Statistical Analysis Plan

Protocol SIN-US-001

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

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1.0 INTRODUCTION

The BuMA Supreme Biodegradable Drug Coated Coronary Stent System (BuMA DES) 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.

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. The PIONEER III 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.

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in the PIONEER III Trial. This document supplements the plans outlined in the protocol; however, any significant modification to the protocol-specified analyses will also be reflected in a protocol amendment or in the final clinical study report, as appropriate. This plan is based on the study protocol version 8.0 dated March 26, 2020.

1.1 Study Objectives

The primary objective of the PIONEER III Trial 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]) by randomized comparison with commercially-available durable polymer everolimus-eluting stent systems.

1.2 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 SupremeTM 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 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.

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 (TLF) 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.

1.2.1 Trial Hypotheses

1.2.1.1 Primary Safety and Efficacy Hypothesis

The primary hypothesis is that the rate of TLF in the Intervention group is non-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 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.

1.2.1.2 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 post-procedure 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.

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.

2.0 ENDPOINTS: DEFINITIONS AND CONVENTIONS

2.1 Primary Endpoint

The primary safety and efficacy endpoint of the study is target lesion failure (TLF) 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).

All events will be adjudicated and classified by an independent Clinical Events Committee (CEC). Target-vessel myocardial infarction (TV-MI) events will be adjudicated per the modified Third Universal Definition. Details of the primary protocol definition of myocardial infarction are provided in Section 2.2.3.3.

2.2 Secondary Endpoints

2.2.1 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).

2.2.2 Secondary Efficacy Endpoints

2.2.2.1 Lesion Success

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

In-stent residual stenosis, as assessed by the Angiographic Core Laboratory, will be calculated using the following formula based on post-procedure (final) stent measurements:

In-stent Residual Stenosis = 100*(1 – mean (MIN1, MIN2)) / mean (IS1, IS2)

Where

MIN1, MIN2: In-stent minimum lumen diameter from projections 1 and 2, respectively.
IS1, IS2: Interpolated in-stent reference vessel diameter from projections 1 and 2, respectively.

2.2.2.2 Device Success

Device success is defined as attainment of <30% in-stent residual stenosis of the target lesion measured by QCA using the assigned device [evaluated post-procedure]. Lesions treated with multiple stents in which one stent is an assigned device and ≥1 is not the assigned device are considered as device failures.

This analysis is a lesion-level analysis performed in the ITT subject population. The primary analysis will include all target lesions in which implantation of the assigned device is attempted in the denominator. As a secondary analysis, the device success analysis will include all target lesions in the denominator, whether or not an attempt to implant the assigned device was made.

In addition, lesions without device success will be reported according to the following classification adapted from the 2019 EAPCI/ESC position statement (Chang et al. Defining Device Success for Percutaneous Coronary Intervention Trials: A Position Statement from the European Association of Percutaneous Cardiovascular Interventions of the European Society of Cardiology. *Eurointervention* 2019; Jaa-642 2019, doi 10.4244/EIJ-D-19-00552) [1] in a lesion-level analysis:

1) PCI was not attempted
2) No device implanted (with or without implant attempt)
3) Non-assigned device implanted without attempt to use the assigned device
4) Unsuccessful device delivery (i.e., implant attempted but no device ultimately implanted)
   a) Without crossover to non-assigned devices (i.e., attempted implant of assigned device; did not attempt to implant unassigned device)
   b) Crossover to non-assigned devices, but still unsuccessful (i.e., attempted to implant assigned device; attempted implant of unassigned device)
5) Device implanted outside the intended location
6) Non-assigned device implanted after a failed attempt to use the assigned device
7) Non-assigned device implanted after successful implantation of assigned device(s)
8) Residual stenosis above accepted thresholds (NOTE: threshold is ≥30% based on protocol definition of device success)

Reasons for absence of device success will be summarized based on the breakdown listed above and the analysis will be performed in the ITT subject population in 1) all target lesions in which implantation of the assigned device is attempted in the denominator (primary), and 2.) all target lesions (secondary).

2.2.2.3 Procedure Success

Procedure success is defined as lesion success without the occurrence of in-hospital major adverse cardiac events (MACE) [evaluated in-hospital]. MACE is a composite of all-cause death, myocardial infarction, and target vessel revascularization and will be adjudicated by an independent Clinical Events Committee (CEC). The myocardial infarction (MI) events will be adjudicated per the modified Third Universal Definition.

