EluNIR™

Ridaforolimus Eluting Coronary Stent System

INSTRUCTIONS FOR USE

Medinol
Ingenuity for life

CAUTION: Federal law restricts this device to sale by or on the order of a physician

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EXPLANATION OF SYMBOLS ON LABELS AND PACKAGING


Date of Manufacture


Consult Instructions for Use


Do Not Use if Package is Damaged


Keep Dry


Keep Away from Sunlight

Sterilized Using Ethylene Oxide


Do Not Reuse

MR Conditional

Do Not Resterilize

Contains a medicinal substance

Not Made with Natural Rubber Latex


Nonpyrogenic

Medical Device

Unique Device Identifier


Single sterile barrier system with two protective packaging outside


Single sterile barrier system with protective packaging outside


Single sterile barrier system

INSTRUCTIONS FOR USE

EluNIR™ Ridaforolimus Eluting Coronary Stent System

EluNIR™ Ridaforolimus Eluting Coronary Stent System (EluNIR™) and all its components are provided sterile for single use only.

1 PRODUCT DESCRIPTION

The Medinol EluNIR™ Ridaforolimus Eluting Coronary Stent System (EluNIR™) is a single use device/ drug combination product composed of the following device components: the coronary stent and its delivery system, and a drug component (a formulation of ridaforolimus in a polymer coating blend). The EluNIR™ Stent System characteristics are described in **Table 1-1**.

TABLE 1-1: EluNIR™ RIDAFOROLIMUS ELUTING CORONARY STENT SYSTEM PRODUCT DESCRIPTION

AVAILABLE STENT LENGTHS (mm)	8, 12, 15, 17, 20, 24, 28, 33, 38	
AVAILABLE STENT DIAMETERS (mm)	2.25*, 2.5*, 2.75, 3.0, 3.5, 4.0	
STENT MATERIAL	A medical grade L-605 Cobalt Chromium (CoCr), annealed, ASTM F90	
DRUG COMPONENT	A coating of polymers loaded with ridaforolimus in a formulation applied to the entire surface of the stent at a dose of approximately 1.1µg/mm^2 which results in a maximum nominal drug content of 249µg on the largest stent (4.0mm x 38mm)	
DELIVERY SYSTEM WORKING LENGTH (cm)	140	
DELIVERY SYSTEM DESIGN	Single access port to inflation lumen; guidewire exit notch (RX-Port) is located 30cm from distal tip; designed for guidewires ≤ 0.014" (0.36mm)	
STENT DELIVERY SYSTEM	Expandable balloon with two radiopaque markers located on the catheter system balloon shaft to indicate balloon positioning and expanded stent length	
BALLOON INFLATION PRESSURE	Nominal pressure: For diameter 2.25mm: 8 atm (811 kPa) For diameters 2.5-4.0 mm: 10atm (1013 kPa) Rated Burst Pressure (RBP): 18atm (1824kPa)	
MINIMUM GUIDING CATHETER INNER DIAMETER	≥5F (0.056"/1.42mm)	
CATHETER SHAFT OUTER DIAMETER	Proximal	2.1F (0.69mm)
	Distal	2.7F (0.90mm) for products of 8mm - 28mm length
		2.9F (0.97mm) for products of 33mm - 38mm

* The 2.25 & 2.5 mm diameter stents for the EluNIR™ stent system are available in lengths up to 33 mm long.

1.1 DEVICE COMPONENTS DESCRIPTION

The EluNIR™ stent system device consists of a ridaforolimus eluting coronary stent component premounted onto an RX delivery system. The stents are made from a cobalt-based alloy and are coated with a drug/ polymer coating, which consists of a Poly n-Butyl Methacrylate (PBMA) polymer, a CarboSil® 20 55D polymer and the active pharmaceutical ingredient (API) ridaforolimus. The EluNIR™ delivery system provides a means of delivering the stent through the coronary vasculature and, once in the desired location, expands the stent through balloon inflation. The catheter has a hydrophilic coating on the outer surface of the distal shaft.

1.2 DRUG COMPONENT DESCRIPTION

The coating on the EluNIR™ stent consists of a polymer coating blend [Poly n-Butyl Methacrylate (PBMA) and CarboSil® 20 55D (inactive ingredients)], and the active pharmaceutical ingredient (API) ridaforolimus.

1.2.1 RIDAFOROLIMUS

Ridaforolimus is a tetrazole-containing rapamycin analog, a potent immunosuppressant. It is a member of the limus family of drugs, a unique, non-prodrug analog of rapamycin (sirolimus), a natural macrocyclic lactone, which is a fermentation product of Streptomyces hygroscopicus.

The molecular formula is $C_{53}H_{84}NO_{14}P$ and the molecular weight/ mass is 990.22g/mol.
Figure 1-1 illustrates the chemical structure of ridaforolimus.

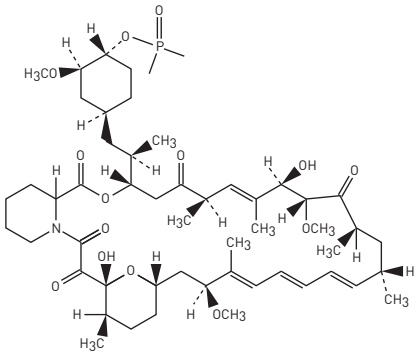

FIGURE 1-1: CHEMICAL STRUCTURE OF RIDAFOROLIMUS

1.2.2 INACTIVE INGREDIENTS (POLYMER COATING BLEND)

The EluNIR™ stent is coated with a polymer blend consisting of CarboSil® 20 55D and Poly n-Butyl Methacrylate (PBMA), (55%w/45%w respectively), combined with the drug ridaforolimus.

1.2.2.1 POLY (N-BUTYL METHACRYLATE)

Poly (n-Butyl Methacrylate) is a biocompatible homopolymer of n-Butyl Methacrylate from the Acrylic family. The molecular formula is $[CH_2CH_2(CH_3)(COOC_4H_9)]$ and the molecular weight/mass is 220-380g/mol. The polymer chemical structure is shown in **Figure 1-2**.

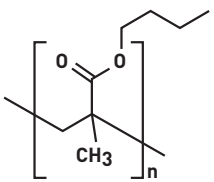

FIGURE 1-2: CHEMICAL STRUCTURE OF POLY (N-BUTYL METHACRYLATE) (PBMA)

1.2.2.2 CarboSil® 20 55D UR THERMOPLASTIC SILICONE-POLYCARBONATE-URETHANE WITH SME®

CarboSil® 20 55D is a medical grade copolymer.

The molecular formula is: SiC_3H_9O-(SiC_2H_6)p-SiC_2H_6-Ri-O-{$[(C_{15}H_{12}N_2O_2)$-O-$(RjCO_3)$n-Rj]O}x-$C_{15}H_{12}N_2O_2$-$[C_4H_8O_2$- $C_{15}H_{12}N_2O_2]$y}z-$SiC_2H_6O_2$Ri-$([SiC_2H_6)pSiC_3H_9$

The molecular weight/mass is ≥200g/mol.

The polymer chemical structure is shown in **Figure 1-3**.

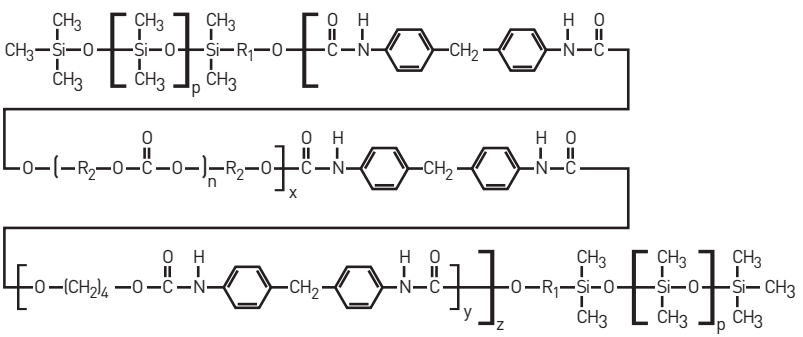

FIGURE 1-3: CHEMICAL STRUCTURE OF CarboSil® 20 55D

1.2.3 PRODUCT MATRIX AND RIDAFOROLIMUS CONTENT

TABLE 1-2: EluNIR™ PRODUCT MATRIX AND NOMINAL TOTAL DOSE OF RIDAFOROLIMUS (µg) PER NOMINAL STENT LENGTH AND DIAMETER

PRODUCT CATALOG NUMBER	NOMINAL EXPANDED STENT ID (mm)	NOMINAL UNEXPANDED STENT LENGTH (mm)	NOMINAL RIDAFOROLIMUS CONTENT (µg)
LUN225L08US	2.25	8	34
LUN225L12US	2.25	12	50
LUN225L15US	2.25	15	66
LUN225L17US	2.25	17	74
LUN225L20US	2.25	20	89
LUN225L24US	2.25	24	104
LUN225L28US	2.25	28	120
LUN225L33US	2.25	33	144
LUN250R08US	2.5	8	34
LUN250R12US	2.5	12	50
LUN250R15US	2.5	15	66
LUN250R17US	2.5	17	74
LUN250R20US	2.5	20	89
LUN250R24US	2.5	24	104
LUN250R28US	2.5	28	120
LUN250R33US	2.5	33	144
LUN275R08US	2.75	8	46
LUN275R12US	2.75	12	67
LUN275R15US	2.75	15	87
LUN275R17US	2.75	17	98
LUN275R20US	2.75	20	119
LUN275R24US	2.75	24	140
LUN275R28US	2.75	28	160
LUN275R33US	2.75	33	192
LUN275R38US	2.75	38	223
LUN300R08US	3.0	8	46
LUN300R12US	3.0	12	67
LUN300R15US	3.0	15	87
LUN300R17US	3.0	17	98
LUN300R20US	3.0	20	119
LUN300R24US	3.0	24	140
LUN300R28US	3.0	28	160
LUN300R33US	3.0	33	192
LUN300R38US	3.0	38	223
LUN350R08US	3.5	8	53
LUN350R12US	3.5	12	83
LUN350R15US	3.5	15	98
LUN350R17US	3.5	17	113
LUN350R20US	3.5	20	128
LUN350R24US	3.5	24	158
LUN350R28US	3.5	28	189
LUN350R33US	3.5	33	219
LUN350R38US	3.5	38	249
LUN400R08US	4.0	8	53
LUN400R12US	4.0	12	83
LUN400R15US	4.0	15	98
LUN400R17US	4.0	17	113
LUN400R20US	4.0	20	128
LUN400R24US	4.0	24	158
LUN400R28US	4.0	28	189
LUN400R33US	4.0	33	219
LUN400R38US	4.0	38	249

2 INDICATIONS FOR USE

The EluNIR™ Ridaforolimus Eluting Coronary Stent System is indicated for improving coronary luminal diameter in patients with symptomatic heart disease due to *de novo* lesions ≤36mm in length in native coronary arteries with reference diameters of 2.25mm to 4.25mm.

3 CONTRAINDICATIONS

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

- Patients who cannot receive recommended antiplatelet and/ or anticoagulation therapy.
- Patients judged to have a lesion which prevents complete inflation of an angioplasty balloon or proper placement of the stent or delivery system.
- Patients with hypersensitivity or allergies to aspirin, heparin, clopidogrel, ticlopidine, drugs such as ridaforolimus or similar drugs, the polymer or its individual components CarboSil® 20 55D (Thermoplastic Silicone-Polycarbonate-Urethane) and Poly n-Butyl Methacrylate (PBMA), cobalt, chromium, nickel, molybdenum or contrast media.

4 WARNINGS

- Please ensure that the inner package has not been opened or damaged as this would indicate that the sterile barrier has been breached.
- The use of this device carries the associated risks of thrombosis, vascular complications and/ or bleeding events.
- This product should not be used in patients who are not likely to comply with the recommended antiplatelet therapy.

5 PRECAUTIONS

5.1 GENERAL PRECAUTIONS

- Stent implantation should only be performed by physicians who have received appropriate training.
- Subsequent restenosis may require repeat dilatation of the arterial segment containing the stent. Long-term outcomes following repeat dilatation of the stent is presently not well characterized.
- Risks and benefits should be considered in patients with severe reaction to contrast agent.
- Patients with known hypersensitivity to the product components [stent substrate, polymer(s), drug substanc]) may suffer an allergic reaction to this implant.
- Do not expose or wipe the product with organic solvents such as alcohol.
- Care should be taken to control the guiding catheter tip during stent delivery, deployment and balloon withdrawal. Before withdrawing the stent delivery system, visually confirm complete balloon deflation by fluoroscopy to avoid guiding catheter movement into the vessel and subsequent arterial damage.
- Stent thrombosis is a low-frequency event that is frequently associated with myocardial infarction (MI) or death.
- When DES are used outside the specified Indications for Use, patient outcomes may differ from the results observed in the EluNIR™ clinical trials.
- Compared to use within the specified Indications for Use, the use of DES in patients and lesions outside of the labeled indications, including more tortuous anatomy, may have an increased risk of adverse events, including stent thrombosis, stent embolization, MI or death.

5.2 ANTIPLATELET REGIMEN

5.2.1 PRE-PROCEDURE ANTIPLATELET MEDICATION

All EluNIR™ clinical trial protocols mandated loading doses of antiplatelet medications to be administered pre-procedure in all patients, as shown below in **Table 5-1**.

TABLE 5-1: PRE-PROCEDURE ANTIPLATELET MEDICATION

AGENT	INSTRUCTIONS
CLOPIDOGREL	A loading dose of clopidogrel 600mg must be administered between 0 to 24 hours prior to PCI or immediately post PCI in patients without ACS (administration prior to PCI is preferred in all patients). For subjects who are already on chronic clopidogrel therapy of 75mg (≥5 days), a loading dose of 300mg is required in all patients between 0 to 24 hours prior to PCI or immediately post PCI in patients without ACS (administration prior to PCI is preferred in all patients).
OR PRASUGREL	At sites in countries where prasugrel is approved and is commercially available, a loading dose of prasugrel 60mg can be used in place of clopidogrel at the investigator's discretion. For subjects already on chronic prasugrel therapy of 10mg a day (5mg if >75 years old or <60kg weight) for ≥5 days, a loading dose of prasugrel 60mg is recommended at the investigator's discretion.
OR TICAGRELOR	At sites in countries where ticagrelor is approved and commercially available, a loading dose of ticagrelor 180mg can be used in place of clopidogrel at the investigator's discretion. For subjects already on chronic ticagrelor therapy of 90mg twice daily for ≥5 days, a loading dose of ticagrelor 180mg is recommended at the investigator's discretion.
ASPIRIN	All subjects already taking daily chronic aspirin therapy will receive 75-325mg or dose per standard hospital practice before the procedure. Subjects not already taking daily chronic aspirin therapy will receive 300 to 325mg (or dose per standard hospital practice) at least two hours and preferably 24 hours before the procedure.

In the BIONICS trial the pre or baseline procedure compliance to ADP antagonists (clopidogrel/ prasugrel/ ticagrelor) was 99.2% and for Aspirin 98.2%.

In the NIREUS trial the pre or baseline procedure compliance to ADP antagonists (clopidogrel/ prasugrel/ ticagrelor) was 94.7% and for Aspirin 98.3%

5.2.2 POST PROCEDURE ANTIPLATELET MEDICATION

All subjects were required to have clopidogrel/ prasugrel/ ticagrelor administration for a minimum of 6 months (12 months recommended) according to national guidelines (such as the ACCF/ AHA/ SCAI recommendations for PCI) and standard of care, as well as aspirin administration indefinitely, unless an intervening medical necessity occurs, such as severe bleeding.

Dual antiplatelet therapy should have been instituted post procedure in all patients, as shown below in **Table 5-2**:

TABLE 5-2: POST PROCEDURE ANTIPLATELET MEDICATION

AGENT	INSTRUCTIONS
CLOPIDOGREL	All subjects who receive a study stent will be treated for a minimum of six months with clopidogrel (75mg/day), according to national guidelines and standard of care. At least 12 months following stent implantation is recommended per the AHA/ ACCF/ SCAI joint guidelines for percutaneous coronary intervention.
OR PRASUGREL	At sites in countries where prasugrel is approved and is commercially available, prasugrel 10mg/day can be used in place of clopidogrel at the investigator's discretion. In subjects weighing less than 60kg or who are over 75 years old, prasugrel should be given at a dose of 5mg/day.
OR TICAGRELOR	At sites in countries where ticagrelor is approved and is commercially available, ticagrelor 90mg bid can be used in place of clopidogrel at the investigator's discretion.
ASPIRIN	Subjects with no aspirin resistance, allergy, or bleeding risk should continue on aspirin (minimum of 75mg/day and up to 162mg/day or dose per standard hospital practice) indefinitely, in accordance with the AHA/ ACC/ SCAI PCI recommendations. Low-dose aspirin (<100mg/day) is preferred in all patients. Higher doses should not be used with ticagrelor.

In the BIONICS trial the compliance to ADP antagonists (clopidogrel/ prasugrel/ ticagrelor) at 6 months was 71.8% and to Aspirin 94.3%. At the 12-month follow-up the compliance to ADP antagonists (clopidogrel/ prasugrel/ ticagrelor) was 76.4% and to Aspirin 93.6%.

In the NIREUS trial the compliance to ADP antagonists (clopidogrel/ prasugrel/ ticagrelor) at 6 months was 96% and to Aspirin 96.7%.

5.2.3 ORAL ANTIPLATELET THERAPY

Dual antiplatelet therapy (DAPT) using a combination treatment of aspirin with a P2Y12 platelet inhibitor after percutaneous coronary intervention (PCI), has been shown to reduce the risk of stent thrombosis and ischemic cardiac events, but increases the risk of bleeding complications.

The optimal duration of DAPT (specifically a P2Y12 platelet inhibitor in addition to aspirin) following DES implantation is unknown, and DES thrombosis may still occur despite continued therapy. It is very important that the patient is compliant with the post-procedural antiplatelet recommendations.

Per ACC/ AHA/ SCAI guidelines, a daily aspirin dose of 81mg is recommended indefinitely after PCI. A P2Y12 platelet inhibitor should be given daily for at least 6 months in stable ischemic heart disease patients and for at least 12 months in patients with acute coronary syndrome (ACS).

In patients at higher risk of bleeding, DAPT discontinuation may be reasonable after 3 months in stable patients or 6 months in ACS patients.

Decisions about duration of DAPT are best made on an individual basis and should integrate clinical judgment, assessment of the benefit/risk ratio and patient preference.

Premature discontinuation or interruption of prescribed antiplatelet medication could result in a higher risk of stent thrombosis, MI or death.

Prior to PCI, if premature discontinuation of antiplatelet therapy is anticipated, physicians should carefully evaluate with the patient whether a DES and its associated recommended DAPT regimen is the appropriate PCI choice.

Following PCI, if elective noncardiac surgery or dental treatment requiring suspension of antiplatelet therapy is considered, the risks and benefits of the procedure should be weighed against the possible risk associated with interruption of antiplatelet therapy.

Patients who require premature DAPT discontinuation should be carefully monitored for cardiac events. At the discretion of the patient's treating physician(s), the antiplatelet therapy should be restarted as soon as possible.

5.3 USE OF MULTIPLE STENTS

A patient's exposure to drug and polymers is proportional to the number and total length of implanted stents. In the EluNIR™ pivotal clinical trials, total stenting length per subject was limited up to 100mm.

NOTE Implanting two stents of different composition in an overlapped configuration creates the potential for accelerated corrosion. The EluNIR™'s performance has not been assessed in an overlapped stent configuration using stents of different composition.

5.4 USE IN CONJUNCTION WITH OTHER PROCEDURES

The safety and effectiveness of using mechanical atherectomy devices (directional atherectomy catheters, rotational atherectomy catheters) or laser angioplasty catheters in conjunction with EluNIR™ stent implantation have not been established.

5.5 BRACHYTHERAPY

EluNIR™ stent safety and effectiveness have not been evaluated in patients with prior target lesion or in-stent restenosis-related brachytherapy.

5.6 USE IN SPECIAL POPULATIONS

5.6.1 PREGNANCY

Pregnancy Category C, see section 6.5 - *Drug Information, Pregnancy*. The EluNIR™ stent has not been tested in pregnant women or in men intending to father children. Effects on the developing fetus have not been studied. Effective contraception should be initiated before implanting an EluNIR™ stent and continued for one year after implantation. While there is no contraindication, the risks and reproductive effects are unknown at this time.

5.6.2 LACTATION

See section 6.6 - *Drug Information, Lactation*. A decision should be made whether to discontinue nursing prior to stent implantation, considering the importance of the stent to the mother.

5.6.3 GENDER

A gender analysis was not pre-specified in the EluNIR™ pivotal clinical studies. However, post-hoc analyses were conducted to evaluate gender-specific outcomes associated with the EluNIR™ stents in the BIONICS clinical study; see section 9.1.1 - *EluNIR™ Clinical Trials, Gender-Based Analysis of the BIONICS Clinical Trial.*

5.6.4 ETHNICITY

Insufficient subject numbers prevent ethnicity-related analyses of the EluNIR™ stent's safety and effectiveness.

5.6.5 PEDIATRIC USE

The safety and effectiveness of the EluNIR™ stent in pediatric subjects have not been established.

5.6.6 GERIATRIC USE

The EluNIR™ clinical studies did not have an upper age limit. Of the 1919 patients in the BIONICS trial, 904 were age 65 or older—46.9% (449/958) in the EluNIR™ arm and 47.3% (455/961) in the Resolute arm. Of the 302 patients in the NIREUS trial, 121 were age 65 or older—36.8% (74/201) in the EluNIR™ arm and 46.5% (47/101) in the Resolute arm.

