colombo A, Macaya C, Richardt, G, Fajadet, J et al. Effect of gender differences on early and mid-term clinical outcome after percutaneous or surgical coronary revascularization in patients with multivessel coronary artery disease: Insights from ARTS I and ARTS II. EuroInterv. 2009; 4(4):492-501.

GENDER-BASED ANALYSIS

Medinol performed a post hoc evaluation of the PIONIR clinical study for possible sex-based differences in baseline characteristics and clinical outcomes. The PIONIR 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 PIONIR study, 66/278 (23.7%) subjects were female and 212/278 (76.3%) were male. In comparison, the prevalence of coronary artery disease (CAD) is estimated at 9.2 million in males and 8.4 million in females for adults age 20 and older in the United States (i.e. the CAD population is estimated to be 52.2% males and 47.7% females).

The disproportionate enrollment distribution in the PIONIR study may be partly attributable to the fact that women have always been underrepresented in clinical trials of coronary interventions. In studies of PCI published between 1990 and 2005, women represented only 15% to 38% (mean = 29.0% women, n = 86,137) of the patient population[6].

Women are also underrepresented in contemporary studies of coronary stenting. Our review of the literature identified only 7 studies with sex-stratified data, with the inclusion of women ranging from 20% to 28% (mean = 25.1% women; n = 2,954).[10, 11, 12, 13, 14, 15, 16]

With the inclusion of 23.7% women, our PIONIR trial of the Presillionä plus Stent System is representative of contemporary studies.

Table 7 and table 8 display baseline demographics and angiographic characteristics, respectively.

TABLE 7: BASELINE DEMOGRAPHICS BY GENDER

	MALE (N = 212)	FEMALE (N = 66)	DIFFERENCE [95% CI]	P-VALUE
AGE (YEARS)	64.3 ± 10.2	69.0 ± 11.0	-4.7 [-7.6,-1.7]	0.002
CURRENT SMOKERS	24.1%	22.7%	1.3% [-10.3%,13.0%]	<.001
HYPERCHOLESTEROLEMIA	75.8%	77.3%	-1.4% [-13.1%,10.2%]	0.870
HYPERTENSION	69.3 %	81.8%	-12.5% [-23.7%,-1.3%]	0.058
PREVIOUS MI	28.3%	26.2%	2.1% [-10.1%,14.4%]	0.874
DIABETES	19.8%	22.7%	-2.9% [-14.4%,8.5%]	0.604
DIET CONTROLLED	4.7%	1.5%	3.2% [-0.9%,7.3%]	0.468
ORAL HYPOGLYCEMICS	10.4%	18.2%	-7.8% [-18.0%,2.4%]	0.130
INSULIN	4.7%	3.0%	1.7% [-3.3%,6.7%]	0.737

TABLE 8: ANGIOGRAPHIC CHARACTERISTICS BY GENDER

MEASURE	MALE (N = 212)	FEMALE (N = 66)	DIFFERENCE [95% CI]	P-VALUE
VESSEL LOCATION				
LAD	35.2% (75/213)	38.8% (26/67)	-3.6%[-16.9%,9.7%]	0.237
LCX	29.1% (62/213)	31.3% (21/67)	-2.2%[-14.9%,10.4%]	
RCA	35.7% (76/213)	28.4% (19/67)	7.3%[-5.2%,19.9%]	
LCMA	0.0% (0/213)	1.5% (1/67)	-1.5%[-4.4%,1.4%]	
LENGTH				
1 - 10 mm	54.9% (117/213)	50.7% (34/67)	4.2%[-9.5%,17.9%]	0.805
10 - 20 mm	40.4% (86/213)	43.3% (29/67)	-2.9%[-16.5%,10.7%]	
> 20 mm	4.7% (10/213)	6.0% (4/67)	-1.3%[-7.6%,5.1%]	
THROMBUS				
	0.9% (2/213)	0.0% (0/67)	0.9%[-0.4%,2.2%]	1.000
CALCIFICATION				
MILD	82.2% (175/213)	71.6% (48/67)	10.5%[-1.4%,22.5%]	0.003
MODERATE	13.6% (29/213)	11.9% (8/67)	1.7%[-7.4%,10.7%]	
SEVERE	4.2% (9/213)	16.4% (11/67)	-12.2%[-21.5%,-2.9%]	

10. Mehilli J, Kastrati A, Bollwein H, et al. Gender and restenosis after coronary artery stenting. Eur Heart J 2003;24:1523-30.
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In the post-hoc analysis conducted on the intention-to-treat population, the only significant sex difference observed was a lower rate of target vessel myocardial infarction in women at the 270-day follow-up (1.9% vs 7.6%, p = 0.038). Although not significant (p = 0.057), the rate of cardiac death at 180-day and 270- day follow-up was higher in women (3.3%) than men (0.0%). Due to the modest sample size of this study, this analysis and any interpretation are limited.

