September 1, 2021
Medical Device Evaluation Division
Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Report on the Deliberation Results

Classification	Instrument & Apparatus 7, Organ Function Replacement Device
Term Name	Coronary stent
Brand Name	EluNIR Drug-Eluting Stent
Applicant	Medinol Ltd.
Designated Marketing Authorization Holder	Micren Healthcare Co., Ltd.
Date of Application	February 28, 2019 (Application for marketing approval of a medical device manufactured in a foreign country)

Results of Deliberation

In its meeting held on September 1, 2021, the Committee on Medical Devices and *In-vitro* Diagnostics reached the following conclusion, and decided that this conclusion should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is not designated as a medical device subject to a use-results survey. The product should be approved. The product is not classified as a biological product or a specified biological product.

Review Report

August 6, 2021
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following medical device submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

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Reviewing Office	Office of Medical Devices I

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Results of Review

EluNIR Drug-Eluting Stent is a stent system for percutaneous coronary stenting (hereinafter referred to as EluNIR). EluNIR consists of (a) a stent that is placed at a lesion to maintain the vascular patency and (b) a delivery catheter used to deliver the stent to the lesion. The stent surface is coated with ridaforolimus to prevent restenosis.

The applicant submitted nonclinical data supporting the physicochemical properties, biological safety, stability and durability, and performance of EluNIR. There was no particular problem in the submitted data.

The applicant submitted the results of the following clinical studies of EluNIR: the BIONICS study (a foreign clinical study), the BIONICS-PK study (a foreign pharmacokinetic study), and the JNIR study (a Japanese clinical study). In the BIONICS study, "the target lesion failure rate at 1 year after procedure," the primary endpoint, was 5.4% in the EluNIR group and 5.4% in the control group that received the control device (an approved similar device "Resolute Integrity Coronary Stent System" [Approval number 22400BZX00176000]); thus EluNIR was shown to be non-inferior to the control device. In the JNIR study, "the target lesion failure rate at 1 year after procedure," the primary endpoint, was 1.9% in the EluNIR group and 5.3% in the control group (which consisted of subjects receiving EluNIR in the BIONICS study who were matched for patient characteristics to the subjects of the JNIR study); thus EluNIR was shown to be non-inferior to the control device.

PMDA comprehensively reviewed these study results in view of comments from the Expert Discussion, and concluded that EluNIR was shown to have efficacy and safety.

As a result of its review, PMDA has concluded that EluNIR may be approved for marketing for the intended use shown below with the following approval condition, and that this conclusion should be presented to the Committee on Medical Devices and *In-vitro* Diagnostics for further deliberation.

Intended Use

EluNIR Drug-Eluting Stent is used for the treatment of patients with symptomatic ischemic heart disease who have de-novo lesions (≤42 mm in length) in native coronary arteries with reference vessel diameters of 2.50 to 4.25 mm.

Approval Condition

The applicant is required to (a) submit the analysis results of long-term outcomes of the patients included in a clinical study submitted for the present application, to the Pharmaceuticals and Medical Devices Agency, and (b) take appropriate actions as necessary.

Review Report

August 6, 2021

Product for Review

Classification	Instrument & Apparatus 7, Organ Function Replacement Device
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Brand Name	EluNIR Drug-Eluting Stent
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Designated Marketing Authorization Holder	Micren Healthcare Co., Ltd.
Date of Application	February 28, 2019 (Application for marketing approval of a medical device manufactured in a foreign country)
Proposed Intended Use	EluNIR Drug-Eluting Stent is used for the treatment of patients with symptomatic ischemic heart disease who have de-novo lesions (≤42 mm in length) in native vessels with reference vessel diameters of 2.50 to 4.25 mm.

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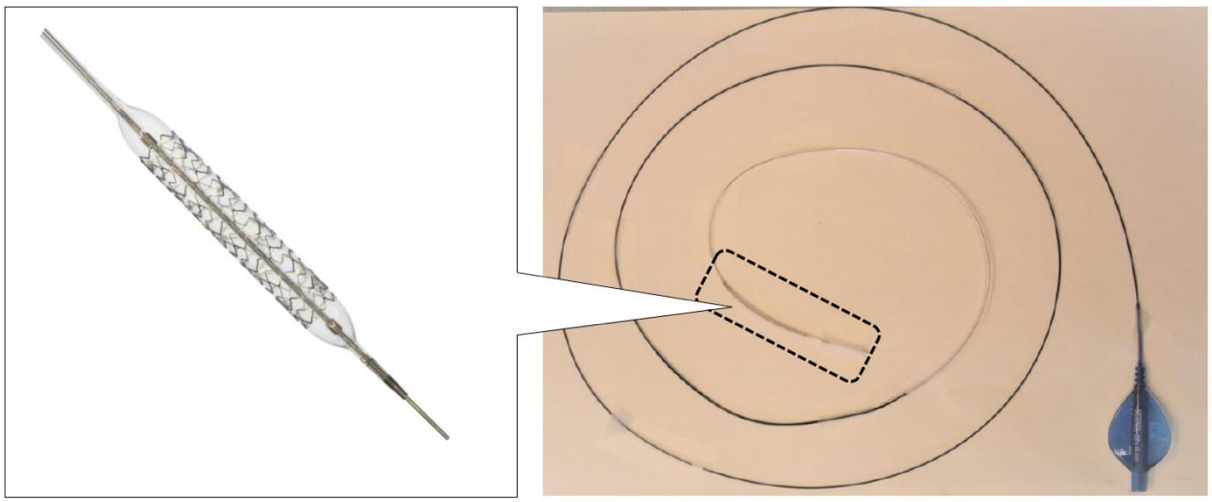
List of Abbreviations

ACC	American College of Cardiology
AHA	American Heart Association
BHT	Butylated Hydroxytoluene
BMI	Body Mass Index
BMS	Bare Metal Stent
CCS	Canadian Cardiovascular Society
CYP	Cytochrome P450
DAPT	Dual Antiplatelet Therapy
DES	Drug Eluting Stent
FKBP12	FK506 Binding Protein
HERG	Human ether-a-go-go related gene
IC_{50}	Half Maximal Inhibitory Concentration
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ISO	International Organization for Standardization
MACE	Major Adverse Cardiac Events
MRI	Magnetic Resonance Imaging
mTOR	Mammalian Target of Rapamycin
PCI	Percutaneous Coronary Intervention
Pgp	P-glycoprotein
PK	Pharmacokinetics
SD	Standard Deviation
TLF	Target Lesion Failure
TLR	Target Lesion Revascularization
TVF	Target Vessel Failure
TVR	Target Vessel Revascularization

I. Product Overview

EluNIR Drug-Eluting Stent is a stent system for percutaneous coronary stenting (hereinafter referred to as EluNIR). EluNIR consists of a cobalt chromium (L-605) stent that is placed at a lesion to maintain the vascular patency and a delivery catheter used to deliver the stent to the lesion (Figure 1). Table 1 shows the available size variation of the EluNIR stents.



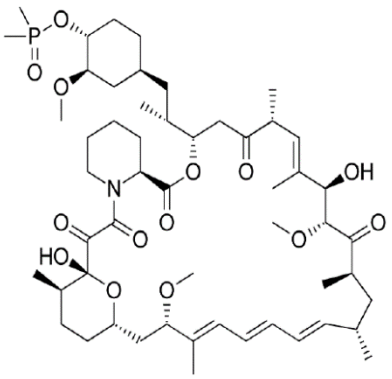
Delivery catheter working length, 1400 mm

Figure 1. Appearance of EluNIR

Table 1. Size variation of the stent

		Length (mm)									
		8	12	15	17	20	24	28	33	38	44
Diameter (mm)	2.50	✓	✓	✓	✓	✓	✓	✓	✓	-	-
	2.75	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	3.00	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	3.50	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	4.00	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

The stent surface is coated with polymers loaded with ridaforolimus (Figure 2), which is a sirolimus analog, to prevent local neointimal hyperplasia, which is considered to cause in-stent restenosis. The proposed quality specifications for ridaforolimus include appearance, identification, impurities, assay, residual solvents, content of butylated hydroxytoluene (BHT), degree of crystallinity, moisture content, bacterial endotoxins, and mean residue on ignition. The selected polymers are a poly n-butyl methacrylate, which is used in approved drug-eluting stents (DESs) similar to the EluNIR stent, and a thermoplastic polyurethane elastomer, which is widely used in medical devices. Ridaforolimus has not been approved as a drug in or outside Japan.



Molecular formula, $C_{53}H_{84}NO_{14}P$; molecular weight, 990.22

Figure 2. Chemical structure of ridaforolimus

II. Summary of the Data Submitted and Outline of the Review Conducted by the Pharmaceuticals and Medical Devices Agency

The data submitted for the present application by the applicant and the applicant's responses to the inquiries from the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined below.

The expert advisors present during the Expert Discussion on EluNIR declared that they did not fall under the Item 5 of the Rules for Convening Expert Discussions, etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1. History of Development, Use in Foreign Countries, and Other Information

1.A Summary of the data submitted

1.A.(1) History of development

Coronary stenting is widely used for endovascular treatment of ischemic heart disease. However, placement of a stent in a blood vessel may damage the vessel wall and induce inflammatory reactions due to foreign body reactions, etc. In the healing process of the vascular wall after stent placement, vascular smooth muscle cell proliferation may induce neointimal hyperplasia, which is associated with the risk of restenosis. To prevent neointimal hyperplasia, many stents currently available in clinical practice are coated with a drug on their surfaces. The drug-coated stents have been shown to result in excellent clinical outcomes. These drug-loaded stents are called drug-eluting stents (DESs), including the EluNIR stent.

Almost all drugs currently loaded on DESs are sirolimus, which is a "limus" drug, and its analogs (everolimus, zotarolimus, and biolimus A9). Ridaforolimus loaded on the EluNIR stent also belongs to the "limus" family and has a similar mechanism of action to that of other "limus" drugs. Ridaforolimus infiltrates the cellular membrane, and binds to a protein called FK506 binding protein (FKBP12) in the cell and then to the mammalian target of rapamycin (mTOR), which is a signaling protein that plays an important role in cell cycle regulation, to inhibit the activity of the mTOR.

Sirolimus consists of a functional domain binding to FKBP12 and mTOR, and a non-functional domain. In general, all sirolimus analogs including ridaforolimus are manufactured using sirolimus as the starting material. In the subsequent chemical replacement process, the non-functional domain of the molecule is slightly modified. For this reason, all members of the "limus" family have a very similar mechanism of action.

"Limus" drugs having a less inhibitory effect on the proliferation of endothelial cells, which are involved in vascular healing after angioplasty, have a better safety profile. The half maximal inhibitory concentration (IC_{50}) of ridaforolimus in vascular smooth muscle cells and endothelial cells is similar to that of zotarolimus [see Section "2.(5).A.1).(a) Inhibition of the proliferation of smooth muscle and endothelial cells"], suggesting that ridaforolimus can be used in DESs.

Sirolimus and "limus" analogs are approved as drugs around the world. Ridaforolimus for the treatment of sarcoma was also investigated in clinical studies in and outside Japan. The studies showed that ridaforolimus had a safety profile comparable to the other "limus" drugs, but failed to demonstrate adequately its efficacy; this led to the termination of clinical development of ridaforolimus. Therefore ridaforolimus has not been approved as a drug anywhere in the world.

1.A.(2) Use in foreign countries

Table 2 shows information regarding the use of EluNIR in foreign countries as of July 2021.

Table 2. Approvals and sales performance outside Japan

Country/ region	Intended use	Approved in	Sales performance
EU	EluNIR is used for the treatment of patients with symptomatic ischemic heart disease who have de-novo lesions (≤42 mm in length) in native coronary arteries with reference vessel diameters of 2.25 to 4.25 mm.	August 2017	[redacted]
US	EluNIR is used for the treatment of patients with symptomatic ischemic heart disease who have de-novo lesions (≤36 mm in length) in native coronary arteries with reference vessel diameters of 2.50 to 4.25 mm.	November 2017	[redacted]
Others	-	-	[redacted]
		Total	[redacted]

1.A.(3) Malfunctions and adverse events in foreign countries

Table 3 shows malfunctions and adverse events of EluNIR reported in the EU and the US as of July 2021.

