The PIONEER III Trial

A Prospective Multicenter Global Randomized Controlled Trial Assessing the Safety and Efficacy of the BuMA Supreme™ Biodegradable Drug Coated Coronary Stent System for Coronary Revascularization in Patients with Stable Coronary Artery Disease or Non-ST Segment Elevation Acute Coronary Syndromes

Protocol # SIN-US-001

Clinical Investigation Plan

Version 8.0

26 March 2020

Sponsor: Sino Medical Sciences Technology, Inc. (SINOMED)
2nd Floor, Building B, TEDA BioPharm Res., #5
Tianjin 300457, People's Republic of China

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1.0 Document Control

1.1 Version History

Version (Date)	Description
1.0 (30 June 2016)	Initial submission to PMDA (Japan)
2.0 (15 September 2016)	Initial submission to US FDA. Active control group expanded to include additional commercially-available durable polymer everolimus-eluting stents; randomization stratification by diabetes status added; protocol MI definition revised; 6-month follow-up time point added; additional minor changes.
3.0 (07 January 2017)	Revised according to US FDA recommendations, with additional minor changes. Correction to BuMA DES stent size matrix (3.25 mm stent diameter added); inclusion criterion for lesion length modified from ≤33 mm to ≤31 mm; exclusion criterion for planned staged procedures revised from within 30 days to any planned staged procedure; primary protocol definition of PCI-related MI revised to use cTn elevation cutoff of >5 × 99th percentile URL (rather than >10); broadened allowable ECG type (from 12-lead to per standard clinical practice); index procedure description expanded (pre-dilatation recommendation, management of unplanned staged procedures); clarified statistical methodology (treatment of subject- and lesion-level events in the primary endpoint analysis, secondary hypothesis-driven endpoint analysis, sequence of hypothesis testing, pooling results across sites); minor administrative changes.
4.0 (10 April 2017)	Revised according to US FDA recommendations, with additional minor changes. Modified BuMA DES stent size matrix (4.0 mm diameter stent removed), with corresponding changes to angiographic inclusion criteria (visually estimated reference vessel diameter now ≥2.25 mm to ≤3.50) and intended use statement; corrected lesion length criterion in intended use statement (from ≤ 35 mm to ≤ 31 mm) to match trial inclusion criteria; added XIENCE PRO to listing of commercially-available durable polymer everolimus-eluting stent systems serving as the control comparator; modified dual antiplatelet therapy recommendations to include 600 mg loading dose of clopidogrel and to provide additional guidance regarding the management of patients receiving chronic aspirin or $P2Y_{12}$ inhibitor therapy prior to the procedure; modified statistical methodology (multiplicity adjustment in primary and secondary endpoint hypothesis testing, significance level for assessing site poolability); restored requirement for 12-lead ECG at screening/baseline, post-procedure/pre-discharge, and 30-day and 12-month follow-up assessment time points; revised assessment window for screening/baseline ECG (from up to 72 hours pre-procedure to up to 21 days pre-procedure, except when there is evidence of acute or recent MI or UA, in which case the ECG must be performed within 24 hours prior to the index procedure); minor administrative changes.

5.0 (27 April 2018)	Minor modifications and clarifications to study eligibility criteria, including: Added upper age limit of 99 years to general inclusion criteria; added that when treatment of 2 target lesions in a single vessel is planned, there must be adequate separation between lesions to ensure a gap of ≥10 mm between study stents; clarified that known other medical illness or known history of substance abuse that may cause non-compliance with prescribed medications excludes a potential subject from study participation; clarified that lesions accessed via arterial or saphenous vein grafts are not eligible target lesions; clarified that vascular brachytherapy is not permitted as part of the index procedure treatment plan. Minor modifications to study procedures and assessments, including: Clarified that assessments performed as part of standard medical care prior to study enrollment are valid sources of data for verifying study eligibility and (after informed consent has been obtained) collecting baseline study data; clarified that laboratory testing of CBC and serum creatinine should be performed only if part of the site standard of care; clarified that antiplatelet therapy loading dose, loading dose timing, and maintenance dosage may vary based on applicable regional guidelines; clarified that a major protocol deviation is any deviation that may affect the scientific soundness of the protocol or the rights, safety, or welfare of the patients, and that the stated examples of major protocol deviations are not exhaustive. Minor administrative updates and editorial corrections, including: Editorial correction for consistency of study title; updated anticipated study timelines; updated study contacts; updated Angiographic Core Laboratory submission information.
6.0 (19 February 2019)	Not implemented. Modified BuMA DES stent size matrix (4.0 mm diameter stent added), with corresponding changes to angiographic inclusion criteria (visually estimated reference vessel diameter now ≥2.25 mm to ≤4.00 mm) and intended use statement. Anticipated study timelines updated.
7.0 (29 May 2019)	Includes all changes from Version 6.0 (as approved by US FDA), with the following additional minor changes: • Time frame for 30-day follow up clinic visit modified from “30 days (+ 7 days) post-procedure” to “30 days (± 7 days) post-procedure” due to operational considerations • Updated anticipated study timelines • Updated Angiographic Core Laboratory contact email

8.0 (26 March 2020)	Protocol revised to permit telephone or virtual follow-up visits at 12 months if necessary to assure the safety of trial participants in the context of the Coronavirus Disease 2019 pandemic. Modified protocol sections include: • Section 5.1 (Study Design Overview) • Section 7.1 (Schedule of Procedures and Assessments) • Section 7.7 (Twelve-Month Follow-up [Clinic Visit or Optional Telephone Contact / Virtual Visit])

1.2 Protocol Approval Page

Study title: The PIONEER III Trial

A prospective, multicenter, global randomized controlled trial assessing the safety and efficacy of the BuMA Supreme™ Biodegradable Drug Coated Coronary Stent System for coronary revascularization in patients with stable coronary artery disease or non-ST segment elevation acute coronary syndromes

Protocol version: 8.0

Protocol date: 26 March 2020

[redacted]

4/1/2020.

[redacted]

1.3 Investigator Signature Page

Study title: The PIONEER III Trial

A prospective, multicenter, global randomized controlled trial assessing the safety and efficacy of the BuMA Supreme™ Biodegradable Drug Coated Coronary Stent System for coronary revascularization in patients with stable coronary artery disease or non-ST segment elevation acute coronary syndromes

Protocol version: 8.0

Protocol date: 26 March 2020

Investigator's Responsibility

As the site Principal Investigator, I understand that I must obtain written approval from my Institutional Review Board/Ethics Committee prior to participation in the trial. This approval must include my name and a copy must be provided to SINOMED (or designee), along with the approved Patient Information and Consent Form prior to the first enrollment at my study site.

As the site Principal Investigator, I must also:

1. Conduct the study in accordance with the study protocol, the signed Clinical Investigation Agreement, applicable laws, 21 CFR Part 812 and other applicable United States Food and Drug Administration (FDA) regulations, any conditions of approval imposed by the FDA or IRB/EC, local regulations where applicable, International Conference on Harmonization (ICH) Good Clinical Practice guidelines, and the Declaration of Helsinki, and ensure that all study personnel are appropriately trained prior to any study activities.
2. Ensure that the study is not commenced until all approvals have been obtained.
3. Supervise all use of the BuMA Supreme Biodegradable Drug Coated Coronary Stent System at my institution.
4. Ensure that written informed consent is obtained from each subject prior to any data collection, using the most recent Institutional Review Board/Ethics Committee approved Patient Information and Consent Form.
5. Provide all required data and reports and agree to source document verification of study data with patient's medical records by SINOMED (or designee) and any regulatory authorities.
6. Allow SINOMED personnel or its designees, as well as regulatory representatives, to inspect and copy any documents pertaining to this clinical investigation according to national data protection laws.

2.0 Study Contacts

Sponsor

Site [redacted]

[redacted]

3.0 Protocol Synopsis

<table>
<tr><td>Study Title</td><td>The PIONEER III Trial

A prospective, multicenter, global randomized controlled trial assessing the safety and efficacy of the BuMA Supreme™ Biodegradable Drug Coated Coronary Stent System for coronary revascularization in patients with stable coronary artery disease or non-ST segment elevation acute coronary syndromes</td></tr>
<tr><td>Study Device</td><td>The BuMA Supreme™ Biodegradable Drug Coated Coronary Stent System (BuMA DES), manufactured by Sino Medical Sciences Technology, Inc. (Tianjin, People's Republic of China), is a device / drug combination product consisting of a drug-coated balloon expandable stent and a rapid exchange delivery system. The cobalt chromium (CoCr) stent is coated with a very thin, non-erodable layer of poly n-butyl methacrylate (PBMA) covalently bonded to the metal surface. A topcoat is then applied that contains sirolimus, the active ingredient, embedded in a biodegradable polymer, poly lactic co-glycolic acid (PLGA).

The BuMA stent will be available in a range of lengths (10-35 mm) and diameters (2.25-4.0 mm) according to the following matrix of currently available stent lengths and diameters:

<table>
<tr><td rowspan="2">Stent Diameter (mm)</td><td colspan="6">Stent Length (mm)</td></tr>
<tr><td>10</td><td>15</td><td>20</td><td>25</td><td>30</td><td>35</td></tr>
<tr><td>2.25</td><td>√</td><td>√</td><td>√</td><td>√</td><td>√</td><td>√</td></tr>
<tr><td>2.5</td><td>√</td><td>√</td><td>√</td><td>√</td><td>√</td><td>√</td></tr>
<tr><td>2.75</td><td>√</td><td>√</td><td>√</td><td>√</td><td>√</td><td>√</td></tr>
<tr><td>3.0</td><td>√</td><td>√</td><td>√</td><td>√</td><td>√</td><td>√</td></tr>
<tr><td>3.25</td><td>√</td><td>√</td><td>√</td><td>√</td><td>√</td><td>√</td></tr>
<tr><td>3.5</td><td>√</td><td>√</td><td>√</td><td>√</td><td>√</td><td>√</td></tr>
<tr><td>4.0</td><td>√</td><td>√</td><td>√</td><td>√</td><td>√</td><td>√</td></tr>
</table>
</td></tr>
<tr><td>Comparator Device</td><td>The control comparator is commercially-available durable polymer everolimus-eluting stent systems (DP EES), consisting of the XIENCE™ family of cobalt chromium everolimus-eluting coronary stent systems (Abbott Vascular, Santa Clara, CA, USA), including the Xience V, XIENCE PRIME, XIENCE Xpedition, XIENCE Alpine, and XIENCE PRO stent systems, and the PROMUS Element™ family of everolimus-eluting platinum chromium coronary stent systems (Boston Scientific Corporation, Maple Grove, MN, USA), including the PROMUS Element Plus and Promus PREMIER stent systems.</td></tr>
<tr><td>Objective</td><td>The primary objective is to demonstrate the safety and efficacy of the BuMA DES in patients with functionally significant ischemia requiring percutaneous coronary intervention (PCI) with implantation of drug eluting stents for the treatment of stable coronary artery disease or acute coronary syndromes without ST-segment elevation (unstable angina [UA] and non-ST-segment elevation myocardial infarction [NSTEMI])</td></tr>
</table>

	by randomized comparison with commercially-available durable polymer everolimus-eluting stent systems.
Study Design	This prospective, multicenter study will enroll up to 1632 subjects at up to 130 investigational sites in North America, Japan, and Europe. Patients presenting with symptomatic ischemic heart disease (including chronic stable angina with evidence of ischemia, unstable angina, or non-ST segment elevation myocardial infarction) who require elective or urgent percutaneous coronary intervention (PCI) to treat up to 3 native coronary artery lesions in up to 2 major coronary arteries, in vessel diameters of ≥2.25 mm to ≤4.00 mm and lesion lengths ≤31 mm, and who meet all eligibility criteria will be enrolled in the study and randomized 2:1 (stratified by presentation [acute coronary syndrome vs. non-ACS], diabetes status [with vs. without medically-treated diabetes mellitus], and study site) to the following treatment groups: • **Intervention**: Coronary revascularization with the BuMA Supreme™ Biodegradable Drug Coated Coronary Stent System (BuMA DES) • **Control**: Coronary revascularization with commercially-available durable polymer everolimus-eluting stent systems (DP EES) Subjects will have clinical follow-up in-hospital and at 30 days, 6 months, 12 months, and 2, 3, 4, and 5 years. Follow-up at 30 days and 12 months* will be clinic visits, while the 6-month follow-up and annual follow-up at 2-5 years will be via telephone contact (or optional clinic visit). Subjects in whom no study stent is implanted will be followed to 12 months only. *NOTE: For the duration of the Coronavirus Disease 2019 (COVID-19) pandemic, phone follow-up or virtual visit at 12 months is permitted if necessary to assure the safety of trial participants.
Sites and Geography	Up to 130 sites in North America, Japan, and Europe. A minimum of 50% of subjects will be enrolled at North American sites, and no single center will enroll more than 10% of all subjects.
Primary Safety and Efficacy Endpoint	**Target lesion failure at 12 months** Target lesion failure (TLF) is defined as the composite of cardiac death, target vessel-related myocardial infarction (TV-MI), and clinically-driven target lesion revascularization (TLR).
Secondary Endpoints	All secondary endpoints will be compared in the BuMA DES group versus the DP EES group. All endpoints will be evaluated in-hospital and at 30 days, 6 months, 12 months, and 2, 3, 4, and 5 years unless specified otherwise. **Powered Secondary Endpoint** **Long-term Safety and Efficacy,** defined as target lesion failure (TLF) between 12 months and 5 years by landmark analysis. TLF is defined as the composite of cardiac death, target vessel-related myocardial infarction (TV-MI), and clinically-driven target lesion revascularization (TLR). **Secondary Safety Endpoints** 1. **Major adverse cardiac events (MACE)**, defined as a composite of all-cause death, myocardial infarction, and target vessel revascularization

	2. **Mortality**, classified as cardiac or non-cardiac, and reported cumulatively and individually 3. **Myocardial infarction (MI)**, defined according to the modified Third Universal Definition 4. **Stent thrombosis**, definite or probable (ARC-defined), classified as early, late, or very late 5. **Bleeding complications** (BARC definitions), evaluated as components and as a composite of BARC Type 3 and 5 bleeding **Secondary Efficacy Endpoints** 1. **Lesion success**, defined as attainment of <30% residual stenosis, as measured by quantitative coronary angiography (QCA) using any percutaneous method [evaluated post-procedure] 2. **Device success**, defined as attainment of <30% residual stenosis of the target lesion measured by QCA using the assigned device [evaluated post-procedure] 3. **Procedure success**, defined as lesion success without the occurrence of in-hospital MACE [evaluated in-hospital] 4. **Clinically-driven target lesion revascularization (TLR)** [evaluated in-hospital and at 30 days, 6 months, and 1, 2, 3, 4, and 5 years] 5. **Clinically-driven target vessel revascularization (TVR)** [evaluated in-hospital and at 30 days, 6 months, and 1, 2, 3, 4, and 5 years] 6. **Target vessel failure (TVF)**, defined as cardiac death, target vessel-related MI, or clinically-driven target vessel revascularization [evaluated in-hospital and at 30 days, 6 months, and 1, 2, 3, 4, and 5 years] 7. **Target Lesion Failure (TLF)**, defined as cardiac death, target vessel-related MI, or clinically-driven target lesion revascularization [evaluated in-hospital and at 30 days, 6 months, and 2, 3, 4, and 5 years]
Patient Population	The patient population will consist of up to 1632 male and female adults presenting with symptomatic ischemic heart disease, including chronic stable angina with evidence of ischemia or acute coronary syndromes (UA or NSTEMI), requiring elective or urgent percutaneous coronary intervention (PCI) with drug-eluting stents. Patients meeting all inclusion and no exclusion criteria will be enrolled and randomized 2:1 to coronary revascularization with the BuMA DES or DP EES.
Subject Follow-up	Subjects will have clinical follow-up prior to discharge from the index intervention and at 30 days, 6 months, 12 months*, and 2, 3, 4, and 5 years. Follow-up at 30 days and 12 months will be clinic visits, while the 6-month follow-up and annual follow-up at 2-5 years will be via telephone contact (or optional clinic visit). Subjects in whom no study stent is implanted will be followed to 12 months only. *NOTE: For the duration of the Coronavirus Disease 2019 (COVID-19) pandemic, phone follow-up or virtual visit at 12 months is permitted if necessary to assure the safety of trial participants.