2.2.2.4 Clinically Driven Target Lesion Revascularization

Target lesion revascularization (TLR) is defined as 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:

(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 TLRs will be adjudicated and categorized by the CEC as clinically indicated or not clinically indicated based on the above protocol definition and will be evaluated in-hospital and at 30 days, 6 months, and 1, 2, 3, 4, and 5 years.

2.2.2.5 Clinically Driven Target Vessel Revascularization

Target vessel revascularization (TVR) is defined as 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:

(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 TVRs will be adjudicated and categorized by the CEC as clinically indicated or not clinically indicated based on the above protocol definition and will be evaluated in-hospital and at 30 days, 6 months, and 1, 2, 3, 4, and 5 years.

2.2.2.6 Target Vessel Failure

Target vessel failure (TVF) is defined as the composite of cardiac death, target vessel-related myocardial infarction (TV-MI), and clinically-driven target vessel revascularization (TVR).

All events will be adjudicated and classified by the CEC. Target-vessel myocardial infarction (TV-MI) events will be adjudicated per the modified Third Universal Definition. TVF will be evaluated in-hospital and at 30 days, 6 months, and 1, 2, 3, 4, and 5 years.

2.2.2.7 Target Lesion Failure

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). TLF will be evaluated as a secondary efficacy endpoint at the following time points: in-hospital, and at 30 days, 6 months 2, 3, 4, and 5 years.

2.2.3 Secondary Safety Endpoints

2.2.3.1 Major Adverse Cardiac Events

A major adverse cardiac event (MACE) is defined as a composite of all-cause death, myocardial infarction, and target vessel revascularization. MACE will be evaluated in-hospital and at 30 days, 6 months, and 1, 2, 3, 4, and 5 years.

All events will be adjudicated and classified by the CEC. Myocardial infarction (MI) events will be adjudicated per the modified Third Universal Definition.

2.2.3.2 Mortality

All death events will be adjudicated and classified by the CEC into the following categories (ARC-defined):

- **Cardiac:** 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 caused by non-coronary vascular causes, such as cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular diseases.
- **Non-cardiovascular:** Any death not covered by the above definitions, such as death caused by infection, malignancy, sepsis, pulmonary causes, accident, suicide, or trauma.

All death events will be reported and evaluated in-hospital and at 30 days, 6 months, and 1, 2, 3, 4, and 5 years, cumulatively and by individual categories.

2.2.3.3 Myocardial Infarction

The primary protocol definition of myocardial infarction (MI) is the modified Third Universal Definition, provided in Table 1 below, which will be adjudicated and classified by an independent CEC.

Table 1: Protocol Definition of Myocardial Infarction

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

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 described in the protocol.

2.2.3.4 Stent Thrombosis (Definite or Probable)

Stent thrombosis is 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:

- 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 thromboses include primary as well as secondary late stent thrombosis; secondary late stent thrombosis is a stent thrombosis after a target lesion revascularization.

2.2.3.5 Bleeding Complications

Bleeding is defined according to the following BARC definitions. All bleeding complications will be evaluated as components and as a composite of BARC Type 3 and 5 bleeding.

- **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:

  Overt 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

2.3 Angiographic Core Laboratory Variables

Pre-and post-procedure (final) coronary angiographic images will be analyzed by an independent Core Laboratory. Angiographic core lab variables include lesion morphology and/or QCA data as provided below:

- Pre-procedure morphology and QCA
- Final (post-procedure) morphology and QCA
- Final stent measurements
- Final stent edge measurements
- Final stent overlap/gap measurements

Pre-procedure and final QCA variables will be derived based on the following parameters from the Angiographic Core Laboratory (ACL) case report form:

