Rationale and Design of the PARTHENOPE Trial: A Two-by-Two Factorial Comparison of Polymer-Free vs. Biodegradable-Polymer Drug-Eluting Stents and Personalized vs. Standard Duration of Dual Antiplatelet Therapy in All-Comers Undergoing PCI

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Abstract

Background: Over the past few decades, percutaneous coronary intervention (PCI) has undergone significant advancements as a result of the combination of device-based and drug-based therapies. These iterations have led to the development of polymer-free drug-eluting stents. However, there is a scarcity of data regarding their clinical performance. Furthermore, while various risk scores have been proposed to determine the optimal duration of dual antiplatelet therapy (DAPT), none of them have undergone prospective validation within the context of randomized trials.

Design: The PARTHENOPE trial is a phase IV, prospective, randomized, multicenter, investigator-initiated, assessor-blind study being conducted at 13 centers in Italy (NCT04135989). It includes 2,107 all-comers patients with minimal exclusion criteria, randomly assigned in a 2-by-2 design to receive either the Cre8 amphilimus-eluting stent or the SYNERGY everolimus-eluting stent, along with either a personalized or standard duration of DAPT. Personalized DAPT duration is determined by the DAPT score, which accounts for both bleeding and ischemic risks. Patients with a DAPT score <2 (indicating higher bleeding than ischemic risk) receive DAPT for 3 or 6 months for chronic or acute coronary syndrome, respectively, while patients with a DAPT score ≥2 (indicating higher ischemic than bleeding risk) receive DAPT for 24 months. Patients in the standard DAPT group receive DAPT for 12 months. The trial aims to establish the non-inferiority between stents with respect to a device-oriented composite endpoint of cardiovascular death, target-vessel myocardial infarction, or clinically-driven target-lesion revascularization at 12 months after PCI. Additionally, the trial aims to demonstrate the superiority of personalized DAPT compared to a standard approach with respect to a net clinical composite of all-cause death, any myocardial infarction, stroke, urgent target-vessel revascularization, or type 2 to 5 bleeding according to the Bleeding Academic Research Consortium criteria at 24-months after PCI.

Summary: The PARTHENOPE trial is the largest randomized trial investigating the efficacy and safety of a polymer-free DES with a reservoir technology for drug-release and the first trial evaluating a personalized duration of DAPT based on the DAPT score. The study results will provide novel insights into the optimizing the use of drug-eluting stents and DAPT in patients undergoing PCI.

Introduction

Percutaneous coronary intervention (PCI) has undergone significant advancements in recent years, becoming the most commonly used treatment for coronary artery disease.(1,2) The advancements in stent technology and antithrombotic therapy have broadened the application of PCI to a wider range of patients and lesions.(3,4) Newer drug-eluting stents (DES) release sirolimus or its analogues from a metallic platform based on biocompatible polymer or polymer-free elution technologies. Despite their potential to overcome polymer-related issues, polymer-free DES have shown conflicting results in terms of efficacy, with some evidence suggesting lower antirestenotic efficacy compared to other new-generation DES.(5–9) Regarding the antiplatelet therapy, the use of long-term dual antiplatelet therapy (DAPT) has demonstrated improved protection against ischemic events, but this benefit comes at the expense of an increased risk of bleeding.(10,11) Considering that both ischemic and bleeding events have similar negative impacts on patient outcomes(12–15), it is important to identify which patients may benefit most from prolonged DAPT and which may be harmed by it. Despite the development of several risk scores to guide DAPT duration in PCI patients, none of them have undergone prospective validation through randomized studies.(16–18)

To address these uncertainties, we have designed a 2-by-2 randomized trial aiming to compare the clinical performance of polymer-free DES vs. biodegradable-polymer DES at 12 months. Additionally, we aim to evaluate whether a personalized DAPT duration (3, 6 or 24 months), based on a risk score, is superior to a standard duration of 12-months DAPT at 24 months of follow-up. The purpose of this study is to provide a better understanding of the relative benefits and risks of these treatments to inform clinical decision-making after PCI.