Table 9 below displays effectiveness and safety results by gender.

TABLE 9: EFFECTIVENESS AND SAFETY RESULTS BY GENDER

	MALE (N = 212)	FEMALE (N = 66)
PRIMARY ENDPOINT		
TVF-FREE AT 270 DAYS	92.4%	87.9%
EFFECTIVENESS MEASURES		
LESION SUCCESS	100.0% (214/214)	100.0% (67/67)
DEVICE SUCCESS	98.1% (210/214)	98.5% (66/67)
PROCEDURE SUCCESS	98.6% (209/212)	95.5% (63/66)
TVF-FREE AT 30 DAYS	98.1%	95.5%
CLINICALLY DRIVEN TLR-FREE AT 30 DAYS	99.1%	98.5%
CLINICALLY DRIVEN TVR-FREE AT 30 DAYS	99.1%	98.5%
CLINICALLY DRIVEN TLR-FREE AT 270 DAYS	94.8%	95.4%
CLINICALLY DRIVEN TVR-FREE AT 270 DAYS	93.8%	92.3%
SAFETY MEASURES		
TVF TO 30 DAYS	1.9% (4/211)	4.5% (3/66)
ALL DEATH TO 30 DAYS	0.0% (0/211)	1.5% (1/66)
TARGET VESSEL MI TO 30 DAYS	1.9% (4/211)	4.5% (3/66)
TVF TO 270 DAYS	7.6% (16/210)	12.1% (8/66)
ALL DEATH TO 270 DAYS	1.0% (2/210)	3.0% (2/66)
TARGET VESSEL MI TO 270 DAYS	1.9% (4/210)	7.6% (5/66)
STENT THROMBOSIS TO 270 DAYS	1.0% (2/210)	1.5% (1/66)
BLEEDING COMPLICATIONS AT DISCHARGE	0.0% (0/212)	0.0% (0/66)
VASCULAR COMPLICATIONS AT DISCHARGE	1.9% (4/212)	0.0% (0/66)

7.1.6 CONCLUSION

The 9-month results of the PIONIR study demonstrate Presillion™/Presillion™ plus Stent Systems to be safe and effective in the treatment of de novo stenotic lesions in native coronary arteries, when compared to a performance goal derived using a meta-analysis of peer-reviewed literature on coronary stenting with bare metal stents.

7.2 THE BLAST STUDY

7.2.1 STUDY OVERVIEW

The BLAST was a Phase II, randomized, multi-center, prospective, double blind clinical study of the Presillion stent System in combination with Liposomal Alendronate compared to the Presillion Stent System alone The main objective of this study was to assess the safety and efficacy of Liposomal Alendronate in the treatment of de novo stenotic lesions in native coronary arteries in a population undergoing PCI.

The data from the Presillion-only treatment arm provide supportive information regarding the safety and effectiveness of the PIONIR stent.

The primary efficacy endpoint of this study was the 180 days in-stent late lumen loss, as measured by QCA.

The follow-up rate in the per protocol population of 57 patients randomized to placebo was 98.2%(56/57) at 60 months.

An independent Clinical Events Committee adjudicated all SAEs and endpoint AEs.

TABLE 10: SUMMARY OF THE BLAST STUDY

STUDY TYPE	• Prospective • Multi-center study (n=11), performed in Israel • Double blind • Randomized, 3 arms on 1:1:1 basis: ° High LA dose + Presillion Stent System ° Low LA dose + Presillion Stent System ° Placebo IV saline infusion + Presillion Stent System
NUMBER OF PATIENTS	• Total: 226 • Placebo group: 57
LESION CRITERIA	Up to 2 de novo stenotic lesions in native coronary arteries (length ⩽ 30mm) with a reference vessel diameter of 2.50mm to 3.50mm
ANTI-PLATELET THERAPY	• Aspirin indefinitely • Clopidogrel for a minimum of 1 month
FOLLOW UP	• Clinical follow up at 30 days • Clinical and angiographic (stent) follow up at baseline and 180 days, including Quantitative Coronary Angiography (QCA). • IVUS at baseline at 180 days for pre-specified patients. • Yearly contact through 1-5 years
SPONSOR	BIOrest Ltd

7.2.2 PATIENT CHARACTERISTICS

The following table provides a summary of characteristics of the patient cohort.