Table 3. Malfunctions and adverse events of EluNIR reported in EU and US

Malfunction or event reported	Number of malfunctions or events	Incidence (%)
Tracking difficulties	[redacted]	0.01963
Stent dislocation	[redacted]	0.01554
Strut protrusion	[redacted]	0.00572
Damage to catheter spring tip	[redacted]	0.00491
Contrast medium leakage from delivery catheter	[redacted]	0.00491
Difficulties in balloon dilation	[redacted]	0.00245
Delivery catheter rupture	[redacted]	0.00164
Catheter spring tip separation	[redacted]	0.00082
Stent migration	[redacted]	0.00082
Balloon burst	[redacted]	0.00082
Stent thrombosis	[redacted]	0.00491
Myocardial infarction	[redacted]	0.00327
Coronary artery dissection	[redacted]	0.00164
Death	[redacted]	0.00164
Stent embolism	[redacted]	0.00082

1.B Outline of the review conducted by PMDA

PMDA concluded that the malfunctions and adverse events of EluNIR reported in EU and the US were not particularly problematic because they are common to DESs and their incidence was low.

2. Design and Development

2.(1) Performance and safety specifications

2.(1).A Summary of the data submitted

The proposed performance and safety specifications for EluNIR were determined with reference to the "Handling of Applications for Coronary Stents (in Japanese)" (PFSB/ELD Notification No. 0904001 dated September 4, 2003), the "Establishment of Approval Standards for Percutaneous Coronary Angioplasty Catheters (in Japanese)" (PFSB Notification No. 0401038 dated April 1, 2005), and the US FDA guidance "Guidance for Industry and FDA Staff – Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems, April 2010," "FDA Guidance: Class II Special Controls Guidance Document for Certain Percutaneous Transluminal Coronary Angioplasty (PTCA) Catheters, September 2010," and "FDA Guidance: Coronary Drug-Eluting Stents – Nonclinical and Clinical Studies, March 2008."

(a) Performance specifications for the stent

The proposed performance specifications include stent over-expanded diameter, bare metal stent (BMS) integrity, percentage of the metal to the artery-contacting area, recoil, radial stiffness and strength (compression resistance), stress and strain analysis, fatigue analysis, accelerated durability, corrosion resistance, galvanic corrosion resistance, corrosion resistance after durability testing, magnetic resonance imaging (MRI) safety/compatibility, and radiopacity.

(b) Performance specifications for the whole system consisting of the stent and the delivery system

The proposed performance specifications for the whole system include crossing profile, stent inner diameter at nominal pressure, maximum allowable diameter (maximum inner diameter of the stent with the maximum nominal diameter), delivery performance, guidewire compatibility, guiding catheter compatibility, force required for retrieving the catheter from the deployed stent into the guiding catheter, balloon compliance, minimum balloon burst pressure, balloon fatigue (repeated dilatation of the system), balloon inflation time, balloon deflation time, rupture strength (strength at catheter junction), tip tensile strength, system flexibility and kink resistance, hydrophilic coating, early particulate matter analysis (at baseline and over-expansion in beaker), early particulate matter analysis (after simulated use), stent radial force, torque, stent shortening and elongation, stent deployment heterogeneity, radiopacity and visibility, and catheter corrosion resistance.

(c) Performance specifications for the stent coating

The proposed performance specifications for the stent coating include stent appearance, early integrity of coating surface, long-term integrity of coating (after durability testing), coating adhesiveness, assay/identification/dosage unit uniformity of the drug, drug release, degradation products/drug impurities, and particulate materials.

(d) Safety specifications for EluNIR

The proposed safety specifications for EluNIR include sterility assurance, ethylene oxide sterilization residuals, endotoxins, and biological safety.

2.(1).B Outline of the review conducted by PMDA

PMDA reviewed the data supporting the performance and safety specifications for the appropriateness of the tests and specification limits, and concluded that there was no particular problem in the submitted data.

2.(2) Physicochemical properties

2.(2).A Summary of the data submitted

The tests defined in the performance and safety specifications were conducted.

The MRI compatibility tests (heat generation, magnetically induced displacement force, torque, and image artifacts during the use of 1.5- and 3-Tesla MR system) were conducted using a single EluNIR stent, or 2 or 3 EluNIR stents (overlapping each other), of the maximum length and diameter. The tests showed patients implanted with the device can undergo MRI examinations under predefined conditions. The applicant appropriately raised awareness of the conditions required for MRI imaging by listing them in Information on Precautions, etc., which was published or provided to users.

In addition to the tests defined in the proposed performance and safety specifications, the following tests were conducted:

- The stent was tested for chemical analysis, mechanical properties, extractables, drug coating homogeneity, and coating thickness. The applicant submitted data indicating no particular problem.
- The whole system consisting of the stent and the delivery catheter was tested for direct stenting, flexibility, delivery preparation, and system dimensions. The applicant submitted data indicating no particular problem.

2.(2).B Outline of the review conducted by PMDA

PMDA reviewed the data supporting the physicochemical properties of EluNIR, and concluded that there was no particular problem in the submitted data.

2.(3) Biological safety

2.(3).A Summary of the data submitted

2.(3).A.1) Biological safety of EluNIR

To support the biological safety of EluNIR, the applicant submitted the results of biological safety studies that were conducted in accordance with the "Basic principles of biological safety evaluation required for marketing application for medical devices (in Japanese)" (PFSB/ELD/OMDE Notification No. 0301-20, dated March 1, 2012) and the International Organization for Standardization (ISO) 10993-1.

The DES and BMS of EluNIR were tested for cytotoxicity, sensitization, intracutaneous reactivity, acute systemic toxicity, subchronic toxicity, reverse mutation, mouse lymphoma, mouse micronucleus, rabbit intramuscular implantation (6 weeks), rabbit intramuscular implantation (12 weeks), pyrogenicity, hemolysis, C3a complement activation, and SC5b-9 complement activation. The applicant submitted data indicating no particular problem.

The delivery catheter of EluNIR was tested for cytotoxicity, sensitization, intracutaneous reactivity, acute systemic toxicity, pyrogenicity, hemolysis, C3a complement activation, and SC5b-9 complement activation. The applicant submitted data indicating no particular problem.

The flushing tool, an accessory of EluNIR, was tested for cytotoxicity, sensitization, intracutaneous reactivity, acute systemic toxicity, pyrogenicity, and hemolysis. The applicant submitted data indicating no particular problem.

The *in vivo* thrombotic potential of EluNIR was assessed in animal studies of the device [see Section "2.(5).A.5) Performance studies in animals"] conducted to support its performance.

2.(3).A.2) Toxicity of ridaforolimus

Table 4 shows the toxicity studies of ridaforolimus conducted for the present application. These studies are commonly conducted in the development of drugs. Toxicological findings from these studies were consistent with those reported with "limus" drugs that are commercially available in and outside Japan.[1,2,3] The dose of ridaforolimus is calculated to be [redacted] mg/kg if a human weighing 60 kg, the average human body weight, is implanted with multiple EluNIR stents of the maximum diameter (4.0 mm) so that the total stent length is approximately 100 mm. The results of the studies in Table 4 show that the toxicity risk of ridaforolimus loaded on the EluNIR stent is controlled at a very low level.

Table 4. Toxicity studies of ridaforolimus included in the present application

Study title	Outline
(a) Single-dose toxicity	• Single intravenous dose toxicity study in mice • Single intravenous dose toxicity study in rats • Single intravenous dose toxicity study in monkeys • Oral dose toxicity study in mice (reference data) • Oral dose toxicity study in rats (reference data)
(b) Repeated-dose toxicity	• Repeated intravenous dose toxicity study in rats • Four-cycle intravenous dose toxicity study in rats • Four-cycle intravenous dose toxicity study in monkeys • Twenty-one-day oral dose toxicity study in rats (reference data) • Twenty-eight-day oral dose toxicity study in rats (reference data) • Six-month oral dose toxicity study in rats (reference data) • Twenty-eight-day oral dose toxicity study in monkeys (reference data) • Thirteen-week oral dose toxicity study in monkeys (reference data) • Six-month oral dose toxicity study in monkeys (reference data)
(c) Developmental toxicity and genotoxicity	• Developmental toxicity study by oral dose in rats • Developmental dose-finding toxicity study by oral dose in rats (reference data) • Reverse mutation assay • Chromosome aberration assay • Micronucleus assay
(d) Local tolerance	• Acute intravenous and peri-intravenous dose tolerance study in rabbits
(e) Phototoxicity	• Oral dose phototoxicity study in pigmented rats

2.(3).A.2).(a) Single-dose toxicity

A single intravenous dose toxicity study in mice was conducted to investigate the toxicity of ridaforolimus 5, 10, 25, or 50 mg/kg for 14 days after intravenous administration to mice. Toxicological findings observed were decreased testis weight, decreased brain weight, increased lung-to-brain weight ratio, and decreased liver-to-body weight ratio.

A single intravenous dose toxicity study in rats was conducted to investigate the toxicity of ridaforolimus 5, 10, 20, or 30 mg/kg for 14 days after intravenous administration to rats. Toxicological findings observed were body weight losses, hematological data outside the normal ranges (decreased

reticulocyte count, increased sodium, increased glucose, and decreased testosterone), decreased thymus gland weight, decreased seminal vesicle weight, decreased heart weight, and increased lung weight.

A single intravenous dose toxicity study in monkeys was conducted to investigate the toxicity of ridaforolimus 5, 10, or 15 mg/kg for 14 days after intravenous administration to monkeys. Toxicological findings observed were hematological data outside the normal ranges (increased alanine aminotransferase and increased aspartate aminotransferase), and decreased thymus gland weight.

2.(3).A.2).(b) Repeated-dose toxicity

A repeated intravenous dose toxicity study in rats was conducted to investigate the toxicity of ridaforolimus 5, 10, or 20 mg/kg administered intravenously to rats once daily for 28 days. Death occurred in 1 male in the 20 mg/kg group 2 days after the start of administration and 1 female in the 10 mg/kg group 28 days after the start of administration. Neither dead animal had abnormal clinical signs before death. The following toxicological findings were observed in the surviving animals: injection site lesions, body weight losses, hematological data outside the normal ranges (decreased mean corpuscular hemoglobin concentration, increased reticulocyte count, increased reticulocyte percentage, decreased platelet count, decreased basophil count, increased monocyte count, decreased eosinophil count, increased fibrinogen, increased blood urea nitrogen, increased cholesterol, decreased albumin, increased globulin, decreased total protein, decreased potassium, decreased chloride, decreased calcium, increased glucose, and decreased testosterone), decreased organ weights (brain, epididymides, heart, kidneys, liver, pituitary gland, prostate, slavery gland, seminal vesicles, spleen, testes, thymus gland, thyroid gland, ovaries, and uterus), lymphocyte depletion (thymus gland, spleen, lymph nodes, and gut-associated lymphoid tissue), lens degeneration, myocardial necrosis, myocardial fibrosis, testicular degeneration, uterine atrophy, telogen follicle, increased diffuse alveolar macrophage, red blood cells in the sinusoidal area in mesenteric lymph node, urinary protein, urinary glucose, and blood urine.

A 4-cycle intravenous dose toxicity study in rats was conducted to investigate the toxicity of ridaforolimus. A cycle consisted of intravenous administration of ridaforolimus 5, 10, or 20 mg/kg once daily for 5 consecutive days. A total of 4 cycles were performed with a 2-week interval between cycles. Death occurred in 12 animals before the scheduled day of euthanasia. Ten of them died from anesthesia or stress associated with blood sampling. One of the 2 remaining animals was in the 20 mg/kg group. This animal had a lateral position and no reaction 17 days after the start of administration (during the second cycle), and died on the same day. The cause of death was acute urinary tract inflammation, which was considered to have developed spontaneously. The remaining 1 animal was in the 5 mg/kg group, and was found moribund 7 days after the start of administration and

was euthanized. Prior to euthanasia, the animal had rapid respiration, lateral position, contact hypersensitivity, and tremor. Neither food nor water intake was observed. The cause of death was unknown. The following toxicological findings were observed in the surviving animals: body weight losses, hematological data outside the normal ranges (decreased mean corpuscular volume, decreased platelet count, increased hematocrit, increased monocyte count, decreased white blood cell count, decreased circulating lymphocyte percentage, decreased mean corpuscular hemoglobin concentration, increased fibrinogen, prolonged prothrombin time, decreased alkali phosphatase, increased blood urea nitrogen, increased cholesterol, increased globulin, decreased albumin, decreased phosphorous, decreased magnesium, increased sodium, decreased chloride, increased alanine aminotransferase, increased glucose, decreased potassium, decreased total protein, and decreased testosterone), decreased organ weights (brain, epididymides, heart, kidneys, liver, pituitary gland, prostate, slavery gland, seminal vesicles, spleen, testes, thymus gland, thyroid gland, ovaries, and uterus), organ atrophy (thymus gland, testes, seminal vesicles, ovaries, and uterus), lens degeneration, cardiomyopathy, alveolar histiocytosis, increased foamy macrophages in mesenteric lymph node, lymphocyte depletion in thymus gland, femur bone marrow depletion, injection site lesions, testicular duct degeneration, decreased sperm in epididymis, mammary gland hyperplasia, and gastric adenocarcinoma.