Methods

Study design and population

The PARTHENOPE trial (comparisons of a Personalized vs. stAndard duRation of dual antiplatelet THErapy and New-generation pOlymer-free vs. biodegradable-Polymer dEs; ClinicalTrials.gov Identifier: NCT04135989) is a phase IV, prospective, randomized, multicenter, investigator-initiated, assessor-blind trial being conducted at 13 centers in Italy. Patients undergoing PCI are randomized in a 2-by-2 design to receive either the Cre8 amphilimus-eluting stent (AES; Alvimedica, Instanbul, Turkey) or the SYNERGY everolimus-eluting stent (EES; Boston Scientific Corporation, Marlborough, MA, USA) and to receive either a personalized or standard DAPT duration (**Figure 1**). The DAPT score is used to personalize the duration of DAPT. The PARTHENOPE trial has

an all-comers design, with minimal exclusion criteria to better reflect clinical practice (**Table 1**). The main exclusion criterion is the indication to oral anticoagulant therapy known prior to PCI.

Randomization and follow-up

After undergoing diagnostic coronary angiography and meeting all general and angiographic inclusion and exclusion criteria, subjects in whom the first target-lesion is successfully crossed with a coronary guidewire are randomly assigned to receive either the Cre8 AES or the SYNERGY EES, along with either a personalized or standard DAPT regimen. Randomization is performed using a computer-generated sequence stratified by center, with a block size of either 4 or 8. The stratification by center is implemented to ensure that the treatment groups are balanced across centers, while the block design with variable block size aims to reduce the predictability and enhance allocation concealment. The sequence of block sizes is also randomly generated to further enforce concealment. The randomization scheme follows a 2-by-2 design, with each subject having an equal probability of being assigned to one of the four treatment combinations. A written informed consent is required for all patients. Patients can be consented before invasive coronary angiography is performed until the target vessel has been wired. Patients can also provide an initial oral consent and then sign a written informed consent, which is however required for all patients within 72 hours. The aim of using an initial oral consent with a subsequent standard written informed consent is to enhance the recruitment of an all-comer population, potentially offering a more comprehensive representation of real-world clinical practice. After hospital discharge, clinical follow-up is performed by office visit (preferred, particularly in case of DAPT discontinuation) or telephone visit at 3, 6, 12, and 24 months after PCI.

DES comparison

In the experimental DES group, patients undergo PCI with the Cre8 AES, a thin-strut (80 μm), cobalt-chromium stent with a polymer-free design and a proprietary reservoir technology. The stent's outer surface has reservoirs that control the release of the Amphilimus formulation, which is based on sirolimus and formulated with a non-polymeric mixture of long-chain fatty acid as a carrier.(19) The Cre8 AES also has an ultra-thin (<3 μm) and high-density carbon film that enhances hemocompatibility and causes minimal platelet activation and endothelialization.(20) The reservoirs on the stent modulate the release kinetics, resulting in a peak drug tissue concentration in the first few days after implantation, 50% drug elution after approximately 18 days, 65-70% elution within 30 days, and complete drug elution within 90 days.(19) In the control DES group, patients undergo

PCI with the SYNERGY EES, a thin-strut (74-81 μm) platinum chromium metal alloy stent with an abluminal PLGA (Poly-lactic co-glycolic acid) polymer that elutes everolimus (100 μg/cm^2). The drug release kinetics of the SYNERGY EES are similar to those of the Cre8 AES, with complete release of everolimus occurring by 90 days and biodegradation of the PLGA completing shortly thereafter.(21) The SYNERGY platform is based on the PROMUS Premier platform, but with several differences, including the use of an ultrathin (4 μm) and lighter (200 μg load per 16 mm of stent) bioresorbable PLGA polymer with the coating limited to the abluminal strut surface and thinner stent struts. Additionally, the end rings of the SYNERGY EES are reinforced with four connectors instead of two throughout the body of the stent to prevent longitudinal compression.(3) The safety and efficacy of the SYNERGY EES has been proven across many different patient populations.(22–24) The DES assigned in a randomized manner is used for both index and staged procedures. It is recommended that all staged procedures be completed within a period of two months, though a shorter timeframe (within the same index hospitalization) is preferable. If the assigned study stent is unable to be implanted, it is permitted to switch to another new-generation DES, but crossover is not allowed.

