

SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Drug Eluting Coronary Stent System

Device Trade Name: EluNIR™ Ridaforolimus Eluting Coronary Stent System

Device Prococode: NIQ

Applicant's Name and Address: Medinol LTD
Kiryat Atidim, Building 8
POB 58165
Tel Aviv 6158101
Israel

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P170008

Date of FDA Notice of Approval: November 28, 2017

II. 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 ≤30mm in length in native coronary arteries with reference diameters of 2.50mm to 4.25mm.

III. 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.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the EluNIR™ Ridaforolimus Eluting Coronary Stent System labeling.

V. DEVICE DESCRIPTION

The EluNIR Ridaforolimus Eluting Coronary Stent System is a single use device/drug combination product comprising the following components:

1. Device Components ([Section V.A](#)):
 - 1.1 Stent: Cobalt Chromium (CoCr) alloy
 - 1.2 Delivery System: Rapid Exchange (RX) Coronary System
2. Drug Components (Coating Formulation):
 - 2.1 Drug (the active pharmaceutical ingredient (API)):

Ridaforolimus CAS Registry Number: 572924-54-0 (formerly Deforolimus and AP23573) [Section V.B1](#)
 - 2.2 Polymer Coating Blend (Inactive Ingredients, [Section V.B2](#)): Poly n-Butyl Methacrylate (PBMA), [Section V.B2.1](#) CarboSil[®] 20 55D (CS), [Section V.B2.2](#)

[Table 1](#) describes the characteristics of the EluNIR[™] stent system.

Table 1: EluNIR Ridaforolimus Eluting Coronary Stent System: Product Description

Available Stent Lengths (mm)	8, 12, 15, 17, 20, 24, 28, 33	
Available Stent Diameters (mm)	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 1.1 µg/mm ² which results in a maximum nominal drug content of 219µg on the largest stent (4.0mm x 33mm)	
Delivery System Working Length	140cm	
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 (2) radiopaque markers located on the catheter system balloon shaft to indicate balloon positioning and expanded stent length	
Balloon Inflation Pressure	For all diameters: Nominal Pressure: 10atm (1013 kPa) Rated Burst Pressure (RBP): 18atm (1824 kPa)	
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 length

A. Device Component Description

The EluNIR[™] device component consists of a ridaforolimus eluting coronary stent pre-mounted 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 EluNIR™ uncoated (bare metal) stent and delivery system are identical to Medinol's PMA approved NIRxcell™ CoCr Coronary Stent on RX System (P110004 and its supplements).

B. Drug Component Description

The drug 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.

B1. Ridaforolimus

Ridaforolimus (CAS Registry Number: 572924-54-0, formerly Deforolimus and AP23573) is the active pharmaceutical ingredient in the EluNIR™ stent. It is a member of the limus family of drugs, a unique, non-prodrug analog of rapamycin (also referred to as sirolimus), a natural macrocyclic lactone, which is a fermentation product of *Streptomyces hygroscopicus*. Like rapamycin, ridaforolimus is an immunosuppressant.

Table 2 provides the nominal dose of ridaforolimus per nominal stent length/diameter for the product matrix. The drug load for all stent designs is 1.1 µg/mm² of ridaforolimus.

Ridaforolimus is a clean, white to off-white amorphous powder that is freely soluble in acetone, ethanol, tetrahydrofuran, and acetonitrile. It is insoluble in heptane.

Ridaforolimus has 15 chiral centers. The molecular formula is C₅₃H₈₄NO₁₄P and the molecular weight/mass is 990.22 g/mol.

Figure 1 illustrates the chemical structure of ridaforolimus.

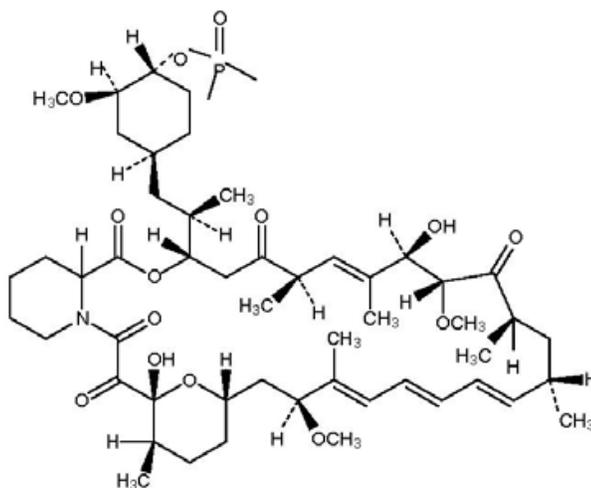


Figure 1: Chemical structure of ridaforolimus

B2. Inactive Ingredients (Polymer Coating Blend)

The bare metal 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.

B2.1 PBMA

PBMA is a biocompatible homopolymer of n-Butyl Methacrylate from the Acrylic family.

PBMA is known for a variety of biomedical uses: in ophthalmological devices (contact lenses, crystalline lenses); for odonatological applications (maxillofacial prostheses, mouth guards); in combination with other biomedical elastomers (polyurethanes, SEBS, etc.) to produce linear and graft copolymers; and as a component of the coating formulation of the following PMA approved drug eluting stents: Cypher™ drug eluting stent (Cordis, USA, PMA P020026) and XIENCE PRIME drug eluting stent (Abbott, USA, PMA P110019).

PBMA is a white amorphous solid that is soluble in ethyl acetate, tetrahydrofuran, chloroform, methylene chloride, acetone, and toluene, and sparingly soluble in alcohols – methanol, isopropanol. The molecular formula is $[\text{CH}_2\text{CH}(\text{CH}_3)(\text{COOC}_4\text{H}_9)]_n$ and the molecular weight/mass is 220-380g/mol.

Figure 2 illustrates the polymer chemical structure.

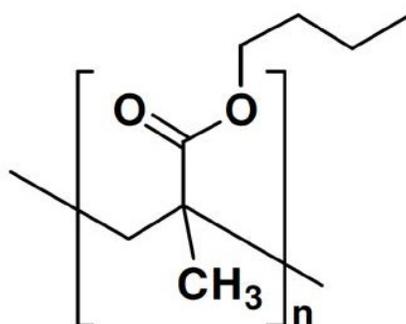


Figure 2: Chemical Structure of PBMA

B2.2 CarboSil® 20 55D UR Thermoplastic Silicone-Polycarbonate-urethane with SME®

CarboSil® 20 55D is a medical grade copolymer.

CarboSil® TSPCU is used in a wide range of medical applications, including the CE-marked nervous system electrostimulation (AxioMed Freedom® Lumbar Disc and Freedom® Cervical Disc); the biliary covered stent (X-Suit NIR® Biliary Metallic Stent); and other typical medical applications, including leads, grafts, balloons, shunts, and cardio-assist devices.

Numerous studies have demonstrated that CarboSil® is both biocompatible and safe for its intended use. The expected chemical additives and degradation products from CarboSil® and other polyurethanes have been thoroughly studied and reported in peer reviewed publications¹⁻⁷. The molecular formula is: $\text{SiC}_3\text{H}_9\text{O}-(\text{SiC}_2\text{H}_6)_p-\text{SiC}_2\text{H}_6-\text{Ri}-\text{O}-\{(\text{C}_{15}\text{H}_{12}\text{N}_2\text{O}_2)-\text{O}-(\text{R}_j\text{CO}_3)_n-\text{R}_j\text{O}\}_x-\text{C}_{15}\text{H}_{12}\text{N}_2\text{O}_2-[\text{C}_4\text{H}_8\text{O}_2-\text{C}_{15}\text{H}_{12}\text{N}_2\text{O}_2]_y-\text{z}-\text{SiC}_2\text{H}_6\text{O}_2\text{Ri}-([\text{SiC}_2\text{H}_6)_p\text{SiC}_3\text{H}_9$

The molecular weight/mass is ≥ 200 g/mol. Figure 3 illustrates CarboSil® 20 55D chemical structure.

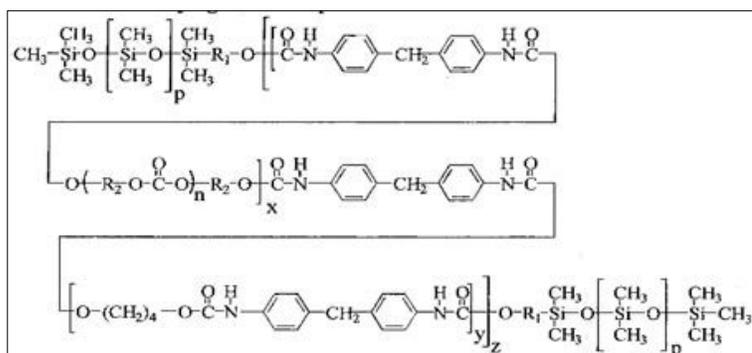


Figure 3: Chemical structure of CarboSil® 20 55D

The EluNIR Ridaforolimus Eluting Coronary Stent System is available in multiple stent sizes (diameters and lengths), containing a range nominal drug doses, as listed in Table 2.

Table 2: 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)
LUN250R08US	2.50	8	34
LUN250R12US	2.50	12	50
LUN250R15US	2.50	15	66
LUN250R17US	2.50	17	74
LUN250R20US	2.50	20	89
LUN250R24US	2.50	24	104
LUN250R28US	2.50	28	120
LUN250R33US	2.50	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
LUN300R08US	3.00	8	46
LUN300R12US	3.00	12	67

Product Catalog Number	Nominal Expanded Stent ID (mm)	Nominal Unexpanded Stent Length (mm)	Nominal Ridaforolimus Content (µg)
LUN300R15US	3.00	15	87
LUN300R17US	3.00	17	98
LUN300R20US	3.00	20	119
LUN300R24US	3.00	24	140
LUN300R28US	3.00	28	160
LUN300R33US	3.00	33	192
LUN350R08US	3.50	8	53
LUN350R12US	3.50	12	83
LUN350R15US	3.50	15	98
LUN350R17US	3.50	17	113
LUN350R20US	3.50	20	128
LUN350R24US	3.50	24	158
LUN350R28US	3.50	28	189
LUN350R33US	3.50	33	219
LUN400R08US	4.00	8	53
LUN400R12US	4.00	12	83
LUN400R15US	4.00	15	98
LUN400R17US	4.00	17	113
LUN400R20US	4.00	20	128
LUN400R24US	4.00	24	158
LUN400R28US	4.00	28	189
LUN400R33US	4.00	33	219

C. Mechanism of Action

The mechanism by which the EluNIR Ridaforolimus 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.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the treatment of patients with coronary artery disease, including exercise, diet, drug therapy, percutaneous coronary interventions (i.e., balloon angioplasty, atherectomy, bare metal stents, coated stents, and other drug-eluting stents), and coronary artery bypass grafting (CABG) surgery. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

Table 3 lists countries where the product is currently commercially available. No products have been withdrawn from the market in any country for any reason.

**Table 3: Countries with EluNIR™ Ridaforolimus Eluting Coronary Stent System
Commercial availability**

• Austria	• Estonia	• Luxembourg	• Sweden
• Belgium	• Finland	• Malta	• United Kingdom
• Bulgaria	• Germany	• Netherlands	• Iceland
• Cyprus	• Hungary	• Romania	• Liechtenstein
• Czech Republic	• Ireland	• Slovenia	• Norway
• Denmark	• Italy	• Spain	• Switzerland

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the 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^a
- 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^b
- 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
- ^a Includes arteriovenous fistula, hematoma, infection, nerve injury, pain, peripheral ischemia, phlebitis, pseudoaneurysm
- ^b 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 X](#) below.

IX. SUMMARY OF NON-CLINICAL STUDIES

A series of non-clinical laboratory studies and pharmacokinetic studies related to the product were performed. Studies included those performed on the drug substance (i.e., ridaforolimus), the coated stent alone, the polymer-only coated stent alone, the delivery system, and the finished combination products (i.e., EluNIR Ridaforolimus-Eluting Coronary Stent System).

A. Laboratory Studies

A1. In Vitro Engineering Testing

In vitro engineering testing, in accordance with FDA's "Guidance for Industry and FDA Staff:

Non-Clinical Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems" (April, 2010), was conducted on the EluNIR stent. Some in vitro engineering tests were performed on the uncoated, bare metal version of the EluNIR stent, since there was no change to the stent substrate. An appropriate rationale was provided where the testing of the bare metal stent provided a worst case representative condition for the attributes evaluated. The effect of the coating is assumed to be negligible when evaluated against measurement and manufacturing tolerances. Supplementary in vitro engineering tests were also performed on the EluNIR delivery systems containing the EluNIR stent mounted on a delivery catheter.