5.7 LESION/ VESSEL CHARACTERISTICS

The safety and effectiveness of the EluNIR™ stent have not been established for subject populations with the following clinical settings:

- Occlusive thrombus and/ or a thrombus requiring thrombectomy in a target vessel
- Coronary artery reference vessel diameters < 2.25mm or > 4.25mm
- Unprotected left main lesions ≥30% or planned unprotected left main intervention
- Ostial LAD or LCX lesions (stenting of any diseased segment within 5mm of the unprotected left main coronary artery)
- Planned stenting of lesions in more than two (2) major coronary arteries (i.e., two of LAD, LCX, RCA) and their respective branches (the Ramus Intermedius is defined as a branch of the LCX)
- Planned stenting of more than two lesions per vessel (two lesions separated by less than 10mm and which can be covered by a single stent are considered as one lesion)
- Bifurcation lesions with planned dual stent implantation
- Recent acute myocardial infarction (STEMI)
- Stenting of lesions due to DES restenosis

5.8 DRUG INTERACTIONS

See section 6.3 - *Drug Information, Drugs Interactions*

Several drugs are known to affect ridaforolimus metabolism, and other drug interactions may also occur. Ridaforolimus is known to be a substrate for both cytochrome P4503A4 (CYP3A4) and P-glycoprotein (PgP). Ridaforolimus absorption and subsequent elimination may be influenced by drugs that affect these pathways. Formal drug interaction studies have not been performed with the EluNIR™ stent because of limited systemic exposure to ridaforolimus eluted from the EluNIR™ stent (see section 6.2 - *Drug Information, Pharmacokinetics*). Therefore, due consideration should be given to the potential for both systemic and local drug interactions in the vessel wall, when deciding to place the EluNIR™ stent in a patient taking a drug with known interaction with ridaforolimus, or when deciding to initiate therapy with such a drug in a patient who has recently received a EluNIR™ stent.

5.9 MAGNETIC RESONANCE IMAGING (MRI) SAFETY INFORMATION

Non-clinical testing has demonstrated that the EluNIR™ stent is MR Conditional for single and overlapping stents up to 120mm. A patient with an implant from this family can be scanned safely in an MR system meeting the following conditions:

- Static magnetic field of 1.5-Tesla and 3-Tesla, only
- Maximum spatial gradient magnetic field of 3,000-gauss/cm (30-T/m) or less
- Maximum MR system reported, whole body averaged specific absorption rate (SAR) of 2-W/kg in the Normal Operating Mode

Under the scanning conditions defined, the EluNIR™ stent is expected to produce a maximum temperature rise of 3°C after 15 minutes of continuous scanning (i.e., per pulse sequence).

In non-clinical testing, the image artifact caused by the EluNIR™ stent extends approximately 8mm from this EluNIR™ stent when imaged with a gradient echo pulse sequence and a 3-Tesla MR system. The artifact obscures the device lumen.

5.10 STENT HANDLING

- **Each stent is for single use only**. Do not re-sterilize or reuse this device. Note the "Use by" (expiration) date on the product label.
- **The foil pouch is not a sterile barrier**. The inner header bag pouch within the foil pouch is the sterile barrier. **Only the contents of the inner sterilization pouch should be considered sterile. The outside surface of the inner sterilization pouch is NOT sterile.**
- **Do not remove the stent from the delivery system**. Removal may damage the stent and/ or lead to stent embolization. These components are intended to perform together as a system.
- The delivery system should not be used in conjunction with other stents.
- Special care must be taken not to handle or disrupt the stent on the balloon, particularly during delivery system removal from packaging, placement over the guide wire and advancement through the rotating hemostatic valve adapter and guiding catheter hub. Manipulation, e.g. rolling the mounted stent with your fingers, may loosen the stent from the delivery system balloon and cause dislodgment.
- When loading the catheter on the guidewire, provide adequate support to shaft segments.
- **Do not manipulate, touch or handle the stent with your fingers**, which may cause coating damage, contamination or stent dislodgement from the delivery balloon.

Use only the appropriate balloon inflation media (see section 12.4.3 - *Operator's Instructions, Delivery System Preparation*). Do not use air or any gaseous medium to inflate the balloon as this may cause uneven expansion and difficulty in stent deployment.

5.11 STENT PLACEMENT

5.11.1 STENT PREPARATION

- **Do not prepare or pre-inflate the delivery system prior to stent deployment other than as directed**. Use the balloon purging technique described in section 12.4.3 - *Operator's Instructions, Delivery System Preparation*.
- **While introducing the delivery system into the vessel, do not induce negative pressure on the delivery system**. This may cause dislodgement of the stent from the balloon.
- Use guiding catheters with lumen sizes suitable to accommodate the introduction of the stent delivery system (see section 1.1 - *Product Description, Device Components Description*).

5.11.2 STENT IMPLANTATION

- The decision to pre-dilate the lesion with an appropriate sized balloon should be carefully based on patient and lesion characteristics. The EluNIR™ pivotal clinical trials demonstrated that in a real-world setting, direct stenting with EluNIR™ stents in single-lesion treated patients who did not have a staged procedure was safe.
- Do not expand the stent if it is not properly positioned in the vessel (see section 5.12 - *Precautions, Stent System Removal*).
- 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 (Coronary artery bypass grafting (CABG), further dilatation, placement of additional stents or other).
- When treating multiple lesions, consider stenting the distal lesion first, followed by stenting of the proximal lesion. Stenting in this order obviates the need to cross the proximal stent when placing the distal stent and reduces the chances of dislodging the proximal stent.
- Additional expansion of a deployed stent may cause a flow limiting dissection. This may be treated by implantation of another stent. When multiple stents are implanted, the ends should overlap slightly.
- Stent placement may compromise side branch patency.
- **Do not exceed Rated Burst Pressure (RBP) as indicated on product label**. See **Table 13-1**. Balloon pressures should be monitored during inflation. Applying pressures higher than those specified on the product label may result in a ruptured balloon with possible arterial damage and dissection. The stent inner diameter should approximate 1.1 times the reference diameter of the vessel.
- An unexpanded stent may be retracted into the guiding catheter one time only. An unexpanded stent should not be reintroduced into the artery once it has been pulled back into the guiding catheter. Subsequent movement in and out through the distal end of the guiding catheter should not be performed, as the stent may be damaged when retracting the undeployed stent back into the guiding catheter.
- Should **resistance** be felt **at any time** during either lesion access or withdrawal of the pre-stent implantation, the system should be removed per instructions in section 5.12 - *Precautions, Stent System Removal.*
- Stent retrieval methods (e.g., using 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.
- Although the stent delivery system balloon is strong enough to expand the stent without rupture, a circumferential balloon tear distal to the stent and prior to complete stent expansion, could cause the balloon to become tethered to the stent, requiring surgical removal. In case of balloon rupture, it should be withdrawn and, if necessary, a new dilatation catheter exchanged over the guidewire to complete the expansion of the stent.
- Ensure the stented area covers the entire lesion/ dissection site and that no gaps exist between stents.
- Do not torque the catheter more than one (1) full turn.
- If reinserting the catheter, flush the guidewire lumen before reinsertion.

5.12 STENT SYSTEM REMOVAL

5.12.1 STENT DELIVERY SYSTEM REMOVAL PRIOR TO STENT DEPLOYMENT

If removal of a stent system is required prior to stent deployment, ensure that the guiding catheter is coaxially positioned relative to the stent delivery system and cautiously withdraw the stent delivery system into the guiding catheter. Should unusual resistance be felt at any time when withdrawing the stent towards the guiding catheter, the stent delivery system and the guiding catheter should be removed as a single unit. This should be done under direct visualization with fluoroscopy.

5.12.2 WITHDRAWAL OF THE STENT DELIVERY SYSTEM FROM THE DEPLOYED STENT

1. Deflate the balloon by pulling negative on the inflation device. Larger and longer balloons will take more time (up to 30 seconds) to deflate than smaller and shorter balloons. Confirm balloon deflation under fluoroscopy and wait 10 - 15 seconds longer.
2. Position the inflation device to "negative" or "neutral" pressure.
3. Stabilize guiding catheter position just outside coronary ostium and anchor in place. Maintain guide wire placement across stent segment.
4. Gently remove the stent delivery system with slow and steady pressure.
5. Confirm adequate sealing of the hemostatic valve.

If during withdrawal of the delivery system resistance is encountered, use the following steps to improve balloon rewrap:

- Re-inflate the balloon up to nominal pressure.
- Repeat steps 1 through 5 above.

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

If it is necessary to retain guidewire position for subsequent artery/lesion access, leave the guidewire in place and remove all other system components.

Stent retrieval methods (i.e., additional wires, snares, and/ or forceps) may result in additional trauma to the coronary vasculature and/ or the vascular access site. Complications may include, but are not limited to bleeding, hematoma, pseudoaneurysm or vessel perforation.

5.13 POST PROCEDURE

- When crossing a newly deployed stent with an intravascular ultrasound (IVUS) catheter, a coronary guidewire, an optical coherence tomography (OCT) catheter, a balloon catheter or delivery system, exercise care to avoid disrupting the stent placement, apposition and geometry.
- Post-dilatation: All efforts should be made to assure that the stent is not under-dilated. If the deployed stent is not fully apposed to the vessel wall, the stent may be expanded further with a larger diameter balloon that is slightly shorter (about 2mm) than the stent. The post-dilatation can be done using a low-profile, high pressure, non-compliant balloon catheter. The balloon should not extend outside of the stented region. Do not use the stent delivery balloon for post-dilatation.
- Antiplatelet therapy should be administered post-procedure (see section 5.2 - *Precautions, Antiplatelet Regimen*). Patients who require early discontinuation of antiplatelet therapy (e.g., secondary to active bleeding) should be monitored carefully for cardiac events. At the discretion of the patient's treating physician, the antiplatelet therapy should be restarted as soon as possible.
- If the patient requires imaging, see section 5.9 - *Precautions, Magnetic Resonance Imaging (MRI) Safety Information.*

6 DRUG INFORMATION

6.1 MECHANISM OF ACTION

The mechanism by which the EluNIR™ stent inhibits neointimal growth as seen in pre-clinical and clinical studies has not been established. At the cellular level, ridaforolimus inhibits growth factor-stimulated cell proliferation. At the molecular level, ridaforolimus forms a complex with the cytoplasmic protein FKBP-12 (FK 506 Binding Protein). This complex binds to and interferes with FKBP-12 Rapamycin Associated Protein (FRAP), also known as mammalian target of rapamycin (mTOR), leading to inhibition of cell metabolism, growth and proliferation by arresting the cell cycle at the late G1 stage.

6.2 PHARMACOKINETICS

The pharmacokinetics (PK) of ridaforolimus delivered from the EluNIR™ Stent has been determined in 12 patients with coronary artery disease after stent implantation in the BIONICS-PK Trial (CIP Number: BIONICS-PK-001), see section 7.3 - *Overview of Clinical Studies, BIONICS-PK Trial*. The dose of ridaforolimus was calculated per stent unit surface area and the key pharmacokinetic parameters determined from these patients are provided in **Table 6-1**.

TABLE 6-1: WHOLE BLOOD RIDAFOROLIMUS PHARMACOKINETICS PARAMETERS IN PATIENTS FOLLOWING EluNIR™ STENT IMPLANTATION

Parameter*	Total Dose	Cmax	Cmax/D	Tmax	Tlast[a]	Clast[a]	AUC0-tlast	AUC0-tlast/D	AUC0-t∞	AUC0-t∞/D	t1/2	CL/F
	(µg)	(ng/mL)	(ng/mL/µg)	(hr)	(hr)	(ng/mL)	(hr*ng/mL)	(hr*ng/mL/µg)	(hr*ng/mL)	(hr*ng/mL/µg)	(hr)	(L/hr/kg)
LOW DOSE GROUP (<130 µg), N=6												
Mean	114	0.438	0.00399	1.92	371	0.0500	51.0	0.456	62.6	0.563	161	2.36
SD	19.7	0.147	0.00154	1.21	185	0.000	34.2	0.285	38.3	0.324	61.2	1.48
CV%	17.3	33.5	38.7	63.0	49.8	0.000	67.1	62.3	61.2	57.5	37.9	62.8
MID DOSE GROUP (130 TO 300 µg), N=4												
Mean	154	0.565	0.00369	1.51	719	0.0500	104	0.682	124	0.814	280	1.24
SD	9.00	0.115	0.000754	0.583	4.97	0.000	14.6	0.102	13.6	0.0973	29.2	0.169
CV%	5.9	20.3	20.5	38.6	0.7	0.000	14.0	14.9	11.0	12.0	10.4	13.6
HIGH DOSE GROUP (>300 µg), N=2												
Mean	442	1.75	0.00396	2.00	718	0.153	311	0.702	374	0.844	285	1.19
SD	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
CV%	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

a. The first value that was BQL after the Cmax was assigned a value equal to one-half the lower limit of quantitation and subsequent BQL was assigned a value of zero (0).

*** EVALUATED/ CALCULATED PARAMETERS:**

$AUC_{0-t\infty}$ (hour*ng/mL)	AUC computed from time zero extrapolated to infinity.
$AUC_{0-tlast}$ (hour*ng/mL)	AUC computed from time zero to the time of the last positive Y value.
CL/F (mL/min/kg or L/hr/kg)	Total body clearance. CL = Dose / $AUC_{0-\infty}$
C_{last} (ng/mL)	The concentration of the latest time point.
C_{max} (ng/mL)	The maximum concentration observed.
$t_{1/2}$ (hr)	Apparent terminal half-life = ln (2) / λ_Z.
λ_Z (1/hr)	First order rate constant associated with the apparent terminal (log-linear) elimination phase. This is estimated via linear regression of time vs. log concentration.
T_{last} (hr)	The latest time point.
Rsq	Goodness of fit statistic for the terminal elimination phase.
T_{max} (hr)	The time of peak concentration.

Six subjects received a mean total dose of 114µg, four subjects received a mean total dose of 154µg and two subjects received a mean total dose of 442µg. Whole blood Cmax increased with increasing dose and ranged from 0.438 to 1.75 ng/mL by dose-group, with individual mean Cmax ranging from 0.308 to 1.80ng/mL. Tmax was similar among dose groups ranging from 1.51 to 2.00 hrs, with individual Tmax ranging from 0.500 to 4.03 hrs. All AUC estimates increased with increasing dose and were slightly supra-proportional. The apparent t½ of ridaforolimus for individual subject t½ ranged from 75.3 to 311 hrs across all dose levels, with mean t½ values of 161 hrs for the low-dose group, 280 hrs for the mid-dose group and 285 hrs for the high-dose group. The apparent systemic clearance was evaluated with individual subject CL/F ranging from 0.875 to 5.16 L/hr/kg across all dose levels, with mean CL/F values of 2.36 L/hr/kg for the low-dose group, 1.24 L/hr/kg for the mid-dose group and 1.19 L/hr/kg for the high-dose group.

6.3 DRUG INTERACTIONS

Ridaforolimus is extensively metabolized by the cytochrome P4503A4 (CYP3A4) in the liver,and is a substrate for the counter transporter P-glycoprotein (PgP). Therefore, absorption and subsequent elimination of ridaforolimus may be influenced by drugs that also affect CYP3A4 and PgP pathways. Formal drug interaction studies have not been performed with the EluNIR™ stent because of limited systemic exposure to ridaforolimus eluted from EluNIR™ (see section 6.2 - *Drug Information, Pharmacokinetics*). However, consideration should be given to the potential for both systemic and local drug interactions in the vessel wall when deciding to place the EluNIR™ stent in a subject taking a drug with known interaction with ridaforolimus.

Ridaforolimus, when prescribed as an oral medication, may interact with CYP3A4/PgP inhibitors and/ or CYP3A4/PgP inducers. Medications that are strong inhibitors of CYP3A4 or PgP might reduce ridaforolimus metabolism in vivo. Hence, co-administration of strong inhibitors of CYP3A4 or PgP may increase the blood concentrations of ridaforolimus. Medications that are strong inducers of CYP3A4 or PgP might increase ridaforolimus metabolism in vivo resulting in decreased blood concentrations of ridaforolimus.

6.4 MUTAGENESIS, CARCINOGENICITY AND REPRODUCTIVE TOXICITY

6.4.1 MUTAGENESIS

The mutagenic potential of the EluNIR™ stent was evaluated in three separate assays, in bacteria and in mammalian cells. The potential to reverse mutations in S. typhimurium and E. coli strains was assessed *in vitro* in the standard Ames assay. Mouse lymphoma L5178Y/TK$^{+/-}$ cells were also used to evaluate, in vitro, the potential to induce forward mutations at the thymidine kinase (Tk) locus Lastly, the potential clastogenic effects of the EluNIR™ stent were determined in vivo using the Mouse Micronucleus Test. No evidence of mutagenic potential was observed in these studies.

6.4.2 CARCINOGENICITY

Formal carcinogenicity testing was not conducted on the EluNIR™ Stent. The carcinogenic potential of the EluNIR™ stent is minimal based on the limited period of ridaforolimus release, on the types and quantities of materials present, and on the favorable outcomes and results of the mutagenesis testing.

6.4.3 REPRODUCTIVE TOXICITY

Formal reproductive toxicity testing was not conducted on the EluNIR™ Stent. The reproductive potential of the EluNIR™ stent is minimal based on the limited period of ridaforolimus release, on the types and quantities of materials present.

6.5 PREGNANCY

Pregnancy Category C: There are no adequate and well-controlled ridaforolimus or EluNIR™ stent related studies in pregnant women.

Effects of ridaforolimus on prenatal rat development were no different than the controls (*see section 6.4 - Drug Information, Mutagenesis, Carcinogenicity and Reproductive Toxicity*). When administered at oral doses of 2.0mg/kg or above, ridaforolimus showed effects on rat development limited to increased incidence of skeletal alterations, slight body weight changes and fetal survival, without any specific toxic potential. The described effects were observed at ridaforolimus dosage approximately 200-fold the maximum dose allowed per the protocols of the EluNIR™ clinical studies (maximal patient exposure to ridaforolimus: 100mm of stenting = 657µg).

Effective contraception should be initiated before implanting an EluNIR™ stent and continued for one year post-implantation. The EluNIR™ stent should be used in pregnant women only if potential benefits outweigh potential risks.

The safety of the EluNIR™ stent has not been evaluated in males intending to father children.

6.6 LACTATION

It is unknown whether ridaforolimus is distributed in human milk. Also, ridaforolimus pharmacokinetic and safety profiles have not been determined in infants. Consequently, mothers should be advised of potential serious adverse reactions to ridaforolimus in nursing infants. Prior to EluNIR™ stent implantation, decisions should be made regarding whether to discontinue nursing or conduct an alternate percutaneous coronary intervention procedure.

7 OVERVIEW OF CLINICAL STUDIES

The EluNIR™ clinical program aims at assessing the safety and efficacy of the EluNIR™ Ridaforolimus eluting coronary stent system for its intended use of improving coronary luminal diameter in patients with symptomatic heart disease due to *de novo* lesions ≤36mm in length in native coronary arteries with reference diameters of 2.25mm to 4.25mm.

The 2422-patient program is composed of the pivotal BIONICS clinical trial, the BIONICS-PK clinical trial and supplementary studies, NIREUS, BIONICS-Israel, BIONICS 38mm and BIONICS Small Vessles. See details below:

7.1 THE BIONICS TRIAL

BIONICS was a prospective, multi-center, single-blind, two-arm, 1:1 randomized clinical trial with 1919 enrolled patients with a wide spectrum of PCI indications (stable angina as well as ACS, including subacute STEMI (>24 hours since first hospital presentation), "more comers" concept. The trial was aimed at assessing the EluNIR™ stent in comparison (non-inferiority design) to the Medtronic Resolute stent. It was performed at 76 sites in the US, Canada, Europe and Israel.

The primary clinical endpoint was target lesion failure (TLF) at one year, with an additional angiographic endpoint of in-stent late lumen loss evaluated in a sub-set of 202 (158 evaluable) patients at 13 months. Among the patients of this subset, 155 (111 evaluable) were also evaluated by intravascular ultrasound (IVUS) at baseline and at the 13-month follow-up.

Randomization was stratified by the presence of medically treated diabetes vs. no medically treated diabetes, acute coronary syndrome (ACS) vs. no ACS (i.e., stable coronary artery disease) and by site.

Clinical follow-up was performed at 30 days, 6 months and annually at 1–5 years post procedure.

A. Periprocedural MIs are included per SCAI definitions as follows:

- In patients with normal baseline CK-MB: The peak CK-MB measured within 48 hours of the procedure rises to ≥10x the local laboratory ULN, or to ≥5x ULN with new pathologic Q-waves in ≥2 contiguous leads or new persistent LBBB, OR in the absence of CK-MB measurements and a normal baseline cTn, a cTn (I or T) level measured within 48 hours of the PCI rises to ≥70x the local laboratory ULN, or ≥35x ULN with new pathologic Q-waves in ≥2 contiguous leads or new persistent LBBB.
- In patients with elevated baseline CK-MB (or cTn) in whom the biomarker levels are stable or falling: The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above from the most recent pre-procedure level.
- In patients with elevated CK-MB (or cTn) in whom the biomarker levels have not been shown to be stable or falling: The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above plus new ST-segment elevation or depression plus signs consistent with a clinically relevant MI, such as new onset or worsening heart failure or sustained hypotension.

THE BIONICS POST APPROVAL STUDY

The 2-5 years follow-up visits data of the BIONICS study is considered as a Post-Approval study and fulfills the requirement for the long-term safety and effectiveness of the EluNIR Stent System in the United States (US), presenting additional information about BIONICS patients up to 5 years follow-up. The follow-up period was completed.

7.2 NIREUS TRIAL

The **NIREUS** clinical trial was aimed at assessing the angiographic outcomes of the EluNIR™ in comparison to the Resolute stent. It was performed at 31 sites in Europe and Israel.

NIREUS was a prospective, multi-center, single-blind, two-arm, 2:1 randomized clinical trial (2 EluNIR™ : 1 Resolute) encompassing 305 patients with a wide spectrum of percutaneous coronary intervention (PCI) indications (stable angina as well as acute coronary syndrome [ACS], including subacute ST segment elevation myocardial infarction [STEMI]).

Randomization was stratified by the presence of medically treated diabetes vs. no medically treated diabetes and by site.

The primary endpoint was angiographic in-stent late loss at 6 months. Clinical follow-up was performed at 30 days, 6 months and annually at 1–5 years post procedure. Study follow-up was completed.

7.3 BIONICS-PK TRIAL

The study is a prospective, multicenter, single-arm, observational study involving two centers in the US.

Twelve (12) consecutive patients referred for PCI or possible PCI with suspected or proven coronary artery disease were screened and consented. Patients with ACS were not eligible. At least 30% (4 subjects) received more than one stent or a sufficiently long stent so that the total implanted stent dose is >1.5 times the ridaforolimus dose of the workhorse EluNIR™ stent (3.0x17mm).