A 4-cycle intravenous dose toxicity study in monkeys was conducted to investigate the toxicity of ridaforolimus. A cycle consisted of intravenous administration of 3, 6, or 12 mg/kg once daily for 5 consecutive days. A total of 4 cycles were performed with a 2-week interval between cycles. One animal in the 3 mg/kg group was found moribund and euthanized 43 days after the start of administration (after the end of third cycle). One animal in the 6 mg/kg group was found moribund and euthanized 57 days after the start of administration (after the end of fourth cycle). Both animals became moribund because of systemic bacterial infection. The following toxicological findings were observed in the surviving animals: soft feces, diarrhea, dry skin with exfoliation, urticaria, body weight losses, hematological data outside the normal ranges (increased white blood cell count, increased neutrophil count, decreased eosinophil count, and increased fibrinogen), urinary test abnormalities (bilirubin, ketones, occult blood, glucose, protein, nitrite, and others), decreased organ weights (testes, seminal vesicles, thymus gland, lungs, kidneys, brain, and spleen), lymphocyte depletion (thymus gland, spleen, lymph nodes, and gut-associated lymphoid tissue), and hydrocephalus.

2.(3).A.2).(c) Developmental toxicity, and genotoxicity

A developmental toxicity study by oral dose in rats was conducted to investigate the developmental toxicity of ridaforolimus 0.1, 0.5, or 2.0 mg/kg after oral administration to probably pregnant female rats once daily from probable gestation days 7 to 17.

Maternal animals in the 2 mg/kg/day group had body weight losses. Increased post-implantation embryonic losses and accompanying reduced litter sizes were observed in the 2 mg/kg/day group, and fetal body weight losses in the 0.5 and 2 mg/kg/day groups. These findings suggested the developmental toxicity of ridaforolimus. The increased incidence of fetal skeleton changes and delayed ossification were also observed in the 2 mg/kg/day group. The mean of the number of corpora lutea, number of implantations, number of late resorptions, and the percentage of live male fetuses in the litter were comparable across all doses up to 2 mg/kg/day. No dead fetus was found. All of the maternal animals of live fetuses had a normal placenta.

Ridaforolimus was negative for genotoxicity in the reverse mutation, chromosomal aberration, and micronucleus assays.

2.(3).A.2).(d) Local tolerance

An acute tolerance study by intravenous dose in rabbits was conducted to investigate the toxicity of ridaforolimus 2.5 mg/kg after intravenous administration into the auricular vein of each rabbit. There was no evidence of irritation at the injection site.

2.(3).A.2).(e) Phototoxicity

A 3-day oral dose phototoxicity study in pigmented rats was conducted to investigate the toxicity of ridaforolimus in the skin and eyes exposed to ultraviolet in pigmented rats given oral ridaforolimus 25 or 75 mg/kg once daily for 3 days. There was neither skin reaction nor ocular findings suggestive of the phototoxicity of ridaforolimus.

2.(3).B Outline of the review conducted by PMDA

PMDA reviewed the data supporting the biological safety of EluNIR and concluded that the toxicological findings from the toxicity studies of ridaforolimus would not pose a particular problem to EluNIR, because the toxicological findings are consistent with those of the other “limus” drugs used in existing DESs, and because the dose loaded on the EluNIR stent is very low [see Section “6.B.(1).(b) Safety”].

2.(4) Stability and durability

2.(4).A Summary of the data submitted

2.(4).A.1) Stability of ridaforolimus coated on the EluNIR stent

The stability of ridaforolimus coated on the EluNIR stent was investigated in stability studies conducted under long-term storage conditions for 2 years and accelerated conditions for 6 months in accordance with the International Council for Harmonisation of Technical Requirements for

Pharmaceuticals for Human Use (ICH) Guideline Q1A (R2) (Stability Testing of New Drug Substances and Products).

All of the tests on stent appearance, drug assay, degradation products, drug-derived impurities, drug release, particulate materials, BHT, and bacterial endotoxins met their respective proposed specifications.

2.(4).A.2) Stability of the stent and the delivery system

The stability of the stent and the delivery system was investigated in stability testing under accelerated conditions equivalent to 2 years of storage.

All of the following tests met their respective proposed specifications: Coating adhesion, coating surface integrity, particulate matter analysis, size (catheter), crossing profile, visual inspection (lure lock compatibility, catheter kink, stent position, stent integrity, readability of the print on the hub, and tip shape/processing), stent inner diameter at nominal pressure, maximum allowable diameter, minimum balloon burst pressure, simulated use (balloon inflation time, delivery performance, guidewire compatibility, guiding catheter compatibility, stent positioning accuracy, effectiveness of fixation, maximum outer diameter of the deflated balloon, and lumen flushing), balloon deflation time, balloon fatigue, force required for retrieving the catheter from the deployed stent into the guiding catheter, balloon compliance, stent shortening and elongation, stent deployment heterogeneity, stent radial strength, rupture strength (strength at catheter junction), tip tensile strength, system flexibility and kink resistance, catheter coating integrity, torque, and catheter corrosion resistance.

2.(4).A.3) Stability of ridaforolimus drug substance

The stability of ridaforolimus drug substance was investigated in stability testing under long-term storage, accelerated, and stress conditions in accordance with the ICH Guideline Q1A (R2) (Stability Testing of New Drug Substances and Products), Q1B (Photostability Testing of New Drug Substances and Products), and Q1E (Evaluation of Stability Data).

The stress testing showed that ridaforolimus was photosensitive and therefore EluNIR needs to be stored protected from light. On the basis of this finding, the aluminum pouch was selected as the final packaging form of EluNIR.

2.(4).B Outline of the review conducted by PMDA

PMDA reviewed the data supporting the stability and durability and concluded that there was no particular problem about the shelf life of 2 years proposed by the applicant.

2.(5) Performance

2.(5).A Summary of the data submitted

To support the performance of EluNIR, the applicant submitted pharmacological, safety pharmacological, and pharmacokinetic data of ridaforolimus, and pharmacokinetic and performance data in pigs implanted with the EluNIR stent.

2.(5).A.1) Pharmacology of ridaforolimus

For the evaluation of the efficacy of ridaforolimus loaded on a DES, the applicant submitted data on inhibition of the proliferation of smooth muscle and endothelial cells, and data on cell signaling inhibition.

2.(5).A.1).(a) Inhibition of the proliferation of smooth muscle and endothelial cells

The half maximal inhibitory concentrations (IC_{50}) of ridaforolimus, sirolimus, everolimus, and zotarolimus in human aortic smooth muscle cells and human aortic endothelial cells were assessed *in vitro*. Drugs loaded on DESs are required to selectively inhibit the proliferation of smooth muscle cells while protecting endothelial cells. As shown in Table 5, ridaforolimus inhibited the proliferation of endothelial cells more weakly than everolimus, and comparably to sirolimus and zotarolimus. On the other hand, ridaforolimus inhibited the proliferation of smooth muscle cells more potently than sirolimus and everolimus, and comparably to zotarolimus. These findings showed that ridaforolimus had a similar inhibitory effect to that of zotarolimus in terms of the performance required for a drug loaded on DESs.[4]

Table 5. Half maximal inhibitory concentration (IC_{50}) in smooth muscle and endothelial cells

IC_{50} (M)	Smooth muscle cell	Endothelial cell
Sirolimus	10^{-4}	10^{-4}
Everolimus	10^{-5}	10^{-5}
Zotarolimus	10^{-8}	10^{-4}
Ridaforolimus	10^{-8}	10^{-4}

2.(5).A.1).(b) Cell signaling inhibition

Ridaforolimus 0.1, 1, or 10 mg/kg was administered intraperitoneally to cancer-bearing nude mice. Phosphorylated 4E-BP1 and phosphorylated S6 protein, which exists in the downstream of mTOR in the cell signaling pathway, were measured by western blotting (immunoblotting). Each protein decreased in a ridaforolimus dose-dependent manner, suggesting that ridaforolimus inhibits mTOR signaling pathway.

2.(5).A.2) Safety pharmacology of ridaforolimus

Safety pharmacology studies were conducted to investigate the effects of ridaforolimus on the central nervous system, cardiovascular system, respiratory system, and kidneys. The results of the study on gastrointestinal effects were submitted as reference data.

2.(5).A.2).(a) Central nervous system

A single dose of ridaforolimus 5, 10, or 20 mg/kg was administered intravenously to mice. The 20 mg/kg group had a decrease in locomotor activity. No other particular neuropharmacological effect was observed.

2.(5).A.2).(b) Cardiovascular system

A single dose of ridaforolimus 5, 15, or 45 mg/kg was administered orally to monkeys. The results showed no particular effects on hemodynamics (heart rate, blood pressure, and core temperature) or electrocardiogram.

A single dose of ridaforolimus 3 mg/kg was administered intravenously to dogs. The results showed no particular effects on cardiac function (electrocardiogram) or cardiovascular function (heart rate, diastolic arterial pressure, systolic arterial pressure, and mean arterial pressure).

In vitro, the rate of inhibition of the human ether-a-go-go related gene (HERG) channel (myocardial potassium ion channel) activity by ridaforolimus was similar to that by sirolimus.

2.(5).A.2).(c) Respiratory system

A single dose of ridaforolimus 5, 10, or 20 mg/kg was administered intravenously to guinea pigs. The results showed no particular effects on pulmonary function (airway resistance [cm H_2O/mL/s], dynamic lung compliance [mL/cm H_2O], respiratory rate [breaths/min], tidal volume [mL], and minute ventilation [mL/min]).

2.(5).A.2).(d) Kidneys

A single dose of ridaforolimus 5, 10, or 20 mg/kg was administered intravenously to rats. All of the groups had increases in urine output and electrolyte excretion. No effect on urinary pH or electrolyte levels was observed.

2.(5).A.2).(e) Tolerability of gastrointestinal administration (reference data)

One film-coated tablet or enteric-coated tablet containing ridaforolimus 10 mg was administered orally to miniature pigs once daily for 7 days. No evidence of gastrointestinal irritation was observed.

2.(5).A.3) Pharmacokinetics of ridaforolimus

The pharmacokinetics (absorption, distribution, metabolism, and excretion) of ridaforolimus was investigated in animals. The key study results are presented below.

2.(5).A.3).(a) Absorption

Intravenous dose studies were conducted in rats and monkeys. Although the applicant submitted also the results of oral dose studies as reference data, this review report shows only the results of the intravenous dose studies (summarized in Table 6) because the EluNIR stent is a coronary stent.