Table 2: Derivation of QCA Data

	Pre-Procedure Pre-procedure QCA section of the ACL Case Report Form	In-Segment Final QCA section of the ACL Case Report Form	In-Stent Final Stent Measurements section of the ACL Case Report Form
Minimum Lumen Diameter (MLD) [mm]	Pre-procedure MLD = Mean of pre-procedure QCA MLDs from Projections 1 and 2	In-segment MLD = Mean of Final QCA MLDs from Projections 1 and 2	In-stent MLD = Mean of Min Stent from Projection 1 and Min Stent from Projection 2
Reference Vessel Diameter (RVD) [mm]	Pre-procedure RVD (mm) = Mean of pre-procedure QCA interpolated RVDs (Inter Normal) from Projections 1 and 2	In-segment RVD (mm) = Mean of Final QCA Interpolated RVDs (Inter Normal) from Projections 1 and 2	In-stent RVD (mm) = Mean of Interpolated RVDs (Inter Stent) from Projections 1 and 2
Diameter Stenosis (DS) [mm]	%DS = 100*(1 – Pre-procedure MLD / Pre-procedure RVD)	%DS = 100*(1 - In-segment MLD / In-segment RVD)	%DS = 100*(1-In-stent MLD / In-stent RVD)
Acute Gain (mm)	N/A	Post-procedure In-segment MLD – Pre-procedure MLD	Post-procedure In-stent MLD – Pre-procedure MLD

2.4 Additional Safety Endpoints

2.4.1 Adverse Events and Serious Adverse Events

2.4.1.1 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. 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.

2.4.1.2 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.

2.4.1.3 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

2.4.1.4 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.

2.4.1.5 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).

2.4.1.6 Device Deficiencies, Malfunctions, and Use Error

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.

2.4.2 Laboratory Data

Laboratory variables will be collected at Screening/Baseline visit, post-procedure/pre-discharge, at 30 days follow-up, and at 12-month follow-up visits. The testing will be performed per site standard practice and will include CBC (white blood cell count (WBC), platelet count, hemoglobin, hematocrit, and red blood cell count (RBC)) and serum creatinine. Creatinine clearance will not be collected by sites, but will be calculated by Cockcroft-Gault equation. The following additional laboratory variables may also be collected:

- Blood urea nitrogen (BUN)
- Total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides
- Electrolytes (sodium, potassium, chloride, bicarbonate).

Cardiac biomarkers (preferably troponin [cTn] I or T; if not available, then CKMB is acceptable) will be collected at screening/baseline visit and post-procedure/pre-discharge per the protocol specified guidelines.

2.4.3 Electrocardiogram

An ECG will be performed at screening/baseline visit, within 24 hours post procedure or prior to hospital discharge (whichever occurs first), and at 30-day and 12-month follow-up visits per the protocol. Any

abnormal findings and/or significant changes compared to prior time points will be recorded in the electronic case report forms.

2.4.4 Anginal Status

Anginal status (CCS classification, Braunwald classification of unstable angina, or silent ischemia) will be collected at screening/baseline, post-procedure or pre-discharge, and at 30 days, 6 months, and 1, 2, 3, 4, and 5 years.

2.4.5 Concomitant Medications

Dual antiplatelet therapy (DAPT) and anticoagulation therapy administered during the index procedure will be recorded in electronic case report forms.

Use of any antiplatelet therapy (Aspirin, P2Y12) and other medications including ACEI/ARB/Neprilysin inhibitors, beta blockers, calcium channel blockers, nitrates, statins, non-statin lipid lowering medications, warfarin, NOACs, other anti-anginal medications and diuretics will be collected at all visits.

3.0 ANALYSIS SETS

The statistical analysis for the PIONEER III Trial will be presented on the following analysis populations. Data for all subjects will be assessed to determine if subjects meet the criteria for inclusion in each analysis population prior to unblinding.

3.1 Intention to Treat (ITT) Analysis Population

The Intention to Treat (ITT) analysis population will include all randomized subjects in the treatment groups to which they are randomized, 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.

3.2 Per Protocol (PP) Analysis Population

The Per Protocol (PP) analysis population is defined as subjects enrolled in the trial, who meet all major eligibility criteria, and in whom an attempt to implant an assigned study stent has been made. For the purposes of defining the PP population, the following eligibility criteria are defined as “major eligibility criteria”:

- 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)
- 6.2.1.2.2 Target lesion(s) must be de novo or previously unstented restenotic native coronary artery lesions (no in-stent restenotic lesions permitted)
- 6.2.2.1.5 [Subject does not have] ST-segment elevation myocardial infarction (STEMI) at index presentation or within 7 days prior to randomization

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.