Table 4 summarizes this testing. "Pass" denotes that the test results met product specifications and/or the recommendations in the above referenced guidance document.

Additional tests were conducted to support the integrity of the coating on the EluNIR™ Ridaforolimus Eluting Coronary Stent System and are summarized separately in Section IX.A2.

Table 4: In vitro engineering testing supporting performance of EluNIR Stent and Delivery System

Test	Test Description	Test Article	Results
Material Characterization			
Bare Metal Stent Material Analysis – Chemical Composition	This test was conducted on a CoCr L605 sheet provided by material supplier prior to any processing to confirm that chemical composition is in accordance with ASTM F90. The test confirmed that EluNIR bare metal stents are produced from material that conforms in chemical composition to ASTM F90.	A medical grade L-605 CoCr alloy sheet	Pass
Bare Metal Stent Material Analysis – Mechanical Properties (Tensile Strength and Elongation)	This test was performed on the metal stent source material (CoCr L605 sheet) prior to any processing. The tensile and yield strength and elongation met acceptance criteria.	A medical grade L-605 CoCr alloy sheet	Pass
Delivery System Material Analysis	Raw material lots are not released prior to successfully passing the tests detailed in incoming inspection procedures.	EluNIR Stent System	Pass
Stent Dimensional and Functional Attributes			
Pitting Corrosion	This test was conducted according to ISO 25539-2 and ASTM F2129 on EluNIR stents to confirm that they possess sufficient Pitting Corrosion resistance. Results met acceptance criteria and demonstrate sufficient Pitting Corrosion resistance.	EluNIR Stent	Pass

Test	Test Description	Test Article	Results
Fretting and Crevice Corrosion	This test was conducted according to ISO 25539-2 and ASTM F2129 on EluNIR stents following accelerated durability testing in overlapped stent conditions to determine potential for Fretting and Crevice Corrosion. The results met acceptance criteria and indicate that the stents possess a high resistance to Fretting and Crevice Corrosion.	EluNIR Stents	Pass
Galvanic Corrosion	This test was conducted according to ISO 25539-2, ASTM F3044, and ASTM F2129 on EluNIR stents coupled with marketed stainless-steel PMA approved (P020040) NIRFLEX stents to confirm that EluNIR stents possess sufficient Galvanic Corrosion resistance. The results met all acceptance criteria and indicate that the stents possess a high resistance to Galvanic Corrosion.	EluNIR Stent; NIRFLEX Stent	Pass
Stent Weight	100% in process inspection of stent weight: any stent failing the inspection is rejected. All stents met acceptance criteria.	EluNIR Stent	Pass
Percent Surface Area	This test determined the percentage of vessel contact stent area to the total area of the vessel. Vessel contact stent area was calculated using measured stent dimensions and divided to theoretical total surface area of vessel at desired diameter for each stent design. The results met acceptance criteria.	EluNIR Stent	Pass
Dimensional Verification: Stent Inner Diameter (ID)	This test demonstrated that the stent inner diameter is consistent with labeling when deployed at nominal pressure. Each stent was deployed to nominal pressure, and the stent inner diameter was measured at the distal, middle, and proximal sections of the stent. The results indicate that the inner diameter of EluNIR stents is consistent with labeling.	EluNIR Stent	Pass
Maximum indicated diameter (Largest stent ID of largest labeled diameter) (formally named upper indication diameter)	This test demonstrated that the stent Maximal indicated inner diameter is consistent with labeling when deployed at Maximum labeled pressure. Each stent was deployed to Maximum labeled pressure, and the stent inner diameter was measured at the distal, middle, and proximal sections of the stent. Testing was conducted based on ASTM F2081 and ISO 25539-1. The results indicate that the Maximal indicated inner diameter of EluNIR stents is consistent with labeling.	EluNIR Stent	Pass
Non-Uniformity of Stent	This test demonstrated stent inner diameter uniformity when deployed at Nominal, Rated Burst, and Maximum pressures. Testing was conducted based on ASTM F2081 and ISO 25539-2. All results met acceptance criteria.	EluNIR Stent	Pass
Stent Foreshortening /Elongation	This test measured the change in stent length from the catheter-loaded (crimped stent) condition to deployment at Nominal, Rated Burst, and Maximum pressures. Testing was conducted based on ASTM F2081 and ISO 25539-2. All results met acceptance criteria.	EluNIR Stent	Pass

Test	Test Description	Test Article	Results
Recoil for Balloon Expandable Stents	This test quantified the amount of elastic recoil for the stent after expansion at Nominal and Rated Burst pressures. The system was inflated to either Nominal or Rated Burst pressure and stent diameter was measured at distal, middle and proximal sections of the stent. The system was deflated and the same measurements were performed. The percent recoil is calculated by subtracting the average stent diameter without the balloon from the average stent with the balloon, dividing by the average stent diameter with the balloon and multiplying by 100. Testing was conducted based on ASTM F2079 and ISO 25539-2. All results met acceptance criteria.	EluNIR Stent	Pass
Stent Integrity	This test determined whether deployment of the stent from catheter-loaded (crimped) conditions to either Nominal or Maximum labeled stent diameter can produce mechanical damage to the stent. Each deployed stent was examined under microscope for broken, cracked and/or missed stent struts. All results met acceptance criteria with no visible cracks, breakages or deformations. Testing was conducted based on ISO 25539-2.	EluNIR Stent	Pass
Radial Stiffness and Radial Strength	This test determined stent resistance to radial compression load. The stents were deployed to nominal stent diameter and placed in radial resistance tester. All results met acceptance criteria. Testing was conducted based on ISO 25539-2.	EluNIR Stent	Pass
Conformability	This test determined stent flexibility under 2-point bending. The stents were deployed to stent nominal diameter and placed on flexibility tester. All results met acceptance criteria.	EluNIR Stent	Pass
Finite Element Analysis (FEA) – Stress /Strain	This analysis was conducted to ensure that implant conditions to which the stent would be subjected would not result in failure. FEA evaluated the structural integrity of the EluNIR stent when subjected to the expected loading conditions during stent manufacturing, delivery, implantation and clinical loading. Two (2) overlapped stents deployed in a curved vessel were analyzed. The analysis showed that no failure is predicted throughout the stent simulated use. Testing was conducted based on ISO 25539-2 and FDA guidance <i>"Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems"</i> issued on: April 18, 2010, and <i>"Reporting of Computational Modeling Studies in Medical Device Submissions"</i> issued on: September 21, 2016.	EluNIR Bare Metal Stent	Pass

Test	Test Description	Test Article	Results
Finite Element Analysis (FEA) – Fatigue	<p>This analysis evaluated the structural integrity of EluNIR stents when subjected to pulsatile loading conditions.</p> <p>Loading during stent manufacturing, delivery and implantation were taken into account. Two overlapped stents deployed in a curved vessel were analyzed.</p> <p>The analysis showed that cyclic pulsatile loading of the EluNIR stent would not result in stent failure due to fatigue. Testing was conducted based on ISO 25539-2 and FDA guidance <i>Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems</i> issued on: April 18, 2010, and <i>Reporting of Computational Modeling Studies in Medical Device Submissions</i> issued on: September 21, 2016.</p>	EluNIR Bare Metal Stent	Pass
Accelerated Durability Testing (Fatigue)	<p>This test evaluated the durability of EluNIR stents under cyclic loading conditions in an overlapped configuration, on a static bend of 15mm, simulating 10 years of pulsatile fatigue, at physiological conditions.</p> <p>After undergoing tracking and simulated use, the EluNIR stents were deployed into simulated vessel in overlapped configuration and dynamically cycled for 420 million cycles. The test procedure was based on ISO 25539-2.</p> <p>Chronic particulates analysis was performed during accelerated durability testing.</p> <p>Following the accelerated durability testing, the stent appearance was examined microscopically for cracks and/or breakage. Stent chronic coating integrity and corrosion resistance (pitting, crevice, and fretting corrosion resistance) were tested based on ASTM F2129.</p> <p>The EluNIR stent withstood accelerated pulsatile durability under clinically relevant conditions, including bending, overlapping, and pulsatile fatigue without showing signs of mechanical failure, for a lifespan of at least 10 years (as simulated by 420 million cycles).</p> <p>All results of particulate analysis, chronic coating integrity, and corrosion resistance (pitting, crevice and fretting corrosion resistance) met acceptance criteria.</p>	EluNIR Stent	Pass

Test	Test Description	Test Article	Results
Magnetic Resonance Imaging (MRI) Safety and Compatibility	This test, performed with single and in combinations of up to three (3) overlapped stents, demonstrated that the EluNIR stent is MR conditional at 1.5-T and 3-T static magnetic field. Maximum temperature rise of 4.5°C; small image artifacts (max. 8mm). Testing was conducted based on ISO 25539-2 and ASTM F2503 and FDA guidance <i>"Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems"</i> Document issued on: April 18, 2010.	EluNIR Stent	Pass
Radiopacity	This test evaluated the radiopacity of the EluNIR stents prior to deployment and angiographic appearance of the stent post deployment to ensure safe and effective delivery of EluNIR stents to the target vessel location. Testing was conducted based on ISO 25539-2. The EluNIR stent design is based on the PMA approved PIONIR stent (P110004). Radiopacity is not affected by the stent coating; thus the results of the approved products are applicable.	PIONIR Bare Metal Stent	Pass
Delivery System Dimensional and Functional Attributes			
Dimensional Verification: Delivery System	The following characteristics were tested to conform to the applicable specifications: Distal Tip: total length, Tip Fuse length; Balloon: working length, Outer Diameters (OD), double wall thickness (DTW), Balloon Cones: length; Balloon Shoulder: lengths, OD, Inner Diameters (ID); Radiopaque Marker Bands: Distance between markers, Balloon to marker alignment; Distal Outer Shaft: length; Proximal Shaft: Marker locations (Femoral Marker & Brachial Marker); Delivery System: Total catheter length, Placement; Delivery System Outer Diameters (Distal Shaft OD, Transition Shaft OD, Proximal Shaft OD, Tip Entry OD).	EluNIR Delivery System	Pass
Delivery, Deployment and Retraction	This test verified the ability of the delivery system to be prepared and tracked through a tortuous simulated use model. The following characteristics were tested: <ul style="list-style-type: none"> • Guidewire compatibility • Guiding catheter compatibility • Deliverability • Balloon inflation time* • Deployment accuracy (for information only) • Fixation effectiveness (for information only) • Flushing the inner lumen • Maximum deflated balloon outer diameter (for characterization only) This test also measured the retraction forces of the delivery system after deployment of the stent. All results met acceptance criteria. Testing was conducted based on ISO 25539-2 and ASTM F2394.	EluNIR Delivery System	Pass

Test	Test Description	Test Article	Results
Balloon Rated Burst Pressure	This test statistically verified with probability/confidence 99.9%/95% that the EluNIR stent system will not rupture below the Rated Burst Pressure. All results met acceptance criteria. Testing was conducted based on ISO 25539-2.	EluNIR Delivery System	Pass
Balloon Fatigue	This test verified that 90% of balloons withstand a minimum of 10 repeated inflations to Rated Burst Pressure with confidence level of 95%. All results met acceptance criteria. Testing was conducted based on ISO 25539-2.	EluNIR Delivery System	Pass
Balloon Compliance (Stent diameter vs. balloon pressure)	This test determined variations of inner stent diameter with applied balloon pressure. Testing was conducted based on ASTM F2081 and ISO 25539-1. All results met acceptance criteria.	EluNIR Delivery System	Pass
Balloon Inflation* and Deflation Time	This test determined the amount of time required to inflate or deflate the delivery catheter balloon. All results met acceptance criteria. Testing was conducted based on ISO 25539-2.	EluNIR Delivery System	Pass
Catheter Bond Strength	This test determined balloon bond tensile strengths. Hub, body, proximal fuse, and RX-port bonds were measured. All results met acceptance criteria. Testing was conducted based on ISO 10555-1.	EluNIR Delivery System	Pass
Tip Pull Test	This test determined tensile strength of the system tip. All results met acceptance criteria. Testing was conducted based on ISO 10555-1.	EluNIR Delivery System	Pass
Flexibility and Kink Test	This test demonstrated the smallest radius that the EluNIR system can conform to prior to kinking. All results met acceptance criteria. Testing was conducted based on ISO 25539-2 and ASTM-F2394.	EluNIR Delivery System	Pass
Torque Strength	This test demonstrated the number of rotations the catheter can withstand prior to fracture. All results met acceptance criteria. Testing was conducted based on ISO 25539-2.	EluNIR Delivery System	Pass
Coating Integrity: Hydrophilic Coating	This test demonstrated that hydrophilic coating on the distal shaft and the transition shaft of the EluNIR system does not delaminate from the tube's surface during tracking through simulated use model. All results met acceptance criteria.	EluNIR Delivery System	Pass
Stent Securement	This test measures the force required to displace a stent in both distal and proximal directions from its original crimped position on the delivery system balloon after the pre-conditioning step when the system was tracked through a simulated use model. All results met acceptance criteria. Testing was conducted based on ISO 25539-2 and ASTM-F2394.	EluNIR Delivery System	Pass