Study Committees	**Clinical Events Committee** An independent Clinical Events Committee (CEC) will adjudicate all site-reported adverse events that represent a potential endpoint event in an ongoing fashion during the trial. Relationship of these events to the study device will also be adjudicated. **Data Safety Monitoring Committee** An independent Data Safety Monitoring Committee (DSMC) will be responsible for the oversight and safety monitoring of the study. The DSMC will advise the Sponsor regarding the continuing safety of the trial subjects and those yet to be recruited to the trial, as well as the continuing validity and scientific merit of the trial.
Antiplatelet Therapy	Dual antiplatelet therapy (DAPT) will be administered according to physician preference in accordance with published guidelines[1, 2] and local standards of care. Patients with stable ischemic heart disease will be required to receive DAPT for at least 6 months in the absence of contraindications; discontinuation of DAPT after 3 months is permitted (but not required) in patients with a high risk of bleeding. Patients with ACS will be required to receive DAPT for at least 12 months in the absence of contraindications; discontinuation of DAPT after 6 months is permitted (but not required) in patients with a high risk of bleeding. The following doses are recommended: • ASA 300 to 325 mg oral or 250 mg IV loading dose and ASA 75-100 mg maintenance dose indefinitely. NOTE: Aspirin loading is recommended regardless of whether or not the patient was receiving chronic aspirin therapy prior to the procedure. AND • Clopidogrel 600 mg loading dose before procedure and 75 mg daily maintenance dose OR prasugrel 60 mg loading dose and 10 mg daily OR ticagrelor 180 mg loading dose and 90 mg twice daily. NOTE: For patients receiving chronic clopidogrel therapy prior to the procedure, pre-procedure re-loading with clopidogrel (600 mg) is recommended. For patients receiving chronic prasugrel or ticagrelor therapy prior to the procedure, re-loading is at the discretion of the operator. Recommended loading dose, loading dose timing, and maintenance dosage may vary based on physician discretion and applicable regional clinical guidelines. Approved adjunctive therapies (e.g., GP IIb/IIIa inhibitors, cangrelor) may be used according to physician preference in accordance with local standards of care. Each site is encouraged to commit to a consistent antiplatelet regimen to be applied to all subjects enrolled in the trial, independent of treatment group.
Inclusion Criteria	Potential subjects must meet **ALL** of the following criteria to be eligible for inclusion in the study: ***General Inclusion Criteria*** 1. The patient is a male or non-pregnant female ≥20 years of age and not greater than 99 years of age

	2. The patient has symptomatic ischemic heart disease, including chronic stable angina (and/or objective evidence of myocardial ischemia on functional study or invasive fractional flow reserve [FFR] measurement) or acute coronary syndromes (UA or NSTEMI), that requires elective or urgent percutaneous coronary intervention (PCI). 3. The patient is an acceptable candidate for percutaneous coronary intervention (PCI) with drug-eluting stents, and for emergent coronary bypass graft (CABG) surgery 4. The patient is willing to comply with specified follow-up evaluations 5. The patient or legally authorized representative has been informed of the nature of the study, agrees to its provisions, and has been provided written informed consent approved by the appropriate Institutional Review Board (IRB) or Ethics Committee (EC) ***Angiographic Inclusion Criteria*** 1. Target vessel(s) must be major coronary artery or branch vessels with a visually estimated reference diameter of ≥2.25 mm to ≤4.00 mm. Treatment is limited to a maximum of 2 target vessels per subject, a maximum of 2 target lesions per epicardial vessel, and a maximum of 3 target lesions per subject. 2. Target lesion(s) must be *de novo* or previously unstented restenotic native coronary artery lesions (no in-stent restenotic lesions permitted) 3. Target lesion(s) must have a visually estimated diameter stenosis of ≥50% and <100% 4. Target lesion(s) must measure 31 mm or less in length by visual estimation, and must be treatable with a single study stent. 5. In subjects in whom treatment of 2 target lesions in a single epicardial vessel is planned, there must be adequate separation between lesions to ensure a gap of ≥10 mm between study stents
Exclusion Criteria	Potential subjects will be excluded if **ANY** of the following conditions apply: ***General Exclusion Criteria*** 1. Pregnant or nursing patients and those who plan pregnancy in the period up to 1 year following index procedure. Female patients of childbearing potential must have a negative pregnancy test done within 7 days prior to index procedure per site standard test. 2. Patients with a history of bleeding diathesis or coagulopathy, contraindications to anti-platelet and/or anticoagulant therapy, or who will refuse transfusion 3. Patients who are receiving or will require chronic anticoagulation therapy for any reason 4. Known hypersensitivity or contraindication to aspirin, heparin/bivalirudin, ADP receptor antagonists (clopidogrel, prasugrel, ticagrelor, ticlopidine), cobalt chromium, 316L stainless steel or platinum, sirolimus or its analogues, and/or contrast sensitivity that cannot be adequately pre-medicated

	5. ST-segment elevation myocardial infarction (STEMI) at index presentation or within 7 days prior to randomization 6. Known LVEF <30% or cardiogenic shock requiring pressors or mechanical circulatory assistance (e.g., intra-aortic balloon pump, left ventricular assist device, other temporary cardiac support blood pump) 7. Renal insufficiency, defined as estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 (by the Modification of Diet in Renal Disease equation or Cockcroft-Gault formula) or dialysis at the time of screening 8. Target vessel percutaneous coronary intervention with stent placement in the previous 3 months 9. Planned elective surgery that would require discontinuation of DAPT within 6 months of the index procedure 10. Past or pending heart or any other organ transplant, or on the waiting list for any organ transplant 11. Patients who are receiving immunosuppressant therapy, or who have known immunosuppressive or severe autoimmune disease that will require chronic immunosuppressive therapy. NOTE: Corticosteroid use is permitted. 12. Known other medical illness or known history of substance abuse that may cause non-compliance with the protocol or prescribed medications, confound data interpretation, or is associated with a life expectancy of less than 1 year 13. Current participation in another investigational drug or device study ***Angiographic Exclusion Criteria*** 1. Target lesion contains a total occlusion (TIMI 0 flow) 2. Target lesion is in an unprotected left main coronary artery location 3. Target lesion is located within an arterial or saphenous vein graft or graft anastomosis, or in a native artery location that requires traversal of an arterial or saphenous vein graft to access 4. Target lesion involves a previously stented segment (in-stent restenosis) or is ≤10 mm from a previously implanted stent 5. Target lesion involves a bifurcation in which 2-vessel stenting is planned 6. Index procedure treatment plan for the target lesion includes stent overlapping 7. Index procedure treatment plan for the target vessel includes treatment of 2 target lesions that would result in 2 study stents placed <10 mm apart 8. Index procedure treatment plan for the target vessel includes vessel preparation other than balloon pre-dilatation (e.g., cutting balloon, atherectomy, thrombectomy, excimer laser angioplasty, brachytherapy) 9. Treatment plan includes repeat intervention (staged procedure)
Blinding	This is a single-blind study. The following individuals will be blinded to the subject's treatment allocation:

	• Subject and his/her family members • Site personnel conducting follow-up evaluations will not have access to randomization eCRFs, and every effort will be made to ensure that medical records use a non-specific term to identify the treatment device (e.g., "DES") to avoid revealing treatment group assignment • Members of the Clinical Events Committee • Angiographic Core Laboratory technicians performing the analysis Un-blinding will occur only after the database has been locked for the analysis of the primary endpoint or to protect subject rights, welfare, or well-being at the request of the DSMC. A site investigator may also reveal treatment allocation to an individual subject if deemed necessary due to complication or injury.
Analysis Plan	***Primary Endpoint Analysis*** The primary analysis will be a test for non-inferiority of the BuMA DES compared with DP EES for the primary endpoint of TLF at 12 months, performed in the Per Protocol (PP) and Intention to Treat (ITT) populations using the Farrington-Manning test. The PP population is defined as subjects who meet all inclusion criteria and no exclusion criteria, have provided written informed consent, and in whom an assigned study stent has been implanted. The ITT population is defined as all subjects enrolled in the study, analyzed by assigned treatment, regardless of the treatment actually received. A total of 1551 evaluable subjects (1034 Intervention: 517 Control) will provide 80% power to demonstrate non-inferiority of the BuMA DES, assuming a 6.5% rate of TLF at 12 months in the DP EES group, no difference between treatments, a one-sided alpha of 0.025, and an absolute non-inferiority margin of 3.575%. The sample size has been increased to 1632 subjects (1088 Intervention: 544 Control) to account for an expected 5% loss to follow-up at 12 months, inclusive of dropout from the PP analysis population. If non-inferiority for the primary endpoint is met and superiority for the powered secondary endpoint is met, formal superiority testing will be performed for the primary endpoint. The primary endpoint will be evaluated in both the PP and ITT populations. For the primary analyses, only subjects who experienced a primary endpoint event or who had at least 11 months follow-up (1 year minus the allowable 30 day window) and who meet the applicable analysis population definition will be included in the analysis. As an additional analysis, to account for any missing data in the primary endpoint, a tipping point analysis will be conducted. A sensitivity analysis for the primary endpoint will also be conducted according to various alternate biomarker thresholds for PCI-related MI. In addition, to assess the appropriateness of pooling results between study regions (North America vs. Japan vs. Europe), an assessment of the effect of region on the primary endpoint will be carried out in the PP population using interaction testing from the logistic regression with a 0.15 level of significance. ***Secondary Endpoints Analysis*** **Powered Secondary Endpoint** The powered secondary endpoint of long-term safety and efficacy, defined as TLF between 12 months and 5 years by landmark Kaplan-Meier analysis, will be a test for

	superiority of the BuMA DES group to the DP EES group via the log-rank test in the ITT population. The analysis will be performed when the last enrolled subject has completed his/her 5 year clinical follow-up visit, and will be performed only if non-inferiority for the primary endpoint has been met. Assuming a TLF rate of 8% between 12 months and 5 years in the DP EES group and a hazard ratio (HR) of 0.52 in the BuMA DES group compared with the DP EES group, the study sample size of 1444 evaluable subjects at 1 year (accounting for an estimated 5% loss to follow-up at 1 year, a 6.5% rate of TLF prior to 1 year, and a continued annual loss to follow-up of 5%) will provide approximately 80% power to demonstrate superiority of the BuMA DES. **Secondary Safety Endpoints** All secondary safety endpoints will be evaluated in the ITT population using appropriate descriptive statistics. No formal hypothesis testing will be performed. Statistics for continuous variables will include mean, median, standard deviation, minimum, maximum, and sample size for each treatment group. Binary variables will be summarized using frequencies, percentages, and sample size for each treatment group. As a secondary analysis, all secondary safety endpoints will be evaluated in the PP population. **Secondary Efficacy Endpoints** All secondary efficacy endpoints will be evaluated in the ITT population using appropriate descriptive statistics. No formal hypothesis testing will be performed. Statistics for continuous variables will include mean, median, standard deviation, minimum, maximum, and sample size for each treatment group. Binary variables will be summarized using frequencies, percentages, and sample size for each treatment group. As a secondary analysis, all secondary efficacy endpoints will be evaluated in the PP population. ***Subgroup Analyses:*** Subgroup analyses will be performed for all primary and secondary endpoints in their respective primary analysis populations for the following subgroups: • Enrollment region (North America vs. Japan vs. Europe) • Presentation (stable coronary artery disease vs. acute coronary syndromes) • Single- versus multi-vessel disease (1 vs. 2 target vessels) • Diabetes status (subjects with vs. without medically-treated diabetes mellitus) • Subject gender (male vs. female)
Anticipated Timelines	First subject enrolled: October 2017 Last subject enrolled: August 2019 30 day follow-up: September 2019 6 month follow-up: February 2020 12 month follow-up: August 2020 2 year follow-up: August 2021

	3 year follow-up:	August 2022
	4 year follow-up:	August 2023
	5 year follow-up:	August 2024

4.0 Background

4.1 Clinical Background

Percutaneous coronary intervention (PCI) with drug eluting stents (DES) is a mainstay of treatment for patients with coronary artery disease (CAD), including stable angina, silent ischemia, and acute coronary syndromes (ACS).[1, 3-5] Compared with bare metal stents (BMS), DES reduce restenosis and the consequent need for repeat revascularization via the inhibition of neointimal hyperplasia.[6] However, even with the use of DES repeat intervention is required in >10% of all patients within 1 year,[7] and DES use has been associated with a small incremental risk of late (>30 days to 1 year post-implantation) and very late (>1 year post-implantation) stent thrombosis. Although rare, stent thrombosis is a devastating complication, usually associated with myocardial infarction or death.[8] Extended duration dual antiplatelet therapy (DAPT) is required after DES implantation, with an attendant risk of bleeding complications;[2] however, the risk of stent thrombosis persists following DAPT discontinuation.[9]

DES are also associated with delayed vascular healing, as evidenced by histologic data from autopsy studies of stent thrombosis that reveal persistent fibrin deposition and poor re-endothelialization.[10, 11] While the mechanisms by which DES cause a prolongation of arterial healing are incompletely understood, the permanent presence of a non-erodable polymer drug release matrix is thought to be a contributor to both late stent thrombosis and late restenosis.[12] The polymer has also been implicated in localized hypersensitivity reactions and adverse late vessel wall remodeling.[13, 14] Although second-generation DES with more biocompatible polymers and reduced strut dimensions have improved the extent of endothelialization, concerns regarding late stent thrombosis and delayed vascular healing remain,[15] and a persistent inflammatory response continues to be observed.[16, 17]

To address the issue of permanent polymer as a contributor to inflammation, stent thrombosis, and restenosis, DES using erodible polymers for drug delivery have been developed. Long-term follow-up has demonstrated that this technology is capable of reducing (but not eliminating) the occurrence of very late stent thrombosis; however, major adverse cardiac event rates are comparable to those observed with durable polymer DES.[18, 19] In addition, limitations remain in the implementation of erodible polymers in currently available DES. The polymer composition required for biodegradation conflicts with the optimal adhesive and mechanical properties of balloon-expandable coronary stent coatings, creating the potential for cracking and delamination upon stent placement and over time as the polymer degrades; these effects may impair re-endothelialization and serve as a substrate for the observed thrombosis and inflammation.[20, 21] Furthermore, optimization of the timeframes for drug elution and polymer resorption have the potential to improve early vascular healing and thereby reduce long-term adverse events.[22]

For these reasons, the development of new-generation DES that incorporate erodible polymers to prevent restenosis, while improving the speed and completeness of re-endothelialization and restoration of normal vascular function, is desirable to improve the outcomes of patients undergoing PCI for the treatment of CAD.

4.2 Investigational Device

4.2.1 **Name of the Investigational Device**

The BuMA Supreme™ Biodegradable Drug Coated Coronary Stent System, herein referred to as the "BuMA DES." The BuMA DES is manufactured by Sino Medical Sciences Technology, Inc. (Tianjin, People's Republic of China).

4.2.2 **Intended Use**

The BuMA Supreme Biodegradable Drug Coated Coronary Stent System is indicated for improving coronary luminal diameter in patients with symptomatic heart disease due to de novo native coronary artery lesions (length ≤ 31 mm) with reference vessel diameters of 2.25 mm to 4.0 mm.

4.2.3 **Regulatory Status**

The BuMA DES is for investigational use only.

4.2.4 **Device Description**

The following is a summary description of the Investigational Device. For additional information, please refer to the Instructions for Use.

4.2.4.1 Overview

The BuMA Supreme Biodegradable Drug Coated Coronary Stent System is a device / drug combination product consisting of a drug-coated balloon expandable stent and a rapid exchange delivery system. The cobalt chromium (CoCr) stent is coated with a very thin, non-erodable layer of poly n-butyl methacrylate (PBMA) that is covalently bonded to the metal surface through a proprietary electro-grafting (eG™) process. A topcoat is then applied that contains sirolimus, the active ingredient, embedded in a biodegradable polymer, poly lactic *co*-glycolic acid (PLGA). In addition to the stent, the BuMA Supreme system includes a rapid exchange balloon expandable delivery system.

The BuMA DES is designed to de-couple the therapeutic goals of restenosis prevention and optimal vascular healing by providing controlled and complete drug delivery via a biodegradable polymer matrix, leaving behind a stent with an extremely thin and uniform coating that promotes early and complete re-endothelialization.

4.2.4.2 Stent Platform

The BuMA DES stent platform is a laser-cut L605 CoCr alloy tube, subjected to acid descaling and then electro-polished to a nominal strut thickness of 80 µm. Figure 1 shows an image of an expanded BuMA DES.

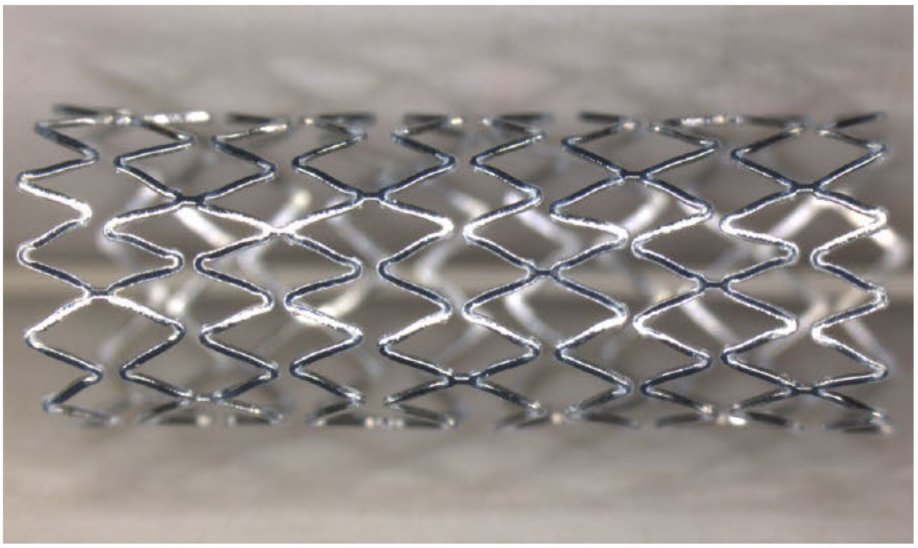

Figure 1. Expanded BuMA DES

The BuMA stent is available in a range of lengths (10-35 mm) and diameters (2.25-4.0 mm) according to the matrix provided in Table 1.

Table 1. BuMA DES stent size matrix

Stent Diameter (mm)	Stent Length (mm)					
	10	15	20	25	30	35
2.25	√	√	√	√	√	√
2.5	√	√	√	√	√	√
2.75	√	√	√	√	√	√
3.0	√	√	√	√	√	√
3.25	√	√	√	√	√	√
3.5	√	√	√	√	√	√
4.0	√	√	√	√	√	√

4.2.4.3 Stent Coating

The stent coating consists of two layers: a very thin (100-200 nm) non-erodable PBMA base layer, and a bioabsorbable PLGA topcoat containing the anti-proliferative drug sirolimus. The structure of the BuMA DES coating is depicted in Figure 2.

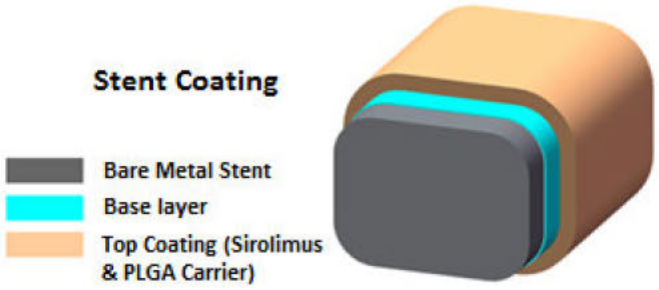

Figure 2. Coating Structure of the BuMA DES

The PBMA base layer is covalently bonded to the CoCr stent surface using SINOMED's proprietary electro-grafting (eG) technology. The very thin durable base layer is designed to secure adhesion of the topcoat, preventing cracking and delamination upon initial stent expansion and over time, in addition to suppressing corrosion and heavy metal ion release, while maintaining a thin strut profile and optimal surface properties to facilitate rapid re-endothelialization. The topcoat (3-10 µm thick) consists of a PLGA carrier matrix containing sirolimus; the polymer is completely resorbed within 2-3 months. PMBA has been widely used in FDA approved drug eluting stents, and PLGA is a well-characterized bioabsorbable biomaterial used in FDA-approved vascular implants.

4.2.4.4 Drug Component

The stent coating elutes the drug sirolimus (rapamycin), a macrocyclic lactone produced by the bacterium *Streptomyces hygroscopicus*. Sirolimus is widely used in drug eluting stents for the suppression of neointimal hyperplasia, and its safety and effectiveness in this application have been demonstrated during more than 14 years of commercial experience.

The sirolimus dose is approximately 1.2 µg/mm^2, with total dose per stent ranging from 59 µg (2.25 mm X 10 mm) to 285 µg (4.0 mm X 35 mm). The drug is fully eluted from the carrier matrix within approximately 45 days.