3.3 Modified Per Protocol (MPP) Analysis Population

The Modified Per Protocol (PP) analysis population will include all randomized subjects who receive the assigned treatment per randomization and who have no major protocol deviations. The following will be excluded from the MPP population as specified below:

- Subjects with major inclusion or exclusion criteria deviations (as defined in the PP population definition)
- Subjects whose informed consent was not obtained
- Subjects for whom the randomization assignment was not followed (e.g., subject randomized to BuMA DES but treated with DP EES by error)
- Subjects for whom an incorrect stratification was declared for randomization (e.g., incorrect reporting of a subject's diabetes status or clinical presentation in the randomization from prior to randomization)
- An unplanned staged procedure of a target lesion performed with a device other than the previously implanted device(s)

The MPP population will be used in a sensitivity analysis for the primary safety and efficacy endpoint.

3.4 As Treated (AT) Analysis Population

As Treated analysis population will include all randomized subjects as well as all non-randomized subjects treated with a study stent, classified into treatment according to the treatment actually received. The AT population will be the primary analysis population for all adverse event analyses.

4.0 GENERAL METHODOLOGY AND CONVENTIONS

Statistical analyses will be performed by the Cardiovascular Research Foundation using SAS® Software version 9.4 or higher. An independent programmer will validate all derived variables and analyses as defined in this SAP.

The primary safety and efficacy endpoint analysis will be performed after all eligible subjects have completed the 12 month follow-up assessment or reached the end of the assessment window. The secondary long-term safety and efficacy endpoint analysis will be performed after all patients have completed the 5 year follow-up assessment.

4.1 Sample Size and Controlling for Multiplicity

4.1.1 Sample Size - 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%
- No difference between treatments (the true rate of TLF in the Intervention group at 12 months = 6.5%)
- Non-inferiority margin (Δ) = 3.575%
- 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)
- $\alpha = 0.025$ (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.

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). 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%. Details and rationale for assumption with regards to the expected control event rate are provided in Protocol Section 11.3.3.1.

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. 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.

4.1.2 Sample Size - 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%
- The rate of TLF in the control group at 12 months = 6.5%
- 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.

4.1.3 Controlling for Multiplicity

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. For the non-inferiority testing of the primary endpoint, 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 formally tested if the secondary powered endpoint hypothesis is confirmed.

4.2 Interim Analyses and Summaries

No interim analyses for this study are planned.

4.3 General Methods

All data collected will be summarized overall and by treatment. Descriptive statistics of continuous variables will include mean, standard deviation, median, quartiles, range, and sample size. Differences between the treatment arms, where specified, will be summarized with the differences of the two means, 95% confidence intervals for the difference between the means, and p-values based on a t-test. The distributions within each group will be tested for normality using the Shapiro-Wilks test and if normality cannot be assumed then a Wilcoxon rank-sum test for medians will be performed. The confidence interval for the difference of two means will be calculated under the assumption of unequal variances.

For categorical variables, descriptive statistics will include count, percentage, and sample size. Categorical data will be presented as n/N (%), and percentages will be rounded and reported to a single decimal point (xx.x %). Unless otherwise noted, subjects with missing data will be excluded from the denominator. Differences between the two treatment arms, where specified, will be summarized with the difference in percentages, the asymptotic 95% confidence interval for the difference of two percentages, and a p-value based on a chi-squared test. If 20% or more of the expected cell frequencies are less than 5 then a Fisher's Exact Test will be used to test for differences in proportions.

Survival analysis techniques will be used to analyze the time-to-event variables that occur at or after 30 days of follow-up. Time to event analysis will be performed for each time point separately (i.e. up to 30 days, 6-months (180 days), 1 year (365 days), 2 years (730 days), 3 years (1095 days), 4 years (1460 days), and 5 years (1825 days)) and summarized using the Kaplan-Meier estimated event rates and number of events. The log-rank test will be used for comparing treatments. Hazard ratios and the associated two sided confidence intervals (Wald's CI) will be estimated by Cox proportional hazards model, including treatment as a covariate.

All time-to-event analyses will be performed with time defined from date of randomization to first occurrence of an event. Subjects without events will be censored at their early withdrawal date or the last known event-free time point. If this event-free time point occurs after the analysis time point, the days to event variable will be set equal to the analysis time point so that the patient will be included in the analysis (e.g. if the last data point was collected at 1 year and 2 weeks post-procedure, for the 1-year analysis, this subject will be censored at exactly 1 year (365 days)). When analyzing composite endpoints, time is measured from randomization to the first event (days).