Test	Test Description	Test Article	Results
Crossing Profile	This test verified that the crossing profile of the EluNIR stent system is consistent with label claims. Measurements of the EluNIR stent crimped on the balloon were taken at distal, middle, and proximal sections of the stent. The average value of the crimped stent outer diameter was calculated. All results met acceptance criteria.	EluNIR Delivery System	Pass
Visual and Handling	This test verified preparation of the EluNIR delivery system. The following characteristics were tested: <ul style="list-style-type: none"> • Luer Lock compatibility • System Cleanliness (Maximal particle size & Maximal fiber length) • Flushing Tool Cleanliness (Max. particles & fiber size) • Catheter Kinks • Stent Position • Hub Legibility • Non-traumatic Tip All results met acceptance criteria. Testing was conducted based on ISO 25539-2.	EluNIR Delivery System	Pass
Catheter Corrosion Resistance	This test verified that the EluNIR system catheter built from non-corrosive materials does not demonstrate any sign of corrosion. All results met acceptance criteria. Testing was conducted based on ASTM-F2129.	EluNIR Delivery System	Pass
Acute Particulates Analysis (after simulated use) (formally named Particulate matter: over-expansion after simulated use in overlapped conditions)	This test determined the particulate matter after navigating through a simulated use model and following deployment to Rated Burst Pressure inside simulated vasculature. The second stent was then tracked and deployed over the first in an overlapping configuration. Water was drawn through the vasculature and the particle quantities and sizes were counted and recorded. The results of the particulate testing and coating integrity are for characterization. All results met acceptance criteria.	EluNIR Delivery System	Pass

A2. Coating Characterization Testing

The following methods were developed to characterize and set initial specifications for the EluNIR Ridaforolimus Eluting Coronary Stent System. The coating characterization testing conducted on the device includes those tests summarized in [Table 5](#).

Table 5: Coating characterization testing

Test	Test Description	Test Article	Results
Coating materials: Polymers (Poly n-Butyl Methacrylate, CarboSil® 20 55D) and Drug Substance (Ridaforolimus)	Raw material lots are not released prior to successfully passing the tests.	EluNIR Stent	Pass

Test	Test Description	Test Article	Results
Appearance of Stent	This test verified that the EluNIR stent mounted on the catheter has a metallic appearance, with a transparent coating of smooth texture. All results met acceptance criteria.	EluNIR Stent	Pass
Coating Adhesion	This test characterized the adhesion of stent coating to metal strut. No coating delamination was detected after EluNIR system tracking through a simulated use model and deployment to maximal labeled diameter. All results met acceptance criteria.	EluNIR Stent	Pass
Acute Stent Coating Integrity	This test determined coating integrity in the following configurations: <ul style="list-style-type: none"> At baseline – without expansion and after expansion to stent nominal and over-expansion diameter After tracking through a simulated use model and deployment to maximal labeled diameter Stent coating was examined using light and scanning electron microscopes; all detected coating imperfections were recorded and measured. Any compromised coating area was calculated as a percentage of entire coated stent surface. All results met acceptance criteria.	EluNIR Stent	Pass
Chronic Coating Integrity (after durability test)	This test determined the coating integrity of the EluNIR stent after the accelerated durability test: 420 million cycles of radial pulsated loading in an overlapped configuration on a static bend of 15mm, simulating 10 years of pulsatile fatigue at physiological conditions. Light and scanning electron microscopes were used. All results met acceptance criteria.	EluNIR Stent	Pass
Coating Thickness	This test determined coating thickness measured on the stent cross sections prepared from the distal, middle, and proximal stent areas. Coating thickness was demonstrated to be uniform and consistent along the stent's length, as well as on different stent surfaces (inner, outer, side surfaces). For characterization only.	EluNIR Stent	Pass
Coating Uniformity Along Stent Length (formally named Drug Coating Uniformity along Stent Length)	This test evaluated coating uniformity by measuring the coated drug at various locations of the stent. Longitudinal and circumferential coating uniformity were tested using separate stents of the same size. Multiple stent segments were cut in longitudinal and circumferential stent directions, and drug amount was determined for each segment. Variations of drug content in each segment were calculated as a percentage of nominal fractional drug amounts for segments. Uniformity of drug distribution along the stent length and in circumferential directions was demonstrated. All results met acceptance criteria.	EluNIR Stent	Pass
Acute Particulates Analysis (at baseline and over-expansion in beaker) (formally named Particulate matter – baseline acute stent particulate analysis)	This test evaluated the particulate matter generated during deployment and over-expansion of the EluNIR stent in a beaker of water. The distal end (balloon and stent) was inserted into glassware filled with clean water and the stent was deployed to nominal and then to maximum labeled diameter. After agitation, aliquots of the water were withdrawn and the particle quantities and sizes were counted and recorded. The results of the particulate testing and coating integrity are for characterization. All results met acceptance criteria.	EluNIR Stent	Pass

Test	Test Description	Test Article	Results
Acute Particulates Analysis (after simulated use) (formally named Particulate matter: over- expansion after simulated use in overlapped conditions)	This test determined particulate matter after navigation through a simulated use model and following deployment to Rated Burst Pressure inside simulated vasculature. A second stent was then tracked and deployed over the first in an overlapping configuration. Water was drawn through the vasculature and the particle quantities and sizes were counted and recorded. The results of the particulate testing and coating integrity are for characterization. All results met acceptance criteria	EluNIR Stent	Pass
Chronic Particulates Analysis (during accelerated durability test)	This test determined particulate matter after the accelerated durability test: 420 million cycles of radial pulsatid loading in an overlapped configuration on a static bend of 15mm, simulating 10 years of pulsatile fatigue at physiological conditions. Particle quantities and sizes were counted and recorded for each pair of stents. The results of particulate testing and coating integrity are for characterization. All results met acceptance criteria.	EluNIR Stent	Pass
Particulate Matter (formally named Particulate matter – chemical characterization: Acute and Chronic)	This test characterized and identified particulates collected from EluNIR stents that had been tracked through a simulated use model and deployed to maximum labeled diameter in an overlapped configuration. Particulates that had been collected from EluNIR stents during accelerated durability testing also were analyzed for chemical identification.	EluNIR Stent	Pass
Assay (Drug Content) (formally named Drug Assay)	An assay test was conducted to quantitatively verify the total amount of drug on the EluNIR stent. All results met acceptance criteria.	EluNIR Stent	Pass
Drug Identification	All results met acceptance criteria.	EluNIR Stent	Pass
Uniformity of Dosage Units (formally named Drug content uniformity)	This test verified uniformity of the drug content between individual stents. Multiple stents were tested for verification. All results met acceptance criteria.	EluNIR Stent	Pass
Degradation Products/Drug Impurities (formally named Drug Impurities and degradation products)	This test quantitatively verified the amount and type of degradation products. All results met acceptance criteria.	EluNIR Stent	Pass
Drug Elution	This in vitro test determined the drug release profile of the drug substance. All results met acceptance criteria.	EluNIR Stent	Pass
Antioxidant Preservative- Butylated Hydroxy Toluene (BHT)	This test determined the amount of BHT in the EluNIR stent. All results met acceptance criteria.	EluNIR Stent	Pass
Residual Solvents – Tetrahydrofuran (THF)	This test determined the amount of residual solvent in the EluNIR stent. All results met acceptance criteria.	EluNIR Stent	Pass

A3. Chemistry Manufacturing and Controls (CMC) Testing

Where applicable, International Conference on Harmonization (ICH) guidelines were followed for the testing routinely performed on EluNIR stents as part of CMC. This testing is summarized in [Table 6](#). Information to support the stability of the EluNIR stent is summarized separately in [Section IX A4](#).

Table 6: Stent release test

Test	Test Description	Test Article
Appearance of Stent	A visual inspection is conducted to verify that the EluNIR stent meets the product's appearance specifications.	EluNIR Stent
Drug Identity	Assay is conducted to verify the identity of the drug substance, ridaforolimus, on the EluNIR Stent.	EluNIR Stent
Drug Content	Assay is conducted to quantitatively verify that the total amount of drug on the EluNIR stent met specifications for finished goods release.	EluNIR Stent
Uniformity of Dosage Units	Multiple stents are tested to verify that the uniformity of the drug content between individual stents was within specifications established for finished goods release.	EluNIR Stent
Degradation Products / Drug Impurities	HPLC analysis is conducted to quantitatively verify the amount and type of degradation products on the EluNIR Stent.	EluNIR Stent
Drug Elution	The <i>in vitro</i> release profile for ridaforolimus is measured on the EluNIR stent. Specifications are based on the elution characteristics of clinical and stability data. The product meets specifications established for finished goods release.	EluNIR Stent
Particulate Matter	Particulate levels are monitored to verify that they remain below acceptable levels as established in the product's specifications.	EluNIR Integrated Stent System (Stent mounted on Delivery System)
Residual Solvent*	The amount of Tetrahydrofuran (THF) on the EluNIR stent is determined to verify that the residual level of the solvent used in the manufacturing process is within the specification limits established for finished goods release.	EluNIR Stent
Antioxidant Preservative*	The levels of Butylated Hydroxy Toluene (BHT) on the EluNIR stent is quantified to verify that it is within the specification limits established for finished goods release.	EluNIR Stent
Bacterial Endotoxins Test	The amount of bacterial endotoxins is verified to be within the specification limits established for finished goods release.	EluNIR Integrated Stent System (Stent mounted on Delivery System)
Sterility Biological Indicator	The release of each lot of EluNIR Stent System is based on verification that the sterilization load complies with validated sterilization cycle parameters and satisfies the requirement for labeling the finished goods as sterile.	EluNIR Integrated Stent System (Stent mounted on Delivery System)

*Not a release test

A4. Stability/Shelf Life

A formal stability study was conducted to establish a shelf life expiration date for the EluNIR Stent System. Testing included appearance of stent, drug assay, degradation products / drug impurities, drug elution, particulate matter, antioxidant preservative (BHT), product sterility and packaging integrity (visual inspection, tensile strength [peel test], seal integrity [bubble leak test], dye penetration and bacterial endotoxin).

Testing to establish container closure integrity was conducted to ensure sterility was maintained during the shelf life of the product. Functional testing of the stent system was conducted on aged products. The data generated to date support a shelf life of 24 months.

A5. Sterilization

The EluNIR Stent System is sterilized using ethylene oxide (EO) sterilization. The cycle is validated per ISO 11135 “Medical Devices-Validation and Routine Control of Ethylene Oxide Sterilization”. Results obtained from the sterilization studies show that the product satisfies a minimum Sterility Assurance Level (SAL) of 10^{-6} and the requirements of ISO 10993-7 “Ethylene Oxide Sterilization Residuals”. In addition, the amount of bacterial endotoxins was verified to be within the specification limits.

B. Animal Studies

B1. Major Supportive Animal Studies

Detailed arterial histopathology and histomorphometry are not obtainable through human clinical trials. Consequently, a series of animal studies were conducted to evaluate safety, efficacy (proof of concept dosing), and overall product performance.

All animal studies (feasibility, safety, pharmacokinetic and acute) were conducted in accordance with §21CFR 58 (Good Laboratory Practices). The results of these studies support the safety and biocompatibility of the EluNIR Ridaforolimus Eluting Coronary Stent System. [Table 7](#) includes summaries of the major animal studies performed to support product safety.