4.2.4.5 Delivery System

The BuMA DES is delivered using a rapid exchange balloon expandable delivery system with 145 cm working length, compatible with guide wires ≤ 0.014" and guide catheter inner diameters ≥ 5 F (0.056"). Radiopaque markers located on the catheter shaft indicate the working length of the balloon. A schematic of the delivery system is provided in Figure 3.

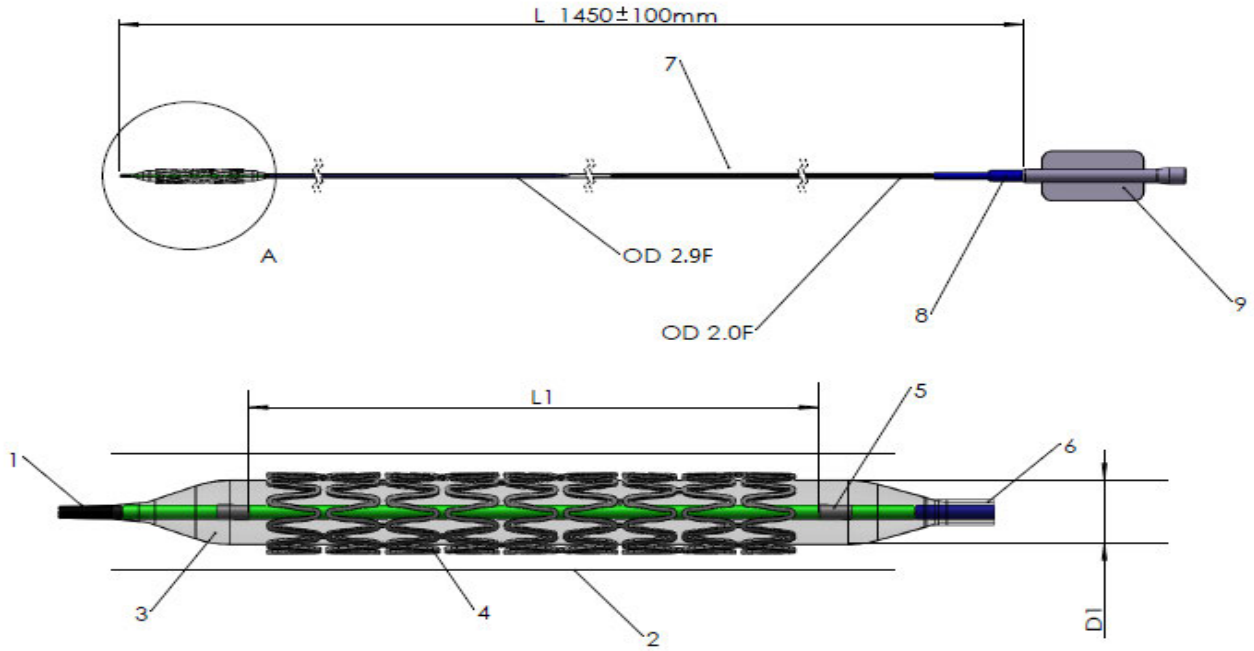

Figure 3. BuMA DES delivery system. 1. Balloon Tip; 2. Protective sleeve; 3. Balloon; 4. BuMA Supreme stent; 5. Radiopaque marker bands; 6. Catheter tubing; 7. Hypotube shaft; 8. Anti-kink protective tubing; 9. Luer lock.

4.2.5 **Previous and Ongoing Clinical Studies**

The first generation BuMA stent, utilizing the same coating and drug but a different stent platform (S-link 316L stainless steel) and delivery system, is market approved in China, and has been implanted in more than 200,000 patients worldwide. Data from the BuMA-OCT randomized trial (N=80) demonstrated superior strut coverage at 3 months compared with the EXCEL biodegradable polymer SES (JW Medical Systems, Weihai, China).[23] In addition, the PANDA III all-comers randomized trial (N=2348) demonstrated non-inferiority to Excel SES for target lesion failure at 1 year (6.4% vs. 6.4%); the secondary endpoint of ARC definite/probable stent thrombosis at 1 year occurred less often in the BuMA group (0.5% vs. 1.3%, p=0.048).[22]

The current generation BuMA DES, with a thinner-strut CoCr stent platform and improved delivery system, is being evaluated in the first-in-human PIONEER trial in Europe and the PIONEER II trial in China. The PIONEER trial (NCT02236975) is an ongoing multicenter randomized trial (N=168) at 14 European centers, comparing the BuMA DES with the Resolute Integrity DES (Medtronic, Minneapolis, MN, US) for the primary endpoint of late lumen loss at 9 months by quantitative coronary angiography. Enrollment in this trial is complete and clinical follow-up continues to 3 years. The PIONEER II trial (N=1319) is a prospective, multicenter, randomized trial comparing the BuMA DES with the first generation BuMA stent, currently enrolling in China.

For additional information, please refer to the Investigator's Brochure / Report of Prior Investigations.

4.3 Control Device

The control comparator is durable polymer everolimus-eluting stent systems (DP EES), consisting of the Xience™ family of durable polymer cobalt chromium everolimus-eluting coronary stent systems (Abbott Vascular, Santa Clara, CA, USA), including the Xience V, XIENCE PRIME, XIENCE Xpedition, XIENCE Alpine, and XIENCE PRO stent systems, and the PROMUS Element™ family of everolimus-eluting platinum chromium coronary stent systems (Boston Scientific Corporation, Maple Grove, MN, USA), including the PROMUS Element Plus and Promus PREMIER stent systems. These commercially-available DES have well-documented safety and effectiveness.[24-27]

Currently available stent sizes and product names may vary by region, but may include the following (Table 2). For additional information, please refer to the Instructions for Use for the relevant region.

Table 2. Currently available DP EES stent sizes

Product	Stent Diameter (mm)	Stent Length (mm)
XIENCE V (rapid-exchange)	2.25, 2.5, 2.75, 3.0, 3.5, 4.0	8, 12, 15, 18, 23, 28
XIENCE V (over-the-wire)	2.5, 2.75, 3.0, 3.5, 4.0	8, 12, 15, 18, 23, 28
XIENCE PRIME	2.25, 2.5, 2.75, 3.0, 3.5, 4.0	8, 12, 15, 18, 23
XIENCE PRIME LL	2.25, 2.5, 2.75, 3.0, 3.5, 4.0	28, 33, 38
XIENCE Xpedition	2.5, 2.75, 3.0, 3.25, 3.5, 4.0	8, 12, 15, 18, 23, 28
XIENCE Xpedition SV	2.25	8, 12, 15, 18, 23, 28
XIENCE Xpedition LL	2.5, 2.75, 3.0, 3.25, 3.5, 4.0	33, 38
XIENCE Alpine	2.25, 2.5, 2.75, 3.0, 3.25, 3.5, 4.0	8, 12, 15, 18, 23, 28, 33, 38
XIENCE PRO	2.25, 2.5, 2.75, 3.0, 3.5, 4.0	8, 12, 15, 18, 23, 28
XIENCE PRO LL	2.5, 2.75, 3.0, 3.5, 4.0	33, 38

XIENCE PRO^X	2.0, 2.25, 2.5, 2.75, 3.0, 3.25, 3.5, 4.0	8, 12, 15, 18, 23, 28, 33, 38
PROMUS Element Plus	2.25, 2.5, 2.75, 3.0, 3.5, 4.0	8, 12, 16, 20, 24, 28, 32, 38
Promus PREMIER	2.25, 2.5, 2.75, 3.0, 3.5, 4.0	8, 12, 16, 20, 24, 28, 32, 38

4.4 Rationale

The BuMA DES is designed to provide the benefits of conventional DES for the prevention of restenosis while facilitating early and complete vascular healing to prevent long-term adverse events. This study will evaluate the safety and effectiveness of the BuMA DES at 1 year by randomized comparison with state-of-the-art commercially available durable polymer DES, and will also evaluate the potential benefits of BuMA DES for the reduction of late adverse events.

5.0 Study Design

5.1 Study Design Overview

This prospective, multicenter study will enroll up to 1632 subjects at up to 130 investigational sites in North America, Japan, and Europe. A minimum of 50% of subjects will be enrolled at North American sites, and no single center will be permitted to enroll more than 10% of all subjects.

Patients presenting with symptomatic ischemic heart disease (including chronic stable angina with evidence of ischemia, unstable angina, or non-ST segment elevation myocardial infarction) who require elective or urgent percutaneous coronary intervention (PCI) to treat up to 3 native coronary artery lesions in up to 2 major coronary arteries, in vessel diameters of ≥2.25 mm to ≤4.00 mm and lesion lengths ≤31 mm, and who meet all eligibility criteria will be enrolled in the study and randomized 2:1 (stratified by presentation [acute coronary syndrome vs. non-ACS], diabetes status [with vs. without medically-treated diabetes mellitus], and study site) to the following treatment groups:

- **Intervention**: Coronary revascularization with the BuMA Supreme Biodegradable Drug Coated Coronary Stent System (BuMA DES)
- **Control**: Coronary revascularization with the commercially-available durable polymer everolimus-eluting stent systems (DP EES)

Subjects will have clinical follow-up in-hospital and at 30 days, 6 months, 12 months*, and 2, 3, 4, and 5 years. Follow-up at 30 days and 12 months will be clinic visits, while 6-month follow-up and annual follow-up at 2-5 years will be via telephone contact (or optional clinic visit). Subjects in whom no study stent is implanted will be followed to 12 months only. *NOTE: For the duration of the Coronavirus Disease 2019 (COVID-19) pandemic, phone follow-up or virtual visit at 12 months is permitted if necessary to assure the safety of trial participants.

The primary analysis will be a non-inferiority test comparing BuMA DES to DP EES for the primary safety and efficacy endpoint of target lesion failure at 12 months in the Intention to Treat and Per Protocol patient populations. As a secondary hypothesis-driven analysis, a superiority test comparing BuMA DES to DP EES will be performed for the powered secondary endpoint of long-term safety and efficacy, defined as target lesion failure between 12 months and 5 years by landmark analysis. The study will also report additional secondary safety and efficacy endpoints.

Clinical endpoint data will be adjudicated by an independent Clinical Event Committee, and an independent Data Safety Monitoring Committee will monitor the safety of subjects throughout the trial. Index procedure and event-driven angiographic data will be analyzed by an independent Angiographic Core Laboratory.

5.2 Study Objective

The primary objective of the trial is to evaluate the safety and efficacy of the BuMA DES in patients with functionally significant ischemia requiring percutaneous coronary intervention (PCI) with implantation of drug eluting stents for the treatment of stable coronary artery disease or acute coronary syndromes without ST-segment elevation (unstable angina [UA] and non-ST-segment elevation myocardial infarction [NSTEMI]) by randomized comparison with commercially-available durable polymer everolimus-eluting stent systems.

5.3 Endpoints

5.3.1 **Primary Endpoint**

The primary safety and efficacy endpoint of the study is target lesion failure at 12 months. Target lesion failure (TLF) is defined as the composite of cardiac death, target vessel-related myocardial infarction (TV-MI), and clinically-driven target lesion revascularization (TLR).

5.3.2 **Secondary Powered Endpoint**

The powered secondary hypothesis-driven endpoint is long-term safety and efficacy, defined as target lesion failure (TLF) between 12 months and 5 years by landmark analysis. TLF is defined as the composite of cardiac death, target vessel-related myocardial infarction (TV-MI), and clinically-driven target lesion revascularization (TLR).

5.3.3 **Additional Secondary Endpoints**

All endpoints will be evaluated in-hospital and at 30 days, 6 months, 12 months, and 2, 3, 4, and 5 years unless specified otherwise.

5.3.3.1 Secondary Safety Endpoints

5.3.3.1.1 **Major adverse cardiac events (MACE)**, defined as a composite of all-cause death, myocardial infarction, and target vessel revascularization

5.3.3.1.2 **Mortality**, classified as cardiac or non-cardiac, and reported cumulatively and individually

5.3.3.1.3 **Myocardial infarction (MI)**, defined according to the modified Third Universal Definition

5.3.3.1.4 **Stent thrombosis**, definite or probable (ARC-defined), classified as early, late, or very late

5.3.3.1.5 **Bleeding complications** (BARC definitions), evaluated as components and as a composite of BARC Type 3 and 5 bleeding

5.3.3.2 Secondary Efficacy Endpoints

5.3.3.2.1 **Lesion success**, defined as attainment of <30% residual stenosis, as measured by quantitative coronary angiography (QCA) using any percutaneous method [evaluated post-procedure]

5.3.3.2.2 **Device success**, defined as attainment of <30% residual stenosis of the target lesion measured by QCA using the assigned device [evaluated post-procedure]

5.3.3.2.3 **Procedure success**, defined as lesion success without the occurrence of in-hospital MACE [evaluated in-hospital]

5.3.3.2.4 **Clinically-driven target lesion revascularization (TLR)** [evaluated in-hospital and at 30 days, 6 months, and 1, 2, 3, 4, and 5 years]

5.3.3.2.5 **Clinically-driven target vessel revascularization (TVR)** [evaluated in-hospital and at 30 days, 6 months, and 1, 2, 3, 4, and 5 years]

5.3.3.2.6 **Target vessel failure (TVF)**, defined as cardiac death, target vessel-related MI, or clinically-driven target vessel revascularization [evaluated in-hospital and at 30 days, 6 months, and 1, 2, 3, 4, and 5 years]

5.3.3.2.7 **Target Lesion Failure (TLF)**, defined as cardiac death, target vessel-related MI, or clinically-driven target lesion revascularization [evaluated in-hospital and at 30 days, 6 months, and 2, 3, 4, and 5 years]

6.0 Subject Selection and Withdrawal

6.1 Patient Population

The patient population from which subjects for this trial will be recruited consists of male and female adults in the general interventional cardiology population. The trial will enroll up to 1632 subjects presenting with symptomatic ischemic heart disease, including chronic stable angina with evidence of ischemia or acute coronary syndromes (UA or NSTEMI), requiring elective or urgent percutaneous coronary intervention (PCI) with drug-eluting stents.

6.2 Eligibility Criteria

6.2.1 **Inclusion Criteria**

Potential subjects must meet ALL of the following criteria to be eligible for enrollment into the study:

6.2.1.1 General Inclusion Criteria

6.2.1.1.1 The patient is a male or non-pregnant female ≥20 years of age and not greater than 99 years of age

6.2.1.1.2 The patient has symptomatic ischemic heart disease, including chronic stable angina (and/or objective evidence of myocardial ischemia on functional study or invasive fractional flow reserve [FFR] measurement) or acute coronary syndromes (UA or NSTEMI), that requires elective or urgent percutaneous coronary intervention (PCI).

6.2.1.1.3 The patient is an acceptable candidate for percutaneous coronary intervention (PCI) with drug-eluting stents, and for emergent coronary bypass graft (CABG) surgery

6.2.1.1.4 The patient is willing to comply with specified follow-up evaluations

6.2.1.1.5 The patient or legally authorized representative has been informed of the nature of the study, agrees to its provisions, and has been provided written informed consent approved by the appropriate Institutional Review Board (IRB) or Ethics Committee (EC)

6.2.1.2 Angiographic Inclusion Criteria

6.2.1.2.1 Target vessel(s) must be major coronary artery or branch vessels with a visually estimated reference diameter of ≥2.25 mm to ≤4.00 mm. Treatment is limited to a maximum of 2 target vessels per subject, a maximum of 2 target lesions per epicardial vessel, and a maximum of 3 target lesions per subject.

6.2.1.2.2 Target lesion(s) must be *de novo* or previously unstented restenotic native coronary artery lesions (no in-stent restenotic lesions permitted)

6.2.1.2.3 Target lesion(s) must have a visually estimated diameter stenosis of ≥50% and <100%

6.2.1.2.4 Target lesion(s) must measure 31 mm or less in length by visual estimation, and must be treatable with a single study stent.

6.2.1.2.5 In subjects in whom treatment of 2 target lesions in a single epicardial vessel is planned, there must be adequate separation between lesions to ensure a gap of ≥10 mm between study stents

6.2.2 **Exclusion Criteria**

Potential subjects will be excluded if ANY of the following criteria apply:

6.2.2.1 General Exclusion Criteria

6.2.2.1.1 Pregnant or nursing patients and those who plan pregnancy in the period up to 1 year following index procedure. Female patients of childbearing potential must have a negative pregnancy test done within 7 days prior to index procedure per site standard test.

6.2.2.1.2 Patients with a history of bleeding diathesis or coagulopathy, contraindications to anti-platelet and/or anticoagulant therapy, or who will refuse transfusion

6.2.2.1.3 Patients who are receiving or will require chronic oral anticoagulation therapy for any reason

6.2.2.1.4 Known hypersensitivity or contraindication to aspirin, heparin/bivalirudin, ADP receptor antagonists (clopidogrel, prasugrel, ticagrelor, ticlopidine), cobalt chromium, 316L stainless steel or platinum, sirolimus or its analogues, and/or contrast sensitivity that cannot be adequately pre-medicated

6.2.2.1.5 ST-segment elevation myocardial infarction (STEMI) at index presentation or within 7 days prior to randomization

6.2.2.1.6 Known LVEF <30% or cardiogenic shock requiring pressors or mechanical circulatory assistance (e.g., intra-aortic balloon pump, left ventricular assist device, other temporary cardiac support blood pump)

6.2.2.1.7 Renal insufficiency, defined as estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 (by the Modification of Diet in Renal Disease equation or Cockcroft-Gault formula) or dialysis at the time of screening

6.2.2.1.8 Target vessel percutaneous coronary intervention with stent placement in the previous 3 months

6.2.2.1.9 Planned elective surgery that would require discontinuation of DAPT within 6 months of the index procedure

6.2.2.1.10 Past or pending heart or any other organ transplant, or on the waiting list for any organ transplant

6.2.2.1.11 Patients who are receiving immunosuppressant therapy, or who have known immunosuppressive or severe autoimmune disease that will require chronic immunosuppressive therapy. NOTE: Corticosteroid use is permitted.