TABLE 11: SUMMARY OF PATIENT CHARACTERISTICS IN THE BLAST STUDY

	% OF NUMBER OF PATIENTS (N = 57)
AGE (YEARS)	58.1 ± 8.2
MALE	87.7%
CURRENT SMOKERS	42.6%
HYPERCHOLESTEROLEMIA	75.4%
HYPERTENSION	66.7%
PREVIOUS MI	30.4%
DIABETES	38.6%
DIET CONTROLLED	22.7%
ORAL HYPOGLYCEMICS	68.2%
INSULIN	9.1%

7.2.3 EFFECTIVENESS AND SAFETY – RESULTS

180 DAYS DATA:

The mean (±SD) of in-stent late lumen loss at 180 days for the 57 per-protocol (PP) placebo arm patients was 0.86mm (± 0.60mm).

The overall MACE rate at 180 days for the placebo group was 25.0% (14/56) with 19.65% (11/56) MIs (all being target vessel non ST elevation MIs) and 7.1% (4/56) clinically driven TLR events. (A patient may have experienced more than one such event). There were no deaths or emergent CABG events reported through 180 days.

The overall rate of TLF at 180 days was 25.0% (14/56) as was the overall rate of TVF. There was only one (1.8%) late stent thrombosis event through 180 days of follow-up in the placebo group.

The rate of peri-procedural TV-MI in the BLAST study was 17.5% compared to a rate of 2.2% in the PIONIR study. The difference in these rates is largely attributable to differences in definitions utilized in the two studies. The PIONIR study used the historical WHO definition based on total CK, whereas the BLAST study used the ARC definition utilizing levels of troponin, a more sensitive biomarker. When the events in the PIONIR study are adjudicated against the ARC definition, the resulting rate is 12.6%. Additionally, when patient and lesion characteristics are considered, the BLAST patient study enrolled a more complex patient population compared to the PIONIR study, with higher rates of unstable angina and diabetes and more complex lesion characteristics. Given these differences between studies, the difference in MI rates between studies did not raise a safety concern.

1800 days safety data:

The overall MACE rate at 1800 days for the placebo group was 38.6% (22/57) with 24.6% (14/57) MIs and 21.1% (12/57) clinically driven TLR events. (A patient may have experienced more than one such event). There were 2 deaths and 0 emergent CABG events reported through 1800 days.

The overall rates of TLF and TVF were 36.8% (21/57) and 38.6% (22/57), respectively, at 1800 days. There was only one (1.8%) late stent thrombosis event through 1800 days of follow-up in the placebo group.

Table 12 shows the principal effectiveness and safety results.

TABLE 12: PRINCIPAL EFFECTIVENESS AND SAFETY RESULTS

EFFECTIVENESS MEASURES		
	PLACEBO (N = 57)	[95% CI]
ACUTE SUCCESS		
LESION SUCCESS	100.0% (65/65)	[94.5%,100.0%]
PROCEDURE SUCCESS	82.5% (47/57)	[70.1%,91.3%]
TREATMENT SUCCESS	82.5% (47/57)	[70.1%,91.3%]
FOLLOW-UP (6-MONTH)		
FOLLOW-UP IN-STENT MINIMAL LUMEN DIAMETER (MLD, IN MM)		
MEAN±SD (N)	1.77 ± 0.80 (57)	[1.55,1.98]
RANGE (MIN,MAX)	(0.00,3.41)	
MEDIAN	1.81	
FOLLOW-UP IN-STENT PERCENT DIAMETER STENOSIS (% DS)		
MEAN±SD (N)	36.64 ± 24.88 (57)	[30.04,43.24]
RANGE (MIN,MAX)	(-6.40,100.00)	
MEDIAN	35.40	
FOLLOW-UP IN-SEGMENT MINIMAL LUMEN DIAMETER (MLD, IN MM)		
MEAN±SD (N)	1.68 ± 0.72 (57)	[1.49,1.87]
RANGE (MIN,MAX)	(0.00,3.00)	
MEDIAN	1.61	
FOLLOW-UP IN-SEGMENT PERCENT DIAMETER STENOSIS (% DS)		
MEAN±SD (N)	39.84 ± 21.68 (57)	[34.08,45.59]
RANGE (MIN,MAX)	(3.81,100.00)	
MEDIAN	35.58	
LATE LOSS IN-STENT (MM)		
MEAN±SD (N)	0.86 ± 0.60 (57)	[0.70,1.02]
RANGE (MIN,MAX)	(-0.08,2.24)	
MEDIAN	0.83	
LATE LOSS IN-SEGMENT (MM)		
MEAN±SD (N)	0.68 ± 0.58 (57)	[0.53,0.84]
RANGE (MIN,MAX)	(-0.37,1.81)	
MEDIAN	0.62	
IN-STENT BINARY RESTENOSIS	26.3% (15/57)	[15.5%,39.7%]
IN-SEGMENT BINARY RESTENOSIS	26.3% (15/57)	[15.5%,39.7%]