Table 7: Summary of major supportive animal studies

Study Number	Stent Design	Type/Number of Animals	Number of Stents	Follow-up Duration	Major Endpoints
UWS00025 180-day Safety Study, Overlapping Configuration	Test Article: EluNIR Ridaforolimus Eluting Coronary Stent System (DES), 2.75/3.0 x 12mm Control Article: Presillion Plus (BMS) 2.75/3.0 x 12mm GLP: Yes	Yucatan mini swine/28 (11 Male [castrated] and 17 Female [nulliparous])	Test: 74 (37 pairs) Control: 72 (36 pairs) (LCX, LAD, and/or RCA) Animals received at least one overlapping pair of test stents/SDSs and one overlapping pair of control stents/SDSs in separate vessels. 2 stents/vessel (overlapping) 2-3 overlapping stent pairs/animal (4 to 6 stents/animal)	Up to 180 days (Days 3, 30 and 180)	<ol style="list-style-type: none"> 1. Device Deployment and Acute Performance 2. Thromboresistance Assessment 3. Activated Clotting Times 4. Quantitative Coronary Angiography 5. Animal Observations <ol style="list-style-type: none"> 5.1 Mortality/Moribundity 5.2 Clinical Observations 5.3 Body Weights and Body Condition Score 6. Clinical Pathology <ol style="list-style-type: none"> 6.1 Hematology 6.2 Fibrinogen 6.3 Serum Chemistry 7. Anatomic Pathology <ol style="list-style-type: none"> 7.1 SEM Analysis 7.2 Histomorphometry 7.3 Histopathology
UWS00024 360-day Safety Study, Single Configuration	Test Article: EluNIR Ridaforolimus Eluting Coronary Stent System, multiple doses (DES) 2.75/3.0 x 17mm 2.75/3.0 x 33mm Control Article: Presillion Plus (BMS) 2.75/3.0 x 17mm GLP: Yes	Yucatan mini swine/62 (47 Male [castrated] and 15 Female [nulliparous]) Note: 2 males were early dead on Day 0; did not reach protocol time point.	Test: 87 (DES=55 [excluding 2 early dead], High dose DES (5x drug load, 2x polymer load)=16, Long stent DES=16 [excluding 1 early dead]) Control: 51 [excluding 1 early dead] (LCX, LAD, RCA) Animals received both test and control (up to 3 stents (DES, BMS, long DES, or high dose DES)). 1 stent/vessel 2 to 3 stents/animal	Up to 360 days (Days 3, 30, 90, 180, and 360)	<ol style="list-style-type: none"> 1. Device Deployment and Acute Performance 2. Thromboresistance Assessment 3. Activated Clotting Times 4. Quantitative Coronary Angiography 5. Animal Observations <ol style="list-style-type: none"> 5.1 Mortality/Moribundity 5.2 Clinical Observations 5.3 Body Weights and Body Condition Score 6. Clinical Pathology <ol style="list-style-type: none"> 6.1 Hematology 6.2 Fibrinogen 6.3 Serum Chemistry 7. Anatomic Pathology <ol style="list-style-type: none"> 7.1 SEM Analysis 7.2 Histomorphometry 7.3 Histopathology

Study Number	Stent Design	Type/Number of Animals	Number of Stents	Follow-up Duration	Major Endpoints
UWS00033, Acute Performance Study, Stent Delivery System (SDS)	<p>Test Article: EluNIR Ridaforolimus Eluting Coronary Stent System, multiple doses (Modified Process-DES, 3.0 x 17 mm)</p> <p>Control:</p> <ul style="list-style-type: none"> • EluNIR Ridaforolimus Eluting Coronary Stent System (DES, 3.0 x 17mm) • Resolute Integrity Stent Systems (DES, 3.0 x 18mm) <p>GLP: Yes</p>	Yorkshire swine/2 (Male [castrated])	<p>Test: 12 (EluNIR Modified SDS)</p> <p>Control: 24 (EluNIR SDS=12; Resolute SDS=12) (LCX, LAD, RCA)</p> <p>Animals received both test and control.</p> <p>6 stents (n=2/type)/vessel tracked including 2 deployed</p> <p>18 stent/animal</p>	Acute	<ol style="list-style-type: none"> 1. Device Deployment and Acute Performance 2. Activated Clotting Times 3. Quantitative Coronary Angiography 4. Animal Observations <ol style="list-style-type: none"> 4.1 Mortality/Moribundity

Study Number	Stent Design		Type/ Number of Animals	Number of Stents	Follow-up Duration	Major Endpoints
UWS00035 Acute Performance Study, Stent Delivery System (SDS)	Test Article:		Yorkshire swine/5 (Male)	<p>Test: 12 (Improved BioNIR 2.5x8mm); 12 (Improved BioNIR 4.0x33mm); 12 (BioNIR 2.75x44mm); 12 (BioNIR 4.0x44mm); 12 (Improved NIRxcell 2.5x8mm); 12 (Improved NIRxcell 4.0x33mm)</p> <p>Control: 12 (Control BioNIR 2.5x8 mm); 12 (Control BioNIR 4.0x33mm); 12 (Control NIRxcell 2.5x8mm); 12 (Control NIRxcell 4.0x33mm)</p> <p>(RCA, LAD, LCX and/or and branches thereof). BioNIR test articles (2.75x44mm and 4.0x44mm) will be tracked through a coronary artery and two will be implanted in a vessel of appropriate length and diameter (e.g., mammary artery, subclavian artery, etc.)</p> <p>Animals received both test and control.</p> <p>Up to 8 stents tracked and 2 stents implanted/vessel tracked up to 20 stents/animal</p>	Acute	<ol style="list-style-type: none"> 1. Device Deployment and Acute Performance 2. Activated Clotting Times 3. Quantitative Coronary Angiography 4. Animal Observations <ol style="list-style-type: none"> 4.1 Mortality/Moribundity 4.2 Clinical Observations 4.3 Body Weights and Body Condition Score
	Identification and Description	Size				
	Modified EluNIR; Smallest/ shortest (DES)	2.5x8mm				
	Modified EluNIR; Largest/ longest (DES)	4.0x33mm				
	Modified EluNIR; Smallest long (DES)	2.75x44mm				
	Modified EluNIR; Largest long (DES)	4.0x44mm				
	Modified NIRxcell; Smallest/shortest (BMS)	2.5x8mm				
	Modified NIRxcell; Largest/ longest (BMS)	4.0x33mm				
	Control Article:					
	Identification and Description	Size				
	Control EluNIR; Smallest/shortest (DES)	2.5x8mm				
	Control EluNIR; Largest/ longest (DES)	4.0x33mm				
	Control NIRxcell; Smallest/shortest (BMS)	2.5x8mm				
	Control NIRxcell; Largest/ longest (BMS)	4.0x33mm				
GLP: Yes						

Study Number	Stent Design	Type/ Number of Animals	Number of Stents	Follow-up Duration	Major Endpoints
UWS00020 Local/Systemic pharmacokinetics (PK) Study	Test Article: EluNIR Ridaforolimus Eluting Coronary Stent System (DES), 2.75/3.0 x 17mm Control Article: N/a GLP: Yes	Yucatan mini swine/27 (10 Male [castrated] and 1 Female [nulliparous])	Test: 73 Control: N/a (RCA, LAD, LCX and/or branches thereof). 1 stent/vessel 2 to 3 stents/animal	Up to 456. (Days 1, 3, 7, 14, 30, 60, 90, 180, and 456)	<ol style="list-style-type: none"> 1. Device Deployment 2. Activated Clotting Times 3. Quantitative Coronary Angiography 4. Animal Observations <ol style="list-style-type: none"> 4.1 Mortality/Moribundity 4.2 Clinical Observations 4.3 Body Weights and Body Condition Score 5. Clinical Pathology <ol style="list-style-type: none"> 5.1 Hematology 5.2 Fibrinogen 5.3 Serum Chemistry 6. Ridaforolimus Extraction and Bioanalysis <ol style="list-style-type: none"> 6.1 Systemic Drug Levels 6.2 Drug Release Profile (Stent Drug Levels) 6.3 Arterial Tissue Drug Levels 6.4 Myocardial Tissue Levels 7. Anatomic Pathology <ol style="list-style-type: none"> 7.1 Gross Necropsy

B2. Biocompatibility Studies

A series of GLP biocompatibility tests and USP Physicochemical tests were conducted to demonstrate that the components of the EluNIR Ridaforolimus Eluting Coronary Stent System are non-toxic and biocompatible. Tests were conducted on final, ethylene oxide-sterilized EluNIR coated stents, polymer-only coated stents, stent delivery systems (delivery system and modified delivery system), stent protector sleeve and the flushing tool. These test articles were processed in the same manner as the finished EluNIR product. In all of these test systems, the materials were non-reactive and met all acceptance criteria. The results of the biocompatibility studies indicated that the EluNIR Coronary Stent System was biologically safe and acceptable for clinical use:

- The **EluNIR Stent** was categorized as an implant device with permanent contact duration with circulating blood (>30 days).
- The **Delivery System** was categorized as an externally communicating device with limited contact duration with circulating blood (<24 hours).
- The **Packing System** was categorized as follows:
 - The Stent Protector Sleeve (sleeve segment), the primary immediate packaging component which directly interacts with the coating formulation, is a non-contact device that does not contact the patient's body directly or indirectly
 - The Flushing Tool, the associated component included in the Coronary Hoop packaging component, does not come in direct contact with the patient's body; however, since there is indirect blood path contact, it is considered to be an externally communicating device with limited (< 24 hours), indirect contact with blood.

All biocompatibility testing was conducted in accordance with one or more of the following general regulations, standards and guidance documents:

- Good Laboratory Practices Regulations (21 CFR § 58)
- Guidance for Industry: "Coronary Drug-Eluting Stents-Nonclinical and Clinical Studies" (March 2008)
- Guidance for Industry and FDA Staff: "Select Updates for Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems"
- Blue Book Memorandum #G95-1 "Use of International Standard ISO-10993, 'Biological Evaluation of Medical Devices Part 1: Evaluation and Testing,'" (May 1, 1995)
- ISO 10993-1, "Biological Evaluation of Medical Devices: Evaluation and Testing within a Risk Management Process"
- ISO 14971, Medical devices: "Application of Risk Management to Medical Devices"
- USP "Physicochemical Test – Containers Plastics" <661>
- FDA Guidance for Industry: "Container Closure Systems for Packaging Human Drugs and Biologics"

Table 8 provides a summary of the biocompatibility testing conducted to support the EluNIR Ridaforolimus Eluting Coronary Stent System.