For each patient, a total of up to 14 blood samples were collected at the following time points: immediately prior to the first stent implant as time 0, at 10 and 30 minutes, and at 1, 2, 4, 8, 12, 24±6, 48±12, 72±12, 168±36 hours (7 days), 336±36 hours (14 days) and 720±36 hours (30 days) after the first EluNIR™ stent implantation. Whole blood concentration of ridaforolimus was determined.

7.4 BIONICS-ISRAEL TRIAL

BIONICS-Israel was a prospective, multi-center, single-arm, open-label clinical trial conducted at 3 sites in Israel, with 58 enrolled patients undergoing a wide spectrum of PCI indications (stable angina as well as ACS, including subacute STEMI (>24 hours since first hospital presentation), "more comers" concept. Clinical follow-up was performed at 30 days. Follow-up by phone was performed at 6 months and 1 year post procedure.

The trial aimed to assess the safety and efficacy of the EluNIR™ with the modified delivery system. The primary clinical endpoint was acute device success in the target lesion, as determined by the Angiographic Core Laboratory. Study follow-up was completed.

7.5 BIONICS 38MM TRIAL

BIONICS 38mm Trial was a prospective, multi-center, single-arm, open label clinical trial conducted at 7 sites in Israel, with 50 enrolled patients undergoing PCI for angina (stable or unstable), silent ischemia (in absence of symptoms a visually estimated target lesion diameter stenosis of ≥70%, a positive non-invasive stress test or FFR ≤0.80 must be present), NSTEMI and recent STEMI with attempted implantation of 38mm EluNIR™ stent, to further assess the safety and efficacy of long (38mm) Ridaforolimus Eluting Stent - EluNIR™.

The primary endpoint was a combined efficacy and safety endpoint: Device success as determined by the Angiographic Core Lab (ACL) with no 30 day MACE.

The clinical Follow-up was performed at 30 days, 6 months and 1 year post-procedure. Study follow-up was completed.

7.6 BIONICS SMALL VESSELS TRIAL

BIONICS Small Vessels Trial was a prospective, multi-center, single-arm, open label clinical trial conducted at 9 sites in Israel, with 81 enrolled patients undergoing PCI for angina (stable or unstable), silent ischemia (in absence of symptoms a visually estimated target lesion diameter stenosis of ≥70%, a positive non-invasive stress test, or FFR ≤0.80 must be present), NSTEMI, and recent STEMI (>24 hours from initial presentation and stable) with attempted implantation of a 2.25mm diameter EluNIR™ stent.

The primary endpoints were a combined early efficacy and safety endpoint: MACE at 30 days for all enrolled patients; and a combined late efficacy and safety endpoint: Target Lesion Failure (TLF) at 6 months evaluated for the first 50% of patients enrolled.

The Clinical follow-up was performed at 30 days. Follow up by phone was performed at 6 months and at 1 year after the procedure for all patients.

TABLE 7-1: SUMMARY OF EluNIR™ CLINICAL TRIALS PROGRAM

PARAMETER	BIONICS	NIREUS	BIONICS PK	BIONICS ISRAEL	BIONICS 38mm	BIONCS SMALL VESSELS
STUDY TYPE	Prospective, multi-center, single-blind, two-arm, 1:1 randomized study	Prospective, multi-center, single-blind, two-arm, 2:1 randomized study	Prospective, multi-center, single-arm, observational study	Prospective, multi-center, single-arm, open-label study	Prospective, multi-center, single-arm, open-label clinical trial.	prospective, multi-center, single-arm, open label clinical trial.
NUMBER OF PATIENTS ENROLLED	1919	302	12	58	50	81
SPECIFIC LESION CRITERIA	Lesion located in a native coronary artery or bypass graft conduit with visually estimated diameter of ≥2.5mm to ≤4.25mm, a diameter stenosis of ≥70%	Single de novo lesion in a native coronary artery with an estimated diameter of ≥2.5mm to ≤4.25mm, a diameter stenosis of ≥70%	Lesion located in a native coronary artery or bypass graft conduit with visually estimated diameter of ≥2.5mm to ≤4.25mm, a diameter stenosis of ≥70%	Lesion located in a native coronary artery or bypass graft conduit with visually estimated diameter of ≥2.5mm to ≤4.25mm, a diameter stenosis of ≥70%	lesion(s) must be located in a native coronary artery or bypass graft conduit with visually estimated diameter of ≥2.75 mm to ≤4.25 mm, a diameter stenosis of ≥70%	Lesion(s) must be located in a native coronary artery or bypass graft conduit with visually estimated diameter of ≥2.25 mm to ≤2.5 mm, a diameter stenosis of ≥70%
PRODUCT USED	Single use device/drug combination product on a Rapid Exchange Coronary delivery system	Single use device/drug combination product on a Rapid Exchange Coronary delivery system	Single use device/drug combination product on a Rapid Exchange Coronary delivery system	Single use device/drug combination product on a Rapid Exchange Coronary delivery system	Single use device/drug combination product on a Rapid Exchange Coronary delivery system	Single use device/drug combination product on a Rapid Exchange Coronary delivery system
PRIMARY STUDY END POINT	TLF at 12 months	In Stent Late Lumen Loss at 6 months	Pharmacokinetic Parameters See section 7.3 - *BIONICS-PK Trial*.	Acute Device Success (post-procedure)	Combined efficacy and safety endpoint: Device success as determined by the Angiographic Core Lab (ACL) with no 30 day MACE. Device success is defined as achievement of a final in-stent residual diameter stenosis of <30% (by QCA), using the EluNIR™ 38mm stent only and without a device malfunction. MACE is defined as the composite of cardiac death, any MI, or ischemia-driven TLR.	1. combined early efficacy and safety endpoint: MACE at 30 days for all enrolled patients. MACE is defined as the composite of cardiac death, any MI, or ischemia-driven TLR. 2. Combined late efficacy and safety endpoint: Target Lesion Failure (TLF) at 6 months (evaluated for the first 50% of patients enrolled). TLF is defined as the composite of cardiac death, target vessel-related myocardial infarction, or ischemia-driven target lesion revascularization.
NUMBER OF OUS INVESTIGATIONAL SITES	37	31	None	3	7	9
NUMBER OF US INVESTIGATIONAL SITES	39	None	2	None	0	0
ANTIPLATELET THERAPY (POST-PROCEDURE) *For pre-procedure see section 5.2.1- Pre-procedure Antiplatelet Medication*	Aspirin indefinitely and Clopidogerl (for 6-12 months) or Prasugrel or Ticagrelor	Aspirin indefinitely and Clopidogerl (for 6-12 months) or Prasugrel or Ticagrelor	Aspirin indefinitely and Clopidogerl (at least 12 months) or Prasugrel or Ticagrelor	Aspirin indefinitely and Clopidogerl (for 6-12 months) or Prasugrel or Ticagrelor	Post procedure – Aspirin indefinitely and Clopidogrel (for 6-12 months) or Prasugrel or Ticagrelor	Post Procedure: Aspirin indefinitely and Clopidogrel (for 6-12 months) or Prasugrel or Ticagrelor
FOLLOW-UP	30-Day: clinical follow-up	30-Day: clinical follow-up	30-Day: clinical follow-up (in-clinic or telephone visit)	30-Day: clinical follow-up	30-day: Clinical follow up	30-day: Clinical follow up
	6-month: clinical follow-up	6-Month: Angiographic (for all patients) and clinical follow-up	6-month: clinical follow-up (in-clinic or telephone visit)	6-month: clinical follow-up (by phone)	6-month: Clinical follow up (by phone)	6 month: Clinical follow-up (by phone)
	1-Year: clinical follow-up	1-5-year: clinical follow-up	1-Year: clinical follow-up	1-Year: clinical follow-up (by phone)	1-Year: Clinical follow up (by phone)	1 Year: clinical follow up (by phone)
	13-month: Angiographic follow-up in up to 200 patients (and up to 100 patients with IVUS)		2-5 Year: clinical follow-up (in-clinic or telephone visit)			
	The 2-5 years follow-up phase of the BIONICS study is considered the Post Approval Study in the US					

8 ADVERSE EVENTS

8.1 OBSERVED ADVERSE EVENTS

Principal adverse event information is derived from the pivotal BIONICS and NIREUS trials and is shown in **Table 8-1** and **Table 8-2**.

TABLE 8-1: BIONICS TRIAL: PRINCIPAL ADVERSE EVENTS FROM POST-PROCEDURE TO 1-YEAR

EVENT	STATISTIC	EluNIR™ (N=958)	RESOLUTE (N=961)
IN-HOSPITAL EVENTS			
TLF[1]	% (n/N)	2.3%(22/958)	2.7%(26/961)
MACE[2]	% (n/N)	2.5%(24/958)	2.8%(27/961)
TVF[3]	% (n/N)	2.3%(22/958)	2.7%(26/961)
ALL-CAUSE MORTALITY	% (n/N)	0.3%(3/958)	0.0%(0/961)
Cardiovascular Death	% (n/N)	0.3%(3/958)	0.0%(0/961)
Cardiac Death	% (n/N)	0.3%(3/958)	0.0%(0/961)
Vascular Death	% (n/N)	0.0%(0/958)	0.0%(0/961)
Non-Cardiovascular Death	% (n/N)	0.0%(0/958)	0.0%(0/961)
MI	% (n/N)	2.3%(22/958)	2.7%(26/961)
Q-wave	% (n/N)	0.3%(3/958)	0.2%(2/961)
Non Q-wave	% (n/N)	2.0%(19/958)	2.5%(24/961)
TARGET VESSEL MI	% (n/N)	2.1%(20/958)	2.6%(25/961)
Q-wave	% (n/N)	0.3%(3/958)	0.2%(2/961)
Non Q-wave	% (n/N)	1.8%(17/958)	2.4%(23/961)
CLINICALLY DRIVEN REVASCULARIZATION	% (n/N)	0.4%(4/958)	0.3%(3/961)
CLINICALLY DRIVEN TLR	% (n/N)	0.1%(1/958)	0.2%(2/961)
CLINICALLY DRIVEN TVR, NON-TL	% (n/N)	0.1%(1/958)	0.0%(0/961)
DEFINITE/PROBABLE STENT THROMBOSIS (ARC)	% (n/N)	0.1%(1/958)	0.1%(1/961)
POST PROCEDURE EVENTS			
30-day TLF[1]	KM Estimate %(n)	2.6%(25)	3.2%(31)
30-day TVF[3]	KM Estimate %(n)	2.9%(28)	3.4%(33)
30-day MACE[2]	KM Estimate %(n)	3.0%(29)	3.5%(34)
6-Month TLF[1]	KM Estimate %(n)	3.5%(33)	4.2%(40)
6-Month TVF[3]	KM Estimate %(n)	4.1%(39)	5.1%(49)
6-Month MACE[2]	KM Estimate %(n)	4.3%(41)	5.3%(51)
12 - Month TLF (Primary Endpoint)[4]	% (n/N)	5.4%(50/926)	5.4%(50/930)
12 MONTH EVENTS			
MACE[2]	KM Estimate %(n)	6.8%(63)	6.6%(63)
TVF[3]	KM Estimate %(n)	7.1%(66)	6.3%(60)
ALL-CAUSE MORTALITY	KM Estimate %(n)	1.2%(11)	1.0%(10)
Cardiovascular Death	KM Estimate %(n)	0.6%(6)	0.6%(6)
Cardiac Death	KM Estimate %(n)	0.5%(5)	0.2%(2)
Vascular Death	KM Estimate %(n)	0.1%(1)	0.4%(4)
Non-Cardiovascular Death	KM Estimate %(n)	0.5%(5)	0.4%(4)
MI	KM Estimate %(n)	4.6%(43)	4.8%(46)
Q-wave	KM Estimate %(n)	0.5%(5)	0.5%(5)
Non Q-wave	KM Estimate %(n)	4.0%(38)	4.3%(41)
TARGET VESSEL MI	KM Estimate %(n)	3.2%(30)	3.2%(31)
Q-wave	KM Estimate %(n)	0.5%(5)	0.5%(5)
Non Q-wave	KM Estimate %(n)	2.8%(26)	2.7%(26)
CLINICALLY DRIVEN REVASCULARIZATION	KM Estimate %(n)	7.7%(70)	5.9%(55)
CLINICALLY DRIVEN TLR	KM Estimate %(n)	3.2%(28)	2.3%(22)
CLINICALLY DRIVEN TVR, NON-TL	KM Estimate %(n)	2.3%(22)	0.7%(7)
DEFINITE/PROBABLE STENT THROMBOSIS (ARC)[4]	% (n/N)	0.4%(4/921)	0.8%(7/927)

Each Event is confirmed by adjudication
Periprocedural MIs are included per SCAI criteria

1. Target Lesion Failure (TLF; the composite rate of cardiac death, target vessel MI or clinically driven TLR)
2. Major Adverse Cardiac Events (MACE; the composite rate of cardiac death, any MI or clinically driven TLR)
3. Target Vessel Failure (TVF; the composite rate of all-cause death, target vessel related MI or clinically driven TVR)
4. Subjects with appropriate follow up (≥335 days post procedure) and subjects with an event up to 1 year are included in the denominator. Events are included up to the end of the 365 day visit window (+14 days).

TABLE 8-2: NIREUS TRIAL: EluNIR™ PRINCIPAL ADVERSE EVENTS FROM POST-PROCEDURE TO 1-YEAR

EVENT	STATISTIC	EluNIR™ (N=201)	RESOLUTE (N=101)
IN-HOSPITAL EVENTS			
TLF[1]	% (n/N)	0.5%(1/201)	2.0%(2/101)
MACE[2]	% (n/N)	0.5%(1/201)	2.0%(2/101)
TVF[3]	% (n/N)	0.5%(1/201)	2.0%(2/101)
ALL-CAUSE MORTALITY	% (n/N)	0.0%(0/201)	0.0%(0/101)
Cardiovascular Death	% (n/N)	0.0%(0/201)	0.0%(0/101)
Cardiac Death	% (n/N)	0.0%(0/201)	0.0%(0/101)
Vascular Death	% (n/N)	0.0%(0/201)	0.0%(0/101)
Non-Cardiovascular Death	% (n/N)	0.0%(0/201)	0.0%(0/101)
MI	% (n/N)	0.5%(1/201)	2.0%(2/101)
Q-wave	% (n/N)	0.0%(0/201)	0.0%(0/101)
Non Q-wave	% (n/N)	0.5%(1/201)	2.0%(2/101)
TARGET VESSEL MI	% (n/N)	0.5%(1/201)	2.0%(2/101)
Q-wave	% (n/N)	0.0%(0/201)	0.0%(0/101)
Non Q-wave	% (n/N)	0.5%(1/201)	2.0%(2/101)
CLINICALLY DRIVEN REVASCULARIZATION	% (n/N)	0.0%(0/201)	0.0%(0/101)
CLINICALLY DRIVEN TLR	% (n/N)	0.0%(0/201)	0.0%(0/101)
CLINICALLY DRIVEN TVR, NON-TL	% (n/N)	0.0%(0/201)	0.0%(0/101)
DEFINITE/ PROBABLE STENT THROMBOSIS (ARC)	% (n/N)	0.0%(0/201)	0.0%(0/101)
POST PROCEDURE EVENTS (KAPLAN-MEIER ESTIMATE %(n))			
30-day TLF[1]	%(n)	1%(2)	2%(2)
30-day TVF[3]	%(n)	1%(2)	2%(2)
30- day MACE[2]	%(n)	1%(2)	2%(2)
6-Month TLF[1]	%(n)	2.5%(5)	4%(4)
6-Month TVF[3]	%(n)	4.5%(9)	4%(4)
6-Month MACE[2]	%(n)	3.5%(7)	4%(4)
12-Month TLF[1]	%(n)	3.4%(6)	7%(7)
12-Month MACE[2]	%(n)	4.3%(8)	8%(7)
12-Month TVF[3]	%(n)	7.5%(14)	10%(10)
12-Month All-Cause Mortality	%(n)	2.1%(4)	0.0%(0)
12-Month Cardiovascular Death	%(n)	0.5%(1)	0.0%(0)
12-Month Cardiac Death	%(n)	0.5%(1)	0.0%(0)
12-Month Vascular Death	%(n)	0.0%(0)	0.0%(0)
12-Month Non-Cardiovascular Death	%(n)	1.6%(3)	0.0%(0)
12-Month MI	%(n)	2%(4)	3%(3)
12-Month Q-wave	%(n)	0.5%(1)	0.0%(0)
12-Month Non Q-wave	%(n)	2%(4)	3%(3)
12-Month Target Vessel MI	%(n)	1%(2)	3%(3)
12-Month Q-wave	%(n)	0.5%(1)	0.0%(0)
12-Month Non Q-wave	%(n)	1%(2)	3%(3)
12-Month Clinically Driven Revascularization	%(n)	12%(23)	12.9%(13)
12-Month Clinically Driven TLR	%(n)	2.9%(5)	4.0%(4)
12-Month Clinically Driven TVR, Non-TL	%(n)	3.0%(6)	4.0%(4)
12-Month Definite/Probable Stent Thrombosis (ARC)	%(n)	0.5%(1)	0.0%(0)

Each Event is confirmed by adjudication

1. Target Lesion Failure (TLF; the composite rate of cardiac death, target vessel MI or clinically driven TLR)
2. Major Adverse Cardiac Events (MACE; the composite rate of cardiac death, any MI or clinically driven TLR)
3. Target Vessel Failure (TVF; the composite rate of all-cause death, target vessel related MI or clinically driven TVR)

Primary: Occurs in the target lesion or margins after baseline procedure. Secondary: Occurs after revascularization (TLR, TVR or non-TVR)

8.2 STENT THROMBOSIS DEFINITIONS

TABLE 8-3: ARC DEFINITION, CIRCULATION 2007; 115:2344-51

TIMING	Acute	≤ 24 hours post stent implantation
	Subacute	> 24 hours to 30 days post stent implantation
	Late	> 30 days to 1 year post stent implantation
	Very late	> 1 year post stent implantation
TYPE	Primary	Occurs in target lesion or margins after baseline procedure
	Secondary	Occurs after revascularization (TLR, TVR or nonTVR)
CATEGORY	Definite	Definite stent thrombosis is confirmed by either angiographic or pathologic analysis
	Probable	Probable stent thrombosis is considered to have occurred after intracoronary stenting for either: • any unexplained death within the first 30 days, unless that patient had baseline procedure for ST elevation MI • any MI, irrespective of time after baseline procedure, that is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause"
	Possible	Possible stent thrombosis is considered to have occurred with any unexplained death from 30 days after intracoronary stenting until end of trial follow-up

8.3 POTENTIAL ADVERSE EVENTS

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the EluNIR™ Ridaforolimus Eluting Coronary Stent System.

Adverse events (in alphabetical order) which may be associated with percutaneous coronary and treatment procedures, where coronary stents are used in native coronary arteries include, but are not limited to:

- Access site complications*
- Acute myocardial infarction
- Allergic reaction or hypersensitivity to stent components or contrast media
- Aneurysm
- Angina pectoris
- Anxiety
- Bleeding complications which may require transfusions or surgical repair
- Need for CABG- emergent or non-emergent
- Cardiac arrhythmias
- Cardiac failure
- Cardiac tamponade
- Cardiac shock
- Coronary artery complications**
- Death
- Delayed endothelialization
- Distal emboli
- Endocarditis
- Failure to deliver the stent to the intended site
- Fever or pyrogenic reactions
- Hypertension
- Hypotension
- Infections
- Myocardial ischemia
- Nausea and vomiting
- Palpitations
- Perforation of the heart or great vessels
- Pericardial effusion
- Pulmonary failure
- Renal failure
- Stent compression
- Stent misplacement/ migration/ embolization
- Stent thrombosis
- Stroke/ Cerebrovascular Accident (CVA)/ Transient Ischemic Attack (TIA)
- Vasovagal reaction
- Ventricular fibrillation
- Vessel spasm
- Volume overload

* Includes arteriovenous fistula, hematoma, infection, nerve injury, pain, peripheral ischemia, phlebitis, pseudoaneurysm
** Includes abrupt closure, dissection, embolism, injury, perforation, plaque rupture/ shift, restenosis, rupture, spasm, thrombosis, total occlusion

Patient exposure to ridaforolimus is directly related to the total surface area of stents implanted. The actual side effects/ complications that may be associated with the use of ridaforolimus in the setting of drug eluting stents (DES) are not fully known.

The adverse events that have been associated with the intravenous injection of ridaforolimus in humans are based on experience with the drug in phase I oncology based studies conducted by Merck Sharp & Dohme Corp. and Ariad Pharmaceuticals Inc. where there is systemic exposure in concentrations that are 150 times greater than foreseeable with the EluNIR™ stent.

Potential adverse events (AEs) and adverse drug events (ADEs) for systemic exposure of ridaforolimus include but are not limited to:

- Anemia
- Anorexia
- Alopecia
- Aspartate Aminotransferase increased
- Blood Creatine phosphokinase
- Blood Alkaline Phosphatase increased
- Constipation
- Dehydration
- Diarrhea
- Dysgeusia
- Dermatitis acneiform
- Febrile neutropenia
- Fatigue
- Hyperglycemia
- Hypertriglyceridemia
- Hypokalaemia
- Hypercholesterolaemia
- Hypophosphataemia
- Leukopenia
- Mucosal inflammation
- Nausea
- Nail disorder
- Pneumonia
- Pneumonitis
- Pyrexia
- Pruritus
- Paraesthesia
- Renal failure acute
- Rash
- Stomatitis
- Thrombocytopenia
- Vomiting
- Weight decrease

There may be other potential adverse events that are unforeseen at this time.

For the specific adverse events that occurred in the clinical studies, please see section 8.1 - *Adverse Events, Observed Adverse Events.*

9 EluNIR™ CLINICAL TRIALS

The 2422-patient program is composed of the pivotal BIONICS clinical trial, the BIONICS-PK clinical trial and supplementary studies, NIREUS, BIONICS-Israel and BIONICS 38mm and BIONICS Small Vessels.

Core laboratories enabled standardized and objective analysis of the data.

9.1 BIONICS CLINICAL TRIAL

BIONICS was a pivotal clinical trial designed to demonstrate the non-inferiority of the EluNIR™ stent to the Resolute stent; it was conducted at 76 sites in the United States, Canada, Europe and Israel.

PRIMARY OBJECTIVE: To demonstrate clinical and angiographic non-inferiority for the EluNIR™ in comparison to the Resolute Zotarlimus-Eluting Stent.