6.2.2.1.12 Known other medical illness or known history of substance abuse that may cause non-compliance with the protocol or prescribed medications, confound data interpretation, or is associated with a life expectancy of less than 1 year

6.2.2.1.13 Current participation in another investigational drug or device study

6.2.2.2 Angiographic Exclusion Criteria

6.2.2.2.1 Target lesion contains a total occlusion (TIMI 0 flow)

6.2.2.2.2 Target lesion is in an unprotected left main coronary artery location

6.2.2.2.3 Target lesion is located within an arterial or saphenous vein graft or graft anastomosis, or in a native artery location that requires traversal of an arterial or saphenous vein graft to access

6.2.2.2.4 Target lesion involves a previously stented segment (in-stent restenosis) or is ≤10 mm from a previously implanted stent

6.2.2.2.5 Target lesion involves a bifurcation in which 2-vessel stenting is planned

6.2.2.2.6 Index procedure treatment plan for the target lesion includes stent overlapping

6.2.2.2.7 Index procedure treatment plan for the target vessel includes treatment of 2 target lesions that would result in 2 study stents placed <10 mm apart

6.2.2.2.8 Index procedure treatment plan for the target vessel includes vessel preparation other than balloon pre-dilatation (e.g., cutting balloon, atherectomy, thrombectomy, excimer laser angioplasty, brachytherapy)

6.2.2.2.9 Treatment plan includes repeat intervention (staged procedure)

6.3 Subject Screening

Patients requiring elective or urgent PCI will be pre-screened by a member of the research team who has received training on this Clinical Investigation Plan, including a review of the patient's medical history and any testing that has been performed as a part of the patient's routine medical care, to determine whether the patient meets general eligibility criteria (inclusion and exclusion) for participation in the trial.

Potentially eligible subjects will undergo the process of informed consent (§6.4) prior to the performance of any study-specific assessments. After informed consent has been obtained, screening / baseline tests and examinations will be performed to verify eligibility and to collect baseline study data. Assessments performed as part of standard medical care prior to study enrollment are valid sources of data for verifying study eligibility and collecting baseline study data, provided that the previously performed assessments comply with applicable protocol requirements. Potentially eligible subjects will be randomized to a treatment group and enrolled in the study only after it has been confirmed (at the time of the index procedure cardiac catheterization) that the patient meets all angiographic inclusion criteria and no angiographic exclusion criteria, and after treatment of any non-target lesion has been completed successfully without complication.

A screening log will be maintained to document the enrollment and subject number, or reason for non-enrollment of subjects screened but not enrolled in the study. Subjects who receive any study stent during the index procedure (BuMA DES or DP EES) must complete all assigned follow-up assessments (to 5 years); subjects who do not receive any study stent during the index procedure will be followed to 12 months only for safety.

6.4 Informed Consent

Relevant study information will be summarized on a Patient Information and Consent Form ("Informed Consent Form [ICF]") that has been approved by applicable regulatory authorities. This document, or a modification based on local IRB/EC recommendations, must be approved by the applicable IRB/EC and signed by each subject or his/her legal representative prior to the performance of any study-specific procedures or assessments.

Prior to obtaining informed consent, the investigator (or designee) should provide the relevant study information to the patient in both oral and written form, in a language and at a level of complexity understandable to the patient. Patients should not be coerced, persuaded, or unduly influenced to participate or remain in the trial. The patient or his/her legal representative must be given ample time and

opportunity to inquire about details of the trial, and all questions about the trial should be answered to the satisfaction of the patient or the representative.

The written informed consent form should be signed and personally dated by the subject or his/her legal representative, and by the person who conducted the informed consent discussion (investigator or designee), prior to the subject's participation in the trial. If the subject or his/her legal representative is unable to read the consent form, a witness should be present during the entire informed consent discussion. After the informed consent form is read to the subject and signed by the subject or his/her legal representative, the witness should also sign the consent form, attesting that informed consent was freely given by the subject or his/her legal representative. For non-English speaking subjects, the written informed consent should be translated into the subject's native language, or a short form (including the elements of informed consent translated into the subject's native language) should be used. The informed consent process should be documented in each subject's medical record.

The subject or his/her legal representative must be provided with a copy of the signed and dated informed consent form.

The Investigator shall inform the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required, that may be relevant to the subject and his/her willingness to continue participation in the study. The consent form should be updated or amended whenever such new information becomes available and updated consent shall be recorded.

6.5 Subject Enrollment

Potentially eligible subjects who meet all general inclusion criteria and no general exclusion criteria and who have consented to participate in the trial will undergo screening/baseline assessments. At the index procedure cardiac catheterization, the target lesions(s), target vessel(s), and index procedure treatment plan will be evaluated to confirm that all angiographic inclusion criteria (§6.2.1.2) and no angiographic exclusion criteria (§6.2.2.2) are met.

If the subject meets all inclusion and no exclusion criteria, and treatment of any non-target lesion has been completed successfully without complication, the subject will be randomized to a treatment arm (BuMA DES or DP EES in a 2:1 ratio) and enrolled in the trial. Randomization will be stratified by the presence of acute coronary syndrome (i.e., patients with stable angina or silent ischemia versus patients with unstable angina or non-ST segment elevation myocardial infarction), by diabetes status (i.e., subjects with vs. without medically-treated diabetes mellitus), as well as by study center. All target lesion(s) should be treated with the assigned stent type.

The point of enrollment is the moment of randomization. All enrolled subjects will be assigned a study-specific patient identification number via the database system.

No single site will be permitted to enroll more than 10% of the total number of subjects in the trial (i.e., no single site may enroll more than 163 subjects).

6.6 Withdrawal and Replacement of Subjects

Subjects can withdraw from the study at any time; the reason(s) for withdrawal (if given) will be documented. All data available at the time of withdrawal (if any) will be used for analysis, unless the subject has explicitly forbid the use of such data and has documented this preference in accordance with local regulatory requirements. With the exception of ascertainment of survival status (in accordance with applicable legal and ethical considerations), there will be no further follow-up (per this study protocol) on a subject who has withdrawn. Subjects who withdraw from the study will not be replaced. The withdrawal of a subject can be initiated by the Investigator if he/she determines it is in the best interest of the patient.

6.7 Protocol Deviations

All deviations from the requirements of this Clinical Investigation Plan will be considered protocol deviations. In the event of a protocol deviation, a Protocol Deviation form should be completed in the eCRF and submitted to the Sponsor and to the relevant regulatory body (if required by local regulations). Protocol deviations that will be collected include, but are not limited to:

- Failure to obtain informed consent, or failure to obtain informed consent prior to the performance of study-specific procedures or assessments
- Enrollment of a subject who did not meet all study inclusion criteria, or who met one or more study exclusion criteria
- Failure to complete protocol-specified assessments

A major protocol deviation is a protocol deviation that may affect the scientific soundness of the protocol or the rights, safety, or welfare of the patients. Major protocol deviations include, but are not limited to: failure to obtain informed consent, enrollment of a subject not meeting study eligibility criteria, and implantation of a study stent in a patient who has not reached the point of enrollment. Major protocol deviations require immediate reporting to the Study Monitor and the Institutional Review Board/Ethics Committee.

Site-level deviations are those that occur at the study center but are not directly related to a specific patient. The Sponsor reserves the right to terminate the study participation of a site with excessive protocol deviations, or to suspend the site's participation until an adequate system to reduce further deviations has been implemented.

7.0 Study Procedures and Assessments

7.1 Schedule of Procedures and Assessments

Table 3. Study Schedule of Procedures and Assessments

	Screening / Baseline	Index Procedure (day 0)	Post-procedure / Pre-discharge	30 days (30 ± 7 days)	6 months (± 30 days)	12 months (± 30 days)	2, 3, 4, 5 years (± 60 days)
	Clinic Visit	Clinic Visit	Clinic Visit	Clinic Visit	Telephone Contact / Clinic Visit	Clinic Visit / Telephone Contact[9]	Telephone Contact[8,10] / Clinic Visit
General eligibility criteria	●						
Informed consent	●						
Pregnancy test (if applicable)	●[1]						
Medical history	●						
Physical examination	●						
Anginal status	●		●	●	●	●	●
Concomitant medications	●	●	●	●	●	●	●
12-lead ECG[2]	●		●	●		●[9]	
Laboratory testing[3]	●		●	●		●[9]	
Cardiac biomarkers	●[4]		●[5]				
Coronary angiography[6]		●					
Angiographic eligibility criteria		●					
Stent implantation		●					
Adverse events[7]		●	●	●	●	●	●

[1] Female subjects of childbearing potential must have a pregnancy test (performed per site standard practice) within 7 days prior to the index procedure to confirm study eligibility.
[2] The screening/baseline ECG may be performed up to 21 days prior to procedure, except when there is evidence of acute or recent MI or UA, in which case the ECG must be performed within 24 hours prior to the index procedure. An ECG must also be performed within 24 hours post procedure or prior to hospital discharge (whichever occurs first) and at the 30-day and 12-month follow-up visits.
[3] Laboratory testing should be performed per site standard practice; if laboratory testing is part of the standard of care and includes CBC and serum creatinine, these should be recorded.
[4] The pre-procedure blood draw for cardiac biomarkers testing (preferably troponin [cTn] I or T; if not available, then CKMB is acceptable) may be performed within 48 hours prior to the index procedure, except when there is evidence of acute or recent (<7 days) MI or UA, in which case the draw must be performed within 24 hours prior to the index procedure. If the subject does not have a known diagnosis of acute MI or UA within 96 hours prior to the index procedure, assessment of cardiac biomarkers may be obtained after the start of the index procedure but prior to device implantation.
[5] Cardiac biomarkers (preferably cTn I or T; if not available, then CKMB is acceptable) should be measured 2 to 6 (up to 12) hours postprocedure. If cardiac biomarkers are elevated and there is a clinical suspicion of myocardial

ischemia (for example, due to new ischemic ECG changes [such as ischemic ST changes or new pathological Q waves] or new LBBB, angiographic evidence of a flow-limiting complication, or imaging evidence of new loss of viable myocardium or new regional wall motion abnormality), serial measurements should be taken every 6 to 12 hours until a decline is noted.
[6] Angiographic eligibility criteria must be confirmed at the time of the index procedure. All angiographic films for the index procedure and any repeat intervention or repeat diagnostic cardiac catheterization must be forwarded to the Angiographic Core Laboratory (§17.3).
[7] Procedural angiographic images, ECG data, and the results of laboratory testing should be submitted for all repeat revascularizations. For all adverse events that represent a potential endpoint event, all relevant medical information (including clinically relevant imaging data, ECG data, and the results of relevant laboratory testing performed as part of the standard of care) should be collected and retained as part of the research file to support adverse event analysis and adjudication.
[8] Subjects who do not receive a study stent during the index procedure will be followed to 12 months only.
[9] For the duration of the Coronavirus Disease 2019 (COVID-19) pandemic, phone follow-up or virtual visit at 12 months is permitted if necessary to assure the safety of trial participants. The reason for the conduct of the phone follow-up should be documented in the eCRF. Phone follow-ups conducted for other reasons (e.g., to collect all available data in a subject otherwise lost to follow-up) should continue to be recorded as protocol deviations, and details of the protocol deviation must be captured in the appropriate eCRF. Please refer to Section 7.7 for additional considerations related to alternate assessment methods.
[10] For subjects who underwent a phone follow-up at the 12-month time point for any reason, it is preferable that the 2-year follow-up be conducted as an in-clinic visit.

7.2 Screening / Baseline

The following tests and examinations must be performed prior to the procedure to verify eligibility and to collect baseline study data. Note that assessments performed as part of standard medical care prior to study enrollment are valid sources of data for verifying study eligibility and collecting baseline study data, provided that the previously performed assessments comply with applicable protocol requirements.

- Review of general inclusion and exclusion criteria.
- Female patients of childbearing potential must have a pregnancy test performed within 7 days prior to the procedure
- Relevant medical history and patient demographic information
- Physical examination
- Anginal status (CCS, Braunwald classification of unstable angina, or silent ischemia)
- Documentation of all concomitant medications
- A 12-lead electrocardiogram (ECG). The ECG may be performed up to 21 days prior to procedure, except when there is evidence of acute or recent MI or UA, in which case the ECG must be performed within 24 hours prior to the index procedure.

  Laboratory testing per site standard practice; if laboratory testing is part of the standard of care and includes CBC and serum creatinine, these should be recorded. The results of any additional tests performed per site standard practice should also be collected.
- The blood draw for cardiac biomarkers testing (preferably cTn I or T; if not available, then CKMB is acceptable) may be performed within 48 hours prior to the index procedure, except when there is evidence of acute or recent (<7 days) MI or UA, in which case the draw must be performed within 24 hours prior to the index procedure. If the subject does not have a known diagnosis of acute MI or UA within 96 hours prior to the index procedure, assessment of cardiac biomarkers may be obtained after the start of the index procedure but prior to device implantation.

7.3 Index Procedure

7.3.1 **Angiographic Imaging**

The imaging protocol includes angiography pre-intervention, post-stent implantation, and after any post-dilatation (if any), in addition to documentation of any procedural complications. For details, please refer to the Angiographic Imaging Acquisition Guidelines (§17.3). All procedural angiographic imaging should be forwarded to the Angiographic Core Laboratory for analysis.

7.3.2 **Eligibility Confirmation**

At the time of the index procedure, the investigator should confirm the following before the patient is randomized to a treatment arm and enrolled in the trial:

1) The target vessel(s), target lesion(s), and treatment plan meet all angiographic inclusion criteria and no exclusion criteria; AND
2) Treatment of a non-target lesion (if performed) has been successfully completed without complications (see §7.3.3)

7.3.3 **Treatment of Non-target Lesion**

Treatment of a single non-target lesion that does not meet study angiographic eligibility criteria during the index procedure is permitted, provided that all the following conditions are met:

1) The non-target lesion is treated first, prior to randomization.
2) The non-target lesion is located in a separate epicardial vessel from the target lesion(s). The epicardial vessels are defined as the LAD, LCx, and RCA, each including its respective branches; e.g., a patient with a target lesion in the LAD would not be eligible for treatment of a non-target lesion in a diagonal branch. The ramus intermedius is considered a branch of the LCx.
3) The non-target lesion is treated with an approved (FDA-approved, CE-marked, or PMDA-approved, as applicable) commercially available device.
4) Treatment of the non-target lesion was successful, defined as:
    a. Final % diameter stenosis (%DS) ≤30% with final TIMI 3 flow AND
    b. Without the following complications
        i. Residual dissection (NHLBI grade ≥ type B)
        ii. Angiographic complications (e.g., distal embolization, side branch closure)
        iii. Chest pain lasting > 5 minutes
        iv. ST segment elevation or depression lasting > 5 minutes.

If all the above conditions have been met, the patient may be randomized to a treatment arm and enrolled in the trial. The non-target lesion will not be considered in the primary analyses.

7.3.4 **Treatment of Target Lesion(s)**

Implantation of the assigned study stent(s) in the designated target lesion(s) should be performed per site standard practice in accordance with each manufacturer's Instructions for Use. All target lesions should be treated with the assigned study stent type.

Pre-dilatation of the target lesion(s) with an appropriately sized angioplasty balloon is recommended, and should be documented on the eCRF.

The investigator should choose the appropriate diameter and length of the stent(s) to be implanted by visual estimate, ensuring that the selected stent length allows complete coverage of the target lesion with 1-2 mm of healthy vessel overlap at each end. If the stent is under-dilated following initial expansion, post-dilation should be performed with an appropriately sized balloon.

In the event of a need for a bailout device at the target lesion (e.g., edge dissection, unplanned additional device required to cover target lesion), the same device as the implanted device should be used (i.e., BuMA DES for BuMA DES-treated lesions, DP EES for DP EES-treated lesions), with 1-2 mm overlap of the bailout and implanted stents.

Procedural details should be entered into the eCRF. ACT should be measured at the onset of the procedure and at regular intervals throughout the procedure per routine hospital practice.

7.3.5 **Unplanned Staged Procedures**

Subjects with planned staged procedures are not eligible for enrollment in the study (refer to Angiographic Exclusion Criterion #9, §6.2.2.2.9). However, if index procedure complications (excessive contrast load or radiation exposure, blood loss, or patient intolerance) necessitate discontinuation of the procedure, staged treatment of a target lesion is permitted provided the staged procedure is performed >72 hours and <14 days after the index procedure. The same device as the previously implanted device(s) must be used (i.e., BuMA DES for BuMA DES-treated subjects, DP EES for DP EES-treated subjects).

7.3.6 **Concomitant Medical Therapy**

Dual antiplatelet therapy (DAPT) will be administered according to physician standard practice in accordance with published guidelines[1] and local standards of care. Patients with stable ischemic heart disease will be required to receive DAPT for at least 6 months in the absence of contraindications; discontinuation of DAPT after 3 months is permitted (but not required) in patients with a high risk of bleeding. Patients with ACS will be required to receive DAPT for at least 12 months in the absence of contraindications; discontinuation of DAPT after 6 months is permitted (but not required) in patients with a high risk of bleeding.

The following doses are recommended:

- ASA 300 to 325 mg oral or 250 mg IV loading dose and ASA 75-100 mg maintenance dose indefinitely. NOTE: Aspirin loading is recommended regardless of whether or not the patient was receiving chronic aspirin therapy prior to the procedure.

  AND

- Clopidogrel 600 mg loading dose before procedure and 75 mg daily maintenance dose OR prasugrel 60 mg loading dose and 10 mg daily OR ticagrelor 180 mg loading dose and 90 mg twice daily. NOTE: For patients receiving chronic clopidogrel therapy prior to the procedure, pre-procedure re-loading with clopidogrel (600 mg) is recommended. For patients receiving chronic prasugrel or ticagrelor therapy prior to the procedure, re-loading is at the discretion of the operator.

Recommended loading dose, loading dose timing, and maintenance dosage may vary based on physician's discretion and applicable regional clinical guidelines. Approved adjunctive therapies (e.g., GP IIb/IIIa inhibitors, cangrelor) may be used according to physician preference in accordance with local standards of care. Each site is encouraged to commit to a consistent antiplatelet regimen to be applied to all subjects enrolled in the trial, independent of treatment group.

Procedural anticoagulation therapy should be administered according to physician standard practice in accordance with published guidelines and local standards of care.

All medications administered, including the dose and timing, should be recorded in the patient's medical record and the CRF.

7.4 Post-procedure / Pre-discharge Follow-up

The procedure is complete once the last guiding catheter has been removed from the patient. Thereafter, if a guiding catheter is re-introduced, this is considered a repeat intervention, which must be documented.