Table 8: Summary of biocompatibility testing

Test Name	Test Description	Test Article	Results
Cytotoxicity	ISO 10993-5: <i>In Vitro</i> Cytotoxicity (L929 MEM Elution)	<ul style="list-style-type: none"> Coated (drug and polymer blend) stent Polymer only coated stent Delivery system 	Pass (non-cytotoxic)
	MHLW, PFSB/ELD (Iyakushin) Notification No.0213001 (Colony Forming Cell Assay with V79 Chinese hamster lung cells)	<ul style="list-style-type: none"> Modified delivery system Stent Protector Sleeve (sleeve segment) Flushing tool 	Pass (non- cytotoxic)
Pyrogenicity	ISO-10993-11: Systemic Toxicity (Material Mediated Rabbit, Injection)	<ul style="list-style-type: none"> Coated (drug and polymer blend) stent Polymer only coated stent Delivery system Modified delivery system 	Pass (non- pyrogenic)
	USP, General Chapter <151>, Pyrogen Test		
Sensitization	ISO-10993-10: Sensitization (Guinea pig Maximization)	<ul style="list-style-type: none"> Coated (drug and polymer blend) stent Polymer only coated stent Delivery system Modified delivery system Flushing tool 	Pass (non-sensitizing)
Acute Intracutaneous Reactivity	ISO-10993-10: Irritation (Injection)	<ul style="list-style-type: none"> Coated (drug and polymer blend) stent Polymer only coated stent Delivery system Modified delivery system Flushing tool 	Pass (non-irritant)
Acute Systemic Toxicity	ISO-10993-11: Systemic toxicity (Acute, Intravenous)	<ul style="list-style-type: none"> Coated (drug and polymer blend) stent Polymer only coated stent Delivery system Modified delivery system Flushing tool 	Pass (non-toxic)
	ISO-10993-11: Systemic toxicity (Acute, Subcutaneous)	<ul style="list-style-type: none"> Coated (drug and polymer blend) stent Polymer only coated stent 	Pass (non-toxic)
Hemocompatibility /Hemolysis	ISO-10993-4: <i>In Vivo</i> Thromboresistance (see Section XI B2)	<ul style="list-style-type: none"> Stent System 	Pass (non-thrombogenic)
	ISO-10993-4: <i>In Vitro</i> ASTM F756: Hemolytic Properties of Materials	<ul style="list-style-type: none"> Coated (drug and polymer blend) stent 	Pass (non-thrombogenic)

Test Name	Test Description	Test Article	Results
		<ul style="list-style-type: none"> Modified delivery system Stent Protector Sleeve (sleeve segment) Flushing tool 	Pass (non-thrombogenic)
Complement Activation	ISO-10993-4: Complement Activation Test (C3a and SC5b-9)	<ul style="list-style-type: none"> Coated (drug and polymer blend) stent Polymer only coated stent Delivery system Modified delivery system 	Pass
Implantation	ISO-10993-6: Local Effects After Implantation (6 weeks, Rabbit , Intramuscular)	<ul style="list-style-type: none"> Coated (drug and polymer blend) stent Polymer only coated stent 	Pass
	ISO-10993-6: Local Effects After Implantation (12 weeks, Rabbit , Intramuscular)	<ul style="list-style-type: none"> Coated (drug and polymer blend) stent Polymer only coated stent 	Pass
Mutagenesis	ISO-10993-3: Bacterial Reverse Mutation Assay (Ames test)	<ul style="list-style-type: none"> Coated (drug and polymer blend) stent Polymer only coated stent Delivery system 	Pass (non-mutagenic)
	ISO-10993-3: Lymphoma Assay for Mammalian Cell Mutagenicity	<ul style="list-style-type: none"> Coated (drug and polymer blend) stent Polymer only coated stent 	Pass (non-mutagenic)
	ASTM E1280-1997 Standard Guide for Performing the Mouse Lymphoma Assay for Mammalian Cell Mutagenicity		
	OECD Guidelines for the Testing of Chemicals, Section 4, Test No. 476: In vitro Mammalian Cell Gene Mutation Test		
	ISO-10993-3: Mouse Peripheral Blood Micronucleus Study	<ul style="list-style-type: none"> Coated (drug and polymer blend) stent Polymer only coated stent 	Pass (non-mutagenic)
	OECD Guidelines for the Testing of Chemicals, Section 4, Test No. 474: Mammalian Erythrocyte Micronucleus Test		
Material Characterization (USP Physicochemical Testing)	USP Physicochemical Extracts <661> (Aqueous)	<ul style="list-style-type: none"> Coated (drug and polymer blend) stent Delivery system Stent Protector Sleeve (sleeve segment) 	Pass

In vivo animal testing conducted on the EluNIR Stent System evaluated the effects of drug multiple doses and device exposure in a porcine coronary artery for up to 360 days, in lieu of ISO-10993 chronic toxicity and muscle implantation testing. These

studies showed no evidence of local arterial or systemic toxicity. The resulting tissue histology in these studies did not display pathology consistent with drug or polymer-induced toxicity. The animal studies are summarized separately in [Section XI B1](#).

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 (see [Table 8](#)).

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.

Based on *in vitro* analytical and stability testing results, there is no evidence to suggest that, under established processing and storage conditions, any chemical interactions occur between the polymers (CarboSil[®] 20 55D and PBMA) and the ridaforolimus drug that would lead to the formation of covalent bonds or that would alter the structure of the drug in any way to form a new intermediate or molecular entity.

C. Additional Studies

C1. Studies on the Drug Substance - Drug 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 EluNIR stent. 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.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

The principal safety and effectiveness and pharmacokinetics information for the EluNIR[™] Ridaforolimus Eluting Coronary Stent System (EluNIR) were derived from a pivotal clinical trial as well as PK trial, both under IDE# G140107:

- The BIONICS clinical trial CIP#BioNIR-001
- The BIONICS-PK clinical trial CIP# BioNIR-PK-001

A summary of the two (2) clinical studies is presented below.

1) BIONICS CLINICAL TRIAL (CIP#: BioNIR-001)

The BIONICS trial evaluated the safety and efficacy of EluNIR Ridaforolimus in comparison to the Medtronic Zotarolimus-Eluting Resolute Stent, for its indication for use of improving coronary luminal diameter in patients with symptomatic heart disease due to *de novo* lesions ≤ 30 mm in length in native coronary arteries with reference

diameters of 2.5mm to 4.25mm. The trial has reached the primary endpoint. Patient follow-up is ongoing up to five years, per protocol.

A. Study Design:

BIONICS is a prospective, multi-center, single-blind, two-arm, 1:1 randomized clinical trial with 1919 enrolled patients with a wide spectrum of Percutaneous Coronary Intervention (PCI) indications (stable angina as well as ACS, including subacute ST-Elevated Myocardial Infarction (STEMI) (>24 hours since first hospital presentation)), "more comers" concept. It is being performed at 76 sites in the US, Canada, Europe and Israel. Enrollment in the study started on March 12, 2014 and was completed on August 28, 2015.

The study objective was to demonstrate clinical and angiographic non-inferiority for the EluNIR in comparison to the Resolute Zotarolimus-Eluting Stent System.

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 were also evaluated by intravascular ultrasound (IVUS) at baseline and at the 13-month follow-up (111 evaluable at 13-months follow-up).

From recent US trials of best in class DES (Xience V, Promus Element and Resolute), the 1-year TLF rate in patients with non-complex lesions not undergoing routine angiographic follow-up was approximately 4.1%. Using the assumption of the more-comers' design, the 1-year event rate was conservatively increased by ~40% (assuming enrollment rate for complex patients/lesions 40% with double the standard event rate) – thus 5.8%. Therefore, with a one-sided 95% upper bound of the confidence interval of 3.3% (a relative 57% margin) and 1:1 randomization, enrolling 1810 patients (905 per group) provided 90% power to demonstrate non-inferiority. Assuming 95% follow-up rate at 1 year, approximately 1906 patients were enrolled (953 in each group).

Randomization was stratified by the presence of medically treated diabetes vs. no medically treated diabetes, acute coronary syndrome (ACS, unstable angina, non-STEMI and subacute STEMI) vs. no ACS (i.e., stable coronary artery disease), and by site. The primary analysis of the BIONICS data was performed on the Full Analysis Set (FAS) which was defined as all randomized subjects assigned to treatment per randomization, regardless of whether they received the study stent. Subjects were included in the FAS once the study stent has been advanced beyond the guide catheter (de-registered subjects are excluded).

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

Angiographic, IVUS and ECG Core laboratories enabled standardized and objective analysis of the data.

Patients' follow-up is described in the following timelines, per protocol: 30 days, 6 months, 1 year post randomization, and annually thereafter up to 5 years.

The schematic diagram for the study design is displayed in [Figure 4](#).

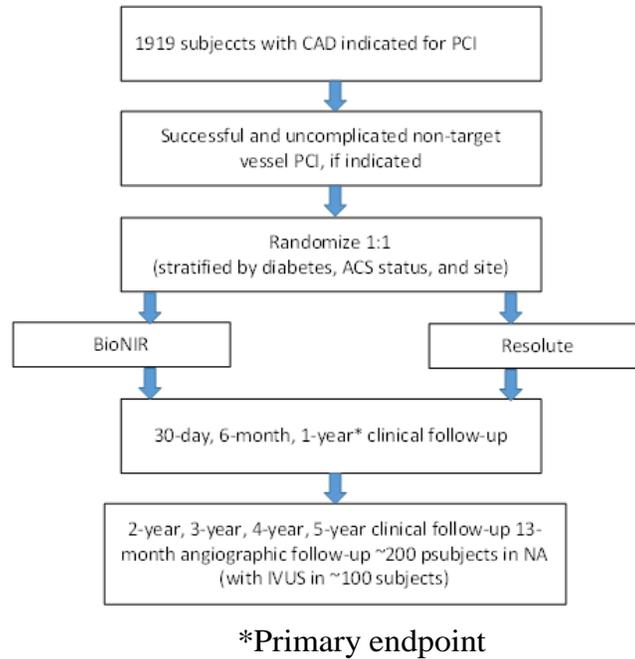


Figure 4: BIONICS Clinical Trial Design

A1. Clinical Inclusion and Exclusion Criteria

Inclusion Criteria

All inclusion criteria must have been present for the patient to be eligible for enrollment.

General Inclusion Criteria:

1. Age ≥ 18 years.
2. An indication for percutaneous coronary intervention (PCI) including angina (stable or unstable), silent ischemia (in absence of symptoms a visually estimated target lesion diameter stenosis (DS) of $\geq 70\%$, a positive non-invasive stress test, or fractional flow reserve (FFR) ≤ 0.80 must be present), non-ST-elevation myocardial infarction (NSTEMI), or recent ST-elevation myocardial infarction (STEMI). For STEMI the time of presentation to the first treating hospital, whether a transfer facility or the study hospital, must have been >24 hours prior to randomization with enzyme levels (creatin kinase-muscle-brain isoenzyme [CK- MB] or Troponin) demonstrating that either or both enzyme levels have peaked.
3. Non-target vessel PCI were allowed prior to randomization depending on the time interval and conditions:

- a. During Baseline Procedure:
 - PCI of non-target vessels performed during the baseline procedure itself immediately prior to randomization if successful and uncomplicated defined as: <50% visually estimated residual DS, Thrombolysis in Myocardial Infarction (TIMI) Grade 3 flow, no dissection \geq type C (National Heart, Lung, and Blood Institute [NHLBI] [coronary artery dissection scale]), no perforation, no persistent ST segment changes, no prolonged chest pain, no TIMI major or Bleeding Academic Research Consortium (ARC) type 3 bleeding.
 - b. Less than 24 hours prior to Baseline Procedure: Not allowed (see [Criteria#2](#)).
 - c. 24 hours-30 days prior to Baseline Procedure:
 - i. PCI of non-target vessels 24 hours to 30 days prior to randomization if successful and uncomplicated as defined above.
 - ii. In addition, in cases where non-target lesion PCI had occurred 24-72 hours prior to the baseline procedure, at least two sets of cardiac biomarkers were drawn at least 6 and 12 hours after the non-target vessel PCI.
 - iii. If cardiac biomarkers were initially elevated above the local laboratory upper limit of normal (ULN), serial measurements must have demonstrated biomarkers were falling.
 - d. Over 30 days prior to Baseline Procedure:
 - i. PCI of non-target vessels performed greater than 30 days prior to procedure whether or not successful and uncomplicated.
4. Subject or legal guardian was willing and able to provide informed written consent and comply with follow- up visits and testing schedule.

Angiographic Inclusion Criteria (visual estimate):

1. Target lesion(s) were located in a native coronary artery or bypass graft conduit with visually estimated diameter of ≥ 2.5 mm to ≤ 4.25 mm.
2. Complex lesions were allowed including calcified lesions (lesion preparation with scoring/cutting and rotational atherectomy were allowed), presence of thrombus that was non-occlusive and did not require thrombectomy, chronic total occlusion (CTO), bifurcation lesions (except planned dual stent implantation), ostial right coronary artery (RCA) lesions, tortuous lesions, bare metal stent (BMS) restenotic lesions, protected left main lesions, and saphenous vein graft (SVG) lesions.
3. Overlapping stents were allowed.

Exclusion Criteria

All exclusion criteria must have been absent for the patient to be eligible for enrollment.

General Exclusion Criteria:

1. STEMI within 24 hours of initial time of presentation to the first treating hospital, whether at a transfer facility or the study hospital, or in whom enzyme levels (either CK-MB or Troponin) had not peaked.
2. PCI within the 24 hours preceding the baseline procedure.

