Statistical Analysis Plan

A Post-Approval Study of the PROMUS PREMIER™ Everolimus-Eluting Platinum Chromium Coronary Stent System in China

PROMUS PREMIER™ China Post-Approval Study

Study Reference # S2384

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1 PROTOCOL SUMMARY

Boston Scientific Corporation (BSC) obtained marketing approval for the PROMUS PREMIER™ Everolimus-Eluting Platinum Chromium Coronary Stent System (PROMUS PREMIER™ Stent System) in China from the China Food and Drug Administration (CFDA) on Feb 10th, 2015. The PROMUS PREMIER™ Stent System is indicated for improving coronary luminal diameter in patients with symptomatic ischemic heart disease due to discrete de novo native coronary artery lesions.

This prospective, open-label, multi-center study is designed to provide post-market surveillance information on the PROMUS PREMIER Stent System.

1.1 Study design

A prospective, open-label, multi-center study designed to observe clinical outcomes in subjects receiving the Promus PREMIER™ Stent System.

1.2 Study objective

To compile real-world clinical outcome data for the Promus PREMIER™ Everolimus-Eluting Platinum Chromium Coronary Stent System (Promus PREMIER™ Stent System) in routine clinical practice in China.

1.3 Number of sites and patients and enrollment

The study will enroll at least 2000 subjects at up to 25 investigational sites in China. Each site will be allowed to enroll up to a maximum of 300 subjects.

1.4 Description of study population

The subjects who are candidates for coronary artery stenting, signed the informed consent form and eligible to receive a Promus PREMIER™ Stent System will be evaluated for enrollment in this study

1.5 Description of device(s) including model numbers used in the study

The Promus PREMIER™ Monorail Everolimus-Eluting Platinum Chromium Coronary Stent System (Promus PREMIER™ Stent System) is indicated for improving coronary luminal diameter in patients with symptomatic ischemic heart disease due to discrete de novo native coronary artery lesions. The characteristics of the Promus PREMIER™ Stent System are described in the table below:

Characteristic	Promus PREMIER Monorail Stent Delivery System
Available Stent Lengths (mm)	8, 12, 16, 20, 24, 28, 32, 38*
Available Stent Diameters (mm)	2.25*, 2.50, 2.75, 3.00, 3.50, 4.00
Stent Material	Platinum Chromium Alloy (PtCr)
Drug Product	A conformal coating of a polymer carrier loaded with 100 µg/mm^2 everolimus applied to the stent with a maximum nominal drug content of 243.0 µg on the largest stent (4.00 x 38 mm)
Delivery System Effective Length	144 cm
Delivery System Ports	Single access port to inflation lumen. Guidewire exit port is located approximately 26 cm from tip. Designed for guidewire ≤0.014 inches (0.36 mm)
Average stent length change at nominal diameter	2.25-4.00 mm; 0.1-1.5 mm
Stent Delivery Balloon	A balloon, with two radiopaque balloon markers, nominally placed 0.4 mm (0.016 inches) beyond the stent at each end.
Balloon Inflation Pressure	Nominal Inflation Pressure: 11 atm -1117 kPa Rated Burst Pressure: 18 atm-1827 kPa for stent diameters 2.25-2.75 (mm) and 16 atm-1620 kPa for stent diameters 3.00-4.00 (mm) diameters
Guide Catheter Inner Diameter	≥0.056 inches (1.42 mm)
Catheter Shaft Outer Diameter	2.1F (0.70 mm) proximal and 2.7F (≤0.95 mm) distal.
Stent Strut Thickness (including coating)	2.25-3.50 mm: 0.093 mm, 4.00 mm: 0.098 mm

*38 mm length is not available in 2.25 mm diameter sizes.

1.6 Follow-up Schedule:

Subject follow up will occur via telephone contact or clinic visit at 30 days, 6 months, 12 months and then annually through 5 years post stent implant, for all enrolled subjects. Enrolled subjects with a Promus PREMIER™ Stent implant failure will be followed through hospital discharge following the initial attempted index procedure. The overall study duration is approximately 6-years.