SAFETY MEASURES				
	180 DAYS		1800 DAYS	
	PLACEBO (N = 57)	[95% CI]	PLACEBO (N = 57)	[95% CI]
IN-HOSPITAL MACE	17.5% (10/57)	[8.7%,29.9%]	17.5% (10/57)	[8.7%,29.9%]
OUT-OF-HOSPITAL MACE	7.1% (4/56)	[2.0%,17.3%]	28.1% (16/57)	[17.0%,41.5%]
MACE	25.0% (14/56)	[14.4%,38.4%]	38.6% (22/57)	[26.0%,52.4%]
TYPE I MI (STEMI, NSTEMI)*	19.6% (11/56)	[10.2%,32.4%]	24.6% (14/57)	[14.1%,37.8%]
TYPE II MI (Q-WAVE, NON-Q-WAVE)*	19.6% (11/56)	[10.2%,32.4%]	24.6% (14/57)	[14.1%,37.8%]
CARDIAC DEATH OR MI	19.6% (11/56)	[10.2%,32.4%]	26.3% (15/57)	[15.5%,39.7%]
CLINICALLY-DRIVEN TARGET LESION REVASCULARIZATION (TLR)	7.1% (4/56)	[2.0%,17.3%]	21.1% (12/57)	[11.4%,33.9%]
TARGET VESSEL FAILURE (TVF)	25.0% (14/56)	[14.4%,38.4%]	38.6% (22/57)	[26.0%,52.4%]
TARGET LESION FAILURE (TLF)	25.0% (14/56)	[14.4%,38.4%]	36.8% (21/57)	[24.4%,50.7%]
BLEEDING COMPLICATIONS	0.0% (0/56)	[0.0%,6.4%]	0.0% (0/57)	[0.0%,6.3%]
VASCULAR COMPLICATIONS	0.0% (0/56)	[0.0%,6.4%]	0.0% (0/57)	[0.0%,6.3%]
STENT THROMBOSIS	1.8% (1/56)	[0.0%,9.6%]	1.8% (1/57)	[0.0%,9.4%]
MACE-FREE†	75.4%	[64.3%,86.6%]	61.4%	[47.5%,75.3%]
CLINICALLY DRIVEN TLR-FREE†	93.0%	[86.4%,99.6%]	78.9%	[67.4%,90.5%]
TVF-FREE†	75.4%	[64.3%,86.6%]	61.4%	[47.8%,75.1%]
TLF-FREE†	75.4%	[64.3%,86.6%]	63.2%	[49.4%,76.9%]

* Each MI was categorized for both groups.
† Kaplan-Meier estimates are based on all PP patients, where patients not experiencing the event were censored at 180/1800-days or last known follow-up, whichever is earlier.

7.2.4 CONCLUSIONS

The outcomes of the PIONIR Stent-only cohort (57 patients) in the BLAST trial at 180 and 1800 days post-procedure are presented above. The Quantitative Angiographic Analysis and clinical outcomes are generally consistent with the outcomes of the PIONIR study.

Long-term safety at 1800 days post-procedure is comparable with that found in the literature[17, 18, 19, 20] for other approved stents.

7.3 THE BELGIAN REGISTRY

7.3.1 STUDY OVERVIEW

This non-randomized, multi-center, single-arm registry was initiated with the objective of capturing 30-day outcomes. At a later stage, the follow up period was prolonged per the Belgian health authority's request to include an additional data point (as close as possible to, but after, the 6-month post procedure date).

