Study Title: Evaluation of a Sirolimus Eluting Bioadaptor as Compared to a Zotarolimus Eluting Stent in *De novo* Native Coronary Arteries

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Title	Evaluation of a Sirolimus Eluting Bioadaptor as Compared to a Zotarolimus Eluting Stent in De novo Native Coronary Arteries (referred to as "Bioadaptor RCT")
Objective	The objective of this study is to verify the safety and efficacy of the investigational device (ELX1805J) for the treatment of ischemic heart disease due to *de novo,* native coronary artery lesions
Study design	A prospective, multicenter, randomized (1:1; DynamX Bioadaptor (ELX1805J): Resolute Onyx), single-blind study, registering approximately 444 subjects at approximately 35 sites within Japan, Europe, and New Zealand to be conducted in two parallel cohorts. The combined Japan Bioadaptor RCT data and European Bioadaptor RCT data are intended to serve as the pivotal trial to support the regulatory approval in Japan with the Pharmaceuticals and Medical Devices Agency (PMDA). Up to 2 *de novo* lesions located in 2 separate native coronary arteries designated as target lesions may be treated. The target lesion(s) must measure between 2.25 mm and 4.0 mm in diameter and ≤ 34 mm in length, to be covered by a single ELX1805J Bioadaptor or a single control device. Patients should not be randomized until after satisfactory pre-dilatation of the target lesion has been performed. A non-target lesion may be treated if located in separate epicardial vessel (RCA, LCX or LAD) using an approved 'olimus drug eluting stent provided the treatment of this non-target lesion is done prior to the treatment of the target lesion(s), and the treatment of the non-target lesion is considered successful. The segment should be located such that any injury that might occur during intervention can be clearly attributable to that treated segment. **Japanese Cohort (222 subjects) & European/New Zealand Cohort (222 subjects)** The study is composed of two cohorts, i.e., the Japanese cohort and the European/New Zealand cohort. For each cohort, at least 222 subjects are randomly allocated in a 1:1 ratio to either the test or control arm. All subjects will receive follow-up clinical assessments at 1, 6 and 12 months and every year for 5 years thereafter. Additionally, imaging follow-up with IVUS and IVUS + OCT are collected in the following imaging subsets. Data from the Bioadaptor RCT European Cohort will be pooled with the data from the Bioadaptor RCT Japan Cohort to support primary and secondary endpoints. The primary endpoint analysis will be performed using the Intent-to-Treat (ITT) population on all subjects at the point of randomization.

	IVUS Imaging Subset (80 subjects in the Japanese cohort) The IVUS imaging subset of approximately 80 subjects undergo angiography and IVUS assessments at baseline and 12 month follow-up. **IVUS + OCT Imaging Subset (20 subjects in the Japanese cohort)** The IVUS + OCT imaging subset of approximately 20 subjects undergo angiography, IVUS + OCT assessments at baseline and 12 month follow-up. **Single-group study (referred to as PK substudy)** Up to 2 *de novo* lesions located in 2 separate native coronary arteries designated as target lesions may be treated. The PK study will enroll 8 Japanese subjects and is being conducted to assess the blood pharmacokinetics of Sirolimus eluted from the ELX1805J Bioadaptor implanted in patients. PK measurement will be conducted at pre-treatment, 10 minutes, 30 minutes, 1, 2, 4, 6, 12, 24, 72 hours, and 7 days. In addition, all subjects will undergo clinical follow-up assessments at 1, 6 and 12 months and every year for 5 years thereafter.
Enrollment/ Number of Sites	Approximately 444 subjects will be enrolled at up to 35 centers in Japan and Europe/New Zealand. Planned: Japanese cohort: 222 European/New Zealand cohort: 222 PK substudy: 8
Study Devices	Investigational device: ELX1805J (Japan); DynamX Sirolimus Eluting Coronary Bioadaptor System (Europe/NZ) Control device: Resolute Onyx Zotarolimus Eluting Coronary Stent System (Medtronic Japan Co., Ltd. or Medtronic per the applicable geography) PK study: Subjects are to receive the ELX1805J device
Clinical Endpoints:	**Primary Endpoint:** Target lesion failure (TLF) assessed at 12 months. TLF is a composite endpoint defined as cardiovascular death, target-vessel MI, and clinically-indicated target lesion revascularization (CI-TLR) **Secondary Endpoints:** **Efficacy endpoints** • Acute success rates: Lesion success rate, device success rate, procedure success rate

