Statistical Analysis Plan

AGENT Japan SV Trial

A 2:1 Randomized Trial Comparing the Agent™ Paclitaxel-Coated PTCA Balloon Catheter (BSJ016A) vs SeQuent® Please Drug Eluting Balloon Catheter for the Treatment of a Small Vessel De Novo Native Coronary Artery Lesion.

[redacted]

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APPROVALS (Check/Complete one below):

☒ Approvals are captured electronically

☐ An electronic system for capturing approvals is not being used for this study; wet signatures are captured below:

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TABLE OF CONTENTS

1 PROTOCOL SUMMARY

AGENT Japan SV: A 2:1 Randomized Trial Comparing the Agent™ Paclitaxel-Coated PTCA Balloon Catheter vs SeQuent® Please Drug Eluting Balloon Catheter for the Treatment of a Small Vessel De Novo Native Coronary Artery Lesion.	
Study Objective(s)	Primary objective is to evaluate the safety and effectiveness of the Agent ™ Paclitaxel-Coated PTCA Balloon Catheter for the treatment of Japanese subjects with a small vessel de novo native atherosclerotic coronary artery lesion or in-stent restenosis (ISR) of a previously treated lesion.
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Study Design	The AGENT Japan SV trial is composed of the following trials: - Trial for small vessel de novo native lesion (called "SV trial" hereinafter): This is a prospective, multicenter, 2:1 randomized (Agent DCB to SeQuent Please DCB), controlled, single-blind, non-inferiority trial. - Sub-study for ISR (called "ISR substudy" hereinafter): This is a prospective, multicenter, single-arm, open-label trial.
Test Device	Agent™ Paclitaxel-Coated PTCA Balloon Catheter
Control Device	Commercially available SeQuent® Please Drug Eluting Balloon Catheter
Device Sizes	The investigational test device and control device matrices consist of the following sizes (balloon diameter and balloon length) for SV trial: Agent™ Paclitaxel-Coated PTCA Balloon Catheter [redacted] SeQuent® Please Drug Eluting Balloon Catheter Commercially available balloons will be used. [redacted] Note : A center may use the SeQuent® Please Neo Drug Eluting Balloon Catheter if it is approved and commercially available. The investigational test device matrices consist of the following sizes (balloon diameter and balloon length) for ISR substudy: Agent™ Paclitaxel-Coated PTCA Balloon Catheter [redacted]

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Primary Endpoint	Primary endpoint: Target Lesion Failure (TLF) rate at 6 months post index-procedure. TLF is defined as any ischemia driven revascularization of the target lesion (TLR), myocardial infarction (MI, Q-wave and non–Q-wave) related to the target vessel, or cardiac death.
Additional Endpoint	[redacted] • Target lesion revascularization (TLR) rate • TLF rate • Target vessel revascularization (TVR) rate • Target vessel failure (TVF) rate • MI (Q-wave and non–Q-wave) rate • Cardiac death rate • Non-cardiac death rate • All death rate • Cardiac death or MI rate • All death or MI rate • All death/MI/TVR rate

	• Thrombosis related to target lesion rate Change in Quality of Life: Functional status of general health-related quality of life measured by changes in EQ-5D scores [redacted] [redacted] • Percent diameter stenosis (%DS) • Late lumen loss • Binary restenosis rate • Minimum lumen diameter (MLD) [redacted] • Technical success rate • Clinical procedural success rate Technical success rate: Technical success is the ability to cross and dilate the lesion to achieve residual angiographic stenosis no greater than 30% as determined by the investigator. The result will be generally confirmed by an angiographic core lab. Clinical procedural success rate: Technical success with no death or MI noted within 24 hours of the index procedure.
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Clinical Inclusion Criteria	CI1. Subject must be at least 20 years of age. CI2. Subject understands the trial requirements and the treatment procedures and provides written informed consent before any study-specific tests or procedures are performed. CI3. Subject is eligible for percutaneous coronary intervention (PCI). CI4. Subject has documented stable angina pectoris or unstable angina pectoris. If subject has documented stable angina pectoris, one of the following criteria meet. - ≥90% diameter stenosis.