Table 6. Single-dose intravenous pharmacokinetics

	Rat	Monkey
Dose (mg/kg)	5	5
C_0 (ng/mL)	2290	3920
$AUC_{0-\infty}$ (ng·h/mL)	2840	8990
CL (L/h/kg)	1.76	0.59
Vd_{ss} (L/kg)	49.8	25.1
$t_{1/2}$ (h)	19.6	29.7

C_0 = Drug concentration in blood at time 0
$AUC_{0-\infty}$ = Area under the curve from 0 to infinity
CL = Blood clearance
Vd_{ss} = Distribution volume at steady state
$t_{1/2}$ = Elimination half-life

2.(5).A.3).(b) Distribution

The binding of ridaforolimus to mouse, rat, monkey, and human plasma proteins, and human liver microsome protein was assessed *in vitro*. The equilibrium distribution of ridaforolimus between plasma and erythrocytes in mouse, rat, monkey, and human whole blood was assessed *in vitro*. The binding of ridaforolimus to mouse, rat, monkey, and human plasma proteins was 99.7%, 95.4%, 95.3%, and 93.8%, respectively. The binding of ridaforolimus to human liver microsome protein was 53.8%. The study on the equilibrium distribution of ridaforolimus between plasma and erythrocytes in whole blood showed no selective binding of ridaforolimus to erythrocytes in mouse whole blood, but suggested the selective binding of ridaforolimus to erythrocytes in rat, monkey, and human whole blood.

An *in vitro* study using a cell line expressing human P glycoprotein (Pgp), which transports compounds out of cells, was conducted. The results suggested the extracellular transport of ridaforolimus by Pgp and also showed that ridaforolimus may inhibit the Pgp-mediated transport of digoxin, an inotropic drug, with IC_{50} of 13.4 ± 5 μM.

A single-dose study was conducted where ^{14}C-ridaforolimus was administered orally to albino rats at a dose of 28.5 mg/kg or pigmented rats at 28.8 mg/kg. The drug concentration peaked at 2 hours post-dose in most tissues of albino and pigmented rats. The following tissues of albino and pigmented rats had particularly high drug concentrations: The small intestine, liver, adrenals, pancreas, renal cortex, brown adipose tissue, cecum, kidneys, thyroid gland, renal medulla, stomach, salivary gland, cardiac muscle, pituitary gland, preputial glands, extra-orbital lacrimal gland, spleen, diaphragm, intra-orbital lacrimal gland, aorta, lungs, bone marrow, prostate, choroid plexus, skeletal muscle, harderian gland, large intestine, lymph node, esophagus, thymus gland, and abdominal adipose tissue.

The drug concentrations in the central nervous system tissues, except for the choroid plexus, were below or around the quantitation limit throughout the entire study period in albino and pigmented rats. Tissue concentrations were almost at the lower limit of quantitation at 168 hours post-dose in albino rats and 672 hours in pigmented rats. Blood concentrations decreased to a level below the quantitation limit within 72 hours post-dose in albino rats and at 24 hours post-dose in pigmented rats. Almost all animals had a blood/plasma concentration ratio of approximately 0.7 at each time point. The tissue/plasma concentration ratio up to 24 hours post-dose was 0.032 (olfactory lobe) to 56.797 (small intestine) in albino rats and 0.035 (olfactory lobe) to 109.874 (small intestine) in pigmented rats.

2.(5).A.3).(c) Metabolism

A single dose of ^{14}C-ridaforolimus 15 mg/kg was administered orally to monkeys. The major radioactive component in whole blood up to 24 hours post-dose was ridaforolimus, which accounted for 44.6% of the total radioactivity. Metabolites of ridaforolimus detected in whole blood were 3 types of mono-hydroxy ridaforolimus and 3 types of *O*-demethylated ridaforolimus, which accounted for 20% and 7.4%, respectively, of the total radioactivity in whole blood. Seco-ridaforolimus accounted for approximately 3% of the total radioactivity in whole blood. Many unidentified polar peaks were detected in urine. Seco-ridaforolimus was the only metabolite identified, which accounted for 18% of the radioactivity in urine. Ridaforolimus accounted for 1.3% of the radioactivity in urine. Many unidentified polar peaks were also detected in feces. Seco-ridaforolimus and metabolites derived from seco-ridaforolimus were identified, and they accounted for 18.9% of the radioactivity in feces. Ridaforolimus accounted for 22.1% of the radioactivity in feces. These findings indicated that ridaforolimus was metabolized in monkeys mainly via hydroxylation, demethylation, and metabolites related to seco-ridaforolimus.

A single dose of ^{14}C-ridaforolimus 38.9 mg/kg was administered orally to bile duct-cannulated rats. The major radioactive component in whole blood up to 24 hours post-dose was ridaforolimus, which accounted for 68.3% of the total radioactivity. Biliary metabolites were mainly due to hydroxylation and demethylation.

The *in vitro* studies using liver microsomes and hepatocytes of rats, monkeys, and humans revealed that the major metabolic pathways of ridaforolimus were mono-hydroxylation, demethylation, and dihydroxylation. Ridaforolimus was mainly metabolized by cytochrome P450 (CYP)3A4.

An *in vitro* study was conducted to evaluate the change in the activity of CYP in primary human hepatocytes treated with ridaforolimus. Ridaforolimus reduced the activity of CYP1A2 and CYP3A4/5.

An *in vitro* study was conducted to investigate the potential of ridaforolimus to inhibit the metabolism of concomitant medications by assessing the inhibitory effect of ridaforolimus on major CYPs in human liver microsomes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5). The results showed that ridaforolimus is a direct inhibitor of CYP2C9, CYP2D6, and CYP3A4/5 with IC_{50} of 21, 16, 21, and 1.4 μM, respectively. Ridaforolimus inhibited CYP2B6 and CYP2C8 by less than 50% (approximately 42% and 26%, respectively) within the concentration range of ridaforolimus assessed (0.03-30 μM); this indicates the IC_{50} of CYP2B6 and CYP2C8 exceeds 30 μM. Ridaforolimus inhibited neither CYP1A2 nor CYP2C19.

2.(5).A.3).(d) Excretion

A single dose of ^{14}C-ridaforolimus 15 mg/kg was administered orally to monkeys. In urine and feces, 2.0% ± 1.5% and 74.5% ± 16.8%, respectively, of the administered dose were excreted up to 168 hours post-dose.

A single dose of ^{14}C-ridaforolimus 38.9 mg/kg was administered orally to bile duct-cannulated rats. In urine, feces, and bile, 2.1%, 52.2%, and 30.8%, respectively, of the administered dose were excreted up to 96 hours post-dose.

2.(5).A.4) Pharmacokinetics in pigs implanted with the EluNIR stent

Two or three EluNIR stents, 2.75 mm in diameter and 17 mm in length or 3.00 mm in diameter and 17 mm in length (loaded with [redacted] μg of ridaforolimus per stent in both sizes), were implanted in the coronary artery of each pig to investigate the pharmacokinetics of ridaforolimus. The blood concentration of ridaforolimus per stent (loaded with [redacted] μg ridaforolimus) peaked (1.1 ng/mL) at several hours post-implantation and was below the detection limit at 144 hours post-implantation. The tissue concentration of ridaforolimus at the implantation site peaked (6.5 ng/mg) at 7 days post-implantation and was below the detection limit between 180 and 450 days post-implantation. The tissue concentration of ridaforolimus in the proximal and distal coronary arteries at the implantation site and in adjacent myocardium peaked within 7 days post-implantation and was almost below the detection limit after 50 days post-implantation.

2.(5).A.5) Performance studies in animals

An acute performance study (immediately after implantation), a long-term safety study of overlapping implantation (180 days post-implantation), and a long-term safety study (360 days post-implantation) were conducted in pigs to support the performance of EluNIR. The EluNIR stent(s) were implanted in the coronary arteries of pigs. The key study results are presented below.

2.(5).A.5).(a) Acute performance study (immediately after implantation)

The EluNIR stent or the "Resolute Integrity Coronary Stent System" (Approval Number, 22400BZX00176000) (hereinafter referred to as Resolute) was implanted in pig coronary arteries. The performance characteristics during the procedure, including the ease of insertion and removal, were assessed by 2 experts. They found no particular problem in any animal. None of the animals had coronary artery dissection or thrombosis adhering to the removed delivery catheter.

The EluNIR stent and its BMS were implanted in pig coronary arteries. The animals were necropsied on the day of completing the procedure. The performance characteristics during the procedure, including the ease of insertion and removal, were assessed by 2 experts. They found no particular problem in any animal. None of the animals had coronary artery dissection or thrombosis adhering to the removed delivery catheter. Histological examination revealed no thrombosis, necrosis, inflammation, or embolic materials in blood vessels or myocardium at the stent placement site or in those in the downstream of the stent placement site.

2.(5).A.5).(b) Long-term safety study of overlapping implantation (180 days post-implantation)

Two EluNIR stents and its 2 BMS were implanted in pig coronary arteries. The 2 EluNIR stents were overlapping each other, and the 2 BMS were overlapping each other. The animals were necropsied at 3, 30, and 180 days post-implantation.

None of the animals had particularly problematic findings. The EluNIR stents and its BMS had sufficient intimal coverage to a similar extent at 30 days post-implantation. Inflammatory reaction at the implantation site almost resolved at 180 days post-implantation.

2.(5).A.5).(c) Long-term safety study (360 days post-implantation)

The EluNIR stent, a high-dose DES (i.e., a stent loaded with ridaforolimus at a dose 5 times that of the EluNIR stent), or the BMS of the EluNIR stent was implanted alone in pig coronary arteries. Necropsy was performed in animals receiving the EluNIR stent or the BMS at 3, 30, 90, 180, and 360 days post-implantation, and in animals receiving the high-dose DES at 30 and 180 days post-implantation.

None of the animals had particularly problematic findings. The EluNIR stent and the high-dose DES had sufficient intimal coverage to a similar extent as the BMS at 30 days post-implantation. Inflammatory reaction at the implantation site almost resolved at 90 days post-implantation in animals receiving EluNIR and BMS.

2.(5).B Outline of the review conducted by PMDA

The safety pharmacology study of ridaforolimus showed a decrease in locomotor activity after intravenous administration of a single dose of ridaforolimus 20 mg/kg to mice. However, the dose of ridaforolimus is calculated to be [redacted] mg/kg if a human weighing 60 kg, the average human body weight, is implanted with multiple EluNIR stents of the maximum diameter (4.0 mm) so that the total stent length is approximately 100 mm. This means that the above finding from the safety pharmacology study does not pose a particular risk of using EluNIR in clinical practice.

There is no particular concern about the pharmacokinetics of ridaforolimus because the relevant information and precautions are provided in the Information on Precautions, etc. based on the study results submitted, including the finding that ridaforolimus was primarily metabolized by CYP3A4 as with the other "limus" drugs.

Assessment of tissue reactions during the implantation of EluNIR revealed no particularly problematic intimal coverage in the pig blood vessels. Inflammatory reaction almost resolved during the observation period. Nevertheless, the performance of EluNIR should be reviewed based not only on the results of the animal studies but also on the results of the clinical studies described later.

PMDA reviewed the data supporting the performance of EluNIR, and concluded that there was no particular problem in the submitted data.

3. Conformity to the Requirements Specified in Paragraph 3 of Article 41 of Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices

3.A Summary of the data submitted

The applicant submitted a declaration of conformity declaring that EluNIR meets the standards for medical devices as stipulated by the Minister of Health, Labour and Welfare in accordance with Paragraph 3 of Article 41 of Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (hereinafter referred to as "the Essential Principles") (MHLW Ministerial Announcement No. 122, 2005).

3.B Outline of the review conducted by PMDA

PMDA reviewed the conformity of EluNIR to the Essential Principles as shown below.

(a) PMDA's view on the conformity to Article 2, which specifies requirements for risk management throughout the product life cycle of medical devices:

As described later in Section "6.B Outline of the review conducted by PMDA," the applicant should report the long-term outcome of patients who participated in the Japanese clinical study to

PMDA in order to confirm the long-term results of EluNIR in the Japanese patients. This requirement is included in the approval conditions.

(b) PMDA's view on the conformity to Article 3, which specifies requirements for the performance of medical devices, and Article 6, which specifies the efficacy of medical devices:
As described later in Section "6.B Outline of the review conducted by PMDA," a clinical study showed the non-inferiority of EluNIR to a similar medical device already approved in Japan, without any adverse event specific to EluNIR. Thus EluNIR conforms to Articles 3 and 6.

(c) PMDA's view on the conformity to Article 4, which specifies the shelf lives of medical devices:
As described earlier in Section "2.(4).B Outline of the review conducted by PMDA," an appropriate shelf life was determined for EluNIR based on the test results on the stability and duration of EluNIR and ridaforolimus. EluNIR thus conforms to Article 4.