	Clinical endpoints Measured at 30 days, 6 months, 12 months, 2, 3, 4 and 5 years: • TLF • Patient Oriented Clinical Endpoint: Overall cardiovascular outcomes from the patient's perspective. This endpoint is a composite endpoint that includes all-cause mortality (cardiac and non-cardiac), stroke, MI (target vessel and non-target vessel) and revascularization (target vessel and non-target vessel) • A composite of all-cause mortality, MI (target vessel or non-target vessel) and revascularization (target vessel or non-target vessel) • Composite of cardiovascular death, target vessel myocardial infarction (TV-MI)*, or clinically-indicated target vessel revascularization (CI-TVR) • Composite of cardiovascular death, stroke, MI (target vessel or non-target vessel) and revascularization (target vessel or non-target vessel) • Composite of cardiovascular death, MI (target vessel or non-target vessel) and revascularization (target vessel or non-target vessel) • Clinically-indicated target lesion revascularization (CI-TLR)TLR • Target vessel revascularization (TVR) • Clinically-indicated TVR (CI-TVR) • Revascularization (target vessel or non-target vessel) • Q-wave MI • Non Q-wave MI • MI (target vessel or non-target vessel) • Target vessel MI • Cardiovascular death • All-cause death • Composite of cardiovascular death or target vessel MI • Composite of all-cause death or MI(target vessel or non-target vessel) • Composite of all-cause death, MI(target vessel or non-target vessel), or TVR • Composite of probable or definite stent thrombosis‡ • Probable stent thrombosis‡ • Definite stent thrombosis‡ ** Defined as myocardial infarction not clearly attributed to a non-target vessel* *‡ Defined as per the Academic Research Consortium (ARC-2) criteria*
Imaging Endpoints	**QCA endpoints:** • Acute recoil • Late lumen loss (in-stent and in-segment) at 12-month follow-up

QCA , IVUS, and OCT	• Change in vessel angulation from baseline, post-stent and 12-month follow-up • MLD post-procedure and 12 months • % DS post-procedure and 12 months **IVUS endpoints:** • Change in mean lumen area from post-procedure to 12-month follow-up • In-stent % neointimal obstruction at 12-month follow-up • In-stent late lumen loss at 12-month follow-up • Acute, persistent and late stent malapposition **OCT Endpoints:** • % Strut coverage • Neointimal thickness • Vessel Pulsatility - % change in Lumen Area and Device Area during systole and diastole by stationary OCT • Additional parameters may be assessed
Key Inclusion Criteria	Patients who meet all of the following criteria are eligible: • Patient must be ≥ 20 years of age. • Patient must have evidence of myocardial ischemia (e.g., stable or unstable angina, silent ischemia, positive functional study or electrocardiogram (ECG) changes consistent with ischemia) • Patients who are able to take dual anti-platelet therapy for 1 year following the index procedure and anticoagulants prior to/during the index procedure • The subject is an acceptable candidate for Percutaneous Transluminal Coronary Angioplasty (PTCA), stenting, and emergent Coronary Artery Bypass Graft (CABG) surgery. • The subject or subject's legally authorized representative has been informed of the nature of the study and agrees to its provisions and has provided written informed consent as approved by the Institutional Review Board or Ethics Committee of the respective clinical site. • Women of childbearing potential with a negative pregnancy test within 7 days and women who are not pregnant or nursing • Patient must agree to undergo all clinical study required follow up visits, angiograms, and imaging testing • Patient must agree not to participate in any other clinical research study for a period of one year following the index procedure