Per protocol, patients may have multiple target lesions treated. For patient level endpoints, only one lesion per subject is required to meet the criteria for the endpoint. All clinical, procedural, and safety endpoints are summarized on a patient level, except when noted. All Angiographic Core Lab variables will be summarized on a lesion level.

4.4 Methods to Manage Missing Data

Reasonable efforts will be made to obtain complete data for all patients; however, missing observations may occur. The reasons for missing data will be reported (e.g., patient is deceased, lost to follow up, withdrew consent, missed follow-up visit, etc.).

The primary endpoint analysis of TLF will be performed using all available data. As a sensitivity analysis, a tipping point analysis will be performed to assess the impact of missing values from subjects with insufficient 12 month follow-up. This analysis will include the worst-case scenario as the most extreme case.

All secondary endpoint analyses will be performed using all available data.

5.0 ANALYSES AND SUMMARIES

5.1 Baseline and Other Summaries and Analyses

5.1.1 Study Conduct and Subject Disposition

The frequency and percentage of subjects enrolled by site will be provided as a table.

A tabulation of patient disposition will be presented overall and by treatment arm, and will include the number of subjects screened, enrolled (randomized), and discontinued, with reasons for discontinuations (e.g., subject died, withdrew consent, was lost to follow-up, etc.) as documented on the case report form. Adherence to study inclusion/exclusion criteria and protocol deviations as documented on the case report form will be descriptively tabulated. A by-subject listing will include the reference data for these tables.

Compliance to 30-day, 6-month, and 1, 2, 3, 4, and 5-year follow-up visit schedules will be summarized for all subjects in the ITT analysis population and by site.

5.1.2 Baseline Summaries

Baseline patient characteristics will be presented descriptively and will be compared between two treatment arms using the methodology described in Section 4.3. Baseline measurements consist of subject demographics, general medical history, cardiovascular disease history, angina status, pre-procedural laboratory testing including cardiac biomarkers, and concomitant medications.

5.1.3 Investigator Reported Index Prcedure, Lesion, and Device Characteristics

Site reported index procedure characteristics, procedural medications, target lesion and device characteristics as reported in the case report forms will be presented descriptively for overall subjects and by treatment arm. Categorical and continuous variables will be compared between treatment arms using the methodology described in Section 4.3.

5.1.4 Core Lab Analyses

The Angiographic Core Lab Analysis will be summarized on a lesion level based on the ITT analysis set, and presented overall and by treatment arm. All angiographic analyses will consider target lesions only.

Continuous QCA variables will be compared between treatment arms using a one-way linear mixed model that accounts for the clustering effect of multiple lesions per subject. The model includes treatment as a fixed effect and subject as a random effect. Two-sided 95% confidence interval for the estimated mean difference between the two treatment arms and p-value from the linear mixed model will be reported for all continuous QCA data.

Binary core lab parameters will be compared between the treatment arms using a generalized linear mixed model that accounts for the clustering effect of multiple lesions per subject. The model includes treatment as a fixed effect and subject as a random effect. Two-sided 95% CI for the estimated difference and p-values will be reported.

5.2 **Primary Endpoint: TLF at 12 Months**

5.2.1 **Primary 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 (non-inferiority margin = 3.575%, one-sided alpha = 0.025).

If the upper bound of the two-sided 95% confidence interval (one-sided 97.5% CI) for the risk difference (BuMA DES – DP EES) is less than the non-inferiority margin of 3.575%, then non-inferiority will have been met and a formal superiority test will be performed for the powered secondary endpoint. If superiority for the powered secondary endpoint is met, formal superiority testing will be performed for

the primary endpoint at alpha = 0.05 (two-sided) and superiority will be declared if the upper bound of the two-sided 95% confidence interval for the risk difference (BuMA DES – DP EES) is less than 0%.

For the primary analysis, only subjects who experienced a primary endpoint event within 12 months (365 days) from randomization 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.

5.2.2 Sensitivity/Robustness Analyses

A sensitivity analysis of the primary safety and efficacy endpoint will be performed on the Modified Per-Protocol (MPP) population. In addition, to support the interpretation of the primary analysis, a tipping point analysis will be performed as a sensitivity analysis. Tipping point analysis involves performing the primary analysis of TLF at 12 months repeatedly for every possible scenario involving the missing outcome data. That is, we will calculate the non-inferiority p-value from the Farrington-Manning test for all possible outcome combinations (event vs no event) for the BuMA DES and DP EES arms.