(d) PMDA's view on the conformity to Article 7, which specifies the selection of materials of medical devices:
As described earlier in Section 2.(1).B to 2.(5).B "Outline of the review conducted by PMDA" and later in Section "6.B Outline of the review conducted by PMDA," the safety, quality, and performance of ridaforolimus were demonstrated, and the safety, equality, and performance of EluNIR as a DES were also demonstrated in the nonclinical and clinical studies. EluNIR thus conforms to Article 7.

(e) PMDA's view on the conformity to Article 8, which specifies prevention of microorganism contamination in medical devices:
As described later in Section "5.B Outline of the review conducted by PMDA," the sterility, etc. of EluNIR was shown to be appropriate. EluNIR thus conforms to Article 8.

(f) PMDA's view on the conformity to Article 9, which specifies considerations when using a medical device in combination with other medical devices:
As described earlier in Section "2.(2).B Outline of the review conducted by PMDA," the MRI compatibility tests showed that patients implanted with the EluNIR stent can undergo MRI examinations under predefined conditions. The conditions for MRI imaging are provided appropriately in the Information on Precaution, etc. Thus EluNIR conforms to Article 9.

(g) PMDA's view on the conformity to Article 17, which specifies dissemination of information to users via the Information on Precautions, etc.:

As described later in Section "6.B Outline of the review conducted by PMDA," information on (1) the toxicity of ridaforolimus and drugs that may interact with ridaforolimus and (2) Dual Antiplatelet Therapy (DAPT) in the clinical studies should be disseminated through the Information on Precautions, etc.

PMDA comprehensively reviewed the conformity of EluNIR to the Essential Principles and concluded that there was no particular problem.

4. Risk Management

4.A Summary of the data submitted

The applicant submitted data summarizing the risk management system and risk management activities conducted for EluNIR in accordance with ISO 14971:2012 "Medical devices – Application of risk management to medical devices."

4.B Outline of the review conducted by PMDA

PMDA comprehensively reviewed the document on risk management taking into account the discussion presented in Section "3.B Outline of the review conducted by PMDA" and concluded that there was no particular problem.

5. Manufacturing Process

5.A Summary of the data submitted

The applicant submitted data on the in-process tests and sterilization methods for EluNIR (sterility assurance, ethylene oxide sterilization residuals, and bacterial endotoxins).

5.B Outline of the review conducted by PMDA

PMDA reviewed the data on the manufacturing process, and concluded that there was no particular problem in the submitted data.

6. Clinical Data or Alternative Data Accepted by the Minister of Health, Labour and Welfare

6.A Summary of the data submitted

The applicant submitted the results of the following studies as evaluation data for EluNIR (Table 7):

- The BIONICS study, a foreign pivotal study
- The BIONICS-PK study, a foreign pharmacokinetics study of ridaforolimus loaded on the implanted EluNIR stent
- The JNIR study, a Japanese bridging study

The applicant submitted the following reference data:

- The results at 5 years post-procedure in the BIONICS study

- The results of the clinical studies conducted for the development of ridaforolimus as a drug

Table 7. Key clinical study results included in the present application

Study title	Country or region (initiated in)	Study device	Outline	Submitted data
BIONICS study	US, Canada, EU, and Israel (2014)	EluNIR	Assessment of non-inferiority of the EluNIR to an approved similar device	• Results at 1 year post-procedure (evaluation data) • Results at 5 years post-procedure (reference data)
BIONICS-PK study	US (2016)	EluNIR	Pharmacokinetic assessment of ridaforolimus from the implanted EluNIR stent	• Results at 30 days post-procedure (evaluation data)
JNIR study	Japan (2017)	EluNIR	Bridging study	• Results at 1 year post-procedure (evaluation data)

6.A.(1) BIONICS study (Studied period, March 2014 to October 2020)

The BIONICS study was conducted in patients eligible for general percutaneous coronary intervention (PCI) at 76 study sites in the US, Canada, EU, and Israel. This was a multicenter, randomized, single-blind comparative study to assess the non-inferiority of EluNIR to Resolute, which is a DES loaded with zotarolimus and is already approved in Japan. Table 8 shows the summary of the study. Tables 9 and 10 show the subject and disease characteristics, respectively. Figure 3 shows the disposition of subjects.

Table 8. Summary of the BIONICS study

	Summary
Study objective	To prove the non-inferiority of EluNIR to Resolute in efficacy and safety
Study design	Prospective, multicenter, single-blind, randomized clinical study
Population	Patients eligible for PCIs, such as those with angina pectoris, asymptomatic ischaemia, non-ST-elevation myocardial infarction, and ST-elevation myocardial infarction
Study device	• EluNIR • Resolute (control)
Number of subjects enrolled	958 in the EluNIR group, 961 in the control group
Number of study sites	76 (US, Canada, EU, and Israel)
Primary endpoint	Rate of target lesion failure (TLF; the composite of cardiac death, target vessel myocardial infarction, or clinically driven target lesion revascularization [TLR]) at 1 year
Secondary endpoints	The following success rates (acute success) were evaluated at the time of baseline procedure: • Device success (final in-stent residual diameter stenosis of <50% using the assigned device only and without a device malfunction [endpoint per lesion]) • Lesion success (final in-stent residual diameter stenosis of <50% using any percutaneous method [endpoint per lesion]) • Procedure success (final in-stent residual diameter stenosis of <50% using the assigned device and/or with any adjunctive devices, without the occurrence of cardiac death, Q wave or non-Q wave myocardial infarction, or repeat TLR during the hospital stay [endpoint per patient]) The incidence of the following events was evaluated at 30 days, 6 months, and 2, 3, 4, and 5 years: • TLF • Major adverse cardiac events (MACE; the composite of cardiac death, any myocardial infarction, and clinically driven TLR) • Target vessel failure (TVF; the composite of death, target vessel myocardial infarction, or clinically driven target vessel revascularization [TVR]) • All-cause death • Cardiac death • Any myocardial infarction • Target vessel myocardial infarction • Clinically driven TLR • Clinically driven TVR • Stent thrombosis
Safety endpoints	Adverse events (including study device-related adverse events, serious adverse events, study device/drug-related serious adverse events, and study device/drug-related known and unknown serious adverse events) were continuously monitored at each study visit and throughout the study period. The other safety parameters monitored: • Pregnancy • Complete blood count, creatinine, and blood urea nitrogen • Lipid profile (total cholesterol, low density lipoprotein, high density lipoprotein, and triglycerides) • Creatine kinase, creatine kinase myocardial isoenzyme, and troponin • 12-Lead electrocardiogram • Concomitant medications
Sub-studies	Approximately the first 200 consecutive subjects who consented to participate in the sub-studies at the study sites in North America underwent angiography at 13 months post-procedure. Of them, the first 100 subjects underwent intravascular ultrasound at the time of procedure and the 13-month post-procedure. • Angiographic assessment of vascular lumen loss (85 in the EluNIR group, 73 in the control group) • Intravascular ultrasonic assessment of neointimal hyperplasia rate and incomplete stent apposition (55 in the EluNIR group, 56 in the control group)

Key inclusion criteria	• Patients eligible for PCI • Target lesion(s) must be located in a native coronary artery or bypass graft conduit with visually estimated diameter of 2.5-4.25 mm.
Key exclusion criteria	• Patients with ST-elevation myocardial infarction at <24 hours since first hospital presentation or in whom myocardial markers have not peaked • Patients who underwent PCI within 24 hours before the baseline procedure • History of stent thrombosis • Cardiogenic shock • Known left ventricular ejection fraction <30% • Contraindication to DAPT for 12 months • Patients with bleeding diathesis or past coagulopathy or those who refuse blood transfusions • Cerebrovascular accident or transient ischemic attack within the past 6 months, or any permanent neurologic defect attributed to cerebrovascular accident • A target lesion present in any of the 3 major coronary arteries or their branches • The total length of the coronary arteries to be covered by the study stents will exceed 100 mm • Occlusive thrombus or a thrombus requiring thrombectomy in a target vessel • Any lesion within 5 mm from the unprotected left main coronary artery • Bifurcation lesions with planned dual stent implantation
Follow-up period	5 years post-procedure

Table 9. Subject characteristics in the BIONICS study

	EluNIR (N = 958)	Control (N = 961)
Age [years (SD)]	63.7 (10.2)	63.1 (10.3)
Men [% (n/N)]	78.3% (750/958)	81.9% (787/961)
BMI [kg/m^2 (SD)]	29.1 (5.0)	29.0 (5.2)
Current smoker [% (n/N)]	23.4% (224/958)	19.4% (186/961)
Hypertension [% (n/N)]	72.4% (687/949)	74.0% (704/951)
Receiving medical treatment	95.2% (654/687)	95.3% (671/704)
Hyperlipidemia [% (n/N)]	80.4% (759/944)	78.1% (744/953)
Receiving medical treatment	89.3% (678/759)	90.2% (671/744)
Diabetes mellitus [% (n/N)]	32.8% (314/958)	32.3% (310/961)
Requiring insulin	29.0% (91/314)	29.0% (90/310)
Requiring oral drug	61.5% (193/314)	59.7% (185/310)
Prior PCI [% (n/N)]	38.8% (372/958)	38.2% (367/961)
Target blood vessel	8.1% (78/958)	7.8% (75/961)
Prior coronary artery bypass [% (n/N)]	8.8% (84/958)	9.6% (92/961)
Target blood vessel	35.7% (30/84)	53.3% (49/92)
History of myocardial infarction [% (n/N)]	31.1% (298/958)	30.5% (293/961)
Family history of early coronary artery disease [% (n/N)]	39.1% (330/843)	40.5% (337/833)
Angina pectoris [% (n/N)]	53.8% (515/958)	53.0% (509/961)
CCS Class I	11.4% (57/499)	8.2% (41/497)
CCS Class II	39.3% (196/499)	41.0% (204/497)
CCS Class III	35.9% (179/499)	36.8% (183/497)
CCS Class IV	13.4% (67/499)	13.9% (69/497)
Number of target lesions		
Mean number of target lesions (SD)	1.3 (0.6)	1.3 (0.6)
1 lesion [% (n/N)]	73.4% (703/958)	74.2% (713/961)
2 lesions [% (n/N)]	20.4% (195/958)	21.7% (209/961)
3 lesions [% (n/N)]	5.9% (57/958)	3.6% (35/961)
4 lesions [% (n/N)]	0.3% (3/958)	0.4% (4/961)

Table 10. Disease characteristics of subjects in the BIONICS study

	EluNIR (N = 958, 1276 lesions)	Control (N = 961, 1277 lesions)
Target blood vessel [% (No. of lesions)]		
Left anterior descending branch	40.7% (519/1276)	39.7% (507/1277)
Right coronary artery	32.0% (408/1276)	32.2% (411/1277)
Left circumflex branch	24.4% (311/1276)	25.1% (320/1277)
Left main coronary trunk	1.1% (14/1276)	0.4% (5/1277)
Lesion morphology [% (No. of lesions)]		
Calcification (moderate)	13.3% (169/1272)	13.5% (172/1274)
Calcification (severe)	13.3% (169/1272)	10.5% (134/1274)
Tortuous (moderate)	4.1% (52/1271)	4.5% (57/1272)
Tortuous (severe)	3.9% (50/1271)	2.8% (35/1272)
Eccentricity	2.0% (25/1273)	2.9% (37/1277)
Thrombus	3.4% (43/1270)	3.0% (38/1275)
ACC/AHA lesion classification [% (No. of lesions)]		
A	10.6% (135/1275)	10.1% (129/1277)
B1	31.9% (407/1275)	31.0% (396/1277)
B2	16.8% (214/1275)	17.5% (223/1277)
C	40.7% (519/1275)	41.4% (529/1277)
B2/C	57.5% (733/1275)	58.9% (752/1277)
Lesion length [mm (SD)]	17.7 (10.8)	17.9 (10.7)
Reference vessel diameter [mm (SD)]	2.73 (0.49)	2.74 (0.49)
Diameter stenosis [% (SD)]	71.5% (13.4)	70.7% (12.8)