The main objective of this study was to evaluate the safety of Presillion Stent System in the treatment of de novo stenotic lesions in native coronary arteries.

The primary safety measure was a composite of MACE [includes cardiac death, MI (Q-wave and Non-Q-wave) and clinically driven Target Lesion Revascularization (TLR)] at 30 days and 180 days post procedure.

TABLE 13: SUMMARY OF THE BELGIAN REGISTRY

STUDY TYPE	• Multi center (n=8), performed in 7 centers in Belgium and 1 center in Luxemburg • Single arm Direct stenting (stent implantation without balloon pre-dilatation) was allowed to most closely address daily routine clinical practice.
NUMBER OF PATIENTS	101 patients enrolled for the study • 30-day follow up: 101 • 6-month to 1-year follow up: 89
LESION CRITERIA	Up to two (2) de novo native coronary artery lesions with a maximum lesion length of 30mm in a maximum of two major coronary arteries with reference vessel diameter ≥ 2.5mm and ≤ 4.0mm by visual estimation
ANTI-PLATELET THERAPY	• Aspirin, indefinitely • Clopidogrel or Ticlopidine, for a minimum of 1 month
FOLLOW UP	• 30 days • Prolonged to 180 days, up to 1 year
SPONSOR	Cordis, a J&J company

7.3.2 PATIENT CHARACTERISTICS

The following table provides a summary of characteristics of the patient cohort.

TABLE 14: SUMMARY OF THE PATIENT CHARACTERISTICS

	% OF NUMBER OF PATIENTS (N = 101)
AGE, MEAN (YEARS)	66.1 ± 10.6
MALE	69.3%
HISTORY OF SMOKING	64.4%
HYPERCHOLESTEROLEMIA	76.2%
PREVIOUS MI	24.8%
HYPERTENSION	71.3%
DIABETES	1.0%

17. Stettler C, Wandel S, Allemann S et al. Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis. Lancet 2007; 370:937-48.
18. Grise MA, Massullo V, Jani S, et al. Five-Year Clinical Follow-Up After Intracoronary Radiation. Results of a Randomized Clinical Trial. Circulation 2002;105:2737-40.
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20. Bangalore et al. Short- and long-term outcomes with drug-eluting and bare-metal coronary stents: a mixed-treatment comparison analysis of 117 762 patient-years of follow-up from randomized trials. Circulation. 2012 Jun 12;125(23):2873-91.

7.3.3 PRINCIPAL SAFETY AND EFFECTIVENESS RESULTS

TABLE 15: 1 MONTH FOLLOW UP (N = 101)

ENDPOINTS	RATE AT 180 DAYS
PRIMARY ENDPOINT	
MACE (CARDIAC DEATH, MYOCARDIAL INFARCTION, TARGET LESION REVASCULARIZATION)	0%
SECONDARY ENDPOINTS	
IN-HOSPITAL MACE	0%
CLINICALLY-DRIVEN TARGET LESION REVASCULARIZATION	0%
CLINICALLY-DRIVEN TARGET VESSEL REVASCULARIZATION	0.99%
TARGET VESSEL FAILURE	0%
MYOCARDIAL INFARCTION	0%
MAJOR BLEEDING	0%
STROKE	0%
PROCEDURAL SUCCESS	99.0%
LESION SUCCESS (N = 111)	100%
DEVICE SUCCESS (N = 111)	97.3%

TABLE 16: 180 DAYS OR BEYOND FOLLOW UP (N = 89)

ENDPOINTS	RATE AT 180 DAYS
MACCE (DEATH, STROKE, MI, CABG, TVR, NON TVR)	7.9%
CARDIAC DEATH	1.1%
NON-CARDIAC DEATH	0%
NON-FATAL QMI	0%
CABG	0%
ISCHEMIA DRIVEN TVR	4.5%
ISCHEMIA DRIVEN NON TVR	1.1%
STROKE	1.1%
STENT THROMBOSIS	1.1%
TVF (CARDIAC DEATH, MI, TVR)	5.6%

7.3.4 CONCLUSION

The information gathered in this registry indicates that the safety profile of the PIONIR stent in the treatment of de novo coronary artery stenosis is generally consistent with the results of the PIONIR study.