CONCLUSIONS: The EluNIR™ stent system was clinically non-inferior to the Resolute stent system for the treatment of coronary artery disease due to lesions in vessels with reference diameters of 2.5 to 4.25mm, and met the primary endpoint for TLF.

DESIGN: This was a prospective, multi-center, single-blind, two-arm, 1:1 randomized clinical trial (EluNIR™: Resolute), Randomization was stratified by the presence of medically treated diabetes vs. no medically treated diabetes, acute coronary syndrome (ACS) vs. no ACS (i.e., stable coronary artery disease) and by site. Lesions planned to be treated were declared and recorded at the time of randomization. Planned staged procedures, if necessary, were declared immediately post procedure.

Clinical follow-up was performed at 30 days, 6 months and 1 to 5 years post randomization. The trial also included an angiographic and IVUS sub studies, with the first 202 consecutive consenting subjects (158 evaluable) at participating North American sites undergoing angiographic follow-up at 13 months after enrollment and the first 155 of these subjects (111 evaluable) undergoing IVUS at baseline and at 13 months following randomization.

The BIONICS Clinical trial was supervised by an independent Data Safety Monitoring Board (DSMB). A dedicated medical monitor reviewed the safety data on an ongoing basis. An independent Clinical Events Committee (CEC) adjudicated all potential clinically significant and relevant cardiac events data.

THE BIONICS POST APPROVAL STUDY: The 2-5 years follow-up visits data of the BIONICS study is considered the Post-Approval Study for the EluNIR™ and fulfills the requirement for the long-term safety and effectiveness of the EluNIR Stent System in the United States (US), presenting additional information about BIONICS patients up to 5 years follow-up. The follow-up period was completed.

DEMOGRAPHICS: Study arms were equivalent regarding baseline characteristics, with the exception of a higher percentage of males in the Resolute treatment group compared to the EluNIR™ treatment group (78.3% EluNIR™, 81.9% Resolute). Lesion characteristics at baseline (measured by the angiographic core lab) were well matched between treatment groups, with the exception of a higher proportion of left main target lesions (1.1% EluNIR™, 0.4% Resolute) and severe calcifications (13.3% EluNIR™, 10.5% Resolute) in the EluNIR™ treatment group.

The demographics and baseline characteristics and risk factors are presented in **Table 9-1**.

TABLE 9-1: BIONICS CLINICAL TRIAL - DEMOGRAPHICS, RISK FACTORS AND BASELINE ANGIOGRAPHIC CHARACTERISTICS

PARAMETER	STATISTIC	EluNIR™ (N=958) (No of lesions=1276) (No of vessels=1142)	RESOLUTE (N=961) (No of lesions=1277) (No of vessels=1157)	OVERALL (N=1919) (No of lesions=2553) (No of vessels=2299)
BASELINE DEMOGRAPHICS				
Age	N	958	961	1919
	Mean(StdDev)	63.7(10.2)	63.1(10.3)	63.4(10.3)
	Median(Q1,Q3)	64.0(57.0,70.0)	64.0(56.0,71.0)	64.0(56.0,70.0)
GENDER				
Male	% (n/N)	78.3%(750/958)	81.9%(787/961)	80.1%(1537/1919)
Female	% (n/N)	21.7%(208/958)	18.1%(174/961)	19.9%(382/1919)
Body Mass Index (kg/m2)	N	958	961	1919
	Mean(StdDev)	29.1(5.0)	29.0(5.2)	29.1(5.1)
	Median(Q1,Q3)	28.5(25.7,31.9)	28.3(25.5,31.9)	28.4(25.6,31.9)
BASELINE RISK FACTORS				
ACUTE CORONARY SYNDROME				
Yes	% (n/N)	40.7%(390/958)	38.7%(372/961)	39.7%(762/1919)
DIABETES				
Yes	% (n/N)	32.8%(314/958)	32.3%(310/961)	32.5%(624/1919)
Controlled by:				
Insulin	% (n/N)	29.0%(91/314)	29.0%(90/310)	29.0%(181/624)
Oral Medication	% (n/N)	61.5%(193/314)	59.7%(185/310)	60.6%(378/624)
Diet / Other	% (n/N)	9.6%(30/314)	11.3%(35/310)	10.4%(65/624)
HYPERLIPIDEMIA				
Yes	% (n/N)	80.4%(759/944)	78.1%(744/953)	79.2%(1503/1897)
Medically Treated	% (n/N)	89.3%(678/759)	90.2%(671/744)	89.8%(1349/1503)
HYPERTENSION				
Yes	% (n/N)	72.4%(687/949)	74.0%(704/951)	73.2%(1391/1900)
Medically Treated	% (n/N)	95.2%(654/687)	95.3%(671/704)	95.3%(1325/1391)
FAMILY HISTORY OF PREMATURE CORONARY DISEASE				
Yes	% (n/N)	39.1%(330/843)	40.5%(337/833)	39.8%(667/1676)
HISTORY OF ANGINA PECTORIS				
Yes	% (n/N)	53.8%(515/958)	53.0%(509/961)	53.4%(1024/1919)
CCS: Class I	% (n/N)	11.4%(57/499)	8.2%(41/497)	9.8%(98/996)
CCS: Class II	% (n/N)	39.3%(196/499)	41.0%(204/497)	40.2%(400/996)
CCS: Class III	% (n/N)	35.9%(179/499)	36.8%(183/497)	36.3%(362/996)
CCS: Class IV	% (n/N)	13.4%(67/499)	13.9%(69/497)	13.7%(136/996)
PREVIOUS MI				
Yes	% (n/N)	31.1%(298/958)	30.5%(293/961)	30.8%(591/1919)
Previous PCI	% (n/N)	38.8%(372/958)	38.2%(367/961)	38.5%(739/1919)
Target Vessel treated	% (n/N)	8.1%(78/958)	7.8%(75/961)	8.0%(153/1919)
BASELINE RISK FACTORS				
Target Lesion Treated	% (n/N)	4.6%(44/958)	4.1%(39/961)	4.3%(83/1919)
PREVIOUS CABG				
Yes	% (n/N)	8.8%(84/958)	9.6%(92/961)	9.2%(176/1919)
Target Vessel	% (n/N)	35.7%(30/84)	53.3%(49/92)	44.9%(79/176)
Non-Target Vessel	% (n/N)	64.3%(54/84)	46.7%(43/92)	55.1%(97/176)
PREVIOUS CVA				
Yes	% (n/N)	2.6%(25/958)	2.5%(24/961)	2.6%(49/1919)
PREVIOUS TIA				
Yes	% (n/N)	2.1%(20/958)	1.8%(17/961)	1.9%(37/1919)
LESION CHARACTERISTICS				
Target Lesion Vessel	N	1276	1277	2553
LAD	% (n/N)	40.7%(519/1276)	39.7%(507/1277)	40.2%(1026/2553)
RCA	% (n/N)	32.0%(408/1276)	32.2%(411/1277)	32.1%(819/2553)
Circumflex	% (n/N)	24.4%(311/1276)	25.1%(320/1277)	24.7%(631/2553)
Left Main	% (n/N)	1.1%(14/1276)	0.4%(5/1277)	0.7%(19/2553)
LESION TYPE				
B2/C	% (n/N)	57.5%(733/1275)	58.9%(752/1277)	58.2%(1485/2552)
Severe Calcification	% (n/N)	13.3%(169/1272)	10.5%(134/1274)	11.9%(303/2546)
Bifurcation	% (n/N)	28.6%(365/1276)	29.1%(371/1277)	28.8%(736/2553)
Ostial	% (n/N)	6.0%(77/1276)	6.1%(78/1277)	6.1%(155/2553)
VESSEL LEVEL CHARACTERISTICS FROM QCA				
	N	1142	1157	2299
LAD	% (n/N)	41.9%(478/1142)	40.7%(471/1157)	41.3%(949/2299)
RCA	% (n/N)	31.3%(357/1142)	30.9%(358/1157)	31.1%(715/2299)
Circumflex	% (n/N)	24.3%(277/1142)	25.2%(292/1157)	24.7%(569/2299)
Left Main	% (n/N)	1.2%(14/1142)	0.4%(5/1157)	0.8%(19/2299)
SVG	% (n/N)	1.4%(16/1142)	2.7%(31/1157)	2.0%(47/2299)
PRE-PROCEDURE QCA ANALYSIS				
Lesion Length (mm)	N	1199	1219	2418
	Mean(StdDev)	17.7(10.8)	17.9(10.7)	17.8(10.8)
	95% CI	(17.1,18.3)	(17.3,18.5)	(17.4,18.2)
RVD (mm)	N	1272	1276	2548
	Mean(StdDev)	2.73(0.49)	2.74(0.49)	2.74(0.49)
	95% CI	(2.70,2.76)	(2.72,2.77)	(2.72,2.76)
Minimal Lumen Diameter (MLD)- (mm)	N	1272	1276	2548
	Mean(StdDev)	0.78(0.40)	0.81(0.40)	0.80(0.40)
	95% CI	(0.76,0.81)	(0.79,0.83)	(0.78,0.81)
%DS	N	1272	1276	2548
	Mean(StdDev)	71.5(13.4)	70.7(12.8)	71.1(13.1)
	95% CI	(70.8,72.2)	(70.0,71.4)	(70.6,71.6)

RESULTS: The presented study outcomes include primary and secondary endpoint results and long term follow up. The BIONICS primary endpoint results are presented in **Table 9-2**. The primary outcome was 5.4% in both treatment groups (95% CIs of [4.0%, 7.1%] EluNIR™ and [4.0%, 7.0%] Resolute). The primary endpoint for BIONICS was achieved, as the upper bound of the one-sided 95% CI for the risk difference (_, 1.81%) was less than the non-inferiority margin (p=0.0013 for non-inferiority).

TABLE 9-2: BIONICS CLINICAL TRIAL - PRIMARY ENDPOINT ANALYSIS OF TLF AT 1 YEAR FOR NON-INFERIORITY (PERIPROCEDURAL MI PER SCAI) CEC-ADJUDICATED - FULL ANALYSIS SET[B]

PARAMETER	STATISTIC	EluNIR™ (N=958)	RESOLUTE (N=961)	OVERALL (N=1919)	DIFFERENCE UPPER BOUND OF THE 95% CI	*p*-VALUE[1] FOR NON-INFERIORITY
PRIMARY ENDPOINT						
Target Lesion Failure	% (n/N)	5.4%(50/926[2])	5.4%(50/930[2])	5.4%(100/1856[2])	0.02% (_,1.81%)	0.0013
Cardiac Death	% (n/N)	0.5%(5/926)	0.2%(2/930)	0.4%(7/1856)		
Target Vessel MI	% (n/N)	3.2%(30/926)	3.4%(32/930)	3.3%(62/1856)		
Clinically driven TLR	% (n/N)	3.0%(28/926)	2.5%(23/930)	2.7%(51/1856)		

TLF is defined as the composite rate of cardiac death, target vessel MI or clinically driven TLR. Periprocedural MIs are included per SCAI criteria.

Only subjects with a propriate follow up (≥335 days post procedure) and subjects with a TLF event up to 1 year are included in the denominator. Subjects who died from non-cardiac reasons, withdrew consent prior to the 1-year visit window or did not have a 1-year follow-up ≥335 days post procedure (including those who were lost to follow-up) are excluded from the denominator. Events are included up to the end of the 365 day visit window (+14 days).

1. *p*-value and one-sided 95% CI for the risk difference in TLF is derived from Farrington-Manning test of non-inferiority for two binomial proportions with a non-inferiority margin of 3.3% at the one-sided 0.05 level of significance. Non-inferiority of EluNIR™ to Resolute is achieved if the upper bound of the one-sided 95% CI for the risk difference is less than the non-inferiority margin of 3.3%.

B. Periprocedural MIs are included per SCAI definitions as follows:

- In patients with normal baseline CK-MB: The peak CK-MB measured within 48 hours of the procedure rises to ≥10x the local laboratory ULN, or to ≥5x ULN with new pathologic Q-waves in ≥2 contiguous leads or new persistent LBBB, or in the absence of CK-MB measurements and a normal baseline cTn, a cTn (I or T) level measured within 48 hours of the PCI rises to ≥70x the local laboratory ULN, or ≥35x ULN with new pathologic Q-waves in ≥2 contiguous leads or new persistent LBBB.
- In patients with elevated baseline CK-MB (or cTn) in whom the biomarker levels are stable or falling: The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above from the most recent pre-procedure level.
- In patients with elevated CK-MB (or cTn) in whom the biomarker levels have not been shown to be stable or falling: The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above plus new ST-segment elevation or depression plus signs consistent with a clinically relevant MI, such as new onset or worsening heart failure or sustained hypotension.

TABLE 9-3: SUPPLEMENTAL ANALYSIS OF PRIMARY ENDPOINT ANALYSIS OF TLF AT 1 YEAR (PERIPROCEDURAL MI PER UNIVERSAL DEFINITION) - CEC ADJUDICATED - FULL ANALYSIS SET

PARAMETER	STATISTIC	EluNIR™ (N=958)	RESOLUTE (N=961)	OVERALL (N=1919)	DIFFERENCE UPPER BOUND OF THE 95% CI	RELATIVE RISK 95% CI	*p*-VALUE[1]
PRIMARY ENDPOINT							
Target Lesion Failure (TLF)	% (n/N)	6.8%(63/926)	6.6%(61/930)	6.7%(124/1856)	0.24%	1.04	0.0049
	95% CI	[5.3%,8.6%]	[5.1%,8.4%]	[5.6%,7.9%]	(-,2.20%)	(0.74,1.46)	
Cardiac Death	% (n/N)	0.5%(5/926)	0.2%(2/930)	0.4%(7/1856)			
	95% CI	[0.2%,1.3%]	[0.0%,0.8%]	[0.2%,0.8%]			
Target Vessel MI	% (n/N)	4.6%(43/926)	4.7%(44/930)	4.7%(87/1856)			
	95% CI	[3.4%,6.2%]	[3.5%,6.3%]	[3.8%,5.8%]			
Clinically driven TLR	% (n/N)	3.0%(28/926)	2.5%(23/930)	2.7%(51/1856)			
	95% CI	[2.0%,4.3%]	[1.6%,3.7%]	[2.1%,3.6%]			

Exact 95% Confidence intervals are provided around the proportion for each sample.

TLF is defined as the composite rate of cardiac death, target vessel MI or clinically driven TLR. Periprocedural.

Only subjects with appropriate follow up (≥335 days post procedure) and subjects with a TLF event up to 1 year are included in the denominator. Subjects who died from non-cardiac reasons, withdrew consent prior to the 1-year visit window or did not have a 1-year follow-up ≥335 days post procedure (including those who were lost to follow-up) are excluded from the denominator. Events are included up to the end of the 365 day visit window (+14 days).

1. *P*-value and one-sided 95% CI for the risk difference in TLF is derived from Farrington-Manning test of non-inferiority for two binomial proportions with a non-inferiority margin of 3.3% at the one-sided 0.05 level of significance. Non-inferiority of BioNIR to Resolute is achieved if the upper bound of the one-sided 95% CI for the risk difference is less than the non-inferiority margin of 3.3%.

The incidence of revascularization, Major Adverse Cardiac Events (MACE) and any type of death cases appeared to be similar between treatment arms.

The observed rates of 'any ST' occurring within 12 months+ window were 4 (0.4%) and 8 (0.9%) of the EluNIR™ and Resolute subjects, respectively. Definite/probable STs within 12 months+ window occurred in 4 EluNIR™ subjects (0.4%) and 7 Resolute subjects (0.8%). Late ST (>30 days) within 12 months+ window occurred in 0 EluNIR™ subjects (0.0%) and 3 Resolute subjects (0.3%).

Clinical results of the BIONICS Trial and follow-up data (BIONICS Post Approval) are presented in **Tables 9-4-A - 9-4-C**.

TABLE 9-4-A: BIONICS CLINICAL TRIAL RESULTS

	OUTCOMES WITHIN 30 DAYS OF BASELINE PROCEDURE (Data presented in Kaplan-Meier Estimate %[n])*			OUTCOMES OF 6 MONTHS OF BASELINE PROCEDURE (Data presented in Kaplan-Meier Estimate %[n])*		
	EluNIR™ (N=958)	RESOLUTE (N=961)	DIFFERENCE	EluNIR™ (N=958)	RESOLUTE (N=961)	DIFFERENCE
COMPOSITE EFFICACY AND SAFETY						
TLF[1]	2.6%(25)	3%(31)	0.81	3.5%(33)	4.2%(40)	0.83
TVF[3]	2.9%(28)	3.4%(33)	0.85	4.1%(39)	5.1%(49)	0.80
MACE[2]	3.0%(29)	3.5%(34)	0.85	4.3%(41)	5.3%(51)	0.80
EFFICACY						
Clinically-Driven TLR	0.5%(5)	0.5%(5)	1.00	1.4%(13)	1.5%(14)	0.94
TLR, CABG	0.0%(0)	0.1%(1)	N/A	0.1%(1)	0.1%(1)	1.01
Clinically Driven TLR, PCI	0.5%(5)	0.4%(4)	1.26	1.3%(12)	1.4%(13)	0.93
Clinically-Driven TVR, non TL	0.3%(3)	0.2%(2)	1.51	1.1%(10)	0.6%(6)	1.68
SAFETY						
All Death	0.5%(5)	0.2%(2)	2.51	0.7%(7)	0.7%(7)	1.01
Cardiac Death	0.3%(3)	0.1%(1)	3.01	0.4%(4)	0.1%(1)	4.02
Vascular Death	0.1%(1)	0.1%(1)	1.00	0.1%(1)	0.4%(4)	0.25
Non-Cardiovascular Death	0.1%(1)	0.0%(0)	N/A	0.2%(2)	0.2%(2)	1.01
MI	2.8%(27)	3.2%(31)	0.87	3.5%(33)	4.4%(42)	0.79
QMI	0.5%(5)	0.4%(4)	1.26	0.5%(5)	0.5%(5)	1.00
NQMI	2.4%(23)	2.8%(27)	0.85	3.0%(29)	3.9%(37)	0.79
Cardiovascular Death or MI	3.1%(30)	3.4%(33)	0.91	3.8%(36)	4.9%(47)	0.77
Stent Thrombosis-ARC Definite/Probable	0.4%(4)	0.4%(4)	1.00	0.4%(4)	0.6%(6)	0.67
Acute (< 1 day)	0.1%(1)	0.1%(1)	1.00	0.1%(1)	0.1%(1)	1.00
Subacute (1-30 days)	0.3%(3)	0.3%(3)	1.00	0.3%(3)	0.3%(3)	1.00
Late Stent Thrombosis (> 30 days)	N/A	N/A	N/A	0.0%(0)	0.2%(2)	N/A

TABLE 9-4-B: BIONICS CLINICAL TRIAL RESULTS (CONTINUED)[C]

PARAMETER	OUTCOMES WITHIN 12 MONTHS (≤365 DAYS) OF BASELINE PROCEDURE (Data presented in Kaplan-Meier Estimate %[n])*		
	EluNIR™ (N=958)	RESOLUTE (N=961)	DIFFERENCE
COMPOSITE EFFICACY AND SAFETY			
TLF[1]	5.4%(50)	5.1%(49)	1.02
TVF[3]	7.1%(66)	6.3%(60)	1.10
MACE[2]	6.8%(63)	6.6%(63)	1.00
EFFICACY			
Clinically-Driven TLR	3.2%(28)	2.3%(22)	1.28
TLR, CABG	0.8%(7)	0.2%(2)	3.52
TLR, PCI	2.5%(22)	2.1%(20)	1.11
Clinically-Driven TVR, Non TL	2.3%(22)	0.7%(7)	3.18
SAFETY			
All Death	1.2%(11)	1.0%(10)	1.11
Cardiac Death	0.5%(5)	0.2%(2)	2.51
Vascular Death	0.1%(1)	0.4%(4)	0.25
Non-Cardiovascular Death	0.5%(5)	0.4%(4)	1.26
MI	4.6%(43)	4.8%(46)	0.94
QMI	0.5%(5)	0.5%(5)	1.00
NQMI	4.0%(38)	4.3%(41)	0.93
Cardiovascular Death or MI	5.0%(47)	5.5%(52)	0.91
Any Stent Thrombosis	0.4%(4/921)	0.9%(8/928)	-0.4
Stent Thrombosis - ARC Definite/Probable	0.4%(4/921)	0.8%(7/927)	-0.3
Late Stent Thrombosis (≥ 30 day -1 year)	0.0%(0/920)	0.3%(3/926)	-0.3

* Proportional hazards assumption not met. Hazards ratio (95% CI) is based on a Cox model which adjusts for treatment by time interaction
1. Target Lesion Failure (TLF; the composite rate of cardiac death, target vessel MI, or clinically driven TLR)
2. Major Adverse Cardiac Events (MACE; the composite rate of cardiac death, any MI or clinically driven TLR)
3. Target Vessel Failure (TVF; the composite rate of all-cause death, target vessel related MI or clinically driven TVR)

C. Periprocedural MIs are included per SCAI definitions as follows:

- In patients with normal baseline CK-MB: The peak CK-MB measured within 48 hours of the procedure rises to ≥10x the local laboratory ULN, or to ≥5x ULN with new pathologic Q-waves in ≥2 contiguous leads or new persistent LBBB, OR in the absence of CK-MB measurements and a normal baseline cTn, a cTn (I or T) level measured within 48 hours of the PCI rises to ≥70x the local laboratory ULN, or ≥35x ULN with new pathologic Q-waves in ≥2 contiguous leads or new persistent LBBB.
- In patients with elevated baseline CK-MB (or cTn) in whom the biomarker levels are stable or falling: The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above from the most recent pre-procedure level.
- In patients with elevated CK-MB (or cTn) in whom the biomarker levels have not been shown to be stable or falling: The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above plus new ST-segment elevation or depression plus signs consistent with a clinically relevant MI, such as new onset or worsening heart failure or sustained hypotension.