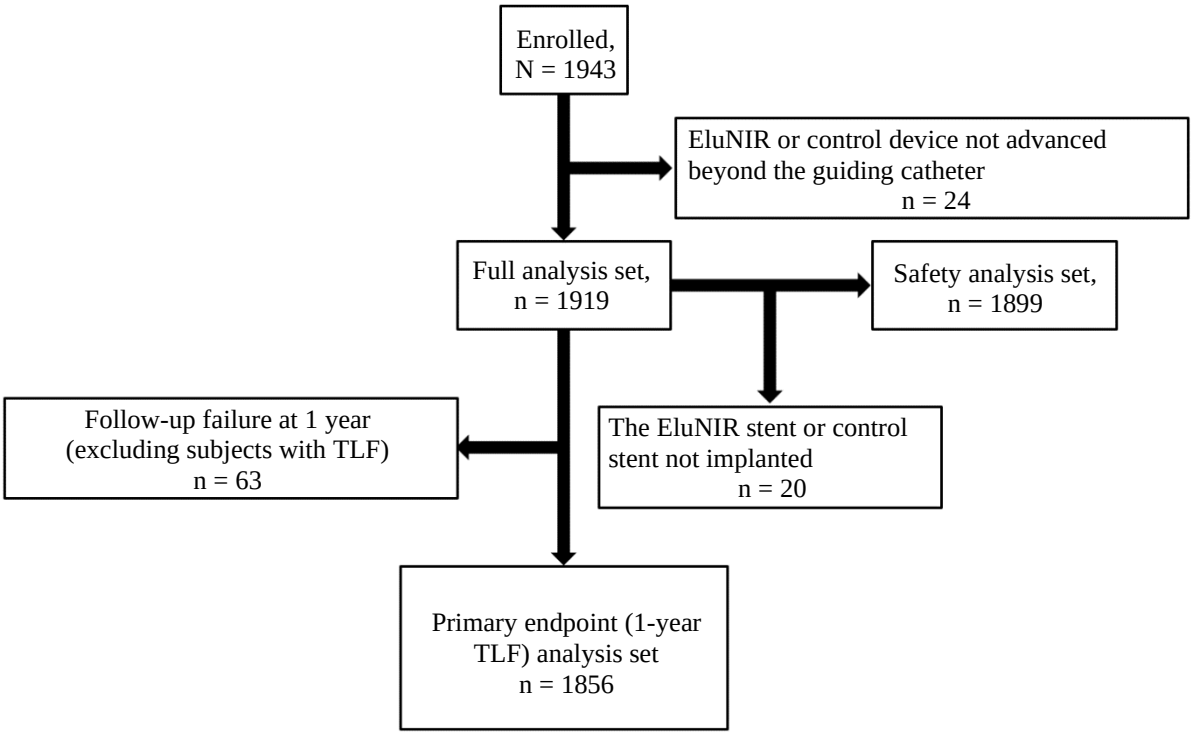


Figure 3. Subject disposition in the BIONICS study

The primary endpoint of the study was the "rate of target lesion failure (TLF) (TLF; the composite of cardiac death, target vessel myocardial infarction, or clinically driven TLR) at 1 year." The 1-year TLF rate was 5.4% (50 of 926 subjects) in the EluNIR group and 5.4% (50 of 930 subjects) in the control group. The difference in TLF rate between the EluNIR and control groups was 0.02%. The upper limit of its 95% confidence interval (CI) was 1.81%, which was less than the non-inferiority margin of 3.3%

(protocol-defined criteria for meeting the primary endpoint). EluNIR was shown to be non-inferior to Resolute (Table 11).

Table 11. Primary endpoint (1 year post-procedure) in the BIONICS study

	EluNIR* (N = 926)	Control* (N = 930)	Between-group Difference (upper limit of 1-sided 95% CI)	Non-inferiority *P*-value
	% (n)			
TLF	5.4% (50)	5.4% (50)	0.02% (1.81%)	0.0013
Cardiac death	0.5% (5)	0.2% (2)	-	-
Target vessel myocardial infarction	3.2% (30)	3.4% (32)	-	-
Clinically driven TLR	3.0% (28)	2.5% (23)	-	-

(non-inferiority margin of 3.3%)

* Only subjects with appropriate follow-up data (≥335 days post-procedure) and subjects with a TLF event up to 1 year are included in the denominator. A sensitivity analysis conducted to assess the effect of excluded data on the study outcome also showed the non-inferiority of EluNIR to Resolute in the primary endpoint (5.6% for the EluNIR group, 5.9% for the control group).

The results of the sub-studies involving some of the subjects of the BIONICS study (Tables 12 and 13) statistically showed the non-inferiority of EluNIR to Resolute in vascular lumen loss and the percentage of neointimal hyperplasia. The secondary endpoints (Table 14) and adverse events (Table 15) did not substantially differ between the EluNIR and control groups.

Table 12. Results of angiographic sub-study (13 months post-procedure) in the BIONICS study

	EluNIR (101 lesions)	Control (93 lesions)	Non-inferiority *P*-value*
Vascular lumen loss (mm)			
Mean (SD)	0.22 (0.41)	0.23 (0.39)	0.0039
Median (Q1, Q3)	0.14 (−0.02, 0.29)	0.12 (0.00, 0.31)	-
Min, Max	−0.28, 2.08	−0.33, 1.71	-

* Non-inferiority margin of 0.20 mm for the upper limit of 1-sided 95% CI of the difference between the EluNIR and control groups

Table 13. Results of intravascular ultrasound sub-study (13 months post-procedure) in the BIONICS study

	EluNIR (54 lesions)	Control (51 lesions)	Non-inferiority *P*-value*
Percentage of neointimal hyperplasia			
Mean (SD)	8.10 (5.81)	8.85 (7.77)	0.0098
Median (Q1, Q3)	6.43 (3.59, 11.47)	6.39 (3.28, 11.37)	-
Min, Max	0.39, 24.53	0.95, 33.02	-

* Non-inferiority margin of 3% for the upper limit of 1-sided 95% CI of the difference between the EluNIR and control groups

Table 14. Secondary endpoints (1 year post-procedure) in the BIONICS study

	EluNIR (N = 958)	Control (N = 961)
Acute success		
Device success*	98.0% (1243 of 1268 lesions)	99.4% (1261 of 1268 lesions)
Lesion success**	99.9% (1257 of 1258 lesions)	99.8% (1262 of 1264 lesions)
Procedure success**	97.6% (929 of 952 subjects)	97.3% (928 of 954 subjects)
Secondary endpoints at 1 year		
MACE***	6.8% (63 subjects)	6.6% (63 subjects)
TVF***	7.1% (66 subjects)	6.3% (60 subjects)
All-cause death***	1.2% (11 subjects)	1.0% (10 subjects)
Myocardial infarction***	4.6% (43 subjects)	4.8% (46 subjects)
Clinically driven TVR***	4.8% (43 subjects)	2.8% (27 subjects)
Stent thrombosis**** (definite or probable)	0.4% (4 of 921 subjects)	0.8% (7 of 927 subjects)

* Lesions with missing angiographic data are excluded, except for those with device failure

** Subjects or lesions with missing angiographic data are excluded.

*** Kaplan-Meier estimates

**** Only subjects with appropriate follow-up data (≥335 days post-procedure) and subjects with stent thrombosis up to 1 year are included in the denominator.

Table 15. Incidence of adverse events (safety analysis set, 1 year post-procedure) in the BIONICS study

	EluNIR (N = 945)	Control (N = 954)
Adverse events	65.3% (617)	63.5% (606)
Serious adverse events	26.1% (247)	25.4% (242)
Serious adverse events occurring in >1% of subjects		
Cardiac disorders		
Angina pectoris	2.5% (24)	2.6% (25)
Myocardial infarction	2.5% (24)	2.1% (20)
Angina unstable	2.8% (26)	1.8% (17)
Acute myocardial infarction	2.1% (20)	1.5% (14)
Atrial fibrillation	1.0% (9)	0.6% (6)
Chest pain	3.8% (36)	4.5% (43)

% (n)

6.A.(2) The BIONICS-PK study (Studied period, ongoing since June 2016)

The BIONICS-PK study was conducted in the US to assess the pharmacokinetics of ridaforolimus after implantation of the EluNIR stent. Table 16 shows the summary of the BIONICS-PK study.

Table 16. Summary of the BIONICS-PK study

	Outline
Population	The same as that of the BIONICS study, except for exclusion of subjects with acute coronary syndrome.
Study device	EluNIR
Number of subjects enrolled	12
Number of study sites	2 (US)
Observation period	10 and 30 minutes, and 1, 2, 4, 8, 12, 24, 48, 72, 168 (7 days), 336 (14 days), and 720 (30 days) hours post-procedure
Follow-up period	Up to 5 years post-procedure

Twelve subjects received 1 or more EluNIR stents so that the total ridaforolimus dose loaded on the stent(s) were <130 μg in 6 subjects, 130 to 300 μg in 4 subjects, and >300 μg in 2 subjects. The EluNIR stent of 3.0 mm in diameter and 17 mm in length, which is the most common stent size, is

loaded with [redacted] μg of ridaforolimus. The EluNIR stent of the maximum diameter and length has [redacted] μg of ridaforolimus.

Blood was collected immediately before implantation of the first EluNIR stent (Time 0), 10 and 30 minutes, and 1, 2, 4, 8, 12, 24, 48, 72, 168 (7 days), 336 (14 days), and 720 (30 days) hours after implantation of the first EluNIR stent.

C_{max} in whole blood increased with increasing dose of ridaforolimus and ranged from 0.438 to 1.75 ng/mL by dose-group, with individual mean C_{max} ranging from 0.308 to 1.80 ng/mL. T_{max} was similar among dose groups ranging from 1.51 to 2.00 hours, with individual T_{max} ranging from 0.500 to 4.03 hours. AUC increased with increasing dose. The $t_{1/2}$ of ridaforolimus in individual subjects ranged from 75.3 to 311 hours across all dose levels, with mean $t_{1/2}$ values of 161 hours in the low-dose group, 280 hours in the mid-dose group, and 285 hours in the high-dose group. The total body clearance (CL/F) was evaluated in each individual subject, and CL/F ranged from 0.875 to 5.16 L/h/kg across all dose levels, with mean CL/F values of 2.36 L/h/kg in the low-dose group, 1.24 L/h/kg in the mid-dose group, and 1.19 L/h/kg in the high-dose group (Table 17).

Table 17. Pharmacokinetics of ridaforolimus in whole blood in subjects implanted with the EluNIR stent

Low-dose group (<130 μg), N = 6							
	Total dose (μg)	**C_{max} (ng/mL)**	**T_{max} (h)**	**$AUC_{0\text{-}tlast}$ (h·ng/mL)**	**$AUC_{0\text{-}t\infty}$ (h·ng/mL)**	**$t_{1/2}$ (h)**	**CL/F (L/h/kg)**
Mean	114	0.438	1.92	51.0	62.6	161	2.36
SD	19.7	0.147	1.21	34.2	38.3	61.2	1.48
Mid-dose group (130-300 μg), N = 4							
	Total dose (μg)	**C_{max} (ng/mL)**	**T_{max} (h)**	**$AUC_{0\text{-}tlast}$ (h·ng/mL)**	**$AUC_{0\text{-}t\infty}$ (h·ng/mL)**	**$t_{1/2}$ (h)**	**CL/F (L/h/kg)**
Mean	154	0.565	1.51	104	124	280	1.24
SD	9.00	0.115	0.583	14.6	13.6	29.2	0.169
High-dose group (>300 μg), N = 2							
	Total dose (μg)	**C_{max} (ng/mL)**	**T_{max} (h)**	**$AUC_{0\text{-}tlast}$ (h·ng/mL)**	**$AUC_{0\text{-}t\infty}$ (h·ng/mL)**	**$t_{1/2}$ (h)**	**CL/F (L/h/kg)**
Mean	442	1.75	2.00	311	374	285	1.19
SD	-	-	-	-	-	-	-

C_{max} = Maximum blood drug concentration, T_{max} = Time to maximum blood drug concentration, $AUC_{0\text{-}tlast}$ = AUC (area under the curve) from time 0 to the last detectable concentration, $AUC_{0\text{-}t\infty}$ = AUC from time 0 to infinity, $t_{1/2}$ = Elimination half-life, CL/F = Total body clearance

As for the pharmacokinetic profile of ridaforolimus in Japanese subjects after implantation of the EluNIR stent, the pharmacokinetics study conducted for the development of ridaforolimus as a drug showed a similar pharmacokinetic profile of ridaforolimus in Caucasian and Japanese subjects.