The post-procedure follow-up must include:

- Anginal status (CCS, Braunwald classification of unstable angina, or silent ischemia)
- Current concomitant medications documentation. If DAPT has been interrupted or terminated the stop date (and resumption date, if applicable) and the reason for interruption/termination should be recorded.
- A 12-lead electrocardiogram (ECG), to be completed within 24 hours post-procedure or prior to hospital discharge (whichever occurs first)
- Laboratory testing per site standard practice; if laboratory testing is part of the standard of care and includes CBC and serum creatinine, these should be recorded. The results of any additional tests performed per site standard practice should also be collected.
- Cardiac biomarkers (preferably cTn I or T; if not available, then CKMB is acceptable) should be measured 2 to 6 (up to 12) hours postprocedure. If cardiac biomarkers are elevated and there is a clinical suspicion of myocardial ischemia (for example, due to new ischemic ECG changes [such as ischemic ST changes or new pathological Q waves] or new LBBB, angiographic evidence of a flow-limiting complication, or imaging evidence of new loss of viable myocardium or new regional wall motion abnormality), serial measurements should be taken every 6 to 12 hours until a decline is noted.
- Documentation of any adverse events/ serious adverse events occurring since the point of enrollment. All clinically significant adverse events should be carefully documented by the research staff using the adverse event data forms. In the event of repeat intervention after the index procedure or repeat diagnostic cardiac catheterization (regardless of whether revascularization was performed), procedural angiographic images should be forwarded to the Angiographic Core Laboratory. For all adverse events that represent a potential endpoint event, all relevant medical information (including clinically relevant imaging data, ECG data, and the results of relevant laboratory testing performed as part of the standard of care) should be collected and retained as part of the research file to support adverse event analysis and adjudication.

Prior to hospital discharge, research staff should review the follow-up requirements with the subject to help ensure that he or she returns to the clinic for the 30-day follow-up visit. Telephone numbers should be obtained from the subject to ensure the ability to contact him or her at the required time. These phone numbers should include all home numbers, work numbers and primary physician numbers. A phone number of a relative or friend should also be requested.

7.5 30-day Follow-up (Clinic Visit)

All subjects will return to the clinic at 30 days (± 7 days) post-procedure for a clinical evaluation. The 30-day follow up visit will include the following assessments:

- Anginal status (CCS, Braunwald classification of unstable angina, or silent ischemia)
- Current concomitant medication documentation. If DAPT has been interrupted or terminated the stop date (and resumption date, if applicable) and the reason for interruption/termination should be recorded.
- A 12-lead electrocardiogram (ECG)

- Laboratory testing per site standard practice; if laboratory testing is part of the standard of care and includes CBC and serum creatinine, these should be recorded. The results of any additional tests performed per site standard practice should also be collected.
- Documentation of any adverse events/ serious adverse events occurring since the previous evaluation. All clinically significant adverse events should be carefully documented by the research staff using the adverse event data forms. In the event of repeat intervention after the index procedure or repeat diagnostic cardiac catheterization (regardless of whether revascularization was performed), procedural angiographic images should be forwarded to the Angiographic Core Laboratory. For all adverse events that represent a potential endpoint event, all relevant medical information (including clinically relevant imaging data, ECG data, and the results of relevant laboratory testing performed as part of the standard of care) should be collected and retained as part of the research file to support adverse event analysis and adjudication.

Prior to concluding the visit, research staff should also review the follow-up requirements with the subject to help ensure that the patient can be reached for the required telephone contact at 6 months, and that the patient returns to the clinic for the 12-month follow-up visit.

7.6 Six-month Follow-up (Telephone Contact/Clinic Visit)

All subjects will be contacted by telephone at 6 months (± 30 days) post-procedure for additional follow-up, to include the following assessments:

- Anginal status (CCS, Braunwald classification of unstable angina, or silent ischemia)
- Current concomitant medication documentation. If DAPT has been interrupted or terminated the stop date (and resumption date, if applicable) and the reason for interruption/termination should be recorded.
- Documentation of any adverse events/ serious adverse events occurring since the previous evaluation. All clinically significant adverse events should be carefully documented by the research staff using the adverse event data forms. In the event of repeat intervention after the index procedure or repeat diagnostic cardiac catheterization (regardless of whether revascularization was performed), procedural angiographic images should be forwarded to the Angiographic Core Laboratory. For all adverse events that represent a potential endpoint event, all relevant medical information (including clinically relevant imaging data, ECG data, and the results of relevant laboratory testing performed as part of the standard of care) should be collected and retained as part of the research file to support adverse event analysis and adjudication.

If a clinic visit occurs as part of the subject's regular medical care during the specified follow-up window, the follow-up assessment may be conducted during this visit, and no separate telephone contact is necessary.

7.7 Twelve-month Follow-up (Clinic Visit or Optional Telephone Contact / Virtual Visit*)

All subjects will return to the clinic at 12 months (± 30 days) post-procedure for a clinical evaluation with the following exceptions:

- For the duration of the Coronavirus Disease 2019 (COVID-19) pandemic, phone follow-up or virtual visit at 12 months is permitted if necessary to assure the safety of trial participants. The reason for the conduct of the phone follow-up should be documented in the eCRF.

The 12-month follow up visit will include the following assessments:

- Anginal status (CCS, Braunwald classification of unstable angina, or silent ischemia).
    - For subjects undergoing this assessment via phone or virtual visit, anginal status should be documented according to patient reporting.
- Current concomitant medication documentation. If DAPT has been interrupted or terminated the stop date (and resumption date, if applicable) and the reason for interruption/termination should be recorded.
    - For subjects undergoing this assessment via phone or virtual visit, concomitant medications should be documented according to patient reporting.
- A 12-lead electrocardiogram (ECG).
    - For subjects undergoing this assessment via phone or virtual visit, the patient should be asked about any recent or planned visits to a healthcare provider. If yes, contact information should be requested and the provider should be contacted to provide any relevant documentation. All documentation should be reviewed with the site Principal Investigator and, if deemed valid, entered into the EDC by the site.
- Laboratory testing per site standard practice; if laboratory testing is part of the standard of care and includes CBC and serum creatinine, these should be recorded. The results of any additional tests performed per site standard practice should also be collected.
    - For subjects being assessed by phone or virtual visit, this data will not be collected.
- Documentation of any adverse events/ serious adverse events occurring since the previous evaluation. All clinically significant adverse events should be carefully documented by the research staff using the adverse event data forms. In the event of repeat intervention after the index procedure or repeat diagnostic cardiac catheterization (regardless of whether revascularization was performed), procedural angiographic images should be forwarded to the Angiographic Core Laboratory. For all adverse events that represent a potential endpoint event, all relevant medical information (including clinically relevant imaging data, ECG data, and the results of relevant laboratory testing performed as part of the standard of care) should be collected and retained as part of the research file to support adverse event analysis and adjudication.
    - For subjects undergoing this assessment via phone or virtual visit, if potential SAEs or AEs are reported, the subject should be asked about any associated healthcare visits; if applicable visits are reported, contact information should be sought and the provider contacted to provide relevant source documentation (including angiographic films, as applicable). All source documentation must be reviewed with the site PI and, if deemed valid, entered into the EDC by the site. All collected angiographic films are provided to the Angiographic Core Laboratory for analysis.

Prior to concluding the visit, research staff should also review the follow-up requirements with the subject to help ensure that the patient can be reached for the required telephone contact (or optional clinic visit) follow-ups at 2, 3, 4, and 5 years. Telephone numbers, including all home, work, and primary physician numbers, should be confirmed.

Note: For subjects who did not receive any study stent during the index procedure (BuMA DES or DP-EES), the 12-month follow-up will be the final follow-up assessment for this protocol.

7.8 Annual Follow-up at 2, 3, 4, and 5 Years (Telephone Contact/Clinic Visit)

All subjects who received any study stent during the index procedure will be contacted by telephone (or optional in-clinic assessment) annually at 2, 3, 4, and 5 years post-procedure for additional follow-up, to include the following assessments:

- Anginal status (CCS, Braunwald classification of unstable angina, or silent ischemia)
- Current concomitant medication documentation. If DAPT has been interrupted or terminated the stop date (and resumption date, if applicable) and the reason for interruption/termination should be recorded.
- Documentation of any adverse events/ serious adverse events occurring since the previous evaluation. All clinically significant adverse events should be carefully documented by the research staff using the adverse event data forms. In the event of repeat intervention after the index procedure or repeat diagnostic cardiac catheterization (regardless of whether revascularization was performed), procedural angiographic images should be forwarded to the Angiographic Core Laboratory. For all adverse events that represent a potential endpoint event, all relevant medical information (including clinically relevant imaging data, ECG data, and the results of relevant laboratory testing performed as part of the standard of care) should be collected and retained as part of the research file to support adverse event analysis and adjudication.

NOTE: For subjects who underwent a phone follow-up at the 12-month time point for any reason, it is preferable that the 2-year follow-up be conducted as an in-clinic visit. For all other subjects, if a clinic visit occurs as part of the subject's regular medical care during the specified follow-up window, the annual follow-up assessment may be conducted during this visit, and no separate telephone contact is necessary.

8.0 Adverse Events and Serious Adverse Events

In this study, patients should be encouraged to report adverse events (AEs) spontaneously or in response to general, non-directed questioning. Any time during the study, the patient may volunteer information that resembles an adverse event (AE). If it is determined that a clinically significant AE has occurred, the investigator should obtain all the information required to complete the AE CRFs. Non-clinically-significant adverse events will not be required post discharge from the initial study procedure.

8.1 Adverse Events (AE)

An adverse event is any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, whether or not related to the study device.

NOTE: This definition includes events related to the study device or to the procedures involved, but does not imply that there is a relationship between the adverse event and the study device.

Pre-Existing Conditions:

Pre-existing medical conditions or a repeat of symptoms reported prior to the procedure will not be recorded as an AE. Pre-existing conditions that worsen during a study are to be considered adverse events. For users or other persons, this classification is restricted to events related to the study device.

8.2 Serious Adverse Events (SAE)

A serious adverse event is an adverse event that:

1. Led to a death
2. Led to a serious deterioration in the health of the subject that:
    a. Resulted in a life-threatening illness or injury
    b. Resulted in a permanent impairment of a body structure or a body function
    c. Required in-patient hospitalization or prolongation of existing hospitalization
    d. Resulted in medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to body structure or a body function.
3. Led to fetal distress, fetal death or a congenital abnormality or birth defect.

8.3 Adverse Device Effect (ADE)

An adverse device effect is an adverse event related to the use of a medical device. This includes:

- Any adverse event resulting from insufficiencies or inadequacies in the Instructions for Use, the deployment, the implantation, the installation, the operation, or any malfunction of the medical device
- Any event that is a result of a use error or intentional misuse

8.4 Serious Adverse Device Effect (SADE)

A serious adverse device effect is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

8.5 Unanticipated Adverse Device Effect (UADE)

An unanticipated adverse device effect is any serious adverse effect on the health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of subjects.

NOTE: An anticipated serious adverse device effect (ASADE) is a serious adverse device effect which by its nature, incidence, severity, or outcome has been identified in the investigational plan or application (including a supplementary plan or application).

8.6 Device Deficiencies, Malfunctions, and Use Error

Investigators are instructed to report all possible device deficiencies, malfunctions, misuse or use error observed during the course of the trial. These incidents will be documented in the case report form provided as follows:

- **Device deficiency**: Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance. NOTE: Device deficiencies include malfunction, use error, and inadequate labeling. They may or may not affect device performance or lead to an adverse event.
    - **Device malfunction**: Failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the Instructions for Use or protocol. NOTE: A device malfunction occurs when the device is used in

compliance with the Instructions for Use, but does not perform as described in the Instructions for Use.

- **Use error:** Act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user. NOTE 1: Use error includes slips, lapses and mistakes. NOTE 2: An unexpected physiological response of the patient does not itself constitute a use error.
  - **Device misuse:** Any use of the investigational device by an investigator that is contradictory to the application described in the Instructions for Use will be categorized as device misuse. This is a form of Use Error.

8.7 Documentation

Adverse events must be listed on the appropriate CRF. All AEs will be characterized by the following criteria:

- Intensity or Severity
- Relatedness
- Outcome
- Treatment or Action Taken

8.7.1 **Intensity or Severity**

The following categories of the intensity of an adverse event are to be used:

Mild	Awareness of a sign or symptom that does not interfere with the patient's usual activity or is transient, resolved without treatment and with no sequelae.
Moderate	Interferes with the patient's usual activity and/or requires symptomatic treatment.
Severe	Symptom(s) causing severe discomfort and significant impact of the patient's usual activity and requires treatment.

8.7.2 **Relatedness**

The investigator will use the following definitions to assess the relationship to the study device or procedure:

Not related	The cause of the AE is known and the event is not related to the study device or procedure.
Unlikely to be related	There is little or no temporal relationship to the study device or procedure, and/or a more likely alternative etiology exists.
Possibly related	There is a reasonable possibility that the event may have been caused by the study device or procedure. The AE has a **timely relationship** to the study device or procedure(s); **however, follows no known pattern of response**, and an alternative cause seems more likely or there is significant uncertainty about the cause of the event.

Related	A **related** event has a **strong temporal relationship** and an alternative cause is unlikely.

If the relationship between any adverse event and the use of the investigational medical device is considered to be possibly related or related, that event will be classified as an ADE or SADE.

8.7.3 **Outcome**

The clinical outcome of the AE or SAE will be characterized as follows:

Death	The SAE CRF must be completed for this outcome
Recovered without sequelae	The patient returned to baseline status
Ongoing	Patient did not recover and symptoms continue
Recovered with sequelae	The patient has recovered but with clinical sequelae from the event
Unknown	The patient outcome is unknown

8.7.4 **Treatment or Action Taken**

The treatment or action taken after the occurrence of an AE or SAE will be reported as:

Interventional Treatment	Surgical, percutaneous or other procedure
Medical Treatment	Medication dose reduction/interruption or discontinuation, or medication initiated for event
None	No action is taken

8.8 Reporting

8.8.1 **General Adverse Event Reporting Procedures**

Investigators are required to keep records on "all relevant observations, including records concerning adverse device effects (whether anticipated or unanticipated)" according to 21 CFR 812.140. Adverse event collection will occur from the point of study enrollment to study closure. All new or worsening (from baseline) clinically significant adverse events will be captured on the AE CRF through the 5-year follow-up visit. It is the responsibility of the Investigator to assess the subject for adverse events and, if it is determined that a clinically significant AE has occurred, to capture the required adverse event information on the AE CRF. Independent monitoring will be conducted (§13.1) to review source documentation and verify the complete and accurate capturing of adverse events.

The general procedure for investigators reporting any adverse event is as follows:

- If an adverse event occurs, complete all sections of the Adverse Event CRF
- Each unique event/diagnosis must be documented separately
- Documented pre-existing conditions are not considered to be reportable AEs unless there is a change in the nature or severity of the condition

- The AE CRF must be reviewed by the investigator

For adverse events not meeting the criteria for an SAE or (potential) UADE, the Sponsor recommends that the Investigator notify the Sponsor within 10 working days of first learning of the AE using the electronic data capture (EDC) CRF. If necessary, the Investigator may be requested to provide de-identified copies of source documentation (e.g., physician/nurse notes or summaries) regarding the event.

The Investigator must also notify the responsible IRB/EC regarding new and significant safety information and any events identified by SINOMED that require expedited FDA or other regulatory authority reporting as serious, unexpected, and related to the investigational device. It is the responsibility of the investigator to ensure site-specific IRB/EC reporting requirement are met.

The sponsor is responsible for reporting SAEs and device deficiencies to regulatory authorities in line with applicable regulatory requirements and for reviewing the risk analysis, determining the need for corrective or preventative action, and informing investigators and regulatory authorities accordingly.

8.8.2 **Serious Adverse Events**

The Sponsor recommends that the Investigator notify SINOMED within 3 working days of first learning of any SAE using the EDC CRF. If necessary, the Investigator may be requested to provide copies of de-identified source documentation (e.g., physician/nurse notes or summaries) regarding the event. The Sponsor will conduct an evaluation of the event and, if it is determined by the Sponsor to be a UADE, it will be reported as described in the following section.

At EU sites, Serious Adverse Device Effects (SADEs) must be reported to the Safety Monitor (Europe) within 48 hours of knowledge if required by local or national regulations; contact details are provided in §2.0.

It is the responsibility of each Investigator to report all serious adverse events and/or serious adverse device effects and device deficiencies that could have led to a serious adverse device effect to the IRB/EC, according to national regulations and IRB/EC requirements. If required by national regulations, the Investigator may also be required to report SAEs to the applicable regulatory authority.

8.8.3 **Unanticipated Adverse Device Effects**

Investigators must report any (potential) unanticipated adverse device effects to the Sponsor and their IRB/EC as soon as possible but no later than within 5 working days after the investigator first learns of the event [21 CFR 812.150]. UADEs should be reported immediately on the eCRF and via telephone to the Sponsor Clinical Project Lead; contact details are provided in §2.0.

Investigators should consider the device labeling and the listing of expected adverse events (§8.9) in determining whether an event may qualify as “unanticipated.”

If an event is determined by SINOMED to be a UADE, the Sponsor will report the event to the FDA, relevant Competent Authorities and/or other regulatory authorities, and the European Databank on Medical Devices in accordance with MEDDEV 2.12-1, as applicable. The Sponsor will also report all UADEs to all investigators to enable reporting to their respective IRB/EC. The Sponsor will provide this notification within 10 days after first receiving notice of the effect [21 CFR 812.150].

If the Sponsor and the DSMC determine that the event presents an unreasonable risk to participating subjects, the Sponsor must terminate all investigations or parts of investigations presenting the risk in the clinical trial not more than 5 working days after making that determination, and not more than 15 working days after the sponsor first received notice of the effect [21 CFR 812.26]. Follow-up visits for enrolled subjects will continue according to the schedule of assessments.

8.9 Expected Adverse Events

The following adverse events have been identified as actual or potential complications associated with percutaneous coronary intervention with drug-eluting stents, categorized below by their estimated frequency at 1 year. It is expected that the nature and frequency of the risks observed with the use of BuMA DES and DP EES in this trial will be similar.