TABLE 9-4-C: BIONICS CLINICAL TRIAL RESULTS (CONTINUED)[C]

PARAMETER	OUTCOMES WITHIN 2 YEARS (730 DAYS) OF BASELINE PROCEDURE (Data presented in Kaplan-Meier Estimate %[n])			OUTCOMES WITHIN 5 YEARS (1825 DAYS) OF BASELINE PROCEDURE (Data presented in Kaplan-Meier Estimate %[n])		
	EluNIR™ (N=958)	RESOLUTE (N=961)	DIFFERENCE	EluNIR™ (N=958)	RESOLUTE (N=961)	DIFFERENCE
COMPOSITE EFFICACY AND SAFETY						
TLF[1]	7.6%(72)	7.2%(68)	1.06	12.5%(116)	11.4%(106)	1.10
TVF[3]	10.6%(100)	9.6%(91)	1.11	18.8%(175)	18.0%(169)	1.05
MACE[2]	9.3%(88)	9.6%(91)	0.97	17.4%(159)	15.8%(146)	1.09
EFFICACY						
Clinically-Driven TLR	4.8%(45)	4.0%(38)	1.20	7.4%(68)	6.8%(63)	1.09
TLR, CABG	1.1%(10)	0.5%(5)	2.02	1.3%(12)	1.0%(9)	1.35
Clinically Driven TLR, PCI	4.0%(37)	3.5%(33)	1.13	6.3%(58)	6.0%(55)	1.06
Clinically-Driven TVR, non TL	3.5%(33)	1.2%(11)	3.05	6.9%(63)	3.9%(35)	1.84
SAFETY						
All Death	2.2%(21)	2.4%(23)	0.92	6.8%(62)	7.6%(70)	0.89
Cardiac Death	1.2%(11)	0.6%(6)	1.85	3.5%(32)	2.4%(21)	1.53
Vascular Death	0.1%(1)	0.5 (5)	0.2	0.1%(1)	0.6%(6)	0.17
Non-Cardiovascular Death	1.0%(9)	1.3%(12)	0.76	3.3%(29)	4.7%(43)	0.68
MI	5.3%(50)	6.6%(63)	0.79	11.0%(99)	10.3%(95)	1.04
QMI	0.6%(6)	0.6%(6)	1.00	2.0%(84)	1.3%(11)	1.47
NQMI	4.8%(45)	6.0%(57)	0.79	9.2%(84)	9.2%(86)	0.97
Cardiovascular Death or MI	6.2%(59)	7.6%(72)	0.82	13.5%(123)	12.4%(115)	1.07
Stent Thrombosis-ARC Definite/Probable	0.5%(5)	0.9%(9)	0.56	1.0%(9)	0.9%(9)	1.00
Very Late Stent Thrombosis (>1 year after stent implantation)	0.1%(1)	0.3%(3)	0.34	0.6%(5)	0.3%(3)	1.68

1. Target Lesion Failure (TLF; the composite rate of cardiac death, target vessel MI, or clinically driven TLR)
2. Major Adverse Cardiac Events (MACE; the composite rate of cardiac death, any MI or clinically driven TLR)
3. Target Vessel Failure (TVF; the composite rate of all-cause death, target vessel related MI or clinically driven TVR)

Acute success rates of the BIONICS Trial are presented in **Table 9-5**, **Table 9-6**, with a residual stenosis of ⩽50% and ⩽20%, respectively.

TABLE 9-5: BIONICS - SUMMARY OF ACUTE SUCCESS RATE DEFINED FROM ANGIOGRAPHIC CORE LAB ASSESSMENT (DS < 50% THRESHOLD) AND CEC ADJUDICATION (FULL ANALYSIS SET)

PARAMETER	STATISTIC	EluNIR™ (N=958 PATIENTS, 1285 LESIONS)	RESOLUTE (N=961 PATIENTS, 1281 LESIONS)	OVERALL (N=1919 PATIENTS, 2566 LESIONS)	DIFFERENCE
Device Success[a]	% (n/N)	98.0%(1243/1268)	99.4%(1261/1268)	98.7%(2504/2536)	-1.4
Lesion Success[b]	% (n/N)	99.9%(1257/1258)	99.8%(1262/1264)	99.9%(2519/2522)	0.1
Procedure Success[c]	% (n/N)	97.6%(929/952)	97.3%(928/954)	97.4%(1857/1906)	0.3

a. Device Success: Final in-stent residual diameter stenosis of <50% (by QCA) in the target lesion, using the assigned device only and without a device malfunction. Device success is assessed among subjects where the randomization assignment was followed. Device success is summarized across all lesions.

b. Lesion Success: Final in-stent residual diameter stenosis of <50% (by QCA) in the target lesion using any percutaneous method. Lesion success is summarized across all lesions.

c. Procedure success: Final in-stent diameter stenosis of <50% (by QCA) using the assigned device and/ or with any adjunctive devices, without the occurrence of cardiac death, Q wave or non-Q wave MI (peri procedural MIs are included according to SCAI criteria) or repeat revascularization of the target lesion during the hospital stay.

TABLE 9-6: BIONICS - SUMMARY OF ACUTE SUCCESS RATE DEFINED FROM ANGIOGRAPHIC CORE LAB ASSESSMENT (DS < 20% THRESHOLD) AND CEC ADJUDICATION (FULL ANALYSIS SET)

PARAMETER	STATISTIC	EluNIR™ (N=958 PATIENTS, 1285 LESIONS)	RESOLUTE (N=961 PATIENTS, 1281 LESIONS)	OVERALL (N=1919 PATIENTS, 2566 LESIONS)	DIFFERENCE
Device Success[a]	% (n/N)	87.7%(1112/1268)	91.3%(1158/1268)	89.5%(2270/2536)	-3.6
Lesion Success[b]	% (n/N)	89.5%(1126/1258)	91.6%(1158/1264)	90.6%(2284/2522)	-2.1
Procedure Success[c]	% (n/N)	90.0%(857/952)	90.4%(862/954)	90.2%(1719/1906)	-0.3

a. Device Success: Final in-stent residual diameter stenosis of <20% (by QCA) in the target lesion, using the assigned device only and without a device malfunction. Device success is assessed among subjects where the randomization assignment was followed. Device success is summarized across all lesions.

b. Lesion Success: Final in-stent residual diameter stenosis of <20% (by QCA) in the target lesion using any percutaneous method. Lesion success is summarized across all lesions.

c. Procedure success: Final in-stent diameter stenosis of <20% (by QCA) using the assigned device and/ or with any adjunctive devices, without the occurrence of cardiac death, Q wave or non-Q wave MI (peri procedural MIs are included according to SCAI criteria), or repeat revascularization of the target lesion during the hospital stay

The results of the Angiographic and IVUS sub-studies are presented in **Table 9-7**.

At 13 months post procedure, in the angiographic sub-study, the observed mean ± standard deviation of in-stent late loss was 0.22mm ±0.41mm for EluNIR™ and 0.23mm ± 0.39mm for Resolute. Non-inferiority of 0.0039.

TABLE 9-7: POWERED SECONDARY ENDPOINTS AT 13 MONTHS AS ASSESSED BY ANGIOGRAPHIC CORE LABS - ANGIOGRAPHIC SUB-STUDY

PARAMETER	STATISTIC	EluNIR™ (N=85 PATIENTS, 105 LESIONS)	RESOLUTE (N=73 PATIENTS, 96 LESIONS)	OVERALL (N=158 PATIENTS, 201 LESIONS)	DIFFERENCE UPPER BOUND OF THE 95% CI	*p*-VALUE[1] OF NON-INFERIORITY
In-stent Late Loss (secondary endpoint) (mm)	N	101	93	194	0.02857	0.0039
	Mean(StdDev)	0.22(0.41)	0.23(0.39)	0.23(0.40)	(,0.1314)	
	Median (Q1, Q3)	0.14(-0.02,0.29)	0.12(0.00,0.31)	0.13(-0.01,0.30)		
	Min, Max	-0.28,2.08	-0.33,1.71	-0.33,2.08		

Angiographic Sub-Study Analysis Set: All subjects in the FAS who consented for the 13-Month Angiographic sub-study and had a qualifying 13-month angiographic follow-up. Subjects whose baseline angiograms could not be analyzed by the Angiographic Core Lab are excluded from the Angiographic Sub-Study Analysis Set.

1. The estimated mean difference [one-sided 95% CI] between treatments and *p*-value is calculated from a one-way linear mixed model that accounts for the clustering effect of multiple lesions per patient. The model includes treatment as a fixed effect and patient as a random effect.

In the IVUS sub-study, the observed percent volume Neointimal Hyperplasia (NIH) was 8.10 for EluNIR™ and 8.85 for Resolute. Non-inferiority was achieved (*p*-value for non-inferiority of 0.0098). No stent fractures were reported.

TABLE 9-8: POWERED SECONDARY ENDPOINTS AT 13 MONTHS AS ASSESSED BY IVUS CORE LABS - IVUS SUB-STUDY

PARAMETER	STATISTIC	EluNIR™ (N=55 PATIENTS, 62 LESIONS)	RESOLUTE (N=56 PATIENTS, 60 LESIONS)	OVERALL (N=111 PATIENTS, 122 LESIONS)	DIFFERENCE UPPER BOUND OF THE 95% CI	*p*-VALUE[1] OF NON-INFERIORITY
Percent Neointimal Hyperplasia (secondary endpoint)	N	54	51	105	-0.34488	0.0098
	Mean(StdDev)	8.10(5.81)	8.85(7.77)	8.47(6.81)	(,2.1681)	
	Median (Q1, Q3)	6.43(3.59,11.47)	6.39(3.28,11.37)	6.39(3.59,11.37)		
	Min, Max	0.39,24.53	0.95,33.02	0.39,33.02		

IVUS Sub-Study Analysis Set: All subjects in the FAS, who consented for the 13-Month IVUS sub-study and had a qualifying 13-Month IVUS follow-up

1. The estimated mean difference [one-sided 95% CI] between treatments and *p*-value is calculated from a one-way linear mixed model that accounts for the clustering effect of multiple lesions per patient. The model includes treatment as a fixed effect and patient as a random effect

9.1.1 GENDER-BASED ANALYSIS OF THE BIONICS CLINICAL TRIAL

Cardiovascular disease is the leading cause of death for both women and men in the U.S.

The 2013 overall rate of death attributable to CVD was 222.9 per 100,000 Americans.

The death rates were 269.8 for males and 184.8 for females. For the first time since 1983, more males (402,851) died of CVD than females (398,086).

On the basis of data from NHANES 2009 to 2012 (NHLBI tabulation), an estimated 15.5 million Americans ≥20 years of age have CHD. Total CHD prevalence is 6.2% in US adults ≥20 years of age. CHD prevalence is 7.6% for men and 5.0% for women.

Based on the aforementioned data, the overall prevalence for MI is 2.8% in US adults ≥20 years of age. MI prevalence is 4.0% for men and 1.8% for women[D].

Medinol performed a post hoc evaluation of the BIONICS clinical trial for possible sex-based differences in baseline characteristics and clinical outcomes. The BIONICS trial was not designed or powered to study safety or effectiveness differences between sexes, so these analyses are considered exploratory without definitive conclusions.

Table 9-9 presents the baseline demographics, risk factors and angiographic characteristics by gender for subjects in the BIONICS trial. The clinical outcomes of the gender based analysis of the BIONICS trial until 12 months, are presented in **Table 9-10**

TABLE 9-9: BIONICS TRIAL DEMOGRAPHICS, RISK FACTORS AND BASELINE ANGIOGRAPHIC CHARACTERISTICS - GENDER BASED ANALYSIS (FULL ANALYSIS SET)

PARAMETER	MALE (N=1537)	FEMALE (N=382)	OVERALL (N=1919)
Age (Mean)	62.5 (±10.2)	67.3(±9.7)	63.4(±10.3)
BODY MASS INDEX (kg/m²)			
Acute Coronary Syndrome	40.1%(617)	38%(145)	39.7%(762)
Diabetes	31.8%(489)	35.3%(135)	32.5%(624)
Diabetes Controlled by Insulin	27.8%(136)	33.3%(45)	29%(181)
Hyperlipidemia	79.1% (1200)	79.7%(303)	79.2%(1503)
Hypertension	70.5%(1072)	83.9%(319)	73.2%(1391)
History of Angina Pectoris	52%(800)	58.6(224)	53.4%(1024)
Previous MI	32.2%(495)	25.1%(96)	30.8%(591)
Previous PCI	39.9%(613)	33%(126)	38.5%(739)
Previous CABG	9.8%(150)	6.8%(26)	9.2%(176)
Current Smoking	22.7%(349)	16%(61)	21.4%(410)
TARGET LESION VESSEL			
LAD	39.9%(830)	41.4%(196)	40.2%(1026)
RCA	31.8%(662)	33.2%(157)	32.1%(819)
Circumflex	25%(519)	23.7%(112)	24.7%(631)
Left Main	0.8%(17)	0.4%(2)	0.7%(19)
PRE-PROCEDURE QCA ANALYSIS MEAN SD			
Lesion Length (mm)	17.8 (10.7)	18.0 (10.9)	17.8(10.8)
RVD (mm)	2.76(0.49)	2.65(0.45)	2.74(0.49)
MLD (mm)	0.8 (0.40)	0.78(0.38)	0.8(0.40)
Diameter Stenosis (%DS)	71.1(13.1)	70.0(13)	71.1(13.1)

D. Mozaffarian D, Benjamin EJ, Go AS,et al. Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. Circulation. 2016 Jan 26;133(4):e38-360. doi: 10.1161/CIR.0000000000000350. Epub 2015 Dec 16

TABLE 9-10: BIONICS TRIAL CLINICAL SAFETY AND EFFECTIVENESS - GENDER BASED ANALYSIS (FULL ANALYSIS SET)

EVENT	STATISTIC	OVERALL (N=1919)	
		MALE N=1537	FEMALE N=382
TLF[1]	% (n/N)	5.3%(80)	5.1%(19)
MACE[2]	% (n/N)	6.9%(104)	5.8%(22)
TVF[3]	% (n/N)	6.6%(99)	7.2%(27)
ALL-CAUSE MORTALITY	% (n/N)	0.9%(14)	1.9%(7)
Cardiovascular Death	% (n/N)	0.5%(7)	1.3%(5)
Cardiac Death	% (n/N)	0.3%(4)	0.8%(3)
Vascular Death	% (n/N)	0.2%(3)	0.5%(2)
Non-Cardiovascular Death	% (n/N)	0.5%(7)	0.5%(2)
MI	% (n/N)	5.0%(76)	3.5%(13)
Q-wave	% (n/N)	0.4%(6)	1.0%(4)
Non Q-wave	% (n/N)	4.6%(70)	2.5%(9)
TARGET VESSEL MI	% (n/N)	3.3%(51)	2.7%(10)
Q-wave	% (n/N)	0.4%(6)	1.0%(4)
Non Q-wave	% (n/N)	3.0%(46)	1.7%(6)
CLINICALLY DRIVEN REVASCULARIZATION	% (n/N)	6.7%(100)	6.9%(25)
PCI	% (n/N)	6.2%(91)	5.9%(22)
CABG	% (n/N)	0.7%(10)	1.3%(4)
CLINICALLY DRIVEN TLR	% (n/N)	2.8%(41)	2.6%(9)
PCI	% (n/N)	2.5%(36)	1.6%(6)
CABG	% (n/N)	0.4%(6)	1.0%(3)
CLINICALLY DRIVEN TVR	% (n/N)	3.8%(56)	4.0%(14)
PCI	% (n/N)	3.4%(50)	2.7%(10)
CABG	% (n/N)	0.5%(7)	1.3%(4)
DEFINITE/PROBABLE STENT THROMBOSIS[4]	% (n/N)	0.6%(9)	0.5%(2)
Primary*	% (n/N)	0.5%(8)	0.8%(3)
Secondary**	% (n/N)	0.1%(1)	0.0%(0)

Each Event is confirmed by adjudication

1. Target Lesion Failure (TLF; the composite rate of cardiac death, target vessel MI or clinically driven TLR)
2. Major Adverse Cardiac Events (MACE; the composite rate of cardiac death, any MI or clinically driven TLR)
3. Target Vessel Failure (TVF; the composite rate of all-cause death, target vessel related MI or clinically driven TVR)
4. Subjects with appropriate follow up (≥335 days post procedure) and subjects with an event up to 1 year are included in the denominator. Events are included up to the end of the 365 days visit window (+14 days)

* Occurs in target lesion or margins after baseline procedure (Per ARC)

**Occurs after revascularization (TLR, TVR or non-TVR) (Per ARC)

9.1.2 SUBGROUP ANALYSIS OF THE PRIMARY ENDPOINT TLF AT 1 YEAR

An exploratory analysis of the primary endpoint was performed within the subgroups in order to examine the homogeneity of the treatment effect across important demographic and baseline characteristics, as presented in **Table 9-11**. There was no indication for difference in the treatment effects across these subgroups.

TABLE 9-11: SUBGROUP ANALYSES OF THE PRIMARY ENDPOINT OF TLF AT 1 YEAR (PERI-PROCEDURAL MI PER SCAI) - CEC ADJUDICATED - FULL ANALYSIS SET[E]

EVENT	STATISTIC	EluNIR™ (N=958)	RESOLUTE (N=961)	OVERALL (N=1919)
Male	%(n/N)	5.5%(40/725)	5.4%(41/762)	5.4%(81/1487)
Female	%(n/N)	5.0%(10/201)	5.4%(9/168)	5.1%(19/369)
Medically Treated Diabetes	%(n/N)	7.9%(22/277)	8.0%(21/264)	7.9%(43/541)
No Medically Treated Diabetes	%(n/N)	4.3%(28/649)	4.4%(29/666)	4.3%(57/1315)
Age≥65	%(n/N)	7.9%(34/433)	6.1%(27/440)	7.0%(61/873)
Age<65	%(n/N)	3.2%(16/493)	4.7%(23/490)	4.0%(39/983)
Acute coronary syndrome	%(n/N)	5.0%(19/380)	5.5%(20/363)	5.2%(39/743)
No acute coronary syndrome	%(n/N)	5.7%(31/546)	5.3%(30/567)	5.5%(61/1113)
Single Lesion	%(n/N)	4.5%(31/687)	4.6%(31/679)	4.5%(62/1366)
Multiple Lesion	%(n/N)	7.9%(19/239)	7.6%(19/249)	7.8%(38/488)
Single Vessel	%(n/N)	4.9%(37/752)	4.8%(35/732)	4.9%(72/1484)
Multiple Vessel	%(n/N)	6.7%(11/163)	7.6%(13/172)	7.2%(24/335)
Single Stent	%(n/N)	5.2%(36/697)	4.8%(34/714)	5.0%(70/1411)
Overlapping Stent	%(n/N)	6.1%(14/229)	7.5%(16/214)	6.8%(30/443)
LAD	%(n/N)	5.2%(24/460)	6.4%(29/456)	5.8%(53/916)
Non-LAD	%(n/N)	5.6%(26/466)	4.4%(21/472)	5.0%(47/938)

TLF is defined as the composite rate of cardiac death, target vessel MI or clinically driven TLR. Periprocedural MIs are included per SCAI criteria. Only subjects with appropriate follow up (≥ 335 days post procedure) and subjects with a TLF event up to 1 year are included in the denominator. Subjects who died from non-cardiac reasons, withdrew consent prior to the 1-year visit window or did not have a 1-year follow-up ≥335 days post procedure (including those who were lost to follow-up) are excluded from the denominator. Events are included up to the end of the 365 day visit window (+14 days).

E.Periprocedural MIs are included per SCAI definitions as follows:

- In patients with normal baseline CK-MB: The peak CK-MB measured within 48 hours of the procedure rises to ≥10x the local laboratory ULN, or to ≥5x ULN with new pathologic Q-waves in ≥2 contiguous leads or new persistent LBBB, or in the absence of CK-MB measurements and a normal baseline cTn, a cTn (I or T) level measured within 48 hours of the PCI rises to ≥70x the local laboratory ULN, or ≥35x ULN with new pathologic Q-waves in ≥2 contiguous leads or new persistent LBBB.
- In patients with elevated baseline CK-MB (or cTn) in whom the biomarker levels are stable or falling: The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above from the most recent pre-procedure level.
- In patients with elevated CK-MB (or cTn) in whom the biomarker levels have not been shown to be stable or falling: The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above plus new ST-segment elevation or depression plus signs consistent with a clinically relevant MI, such as new onset or worsening heart failure or sustained hypotension.

9.2 NIREUS CLINICAL TRIAL

NIREUS was a pivotal clinical trial designed to demonstrate the angiographic non-inferiority of the EluNIR™ stent to the Resolute stent; it was conducted at 31 sites in Europe and Israel.

PRIMARY OBJECTIVE: To demonstrate non-inferiority for the EluNIR™ in comparison to the Resolute for the primary angiographic endpoint of in-stent late lumen loss at 6 months.

CONCLUSIONS: The study met its primary endpoint. The study's result signifies that the EluNIR™ is non-inferior to the comparator stent with regards to the mean in-stent late loss at 6 months.

DESIGN: Prospective, multicenter, single blind, randomized study designed to enroll approximately 300 patients, randomized 2:1 EluNIR™ vs. Resolute.

Randomization was stratified by the presence of medically treated diabetes vs. no medically treated diabetes and by site. Lesions planned to be treated had to be declared and recorded at the time of randomization. Subjects in this study underwent coronary angiography and percutaneous coronary intervention (PCI) with stent implantation for narrowing (stenoses) in the coronary arteries using standard angiographic and stenting techniques. Both radial and femoral approaches were acceptable. Adherence to PCI guidelines issued by professional societies such as the ACCF/ AHA/ SCAI 2011 Guideline for Percutaneous Intervention was recommended.

Angiographic follow-up was performed at 6 months. Clinical follow-up was performed at 30 days, 6 months and at 1, 2, 3, 4 and 5 years post randomization.

The NIREUS Clinical trial was supervised by an independent Data Safety Monitoring Board (DSMB). A dedicated medical monitor reviewed the safety data on an ongoing basis. An independent Clinical Events Committee (CEC) adjudicated all potential clinically significant and relevant cardiac events data.

DEMOGRAPHICS: A total of 305 patients, from the Netherlands, Italy, Israel, Spain, Belgium and Poland were randomized. Two patients in the EluNIR™ arm and 1 patient in the Resolute arm were deregistered (per protocol) because the study stent was not advanced beyond the guiding catheter.

Study arms were balanced with respect to all demographic characteristics. There were no statistically significant differences between the treatment arms in any of the demographic parameters.

In the full analysis set, mean age was 61.8 (±10.1) years, 59.9% under 65 years old. The majority of subjects were males (77.5%) and most women (95.6%) were not of childbearing potential. Most of the study population was white (98.3%).