6.A.(3) The JNIR study (Studied period, ongoing since January 2017)

The JNIR study was a multicenter, single-arm, open-label study that assessed the clinical outcome of the EluNIR stent in Japan, and 104 subjects were enrolled at 10 study sites in Japan. The study was conducted according to almost the same protocol as that of the BIONICS study in order to confirm the

appropriateness of extrapolating the results of the BIONICS study to the Japanese population. Among the subjects in the EluNIR group of the BIONICS study, those having similar patient characteristics to those of the subjects of the JNIR study were extracted using propensity score matching analysis. The extracted subjects were considered as the control group. The ratio of the JNIR group to the control group was 1:4 for data comparisons. Table 18 shows the summary of the study.

Table 18. Summary of the JNIR study

	Summary
Study objective	To assess the non-inferiority of the JNIR group to the EluNIR group of the BIONICS study.
Study design	Prospective, multicenter, single-arm, open-label study
Population	Patients eligible for PCIs, such as those with angina pectoris, asymptomatic ischaemia, non-ST-elevation myocardial infarction, and ST-elevation myocardial infarction (excluding those at <72 hours since first hospital presentation), etc.
Study device	EluNIR
Number of subjects enrolled	104
Number of study sites	10 in Japan
Primary endpoint	Rate of target lesion failure (TLF; the composite of cardiac death, target vessel myocardial infarction, and clinically driven TLR) at 1 year
Secondary endpoints	Similar to those of the BIONICS study
Safety endpoints	Adverse events (including study device-related adverse events, serious adverse events, study device/drug-related serious adverse events, and study device/drug-related known and unknown serious adverse events) are continuously monitored at each study visit and throughout the study period. The other safety parameters monitored: • Creatine kinase, creatine kinase myocardial isoenzyme, and troponin • 12-Lead electrocardiogram • Concomitant medications • Angina pectoris
Key inclusion criteria	Similar to those of the BIONICS study. A major difference is exclusion of patients with target lesion(s) in a bypass graft conduit.
Key exclusion criteria	Similar to those of the BIONICS study. A major difference is that the JNIR study excluded patients with ST-elevation myocardial infarction at <72 hours since first hospital presentation, while the BIONICS study excluded those at <24 hours since first hospital presentation.
Follow-up period	5 years post-procedure

The primary endpoint of the JNIR study is the "1-year TLF rate," which is the same as that of the BIONICS study. The 1-year TLF rate was 1.9% (2 of 104 subjects) in the JNIR group and 5.3% (21 of 395 subjects) in the control group. The difference in 1-year TLF rate between the JNIR and control groups was −3.39%. The upper limit of its 90% confidence interval was −1.31%, which was less than the pre-defined non-inferiority margin of 5.0%. The JNIR group was thus shown to be non-inferior to the EluNIR group of the BIONICS study (Table 19).

Table 19. Primary endpoint (1 year post-procedure) in the JNIR study

	JNIR (N = 104)	EluNIR group of BIONICS study* (N = 395)	Difference (upper limit of 1-sided 90% CI)	Non-inferiority *P*-value
	% (n)			
TLF	1.9% (2)	5.3% (21)	−3.39% (−1.31%)	0.0028
Cardiac death	1.0% (1)	0.5% (2)	-	-
Target vessel myocardial infarction	0.0% (0)	3.8% (15)	-	-
Clinically driven TLR	1.0% (1)	2.5% (10)	-	-

(non-inferiority margin of 5.0%)

* Only subjects with appropriate follow-up data (≥335 days post-procedure) and subjects with a TLF event up to 1 year are included in the denominator.

The secondary endpoints did not substantially differ between the JNIR and control groups (Table 20). No particularly problematic tendency was found in the occurrence of adverse events (Table 21).

Table 20. Secondary endpoints (1 year post-procedure) in the JNIR study

	JNIR (N = 104)	EluNIR group of BIONICS study (N = 410)
Acute success		
Device success	99.1% (115 of 116 lesions)	96.9% (504 of 520 lesions)
Lesion success	99.1% (115 of 116 lesions)	98.5% (512 of 520 lesions)
Procedure success	99.1% (115 of 116 lesions)	95.4% (496 of 520 lesions)
Secondary endpoints at 1 year		
MACE*	1.0% (1 subject)	6.2% (25 subjects)
TVF*	1.0% (1 subject)	6.9% (28 subjects)
All-cause death*	1.0% (1 subject)	1.2% (5 subjects)
Myocardial infarction*	0.0% (0 subjects)	4.7% (19 subjects)
Clinically driven TVR*	0.0% (0 subjects)	4.0% (16 subjects)
Stent thrombosis* (definite or probable)	0.0% (0 subjects)	0.5% (2 subjects)

* Kaplan-Meier estimates

Table 21. Incidence of adverse events (safety analysis set, 1 year post-procedure) in the JNIR study

	JNIR (N = 104)
Adverse events	56.7% (59)
Serious adverse events	20.2% (21)
Serious adverse events occurring in >1% of subjects	
Cardiac disorders	
Angina pectoris	1.9% (2)
Angina unstable	1.0% (1)
Cardiac failure	1.9% (2)
Cardiac failure chronic	1.0% (1)
Myocardial ischaemia	1.0% (1)
Chest pain	1.9% (2)
Eye disorders	1.9% (2)
Gastrointestinal disorders	6.7% (7)
Sudden death	1.0% (1)
Peripheral artery restenosis	1.0% (1)
Spinal cord injury	1.0% (1)
Colon cancer	1.0% (1)
Hepatocellular carcinoma	1.0% (1)
Renal artery stenosis	1.0% (1)
Skin ulcer	1.0% (1)
Peripheral artery stenosis	1.0% (1)
Peripheral embolism	1.0% (1)

% (n)

6.B Outline of the review conducted by PMDA

(1) Efficacy and safety of EluNIR

(2) Antiplatelet therapy after implantation of the EluNIR stent

(3) Use-results survey

6.B.(1) Efficacy and safety of EluNIR

As with the approved coronary DESs, EluNIR is clinically positioned as a device to be used for the treatment of patients eligible for PCIs. On the other hand, ridaforolimus, which is loaded on the EluNIR stent, has not been approved as a drug or for the use with coronary DESs in Japan. For this reason, EluNIR should be shown to be non-inferior to an approved coronary DES in efficacy and safety.

6.B.(1).(a) Efficacy

PMDA's view:

The BIONICS study was designed very similarly to the pivotal study of an approved DES in Japan. This randomized, active device-controlled clinical study has shown the non-inferiority of EluNIR to the approved DES in efficacy as a DES. The JNIR study statistically demonstrated the appropriateness of extrapolating the results of the BIONICS study to the Japanese population.

However, the clinical study data submitted for the present application were the results of the EluNIR stents not longer than 33 mm in length. PMDA asked the applicant to explain the efficacy and safety of the EluNIR stents of 38 and 44 mm in length, which are also included in the present application.

The applicant's explanation:
The BIONICS study included subjects who received overlapping EluNIR stents. Table 22 shows the results in these subjects. Although the number of subjects is limited, no particular problem was found in the results of lesions with lengths equivalent to the 38 or 44 mm EluNIR stent.

Table 22. Primary endpoint (1 year post-procedure, subjects with overlapping stents) in the BIONICS study

		Lesion length (mm)			
		≥30 X ≤35	**>35 X ≤40**	**>40 X ≤45**	**<45 X**
TLF	EluNIR	10.9% (6/55)	2.9% (1/34)	0.0% (0/14)	3.7% (1/27)
	Control	3.8% (2/53)	5.4% (2/37)	10.0% (3/30)	10.7% (3/28)

% (n/N)

According to the foreign safety information of EluNIR, 1 case of difficulty in removal was reported as a malfunction of the 38 mm EluNIR stent, but the patient did not suffer any health hazard. No safety problem, complaint, or malfunction has been reported with the 44 mm EluNIR stent.

PMDA's view:
Although longer stents are generally associated with a poorer outcome, the applicant's explanation is acceptable because the BIONICS study revealed no particular problem in subjects receiving overlapping stents, and because elimination of overlapping parts of stents by using a longer stent may reduce the risk of stent thrombosis or stent breakage. The clinical performance and safety in delivery of a longer EluNIR stent is acceptable because no particularly problematic delivery-related or acute adverse event has been reported from foreign data.

6.B.(1).(b) Safety

PMDA's view:
The results of the sub-studies involving some of the subjects of the BIONICS study (Tables 12 and 13) statistically showed the non-inferiority of EluNIR to Resolute in vascular lumen loss and the percentage of neointimal hyperplasia. There was no substantial difference in adverse events between the EluNIR and control groups in the BIONICS study and the JNIR study (Tables 15 and 21). The secondary endpoints (Tables 14 and 20) also showed no substantial difference. These findings show that EluNIR has a safety profile similar to that of the approved DES in Japan used as a control device.

However, the nonclinical toxicity studies showed the toxicity of ridaforolimus. PMDA asked the applicant to explain the systemic pharmacological action of ridaforolimus derived from the implanted EluNIR stent taking into consideration the results of the BIONICS-PK study.

The applicant's explanation:

As with the approved DESs, ridaforolimus derived from the implanted EluNIR stent is extremely unlikely to cause any systemic pharmacological action, for the following reasons:

- Toxicological findings from the nonclinical studies of ridaforolimus were similar to those reported with other "limus" drugs.[1,2,3]
- The highest ridaforolimus dose ([redacted] μg) loaded on the EluNIR stent is similar to the highest drug doses of the coronary DES already approved in Japan that are loaded with other "limus" drugs.
- C_{max} (1.75 ng/mL) in the highest dose group of the BIONICS-PK study was as very low as 1/100 of C_{max} (195 ng/mL) in the lowest dose group of the clinical studies conducted for the development of ridaforolimus as a drug.

PMDA's view:

For the following reasons in addition to the applicant's explanation, ridaforolimus derived from the implanted EluNIR stent is extremely unlikely to cause any systemic pharmacological action, as with the approved DESs:

(a) The nonclinical studies revealed ridaforolimus had a pharmacokinetic profile, etc. similar to that of other "limus" drugs.[5,6,7]

(b) No systemic pharmacological action has been reported with the coronary DESs already approved in Japan that are loaded with other "limus" drugs.

(c) The BIONICS-PK study revealed that the blood concentration of ridaforolimus peaked immediately after implantation of the EluNIR stent and then acutely decreased.

In addition, relevant information and precautions regarding the use in pregnant women, concomitant medications, etc. are provided in the Information on Precautions, etc. on the basis of the information obtained from the toxicological and pharmacological studies of the drug. There appears to be no particular problem in the safety of EluNIR or the risk mitigation activities for the drug.

Taken together with the comments from the Expert Discussion, PMDA concluded that the efficacy and safety of EluNIR have been demonstrated as with the approved similar devices.

6.B.(2) Antiplatelet therapy after implantation of the EluNIR stent

PMDA's view:

Patients receive DAPT for a certain period of time following implantation of a coronary stent until the stent is sufficiently covered by the neointima in order to prevent thrombosis due to a foreign body

reaction to the stent. It generally takes approximately 30 days after implantation for the neointima to cover a BMS. DESs require more time than BMSs for sufficient neointimal coverage because the drugs loaded on the stents inhibit cell growth.

The latest Japanese guideline revised in March 2020[8] recommends DAPT for 1 to 3 months (short-term DAPT) depending on the patient characteristics. Accordingly, a Ministerial Notification has been issued to ensure that the WARNING section of the instructions for use of DESs includes the following statement:

> "Antiplatelet therapy (APT) after the operation should be performed based on the latest guidelines, such as the 'JCS Guideline on Revascularization of Stable Coronary Artery Disease' and the 'JCS Guideline on Diagnosis and Treatment of Acute Coronary Syndrome' of the Japanese Circulation Society as well as other relevant information."[9]

The latest Japanese guideline was prepared based on many clinical research studies and use experience with the approved DESs in Japan.

On the other hand, no clinical study results of EluNIR with short DAPT are available because the protocol of the BIONICS study recommended "DAPT for 12 months (at least 6 months)" and the protocol of the JNIR study stated "DAPT should be at least 12 months," both according to the guidelines that were in effect at the time of the studies.