Very common (≥10%)

- Angina pectoris (stable or unstable)

Common (1.0% to <10%)

- Access site complications (including pain, hematoma, or hemorrhage)
- Arrhythmia (atrial, ventricular)
- Cardiac, pulmonary, or renal failure
- Coronary artery dissection
- Hypertension
- Hypotension
- Myocardial infarction
- Nausea and vomiting
- Restenosis
- Vascular complications (including access site vascular complications) that may require vessel repair

Uncommon (0.1% to <1.0%)

- Allergic or hypersensitivity reactions (to contrast agent, procedural medications, or device materials)
- Bleeding complications (which may require transfusion)
- Cardiac arrest
- Coronary artery perforation
- Coronary artery spasm
- Distal embolization
- Fever
- Myocardial ischemia (silent)
- Pain or infection at the catheter site
- Palpitations
- Pericarditis
- Peripheral ischemia (due to vascular injury)
- Pseudoaneurysm
- Pulmonary edema

- Requirement for surgery (emergent or non-emergent)
- Stroke or transient ischemic attack
- Total occlusion of a coronary artery
- Ventricular tachycardia
- Ventricular fibrillation
- Vessel dissection

Rare (0.01% to <0.1%)

- Arterial injury
- Arteriovenous fistula
- Cardiac tamponade
- Coronary artery embolism
- Nausea (procedural)
- Pericardial effusion
- Peripheral artery dissection
- Peripheral nerve injury
- Renal insufficiency
- Shock

Very rare (<0.01%)

- Abrupt coronary artery closure
- Arterial rupture
- Coronary artery aneurysm

The nature and frequency of potential adverse events specifically related to the sirolimus drug component as incorporated into the BuMA DES are not known, but are expected to be rare and may include but are not limited to:

- Abnormal liver function tests
- Anemia
- Diarrhea
- Hypercholesterolemia
- Hypersensitivity, including anaphylactic / anaphylactoid type reactions
- Hypertriglyceridemia
- Infections
- Leucopenia
- Pseudoaneurysm
- Renal failure

- Thrombocytopenia

9.0 Benefit: Risk Analysis

9.1 Potential Benefits

The targeted patient population consists of patients presenting with symptomatic ischemic heart disease, including chronic stable angina with evidence of ischemia or acute coronary syndromes, planned to undergo PCI with DES for the treatment of CAD. Compared with traditional durable polymer DES, the combination of a thin durable base layer with a biodegradable polymer drug delivery matrix featured in the BuMA DES may offer improved re-endothelialization, reducing the risk of long-term adverse events.

Subjects in the BuMA US IDE trial may not derive any direct benefit from their participation in the trial; however, subjects may gain satisfaction from having made an altruistic contribution to medical science, and the results of the trial may contribute to improved treatments that could benefit future patients who require PCI for the treatment of CAD.

The potential benefits and risks of study participation will be evaluated on an individual basis and discussed with each patient prior to enrollment in the study.

9.2 Potential Risks and Discomforts

Enrollment in the trial involves exposure to some risks. The risks of trial participation are not expected to be materially different from those encountered by an individual undergoing PCI with DES outside the context of the trial (§8.9). The use of the BuMA DES may pose additional potential risks of an unknown nature or frequency.

9.3 Methods to Minimize Risks

The clinical investigation plan is specifically designed to manage and minimize risks through careful subject selection, thorough training of investigators, adherence to pre-determined time points to assess subject clinical status, and regular clinical monitoring visits by Sponsor-appointed monitoring personnel. In addition, an independent Data Safety Monitoring Committee will meet regularly throughout the trial to monitor the safety of subjects.

10.0 Study Committees

10.1 Executive Committee

The Executive Committee will be comprised of the Study Chairman, the Principle Investigators and Co-Principal Investigators from the US, Europe, and Japan, and one or more Sponsor Representatives. The Executive Committee will be responsible for scientific and operational management of the trial, and will meet regularly prior to and during the trial to monitor trial progress.

10.2 Clinical Events Committee (CEC)

An independent Clinical Events Committee (CEC) will adjudicate all site-reported adverse events that represent a potential endpoint event in an ongoing fashion during the trial. Relationship of these events to the study device and procedure will also be adjudicated.

The CEC will include cardiologists and/or interventional cardiologists experienced in clinical trials who are otherwise independent of the Sponsor and the conduct of the study. Members will not have scientific, financial or other conflicts of interest related to SINOMED or the Investigators. The CEC will operate and

conduct all meetings and event reviews independent of the Sponsor unless specific expert knowledge regarding the characteristics or function of the study device is requested by the CEC from the Sponsor.

The CEC will meet regularly throughout the study to adjudicate events in an ongoing and timely fashion. The adjudication process, event definitions and required source document materials for each type of event will be pre-specified in the CEC Charter prior to the onset of the trial. The adjudication process will include CEC member review of data collected from all relevant medical records, as well as all imaging studies, associated with an event. All adjudication decisions will be made by the CEC in an independent fashion based upon review of all available medical evidence.

10.3 Data Safety Monitoring Committee (DSMC)

An independent Data Safety Monitoring Committee (DSMC) will be responsible for the oversight and safety monitoring of the study. The DSMC will advise the Sponsor regarding the continuing safety of the trial subjects and those yet to be recruited to the trial, as well as the continuing validity and scientific merit of the trial. The DSMC will be composed of leading experts in interventional cardiology and biostatistics who are not participating in the trial and have no affiliation with the Sponsor.

During the enrollment phase of the trial, the DSMC will review accumulating safety data to monitor for the incidence of serious adverse events that would warrant modification or termination of the trial. Any DSMC recommendations for study modification or termination prompted by concerns regarding subject safety or issues relating to data monitoring or quality control will be submitted in writing to the Sponsor for consideration and final decision. However, if the DSMC at any time determines that a potential serious risk exists to subjects in this trial, the DSMC chairman will immediately notify the Sponsor.

The DSMC will meet at regular intervals to review the safety data. DSMC responsibilities, membership, meeting frequencies, and procedures will be outlined in the DSMC charter prior to the onset of the trial.

11.0 Statistical Considerations and Analysis Plan

11.1 Hypotheses

11.1.1 **Primary Safety and Efficacy Hypothesis**

The primary hypothesis is that the rate of TLF in the Intervention group is not inferior to the rate of TLF in the Control group by greater than or equal to the pre-specified non-inferiority margin (Δ). Specifically, the null and alternative hypotheses are:

H_0: $p_I - p_C \geq \Delta$

H_A: $p_I - p_C < \Delta$

Where:

p_I = the true rate of TLF in the Intervention group at 12 months

p_C = the true rate of TLF in the Control group at 12 months

Δ = non-inferiority margin

The non-inferiority criterion is met if the upper bound of the 95% confidence interval (97.5% one-sided confidence interval) of the difference between the Intervention and Control group event rates is less than the specified delta, using the Farrington-Manning approach.

If non-inferiority is demonstrated in the both the Per Protocol (PP) and Intention to Treat (ITT) populations, the trial will be declared a success. Because both analysis populations will be considered simultaneously, no adjustment for alpha is necessary.

11.1.2 **Secondary Powered Endpoint Hypothesis**

If the primary non-inferiority hypothesis is confirmed, the secondary powered endpoint hypothesis will be tested. The secondary powered endpoint hypothesis is that the rate of TLF in the treatment group is superior to the rate of TLF in the control group over the period between 1 and 5 years postprocedure in a landmark analysis. Specifically, the null and alternative hypotheses are:

H_0: $S_I(t) = S_C(t)$ for all t

H_A: $S_I(t) \neq S_C(t)$

Where:

$S_I(t)$ = the survival distribution in the Intervention group and $S_C(t)$ = the survival distribution in the Control group

Superiority will be demonstrated if the survival distributions are not equal using the log-rank test in the Intention to Treat patient population.

11.2 Analysis Populations

11.2.1 **Intention to Treat (ITT) Analysis Population**

The Intention to Treat (ITT) analysis population is defined as all subjects enrolled in the study, by assigned treatment, regardless of the treatment actually received.

The ITT population will be the co-primary analysis population for the primary safety and efficacy endpoint, the primary analysis population for the powered secondary endpoint, and the primary analysis population for all additional secondary safety endpoints and secondary efficacy endpoints.

11.2.2 **Per Protocol (PP) Analysis Population**

The Per Protocol (PP) analysis population is defined as subjects enrolled in the trial who meet all inclusion criteria and no exclusion criteria, have provided written informed consent, and in whom an assigned study stent has been implanted.

The PP population will be the co-primary analysis population for the primary safety and efficacy endpoint and the secondary analysis population for all secondary endpoints.

11.3 Sample Size Calculation and Assumptions

11.3.1 **Primary Endpoint**

The primary safety and efficacy endpoint of the trial is target lesion failure (TLF), defined as the per-subject hierarchical composite of cardiac death, target vessel-related myocardial infarction (TV-MI), and clinically-driven target lesion revascularization (TLR), evaluated at 12 months.

We assume:

- Randomization ratio is 2:1 (BuMA DES: DP EES)
- The true rate of TLF in the Control group at 12 months = 6.5% (§11.3.3.1)
- No difference between treatments (the true rate of TLF in the Intervention group at 12 months = 6.5%)
- Non-inferiority margin (Δ) = 3.575% (§11.3.3.3)
- Loss to follow-up at 1 year (inclusive of dropout from co-primary PP analysis population) = 5% (a standard assumption for contemporary trials of coronary stents)
- α = 0.025 (one-sided)

Given these assumptions, a sample size of 1551 evaluable subjects (1034 Intervention: 517 Control) will provide 80% power to demonstrate non-inferiority of the BuMA DES to DP EES using the Farrington-Manning approach. The sample size has been increased to 1632 subjects (1088 Intervention: 544 Control) to account for an expected 5% loss to follow-up at 12 months.

11.3.2 **Secondary Powered Endpoint**

The powered secondary endpoint of the trial is long-term safety and efficacy, defined as TLF between 12 months and 5 years by landmark analysis. The analysis will be performed when the last enrolled subject has completed his/her 5 year clinical follow-up visit.

We assume:

- Randomization ratio is 2:1 (BuMA DES: DP EES)
- The landmark (between 12 months and 5 years) TLF rate in the Control group = 8% (§11.3.3.2)
- The rate of TLF in the control group at 12 months = 6.5% (§11.3.3.1)
- A constant Hazard Ratio in the Intervention group compared to the Control Group = 0.52
- Loss to follow-up = 5% per year (a standard assumption for contemporary trials of coronary stents)
- $\alpha = 0.05$ (two-sided)

Given these assumptions, the planned study sample size of 1444 evaluable subjects at 1 year (accounting for an estimated 5% loss to follow-up at 1 year, a 6.5% rate of TLF prior to 1 year, and a continued annual loss to follow-up of 5%) will provide approximately 80% power to demonstrate superiority of the BuMA DES to DP EES using the log-rank test.

11.3.3 **Rationale for Assumptions**

11.3.3.1 Expected Control Event Rate – Primary Endpoint

The expected event rate of the primary endpoint (target lesion failure [TLF] at 12 months) in the Control group was estimated based on published data from randomized controlled trials of commercially-available durable polymer everolimus-eluting coronary stent systems (DP EES).

A bibliographic scientific database search (MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials [CENTRAL]) was conducted to identify relevant published clinical data according to the following criteria:

1. Randomized controlled trials (RCTs)
2. Commercially available durable polymer everolimus-eluting coronary stent systems as an investigational device or active comparator, including the XIENCE family of cobalt-chromium everolimus-eluting stent systems (XIENCE EES; including XIENCE V, XIENCE NANO, XIENCE PRIME, XIENCE PRIME LL, XIENCE XPEDITION, XIENCE XPEDITION SV, XIENCE XPEDITION LL, XIENCE Alpine; studies in which a subset of patients in the everolimus-eluting stent arm received cobalt-chromium Promus stents were included) and the PROMUS Element family of everolimus-eluting platinum chromium stent systems (including PROMUS Element, PROMUS Element Plus, and Promus PREMIER).
3. Treatment of native vessel coronary artery disease; studies that were limited solely to the treatment of acute myocardial infarction, chronic total occlusion, in-stent restenosis, or unprotected left main coronary artery disease were excluded.
4. Clinical data reported at ≥12 months
5. Subjects = humans, adults ≥18 years of age
6. $N_{DP\ EES} \geq 200$

The search covered the period from November 2006 to August 1, 2016. Search terms included everolimus eluting stent, Xience, PROMUS, and individual product names; MeSH terms included randomized controlled trial, clinical trial, human, drug eluting stent, eluting stent, everolimus. The bibliographies of all potentially relevant publications were examined to increase the sensitivity of the search.

The literature search identified 35 trials meeting the above selection criteria. Of the 35 potentially applicable trials, 12 were excluded because they did not report the endpoint of interest (SPIRIT II,[28-33] COMPARE,[34, 35] BASE-ACS,[36-39] BASKET PROVE,[40-43] XIMA,[44] APPENDIX-AMI,[45] BASKET-PROVE II,[46, 47] ITALIC,[48] TUXEDO,[49] Lin 2015,[50] BEST,[51] and PROMISE[52]); 3 trials were excluded because they were limited to low-risk patient or lesion subsets not reflective of the target population (TARGET I,[53] PLATINUM,[27] and PLATINUM China[54]); 3 trials were excluded because a substantial proportion (>15%) of subjects presented with ST-segment elevation myocardial infarction (COMPARE II,[55, 56] BIOSCIENCE,[57-59] and DUTCH PEERS[60-62]); 1 trial was excluded for data quality concerns due to a substantially lower event rate compared with concurrent US trial with identical eligibility criteria (ABSORB China[63]); 1 trial was excluded because the high periprocedural MI rate was an outlier (LONG DES V[64]); and 1 trial was excluded because patients received either triple or double-dose dual antiplatelet therapy and no routine post-PCI cardiac enzyme measurement was performed (HOST-ASSURE[65, 66]).

The remaining 14 randomized trials (SPIRIT III,[24, 67-69] SPIRIT IV,[25, 70-72] SPIRIT V DM,[73] RESOLUTE AC,[74-76] SORT OUT IV,[77-81] TWENTE,[82-85] RESET,[86-88] EXCELLENT,[89-91] LONG DES III,[92] ISAR TEST IV,[93-95] NEXT,[96] ABSORB III,[97] IVUS-XPL,[98] AND EVOLVE II[99]), representing a total of 13,833 patients treated with commercially-available DP EES, served as the source of published clinical data for the purpose of estimating the expected primary efficacy endpoint event rate in the control group; sample size and event rate data for these trials are presented below in Table 4.

Table 4. TLF at 1 year in RCTs of DP EES in similar patient populations

Trial	N (DP EES)	Target Lesion Failure (%) at 1 year
SPIRIT III	653	5.2
SPIRIT IV	2416	4.0
SPIRIT V DM	215	11.2
RESOLUTE AC	1126	8.3
SORT OUT IV	1390	4.1
TWENTE	692	6.8
RESET	1597	5.9
EXCELLENT	1067	3.8
LONG DES III	224	12.9
ISAR TEST 4	652	11.5
NEXT	1618	6.6
ABSORB III	677	6.1
IVUS-XPL	700	5.8
EVOLVE II	806	6.5
Simple average	--	**7.05**

Weighted average	--	**6.01**
Meta-analytic average (inverse variance method)	--	**6.50**

Therefore, based on published literature reporting TLF at 1 year in subjects treated with DP EES, the expected event rate for the primary efficacy endpoint in the control group is estimated to be 6.5%.

11.3.3.2 Expected Control Event Rate – Secondary Powered Endpoint

The powered secondary long-term device safety and efficacy endpoint is long-term safety and efficacy, defined as target lesion failure (TLF) between 12 months and 5 years by landmark analysis.

Of the 14 selected randomized trials reporting TLF rates in DP EES at 1 year (§11.2), 8 trials reported data at one or more time points between 2 and 5 years postprocedure (SPIRIT III, SPIRIT IV, RESOLUTE AC, SORT OUT IV, TWENTE, RESET, ISAR TEST 4, and NEXT). Based on this data, a landmark (between 12 months and 5 years) TLF event rate in the control group of 8% was estimated (2% annually).

11.3.3.3 Non-inferiority Margin

A meta-analysis of historical trials determined that a conservative estimate (lower bound of the 90% CI) for the treatment effect of the Control comparator (DP EES) compared to bare metal stents (BMS) was 9.0% for the primary endpoint of TLF at 1 year.[100] The selected non-inferiority margin of 3.575% therefore preserves >60% of the risk reduction provided by the Control using the fixed margin approach. This clinical margin is more conservative than the usual practice in cardiovascular outcomes studies of selecting a non-inferiority margin that preserves 50% of the Control effect size.[101]

11.4 Method of Analysis & Reporting

11.4.1 **General Approach**

Non-inferiority testing for the primary safety and efficacy endpoint will be one-sided and performed at a 0.025 significance level for the comparison of the BuMA DES arm with the DP EES arm. Superiority tests on the secondary powered endpoint of long-term safety and efficacy (if the primary non-inferiority endpoint is met) and the primary safety and efficacy endpoint (if the secondary superiority endpoint is met) will be performed at a two-sided 0.05 significance level.

Analysis of all additional safety and efficacy endpoint results will be summarized using descriptive statistics. For binary variables, descriptive statistics will include counts, percentages, and sample size for each treatment group; p-values may be presented for hypothesis-generating purposes. For continuous variables, descriptive statistics include mean, median, standard deviation, quartiles, minimum, maximum, and sample size for each treatment group. Binary variables will be summarized using frequencies, percentages, and sample size for each treatment group. For time-to-event data, Kaplan-Meier estimates at the indicated time points will be displayed graphically.

Analysis will be conducted using SAS (version 9.3 or greater), unless otherwise noted. Please refer to the formal Statistical Analysis Plan (SAP) for additional details.

11.4.2 **Baseline Characteristics**

The following data will be summarized using descriptive statistics and presented by treatment group for the ITT and PP populations:

- Baseline demographics
- Baseline comorbidities, risk factors, and medical history
- Cardiac risk factors, angina status, and cardiac history
- Procedural characteristics

- Device details

11.4.3 **Primary Endpoint Analysis**

The primary analysis will be a test for non-inferiority of the BuMA DES compared with DP EES for the primary endpoint of TLF at 12 months, performed in the Per Protocol (PP) and Intention to Treat (ITT) populations using the Farrington-Manning test. If non-inferiority for the primary endpoint is met and superiority for the powered secondary endpoint is met, formal superiority testing will be performed for the primary endpoint.

The primary endpoint will be evaluated in both the PP and ITT populations. For the primary analyses, only subjects who experienced a primary endpoint event or who had at least 11 months follow-up (1 year minus the allowable 30 day window) and who meet the applicable analysis population definition will be included in the analysis. Analysis is at the subject level. A subject will be considered a failure for TLF if the subject experiences a cardiac death, a target vessel-related myocardial infarction (TV-MI) in any target vessel, or clinically-driven target lesion revascularization (TLR) in any study target lesion.

As an additional analysis, to account for any missing data in the primary endpoint, a tipping point analysis will be conducted. A sensitivity analysis for the primary endpoint will also be conducted according to the pre-specified alternate biomarker thresholds for PCI-related MI (§17.1).

In addition, to assess the appropriateness of pooling results between study regions (North America vs. Japan vs. Europe), an assessment of the effect of region on the primary endpoint will be carried out in the PP and ITT populations using interaction testing from the logistic regression with a 0.15 level of significance. A non-significant result for region will support the pooling of patients across regions for the primary safety and efficacy analysis. A significant result will require further inspection of the by-region results to assess if poolability is appropriate.