	- Stenosis that is considered a cause of stable effort angina (Only when it's without confirmation of significant stenosis). - Stenosis that is confirmed a cause of functional ischemia with any test. CI5. Subject is an acceptable candidate for coronary artery bypass grafting (CABG). CI6. Subject is willing to comply with all protocol-required follow-up evaluation. CI7. Patients undergoing first or second treatment for ISR lesions for the non-randomized ***ISR substudy***.
Angiographic Inclusion Criteria (visual estimate)	AI1. The target lesion meets all following criteria. - Target lesion length must measure (by visual estimate) ≤28 mm. - Target lesion must be a visually estimated reference vessel diameter (RVD) ≥2.00mm and <3.00 mm (This applys for ***SV trial***. ***For ISR substudy***: RVD ≥2.00mm and ≤4.00 mm.). - Target lesion must be a de novo lesion located in a native coronary artery with visually estimated stenosis ≥75% and <100% (This applies to ***SV trial***. ***For ISR substudy***: Target lesion for ISR must be in-stent restenosis of a previously-treated lesion located in a native coronary artery with visually estimated stenosis ≥75% and <100%.). - Coronary anatomy is likely to allow delivery of an investigational device to the lesions. - Target lesion must be successfully pre-dilated. AI2. Planned treatment of 2 coronary artery lesions in 2 vessels may be treated (*For **SV trial**, up to two lesions per vessel can be treated. For **ISR substudy**, single lesion per vessel can be treated.*).
Clinical Exclusion Criteria	CE1. Subject has had an acute myocardial infarction within 72 hours prior to the index procedure. CE2. Subject has cardiogenic shock, hemodynamic instability requiring inotropic or mechanical circulatory support, intractable ventricular arrhythmia, or ongoing intractable angina. CE3. Subject has severe left ventricular dysfunction with ejection fraction <30%. CE4. Subject has received an organ transplant or is on a waiting list for an organ transplant. CE5. Subject is receiving or scheduled to receive chemotherapy within 30 days before or after the index procedure. CE6. Subject has renal failure with a serum creatinine of > 2.0mg/dL or who is receiving dialysis or chronic immunosuppressant therapy. CE7. Subjects has one of the following. - Not expected to live for the duration of the study (1 year) by investigator's discretion due to other serious medical illness (e.g. cancer, congestive heart failure). - Current problems with substance abuse (e.g., alcohol, cocaine, heroin, etc.). - Planned procedure that may cause non-compliance with the protocol or confound data interpretation.

	CE8. Planned PCI (including staged procedures) or CABG after the index procedure. CE9. Subject previously treated at any time with intravascular brachytherapy. CE10. Subject has a known allergy to contrast (that cannot be adequately premedicated) and/or the investigational device or protocol-required concomitant medications (e.g., paclitaxel, acetyl tributyl citrate (ATBC), iopromide, raw materials of Agent DCB and SeQuent Please DCB, P2Y12 inhibitor or aspirin). CE11. Subject has a platelet count <100,000 cells/mm^3 or >700,000 cells/mm^3. CE12. Subject has a white blood cell (WBC) count < 3,000 cells/mm^3. CE13. Subject has documented or suspected liver disease, including laboratory evidence of hepatitis. CE14. Subject has a history of bleeding diathesis or coagulopathy or will refuse blood transfusions. CE15. Subject has had a history of cerebrovascular accident (CVA) or transient ischemic attack (TIA) within the past 6 months. CE16. Subject has an active peptic ulcer or active gastrointestinal (GI) bleeding. CE17. Target vessel has been treated with Paclitaxel Eluting Stent or Balloon prior to the index procedure. CE18. Target vessel has been treated with any type of PCI (e.g. DES, BMS or PTCA) within 6 months prior to the index procedure. CE19. Target vessel requires the use of adjunctive primary treatment modalities (e.g. laser, atherectomy, other debulking devices, etc.) immediately prior to investigational device's treatment. CE20. Non-target vessel has been treated with any type of PCI within 24 hours prior to the index procedure. CE21. Subject is participating in another investigational drug or device clinical trial that has not reached its primary endpoint. CE22. Subject intends to participate in another investigational drug or device clinical trial within 6 months after the index procedure. CE23. Subject with known intention to procreate within 6 months after the index procedure (women of child-bearing potential who are sexually active must agree to use a reliable method of contraception from the time of screening through 6 months after the index procedure). CE24. Subject is a woman who is pregnant or nursing (a pregnancy test must be performed within 7 days prior to the index procedure in women of child-bearing potential).
Angiographic Exclusion Criteria (visual estimate)	AE1. Target lesion meets any of the following criteria: - Left main location. - Located within 5 mm of the origin of the left anterior descending (LAD) coronary artery or left circumflex (LCX) coronary artery by visual estimate. - > 50% stenosis of an additional lesion proximal or distal to the target lesion (by visual estimate). - Located within a saphenous vein graft or an arterial graft. - Will be accessed via a saphenous vein graft or an arterial graft.