3. Non-target lesion PCI in the target vessel within 12 months of the baseline procedure.
4. History of stent thrombosis (ST).
5. Cardiogenic shock (defined as persistent hypotension [systolic blood pressure <90 millimeters of mercury (mmHg) for more than 30 minutes]) or requiring pressors or hemodynamic support, including intra-aortic balloon pump.
6. Subject was intubated.
7. Known left ventricular ejection fraction (LVEF) <30%.
8. Relative or absolute contraindication to dual antiplatelet therapy (DAPT) for 12 months (including planned surgeries that could not be delayed)
9. Subject had an indication for chronic oral anticoagulant treatment (with either vitamin K antagonists or novel oral anticoagulants)
10. Calculated creatinine clearance <30 milliliters (mL)/minute (min) using Cockcroft-Gault equation (<40 mL/min for subjects participating in the angiographic follow-up sub-study).
11. Hemoglobin <10 grams (g)/deciliter (dL).
12. Platelet count < 100,000 cells/cubic millimeter (mm³) or >700,000 cells/mm³.
13. White blood cell (WBC) count <3,000 cells/mm³.
14. Clinically significant liver disease.
15. Active peptic ulcer or active bleeding from any site.
16. Bleeding from any site within the prior 8 weeks requiring active medical or surgical attention.
17. If femoral access was planned, significant peripheral arterial disease which precluded safe insertion of a 6F sheath.
18. History of bleeding diathesis or coagulopathy or refusal of blood transfusions.
19. Cerebrovascular accident (CVA) or transient ischemic attack (TIA) within 6 months prior to screening, or any permanent neurologic defect attributed to a CVA.
20. Known allergy to the study stent components, whether in the EluNIR or Resolute, e.g., cobalt, nickel, chromium, molybdenum, CarboSil[®], poly-n-butyl-methacrylate (PBMA), BioLinx polymer, or limus drugs (ridaforolimus, zotarolimus, tacrolimus, sirolimus, everolimus, or similar drugs or any other analogue or derivative or similar compounds).
21. Known allergy to protocol-required concomitant medications such as aspirin, or DAPT (clopidogrel, prasugrel, ticagrelor), or heparin and bivalirudin, or iodinated contrast that cannot be adequately pre-medicated.
22. Any co-morbid condition that may have caused non-compliance with the protocol (e.g., dementia, substance abuse) or reduced life expectancy to <24 months (e.g., cancer, severe heart failure, severe lung disease).
23. Subject was participating in or planned to participate in any other investigational drug or device clinical trial that had not reached its primary endpoint.
24. Women who were pregnant or breastfeeding (women of child-bearing potential

[WOCBP] must have had a negative pregnancy test within 1 week before treatment).

25. Women who intended to become pregnant within 12 months after the baseline procedure (WOCBP who were sexually active must have agreed to use a reliable method of contraception from the time of screening through 12 months after the baseline procedure).
26. Subject had received an organ transplant or was on a waiting list for an organ transplant.
27. Subject was receiving or scheduled to receive chemotherapy within 30 days before or any time after the baseline procedure.
28. Subject was receiving oral or intravenous (IV) immunosuppressive therapy or had known life-limiting immunosuppressive or autoimmune disease (e.g., human immunodeficiency virus [HIV]). Corticosteroids were allowed.

Angiographic Exclusion Criteria (visual estimate):

1. Target lesions in more than two major coronary arteries (i.e., 2 of left anterior descending [LAD], left circumflex [LCX], right coronary artery [RCA]) and their respective branches (the Ramus Intermedius was defined as a branch of the LCX).
2. More than two target lesions per target vessel were planned (two lesions separated by less than 10 mm that could have been covered by a single stent were considered one lesion).
3. More than 100 mm length of planned study stenting in the entire coronary tree.
4. Occlusive thrombus and/or a thrombus that required thrombectomy in a target vessel.
5. Unprotected left main lesions; $\geq 30\%$, or planned unprotected left main intervention.
6. Ostial LAD or LCX lesions (stenting of any diseased segment within 5 mm of the unprotected left main coronary artery).
7. Bifurcation lesions with planned dual stent implantation.
8. Stenting of lesions due to drug-eluting stent (DES) restenosis.
9. Another lesion in a target or non-target vessel (including all side branches) was present that required or had a high probability of requiring PCI within 21 months after the baseline procedure.

A2. Follow-up Schedule

Clinical follow-up was performed at 30 days, 6 months, and 1 Year. The next follow up visits will take place at 2, 3, 4, and 5 years post randomization.

The trial also included an angiographic sub-study, with 202 consenting subjects (158 evaluable) at participating North American sites undergoing planned angiographic follow-up at 13 months after enrollment, and the first 155 of these subjects also undergoing intravascular ultrasound (IVUS) at baseline and at 13 months following randomization (111 evaluable at 13 months follow up).

A3. Clinical Endpoints

1. Primary Endpoint:

Target Lesion Failure (TLF) at 12 months defined as the composite of cardiac death, target vessel-related myocardial infarction (MI)¹, or ischemia-driven target lesion revascularization (TLR).

2. Clinical Secondary Endpoint

Secondary endpoints were evaluated at 30 days, 6 months, and 1 year for this analysis, with 2, 3, 4, and 5- year analyses ongoing (except as noted):

- Device, Lesion, and Procedure Success at time of baseline procedure
- TLF at 30 days, 6 months, and 2, 3, 4, and 5 years
- Major adverse cardiac events (MACE; the composite rate of cardiac death, any MI, or ischemia- driven TLR)
- Target vessel failure (TVF; the composite rate of death, target vessel related MI, or ischemia-driven target vessel revascularization [TVR])
- All-cause mortality
- Cardiac death
- MI
- Target vessel related MI
- Ischemia-driven TLR
- Ischemia-driven TVR
- Stent thrombosis (ARC definite and probable)

3. Other Secondary Endpoints

Angiographic Sub-Study

- Angiographic in-stent loss (LL)

IVUS Sub-Study

- In-stent percent neointimal hyperplasia (NIH)
- Stent malapposition

¹ 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 $\geq 10x$ the local laboratory ULN, or to $\geq 5x$ 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 $\geq 70x$ the local laboratory ULN, or $\geq 35x$ 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.

B. Accountability of PMA Cohort

At the time of database lock, of 1919 patients enrolled in the PMA study, 96.7% (1856/1919) patients are available for analysis at the completion of the study, the 12 month post-operative visit.

A total of 4206 patients signed the Informed Consent Form (IFC), of which 2263 were screen failures. In total, 1943 patients were randomized; 974 to EluNIR™ and 969 to Resolute, respectively. For 24 patients; 16 in the EluNIR arm and eight (8) in the Resolute arm, the study stent was not advanced beyond the guiding catheter and the patients were de-registered from the study prior to being implanted with the study stent, leaving 1919 patients enrolled for the study. Twenty-one (21) deaths were reported in the study within the first 12 months (+14 days) after the Baseline procedure; 11 (1.1%) in the EluNIR™ arm, and 10 (1%) in the Resolute arm. Seven (7) patients, five (5) (0.5%) in the EluNIR™ arm, and two (2) (0.2%) in the Resolute arm, withdrew consent, and 21 patients, 11 (1.1%) in the EluNIR™ arm, and 10 (1%) in the Resolute arm, were lost to follow-up within the first 12 months (+14 days) after then Baseline procedure. [Table 9](#) presents the overall disposition of subjects by treatment including reasons for discontinuations.

Table 9: Subject Disposition

Parameter	Statistic	EluNIR	Resolute	Overall
Signed Informed Consent	n			4206
Screen Failure	n			2263
Randomized	n	974	969	1943
De-registered	n	16	8	24
Enrolled (Full Analysis Set)	n	958	961	1919
Discontinued	% (n/N)	1.8%(17/958)	1.2%(12/961)	1.5%(28/1919)
Reason for Discontinuation:				
Subject withdrew consent	% (n/N)	0.5%(5/958)	0.2%(2/961)	0.4%(7/1919)
Physician Withdrew Subject	% (n/N)	0.1%(1/958)	0.0%(0/961)	0.1%(1/1919)
Lost to follow-up	% (n/N)	1.1%(11/958)	1.0%(10/961)	1.1%(21/1919)
Death	% (n/N)	1.1%(11/958)	1.0%(10/961)	1.1%(21/1919)

C. Study Population Demographics and Baseline Characteristics

The demographics of the study population are typical for a pivotal study performed in the US. Study arms appeared to be 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) appeared to be comparable 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.

[Table 10](#) presents the demographics and baseline characteristics, as well as the risk

factors for the study arms.

Table 10: Demographics, baseline characteristics, risk factors

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/m ²)	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				
Target Vessel treated	% (n/N)	8.1%(78/958)	7.8%(75/961)	8.0%(153/1919)
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)

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)
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)

D. DAPT Compliance

All subjects were to receive clopidogrel, prasugrel, or ticagrelor for a minimum of 6 months (12 months recommended) according to professional society guidelines (such as the ACCF/AHA/SCAI recommendations for PCI) and standard of care, as well as aspirin indefinitely (unless an intervening medical necessity such as severe bleeding occurred). There were no differences between treatment arms in the compliance with the DAPT protocol requirements. In accordance with the protocol-required loading dose, at the baseline procedure, 94.6% of patients in the Full Analysis Set received

aspirin and 96.2% received P₂Y₁₂ platelet inhibitors with no differences between treatment groups. Post-procedure, 97.5% of patients received aspirin and 97.4% received P₂Y₁₂ platelet inhibitors. [Table 11](#) below shows that 75% of subjects were taking DAPT at 12 months. The type and frequency of P₂Y₁₂ platelet inhibitors use at 12 months was balanced between treatment groups.

Table 11: Summary of DAPT Use at 12 Months (Full Analysis Set) Parameter

Parameter	Statistic	BioNIR (N=958)	Resolute (N=961)	Overall (N=1899)
Aspirin and P ₂ Y ₁₂ platelet inhibitors	% (n/N)	75.1%(698/929)	75.7%(708/935)	75.4%(1406/1864)
Aspirin	% (n/N)	93.0%(864/929)	94.2%(881/935)	93.6%(1745/1864)
ADP antagonist	% (n/N)	76.3%(709/929)	76.6%(716/935)	76.4%(1425/1864)
Clopidogrel	% (n/N)	17.4%(162/929)	19.1%(179/935)	18.3%(341/1864)
Ticagrelor	% (n/N)	65.3%(607/929)	66.4%(621/935)	65.9%(1228/1864)
Ticlopidine	% (n/N)	7.8%(72/929)	7.8%(73/935)	7.8%(145/1864)
Prasugrel	% (n/N)	15.8%(147/929)	15.8%(148/935)	15.8%(295/1864)

E. Safety and Effectiveness Results

The presented study outcomes include primary and secondary endpoint results from, up to and including the 12-month time point for the clinical outcomes. In addition, 13-month Angiographic and IVUS sub-studies analyses are presented as well.

The BIONICS primary endpoint results are presented in [Table 12](#). The primary outcome was 5.4% in both treatment groups. 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 of 3.3% (p=0.0013 for non-inferiority).

Table 12: BIONICS Trial - Primary Endpoint Analysis of TLF* at 1 year for Non-inferiority (Periprocedural MI per SCAI) CEC-Adjudicated - Full Analysis Set²

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% (.181%)	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)		

*Target Lesion Failure (TLF) is defined as the composite rate of cardiac death, target vessel MI, or clinically driven TLR.

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 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%.

² 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 $\geq 10x$ the local laboratory ULN, or to $\geq 5x$ 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 $\geq 70x$ the local laboratory ULN, or $\geq 35x$ 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 13 below is the primary endpoint using the 3rd Universal definition for peri-procedural MI.

Table 13: Supplemental Analysis of Primary Endpoint Analysis of TLF at 1 year (Periprocedural MI per Universal Definition) - CEC Adjudicated - Full Analysis Set

Parameter	Statistic	BioNIR (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 MIs are included per the Universal definition (Type 4a).

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).

¹P-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 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 four (4) EluNIR™ subjects (0.4%) and seven (7) Resolute subjects (0.8%). Late ST (>30 days) within 12 months+ window occurred in 0 EluNIR™ subjects (0.0%) and three (3) Resolute subjects (0.3%).

Table 14 presents the clinical results of the BIONICS Trial.

Table 14: BIONICS Clinical 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,	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

	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
Subacute (1 – 30 days)	0.3%(3)	0.3%(3)	1.00	0.3%(3)	0.3%(3)	1.00
Late (> 30 days)	N/A	N/A	N/A	0.0%(0)	0.2%(2)	N/A

Table 14: BIONICS Clinical Results (cont'd)³

	Outcomes within 12 months (<=365 Days) of baseline procedure		
	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

³ 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 $\geq 10x$ the local laboratory ULN, or to $\geq 5x$ 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 $\geq 70x$ the local laboratory ULN, or $\geq 35x$ 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.