Median BMI was 27.3KG/m2 (Q1: 24.9, Q3:30.3), mean systolic blood pressure 137.2mmHg (±19.3) and mean diastolic blood pressure 78.0mmHg (±11.8).

Study arms were balanced with respect to all medical history parameters assessed; differences between the treatment arms did not reach statistical significance.

Approximately one third of the patients had a history of acute coronary syndrome and approximately one third had medically treated diabetes. Most subjects had medically treated hyperlipidemia and medically treated hypertension. Approximately half of the study population reported a history of angina pectoris. 126 subjects (41.7%) had a previous PCI, mostly non-target vessel and most were treated by stenting.

There were no subjects with a medical history of bleeding complications and the majority had no history of vascular disease or renal insufficiency.

The demographics and baseline characteristics and risk factors are presented in **Table 9-12**.

TABLE 9-12: NIREUS CLINICAL TRIAL - DEMOGRAPHICS, RISK FACTORS AND BASELINE ANGIOGRAPHIC CHARACTERISTICS

PARAMETER	STATISTIC	EluNIR™ (N=201)	RESOLUTE (N=101)	OVERALL (N=302)
BASELINE DEMOGRAPHICS				
Age	Mean(StdDev)	61.4 (9.9)	62.5 (10.4)	61.8 (10.1)
	Median(Q1,Q3)	61.0 (54.0,68.0)	63.0 (56.0,70.0)	62.0 (54.0,69.0)
GENDER				
Male	% (n/N)	77.6%(156/201)	77.2% (78/101)	77.5% (234/302)
Female	% (n/N)	22.4% (45/201)	22.8% (23/101)	22.5% (68/302)
Body Mass Index (kg/m2)	Mean(StdDev)	28.0 (4.4)	27.7 (4.0)	27.9 (4.3)
	Median(Q1,Q3)	27.2 (25.0,30.4)	27.5 (24.6,29.9)	27.3 (24.9,30.3)
BASELINE RISK FACTORS				
ACUTE CORONARY SYNDROME				
Yes	% (n/N)	30.3% (61/201)	29.7% (30/101)	30.1% (91/302)
DIABETES				
Yes	% (n/N)	26.4% (53/201)	30.7% (31/101)	27.8% (84/302)
Controlled by:				
Insulin	% (n/N)	28.3% (15/53)	29.0% (9/31)	28.6% (24/84)
Oral Medication	% (n/N)	66.0% (35/53)	61.3% (19/31)	64.3% (54/84)
Diet / Other	% (n/N)	3.8% (2/53)	9.7% (3/31)	6.0% (5/84)
HYPERLIPIDEMIA				
Yes	% (n/N)	79.2% (152/192)	84.5% (82/97)	81.0% (234/289)
Medically Treated	% (n/N)	92.1% (140/152)	90.2% (74/82)	91.5% (214/234)
HYPERTENSION				
Yes	% (n/N)	74.5% (149/200)	76.0% (76/100)	75.0% (225/300)
Medically Treated	% (n/N)	94.0% (140/149)	94.7% (72/76)	94.2% (212/225)
FAMILY HISTORY OF PREMATURE CORONARY DISEASE				
Yes	% (n/N)	29.3% (51/174)	33.7% (28/83)	30.7% (79/257)
HISTORY OF ANGINA PECTORIS				
Yes	% (n/N)	52.7% (106/201)	49.5% (50/101)	51.7% (156/302)
CCS: Class I	% (n/N)	13.3% (14/105)	10.2% (5/49)	12.3% (19/154)
CCS: Class II	% (n/N)	33.3% (35/105)	40.8% (20/49)	35.7% (55/154)
CCS: Class III	% (n/N)	35.2% (37/105)	34.7% (17/49)	35.1% (54/154)
CCS: Class IV	% (n/N)	18.1% (19/105)	14.3% (7/49)	16.9% (26/154)
PREVIOUS MI				
Yes	% (n/N)	29.9% (60/201)	32.7% (33/101)	30.8% (93/302)
Previous PCI	Yes	40.3% (81/201)	44.6% (45/101)	41.7% (126/302)
Target Vessel Treated	% (n/N)	9.9% (8/81)	8.9% (4/45)	9.5% (12/126)
Target Lesion Treated	% (n/N)	12.5% (1/8)	0.0% (0/4)	8.3% (1/12)
PREVIOUS CABG				
Yes	% (n/N)	1.5% (3/201)	1.0% (1/101)	1.3% (4/302)
Target Vessel	% (n/N)	0.0% (0/3)	0.0% (0/1)	0.0% (0/4)
PREVIOUS CVA				
Yes	% (n/N)	0.5% (1/201)	3.0% (3/101)	1.3% (4/302)
PREVIOUS TIA				
Yes	% (n/N)	2.0% (4/201)	2.0% (2/101)	2.0% (6/302)
LESION CHARACTERISTICS*		(N=172 Pt's, 206 lesions)	(N=89 Pt's, 105 lesions)	(N=261 Pt's, 311 lesions)
TARGET LESION VESSEL				
LAD	% (n/N)	39.8% (82/206)	35.2% (37/105)	38.3% (119/311)
RCA	% (n/N)	25.7% (53/206)	34.3% (36/105)	28.6% (89/311)
Circumflex	% (n/N)	34.5% (71/206)	30.5% (32/105)	33.1% (103/311)
Left Main	% (n/N)	0.0% (0/206)	0.0% (0/105)	0.0% (0/311)
LESION TYPE				
B2/C	% (n/N)	37.4% (77/206)	41.3% (43/104)	38.7% (120/310)
Severe Calcification	% (n/N)	5.9% (12/204)	6.7% (7/104)	6.2% (19/308)
Bifurcation	% (n/N)	17.5% (36/206)	13.3% (14/105)	16.1% (50/311)
Ostial	% (n/N)	0.5% (1/206)	1.9% (2/105)	1.0% (3/311)
VESSEL LEVEL CHARACTERISTICS FROM QCA		(N=200 vessels)	(N=103 vessels)	(N=303 vessels)
LAD	% (n/N)	40.5% (81/200)	35.0% (36/103)	38.6% (117/303)
RCA	% (n/N)	25.0% (50/200)	34.0% (35/103)	28.1% (85/303)
Circumflex	% (n/N)	34.5% (69/200)	31.1% (32/103)	33.3% (101/303)
Left Main	% (n/N)	0.0% (0/200)	0.0% (0/103)	0.0% (0/303)
PRE-PROCEDURE QCA ANALYSIS				
Lesion Length (mm)	N	206	104	309
	Mean (StdDev)	15.3 (7.1)	13.8 (5.8)	14.8 (6.7)
	95% CI	(14.3,16.3)	(12.7,15.0)	(14.1,15.6)
RVD (mm)	N	206	104	310
	Mean (StdDev)	2.74 (0.48)	2.75 (0.50)	2.74 (0.49)
	95% CI	(2.67,2.81)	(2.65,2.85)	(2.69,2.80)
Minimal Lumen Diameter (MLD) - (mm)	N	205	104	309
	Mean(StdDev)	0.94 (0.35)	0.94 (0.35)	0.94 (0.35)
	95% CI	(0.89,0.98)	(0.87,1.00)	(0.90,0.98)
% DS	N	205	104	309
	Mean(StdDev)	65.6 (11.6)	66.1 (10.7)	65.8 (11.3)
	95% CI	(64.1,67.2)	(64.0,68.2)	(64.5,67.1)

* The numbers representing the qualifying lesions per core lab assessment (angiographic analysis set)

RESULTS: The presented study outcomes include primary and secondary endpoint results from, up to and including the 6-month angiographic outcomes and 12-month time point for the clinical outcomes.

The NIREUS primary endpoint results are presented in **Table 9-13** The primary endpoint of the study was met and the EluNIR™ stent was found to be non-inferior to the Resolute stent for in-stent late lumen loss at 6 months (0.042 ±0.306mm vs. 0.030 ±0.308mm, p<0.0001).

There were no statistically significant differences between the EluNIR™ and Resolute in any of the angiographic secondary endpoints: in-segment late loss; follow-up percent diameter stenosis (in-stent and in-segment); binary restenosis (in-stent and in-segment); and length and patterns of angiographic restenosis.

NIREUS clinical results are presented in **Table 9-14** and **Table 9-15**. There were no statistically significant differences between the EluNIR™ and Resolute in any of the clinical endpoints, including: myocardial infarction, target lesion failure, target vessel failure or Major Adverse Cardiac Events (MACE).

There were no statistically significant differences between the treatment arms in the incidence of peri-procedural myocardial infarctions or in stent thrombosis.

TABLE 9-13: NIREUS TRIAL- PRIMARY ENDPOINT ANALYSIS COMPARISON OF IN-STENT LATE LOSS AT 6 MONTHS FOR NONINFERIORITY AT A MARGIN OF 0.20MM (ANGIOGRAPHIC ANALYSIS SET)

STATISTIC	EluNIR™ (N=172 PATIENTS, 206 LESIONS)	RESOLUTE (N=89 PATIENTS, 105 LESIONS)	OVERALL (N=261 PATIENTS, 311 LESIONS)	DIFFERENCE UPPER BOUND OF THE 97.5% CI	p-VALUE FOR NON-INFERIORITY[1]
N	206	103	309	0.00877	<0.0001
Mean (StdDev)	0.042 (0.306)	0.030 (0.308)	0.038 (0.306)	(, 0.0849)	
Median (Q1, Q3)	0.025 (-0.140, 0.180)	-0.010 (-0.150, 0.210)	0.000 (-0.150, 0.190)		
Min, Max	-0.700,1.490	-0.650,1.370	-0.700,1.490		

1. The estimated mean difference [one-sided 97.5% CI] between treatments and p-value is calculated from a one-way linear mixed model that accounts for the clustering effect of multiple lesions per patient. The model includes treatment as a fixed effect and patient as a random effect

ANGIOGRAPHIC SECONDARY ENDPOINTS

IN SEGMENT LATE LOSS AT 6 MONTHS: The mean late lumen loss in the treated segment was 0.06 (±0.333) in the EluNIR™ arm and 0.051 (±0.368) in the Resolute arm, p=0.9514

PERCENT DIAMETER STENOSIS: The in-segment diameter stenosis was 19.5% (±10.7) and 19.6% (±9.6) in the EluNIR™ and Resolute, respectively, p=0.9286. Within the stent, the mean DS was 14.3% (±9.9) and 12.9% (±9.4) in the EluNIR™ and Resolute, respectively, p=0.2507

BINARY RESTENOSIS: In-segment binary restenosis (DS≥50%) was identified in 7 subjects (3.4%) in the EluNIR™ arm and 4 subjects (3.8%) in the Resolute arm (p=0.8413). In-stent binary restenosis (DS≥50%) was identified in 5 subjects (2.4%) in the EluNIR™ arm and 2 subjects (1.9%) in the Resolute arm (p=0.7795)

TABLE 9-14: NIREUS CLINICAL OUTCOMES - 30 DAYS AND 6 MONTHS[F]

PARAMETER	OUTCOMES WITHIN 30 DAYS OF BASELINE PROCEDURE (Data presented in Kaplan-Meier Estimate %[n])*		OUTCOMES AT 6 MONTHS OF BASELINE PROCEDURE (Data presented in Kaplan-Meier Estimate %[n])*	
	EluNIR™ (N=201)	RESOLUTE (N=101)	EluNIR™ (N=201)	RESOLUTE (N=101)
COMPOSITE EFFICACY AND SAFETY				
TLF[1]	1.0%(2)	2.0%(2)	2.5%(5)	4.0%(4)
TVF[3]	1.0%(2)	2.0%(2)	4.5%(9)	4.0%(4)
MACE[2]	1.0%(2)	2.0%(2)	3.5%(7)	4.0%(4)
EFFICACY				
Clinically-Driven TLR	0.5%(1)	0.0%(0)	2.0%(4)	1.0%(1)
TLR, CABG	0.0%(0)	0.0%(0)	0.0%(0)	0.0%(0)
TLR, PCI	0.5%(1)	0.0%(0)	2.0%(4)	1.0%(1)
Clinically -Driven TVR, Non TL	0.0%(0)	0.0%(0)	2.0%(4)	1.0%(1)
SAFETY				
All Death	0.0%(0)	0.0%(0)	1.0%(2)	0.0%(0)
Cardiac Death	0.0%(0)	0.0%(0)	0.5%(1)	0.0%(0)
Vascular Death	0.0%(0)	0.0%(0)	0.0%(0)	0.0%(0)
Non-Cardiovascular Death	0.0%(0)	0.0%(0)	0.5%(1)	0.0%(0)
MI	1.0%(2)	2.0%(2)	2.1%(4)	3.0%(3)
QMI	0.5%(1)	0.0%(0)	0.5%(1)	0.0%(0)
NQMI	0.5%(1)	0.0%(0)	0.5%(1)	0.0%(0)
Cardiovascular Death or MI	1.0%(2)	2.0%(2)	2.1%(4)	3.0%(3)
StentT hrombosis-ARC Definite/Probable	0.5%(1)	0.0%(0)	0.5%(1)	0.0%(0)
Acute (<1 day)	0.0%(0)	0.0%(0)	N/A	N/A
Subacute (1-30 days)	0.5%(1)	0.0%(0)	N/A	N/A
Late (>30 days)	N/A	N/A	0.5%(1/201)	0.0%(0/101)

1. Target lesion failure (TLF; the composite rate of cardiac death, target vessel MI or clinically driven TLR)
2. Major Adverse Cardiac Events (MACE; the composite rate of cardiac death, any MI or clinically driven TLR)
3. Target Vessel Failure (TVF; the composite rate of all-cause death, target vessel related MI or clinically driven TVR)

* Proportional hazards assumption not met. Hazards ratio (95% CI) is based on a Cox model which adjusts for treatment by time interaction.

F. Periprocedural MIs are included per SCAI definitions as follows:

- In patients with normal baseline CK-MB: The peak CK-MB measured within 48 hours of the procedure rises to ≥10x the local laboratory ULN, or to ≥5x ULN with new pathologic Q-waves in ≥2 contiguous leads or new persistent LBBB, or in the absence of CK-MB measurements and a normal baseline cTn, a cTn (I or T) level measured within 48 hours of the PCI rises to ≥70x the local laboratory ULN, or ≥35x ULN with new pathologic Q-waves in ≥2 contiguous leads or new persistent LBBB.
- In patients with elevated baseline CK-MB (or cTn) in whom the biomarker levels are stable or falling: The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above from the most recent pre-procedure level.
- In patients with elevated CK-MB (or cTn) in whom the biomarker levels have not been shown to be stable or falling: The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above plus new ST-segment elevation or depression plus signs consistent with a clinically relevant MI, such as new onset or worsening heart failure or sustained hypotension.

TABLE 9-15: NIREUS CLINICAL OUTCOMES - 1 YEAR (DATA PRESENTED IN KAPLAN-MEIER ESTIMATE %[N])*[G]

PARAMETER	EluNIR™ (N=201)	RESOLUTE (N=101)
COMPOSITE EFFICACY AND SAFETY		
TLF[1]	3.4%(6)	7.0%(7)
TVF[3]	7.5%(14)	10.0%(10)
MACE[2]	4.3%(8)	8.0%(7)
EFFICACY		
Clinically-Driven TLR	2.9%(5)	4.0%(4)
TLR, CABG	0.0%(0)	0.0%(0)
TLR, PCI	2.9%(5)	4.0%(4)
Clinically-Driven TVR, Non TL	3.0%(6)	4.0%(4)
SAFETY		
All Death	2.1%(4)	0.0%(0)
Cardiac Death	0.5%(1)	0.0%(0)
Vascular Death	0.0%(0)	0.0%(0)
Non-Cardiovascular Death	1.6%(3)	0.0%(0)
MI	2.0%(4)	3.0%(3)
QMI	0.5%(1)	0.0%(0)
NQMI	2.0%(4)	3.0%(3)
Cardiovascular Death or MI	2.0%(4)	3.0%(3)
Any Stent Thrombosis	0.5%(1)	0.0%(0)
Stent Thrombosis - ARC Definite Probable	0.5%(1)	0.0%(0)
Late (>30 days - 1 Year)	0.5%(1)	0.0%(0)

1. Target Lesion Failure (TLF; the composite rate of cardiac death, target vessel MI or clinically driven TLR)
2. Major Adverse Cardiac Events (MACE; the composite rate of cardiac death, any MI or clinically driven TLR)
3. Target Vessel Failure (TVF; the composite rate of all-cause death, target vessel related MI or clinically driven TVR)

* Proportional hazards assumption not met. Hazards ratio (95% CI) is based on a Cox model which adjusts for treatment by time interaction.

G. Periprocedural MIs are included per SCAI definitions as follows:

- In patients with normal baseline CK-MB: The peak CK-MB measured within 48 hours of the procedure rises to ≥10x the local laboratory ULN, or to ≥5x ULN with new pathologic Q-waves in ≥2 contiguous leads or new persistent LBBB, or in the absence of CK-MB measurements and a normal baseline cTn, a cTn (I or T) level measured within 48 hours of the PCI rises to ≥70x the local laboratory ULN, or ≥35x ULN with new pathologic Q-waves in ≥2 contiguous leads or new persistent LBBB.
- In patients with elevated baseline CK-MB (or cTn) in whom the biomarker levels are stable or falling: The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above from the most recent pre-procedure level.
- In patients with elevated CK-MB (or cTn) in whom the biomarker levels have not been shown to be stable or falling: The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above plus new ST-segment elevation or depression plus signs consistent with a clinically relevant MI, such as new onset or worsening heart failure or sustained hypotension.

9.3 BIONICS ISRAEL CLINICAL TRIAL

BIONICS Israel clinical trial aimed at assessing the EluNIR™ stent with modified delivery system.

PRIMARY OBJECTIVE: To assess the Acute Device Success and the Safety of the Ridaforolimus Eluting Stent - EluNIR™ with modified delivery system.

CONCLUSIONS: The EluNIR™ with the modified delivery system showed excellent efficacy with 100% success with the primary endpoint and a lack of safety concern, with few SAEs and no AEs related to the study stent.

DESIGN: This was a prospective, multi-center, single-arm, open-label clinical trial. Clinical follow-up performed at 30 days. Follow-up by phone was performed at 6 months and 1 year after baseline procedure.

Approximately 60 subjects were planned for enrollment in this study in three medical centers in Israel. A total of 58 subjects were enrolled and received the study device.

The BIONICS Israel Clinical trial was supervised by an independent Data Safety Monitoring Board (DSMB). A dedicated medical monitor reviewed the safety data on an ongoing basis. An independent Clinical Events Committee (CEC) adjudicated all potential clinically significant and relevant cardiac events data.

DEMOGRAPHICS: A total of 58 subjects with a mean age of 62.3 (±10.4) years were included in the FAS analysis population, with a majority of subjects being male (84.5%); female subjects constituted 15.5%. All subjects in the study were white and all subjects identified themselves as not Hispanic or Latino.

The demographics and baseline characteristics and risk factors are presented in **Table 9-16**.

TABLE 9-16: BIONICS-ISRAEL CLINICAL TRIAL - DEMOGRAPHICS, RISK FACTORS AND BASELINE ANGIOGRAPHIC CHARACTERISTICS

PARAMETER	STATISTIC	EluNIR™ (N=58)
BASELINE DEMOGRAPHICS		
Age	N	58
	Mean(StdDev)	62.3 ± 10.4
	Median(Q1,Q3)	62.5 [57.0, 69.0]
GENDER		
Male	% (n/N)	84.5% (49/58)
Female	% (n/N)	15.5% (9/58)
Body Mass Index (kg/m2)	N	58
	Mean(StdDev)	28.5 ± 4.6
	Median(Q1,Q3)	27.7 [25.0, 30.7]
BASELINE RISK FACTORS		
Acute Coronary Syndrome	% (n/N)	41.4% (24/58)
Diabetes	% (n/N)	34.5% (20/58)
Controlled by:		
Insulin	% (n/N)	50.0% (10/20)
Non-Insulin	% (n/N)	40.0% (8/20)
Diet / Other	% (n/N)	10.0% (2/20)
Hyperlipidemia	% (n/N)	82.5% (47/57)
Medically Treated	% (n/N)	85.1% (40/47)
Hypertension	% (n/N)	75.9% (44/58)
Medically Treated	% (n/N)	86.4% (38/44)
Family History of premature coronary disease	% (n/N)	33.3% (17/51)
History of Angina Pectoris	% (n/N)	48.3% (28/58)
CCS: Class I	% (n/N)	0.0% (0/20)
CCS: Class II	% (n/N)	25.0% (5/20)
CCS: Class III	% (n/N)	45.0% (9/20)
CCS: Class IV	% (n/N)	30.0% (6/20)
Previous MI	% (n/N)	32.8% (19/58)
Previous PCI	% (n/N)	46.6% (27/58)
Target Vessel Treated	% (n/N)	11.1% (3/27)
Target Lesion Treated	% (n/N)	33.3% (1/3)
Previous CABG	% (n/N)	8.6% (5/58)
Target Vessel	% (n/N)	40.0% (2/5)
Non Target Vessel	% (n/N)	60.0% (3/5)
Previous CVA	% (n/N)	1.7% (1/58)
Previous TIA	% (n/N)	5.2% (3/58)
LESION CHARACTERISTICS		
Target Lesion Vessel	N	58
LAD	% (n/N)	49.3% (37/75)
RCA	% (n/N)	22.7% (17/75)
Circumflex	% (n/N)	24.0% (18/75)
Left Main	% (n/N)	1.3% (1/75)
Lesion Type		
B2/C	% (n/N)	56.0% (42/75)
Severe Calcification	% (n/N)	14.7% (11/75)
Bifurcation	% (n/N)	32.0% (24/75)
Ostial	% (n/N)	2.7% (2/75)
VESSEL LEVEL CHARACTERISTICS FROM QCA		
	N	58
LAD	% (n/N)	48.5% (33/68)
RCA	% (n/N)	23.5% (16/68)
Circumflex	% (n/N)	23.5% (16/68)
Left Main	% (n/N)	1.5% (1/68)
SVG	% (n/N)	2.9% (2/68)
PRE PROCEDURE QCA ANALYSIS		
Lesion Length (mm)	N	75
	Mean(StdDev)	19.5 ± 11.1
RVD (mm)	N	75
	Mean(StdDev)	2.77 ± 0.44
%DS	N	75
	Mean(StdDev)	67.6± 11.8

RESULTS: All currently reported outcomes are based on the 30-day follow-up evaluation time point.