DAPT comparison

In the experimental arm of the study, a personalized duration of DAPT is guided by the DAPT score, which ranges from -2 to 10. The score is calculated by assigning points to patient-related (0 for age <65 years, -1 for age ≥65 and <75 years, -2 for age ≥75 years, 1 for diabetes mellitus, 1 for current smokers, 1 for previous PCI or prior myocardial infarction, 2 for history of congestive heart failure or left ventricular ejection fraction <30%), and procedure-related characteristics (1 for acute myocardial infarction at presentation, 2 for PCI of saphenous vein graft, 1 for implantation of paclitaxel-eluting stent, 1 for stent diameter less than 3 mm). The score was developed by considering two separate models that predict the reduction in ischemic events and the increase in bleeding events with extended DAPT duration. Variables associated with both bleeding and ischemia, such as peripheral artery disease, hypertension, and chronic kidney disease, were excluded from the two models. In general, a low DAPT score (<2) indicates that the risk of bleeding outweighs the benefits of DAPT in terms of preventing ischemic events, whereas a high DAPT score (≥2) indicates that the benefits of DAPT outweigh the bleeding risks. The DAPT score is prospectively collected in all patients, including those randomized to standard DAPT, and is calculated during the hospital stay and before discharge in all cases. In the arm of personalized DAPT duration, patients with a high DAPT score (≥2) receive DAPT for 24 months, while those with a low DAPT score (<2) receive DAPT for 3 or 6 months, followed by aspirin monotherapy until 24 months in the case of

chronic or acute coronary syndrome, respectively. Patients randomized to standard DAPT receive a duration of DAPT for 12 months regardless of their clinical presentation and score. A low dose of aspirin (75 to 162 mg daily) is administered throughout the course of the study. The choice of the oral P2Y12 inhibitor (clopidogrel, prasugrel, or ticagrelor), as well as pretreatment with these drugs, is left to the discretion of the treating physicians. In general, clopidogrel (75 mg daily) is preferred in patients with chronic coronary syndrome or after 12 months of PCI, unless a low-dose of ticagrelor is indicated. Ticagrelor (90 mg twice daily) or prasugrel (10 mg daily, or 5 mg daily in patients weighing less than 60 Kg or who are over 75 years old) are recommended in patients with acute coronary syndrome, while a low-dose of ticagrelor (60 mg twice daily) is recommended in patients with acute coronary syndrome after 12 months in the case of randomization to 24-month DAPT. Switching between oral $P2Y_{12}$ receptor inhibitors should be carried out in accordance with recommendations from an international expert consensus.

Endpoints

The trial has two co-primary endpoints, as outlined in **Table 2**. The first co-primary endpoint is a device-oriented composite endpoint (DOCE), which is defined as the composite of cardiovascular death, myocardial infarction not clearly attributed to a non-target vessel, or clinically-driven target-lesion revascularization. This endpoint will be used to compare the Cre8 AES and the SYNERGY EES and is recommended as composite endpoint for device trials by the Academic Research Consortium-2 consensus document.(25) The second co-primary endpoint is a net adverse clinical endpoint (NACE), which is defined as the composite of all-cause death, any myocardial infarction, stroke, urgent target-vessel revascularization, or type 2 to 5 bleeding according to the Bleeding Academic Research Consortium (BARC) criteria. This endpoint will be used to compare personalized and standard DAPT duration. The definitions of the primary and secondary endpoints are provided in the **Appendix**.

Statistical considerations and sample size

In this trial, all patients who undergo randomization, representing the full analysis population, will be included in the primary and secondary analyses of clinical outcomes in the study arm to which they were originally allocated, according to the intention-to-treat (ITT) principle. In addition, per-protocol analyses will be performed as sensitivity analyses. Continuous variables will be presented as means ± standard deviations (SD) or median and interquartile range (IQR) as appropriate and compared using Student's t-test or Wilcoxon-Mann-Whitney

test as appropriate. Categorical variables will be presented as frequencies (percentage) and compared using the chi-squared test or Fisher's exact test as appropriate. The cumulative event rates for the primary and secondary endpoints will be represented using the Kaplan-Meier method. Hazard ratios (HRs) and 95% confidence intervals (CI) will be calculated using Cox-regression analysis. P-values of the secondary endpoints will be interpreted using the Benjamini-Hochberg method.

Landmark analyses will be conducted using three pre-specified points at 3, 6, and 12 months, with HR calculated separately for each of the periods. For each type of event, patients will be censored at the time of the first event. For example, a patient experiencing an event contributing to the primary composite endpoint during the first 12 months will be censored at the time of the event and excluded from the analysis after the 12-month landmark point. An interaction test will be performed to the treatment effect of the randomized comparison between the time periods (correcting for random patient ID effects).