11.4.4 **Secondary Powered Endpoint Analysis**

The powered secondary endpoint of long-term safety and efficacy, defined as TLF between 12 months and 5 years by landmark Kaplan-Meier analysis, will be a test for superiority of the BuMA DES group to the DP EES group via the log-rank test in the ITT population. Subjects who experience TLF prior to 12 months will be excluded from this analysis. The analysis will be performed when the last enrolled subject has completed his/her 5 year clinical follow-up visit, and will be performed only if non-inferiority for the primary endpoint has been met.

11.4.5 **Additional Secondary Endpoints Analysis**

11.4.5.1 Secondary Safety Endpoints

All secondary safety endpoints will be evaluated in the ITT population using appropriate descriptive statistics. No formal hypothesis testing will be performed. Statistics for continuous variables will include mean, median, standard deviation, minimum, maximum, and sample size for each treatment group. Binary variables will be summarized using frequencies, percentages, and sample size for each treatment group.

As a secondary analysis, all secondary safety endpoints will be evaluated in the PP population.

11.4.5.2 Secondary Efficacy Endpoints

All secondary efficacy endpoints will be evaluated in the ITT population using appropriate descriptive statistics. No formal hypothesis testing will be performed. Statistics for continuous variables will include mean, median, standard deviation, minimum, maximum, and sample size for each treatment group. Binary variables will be summarized using frequencies, percentages, and sample size for each treatment group.

As a secondary analysis, all secondary efficacy endpoints will be evaluated in the PP population.

11.4.6 **Subgroup Analyses**

Subgroup analyses will be performed for all primary and secondary endpoints in their respective primary analysis populations for the following subgroups, and results will be reported by treatment group using descriptive statistics:

- Enrollment region (North America vs. Japan vs. Europe)
- Presentation (stable coronary artery disease vs. acute coronary syndromes)
- Single- versus multi-vessel disease (1 vs. 2 target vessels)
- Diabetes status (subjects with vs. without medically-treated diabetes mellitus)
- Subject gender (male vs. female)

The interaction p-value for the subgroup by treatment effect will be presented.

11.4.7 **Additional Analyses**

The following data will be summarized using descriptive statistics presented by treatment group in the ITT and PP populations:

- Subject enrollment and data compliance by site and visit (data compliance at each visit is the percentage of patients whose data forms have been collected and entered divided by the percentage of patients whose forms should have been collected and entered)
- Frequency (number and percentage of patients) with each type of concomitant medication
- Frequency (number and percentage of patients) with each site-reported Treatment Emergent AE overall and by MedDRA system organ class and preferred term (a treatment emergent AE is an AE that started or worsened during or after the index procedure)
- Frequency (number and percent of patients) with each site-reported Treatment Emergent Serious AE overall and by MedDRA system organ class and preferred term
- Frequency (number and percent of patients) with each site-reported Treatment Emergent AE or SAE, by CEC-adjudicated relationship to the investigational device or procedure
- Protocol deviations (number and percentage of patients with each deviation type)
- Detailed listings on primary and secondary endpoints, site-reported AE, and protocol deviations

11.4.8 **Handling of Multiplicity Issues**

The primary safety and efficacy endpoint will be evaluated simultaneously in the co-primary PP and ITT populations, and trial success requires meeting the non-inferiority criterion in both analyses. Therefore, adjustment for Type I error is not necessary.

The secondary powered endpoint hypothesis will only be tested if the primary endpoint non-inferiority hypothesis is met. Superiority for the primary endpoint will be tested if the secondary powered endpoint hypothesis is confirmed.

11.4.9 **Multicenter Studies**

The appropriateness of pooling data across sites will be assessed by including a random effect for site in a random effects model assessing the primary endpoint using the logit link. If a test of the variance from the mixed effects model is significant at alpha=0.15, then it will be determined that heterogeneity by site exists. If this occurs, the primary endpoint results will be presented by site and the final analysis will be stratified by site. Sites with less than 10 subjects will be pooled according to study region as defined previously.

11.5 Measures to Minimize Bias

11.5.1 **Randomization**

Subjects will be randomly assigned to a treatment group in a 2:1 ratio (BuMA DES : DP EES) after eligibility criteria have been confirmed (at the time of the index procedure). Randomization will be stratified by presentation (acute coronary syndrome vs. non-ACS) and diabetes status (subjects with vs. without medically-treated diabetes mellitus) given the influence of clinical presentation and diabetes status on the outcome of subjects with CAD. Randomization will also be stratified by study site to avoid introducing bias as a result of site-specific factors.

11.5.2 **Blinding**

This is a single-blind study. The following individuals will be blinded to the subject's treatment allocation:

- Subject and his/her family members
- Site personnel conducting follow-up evaluations will not have access to randomization eCRFs, and every effort will be made to ensure that medical records use a non-specific term to identify the treatment device (e.g., "DES") to avoid revealing treatment group assignment
- Members of the Clinical Events Committee
- Angiographic Core Laboratory technicians performing the analysis

Un-blinding will occur only after the database has been locked for the analysis of the primary endpoint or to protect subject rights, welfare, or well-being at the request of the DSMC.

If a site investigator determines it is necessary to reveal treatment allocation to the subject as a result of complication or injury, he or she is requested to notify the Sponsor.

11.5.3 **Independent Assessments**

To decrease the variability of clinical outcome measurements, all adverse events, including all potential endpoint events, will be adjudicated by an independent CEC according to standardized endpoint definitions, and the relationship of these events to the study device will also be adjudicated. In addition, an independent Angiographic Core Laboratory analysis will be performed by technicians who are blinded to subject treatment assignment to provide accurate and unbiased determinations of lesion and device success, as well as to determine if revascularizations meet the diameter stenosis criteria for classification as clinically-driven.

12.0 Publication Policy

The Sponsor and the Principal Investigators are committed to the publication and widespread dissemination of the results of the study in the scientific community. This study represents a joint effort between the Sponsor and the Principal Investigators and Co-Principal Investigators; as such, the parties agree that the recommendation of any party concerning manuscript or text shall be taken into consideration in the preparation of final scientific documents for publication or presentation.

All parties agree that the Investigators will do publications and/or presentations. The number of authors will be determined according to the rules of the addressed scientific journal and by decision of the Executive Committee. Abstracts and articles shall be submitted to the Sponsor in advance of their publication. An agreement on the final form of abstracts and articles shall be obtained within an appropriate time frame of 60 days. In the event that diverging opinions on presentation of the data cannot be reconciled, the Executive Committee will make a final decision.

Any and all information supplied or obtained during this study by or on behalf of any party involved in the study (in whatever form) shall be treated as confidential, shall not be disclosed to any third party unless with the prior written consent of the Sponsor in each case. Any documents, papers, drawings or other materials which are released or created by any party involved in this study are and shall remain at all times the property of the Sponsor excluding publications which are approved in writing by the Sponsor. Such materials shall not be reproduced in any form without the prior written consent of the Sponsor and must be returned to the Sponsor immediately upon request, or upon completion of the evaluation of such materials, whichever occurs first.

All clinical data or any other information gathered during or after this study related to the study, the people involved, or the materials involved will be considered confidential. Confidential information will remain confidential for a period of 36 months following study completion.

13.0 Data Collection and Monitoring

13.1 Data Collection and Monitoring

All required data for this study will be collected on standardized Case Report Forms (CRFs) using an electronic data capture system (EDC). The investigator (or designated hospital staff) will assure primary data collection based on source-documented hospital chart reviews.

Independent monitoring will be performed to ensure that the investigator and his/her study team conduct the clinical investigation in accordance with contract specifications, this protocol, the Declaration of Helsinki, ICH-GCP, ISO 14155, 21 CFR Part 812, and other applicable FDA and local regulations, and to ensure adequate protection of the rights and safety of subjects and the quality and integrity of the resulting data. Submitted trial data will be verified against patient charts and other sources containing original records of patient data. Source document verification will occur in accordance with the pre-specified Monitoring Plan.

Progress of the trial will be monitored by:

- On-site review, as deemed appropriate by the Sponsor
- Telephone communications between site personnel (e.g., Site Investigator, Trial Coordinator) and trial monitors
- Review of CRFs and associated clinical records
- Review of regulatory documents

Entities responsible for monitoring in the US, Europe, and Japan are listed in §2.0.

If a monitor becomes aware that an Investigator is not complying with the requirements mentioned above, the sponsor will be notified by the monitor. The Sponsor will evaluate the non-compliance and if necessary, immediately either secure compliance or discontinue shipments of the investigational device to the Investigator and terminate the Investigator's participation in continued enrollment in the investigation. The Investigator will be required to return all unused devices to the Sponsor.

13.2 Source Documentation

Auditors, monitors, IRBs/ECs, the Sponsor, and the FDA and other regulatory authorities may have access to the medical records related to this study. Original or certified copies of all relevant clinical findings, observations, and other activities throughout the clinical investigation must be recorded and maintained in the medical file of each enrolled patient (no source documentation will be recorded directly on the CRF). At a minimum, the following must be included in each patient's file:

- Sufficient medical history and current physical condition, including any medication(s) the patient is taking at the time of the procedure to assess the patient's eligibility;
- The medical file should reveal the patient's participation in this study, including documentation of written informed consent;
- Dated report of the index procedure including medication, material usage, and complications, if applicable;
- Dated reports of the post-procedure / pre-discharge and follow-up assessments;
- Dated results of required laboratory tests;
- Any adverse event(s), the resultant action or treatment, and outcome, if applicable; and
- In the case of withdrawal of patient consent, the reason and patient status at time of withdrawal.

The Site Investigator will permit study-related monitoring, audits, IRB/EC review, and FDA and other applicable regulatory authority inspections by allowing direct access to the source data.

In case of electronic source data, periodic access will be allowed for full safety review. The review will be specific to study subjects and the records that would contain potential safety data. Dated print-outs are acceptable for preliminary review of safety information. Print-outs will not be limited to cardiac data only, but should include all available data related to the identified patient(s).

13.3 Auditing

As a quality assurance measure, investigational sites may be audited during the trial or following trial completion. The purpose of an audit is to provide an independent evaluation of trial conduct and protocol and GCP compliance, separate from routine monitoring and quality control functions. The audit may be conducted by SINOMED personnel (or designee), the FDA, or another regulatory body.

Site Investigators are requested to notify the Sponsor if the FDA or another regulatory body requests an audit. The site investigator and/or institution shall permit SINOMED and regulatory bodies direct access to source data and all other relevant documents.

14.0 Device Accountability

The Site Principal Investigator is responsible for device accountability at his/her trial site and must maintain associated trial records according to 21 CFR Part 812.140. The investigator may assign the responsibility for device accountability to an appropriate study staff member, but remains the final responsible person.

The Principal Investigator or designed research staff must store all investigational product in a secure location and in compliance with Institutional Policies, and access to the investigational product must be monitored and limited to research staff. The investigator will maintain device use/disposition records that document device delivery to the trial site, the inventory at the site, administration to each patient as well as any device that was opened but not used. These records must include dates, quantities, batch/serial numbers, expiration dates, and the unique code numbers assigned to the trial patients. The investigator must maintain records that adequately document which device was used (or exposed to the circulation) of each subject and any device malfunctions.

At the trial closeout visit, the Investigator must return to the Sponsor any unused devices and a copy of the completed device inventory. The Investigator's copy of the device reconciliation records must document all device usage (including devices that were opened but not used) and any unused devices that have been returned to the Sponsor.

15.0 Ethical and Regulatory Considerations

15.1 Applicable Regulations

This trial will be conducted in compliance with this protocol, the Sponsor's standard operating procedures and/or guidelines, FDA regulations, PMDA regulations, local regulations where applicable, ICH GCP guidelines, the Declaration of Helsinki, Annex X of the European Medical Devices Directive, and EN/ISO 14155:2011. In the event of conflict between provisions of the cited regulations, the applicable regional or national law or regulation shall prevail.

15.2 Institutional Review Board / Ethics Committee

This trial will be conducted in accordance with 21 CFR 56 Institutional Review Boards. The investigator will assure that an appropriately constituted Institutional Review Board (IRB) or Ethics Committee (EC) complies with the requirements of the International Conference on Harmonization Guideline. Prior to initiation of the study, the investigator will forward copies of the protocol, Investigators Brochure, informed consent form and all other appendices to be used for the study to the IRB/EC for its review and approval. A copy of the written IRB/EC approval must be provided to the Sponsor (or designee) and should include the following:

- A statement of IRB/EC approval for the proposed study at the institution;
- The date the study was approved and the duration of approval (if applicable);
- Identification of the approved documents including version dates and/or other references. At a minimum, the following documents should be listed:
    - Study protocol
    - Patient information and consent form
    - Any additional written information to be provided to the patient
- A listing of any conditions attached to the approval (if applicable);
- Identification of the approved primary investigator;
- The signature of the IRB/EC chairperson;
- Acknowledgement of the sub-Investigators.

Any amendments to the protocol, as well as possible associated information and consent form changes, will be submitted to the IRB/EC and written approval obtained prior to implementation. Substantive changes will be submitted to the FDA (and other local regulatory authorities as applicable) for approval prior to implementation, and the FDA (and other local regulatory authorities as applicable) will be notified of any changes not requiring approval according to applicable guidelines.

15.3 Insurance

The Sponsor will maintain clinical trial insurance coverage for the duration of the study in accordance with applicable local laws and regulations. Details of insurance, indemnity, compensation, and reimbursement shall be addressed in a separate agreement approved by the interested parties.

15.4 Regulatory Approval

The Sponsor is responsible for notifying the study to the FDA and any other relevant authorities (as applicable) according to regulatory requirements. Investigators may not commence enrollment of

subjects until they have met any local IRB/EC and hospital management requirements and have received confirmation from the Sponsor that the appropriate regulatory approvals have been obtained.

15.5 Trial Registration

This trial meets the definition of an “applicable clinical trial” according to Section 801 of the Food and Drug Administration Amendments Act. The Sponsor affirms that it will serve as the Responsible Party and fulfill all requirements regarding trial registration, the provision of clinical trial information, and results reporting through the ClinicalTrials.gov registry data bank.

Clinical trial information will be submitted no more than 21 days after the first subject is enrolled in the trial, and results information will be submitted no later than 1 year after completion of the trial or no later than 30 days after the device is approved, licensed, or cleared by the FDA.

15.6 Records and Reports

Sponsor and investigator will maintain records related to this study for 7 years (or longer according to local requirements) after the end of this study.

Records maintained by the Sponsor will include:

- All essential correspondence related to the clinical trial
- Signed Investigator Agreement
- *Curriculum vitae* for each Investigator
- Records of device shipment and disposition (shipping receipts, material destruct records, etc.)
- Adverse event information
- Complaint documentation
- All data forms prepared and signed by the Investigators and all received source documentation and core laboratory reports
- Clinical Investigation Plan (CIP) and any amendments
- Investigators Brochure / Report of Prior Investigations
- Site monitoring reports
- Financial disclosure information

Records maintained by each Site Investigator (the investigator may delegate responsibility for record maintenance to a member of his/her study team, but remains the ultimate responsible person) will include:

- All essential correspondence related to the clinical trial
- Device use/disposition records
- Records of each subject’s case history and exposure to the device. Case histories include the CRFs and supporting data (source documentation).
- Signed Investigator Agreement
- *Curriculum vitae*
- Clinical Investigation Plan (CIP) and any amendments

The Sponsor and Site Investigators are each responsible for the preparation, review, and submission of all required reports in accordance with local laws and regulations, the requirements of the FDA and other regulatory authorities as applicable, and the requirements of local IRB/ECs.

15.7 Protocol Amendments

Any protocol amendments will be approved by the Sponsor, the Principal Investigators, the IRB/EC and any necessary regulatory body before it can be implemented. Substantive changes will be submitted to the FDA (and other regulatory authorities as applicable) for approval prior to implementation, and the FDA (and other regulatory authorities as applicable) will be notified of any changes not requiring approval in accordance with relevant guidelines.

15.8 Informed Consent

Informed consent will be obtained and documented as described in §6.4 prior to the performance of any study-specific procedures or assessments in accordance with 21 CFR Part 50, other applicable laws and regulations, and local IRB/EC requirements.

15.9 Termination of the Study

The Sponsor reserves the right to terminate the study but intends only to exercise this right for valid scientific or administrative reasons and reasons related to protection of patients. Possible reasons for early trial termination include:

- Unanticipated Adverse Device Effects (UADEs) present an unreasonable risk to patients
- Recommendation from the DSMC

If the trial is terminated early, the Sponsor will provide a written statement to the Investigators to enable notification of the IRBs/ECs. The Sponsor will also inform the FDA (and the relevant Competent Authority and/or other regulatory authorities where required). In the case of early termination of trial enrollment, follow-up visits will continue for all enrolled subjects.

The Sponsor may terminate an investigator's or site's participation in the study if there is evidence of an investigator's failure to maintain adequate clinical standards or evidence of an investigator or staff's failure to comply with the protocol. Should investigator or site participation be considered for termination, the Sponsor (or designee) will ensure appropriate follow-up for any subjects enrolled, including transferal to the supervision of an approved investigator and approval of transfer of subject oversight and follow-up by the appropriate IRB/EC. Notification of study site suspension or termination will occur no later than five (5) working days after the Sponsor makes the determination. A suspended or terminated study site may not be reinitiated without approval of the reviewing IRB/EC. The investigator should notify the IRB/EC in writing as soon as possible but no later than within 10 days if the premature termination is related to safety or compliance issues. The same procedure will be applied to the Competent Authority and other applicable regulatory authorities where required.

15.10 Patient Privacy

The Sponsor affirms and upholds the principle of patient confidentiality. Throughout this study, all data provided to SINOMED or its designee(s) will only be identified by a study-specific subject identification number. "Protected Health Information" will be maintained in compliance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and applicable local regulations.

The investigator agrees that representatives of SINOMED, its designee(s), and regulatory authorities may inspect included patients' records to verify trial data, provide the data are treated as confidential and that the subject's privacy is maintained.

16.0 References

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17.0 Appendices

17.1 Appendix A: Definitions

Adverse Device Effect (ADE)

An adverse device effect is an adverse event related to the use of a medical device. This includes:

- Any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the medical device
- Any event that is a result of a use error or intentional misuse

Anticipated Serious Adverse Device Effect (ASADE)

An anticipated serious adverse device effect is a serious adverse device effect which by its nature, incidence, severity, or outcome has been identified in the investigational plan or application (including a supplementary plan or application).