The primary endpoint of this study, acute device success (defined as the achievement of a final in-stent residual diameter stenosis of <50% (by QCA), using the assigned device only and without a device malfunction), was met 100%.

Key secondary endpoints included lesion and procedure success. Lesion success was 100.0% in this study and procedure success was 96.6%.

Acute success rates of the BIONICS-Israel Trial are presented in **Table 9-17** and **Table 9-18**, with a residual stenosis of ≤50% and ≤20%, respectively.

TABLE 9-17: BIONICS ISRAEL PRIMARY ANALYSIS - SUMMARY OF ACUTE SUCCESS RATE DEFINED FROM ANGIOGRAPHIC CORE LAB ASSESSMENT (DS < 50% THRESHOLD) AND CEC ADJUDICATION (FULL ANALYSIS SET)

PARAMETER	STATISTIC	EluNIR™ (N=58 PATIENTS, 75 LESIONS)
Device Success[a]	% (n/N)	100.0% (74/74)
	95% CI	[95.1%, 100.0%]
Lesion Success[b]	% (n/N)	100.0% (74/74)
	95% CI	[95.1%, 100.0%]
Procedure Success[c]	% (n/N)	96.6% (56/58)
	95% CI	[88.1%, 99.6%]

Exact 95% Confidence intervals are provided around the proportion for each sample.

a. Device Success: Final in-stent residual diameter stenosis of < 50% (by QCA) in the target lesion, using the assigned device only and without a device malfunction. Device success is assessed among subjects where the randomization assignment was followed. Lesions not treated according to randomization assignment are excluded.

b. Lesion Success: Final in-stent residual diameter stenosis of < 50% (by QCA) in the target lesion using any percutaneous method.

c. Procedure success: Final in-stent diameter stenosis of < 50% (by QCA) using the assigned device and/ or with any adjunctive devices, without the occurrence of cardiac death, Q wave or non-Q wave MI (peri procedural MIs are included according to SCAI criteria), or repeat revascularization of the target lesion during the hospital stay.

TABLE 9-18: BIONICS-ISRAEL - SUMMARY OF ACUTE SUCCESS RATE DEFINED FROM ANGIOGRAPHIC CORE LAB ASSESSMENT (DS < 20% THRESHOLD) AND CEC ADJUDICATION (FULL ANALYSIS SET)

PARAMETER	STATISTIC	EluNIR™ (N=58 PATIENTS, 75 LESIONS)
Device Success[a]	% (n/N)	85.1% (63/74)
	95% CI	[75.0%, 92.3%]
Lesion Success[b]	% (n/N)	85.1% (63/74)
	95% CI	[75.0%, 92.3%]
Procedure Success[c]	% (n/N)	82.8% (48/58)
	95% CI	[70.6%, 91.4%]

Exact 95% Confidence intervals are provided around the proportion for each sample.

a. Device Success: Final in-stent residual diameter stenosis of < 20% (by QCA) in the target lesion, using the assigned device only and without a device malfunction. Device success is assessed among subjects where the randomization assignment was followed. Lesions not treated according to randomization assignment are excluded.

b. Lesion Success: Final in-stent residual diameter stenosis of < 20% (by QCA) in the target lesion using any percutaneous method.

c. Procedure success: Final in-stent diameter stenosis of < 20% (by QCA) using the assigned device and/ or with any adjunctive devices, without the occurrence of cardiac death, Q wave or non-Q wave MI (peri procedural MIs are included according to SCAI criteria), or repeat revascularization of the target lesion during the hospital stay.

Secondary endpoints related to the safety evaluation of the EluNIR™ Ridaforolimus Eluting Coronary Stent System included the following:

- TLF defined as the composite of cardiac death, target vessel-related MI or ischemia driven TLR (3.6%).
- Major adverse cardiac events (MACE; the composite rate of cardiac death, any MI or ischemia-driven TLR) (3.6%).
- All-cause mortality (0.0%)
- Cardiac death (0.0%)
- Myocardial infarction (3.6%)
- Target vessel related MI (3.6%)
- Ischemia-driven TLR (0.0%)
- Ischemia-driven TVR (1.8%)
- Stent thrombosis (ARC definite and probable) (0.0%)

9.4 BIONICS 38MM TRIAL

BIONICS 38mm Trial was aimed at assessing the safety and efficacy of long (38mm) Ridaforolimus Eluting Stent - EluNIR™.

STUDY DESIGN: This was a prospective, multi-center, single-arm, open label clinical trial conducted at 7 sites in Israel, with 50 enrolled patients undergoing PCI for angina (stable or unstable), silent ischemia (in absence of symptoms a visually estimated target lesion diameter stenosis of ≥70%, a positive non-invasive stress test or FFR ≤0.80 must be present), NSTEMI and recent STEMI with attempted implantation of 38mm EluNIR™ stent.

The BIONICS 38mm Clinical trial was supervised by an independent Data Safety Monitoring Board (DSMB). A dedicated medical monitor reviewed the safety data on an ongoing basis. An independent Clinical Events Committee (CEC) adjudicated all potential clinically significant and relevant cardiac events data.

CLINICAL FOLLOW-UP: Was performed at 30 days. Follow-up by phone was performed at 6 months and 1 year after the baseline procedure.

PRIMARY OBJECTIVE: To further assess the safety and efficacy of long (38mm) Ridaforolimus Eluting Stent - EluNIR™.

PRIMARY ENDPOINT: Combined efficacy and safety endpoint: Device success as determined by the Angiographic Core Lab (ACL) with no 30 day MACE.

CONCLUSIONS: The EluNIR™ 38mm stent performed as intended in this multi-center trial of 50 subjects.

The MACE rate was 6% and the primary endpoint of device success with no 30-day MACE was achieved in 88% (44/50 subjects; 95% CI 75.7%-95.5%) using a<30% residual stenosis threshold. These results are in line with data for the RESOLUTE 38mm stent, in which the MACE rate at 1 month was 4.5%. Using a similar threshold as in RESOLUTE trial of <50 % residual stenosis the comparative device and procedure success rates were 97% and 96% with RESOLUTE and 98% and 94% with EluNIR™ respectively.

DEMOGRAPHICS: Fifty (50) subjects were enrolled with a mean age of 64.6 (±9.7) years. Majority of subjects were males.

The demographics and baseline characteristics and risk factors are presented in **Table 9-19**

TABLE 9-19: BIONICS 38MM CLINICAL TRIAL - DEMOGRAPHIC, RISK FACTORS AND BASELINE ANGIOGRAPHIC CHARACTERISTICS

PARAMETER	STATISTIC	OVERALL
BASELINE DEMOGRAPHICS		
Age (years)	N	50
	Mean(StdDev)	64.6 ± 9.7
	Median(Q1,Q3)	63.5 (59.0, 71.0)
GENDER		
Male	% (n/N)	76.0% (38/50)
Female	% (n/N)	24.0% (12/50)
BMI (kg/m2)	N	49
	Mean ± StdDev	28.16 ± 5.20
	Median (Q1,Q3)	27.62 (24.30, 29.74)
BASELINE RISK FACTORS		
Acute Coronary Syndrome	% (n/N)	28.0% (14/50)
Diabetes	% (n/N)	40.0% (20/50)
Type		
Type I	% (n/N)	0.0% (0/20)
Type II	% (n/N)	100.0% (20/20)
Controlled by:		
Medically Treated	% (n/N)	85.0% (17/20)
Insulin	% (n/N)	20.0% (4/20)
Non-Insulin Medication	% (n/N)	70.0% (14/20)
Diet Controlled/Untreated	% (n/N)	15.0% (3/20)
Pevious MI	% (n/N)	34.0% (17/50)
History of Angina Pectoris	% (n/N)	24.0% (12/50)
CCS: Class I	% (n/N)	8.3% (1/12)
CCS: Class II	% (n/N)	16.7% (2/12)
CCS: Class III	% (n/N)	25.0% (3/12)
CCS: Class IV	% (n/N)	50.0% (6/12)
Previous PCI	% (n/N)	36.0% (18/50)
Target Vessel involved	% (n/N)	16.7% (3/18)
Target Lesion treated	% (n/N)	0.0% (0/3)
Stent implanted	% (n/N)	100.0% (18/18)
Previous CABG	% (n/N)	8.0% (4/50)
Target Vessel	% (n/N)	50.0% (2/4)
Previous TIA	% (n/N)	4.0% (2/50)
Previous CVA	% (n/N)	8.0% (4/50)
Congestive Heart Failure	% (n/N)	6.0% (3/50)
NYHA Class:		
I	(n/N)	0.0% (0/3)
II	(n/N)	33.3% (1/3)
III	(n/N)	33.3% (1/3)
Vascular Disease	% (n/N)	12.2% (6/49)
Hyperlipidemia	% (n/N)	77.6% (38/49)
Medically Treated	% (n/N)	89.5% (34/38)
Hypertension	% (n/N)	70.0% (35/50)
Medically Treated	% (n/N)	94.3% (33/35)

PARAMETER	STATISTIC	OVERALL
LESION CHARACTERISTICS		
Target Lesion Vessel		
LAD	% (n/N)	34.0% (17/50)
RCA	% (n/N)	38.0% (19/50)
Circumflex	% (n/N)	24.0% (12/50)
SVG	% (n/N)	4.0% (2/50)
Lesion Location		
Ostial	% (n/N)	2.0% (1/50)
Anastomosis	% (n/N)	0.0% (0/50)
Eccentric	% (n/N)	0.0% (0/49)
Angulation > 45 degrees	% (n/N)	10.6% (5/47)
Thrombus	% (n/N)	0.0% (0/49)
Tortuosity		
None	% (n/N)	95.9% (47/49)
Moderate	% (n/N)	4.1% (2/49)
Severe	% (n/N)	0.0% (0/49)
Calcification		
None or Mild	% (n/N)	71.4% (35/49)
Moderate	% (n/N)	10.2% (5/49)
Severe	% (n/N)	18.4% (9/49)
Ulcerated	% (n/N)	10.2% (5/49)
Aneurysm	% (n/N)	0.0% (0/49)
Intimal Flap	% (n/N)	0.0% (0/49)
Ectasia	% (n/N)	4.1% (2/49)
Medina Bifurcations Any Bifurcation	% (n/N)	26.0% (13/50)
Side branch diameter stenosis (%DS)	N	13
	Mean ± StdDev	30.5 ± 16.4
	Median (Q1,Q3)	32.0 (14.0, 40.0)
MACC Score B2/C	% (n/N)	92.0% (46/50)
PRE- PROCEDURE VESSEL LEVEL CHARACTERISTICS (QCA)		
Vessel		
LAD	% (n/N)	34.0% (17/50)
RCA	% (n/N)	38.0% (19/50)
Circumflex	% (n/N)	24.0% (12/50)
Left Main	% (n/N)	0.0% (0/50)
SVG	% (n/N)	4.0% (2/50)
PRE-PROCEDURE (BASELINE) QCA MEASUREMENTS		
Lesion Length (mm)	N	46
	Mean ± StdDev	32.4 ± 8.3
RVD (mm)	N	49
	Mean ± StdDev	2.88 ± 0.45
Minimal Lumen Diameter (MLD)	N	49
	Mean ± StdDev	0.80 ± 0.41
%DS	N	49
	Mean ± StdDev	72.6 ± 13.2

RESULTS: The presented study outcomes include primary endpoint results up to 30-days follow-up.
The primary endpoint of the BIONICS 38mm Trial was the combined efficacy and safety endpoint of device success as determined by the Angiographic Core Laboratory (ACL) with no 30-day MACE. Device success was defined as achievement of a final in-stent residual diameter stenosis of <30% (by QCA), using the EluNIR™ 38 mm stent only and without a device malfunction.

The primary endpoint was achieved in 88% (44/50) of the subjects in the FAS (95% Exact CI: 75.7% - 95.5%) (**Table 9-20**) and 90% (36/40) of the subjects in the Per-Protocol Analysis Set (95% Exact CI: 76.3% - 97.2%) (**Table 9-21**).

TABLE 9-20: SUMMARY OF PRIMARY AND SECONDARY ENDPOINTS OF ACUTE SUCCESS (DEVICE SUCCESS WITH NO 30 DAY MACE AND DEVICE, LESION, PROCEDURE SUCCESS) – FULL ANALYSIS SET

PARAMETER	STATISTIC	OVERALL
Primary Endpoint Device Success with no 30-day MACE[1]	% (n/N) 95% CI	88.0% (44/50) (75.7%, 95.5%)
Secondary Endpoint Device Success[2]	% (n/N) 95% CI	92.0% (46/50) (80.8%, 97.8%)
Lesion Success[3]	% (n/N) 95% CI	94.0% (47/50) (83.5%, 98.8%)
Procedure Success[4]	% (n/N) 95% CI	88.0% (44/50) (75.7%, 95.5%)

Full Analysis Set (FAS): All subjects who have been enrolled into the trial, regardless of whether they received the study stent or not. Subjects are included in the FAS once the EluNIR™ 38mm stent has been advanced beyond the guide catheter.

Exact 95% Confidence intervals are provided around the proportion for each sample

1. MACE is defined as the composite of cardiac death, any MI or ischemia-driven TLR
2. Device success is defined as achievement of a final in-stent residual diameter stenosis of <30% (by QCA), using the assigned device only and without a device malfunction.
3. Lesion success is defined as achievement of a final in-stent residual diameter stenosis of <30% (by QCA) using any percutaneous method.
4. Procedure success is defined as achievement of a final in-stent diameter stenosis of <30% (by QCA) using the assigned device and/ or with any adjunctive devices, without the occurrence of cardiac death, Q wave or non-Q wave MI or repeat revascularization of the target lesion during the hospital stay.

TABLE 9-21: SUMMARY OF PRIMARY AND SECONDARY ENDPOINTS OF ACUTE SUCCESS (DEVICE SUCCESS WITH NO 30 DAY MACE AND DEVICE, LESION, PROCEDURE SUCCESS) – PER-PROTOCOL ANALYSIS SET

PARAMETER	STATISTIC	OVERALL
Primary Endpoint Device Success with no 30-day MACE[1]	% (n/N) 95% CI	90.0% (36/40) (76.3%, 97.2%)
Secondary Endpoint Device Success[2]	% (n/N) 95% CI	92.5% (37/40) (79.6%, 98.4%)
Lesion Success[3]	% (n/N) 95% CI	95.0% (38/40) (83.1%, 99.4%)
Procedure Success[4]	% (n/N) 95% CI	90.0% (36/40) (76.3%, 97.2%)

Per-Protocol (PP) Analysis Set: All subjects in the Full Analysis Set (FAS) with no major protocol deviations as identified by the Medical Monitor.

Exact 95% Confidence intervals are provided around the proportion for each sample

1. MACE is defined as the composite of cardiac death, any MI or ischemia-driven TLR
2. Device success is defined as achievement of a final in-stent residual diameter stenosis of <30% (by QCA), using the assigned device only and without a device malfunction.
3. Lesion success is defined as achievement of a final in-stent residual diameter stenosis of <30% (by QCA) using any percutaneous method.
4. Procedure success is defined as achievement of a final in-stent diameter stenosis of <30% (by QCA) using the assigned device and/ or with any adjunctive devices, without the occurrence of cardiac death, Q wave or non-Q wave MI or repeat revascularization of the target lesion during the hospital stay..

9.5 BIONICS SMALL VESSELS TRIAL

BIONICS Small Vessels trial aimed at assessing the safety and efficacy of the small diameter (2.25mm) Ridaforolimus Eluting Stent.

STUDY DESIGN: This was a prospective, multi-center, single-arm, open label clinical trial conducted at 9 sites in Israel, with 81 enrolled patients undergoing PCI for angina (stable or unstable), silent ischemia (in absence of symptoms a visually estimated target lesion diameter stenosis of ≥70%, a positive non-invasive stress test, or FFR ≤0.80 must be present), NSTEMI, and recent STEMI (>24 hours from initial presentation and stable) with attempted implantation of a 2.25mm diameter EluNIR™ stent.

A dedicated medical monitor reviewed the safety data on an ongoing basis. An independent Clinical Events Committee (CEC) adjudicated all potential clinically significant and relevant cardiac events data.

CLINICAL FOLLOW UP: The Clinical follow-up was performed at 30 days. Follow up by phone was performed at 6 months and at 1 year after the procedure for all patients.

PRIMARY OBJECTIVE: To further assess the safety and efficacy of the small diameter (2.25 mm) Ridaforolimus Eluting Stent - EluNIR™.

PRIMARY ENDPOINTS: Combined early efficacy and safety endpoint: MACE at 30 days for all enrolled patients.

Combined late efficacy and safety endpoint: Target Lesion Failure (TLF) at 6 months (evaluated for the first 50% of enrolled patients).

CONCLUSIONS: The EluNIR™ 2.25 mm stent performed as intended in this multi-center trial of 81 subjects.

Event rates were low, with only one patient with MACE at 30 days (1/81) (Primary early safety and efficacy Endpoint) and in only one patient with TLF at 6 months (1/41) (Primary late safety and efficacy endpoint). These results confirm the safety and efficacy of the EluNIR™ 2.25 stent.

At 1 year after the baseline procedure, MACE, TLF and TVF rates were 2.5%, 1.2%, and 1.2%, respectively in the full patient cohort. There was one noncardiovascular death between 6 months and 1 year of the baseline procedure. There were no stent thrombosis events.

DEMOGRAPHICS: Eighty-one (81) subjects were enrolled with a mean age of 63.6 (±10.2) years. Majority of subjects were males. The demographics and baseline characteristics and risk factors are presented in Table 9-22.

TABLE 9-22: BIONICS SMALL VESSELS CLINICAL TRIAL - DEMOGRAPHIC, RISK FACTORS AND BASELINE ANGIOGRAPHIC CHARACTERISTICS

PARAMETER	STATISTIC	OVERALL (N=81)
BASELINE DEMOGRAPHICS		
Age (years)	N	81
	Mean ± StdDev	63.6 ± 10.2
	Median(Q1,Q3)	64.0 (55.0, 70.0)
GENDER		
Male	71.6% (58/81)	71.6% (58/81)
BMI (kg/m2)	N	81
	Mean ± StdDev	29.4 ± 5.5
	Median (Q1,Q3)	28.7 (25.3, 32.9)
BASELINE RISK FACTORS		
Acute Coronary Syndrome	% (n/N)	33.3% (27/81)
Current at admission	% (n/N)	85.2% (23/27)
Diabetes	% (n/N)	43.8% (35/80)
Type		
Type I	% (n/N)	0.0% (0/35)
Type II	% (n/N)	100.0% (35/35)
Controlled by:		
Medically Treated	% (n/N)	91.4% (32/35)
Insulin	% (n/N)	9.4% (3/32)
Non-Insulin Medication Only	% (n/N)	90.6% (29/32)
Diet Controlled/Untreated Only	% (n/N)	8.6% (3/35)
Pevious MI	% (n/N)	46.8% (37/79)
Current at admission	% (n/N)	37.8% (14/37)
History of Angina Pectoris	% (n/N)	79.5% (62/78)
Current at admission	% (n/N)	48.1% (13/27)

TABLE 9-22 (Continue): BIONICS SMALL VESSELS CLINICAL TRIAL - DEMOGRAPHIC, RISK FACTORS AND BASELINE ANGIOGRAPHIC CHARACTERISTICS

PARAMETER	STATISTIC	OVERALL (N=81)
BASELINE RISK FACTORS (Continue)		
Type of Angina at the time of diagnosis	% (n/N)	
Stable angina (CCS class)		22.2% (12/54)
Class I	% (n/N)	45.5% (5/11)
Class II	% (n/N)	45.5% (5/11)
Class III	% (n/N)	9.1% (1/11)
Class IV	% (n/N)	0.0% (0/11)
Unstable angina (Braunwald Class)	% (n/N)	77.8% (42/54)
Class I		38.5% (15/39)
Class II		35.9% (14/39)
Class III		25.6% (10/39)
Prior PCI		62.5% (50/80)
Target Vessel involved	% (n/N)	30.0% (15/50)
Prior CABG	% (n/N)	9.9% (8/81)
Target Vessel	% (n/N)	50.0% (4/8)
History of TIA	% (n/N)	2.5% (2/81)
History of CVA	% (n/N)	1.2% (1/81)
Congestive Heart Failure (CHF)	% (n/N)	9.9% (8/81)
I	% (n/N)	0.0% (0/5)
II	% (n/N)	40.0% (2/5)
III	% (n/N)	60.0% (3/5)
IV	% (n/N)	0.0% (0/5)
Vascular Disease	% (n/N)	7.5% (6/80)
Hyperlipidemia	% (n/N)	83.8% (67/80)
Medically Treated	% (n/N)	94.0% (63/67)
Hypertension	% (n/N)	80.2% (65/81)
Medically Treated	% (n/N)	89.2% (58/65)
Family History of Premature Coronary Disease	% (n/N)	47.6% (30/63)
Smoking Status		
Never	% (n/N)	46.3% (37/80)
Current	% (n/N)	26.3% (21/80)
Former	% (n/N)	27.5% (22/80)
Number of years Smoking:	N	29
	Mean ± StdDev	27.90 ± 12.97
	Median (Q1,Q3)	30.00 (20.00, 35.00)
	Min, Max	5.00, 56.00
Average Number of Cigarettes per day	N	27
	Mean ± StdDev	18.81 ± 10.63
	Median (Q1,Q3)	20.00 (10.00, 20.00)
	Min, Max	3.00, 40.00
Alcohol Abuse		
Never	% (n/N)	100.0% (81/81)
Current	% (n/N)	0.0% (0/81)
Former	% (n/N)	0.0% (0/81)
Atrial Fibrillation	% (n/N)	9.9% (8/81)
Paroxysmal (lasts 7 days or less)	% (n/N)	60.0% (3/5)
Persistent (lasts more than 7 days but no more than 12 months)	% (n/N)	0.0% (0/5)
Long standing persistent (lasts more than 12 months)	% (n/N)	20.0% (1/5)
Other	% (n/N)	20.0% (1/5)
Atrial Fibrillation - Medically treated	% (n/N)	62.5% (5/8)
History of Bleeding Complications	% (n/N)	2.5% (2/81)
Renal Insufficiency	% (n/N)	7.4% (6/81)

PARAMETER	STATISTIC	OVERALL (N=81)
LESION CHARACTERISTICS		
Target Lesion Vessel		
LAD	% (n/N)	27.6% (24/87)
RCA	% (n/N)	25.3% (22/87)
Circumflex	% (n/N)	44.8% (39/87)
Left Main	% (n/N)	0.0% (0/87)
Graft	% (n/N)	2.3% (2/87)
Lesion Location		
Proximal	% (n/N)	50.6% (44/87)
Mid	% (n/N)	39.1% (34/87)
Distal	% (n/N)	3.4% (3/87)
Ostial	% (n/N)	5.7% (5/87)
Anastomosis	% (n/N)	1.1% (1/87)
Eccentric	% (n/N)	9.2% (8/87)
Angulation > 45 degrees	% (n/N)	12.6% (11/87)
Thrombus	% (n/N)	2.3% (2/87)
Tortuosity		
None	% (n/N)	87.4% (76/87)
Moderate	% (n/N)	9.2% (8/87)
Severe	% (n/N)	3.4% (3/87)
Calcification		
None or Mild	% (n/N)	67.8% (59/87)
Moderate	% (n/N)	16.1% (14/87)
Severe	% (n/N)	16.1% (14/87)
Ulcerated	% (n/N)	0.0% (0/87)
Aneurysm	% (n/N)	0.0% (0/87)
Intimal Flap	% (n/N)	0.0% (0/87)
Ectasia	% (n/N)	1.1% (1/87)
Medina Bifurcations	% (n/N)	16.1% (14/87)
Side Branch diseased	% (n/N)	10.3% (9/87)
Side branch diameter stenosis (%DS)	N	14
	Mean ± StdDev	51.93 ± 32.19
	Median (Q1,Q3)	59.50 (22.00, 77.00)
PRE PROCEDURE VESSEL LEVEL CHARACTERISTICS (QCA)		
Vessel		
LAD	% (n/N)	29.3% (24/82)
RCA	% (n/N)	24.4% (20/82)
Circumflex	% (n/N)	45.1% (37/82)
Left Main	% (n/N)	0.0% (0/82)
Graft	% (n/N)	1.2% (1/82)
PRE-PROCEDURE (BASELINE) QCA MEASUREMENTS		
Baseline (Pre-Procedure)		
Lesion Length (mm)	N	86
	Mean ± StdDev	16.97 ± 8.78
RVD (mm)*	N	87
	Mean ± StdDev	2.22 ± 0.23
Minimal Lumen Diameter (MLD)- (mm)	N	87
	Mean ± StdDev	0.66 ± 0.28
%DS*	N	87
	Mean ± StdDev	70.20 ± 11.73

RESULTS: The presented study outcomes include the primary endpoints results up to 6 months follow-up. The primary endpoints of the BIONICS Small Vessels Trial were the combined early efficacy and safety endpoint of MACE at 30 days (all enrolled subjects), and the combined late efficacy and safety endpoint of TLF at 6 months (evaluated for the first 50% of subjects enrolled). MACE was defined as the composite of cardiac death, any MI, or ischemia-driven TLR as adjudicated by the CEC. TLF was defined as the composite of cardiac death, target vessel related MI, or ischemia-driven TLR. For both endpoints, the peri-procedural MIs were adjudicated per the SCAI definition.