	Angiographic inclusion criteria- Target Lesion/Vessel
	
	Confirmed in QCA assessment:
	• Target lesion(s) must be de novo and located in a native coronary artery with a vessel mean diameter of ≥ 2.25 and ≤ 4.0 mm assessed
	Confirmed by visual assessment:
	• Target lesion(s) must be in a major artery or branch with a visually estimated stenosis of ≥ 50% and < 100% with a TIMI flow of >1. When two target lesions are treated, they must be located in separate major epicardial vessels
	• The visually estimated target lesion length is ≤ 34 mm and must be able to be covered by a single 14/15/18/23/28/32/38 mm ELX1805J stent and have at least 2 mm of healthy vessel on either side, OR
	• The visually estimated target lesion length is ≤ 34 mm and must be able to be covered by a single 15/18/22/30/34/38 mm ZES stent respectively and have at least 2 mm of healthy vessel on either side
	• The lesion(s) must be successfully pre-dilated prior to enrollment
	• Mandatory pre-dilatation includes the use of 2 orthogonal views to confirm lesion inclusion and exclusion criteria. Successful pre-dilatation of a minimum of 1 Target Lesion, defined as no waist in the inflated pre-dilatation balloon (using two orthogonal views) with a pre-dilatation balloon diameter size approximately 0.25 mm smaller than reference vessel diameter but not more than 0.5 mm smaller than the reference vessel diameter. A residual diameter stenosis prior to study device implantation by visual estimate is recommended to be <30%.
	• Percutaneous intervention of lesions in a non-target vessel if:
	  ○ Not part of another clinical investigation
	  ○ ≥ 30 days prior to the study index procedure
	  ○ ≥ 6 months after the study index procedure (planned)
	• Percutaneous intervention of lesions located in the target vessel if:
	  ○ Not part of a clinical investigation
	  ○ ≥ 6 months prior to the study index procedure
	  ○ ≥ 12 months after the study index procedure (planned)
	  ○ Previous intervention was distal to and >10 mm from the target lesion
	
	Additional inclusion Criteria for PK study
	Patients participating in PK study may be treated with only ELX1805J

Key Exclusion Criteria	Patients must not have any of the following: • The patient was diagnosed with an acute myocardial infarction within the past 72 hours and the CK and CKMB have not returned to normal (or cTn >15x ULN) and the patient is experiencing clinical symptoms indicative of ongoing ischemia

	• Patient has a known hypersensitivity or contraindication to aspirin, both heparin and bivalirudin, clopidogrel, prasugrel or ticagrelor, cobalt, nickel, chromium, molybdenum, PLLA polymers or contrast sensitivity that cannot be adequately pre-medicated • Patients with a history of allergic reaction or serious hypersensitivity to drugs exhibiting interactions with sirolimus, zotarolimus, everolimus, tacrolimus, temsirolimus, biolimus and other rapamycin, derivatives or analogues) or similar drugs • Elective surgery is planned within the first 6 months after the procedure that will require discontinuing either aspirin or clopidogrel or other P2Y12 inhibitors • Patient presenting with chronic (permanent) atrial or ventricular arrhythmia or current unstable ventricular arrhythmias • Patient has a known left ventricular ejection fraction (LVEF) < 30% • Patient has received a heart or other organ transplant or is on a waiting list for any organ transplant • Patient has a malignancy that is not in remission. • Patient is receiving immunosuppression therapy other than steroids and has known immunosuppressive or autoimmune disease (e.g. human immunodeficiency virus, systemic lupus erythematosus etc.) • Patient is receiving chronic anticoagulation therapy (e.g., heparin, coumadin) that cannot be stopped and restarted according to local hospital standard procedures • Patient has a platelet count < 100,000 cells/mm3 or > 700,000 cells/mm3, a WBC of < 3,000 cells/mm3, or documented or suspected to have cirrhosis of Child-Pugh ≥ Class B within 7 days before study procedure • Patient has known renal insufficiency (e.g., serum creatinine level of more than 2.5 mg/dL within 7 days before study procedure, or patient on dialysis) • Patient has a history of bleeding diathesis or coagulopathy or will refuse blood transfusions • Patient has had a cerebrovascular accident (CVA) or transient ischemic neurological attack (TIA) within the past six months • Patient has had a significant GI or urinary bleed within the past six months • Patient has severe symptomatic heart failure (i.e., NYHA class IV) • Patient has a medical condition that precludes safe 6 French sheath insertion • Patient has other medical illness or known history of substance abuse (alcohol, cocaine, heroin etc.) that may cause non-