For the stent comparison, the trial will test the non-inferiority of the Cre8 AES compared to the SYNERGY EES at 12 months. With an assumed event rate of 8% for DOCE in the control group, a total sample size of 2,024 patients (1,012 patients per arm) will provide 80% power to detect non-inferiority of the Cre8 AES compared to the SYNERGY EES, on a risk difference scale of 3%, which corresponds to a risk ratio scale of 1.375 at a one-sided alpha (α) of 0.05. For the duration of DAPT comparison, the trial will test the superiority of a personalized DAPT duration compared to standard DAPT duration at 24 months. With an assumed event rate of 13.0% for NACE in the reference DAPT arm at 24 months, the total sample size of 2,022 patients will provide 80% power to detect a risk ratio of 0.70, corresponding to a 30% relative risk reduction of the experimental DAPT regimen compared to the reference DAPT regimen, at a two-sided α of 0.05. Based on an assumed attrition rate of 4%, the total sample size is driven by the stent comparison and is estimated to be 2,106 patients (1,053 per arm). The rates of primary endpoints are based on Kaplan-Meier estimates calculated from the date of randomization to 365 days after randomization for DOCE and from the date of randomization to 730 days after randomization for NACE. The assumed event rate for DOCE in the control arm is in line with the rate observed in the LEADERS (26) and RESOLUTE trials (27) that had a similar, all-comers design. The assumed event rate for NACE is consistent with the rate reported in the PRODIGY trial,(28) as well as with the control arm of the GLASSY substudy, which is similar to the control arm of the PARTHENOPE trial in terms of DAPT regimen (DAPT for 12 months followed by aspirin monotherapy) and length of follow-up (2 years).(29)

Subgroup analyses

Subgroup analyses of the primary and secondary endpoints will be conducted in the intention-to-treat population. The following pre-specified subgroups will be analyzed: age (≥65 years vs. <65 years and ≥75 years vs. <75 years), sex (male vs. female), diabetes, clinical presentation (acute vs. chronic coronary syndrome and ST-segment elevation myocardial infarction vs. non-ST-elevation acute coronary syndrome), high-bleeding risk status, DAPT score (high vs. low), complexity of PCI, prior myocardial infarction, chronic kidney disease, and peripheral artery disease.

Current study status

The PARTHENOPE trial is an ongoing clinical study that enrolled the first patient in January 2020 and the last patient in June 2022, for a total of 2,107 participants. The primary outcomes of the trial will be analyzed after the completion of the 12-months and 24-months follow-up periods, with the results of the comparison between the Cre8 AES and SYNERGY EES expected in the fall of 2023 and the results of the comparison between personalized and standard DAPT duration expected in the summer of 2024.

Funding and Study Management

PARTHENOPE is sponsored by the Department of Advanced Biomedical Sciences at the University of Naples “Federico II”. No extramural funding was used to support this work. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.
The study data are managed using REDCap electronic data capture, which is hosted at the University of Naples “Federico II”. The responsibility for reporting the results, drafting, and editing this and subsequent manuscripts lies with the steering committee members. All primary and secondary outcomes after randomization are adjudicated by an independent clinical events committee (CEC), which remains blinded to treatment assignment. Additionally, an independent data and safety monitoring board (DSMB) monitors patient safety and has access to unblinded data.

The Clinical Research Unit at the University of Naples 'Federico II' oversees site management, monitoring, and data cleaning. Central monitoring and on-site visits are conducted for data monitoring on all participants. The study adheres to the ethical principles outlined in the Declaration of Helsinki, the specifications of the International Conference of Harmonization, and the guidelines of Good Clinical Practice. Furthermore, the study has received approval from the ethics committee at each site.

Summary

The PARTHENOPE trial is a randomized, all-comers study designed to evaluate the efficacy and safety of two new-generation DES and two different durations of DAPT in patients undergoing PCI. Although there is a higher risk of failing to demonstrate the non-inferiority hypothesis, the sample size for testing the non-inferiority between the two devices is based on a power assumption of 80%, which reduces the required sample size by approximately 25% in comparison to a 90% power,(30) but facilitated trial feasibility by enabling successful enrollment and completion of the trial. To date, there have been few randomized trials on the Cre8 AES; these have been limited to the inclusion of diabetic patients or have had a smaller sample size (n=1,502) and compared the Cre8 AES to a permanent polymer DES.(31,32) Moreover, the Cre8 AES yielded similar outcomes compared with early-generation paclitaxel-eluting stents at 5-year follow-up requiring therefore additional clinical investigation.(33) In this context, the PARTHENOPE trial will be the largest study to assess the Cre8 AES in an all-comers setting. The SYNERGY EES, a biodegradable polymer DES with a shorter biodegradation time following drug elution, will serve as the reference arm for comparison with the Cre8 AES. After its original development in a population predominantly treated with clopidogrel, the DAPT score has undergone further evaluation in retrospective studies or has been retrospectively applied in prospective studies with inconsistent results.(34–38) The PARTHENOPE trial will prospectively evaluate the use of the DAPT score as a tool to personalize the duration of DAPT after PCI, considering the contemporary use of oral P2Y12 inhibitors as the background therapy. This trial will also be the first to apply the DAPT score around the time of PCI, as opposed to the original study that implemented its use at 12 months after PCI in patients not sustaining major bleeding or ischemic events. The feasibility of early implementation of the DAPT score at 1 month after PCI has been previously reported in a post-hoc analysis of a randomized study,(34) and based on those findings, this trial will test this hypothesis prospectively.