8 PATIENT SELECTION AND TREATMENT

8.1 INDIVIDUALIZATION OF TREATMENT

The risks and benefits should be considered for each patient before use of NIRxcell™ Stent System. Patient selection factors to be assessed should include a judgment regarding risk of antiplatelet therapy.

Special consideration should be given to those patients with recently active gastritis or peptic ulcer disease.

Co-morbidities that increase the risk of poor initial results or the risks of emergency referral for bypass surgery (diabetes mellitus, renal failure, and severe obesity) should be reviewed.

Thrombosis following stent implantation is affected by several baseline angiographic and procedural factors. These include vessel diameter less than 3mm, intra-procedural thrombus, and dissection following stent implantation.

9 HOW SUPPLIED

- **STERILE.** This device is sterilized with Ethylene Oxide (ETO) gas and is non-pyrogenic.
  For single use only. Do not re-sterilize. Do not use the device if the package is opened or damaged.
- Use prior to the expiration date ("Use By" date).
- **CONTENTS:**
  One NIRxcell Stent System
  One Flushing tool
- **STORAGE.** Store in a cool, dark, dry place.

10 OPERATOR'S MANUAL

10.1 INSPECTION PRIOR TO USE

Before opening, carefully inspect the stent delivery system package for damage to the sterile barrier. **Do not use the device if there is any damage to the packaging.**

Prior to using the device, carefully remove the system from the package and inspect for bends, kinks, and other damage.

Verify that the stent is located between the radiopaque markers.

CAUTION: Do not use if any defects are noted.

10.2 MATERIALS REQUIRED

The following table lists the materials required for the procedure.

TABLE 17: REQUIRED MATERIALS

QUANTITY	MATERIAL
N/A	Appropriate guiding catheter(s)
2-3	10-20 cc syringes
1,000 U / 500 CC	Sterile Heparinized Normal Saline (HepNS)
1	0.014" (0.36mm) diameter guidewire (min length 175 cm)
1	Introducer sheath
1	Rotating hemostatic valve with an appropriate internal diameter
N/A	Contrast diluted 1:1 with normal saline
1	Inflation device
1	Three-way stopcock
N/A	Appropriate anticoagulation and anti-platelet drugs
1	Guidewire introducer
1	PTCA catheter

10.2.1 PREPARATION

Carefully remove the shipping mandrel (stainless steel rod), as one unit with the stent protector (PTFE sleeve) from the tip (distal end of system), by gripping the catheter proximally to the sleeve edge, and with the other hand grip the stent protector and gently remove distally.

CAUTION: If unusual resistance is felt during mandrel removal, do not use this product.

10.2.2 CATHETER RINSE

Rinse the catheter with sterile heparinized saline solution.

10.2.3 STENT SYSTEM GUIDEWIRE LUMEN FLUSH

Flush the stent system guidewire lumen with HepNS using flushing tool.

CAUTION: AVOID manipulation of stent during flushing of guidewire lumen, as this may disrupt the placement of the stent on the balloon.

10.2.4 DELIVERY SYSTEM PREPARATION

1. Prepare inflation device/syringe with diluted contrast medium.
2. Attach inflation device/syringe to stopcock; attach to hub (balloon inflation port).
3. Open stopcock to stent delivery system.
4. Apply negative pressure for 30 seconds, release inflation device/syringe, and leave on neutral for contrast fill.
5. Close the stopcock to the delivery system; purge the inflation device/syringe of all air.
   CAUTION: If air is seen in the shaft, repeat Delivery System Preparation to prevent uneven stent expansion.
6. If the syringe was used replace it with inflation device.
7. Open the stopcock to the delivery system and leave on neutral.

10.3 DELIVERY PROCEDURE

1. Prepare vascular access site according to standard practice.
2. Pre-dilate lesion site with PTCA catheter.
3. Maintain neutral pressure on inflation device. Open rotating hemostatic valve as widely as possible.
4. Backload delivery system onto proximal portion of guidewire while maintaining guidewire position across target lesion.
5. Advance the stent delivery system over guidewire to target lesion. Utilize radiopaque balloon markers to position stent across lesion; perform angiography to confirm stent position.

CAUTION: While introducing the delivery system into the vessel, do not induce negative pressure on the delivery system. This may cause dislodgment of the stent from the balloon.

NOTE: Should any resistance be felt at any time during either lesion access pre-stent implantation or removal of the stent delivery system post-stent implantation, the entire system should be removed as a single unit. See section 5.4 Stent/System Removal - Precautions for specific stent delivery system removal instructions.