1.7 Recommended Antiplatelet Therapy

Based on the American College of Cardiology (ACC)/American Heart Association (AHA)/Society for Cardiovascular Angiography and Interventions (SCAI) guidelines and supported by the European Society of Cardiology (ESC) guidelines, dual antiplatelet therapy with aspirin and a clopidogrel is prescribed as follows to reduce the risk of thrombosis.

i. Aspirin

- Subjects must be treated with aspirin indefinitely after the index procedure.

ii. Thienopyridine

- For subjects who have been taking clopidogrel for ≥72 hours at the time of the index procedure, a loading dose is not required.
- For subjects who have not been taking clopidogrel for ≥72 hours at the time of the index procedure, a loading dose is required. It is recommended that the loading dose be administered prior to the index procedure. However, in all cases, the loading dose is required to be administered not more than 2 hours after the index procedure.

The following loading doses are recommended:

Clopidogrel: A peri-procedural loading dose of 600 mg is recommended.

- Subjects must be treated with clopidogrel for at least 6 months following the index procedure. In subjects not at high risk of bleeding, clopidogrel treatment should continue for at least 12 months following the index procedure.

1.8 Key Inclusion and Exclusion criteria

i. Inclusion criteria

- Subject must be at least 18 years of age
- Subject understands and provides written informed consent
- Subject who is clinically indicated and will have an attempt of at least one Promus PREMIER™ Stent
- Subject who is clinically indicated and was implanted with at least one Promus PREMIER™ Stent
- Subject is willing to comply with all protocol-required follow-up evaluation

ii. Exclusion criteria

- Exclusion criteria are not required in the PE PREMIER™ China Post-Approval Study which is an “all comers” study.

1.9 Safety Parameters

All serious adverse events (SAE), adverse device effects (ADE), major adverse cardiac events (MACE) and stent thrombosis will be collected up to 5 years follow-up intervals. A clinical events committee (CEC) will adjudicate for MACE and stent thrombosis through the 5-year follow- up.

2 INTRODUCTION

This statistical analysis plan addresses the planned analyses for **PROMUS PREMIER™ China Post-Approval Study** based on protocol version AB. Specified analyses may be used for scientific presentations and/or manuscripts, and regulatory submissions. This prospective, open-label, multi-center study is designed to provide post-market surveillance information on the PROMUS PREMIER Stent System. The study will evaluate clinical outcomes of subjects receiving the PROMUS PREMIER™ stents over 5 years in a real world setting according to post approval requirements by CFDA. The primary analysis will be based on the data through 12 Month follow up.

3 ENDPOINT ANALYSIS

The endpoint analyses include the primary endpoint (12-month major adverse cardiac event (MACE) rate; see Section 3.1) and secondary endpoints (see Section 3.2).

3.1 Primary Endpoint

The primary endpoint is the 12-month major adverse cardiac event (MACE) rate defined as cardiac death, myocardial infarction (MI) and target vessel revascularization (TVR). The primary endpoint is summarized with counts and percentage and based on binomial proportion 95% CI will be presented for 12 Months MACE and thus summarized based on the MACE definition by Cardiac death, Myocardial Infraction, Target Vessel Revascularization. The endpoint will be analyzed based on both ITT and PP population definitions.

3.1.1 Hypotheses

There is no specific hypothesis planned for this study.

3.1.2 Sample Size

The sample size is determined based on the SFDA Guideline for Coronary Drug-Eluting Stent Clinical Trials. For a post market clinical study, the sample size required is for a minimum of 2,000 subjects with investigational device at enrollment and followed up to 5 years.

3.1.3 Statistical Methods

Descriptive statistics (i.e. frequency tables or Kaplan-Meier rate) will be used to analyze data. Categorical variables will be tabulated with frequencies, percentages and 95% confidence intervals. Continuous variables will be tabulated with mean, median, standard