Bleeding

Defined according to the following BARC definitions[102]

Type 0: no bleeding

Type 1: bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional

Type 2: any overt, actionable sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation

Type 3

Type 3a

Over bleeding plus hemoglobin drop of 3 to <5 g/dL* (provided hemoglobin drop is related to bleed)

Any transfusion with over bleeding

Type 3b

Overt bleeding plus hemoglobin drop ≥5 g/dL* (provided hemoglobin drop is related to bleed)

Cardiac tamponade

Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid)

Bleeding requiring intravenous vasoactive agents

Type 3c

Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal)

Subcategories confirmed by autopsy or imaging or lumbar puncture

Intraocular bleed comprising vision

Type 4: CABG-related bleeding

Perioperative intracranial bleeding within 48 h

Reoperation after closure of sternotomy for the purpose of controlling bleeding

Transfusion of ≥5 U whole blood or packed red blood cells within a 48-h period (NOTE: cell saver products are not counted)

Chest tube output ≥2L within a 24-h period

Type 5: fatal bleeding

Type 5a

Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious

Type 5b

Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

NOTES:

Platelet transfusions should be recorded and reported but are not included in these definitions until further information is obtained about the relationship to outcomes. If a CABG-related bleed is not adjudicated as at least a type 3 severity event, it will be classified as not a bleeding event. If a bleeding event occurs with a clear temporal relationship to CABG (i.e., within a 48-h time frame) but does not meet type 4 severity criteria, it will be classified as not a bleeding event.

* Corrected for transfusion (1 U packed red blood cells or 1 U whole blood = 1 g/dL hemoglobin)

Braunwald classification of unstable angina

Class I: New onset of severe or accelerated angina. Patients with new onset (< 2 months in duration) exertional angina pectoris that is severe or frequent (> 3 episodes/day) or patients with chronic stable angina who develop accelerated angina (that is, angina distinctly more frequent, severe, longer in duration, or precipitated by distinctly less exertion than previously) but who have not experienced pain at rest during the preceding 2 months.

Class II: Angina at rest, subacute. Patients with one or more episodes of angina at rest during the preceding month but not within the preceding 48 hours.

	Class III: Angina at rest, acute. Patients with one or more episodes of angina at rest within the preceding 48 hours.
Canadian Cardiovascular Society (CCS) classification of stable angina	Class I: Ordinary physical activity, such as walking and climbing stairs, does not cause angina. Angina with strenuous, rapid, or prolonged exertion at work or recreation.
	Class II: Slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking up hill, walking or stair climbing after meals, in cold, in wind, or when under emotional stress or during the first few hours after awakening may cause pain. Walking more than two blocks on the level and climbing more than one flight of stairs at a normal pace and in normal conditions.
	Class III: Marked limitation of ordinary physical activity. Walking one-two blocks on a level and climbing one flight of stairs at normal pace results in angina.
	Class IV: Inability to carry on any physical activity without discomfort. Anginal syndrome may be present at rest.
Cardiac death	See “death”
Clinically-driven revascularization	A revascularization is considered clinically driven if angiography at follow-up shows a percent diameter stenosis ≥ 70% (by core lab quantitative coronary angiography assessment) OR percent diameter stenosis ≥ 50% accompanied by one of the following:[103] (1) a positive history of recurrent angina pectoris, presumably related to the target vessel; (2) objective signs of ischemia at rest (ECG changes) or during exercise test (or equivalent) presumably related to the target vessel; (3) abnormal results of any invasive functional diagnostic test (e.g., Doppler flow velocity reserve, fractional flow reserve)
Death	Classified as cardiac, vascular, or noncardiovascular according to the following ARC definitions.[69] All deaths are considered cardiac unless an unequivocal noncardiac cause can be established. Specifically, any unexpected death even in patients with coexisting potentially fatal noncardiac disease (e.g., cancer, infection) should be classified as cardiac. • Cardiac death: Any death due to proximate cardiac cause (e.g., MI, low-output failure, fatal arrhythmia), unwitnessed death and death of unknown cause, and all procedure-related deaths, including those related to concomitant treatment, will be classified as cardiac death. • Vascular death: Death caused by noncoronary vascular causes, such as cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular diseases.

	• Noncardiovascular death: Any death not covered by the above definitions, such as death caused by infection, malignancy, sepsis, pulmonary causes, accident, suicide, or trauma.
Device deficiency	Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance. NOTE: Device deficiencies include malfunction, use error, and inadequate labeling. They may or may not affect device performance or lead to an adverse event.
Device malfunction	Failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the Instructions for Use or protocol. NOTE: A device malfunction occurs when the device is used in compliance with the Instructions for Use, but does not perform as described in the Instructions for Use.
Device misuse	Any use of the investigational device by an investigator that is contradictory to the application described in the Instructions for Use will be categorized as device misuse. This is a form of Use Error.
Device success	Attainment of <30% residual stenosis of the target lesion measured by QCA using the assigned device, evaluated post-procedure
Epicardial vessel	Defined for the purposes of non-target lesion eligibility as the left anterior descending coronary artery, the left circumflex coronary artery, and the right coronary artery, each including its respective branches
Intention to Treat (ITT) Population	All subjects enrolled in the study, by assigned treatment, regardless of the treatment actually received
Lesion success	Attainment of <30% residual stenosis (post-procedure), as measured by QCA using any percutaneous method
Long-term safety and efficacy	Target lesion failure between 12 months and 5 years by landmark analysis
Major adverse cardiac events (MACE)	All-cause death, myocardial infarction, or target vessel revascularization (reported as a composite)
Mortality	See “death”
Myocardial infarction (MI)	The primary protocol definition of myocardial infarction is the modified Third Universal Definition[104] provided in the Table below, which will be adjudicated and classified by an independent CEC. In addition, the CEC will also adjudicate PCI-related MI according to several alternate thresholds of cTn (3, 10, 35, and 70 × 99th percentile URL), and all MI types (except Type 3) will be tabulated according to multiples of the 99th percentile URL of cTn as recommended by Thygesen et al.[104]

Definition of Myocardial Infarction
Criteria for acute myocardial infarction

The term acute MI should be used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia. Under these conditions any one of the following criteria meets the diagnosis for MI:

- Detection of a rise and/or fall of cardiac biomarker values (preferably cTn)* with at least one value above the 99th percentile URL and with at least one of the following:
  - Symptoms of ischemia
  - New or presumed new significant ST–T changes or new LBBB
  - Development of pathological Q waves in the ECG
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
  - Identification of an intracoronary thrombus by angiography or autopsy
- Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased.
- PCI related MI is arbitrarily defined by elevation of cTn values (>5 × 99th percentile URL) in patients with normal baseline values (≤99th percentile URL), or a rise of cTn values >20% if the baseline values are elevated and are stable or falling, within 48 hours of the procedure.* In addition, either (i) new ischemic ECG changes (e.g., ischemic ST changes or new pathological Q waves) or new LBBB, or (ii) angiographic findings consistent with a procedural complication (e.g., loss of patency of a side branch, persistent slow-flow or no-reflow, or embolization) or (iii) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.
- Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile URL.
- CABG related MI is arbitrarily defined by elevation of cardiac biomarker values (>10 × 99th percentile URL) within 48 hours of the procedure in patients with normal baseline biomarker values (≤99th percentile URL).* In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality are required.

Criteria for prior myocardial infarction

Any one of the following criteria meets the diagnosis for prior MI:

- Pathological Q waves with or without symptoms in the absence of non-ischemic causes
- Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischemic cause
- Pathological findings of a prior MI

Criteria for diagnosis of reinfarction

In patients in whom reinfarction is suspected from clinical signs or symptoms following the initial MI, an immediate measurement of cTn is recommended. A second sample should be obtained 3 to 6 hours later.

If the cTn concentration is elevated, but stable or decreasing at the time of suspected reinfarction, the diagnosis of reinfarction requires a 20% or greater increase of the cTn value in the second sample.*

If the initial cTn concentration is normal, the criteria for new acute MI apply.

Classification of Myocardial Infarction

Type 1: Spontaneous myocardial infarction

Spontaneous myocardial infarction related to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus in one or more of the coronary arteries leading to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis. The patient may have underlying severe CAD but on occasion non-obstructive or no CAD.

Type 2: Myocardial infarction secondary to an ischemic imbalance

In instances of myocardial injury with necrosis where a condition other than CAD contributes to an imbalance between myocardial oxygen supply and/or demand, e.g. coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachy-/brady-arrhythmias, anemia, respiratory failure, hypotension, and hypertension with or without LVH.

Type 3: Myocardial infarction resulting in death when biomarker values are unavailable

Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurring before blood samples could be obtained, before cardiac biomarker could rise, or in rare cases when cardiac biomarkers were not collected.

Type 4a: Myocardial infarction related to percutaneous coronary intervention (PCI)

Myocardial infarction associated with PCI is arbitrarily defined by elevation of cTn values >5 × 99th percentile URL in patients with normal baseline values (<99th percentile URL), or a rise of cTn values >20% if the baseline values are elevated and are stable or falling, within 48 hours of the procedure.* In addition, either (i) new ischemic ECG changes (e.g., ischemic ST changes or new pathological Q waves) or new LBBB, or (ii) angiographic loss of patency of a major coronary artery or a side branch or persistent slow- or no-flow or embolization, or (iii) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.

Type 4b: Myocardial infarction related to stent thrombosis

Myocardial infarction associated with stent thrombosis is detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/ or fall of cardiac biomarkers values with at least one value above the 99th percentile URL.

Type 5: Myocardial infarction related to coronary artery bypass grafting (CABG)

Myocardial infarction associated with CABG is arbitrarily defined by elevation of cardiac biomarker values >10 × 99th percentile URL within 48 hours of the procedure in patients with normal baseline biomarker values (≤99th percentile URL).* In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality are required.

*If cTn is not available, CKMB (measured by mass assay) is an acceptable alternative. The CKMB threshold for the diagnosis of PCI-related MI is >5 × 99th percentile URL in patients with normal baseline values.

CABG = coronary artery bypass grafting; CAD = coronary artery disease; CKMB = creatine kinase MB isoform; cTn = cardiac troponin; ECG = electrocardiogram; LBBB = left bundle branch block; LVH = left ventricular hypertrophy; MI = myocardial infarction; PCI = percutaneous coronary intervention; ST–T = ST-segment–T wave; URL = upper reference limit

Per Protocol (PP) population	Subjects who meet all inclusion criteria and no exclusion criteria, have provided written informed consent, and in whom an assigned study stent has been implanted
Procedure success	Lesion success (see definition above) without the occurrence of major adverse cardiac events (see definition above) during the index procedure hospital stay (maximum of 7 days). In the setting of multiple target lesions, all lesions must meet the lesion success criteria to have a patient-level procedure success.
Serious Adverse Device Effect (SADE)	A serious adverse device effect is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Serious Adverse Event (SAE)	A serious adverse event is an adverse event that: 1. Led to a death 2. Led to a serious deterioration in the health of the subject that:

a. Resulted in a life-threatening illness or injury
b. Resulted in a permanent impairment of a body structure or a body function
c. Required in-patient hospitalization or prolongation of existing hospitalization
d. Resulted in medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to body structure or a body function

Led to fetal distress, fetal death or a congenital abnormality or birth defect.

Stent thrombosis

Defined as definite, probable, or possible according to the following ARC definitions, and classified as early, late, or very late according to the timing criteria below:[103]

- Definite stent thrombosis: Confirmed by angiographic or pathological evidence:
  - Angiographic confirmation of stent thrombosis: The presence of an intracoronary thrombus that originates in the stent or in the segment 5 mm proximal or distal to the stent and presence of at least 1 of the following criteria within a 48-hour time window:
    - Acute onset of ischemic symptoms at rest
    - New ischemic ECG changes that suggest acute ischemia
    - Typical rise and fall in cardiac biomarkers (refer to definition of spontaneous MI)
    - Nonocclusive thrombus. Intracoronary thrombus is defined as a (spheric, ovoid, or irregular) noncalcified filling defect or lucency surrounded by contrast material (on 3 sides or within a coronary stenosis) seen in multiple projects, or persistence of contrast material within the lumen, or a visible embolization of intraluminal material downstream.
    - Occlusive thrombus: TIMI 0 or 1 instrastent or proximal to a stent up to the most adjacent proximal side branch or main branch (if originating from the side branch)

    NOTE: The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered a confirmed stent thrombosis (silent occlusion).
  - Pathologic confirmation of stent thrombosis: Evidence of recent thrombus within the stent determined at

autopsy or via examination of tissue retrieved following thrombectomy.

- Probable stent thrombosis: Clinical definition of probably stent thrombosis is considered to have occurred after intracoronary stenting in the following cases:
  - Any unexplained death within the first 30 days
  - Irrespective of the time after the index procedure, any MI that is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause
- Possible stent thrombosis: Clinical definition of possible stent thrombosis is considered to have occurred with any unexplained death from 30 days after intracoronary stenting until end of trial follow-up

Stent thrombosis timing:

- Early stent thrombosis: 0 to 30 days after stent implantation
- Late stent thrombosis: >30 days to 1 year after stent implantation.
- Very late stent thrombosis: >1 year after stent implantation.

NOTE: Late and very late stent thrombosis include primary as well as secondary late stent thrombosis; secondary late stent thrombosis is a stent thrombosis after a target lesion revascularization.

Target lesion failure (TLF)

The composite of cardiac death, target vessel-related myocardial infarction, and clinically-driven target lesion revascularization

Target lesion revascularization (TLR)

Any repeat percutaneous intervention of the target lesion or bypass surgery of the target vessel performed for restenosis or other complication of the target lesion. The target lesion is defined as the treated segment from 5 mm proximal to the stent and to 5 mm distal to the stent.

A revascularization is considered clinically driven if angiography at follow-up shows a percent diameter stenosis ≥ 70% (by core lab quantitative coronary angiography assessment) OR percent diameter stenosis ≥ 50% (by core lab quantitative coronary angiography assessment) accompanied by one of the following:[103]

(1) a positive history of recurrent angina pectoris, presumably related to the target vessel;

(2) objective signs of ischemia at rest (ECG changes) or during exercise test (or equivalent) presumably related to the target vessel;

(3) abnormal results of any invasive functional diagnostic test (e.g., Doppler flow velocity reserve, fractional flow reserve).

	All TLR should be prospectively classified as clinically-driven or non-clinically-driven by the investigator prior to angiography. Where independent core laboratory quantitative coronary angiography (QCA) and the investigator assessment differ with respect to whether percent diameter stenosis requirements are met, the QCA judgment shall prevail.
Target vessel-related myocardial infarction (TV-MI)	Any myocardial infarction (see definition) not clearly attributable to a non-target vessel
Target vessel failure (TVF)	The composite of cardiac death, target vessel-related myocardial infarction, and clinically-driven target vessel revascularization
Target vessel revascularization (TVR)	Any repeat percutaneous intervention or surgical bypass of any segment of the target vessel. The target vessel is defined as the entire major coronary vessel proximal and distal to the target lesion, which includes upstream and downstream branches and the target lesion itself. A revascularization is considered clinically driven if angiography at follow-up shows a percent diameter stenosis ≥ 70% (by core lab quantitative coronary angiography assessment) OR percent diameter stenosis ≥ 50% (by core lab quantitative coronary angiography assessment) accompanied by one of the following:[103] (1) a positive history of recurrent angina pectoris, presumably related to the target vessel; (2) objective signs of ischemia at rest (ECG changes) or during exercise test (or equivalent) presumably related to the target vessel; (3) abnormal results of any invasive functional diagnostic test (e.g., Doppler flow velocity reserve, fractional flow reserve). Where independent core laboratory quantitative coronary angiography (QCA) and the investigator assessment differ with respect to whether percent diameter stenosis requirements are met, the QCA judgment shall prevail.
Total Occlusion	An occlusion with no antegrade filling of contrast to the distal segment (TIMI grade 0)
Unanticipated Adverse Device Effect (UADE)	An unanticipated adverse device effect is any serious adverse effect on the health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of subjects. NOTE: An anticipated serious adverse device effect (ASADE) is a serious adverse device effect which by its nature, incidence, severity, or outcome has been identified in the investigational plan or application (including a supplementary plan or application).

Use Error	Act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user. NOTE 1: Use error includes slips, lapses and mistakes. NOTE 2: An unexpected physiological response of the patient does not itself constitute a use error.

17.2 Appendix B: Acronyms

AE	adverse event
ACS	acute coronary syndromes
ADE	adverse device effect
ADP	adenosine diphosphate
AMI	acute myocardial infarction
ARC	Academic Research Consortium
ASA	acetylsalicylic acid
ASADE	anticipated serious adverse device effect
BARC	Bleeding Academic Research Consortium
BuMA DES	BuMA Supreme biodegradable drug coated coronary stent system
CABG	coronary artery bypass graft surgery
CAD	coronary artery disease
CCS	Canadian Cardiovascular Society (grading scale of angina pectoris)
CEC	clinical events committee
CI	confidence interval
CIP	clinical investigation plan
CK	creatine kinase
CKMB	creatine kinase MB isoform
CRF	case report form
cTn	cardiac troponin
DAPT	dual antiplatelet therapy
DES	drug eluting stent
DICOM	Digital Imaging and Communications in Medicine
DP EES	durable polymer everolimus-eluting stents
DSMC	data safety monitoring committee

EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture (system)
eGFR	estimated glomerular filtration rate
F	French (catheter scale system)
FDA	U.S. Food and Drug Administration
FFR	fractional flow reserve
GCP	good clinical practices
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	informed consent form
ICH	International Conference on Harmonization
IRB	institutional review board
ISO	International Organization for Standardization
ITT	intention to treat
IV	intravenous
LAD	left anterior descending coronary artery
LAO	left anterior oblique
LBBB	left bundle branch block
LCx	left circumflex coronary artery
LVEF	left ventricular ejection fraction
MACE	major adverse cardiac events
MI	myocardial infarction
NSTEMI	non-ST-segment elevation myocardial infarction
PCI	percutaneous coronary intervention
PBMA	poly n-butyl methacrylate

PLGA	poly lactic *co*-glycolic acid
PMDA	Pharmaceuticals and Medical Devices Agency (Japan)
PP	per protocol
QCA	quantitative coronary angiography
RAO	right anterior oblique
RCA	right coronary artery
RCT	randomized controlled trial
SADE	serious adverse device effect
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
STEMI	ST-segment elevation myocardial infarction
TBD	to be determined
TIMI	Thrombolysis in Myocardial Infarction (flow grade)
TLF	target lesion failure
TLR	target lesion revascularization
TV-MI	target vessel-related myocardial infarction
TVF	target vessel failure
TVR	target vessel revascularization
UA	unstable angina
UADE	unanticipated adverse device effect
URL	upper reference limit
US	United States
XIENCE EES	Xience family of durable polymer cobalt chromium everolimus-eluting coronary stent systems

17.3 Appendix C: Angiographic Imaging Acquisition Guidelines

[redacted]