However, when used in the post-marketing setting according to the latest Japanese guideline, EluNIR is unlikely to pose a particularly higher risk of stent thrombosis than the approved similar stents, for the following reasons:

(a) The clinical study showed the non-inferiority of EluNIR to Resolute, an approved similar stent, which should be used according to the latest Japanese guideline.
(b) The animal studies revealed sufficient neointimal coverage of the EluNIR stent at 30 days after implantation without any problem.
(c) In the foreign post-marketing setting, EluNIR has been used without any particular problem according to the foreign guidelines that are similar to the latest Japanese guideline.

Taken together with the comments from the Expert Discussion, PMDA has concluded that there would be no problem in using EluNIR according to the latest Japanese guideline. PMDA instructed the applicant to include the following information in the Information on Precautions, etc.

- The fact that no clinical study data are available regarding the use of EluNIR with short-term DAPT.
- The duration of DAPT conducted in the clinical studies.

The applicant agreed.

6.B.(3) Use-results survey

The applicant's explained that no use-results survey was required for the following reasons:

- EluNIR has been commercially available and commonly used in the EU, the US, and other countries.
- The BIONICS study used the inclusion and exclusion criteria relatively similar to those used in clinical practice.
- In the BIONICS study, 1919 subjects were enrolled and the 5-year follow-up was completed. The long-term efficacy and safety of EluNIR thus have been confirmed.
- A comparison of propensity scores between the JNIR group and the matched EluNIR group of the BIONICS study showed almost no difference between the 2 groups, confirming that those groups were appropriately matched. The incidence of stent thrombosis or hemorrhagic events also did not statistically differ between the groups.
- In addition to follow-up of the JNIR study, pharmacovigilance activities will be conducted in the post-marketing setting.

PMDA's view on the necessity of the use-results survey of EluNIR:

When "Cypher Stent" (Approval number 21600BZY00136000) (hereinafter referred to as Cypher) was approved (Cypher is the first coronary DES ever approved in the world and Japan), a condition requiring a use-results survey that follows up 2000 patients for 5 years was attached, because very limited clinical study data in Japanese patients were available and therefore the effects of ethnic differences were not fully assessed, and because no sufficient safety data regarding the use of "limus" drugs in the coronary arteries were available. In the post-marketing setting, patients receiving Cypher developed late (1 month to 1 year post-procedure) and very late (>1 year post-procedure) stent thrombosis, which were not reported with BMSs. Thereafter, the MAHs of coronary DESs loaded with any drugs that had never been used on a coronary stent were required to conduct a use-results survey that follows up 2000 subjects for 5 years in order to sufficiently investigate stent thrombosis.

Since 2011, when "Nobori" (Approval number: 22300BZX00141000), a coronary DES loaded with a new drug, was approved, no application for marketing approval of a similar device has been submitted until this time for EluNIR. During this period, a large amount of clinical experience and evidence with coronary DESs have been accumulated, with almost no difference in the directions of use or clinical outcome between EU/US and Japan. In addition, the clinical studies of several coronary DESs that are currently commercially available showed similar results although they are loaded with different drugs; these DESs have a substantially lower incidence of stent thrombosis than Cypher.[10,11,12,13,14] The use-results surveys of several coronary DESs loaded with "limus" drugs other than ridaforolimus showed similar incidence of stent thrombosis at 5 years post-procedure.[10,11,12,13]

The 5-year follow-up of the BIONICS study revealed favorable long-term results in approximately 1000 subjects in the EluNIR group, although the EluNIR group of the study included many complicated lesions (i.e., American College of Cardiology [ACC]/American Heart Association [AHA]B2/C lesions were 57.5% [733 of 1275 lesions]). The incidence of stent thrombosis up to 5 years post-procedure was similar in the control group (0.9%, 9 subjects) and the EluNIR group (1.0%, 9 subjects). In the EluNIR group, stent thrombosis occurred within 30 days in 4 subjects and 1 to 5 years in 5 subjects. Very late stent thrombosis, which is of special interest with DESs, rarely occurred. Subjects with stent thrombosis in the EluNIR group included (a) those with relatively poor prognosis based on the site of thrombosis, ACC/AHA lesion classification at the implantation site of the EluNIR stent, medical history, age, etc., (b) those who did not comply with DAPT, and (c) those whose diagnosis of thrombosis was based on insufficient evidence due to lack of angiographic data. The 5-year results of the other evaluation endpoints were also similar in the EluNIR and control groups. Subjects receiving EluNIR in the JNIR study (which was conducted according almost the same protocol as that of the BIONICS study) showed similar 1-year results to those receiving EluNIR in the BIONICS study, and the incidence of stent thrombosis in the JNIR study was 0.0% (0 subjects).

In addition, the clinical studies of ridaforolimus for the treatment of sarcoma in and outside Japan showed that ridaforolimus had a safety profile similar to that of the other “limus” drugs. The animal and clinical studies of EluNIR, and the nonclinical studies of ridaforolimus have demonstrated the local and systemic safety of ridaforolimus loaded on the EluNIR stent, as with the approved similar devices loaded with other “limus” drugs.

In summary, the nonclinical and clinical study data of EluNIR have raised no particular concerns regarding the differences in clinical results between the Japanese and non-Japanese populations, or in the long-term outcome, which have been concerns with the approved coronary DESs. Therefore the use-results survey of EluNIR, if conducted, is very unlikely to detect any significant tendency. The 5-year follow-up data in the JNIR study and normal post-marketing malfunction reports will be sufficient to assure the post-marketing safety of EluNIR in Japan (therefore no use-results survey is needed).

7. Plan for Post-marketing Surveillance etc. Stipulated in Paragraph 1 of Article 2 of Ministerial Ordinance on Good Post-marketing Study Practice for Medical Devices

7.A Summary of the data submitted

The applicant did not plan to conduct any post-marketing surveillance and therefore submitted no post-marketing surveillance plan.

7.B Outline of the review conducted by PMDA

PMDA agreed with the applicant's proposal to omit post-marketing surveillance as discussed in Section 6 above.

8. Documents Relating to Information on Precautions, etc. Specified in Paragraph 1 of Article 63-2 of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices, in Relation to Notification Pursuant to the Same Paragraph of the Act

8.A Summary of the data submitted

The applicant submitted Information on Precautions, etc. (draft) as an attachment in accordance with the Notification titled "Application for Marketing Approval of Medical Devices" (PFSB Notification No. 1120-5, dated November 20, 2014).

8.B Outline of the review conducted by PMDA

On the basis of the conclusion of the Expert Discussion, as described in Section 6, PMDA concluded that there were no particular problems with the proposed Information on Precautions etc., provided that the applicant advises necessary caution.

III. Results of Compliance Assessment Concerning the New Medical Device Application Data and Conclusion Reached by PMDA

PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The medical device application data were subjected to a document-based inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

IV. Overall Evaluation

EluNIR is a coronary DES intended to be used for the treatment of patients with symptomatic ischemic heart disease. PMDA's review of the application for EluNIR focused on (1) its efficacy and safety, and (2) the necessity of use-results survey. Based on comments raised in the Expert Discussion, PMDA reached the following conclusions:

(1) Efficacy and safety of EluNIR

The BIONICS study, a foreign pivotal study, showed that EluNIR was statistically non-inferior in efficacy to a coronary DES already approved in Japan. The JNIR study statistically demonstrated that

the BIONICS study data can be extrapolated to the Japanese population. In the nonclinical and clinical studies of EluNIR, the local safety of EluNIR and the systemic safety of ridaforolimus were evaluated for comparability to those of the approved similar device. The applicant should ensure that the Information on Precautions, etc. includes information on (a) the toxicity of ridaforolimus, (b) drugs that may interact with ridaforolimus, and (c) DAPT used in the clinical studies; these actions constitute sufficient risk mitigation activities.

(2) Necessity of use-results survey

The 5-year follow-up of the foreign BIONICS study, which included many subjects with complicated lesions, revealed good long-term results in approximately 1000 subjects receiving EluNIR. The incidence of stent thrombosis with EluNIR up to 5 years post-procedure was comparable to that with the approved similar device. Only a small number of subjects developed very late stent thrombosis, which is of special interest with coronary DESs. In the JNIR study, which used almost the same protocol as that of the BIONICS study, no stent thrombosis has occurred to date. The animal and clinical studies of EluNIR and the nonclinical studies of ridaforolimus have also demonstrated the local and systemic safety of ridaforolimus loaded on the EluNIR stent, as with the approved similar devices loaded with other “limus” drugs.

On the basis of the above review, PMDA considers that (a) the long-term data of EluNIR can be confirmed based on annually reported data from the JNIR study (a clinical study included in the present application) and therefore the annual reporting of the JNIR study results should be imposed as an approval condition, and that (b) general post-marketing malfunction reporting is sufficient to ensure the post-marketing safety of EluNIR in Japan (therefore no use-results survey is needed).

As a result of the above review, PMDA concludes that EluNIR may be approved for the intended use shown below.

Intended Use

EluNIR Drug-Eluting Stent is used for the treatment of patients with symptomatic ischemic heart disease who have de-novo lesions (≤42 mm in length) in native coronary arteries with reference vessel diameters of 2.50 to 4.25 mm.

Approval Condition

The applicant is required to (a) submit the analysis results of long-term outcomes of the patients included in a clinical study submitted for the present application, to the Pharmaceuticals and Medical Devices Agency, and (b) take appropriate actions as necessary.

The product is not classified as a biological product or a specified biological product. The product is not designated as a medical device subject to a use-results survey.

PMDA has concluded that the present application should be subjected to deliberation by the Committee on Medical Devices and *In-vitro* Diagnostics.

References

[1] Rapamune/sirolimus: Instructions for Use in the US. Philadelphia, PA, Wyeth Pharmaceuticals Inc. Rev 4/2017.

[2] Afinitol/everolimus: Instructions for Use in the US. East Hanover, NJ, Novartis Pharmaceutical Corporation. Rev 10/2010.

[3] Torisel/temsirolimus: Instructions for Use in the US. Philadelphia, PA, Wyeth Pharmaceuticals Inc. Rev 5/2007.

[4] David E. Kandzari, Pieter C. Smits, Michael P. Love, et al. Randomized Comparison of Ridaforolimus- and Zotarolimus-Eluting Coronary Stents in Patients With Coronary Artery Disease. *Circulation.* 2017;136:1304-1314.

[5] Drug Interview Form of "Rapalimus Tablets 1 mg" (Approval number: 22600AMX00763000), September 2020 (Sixth Edition)

[6] Drug Interview Form of "Certican Tablets 0.25 mg" (Approval number: 21900AMX00043000)," "Certican Tablets 0.5 mg" (Approval number: 21900AMX00044000)," and "Certican Tablets 0.75 mg" (Approval number: 21900AMX00045000), July 2019 (11th Edition)

[7] Review Report of "Nobori" (Approval number: 22300BZX00141000)

[8] The Japanese Circulation Society "JCS 2020 Guideline Focused Update on Antithrombotic Therapy in Patients With Coronary Artery Disease"

[9] "Revision of Precautions in the Instructions for Use of Drug-eluting Coronary Stents and Drug-coated Balloon Dilatation Catheters for Coronary Angioplasty" (PSEHB/MDED Notification No. 1010-1 and PSEHB/PSD Notification No. 1010-1, dated October 10, 2019)

[10] Re-examination Report of "Cypher Stent" (Approval number: 21600BZY00136000)

[11] Re-examination Reports of "TAXUS Express 2 Stent" (Approval number: 21900BZX00340000)" and "TAXUS Liberté Stent System" (Approval number: 22100BZX00049000)

[12] Re-examination Reports of "Endeavor Coronary Stent System" (Approval number: 22100BZX00247000)" and "Endeavor Sprint Coronary Stent System" (Approval number: 22200BZX00074000)

[13] Re-examination Reports of "XIENCE V Drug Eluting Stent" (Approval number: 22200BZX00076000)" and "PROMUS Drug-Eluting Stent" (Approval number: 22200BZX00077000)

[14] The Japanese Circulation Society "JCS 2018 Guideline on Revascularization of Stable Coronary Artery Disease"