10.4 DEPLOYMENT PROCEDURE

1. Before deployment, reconfirm the correct position of the stent relative to the target lesion via the radiopaque balloon markers.
2. Under fluoroscopic visualization, inflate the balloon to at least the nominal pressure to deploy the stent, but do not exceed the labeled rated burst pressure.

   NOTE: Refer to product labeling and Table 18 Compliance Chart for in-vitro stent inner diameter, nominal pressure, and RBP. NIRxcell Stent System may be inflated beyond nominal pressure, without repositioning, up to rated burst pressure, to assure complete apposition of the stent to the artery wall.

TABLE 18: NIRxcell STENT SYSTEM COMPLIANCE CHART

PRESSURE (atm)	LABELED DIAMETER (mm)					
	2.50	2.75	3.00	3.50	4.00	
9	2.26	2.55	2.77	3.27	3.77	
10	2.34	2.62	2.85	3.34	3.85	
11	2.42	2.68	2.92	3.42	3.92	
12	2.50	2.75	3.00	3.50	4.00	Diameter at Nominal Pressure
13	2.54	2.79	3.04	3.54	4.04	
14	2.59	2.83	3.09	3.58	4.09	
15	2.63	2.86	3.13	3.62	4.13	
16	2.68	2.90	3.17	3.66	4.18	
17	2.72	2.94	3.22	3.70	4.22	
18	2.77	2.98	3.26	3.75	4.27	Diameter at RBP
19	2.80	3.01	3.29	3.77	4.31	
20	2.84	3.03	3.33	3.80	4.34	

3. Maintain inflation pressure for 15-30 seconds for full expansion of the stent. Optimal expansion requires the stent to be in full contact with the artery wall, with the stent internal diameter matching the size of the reference vessel diameter. Stent wall contact should be verified through routine angiography or intravascular ultrasound.

The compliance data are based on in-vitro bench testing at 37ºC.

NOTE: Balloon pressures should be monitored during inflation. Do not exceed rated burst pressure as indicated on product label as this may result in a ruptured balloon with possible intimal damage and dissection.

4. Deflate the balloon by pulling negative pressure on the inflation device for 30 seconds
5. Confirm adequate stent expansion by angiographic injection through the guiding catheter.

NOTE: All efforts should be made to assure that the stent is not under dilated. If the deployed stent size is still inadequate with respect to vessel diameter, or if full contact with the vessel wall is not achieved, a larger balloon may be used to expand the stent further. The stent may be further expanded using a low profile, high pressure, non-compliant balloon catheter. If this is required, the stented segment should be re-crossed carefully with a prolapsed guidewire to avoid dislodging the stent. The balloon should be centered within the stent and should not extend outside of the stented region.

CAUTION: Do not dilate the stent beyond the following limits:

TABLE 19: MAXIMUM DILATION LIMITS

NOMINAL STENT DIAMETER (mm)	DILATATION LIMITS (mm)
2.50 mm	3.00 mm
2.75 mm	3.75 mm
3.00 mm	3.75 mm
3.50 mm	4.75 mm
4.00 mm	4.75 mm

10.5 REMOVAL PROCEDURE

1. Ensure the delivery system is fully deflated.
2. While maintaining guidewire position and negative pressure on the inflation device, withdraw the stent delivery system.

   NOTE: Should unusual resistance be felt at any time during either lesion access or removal of the stent delivery system pre-stent implantation, the entire system should be removed as a single unit. See section 5.4 Stent/System Removal - Precautions for specific stent delivery system removal instructions.
3. During withdrawal of the delivery system, hold saline-soaked gauze around the exposed catheter shaft and pull the catheter through the gauze to remove blood or any other residues.
4. Repeat angiography to visually assess the vessel and the stented area. If an adequate expansion has not been obtained, exchange back to the original delivery catheter or exchange to another balloon catheter of appropriate balloon diameter to achieve proper stent apposition to the vessel wall.
5. Final internal stent diameter should match reference vessel.
   Assure that the stent is not under dilated.

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Distributed by:
Cordis Corporation
14201 North West 60th Avenue
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USA

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Medinol Ltd.
PO Box 45026, Beck Tech Bldg.
Har-Hotzvim B, Hartom St. 8
Jerusalem 9777508
ISRAEL

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