	compliance with the clinical study plan, confound the data interpretation or is associated with a limited life expectancy (i.e., less than one year) • Patient is already participating in another clinical research study which has not reached the primary endpoint (long-term follow-up is not an exclusion) • Other patients whom primary investigator or sub-investigator determined to be ineligible for this clinical study **Angiographic exclusion criteria** • Patients with bypass graft to the target vessel or lesion is located in a bypass graft • Patients with stent implanted within 10 mm of proximal or distal end of target lesion • Patients with a target lesion involving a bifurcation of which the side branch will be jailed by the struts and: • Side branch > 2.5 mm in diameter • Side branch requires planned predilatation (including Kissing Balloon Technique), or Side branch has an ostial lesion or lesion with > 50% stenosis • Patients suspected or confirmed with the QCA analysis of having stenotic lesion of more than 50% in target vessel in addition to target lesion • Patients with target lesion in ostia located within 5 mm of origin of LAD, LCX or RCA • Patients with stenotic lesion in left main trunk • Patients with target lesion that is a chronic total occlusion (CTO) or ≤ TIMI 1 coronary flow in the target vessel • Patients with target vessel that contains thrombus as indicated in pre-procedure angiographic, IVUS or OCT images • Excessive tortuosity ≥ two 45° angles or extreme angulation (≥ 90°) proximal to or within the target lesion • Patients with target vessel that has moderate to severe calcification that prevents complete angioplasty balloon (POBA with non-compliant balloon, or scoring balloon,) inflation or requires other devices such as rotational atherectomy, rotablator. • Patients with dissection of Grade A or B that cannot be covered (including 2 mm distal to the dissection) with a single study device or with dissection of Grade C or higher • Patients with 2 or more target lesions on 1 branch or target lesions on 3 branches that need to be treated during study procedure • Target lesion involves a myocardial bridge

	Additional Exclusion Criteria for PK study
	• Patients with following criteria
	  ○ Patient with PCI within 180 days before study procedure
	  ○ Patient with plan to have staged PCI within 90 days after study procedure
	  ○ Patients who have non-target lesion

Statistical Methods	The analysis of primary endpoint and secondary endpoints are performed using the Intention-To-Treat (ITT) population. The analysis of secondary clinical endpoints are conducted with the Per-Treatment Evaluable (PTE) population in addition to the ITT population. <u>Analysis of the Primary Endpoint</u> Study success is defined as successful rejection of the null hypothesis for the primary endpoint. The primary endpoint for the study is TLF at 12 months post treatment. The primary endpoint will be evaluated using the ITT population for study success and may also be carried out on the PTE population. The null hypothesis for this study is that the ELX1805J arm will have a 12-month TLF rate that exceeds that of the control device arm by at least a pre-specified margin of 6 (delta). The alternative hypothesis is that the ELX1805J arm will have a 12-month TLF rate that is no more than that of the control device, or exceeds that of the control device but by less than 6. Rejection of the null hypothesis will signify that the ELX1805J is *non-inferior* to the control device with regard to 12-month TLF. The null hypothesis (Ho) and the alternative hypothesis (Ha) can be expressed as below: Ho: $\pi A \geq \pi C + 8.6\%$ Ha: $\pi A < \pi C + 8.6\%$ Here, πA is a true TLF Rate of investigational device, and πC is a true TLF Rate of control device. Based on non-inferiority test for an endpoint that follows binomial distribution, in addition to difference between TLF rates at 12 months for 2 groups (investigational device - control device), one-sided 95% confidence interval of the difference in TLF is

	calculated. Tests are conducted using normal approximation of binomial distribution. When the upper limit of this confidence interval is less than 8.6% (delta of non-inferiority), the null hypothesis is rejected, confirming non-inferiority of investigational device compared to control device for TLF rate at 12 months. This primary analysis will be conducted using the ITT population. Handling of missing data is described in section 3.4.1. In addition, Kaplan-Meier curve for time till first event considered to be TLF will be done. If multiple TLF occurred in same case, occurrence date of the first TLF is the occurrence date of TLF. During study procedure, up to 2 lesions in different epicardial vessels may be treated with the assigned study device. When there are multiple TLF, in a single case, it is counted per case (counted as single incidence). <u>Analysis of the Secondary Endpoints</u> Time-dependent response variables can be expressed using Kaplan-Meier curve, and differences in these variables between groups are tested using log-rank test. Data for all categorical endpoints (e.g., TLF rate at a specific time point, etc.) are shown with number of patients, percentage and Clopper-Pearson's exact 95% confidence interval. Differences between treatment groups are shown using 95% confidence interval of the difference. Comparison of imaging corelab endpoints (QCA, IVUS and OCT) in the Japanese cohort will also use the difference between treatment groups and the 95% confidence interval of the difference. Analyses of clinical secondary endpoints are conducted with the PTE population in addition to the ITT population.
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