The early efficacy and safety endpoint of MACE at 30 days was observed in one patient (1/81) (1.2%) in the FAS (95% Exact CI: 0.0% - 6.7%). In the Per-Protocol analysis set, the 30-day MACE was observed in one patient (1/76) (1.3%) (95% Exact CI: 0.0% - 7.1%)

The combined late efficacy and safety endpoint of TLF at 6 months was evaluated for the first 41 patients enrolled in the trial. At 6 months, the TLF rate was 2.4% (1/41) (95% Exact CI: 0.1% - 12.9%), and 2.6% (1/38) in the Per-Protocol analysis set (95% Exact CI: 0.1% - 13.8%).

TABLE 9-23: SUMMARY OF PRIMARY ENDPOINTS - FULL ANALYSIS SET

PARAMETER	STATISTIC	OVERALL (N=81)
PRE PROCEDURE VESSEL LEVEL CHARACTERISTICS (QCA)- FINAL		
Primary Endpoint		
MACE at 30 Days	% (n/N)	1.2% (1/81)
	95% CI	(0.0%, 6.7%)
TLF at 6 Months	% (n/N)	2.4% (1/41)
	95% CI	(0.1%, 12.9%)

Full Analysis Set (FAS): All subjects who have been enrolled into the trial, regardless of whether they received the study stent or not. Subjects are included in the FAS once the 2.25 mm EluNIR stent has been advanced beyond the guide catheter, and consent was obtained Exact 95% Confidence intervals are provided around the proportion for each sample.

MACE is defined as the composite of cardiac death, any MI (peri-procedural MI per SCAI definition), or ischemia-driven TLR.

TLF is defined as the composite of cardiac death, target vessel related MI, or ischemia-driven TLR.

TABLE 9-24: SUMMARY OF PRIMARY ENDPOINTS- PER-PROTOCOL ANALYSIS SET

PARAMETER	STATISTIC	OVERALL (N=75)
MACE at 30 Days	% (n/N)	1.3% (1//76)
	95% CI	(0.0%, 7.1%)
TLF at 6 Months	% (n/N)	2.6% (1/38)
	95% CI	(0.1%, 13.8%)

Per-Protocol (PP) Analysis Set: All subjects in the Full Analysis Set (FAS) with no major protocol deviations as identified by the Medical Monitor Exact 95% Confidence intervals are provided around the proportion for each sample.

MACE is defined as the composite of cardiac death, any MI, or ischemia-driven TLR

TLF is defined as the composite of cardiac death, target vessel related MI, or ischemia-driven TLR

10 INDIVIDUALIZATION OF TREATMENT

The risks and benefits should be considered for each patient before using the EluNIR™ stent. Patient selection factors to be assessed should include a judgment regarding risk of long-term antiplatelet therapy. Stenting is generally avoided in those patients at heightened risk of bleeding (e.g., patients with recently active gastritis or peptic ulcer disease) in which anticoagulation therapy would be contraindicated.

Antiplatelet drugs should be used in combination with the EluNIR™ stent. Physicians should use information from the EluNIR™ pivotal clinical trials, coupled with current drug eluting stent (DES) literature and the specific needs of individual patients to determine the specific antiplatelet/ anticoagulation regimen to be used for their patients in general practice. See also section 5.2 - *Precautions, Antiplatelet Regimen, section* 5.6 - *Precautions, Use in Special Populations*, and section 5.7 - *Precautions, Lesion/Vessel Characteristics*.

Premorbid conditions 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.

10.1 PATIENT COUNSELING AND PATIENT INFORMATION

Physicians should consider the following in counseling patients about this product:

- Discuss the risks associated with stent placement
- Discuss the risks associated with an ridaforolimus eluting stent
- Discuss the risks of early discontinuation of the antiplatelet therapy
- Discuss the risks of late stent thrombosis with DES use in higher risk patient subgroups
- Discuss the risk/ benefit issues for this particular patient
- Discuss alternation to current life style immediately following the procedure and over the long term

The following patient materials are provided for this product:

- A Patient Information Guide, including information on coronary artery disease, the implant procedure and the EluNIR™ stent system (provided to physician or by calling customer service 1-888-MEDINOL (633-4665).
- A Stent Implant Card, including both patient information and stent implant information (provided in package).

11 HOW SUPPLIED

STERILE - This device is sterilized with ethylene oxide gas and is non-pyrogenic. It is intended for single use only. Do not resterilize. Do not use if the package is opened or damaged. Use prior to the expiration date ("Use By" date).

CONTENTS - One (1) EluNIR™ Ridaforolimus Eluting Coronary Stent System; one (1) flushing tool (attached to coronary hoop with luer fitting); one (1) stent implant card.

STORAGE - Store in a dry, dark, cool place. Do not remove from carton until ready for use. Store at up to 25°C (77°F), with transient excursions allowed up to 40°C (104°F).

Do not refrigerate or freeze.

12 OPERATOR'S INSTRUCTIONS

12.1 INSPECTION PRIOR TO USE

- Carefully inspect the sterile package before opening and check for damage to the sterile barrier (sterilization pouch). **Do not use if the integrity of the sterile package has been compromised.**
- Do not use after the "Use by" date.
- Tear open the foil pouch and remove the inner pouch.

  NOTE **The outside of the inner sterilization pouch is NOT sterile**. Open the inner sterilization pouch and pass or drop the product into the sterile field using an aseptic technique.

- Prior to using the EluNIR™ stent system, carefully remove the system from the package and inspect for bends, kinks and other damage. Verify that the stent does not extend beyond the radiopaque balloon markers. Do not use if any defects are noted. However, **do not manipulate, touch or handle the stent** with your fingers, which may cause coating damage, contamination or stent dislodgement from the balloon.

NOTE At any time during use of the EluNIR™, if the stainless steel proximal shaft has been bent or kinked, do not continue to use the catheter.

12.2 MATERIALS REQUIRED

The following is a list of the materials required for the procedure:

- Appropriate guiding catheter(s). See Table 1-1
- 2 - 3 syringes (10 - 20ml)
- 1,000u/500ml sterile heparinized normal saline (HepNS)
- 0.014" (0.36mm) x 175cm (minimum length) guidewire
- Rotating hemostatic valve
- Contrast diluted 1:1 with heparinized normal saline
- Inflation device
- Pre-deployment dilatation catheter
- Three-way stopcock
- Torque device
- Guidewire introducer
- Appropriate arterial sheath
- Appropriate anticoagulation and antiplatelet drugs

12.3 INCIDENTS REPORT

In case of a serious incident related to the EluNIR™, please contact Medinol at HYPERLINK "mailto:complainthandling@medinol.com" complainthandling@medinol.com and report to the local health authority.

12.4 PREPARATION

12.4.1 PACKAGING REMOVAL

NOTE **The foil pouch is not a sterile barrier**. The inner header bag (sterilization pouch) within the foil pouch is the sterile barrier. Only the contents of the inner pouch should be considered sterile. The outside surface of the inner sterilization pouch is NOT sterile.

1. Carefully remove the delivery system from its protective tubing for preparation of the delivery system. Do not bend or kink the hypotube during removal.
2. Remove the product mandrel and protective stent sheath by grasping the catheter just proximal to the stent (at the proximal balloon bond site), and with the other hand, grasp the stent protector and gently remove distally. If unusual resistance is felt during product mandrel and stent sheath removal, do not use this product and replace with another. Follow product returns procedure for the unused device.

12.4.2 GUIDEWIRE LUMEN FLUSH

Flush the guidewire lumen with HepNS using the flushing tool supplied with the product. Insert the flushing tool into the tip of the catheter and flush until fluid exits the guidewire exit notch.

NOTE Avoid manipulation of the stent while flushing the guidewire lumen, as this may disrupt the placement of the stent on the balloon.

12.4.3 DELIVERY SYSTEM PREPARATION

1. Prepare an inflation device/ syringe with diluted contrast medium.
2. Attach an inflation device/ syringe to the stopcock; attach it to the inflation port of the product. Do not bend the product hypotube when connecting to the inflation device/ syringe.
3. With the tip down, orient the delivery system vertically.
4. Open the stopcock to the delivery system; pull negative for 30 seconds and then release to neutral for contrast fill.
5. Close the stopcock to the delivery system; purge the inflation device/ syringe of all air.
6. Repeat steps 3 through 5 until all air is expelled. If bubbles persist, do not use the product.
7. If a syringe was used, attach a prepared inflation device to the stopcock.
8. Open the stopcock to the delivery system.
9. Leave on neutral.

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

NOTE If air is seen in the shaft, repeat section 12.4.3 - *Operator's Instructions, Delivery System Preparation*, steps 3 through 5, to prevent uneven stent expansion.

12.5 DELIVERY PROCEDURE

1. Prepare the vascular access site according to standard practice.
2. The decision to pre-dilate the lesion with an appropriate sized balloon should be based on patient and lesion characteristics. **If pre-dilatation is performed**, limit the longitudinal length of pre-dilatation by the PTCA balloon to avoid creating a region of vessel injury that is outside the boundaries of the EluNIR™ stent.
3. For long lesions, size the stent to the diameter of the most distal portion of the vessel.

   NOTE If choosing between two stent diameters for tight lesions, choose the smaller diameter stent and inflate. See section 13 - *Compliance Information*.
4. Maintain neutral pressure on the inflation device attached to the delivery system. Open the rotating hemostatic valve as wide as possible.
5. Backload the delivery system onto the proximal portion of the guidewire while maintaining guidewire position across the target lesion.
6. Carefully advance the delivery system into the guiding catheter and over the guidewire to the target lesion. When using a Rapid Exchange (RX) system, be sure to keep the hypotube straight. Ensure guiding catheter stability before advancing the stent system into the coronary artery.

   NOTE If unusual resistance is felt before the stent exits the guiding catheter, do not force passage. Resistance may indicate a problem and the use of excessive force may result in stent damage or dislodgement. Maintain guidewire placement across the lesion and remove the delivery system and guiding catheter as a single unit.
7. Advance the delivery system over the guidewire to the target lesion under direct fluoroscopic visualization. Utilize the radiopaque balloon markers to position the stent across the lesion. Perform angiography to confirm stent position. If the position of the stent is not optimal, the stent should be carefully repositioned or removed (see section 5.12 - *Precautions, Stent System Removal*). The balloon markers indicate both the stent edges and the balloon shoulders. Expansion of the stent should not be undertaken if the stent is not properly positioned in the target lesion.

   NOTE If removal of a stent system is required prior to deployment, ensure that the guiding catheter is coaxially positioned relative to the stent delivery system, and cautiously withdraw the stent delivery system into the guiding catheter. Should unusual resistance be felt at any time when withdrawing the stent towards the guiding catheter, the stent delivery system and the guiding catheter should be removed as a single unit. This should be done under direct visualization with fluoroscopy.
8. Tighten the rotating hemostatic valve. The stent is now ready to be deployed.

TABLE 12-1: EluNIR™ STENT SYSTEM CROSSING PROFILE SPECIFICATIONS VALUES

NOMINAL STENT DIAMETER (LABELED DIAMETER)	MAX CROSSING PROFILE FOR LABELED DIAMETER*
2.25mm	0.89mm
2.5mm	0.9mm
2.75mm	1.07mm
3.0mm	1.07mm
3.5mm	1.19mm
4.0mm	1.20mm

* The value presented is the maximum crossing profile reliability limits for a given labeled diameter.

12.6 DEPLOYMENT PROCEDURE

CAUTION Refer to **Table 13-1** for in vitro stent inner diameter, nominal pressure, and RBP.

1. Prior to deployment, reconfirm the correct position of the stent relative to the target lesion using the radiopaque balloon markers.
2. Deploy the stent slowly by pressurizing the delivery system in 2atm increments, every 5 seconds, until stent is completely expanded. Fully expand the stent by inflating to nominal pressure at a minimum. Accepted practice generally targets an initial deployment pressure that would achieve a stent inner diameter ratio of about 1.1 times the reference vessel diameter (see **Table 13-1**).
3. For long lesions, size the stent to the diameter of the most distal portion of the vessel and expand the stent to nominal pressure at minimum. Maintain pressure for 30 seconds. If necessary, the delivery system can be re-pressurized or further pressurized to assure complete apposition of the stent to the artery wall.
4. Maintain pressure for 30 seconds for full expansion of the stent. Fluoroscopic visualization during stent expansion should be used in order to properly judge the optimum stent diameter as compared to the proximal and distal native coronary artery diameters (reference vessel diameters). Optimal stent expansion and proper apposition requires that the stent be in full contact with the arterial wall.

   NOTE See section 12.7 - *Removal Procedure* for instructions on withdrawal of the stent delivery system.
5. If necessary, the delivery system can be re-pressurized or further pressurized to assure complete apposition of the stent to the artery wall.

   NOTE Do not exceed the labeled rated burst pressure (RBP) of 18atm (1824kPa).
6. Fully cover the entire lesion and balloon treated area (including dissections) with the EluNIR™ stent, allowing for adequate stent coverage into healthy tissue proximal and distal to the lesion.

7. Deflate the balloon by pulling negative on the inflation device for 30 seconds. Confirm complete balloon deflation before attempting to move the delivery system. If unusual resistance is felt during stent delivery system withdrawal, pay particular attention to guiding catheter position.

NOTE See section 12.7 - *Removal Procedure* for instructions on withdrawal of the stent delivery system.

8. Confirm stent position and deployment using standard angiographic techniques. For optimal results, the entire stenosed arterial segment should be covered by the stent. Fluoroscopic visualization during stent expansion should be used in order to properly judge the optimum expanded stent diameter as compared to the proximal and distal coronary artery diameter(s). Optimal expansion requires that the stent be in full contact with the artery wall. Stent wall contact should be verified through routine angiography or intravascular ultrasound (IVUS).
9. If the deployed stent size is still inadequate with respect to reference vessel diameter, a larger balloon may be used to further expand the stent. If the initial angiographic appearance is suboptimal, the stent may be further expanded using a low profile, high pressure, non-compliant balloon dilatation catheter. If this is required, the stented segment should be carefully re-crossed with a prolapsed guidewire to avoid disrupting the stent geometry. **Deployed stents should not be left under-dilated**.

CAUTION Do not dilate the stent beyond the following limits:

TABLE 12-2: EluNIR™ DILATATION LIMITS

NOMINAL STENT DIAMETER	DILATATION LIMITS
2.25 mm	3.00 mm
2.5 mm	3.00 mm
2.75 mm	3.75 mm
3.5 mm	3.75 mm
3.0 mm	4.75 mm
4.0 mm	4.75 mm

12.7 REMOVAL PROCEDURE

12.7.1 WITHDRAWAL OF THE STENT DELIVERY CATHETER FROM THE DEPLOYED STENT:

1. Deflate the balloon by pulling negative on the inflation device. Larger and longer balloons will take more time (up to 30 seconds) to deflate than smaller and shorter balloons. Confirm balloon deflation under fluoroscopy and wait 10-15 seconds longer.
2. Position inflation device on "negative" or "neutral" pressure.
3. Stabilize the guiding catheter position just outside coronary ostium and anchor in place. Maintain guidewire placement across the stent segment.
4. Gently remove the stent delivery system with slow and steady pressure.
5. Confirm adequate sealing of the hemostatic valve.

If resistance is encountered during withdrawal of the stent delivery catheter, use the following steps to improve balloon rewrap:

- Re-inflate the balloon up to nominal pressure.
- Repeat steps 1 through 5 above.

12.7.2 POST STENT DELIVERY SYSTEM WITHDRAWAL - STENT DEPLOYMENT CONFIRMATION:

1. Confirm stent position and deployment using standard angiographic techniques. For optimal results, the entire stenosed arterial segment should be covered by the stent. Fluoroscopic visualization during stent expansion should be used in order to properly judge the optimum expanded stent diameter as compared to the proximal and distal coronary artery diameter(s). Optimal expansion requires that the stent be in full contact with the artery wall. Stent wall contact should be verified through routine angiography or intravascular ultrasound (IVUS).
2. If more than one EluNIR™ stent is needed to cover the lesion and balloon treated area, it is suggested that, to avoid the potential for gap restenosis, the stents be adequately overlapped.
3. To ensure that there are no gaps between stents, the balloon marker bands of the second EluNIR™ stent should be positioned inside the deployed stent prior to expansion.
4. Reconfirm stent position and angiographic results to assess stented area. Repeat inflations until optimal stent deployment is achieved. If post-dilatation is necessary, ensure that the final stent diameter matches the reference vessel diameter. **Assure that the stent wall is in contact with the artery wall**.

12.8 POST-DEPLOYMENT DILATATION OF STENT SEGMENTS

1. All efforts should be made to assure that the stent is not under-dilated.
2. If the deployed stent size is still inadequate with respect to the vessel diameter, or if full contact with the vessel wall is not achieved, a larger balloon may be used to expand the stent further. This is done by using a low profile, high pressure and noncompliant 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, please refer to **Table 12-2**.

13 COMPLIANCE INFORMATION

The Nominal Pressure for each diameter is indicated by bold font.

TABLE 13-1: EluNIR™ STENT COMPLIANCE

PRESSURE		STENT ID (mm) BY SYSTEM DIAMETER					
atm	kPa	2.25mm	2.5mm	2.75mm	3.0mm	3.5mm	4.0mm
6	608	2.18	-	-	-	-	-
7	709	2.23	-	-	-	-	-
8 (NP)	811	2.29	2.36	2.63	2.84	3.34	3.79
9	912	2.35	2.42	2.69	2.91	3.42	3.88
10 (NP)	1013	2.40	2.48	2.74	2.98	3.49	3.95
11	1115	2.45	2.53	2.78	3.04	3.55	4.02
12	1216	2.48	2.58	2.82	3.09	3.60	4.06
13	1317	2.52	2.62	2.86	3.13	3.64	4.11
14	1419	2.55	2.65	2.89	3.16	3.68	4.15
15	1520	2.58	2.68	2.92	3.20	3.71	4.18
16	1621	2.62	2.71	2.95	3.23	3.74	4.22
17	1723	2.64	2.73	2.97	3.25	3.77	4.24
18 (RBP)*	1824	2.67	2.75	3.00	3.28	3.79	4.28
19	1925	2.70	2.78	3.02	3.31	3.82	4.30
20	2027	2.72	2.81	3.04	3.33	3.85	4.33

NOTE These nominal data are based on in vitro testing at 37°C and do not take into account lesion resistance.
Ensure full deployment of the stent (see section 12.6 - *Operator's Instructions, Deployment Procedure*) and confirm the stent sizing angiographically.
* Do not exceed the rated burst pressure (RBP).

14 REUSE PRECAUTION STATEMENT

Do not use if sterile barrier is damaged. If damage is found call your Medinol representative.

For single patient use only. Do not reuse, reprocess, or re-sterilize.

Safe Disposal. After use, dispose of the product and packaging in accordance with hospital, administrative and/or local government policy

15 PATENTS AND TRADEMARKS

This product and/ or its use may be covered by one or more of the following United States Patent Nos.: 6,723,119; 7,141,062; 7,722,658; 7,828,835; 8,202,312; 8,496,699; 9,161,849 and 7,959,664. It also may be covered by one or more of the following United States Patent Application Nos.: US2015/0217083A1 and US2011/0196315A1. Additional patents and patent applications may apply.

EluNIR™ Ridaforolimus Eluting Coronary Stent System is a registered trademark of Medinol Ltd.

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