In addition to tipping point analysis, a sensitivity analysis for the primary endpoint will also be conducted according to the pre-specified alternate biomarker thresholds for PCI-related MIs (see Section 2.2.3.3 for primary MI definition). The alternate thresholds for cTn to be used in the sensitivity analyses are: 3, 10, 35, and 70 x 99^{th} percentile URL.

5.3 Secondary Endpoints

5.3.1 Secondary Powered 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. 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.

5.3.2 Secondary Efficacy Endpoints

Lesion Success will be assessed on a lesion level, performed on the ITT analysis population, and presented for overall subjects and by treatment arm. The analysis of Device Success will include all

target lesions in which the assigned device is attempted in the denominator [1]. As a secondary analysis, the device success analysis will include all target lesions in the denominator, whether or not an attempt to implant the assigned device was made.

No formal hypothesis testing will be performed. Both endpoints will be compared descriptively between the treatment arms using a generalized linear mixed model that accounts for the clustering effect of multiple lesions per subject. The model includes treatment as a fixed effect and subject as a random effect. Two sided 95% CI for the estimated difference and p-values will be reported.

Procedural success and in- hospital TVR, TLR, TVF, and TLF events will be evaluated in the ITT analysis population. No formal hypothesis testing will be performed. Descriptive statistics will include count, percentage, and sample size. Subjects with missing data will be excluded from the denominator. Differences between the two treatment arms will be summarized descriptively with the difference in percentages, the asymptotic 95% confidence interval for the difference of two percentages, and a p-value based on a chi-squared test. If 20% or more of the expected cell frequencies are less than 5 then a Fisher's Exact Test will be used to test for differences in proportions.

Survival analysis techniques, as detailed in Section 4.3, will be used to analyze the TVR, TLR, TVF, and TLF events at 30 days, 6 months, and 1, 2, 3, 4, and 5 years. Summary statistics will include Kaplan-Meier estimated event rates and number of events. The log-rank test will be used for comparing treatments. Hazard ratios and the associated two-sided confidence intervals (Wald's CI) will be estimated by Cox proportional hazards model, including treatment as a covariate.

A secondary analysis of all secondary efficacy endpoints will also be performed in the PP analysis population.

5.3.3 **Secondary Safety Endpoints**

All secondary safety endpoints will be evaluated in the ITT analysis population. No formal hypothesis testing will be performed.

Descriptive statistics for in-hospital events will include count, percentage, and sample size. Subjects with missing data will be excluded from the denominator. Differences in event rates between the two treatment arms will be summarized descriptively with the difference in percentages, the asymptotic 95% confidence interval for the difference of two percentages, and a p-value based on a chi-squared test. If 20% or more of the expected cell frequencies are less than 5 then a Fisher's Exact Test will be used to test for differences in proportions.

Survival analysis techniques, as detailed in Section 4.3, will be used to analyze all secondary safety endpoints at 30 days, 6 months, and 1, 2, 3, 4, and 5 years. Summary statistics will include Kaplan-Meier estimated event rates and number of events. The log-rank test will be used for comparing treatments. Hazard ratios and the associated two-sided confidence intervals (Wald's CI) will be estimated by Cox proportional hazards model, including treatment as a covariate.

A secondary analysis of all secondary safety endpoints will also be performed in the PP analysis population.

5.4 Subgroup Analyses

All Subgroup analyses will be performed for the primary and powered secondary endpoint 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 sex (male vs. female)

No formal hypothesis testing for subgroup analyses will be performed. For the primary endpoint, a descriptive assessment of the effect of subgroup on the primary endpoint will be carried out in the PP and ITT populations using interaction testing for subgroup by treatment effect from a logistic regression model with a 0.15 level of significance. For the powered secondary endpoint, the interaction p-value from a Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction terms as covariates will be presented for descriptive purposes only.

5.5 Multicenter Studies

The appropriateness of pooling data across sites will be assessed using a logistic regression model including a random effect for site to test whether sites have a significant variability in the primary endpoint. If it's determined that heterogeneity by site exists, 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.

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 between region and treatment effect from the logistic regression. 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.

Both tests will be performed at a 15% level of significance level.

