PIONEER III: 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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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...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Coronary artery disorders
Study type	Interventional

Summary

ID

NL-OMON54571

Source
ToetsingOnline

Brief title
PIONEER III Trial.

Condition

- Coronary artery disorders
- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
Coronary artery disease (CAD), heart failure.

Research involving
Human

Sponsors and support

Primary sponsor: Sino Medical Sciences Technology, Inc (SINOMED)
Source(s) of monetary or material Support: Sponsor - SINOMED

Intervention

Keyword: Biodegradable, Coronary, Drug-coated, Stent

Outcome measures

Primary outcome

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 outcome

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]

Study description

Background summary

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 secondgeneration
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.

Study objective

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]) 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 <=3.50 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 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.

Intervention

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).

Study burden and risks

Refer to Section 9.0 of the PIONEER III Trial Clinical Investigation Plan v4.0 and Section 6.0 of the ICF for full details of the risk for human subjects.

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.

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.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

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 <=3.50 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 m2 (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)

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Single blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	18-07-2018
Enrollment:	220
Type:	Actual

Medical products/devices used

Generic name:	BuMa Supreme Biodegradable Drug Coated Coronary Stent System
Registration:	No

Ethics review

Approved WMO

Date:	21-02-2018
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United

	(Nieuwegein)
Approved WMO Date:	23-07-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	22-10-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	05-12-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	08-06-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	22-12-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	12-04-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	25-04-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
ClinicalTrials.gov	NCT03168776
CCMO	NL63692.101.17