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Figure legend

Figure 1. Trial design of the PARTHENOPE trial. DAPT: dual antiplatelet therapy. PCI: percutaneous coronary intervention.

Table 1. Inclusion and exclusion criteria.

Inclusion criteria
1. Age ≥18 years
2. Clinical evidence of coronary artery disease requiring PCI with DES implantation
3. Any coronary lesion sized 2.25–4.5 mm by visual estimation
Exclusion criteria
1. Inability to provide informed consent
2. Active bleeding requiring medical attention (BARC ≥2)
3. Indication to oral anticoagulant therapy
4. Planned surgery within 3 months
5. Known hypersensitivity or allergy to aspirin or any P2Y12 receptor inhibitor (clopidogrel, prasugrel, ticagrelor), heparin, contrast agent, or any DES-components
6. Previous treatment with bioresorbable vascular scaffolds
7. Participation in another study that has not reached the primary endpoint
8. A life expectancy of less than 24 months
9. Female of childbearing potential
10. Under judicial protection, tutorship, or curatorship

BARC: bleeding academic research consortium. DES: drug-eluting stent. PCI: percutaneous coronary intervention.

Table 2. Study endpoints.

Primary endpoints

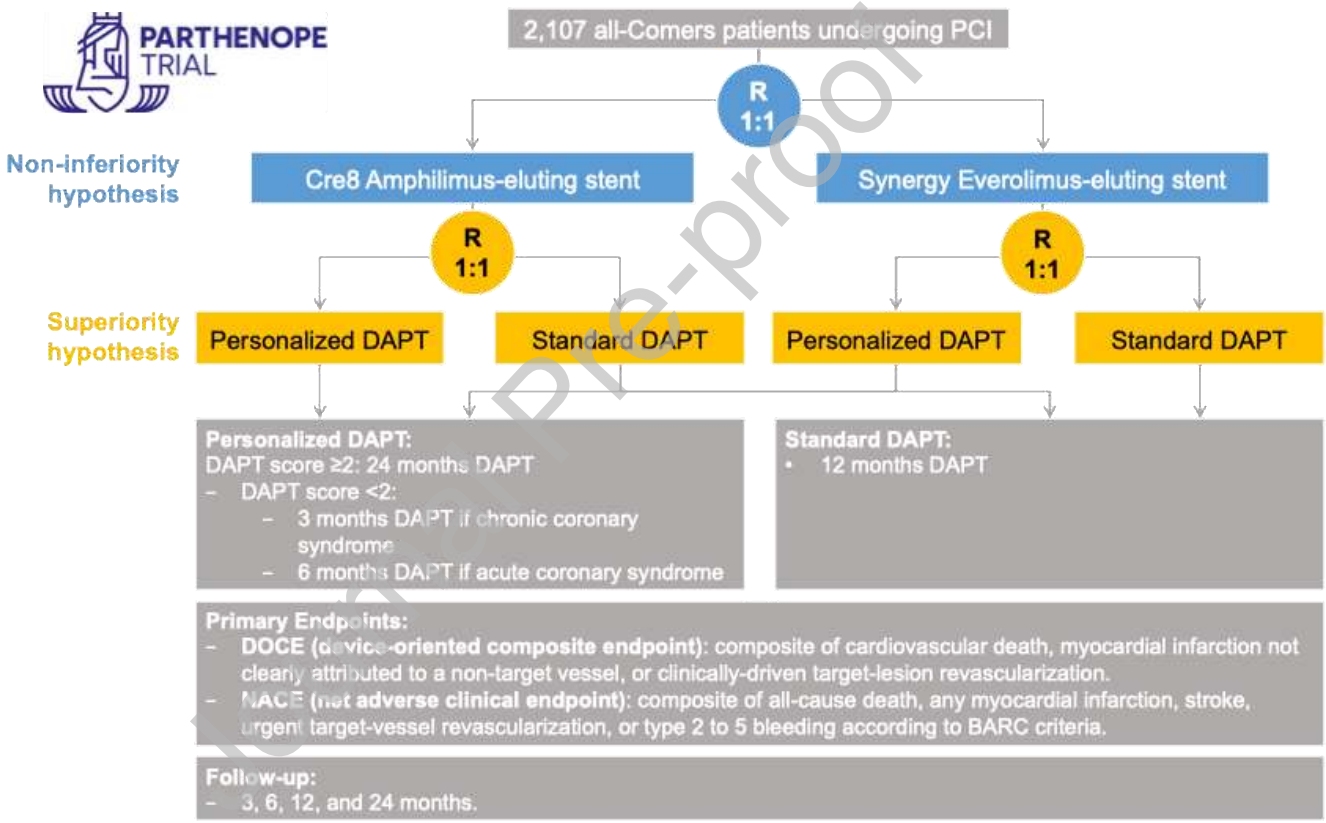
- DOCE* (device-oriented composite endpoint): composite of cardiovascular death, myocardial infarction not clearly attributed to a non-target vessel, or clinically-driven target-lesion revascularization
- NACE† (net adverse clinical endpoint): composite of all-cause death, any myocardial infarction, stroke, urgent target-vessel revascularization, or type 2 to 5 bleeding according to BARC criteria.