	Outcomes within 12 months (<=365 Days) of baseline procedure		
	EluNIR (N = 958)	Resolute (N = 961)	Difference
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

¹Target lesion failure (TLF; the composite rate of cardiac death, target vessel MI, or clinically driven TLR)

²Major Adverse Cardiac Events (MACE; the composite rate of cardiac death, any MI or clinically driven TLR)

³Target 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 15](#) and [Table 16](#), with a residual stenosis of ≤50% and ≤20%, respectively.

Table 15: 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[-2.4,-0.5]
Lesion Success ^b	% (n/N)	99.9% (1257/1258)	99.8% (1262/1264)	99.9% (2519/2522)	0.1[-0.3,0.4]
Procedure Success ^c	% (n/N)	97.6% (929/952)	97.3% (928/954)	97.4% (1857/1906)	0.3[-1.2,1.8]

^aDevice 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.

^bLesion 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.

^cProcedure 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 16: 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[-6.1,-1.2]----
Lesion Success ^b	% (n/N)	89.5% (1126/1258)	91.6% (1158/1264)	90.6% (2284/2522)	-2.1[-4.5,0.3]---- -
Procedure Success ^c	% (n/N)	90.0% (857/952)	90.4% (862/954)	90.2% (1719/1906)	-0.3[-3.1,2.4]---- -

^aDevice 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.

^bLesion 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.

^cProcedure 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 sub-study are presented in [Table 17](#).

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

Table 17: Powered Secondary Endpoints at 13 Months as Assessed by Angiographic Core Lab - Angiographic Sub-study

		EluNIR	Resolute	Overall	Difference Upper Bound of the 95%CI	P-value ¹ of noninferiority
		(N=85 patients, 105 lesions)	(N=73 patients, 96 lesions)	(N=158 patients, 201 lesions)		
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.

Table 18 presents the results of the IVUS sub-study.

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 18: Powered Secondary Endpoints at 13 Months as Assessed by IVUS Core Lab - IVUS Sub-study

		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 noninferiority
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.

E1. Subgroup Analysis

1. Gender-Based Analysis

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.^{ref #8}

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 19 presents the baseline demographics, risk factors, and angiographic characteristics by gender for subjects in the BIONICS trial.

Table 19: BIONICS Trial - Demographics, Risk Factors, and Baseline Angiographic Characteristics - Gender Based Analysis

	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/m ²)	29.0(4.8)	29.1(6.3)	29.1(5.1)
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	N = 2080 lesions	N = 473 Lesions	N = 2553 lesions
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)

Table 20 presents the clinical outcomes of the gender based analysis of the BIONICS trial.

Table 20: BIONICS Trial Clinical Safety and Effectiveness - Gender Based Analysis

Event	Statistic	BIONICS Full Analysis Set (N= 1919)	
		Male N=1537	Female N=382
TLF¹	KM Estimate %(n)	5.3%(80)	5.1%(19)
MACE²	KM Estimate %(n)	6.9%(104)	5.8%(22)
TVF³	KM Estimate %(n)	6.6%(99)	7.2%(27)
All-Cause Mortality	KM Estimate %(n)	0.9%(14)	1.9%(7)
Cardiovascular Death	KM Estimate %(n)	0.5%(7)	1.3%(5)
Cardiac Death	KM Estimate %(n)	0.3%(4)	0.8%(3)
Vascular Death	KM Estimate %(n)	0.2%(3)	0.5%(2)
Non-Cardiovascular Death	KM Estimate %(n)	0.5%(7)	0.5%(2)
MI	KM Estimate %(n)	5.0%(76)	3.5%(13)
Q-wave	KM Estimate %(n)	0.4%(6)	1.0%(4)
Non Q-wave	KM Estimate %(n)	4.6%(70)	2.5%(9)
Target Vessel MI	KM Estimate %(n)	3.3%(51)	2.7%(10)
Q-wave	KM Estimate %(n)	0.4%(6)	1.0%(4)
Non Q-wave	KM Estimate %(n)	3.0%(46)	1.7%(6)
Clinically Driven Revascularization	KM Estimate %(n)	6.7%(100)	6.9%(25)
PCI	KM Estimate %(n)	6.2%(91)	5.9%(22)
CABG	KM Estimate %(n)	0.7%(10)	1.3%(4)
Clinically Driven TLR	KM Estimate %(n)	2.8%(41)	2.6%(9)
PCI	KM Estimate %(n)	2.5%(36)	1.6%(6)
CABG	KM Estimate %(n)	0.4%(6)	1.0%(3)
Clinically Driven TVR	KM Estimate %(n)	3.8%(56)	4.0%(14)
PCI	KM Estimate %(n)	3.4%(50)	2.7%(10)
CABG	KM Estimate %(n)	0.5%(7)	1.3%(4)
Definite/Probable Stent Thrombosis⁴	% (n/N)	0.6%(9/1482)	0.5% (2/365)
Primary*	% (n/N)	0.5%(8/1483)	0.8%(3/366)
Secondary**	% (n/N)	0.1%(1/1481)	0.0%(0/365)

Each Event is confirmed by adjudication:

¹Target lesion failure (TLF; the composite rate of cardiac death, target vessel MI,

or clinically driven TLR)

²Major Adverse Cardiac Events (MACE; the composite rate of cardiac death, any MI or clinically driven TLR)

³Target Vessel Failure (TVF; the composite rate of all-cause death, target vessel related MI or clinically driven TVR)

⁴Primary: Occurs in the target lesion or margins after baseline procedure. Secondary: Occurs after revascularization (TLR, TVR, or non- TVR)

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

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

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 21](#). There was no indication for difference in the treatment effects across these subgroups.

Table 21: Subgroup Analyses of the Primary Endpoint of TLF* at 1 Year (Periprocedural MI per SCAI) - CEC Adjudicated – Full Analysis Set⁴

Parameter	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)

⁴ 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.

Parameter	Statistic	EluNIR (N=958)	Resolute (N=961)	Overall (N=1919)
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.

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).

Table 22: Summary of the Primary Endpoint of TLF at 1 Year by Region – CEC Adjudicated – Full Analysis Set⁵

Parameter	Statistic	EluNIR™ (N=958)	Resolute (N=961)	Overall (N=1919)	Difference (%)
United States	% (n/N)	7.1%(14/198)	7.5%(14/188)	7.3%(28/386)	-0.4
Europe	% (n/N)	4.0%(9/224)	3.0%(7/236)	3.5%(16/460)	1.1
Israel	% (n/N)	6.7%(19/282)	5.8%(17/292)	6.3%(36/574)	0.9
Canada	% (n/N)	3.6%(8/222)	5.6%(12/214)	4.6%(20/436)	-2.0
North America (US + Canada)	% (n/N)	5.2%(22/420)	6.5%(26/402)	5.8%(48/822)	-1.2
Out of North America (Europe + Israel)	% (n/N)	5.5%(28/506)	4.5%(24/528)	5.0%(52/1034)	1.0
Out of North America (Canada + Europe + Israel)	% (n/N)	5.0%(36/728)	4.9%(36/742)	4.9%(72/1470)	0.1

Table 22 outlines an exploratory post hoc analysis of TLF rates at 1 year for both EluNIR and Resolute in the US compared to Non-Us regions.

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).

E2. Pediatric Extrapolation

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

⁵ 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 $\geq 10x$ the local laboratory ULN, or to $\geq 5x$ 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 $\geq 70x$ the local laboratory ULN, or $\geq 35x$ 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.

F. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal BIONICS clinical study included 76 investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

2) In Vivo Pharmacokinetics - BIONICS-PK Sub-Study (CIP#: BioNIR-001-PK)

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 sub-study. Enrollment to the sub-study started on June 6, 2016 and was completed on August 25, 2016.

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).

A dedicated medical monitor reviews the safety data on an ongoing basis. An independent Clinical Events Committee (CEC) adjudicates all potential clinically significant and relevant cardiac events data. The sub-study was supervised by an independent Data Safety Monitoring Board (DSMB). Core laboratories enable standardized and objective analysis of the data.

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 per stent unit surface area, using a validated high performance liquid chromatography mass spectrometry/mass spectrometry (HPLC-MS/MS) method. [Table 23](#) provides the pharmacokinetic parameters for the study analysis.

Table 23: Whole blood ridaforolimus pharmacokinetics parameters in patients following EluNIR Stent implantation

Low Dose Group (<130 µg), N=6												
Parameter*	Total Dose	C _{max}	C _{max} /D	T _{max}	T _{last} ^a	C _{last} ^a	AUC _{0-tlast}	AUC _{0-tlast} /D	AUC _{0-t∞}	AUC _{0-t∞} /D	t _{1/2}	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)
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												
Parameter*	Total Dose	C _{max}	C _{max} /D	T _{max}	T _{last} ^a	C _{last} ^a	AUC _{0-tlast}	AUC _{0-tlast} /D	AUC _{0-t∞}	AUC _{0-t∞} /D	t _{1/2}	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)
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												
Parameter*	Total Dose	C _{max}	C _{max} /D	T _{max}	T _{last} ^a	C _{last} ^a	AUC _{0-tlast}	AUC _{0-tlast} /D	AUC _{0-t∞}	AUC _{0-t∞} /D	t _{1/2}	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)
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

^aThe first value that was BQL after the C_{max} was assigned a value equal to one-half the lower limit of quantitation and subsequent BQL was assigned a value of zero (0).

*Terms defined for the Evaluated/Calculated Parameters in Table 23:

AUC _{0-t∞} (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-∞}
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
Rs _q	Goodness of fit statistic for the terminal elimination phase
T _{max} (hr)	The time of peak concentration

The BIONICS PK sub-study results are presented below:

- Six subjects received a mean total dose of 114 µg of ridaforolimus, four (4) subjects received a mean total dose of 154 µg of ridaforolimus, and two (2) subjects received a mean total dose of 442 µg of ridaforolimus.
- Whole blood C_{max} increased with increasing dose and ranged from 0.438 to 1.75 ng/mL of ridaforolimus by dose-group with individual mean C_{max} ranging from 0.308 to 1.80 ng/mL of ridaforolimus.
- T_{max} was similar among dose groups ranging from 1.51 to 2.00 hrs, with individual T_{max} ranging from 0.500 to 4.03 hrs.
- All AUC estimates increased with increasing dose and were slightly supra proportional.
- The apparent t_{1/2} of ridaforolimus for individual subject t_{1/2} ranged from 75.3 to 311 hrs across all dose levels, with mean t_{1/2} 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.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

1) NIREUS Clinical Trial

The **NIREUS** clinical trial was aimed at assessing the angiographic outcomes of the EluNIR in comparison to the Resolute stent. It is being performed at 31 sites in Europe and Israel. Enrollment to the study started on 19-Mar-2014 and was completed on 24-Mar-2015.

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.

The primary endpoint was angiographic in-stent late loss at 6 months.

Secondary clinical endpoints include target lesion failure (TLF) at 30 days, 6 months, 1 year, and yearly thereafter until year 5.

A dedicated medical monitor reviewed the safety data on an ongoing basis. An independent Clinical Events Committee (CEC) adjudicates all potential clinically significant and relevant cardiac events data. The trial was supervised by an independent Data Safety Monitoring Board (DSMB). Core laboratories enable standardized and objective analysis of the data.

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 (wide spectrum of PCI indications (stable angina as well as acute coronary syndrome [ACS], including subacute ST segment elevation myocardial infarction [STEMI])). 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. All subjects were required to have clopidogrel/prasugrel/ticagrelor administration for a minimum of 6 months (recommended 12 months) as well as aspirin administration indefinitely.

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

Demographics: A total of 305 patients, from the Netherlands, Italy, Israel, Spain, Belgium, and Poland were randomized. Two (2) patients in the EluNIR™ arm and one (1) patient in the Resolute arm were deregistered (per protocol) because the study stent was not advanced beyond the guiding catheter. Three hundred and two (302) patients were included in the full analysis set.

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 was 137.2 mmHg (±19.3); and mean diastolic blood pressure was 78.0 mmHg (±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.

[Table 24](#) presents the demographics, baseline characteristics, and risk factors for the two (2) study arms.