	- Involves a complex bifurcation (e.g., bifurcations requiring treatment with more than 1 stent). - TIMI flow 0 (total occlusion) prior to wire crossing. - Excessive tortuosity proximal to or within the lesion. - Extreme angulation proximal to or within the lesion. - Target lesion and/or target vessel proximal to the lesion is severely calcified by visual estimate to expect sub-optimal balloon expansion. - Target lesion and/or target vessel adjacent to the target lesion presents with dissection or aneurysm by visual estimate. - Restenosis from previous intervention (This is applicable only to ***SV trial***.). - PCI within 10 mm proximal or distal to the target lesion (by visual estimate) at any time prior to the index procedure（This is applicable only to ***SV trial***.）. - Planned treatment of a single lesion with more than 1 investigational device - In-stent restenosis due to stent fracture or recoil (This is applicable only to ***ISR substudy***.). AE2. Non-target lesion to be treated during the index procedure meets any of the following criteria: - Located in the target vessel (This is applicable only to ***ISR substudy***.). - Located within a bypass graft (venous or arterial). - Left main location. - Chronic total occlusion. - Involves a complex bifurcation (e.g., bifurcations requiring treatment with more than 1 stent). - Located within 15 mm of the proximal or distal shoulder of the target lesion by visual estimate **in the case of the same vessel with a target lesion for *SV trial***. AE3. Subject has unprotected left main coronary artery disease (>50% diameter stenosis). AE4. Thrombus, or possible thrombus, present in the target vessel. AE5. Subject with known coronary artery spasm.
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2 INTRODUCTION

This statistical analysis plan addresses the planned analyses for the Agent SV Japan pre-approval randomized controlled trial (SV study) and ISR substudy based on the most current version of the protocol. All the specified analyses may not be provided in reports to competent authorities but may be used for scientific presentations and/or manuscripts. The primary analysis will be with regards to the TLF rates based on the data through 6 months post-procedure, to confirm the TLF rate of the Agent DCB group is non-inferior to the SeQuent Please DCB group in SV study and to compare with the study success criteria in ISR substudy.

3 ENDPOINT ANALYSIS

The overall sample size in the SV study is justified by hypothesis parameters and driven by the primary 6-month endpoint to preserve adequate statistical testing power for the primary endpoint, and in the ISR substudy is justified by the study success criteria and other parameters. [redacted]

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event	Total	rate	UCL(normal)	1-alpha	DIFF1
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4 GENERAL STATISTICAL METHODS

4.1 Analysis Sets

The primary and pre-specified additional endpoints/measurements will be analyzed on an intention to treat (ITT) and per-protocol (PP) basis. [redacted]

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5 ADDITIONAL DATA ANALYSES

Descriptive statistics of SV study will be presented on the trial results by treatment group for randomized subjects. For continuous variables, summaries will include the sample size (N), mean, standard deviation, minimum, median and maximum. Frequency tables will be used to summarize discrete variables. The difference between comparison groups and its both sided 95% exact confidence intervals will be calculated. [redacted]

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5.2 Interim Analyses

No formal interim analyses are planned.

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5.4 Justification of Pooling

Not Applicable

5.5 Multivariable Analyses

In the SV study, to explore predictive covariates for primary parameters, univariate and multivariate analyses will be performed (if applicable logistic model for binary variables, cox regression for time-to-event data).

[redacted]

5.6 Other Analyses

Handling dropouts and missing data will depend on their frequency and the nature of the outcome measure. Sensitivity analyses (e.g., tipping-point analysis) will be performed to assess the impact of subjects with inadequate follow-up (i.e., missing data) on the primary endpoint and to assess the robustness of the conclusion of the primary analysis. Statistical models that account for censored data will be employed in appropriate circumstances (e.g., for time-to-event outcomes). Suspected invalid data will be queried and corrected in the database prior to statistical analysis.

5.7 Changes to Planned Analyses

Any changes to the planned statistical analyses made prior to performing the analyses will be documented in a Statistical Analysis Plan approved prior to performing the analyses. Changes from the planned statistical methods after performing the analyses will be documented in the clinical study report along with a reason for the deviation.

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