Secondary endpoints

- Death according to ARC-2 definition:
  - Cardiovascular death
  - Non-cardiovascular death
  - Undetermined cause of death
- Myocardial infarction according to the 4th UDMI‡
- Periprocedural myocardial infarction additionally adjudicated according to the SCAI and ARC-2 criteria
- Stroke (all, ischemic, and hemorrhagic)
- Transient ischemic attack
- Stent thrombosis according to ARC-2 criteria:
  - Definite stent thrombosis
  - Probable stent thrombosis
- Repeat revascularization:
  - Urgent revascularization
  - Target-lesion revascularization
  - Target-vessel revascularization
  - Target-vessel, non-target-lesion revascularization
- Bleeding:
  - BARC criteria (primary bleeding definition)
  - TIMI criteria
  - GUSTO criteria
- Peripheral artery revascularization:
  - Acute limb ischemia
  - Major amputation of vascular etiology
  - Urgent peripheral revascularization
  - Major adverse limb events
- Composite of all-cause death, myocardial infarction, or stroke
- Composite of cardiovascular death, myocardial infarction, or urgent target-lesion revascularization

All primary and secondary endpoints are CEC-adjudicated. BARC: bleeding academic research consortium. CEC: clinical events committee. GUSTO: Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries. SCAI: Society for Cardiovascular Angiography and Interventions. TIMI: Thrombolysis In Myocardial Infarction. UDMI: universal definition of myocardial infarction. *Co-Primary endpoint for the comparison between the amphilimus-eluting stent and everolimus-eluting stent with primary assessment at 12 months follow-up. †Co-Primary endpoint for the comparison between a personalized and standard duration of dual antiplatelet therapy with primary assessment at 24 months follow-up. ‡Type 4a myocardial infarction according to the UDMI is the primary study definition for periprocedural myocardial infarction.

Figure 1


PARTHENOPE TRIAL
2,107 all-Comers patients undergoing PCI
R 1:1
Non-inferiority hypothesis
Cre8 Amphilimus-eluting stent
Synergy Everolimus-eluting stent
R 1:1
R 1:1
Superiority hypothesis
Personalized DAPT
Standard DAPT
Personalized DAPT
Standard DAPT
Personalized DAPT:
DAPT score ≥2: 24 months DAPT
– DAPT score <2:
– 3 months DAPT if chronic coronary syndrome
– 6 months DAPT if acute coronary syndrome
Standard DAPT:
• 12 months DAPT
Primary Endpoints:
– DOCE (device-oriented composite endpoint): composite of cardiovascular death, myocardial infarction not clearly attributed to a non-target vessel, or clinically-driven target-lesion revascularization.
– NACE (net adverse clinical endpoint): composite of all-cause death, any myocardial infarction, stroke, urgent target-vessel revascularization, or type 2 to 5 bleeding according to BARC criteria.
Follow-up:
– 3, 6, 12, and 24 months.