Table 24: 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	% (n/N)	40.3% (81/201)	44.6% (45/101)	41.7% (126/302)
Target Vessel treated				
Yes	% (n/N)	9.9% (8/81)	8.9% (4/45)	9.5% (12/126)
Target Lesion Treated				
Yes	% (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				
Yes	% (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)

Parameter	Statistic	EluNIR (N=201)	Resolute (N=101)	Overall (N=302)
Lesion Characteristics^a		(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	205	104	309
	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)

^aThe 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 26: 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 25 and Table 26. 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 25: NIREUS Trial- Primary Endpoint Analysis Comparison of In-Stent Late Loss at 6 Months for Non- Inferiority 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		

¹The 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.

Table 26: NIREUS Clinical Outcomes – 30 days and 6 months (Data presented in Kaplan-Meier Estimate %[n])*⁶

	Outcomes within 30 days of baseline procedure		Outcomes at 6 months of baseline procedure	
	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)

⁶ 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 $\geq 10x$ the local laboratory ULN, or to $\geq 5x$ 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 $\geq 70x$ the local laboratory ULN, or $\geq 35x$ 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.

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,	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)	2.0% (4)	3.0% (3)
QMI	0.5% (1)	0.0% (0)	0.5% (1)	0.0% (0)
NQMI	0.5% (1)	2.0% (2)	2.0% (4)	3.0% (3)
Cardiovascular Death or MI	1.0% (2)	2.0% (2)	2.0% (4)	3.0% (3)
Stent Thrombosis – ARC Definite/Probable	0	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)

¹Target lesion failure (TLF; the composite rate of cardiac death, target vessel MI, or clinically driven TLR)

²Major Adverse Cardiac Events (MACE; the composite rate of cardiac death, any MI or clinically driven TLR)

³Target 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.

Table 27: NIREUS Clinical Outcomes – 1 year (Data presented in Kaplan-Meier Estimate %[n])*⁷

	EluNIR (N = 201)	Resolute (N = 101)	Difference [95% CI]	P-value
Composite Efficacy and Safety				
TLF ¹	3.4% (6)	7.0% (7)	0.50[0.16,1.55]	0.2279
TVF ³	7.5% (14)	10.0% (10)	0.82[0.34,1.97]	0.6514

⁷ 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 $\geq 10x$ the local laboratory ULN, or to $\geq 5x$ 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 $\geq 70x$ the local laboratory ULN, or $\geq 35x$ 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.

	EluNIR (N = 201)	Resolute (N = 101)	Difference [95% CI]	P-value
MACE ²	4.3% (8)	8.0% (7)	0.67[0.23,1.92]	0.4543
Efficacy				
Clinically -Driven TLR	2.9% (5)	4.0% (4)	0.68[0.15,3.04]	0.6129
TLR, CABG	0.0% (0)	0.0% (0)	N/A	N/A
TLR, PCI	2.9% (5)	4.0% (4)	0.68[0.15,3.04]	0.6129
Clinically-Driven TVR, Non	3.0% (6)	4.0% (4)	1.02[0.26,4.09]	0.9732
Any Revascularization	12.9% (25)	14.9% (15)	0.86[0.45,1.63]	0.6421
Safety				
All Death	2.1% (4)	0.0% (0)	N/A	1.0000
Cardiac Death	0.5% (1)	0.0% (0)	N/A	1.0000
Vascular Death	0.0% (0)	0.0% (0)	N/A	N/A
Non-Cardiovascular Death	1.6% (3)	0.0% (0)	N/A	1.0000
MI**	2.0% (4)	3.0% (3)	0.67[0.15,2.97]	0.5935
QMI	0.5% (1)	0.0% (0)	N/A	1.0000
NQMI	2.0% (4)	3.0% (3)	0.66[0.15,2.97]	0.5922
Cardiovascular Death or MI	2.0% (4)	3.0% (3)	0.67[0.15,2.97]	0.5935
Any Stent Thrombosis	0.5% (1)	0.0% (0)	N/A	0.4784
Stent Thrombosis – ARC Definite /Probable	0.5% (1)	0.0% (0)	N/A	0.4784
Late (> 30 days-1 Year)	0.5% (1)	0.0% (0)	N/A	0.4784

¹Target lesion failure (TLF; the composite rate of cardiac death, target vessel MI, or clinically driven TLR)

²Major Adverse Cardiac Events (MACE; the composite rate of cardiac death, any MI or clinically driven TLR)

³Target 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.

Angiographic Secondary Endpoints:

In-Segment Late Loss at 6 Months: The mean late lumen loss in the treated segment was 0.06 (\pm 0.333) in the EluNIR arm and 0.051 (\pm 0.368) in the Resolute arm, p=0.9514.

Percent Diameter Stenosis: The in-segment diameter stenosis was 19.5% (\pm 10.7) and 19.6% (\pm 9.6) in the EluNIR and Resolute, respectively, p=0.9286. Within the stent, the mean DS was 14.3% (\pm 9.9) and 12.9% (\pm 9.4) in the EluNIR and Resolute, respectively, p=0.2507.

Binary Restenosis: In-segment binary restenosis (DS \geq 50%) was identified in seven (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 \geq 50%) was identified in 5 subjects (2.4%) in the EluNIR arm and two (2) subjects (1.9%) in the Resolute arm (p=0.7795).

2) **BIONICS-Israel Clinical Trial**

The BIONICS Israel clinical trial aims at assessing the safety and efficacy EluNIR™ stent with modified delivery system. Enrollment to the study started on 20-Sep-2016 and was completed on 14-Dec-2016.

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

The primary clinical endpoint is device success in the target lesion, as determined by the Angiographic Core Laboratory.

A dedicated medical monitor reviews the safety data on an ongoing basis. An independent Clinical Events Committee (CEC) adjudicates all potential clinically significant and relevant cardiac events data. The trial was supervised by an independent Data Safety Monitoring Board (DSMB). Core laboratories enable standardized and objective analysis of the data.

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 is a prospective, multi-center, single-arm, open-label clinical trial, conducted at three (3) sites in Israel, with 58 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.

All patients have reached the 30-day follow-up time point. Follow-up by phone is performed at 6 months, and 1 year after baseline procedure.

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.

Table 28 presents the demographics, baseline characteristics, and risk factors.

Table 28: BIONICS-Israel Clinical Trial – Demographics, Risk Factors, and Baseline Angiographic Characteristics

	Statistic	EluNIR (N=58 Patients)
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

	Statistic	EluNIR (N=58 Patients)
	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	75 Lesions
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)

	Statistic	EluNIR (N=58 Patients)
Ostial	% (n/N)	2.7% (2/75)
Vessel Level Characteristics from QCA		
	N	68 Vessels
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 Lesions
	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 up to 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 Trial are presented in [Table 29](#) and [Table 30](#), with a residual stenosis of ≤50% and ≤20%, respectively.

Table 29: BIONICS Israel Primary Analysis - Summary of Acute Success Rate Defined from Angiographic Core Lab Assessment (DS < 50% Threshold) and CEC Adjudication Full Analysis Set

Category	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.

^aDevice 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.

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

^cProcedure 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 30: BIONICS-Israel - Summary of Acute Success Rate Defined from Angiographic Core Lab Assessment (DS < 20% Threshold) and CEC Adjudication Full Analysis Set

Category	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.

^aDevice 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.

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

^cProcedure 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%)

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory Systems Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

The safety and effectiveness of EluNIR™ Ridaforolimus Eluting Coronary Stent System are based on the results obtained from biocompatibility; *in vivo* pharmacokinetics; *in vitro* engineering testing; coating characterization; chemistry, manufacturing, and controls information; *in vivo* animal testing; sterilization and stability testing; and clinical studies. These test results revealed the following:

A. Effectiveness Conclusion

Based on the BIONICS Clinical Trial, the EluNIR was found clinically non-inferior to the Resolute 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. The EluNIR was similar and non-inferior to the Resolute in respect to NIH and in-stent Lumen Loss at 13 months post procedure. Thus, the EluNIR was found to be safe and effective for its intended use.

B. Safety Conclusions

The biocompatibility, *in vivo* pharmacokinetics, and *in vivo* animal testing conducted demonstrate that the acute and chronic *in vivo* performance characteristics of the product provide reasonable assurance of safety and acceptability for clinical use.

The *in vitro* engineering testing conducted on the stents and delivery system(s) demonstrated that the performance characteristics met the product specifications, and the coating characterization testing adequately described the important attributes of the ridaforolimus coating. The chemistry, manufacturing, and controls information ensures that the product will meet specifications upon release.

The test results obtained from the sterilization testing demonstrated that the product can be adequately sterilized and is acceptable for clinical use. The stability testing demonstrated that the product can be labeled with a shelf life of 12 months.

The results of the EluNIR™ clinical studies showed that no safety signals of concern were identified from a review of SAEs and CEC adjudicated events. In addition, the clinical testing conducted demonstrated that the EluNIR™ with the improved delivery system provides a reasonable assurance of safety and effectiveness when used as indicated in accordance with the Directions for Use.

C. Benefit-risk Determination

The probable benefits of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. The probable benefits of the EluNIR™ Ridaforolimus Eluting Coronary Stent System (EluNIR) of improving the patient symptoms outweigh the probable risks associated with use of the device.

Additional factors that were considered in determining the probable risks and benefits of the EluNIR™ included:

- ✓ Key clinical data supporting the safety and effectiveness of the EluNIR™ were obtained from the BIONICS randomized controlled trial, where the primary endpoint of 12-month TLF (target lesion failure) in the EluNIR™ stent was compared to the 12-month TLF rate in the control device (Resolute):
- ✓ The TLF rate for the full analysis set was observed in 5.4% of EluNIR™ and 5.4% Resolute treated subjects (upper bound of the one-sided 95% CI for the risk difference (1.81%) was less than the non-inferiority margin of 3.3% ,p=0.0013 for non-inferiority), and
- ✓ The per protocol TLF rate was observed in 4.8% of EluNIR™ and 5.1% Resolute treated subjects (the upper bound of the one-sided 95% CI for the risk difference (0.28%) for non-inferiority margin was 3.3%; p=0.0007 for non-inferiority).

In addition, the angiographic secondary endpoints were met;

- ✓ The in-stent LL at 13 months, in the angiographic sub-study, was similar between treatments, with no significant differences (0.22mm EluNIR™, 0.23mm Resolute); non-inferiority was achieved with p-value of 0.0039.
- ✓ Also, the IVUS secondary endpoint was met - in the IVUS sub-study, percent NIH was similar between treatments (8.10 EluNIR, 8.85 Resolute), with no significant differences; non-inferiority was achieved (p-value for non-inferiority of 0.0098).

These data demonstrate that the EluNIR™ stent is non-inferior to the Resolute Stent, and is of clinical benefit to patients undergoing PCI procedures. The rates of individual important safety events including death, MI, and stent thrombosis were low and comparable to the control group. Alternative treatments for coronary artery disease, including other coronary stents and both medical and surgical therapy, are available and the risks and benefits of these therapies were carefully considered. The risks and benefits of the EluNIR™ were found to be similar to the risks and benefits of these devices.

1. Patient Perspectives

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

In conclusion, given the available information above, the data support that, for treating de novo lesions in the coronary arteries, the probable benefits of the EluNIR when used as indicated, outweigh the probable risks.

D. Overall Conclusions

The data in this application support a reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use.

Data from the EluNIR Clinical Program support the safety and effectiveness of the EluNIR Coronary Stent System for the treatment of de novo atherosclerotic lesions when used in accordance with the Directions for Use (DFU).

XIV. CDRH DECISION

CDRH issued an approval order on November 28, 2017. The final condition of approval cited in the approval order is described below.

ODE Led PMA Post-Approval Study – Continued Follow-up of BIONICS clinical study. The Office of Device Evaluation (ODE) will have the lead for this clinical study, which was initiated prior to device approval. The BIONICS clinical study (G140107) is a prospective, multi-center, single-blind trial which enrolled 1919 patients and was designed to assess the safety and effectiveness of the EluNIR Ridaforolimus Eluting Coronary Stent System through 5 years post-index procedure. The primary endpoint is Target Lesion Failure (TLF) at 12 months. You must collect and report clinical outcomes to FDA through 5 years post-procedure on patients enrolled in the BIONICS clinical trial.

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

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.

XVI. REFERENCES

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