5.6 Safety Summaries and Analyses

5.6.1 Adverse Events

For site reported adverse events, number of subjects with at least one adverse event will be summarized for all subjects in the AT population overall and by event severity, relation to procedure, and relation to device. In addition, number of subjects with SAEs and UADEs will be summarized for all subjects in the AT population. Subject data listings of all adverse events and serious adverse events, with their relationship to study device/procedure, AE onset date, outcome, and duration will be presented in the data listings.

Site reported death, myocardial infarction, revascularization, stent thrombosis and bleeding events will be summarized in the ITT population as in-hospital events, at 30-days, 6 months, and 1, 2, 3, 4, and 5 years. Descriptive statistics for in-hospital events will include count, percentage, and sample size. Subjects with missing data will be excluded from the denominator. Differences in event rates between the two treatment arms will be summarized descriptively with the difference in percentages, the asymptotic 95% confidence interval for the difference of two percentages, and a p-value based on a chi-squared test. If 20% or more of the expected cell frequencies are less than 5 then a Fisher's Exact Test will be used to test for differences in proportions.

Survival analysis techniques, as detailed in Section 4.3, will be used to analyze the site reported events at 30 days, 6 months, and 1, 2, 3, 4, and 5 years. Summary statistics will include Kaplan-Meier estimated event rates and number of events. The log-rank test will be used for comparing treatments. Hazard ratios and the associated two-sided confidence intervals (Wald's CI) will be estimated by Cox proportional hazards model, including treatment as a covariate.

5.6.2 Device Deficiencies, Malfunctions

All device deficiencies, malfunctions, use errors, and any (serious) adverse events associated with device malfunctions/deficiencies/use errors, as documented in the case report form, will be summarized descriptively by frequency (number and percentage of subjects) in the ITT Population for all subjects and by treatment arm.

5.6.3 Laboratory Data

Analysis of the clinical laboratory data will be performed on the ITT analysis population and summarized descriptively for each visit for all subjects and by treatment arm.

Cardiac biomarkers Troponin (I or T) or CK-MB will be collected at baseline/pre-procedure and post-procedure/discharge. If serial biomarker measurements are taken at a time point, the peak (i.e., the highest) biomarker value will be included in the analysis for that time point.

For cardiac biomarkers, the frequency and percentage of subjects falling into each of the following categories will be presented separately for pre-procedure/baseline and post-procedure/pre-discharge visits:

For CK-MB:

≤ULN, >1 X ULN, ≥ 1-3ULN, ≥ 3 x ULN, ≥ 3-5ULN, ≥ 5 x ULN, ≥5-10ULN, ≥ 10 x ULN

For Troponin (I or T):

≤ULN, >1 X ULN, ≥ 1-3ULN, ≥ 3 x ULN, ≥ 3-5ULN, ≥ 5 x ULN, ≥5-10ULN, ≥ 10 x ULN, ≥ 10-35 ULN, ≥ 35 ULN, ≥35-70XULN, ≥70ULN

5.6.4 Electrocardiogram

Abnormal ECG findings and/or significant ECG changes compared to prior time points will be summarized descriptively by frequency (number and percentage of subjects) in the ITT Population for all subjects and by treatment arm.

5.6.5 Anginal Status

Anginal status (CCS classification, Braunwald classification of unstable angina, or silent ischemia) will be collected at screening/baseline, post-procedure or pre-discharge, and at 30 days, 6 months, and 1, 2, 3, 4, and 5 years and summarized descriptively by frequency (number and percentage of subjects) in the ITT Population for all subjects and by treatment arm.

5.6.6 Concomitant Medications

Concomitant medication use, including compliance to DAPT, will be summarized by frequency (number and percentage of subjects) at each visit for all subjects and by treatment arm based on the ITT analysis population. In addition to concomitant medication use, antiplatelet and anti-coagulant medications administered during baseline procedure will be presented for the procedure visit.

6.0 REFERENCES

1. Chang CC, Kogame N, Onuma Y, et al., Defining Device Success for Percutaneous Coronary Intervention Trials; A Position Statement from the European Association of Percutaneous Cardiovascular Interventions of the European Socieaty of Cardiology. EuroIntervention 2020; 15:1190-1198.

7.0 APPENDICES

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8.0 VERSION HISTORY

This Statistical Analysis Plan (SAP) for study SIN-US-001 is based on the protocol version 8.0.

Table 3 Summary of Major Changes in SAP Amendments

SAP Version	Change	Rationale
1	Not Applicable	Not Applicable