AGENT Japan SV Clinical 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.

CLINICAL INVESTIGATION PLAN

[redacted]

Sponsored By

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Current Version: SEP 30, 2020

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2. Protocol Synopsis

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.
[redacted]	[redacted]
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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Planned Number of Subjects	The following number of subjects are expected to be enrolled: - SV trial: 150 subjects are expected to be enrolled to support a 2:1 randomization. (Investigational test device: Agent DCB, N=100 subjects or Control device: SeQuent Please DCB, N=50 subjects) - ISR substudy: 30 subjects are expected to be enrolled. (Investigational test device: Agent DCB)
[redacted]	[redacted]
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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Participant Duration	Subject participation will be 60 months after the index procedure.
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 applys for ***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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3. Table of Contents

3.1. Table of Figures

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4. Introduction

4.1. Introduction and Background

Coronary artery disease (CAD) is characterized by atherosclerosis in the epicardial coronary arteries. Atherosclerotic plaques, the hallmark of atherosclerosis, progressively narrow the coronary artery lumen and impair antegrade myocardial blood flow. The reduction in coronary artery flow may be symptomatic or asymptomatic, occur with exertion or at rest, and culminate in a myocardial infarction, depending on obstruction severity and the rapidity of development.

Subjects with coronary artery disease have three common therapeutic options 1) medical therapy and risk factor modification, 2) coronary artery bypass graft surgery (CABG), and 3) percutaneous coronary intervention (PCI). As PCI technology and revascularization procedures evolved, balloon angioplasty, bare metal stent (BMS) and drug-eluting stent (DES) succeeded each other as the primary catheter-based treatments for coronary artery disease. The optimal management of subjects presenting with not only de novo small vessel disease but also in-stent restenosis disease that is a sub study in this study remain unclear.

Drug delivery via DCB could result in a more homogeneous administration of the drug instead of creating a peri-strut gradient,[1-5] in reduced vascular smooth muscle cell proliferation[6] and in a reduced rate of restenosis when compared to uncoated balloon treatment.[7] Drug concentrations at the vessel wall with DCB are the highest at the time of injury when the neointimal process is the most vigorous. Afterwards, the absence of drug and polymer (used in stent technologies) could help to facilitate re-endothelialization, thereby reducing the risk of late and very late thrombosis. Another advantage of DCB over DES is the decrease in duration of dual antiplatelet therapy (DAPT) when compared to DES, likely resulting in a reduced rate of bleeding complications[2,5,8]. Furthermore, it is an attractive approach in small vessels or in-stent restenosis, respecting the original anatomy of the arteries[4], thus avoiding further reduction of the lumen diameter with stent struts[7] and avoiding the deployment of a permanent implant/prosthesis that could complicate future revascularization efforts[2,5].

4.2. Clinical Program Development

4.2.1. Agent DCB Platform

The Agent paclitaxel-coated balloon is a paclitaxel-coated Percutaneous Transluminal Angioplasty (PTA) balloon catheter developed as a collaborative effort between BSC and Hemoteq AG [HTQ, Wuerselen, Germany]. The Agent paclitaxel-coated balloon is based on BSC's well characterized Emerge PTA balloon catheters. These catheters are coated with the paclitaxel (active ingredient) drug that is formulated with the excipient acetyltributyl citrate (ATBC) to effectively deliver paclitaxel to the vessel wall. Paclitaxel has been widely used for both stent and DCB applications as a safe and effective drug to inhibit neointimal proliferation and thereby reduce the rate of restenosis.

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4.3. Trial Rationale

PCI is the most common treatment for patients with coronary artery disease. But the optimal management of patients presenting with not only de novo small vessel disease but also in-stent restenosis disease that is a sub study in this study remain unclear and the need for an alternative therapy exists. The Agent DCB aims to address these treatment gaps and clinical outcomes not adequately addressed by POBA, BMS, and DES.

Agent DCB.incorporates design modifications aimed to improve coating durability and drug transfer efficiency, to minimize particulates and systemic PTx levels for patient safety and to optimize arterial PTx concentrations with reduced drug dose density (2 μg/mm^2 vs 3 μg/mm^2) (TransPaxTM Coating Technology).

5. Device Description

5.1. Agent DCB

The Agent Paclitaxel-Coated PTCA Balloon Catheter (Agent DCB) is a Monorail Percutaneous Transluminal Coronary Angioplasty (PTCA) balloon catheter with a semi-compliant balloon coated with a formulation of paclitaxel (drug) and an excipient, Acetyl-Tri-n-Butyl citrate (ATBC) (see Figure 5.1-1). The Agent balloon catheter is designed to inhibit restenosis by delivering drug to diseased arterial tissue.

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The Agent Paclitaxel-Coated PTCA Balloon Catheter is available in a variety of diameters and balloon lengths. Device sizes intended for use in this trial are exhibited in Table 5.1-1. [redacted]

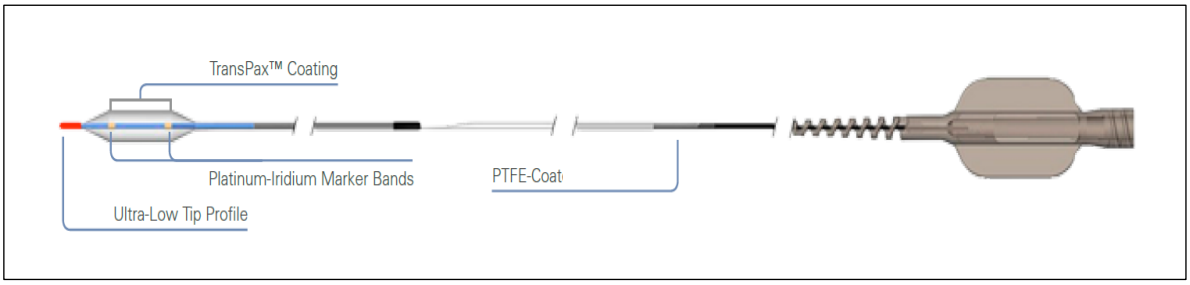

Figure 5.1-1: Agent DCB

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5.2. Drug Components Description

The balloon coating consists of paclitaxel (PTx) and the excipient, acetyltributyl citrate (ATBC).

Paclitaxel (PTx) is the active pharmaceutical ingredient on the Agent DCB. Paclitaxel is a white powder, isolated from a spectrum of TAXUS species and hybrids. It is a terpenoid with a characteristic taxane skeleton of 20 carbon atoms, a molecular weight of 853.91 g/mol, and a molecular formula of $C_{47}H_{51}NO_{14}$. It is highly lipophilic and insoluble in water, but is freely soluble in methanol, ethanol, chloroform, ethyl acetate, and dimethyl sulfoxide.[12,13] The chemical structure of paclitaxel is provided in Figure 5.2-1: Chemical Structure of Paclitaxel.

Paclitaxel is an antiproliferative drug that induces irreversible polymerization of cell microtubules, thus inhibiting mitosis. It is widely used in antineoplastic chemotherapy of cancers; however, doses required in chemotherapeutic treatment are significantly higher per treatment cycle in cancer patients than in coronary artery disease patients.[13] Paclitaxel has been shown to inhibit proliferation and migration of smooth muscle cells, effectively suppressing neointimal hyperplasia after vessel injury.[13,14,15] The drug to excipient formulation ratio in Agent DCB is 80:20 PTx/ATBC. The resulting drug dose density (total weight of drug per unit of balloon surface area) on the coated balloon is 2 µg/mm^2.

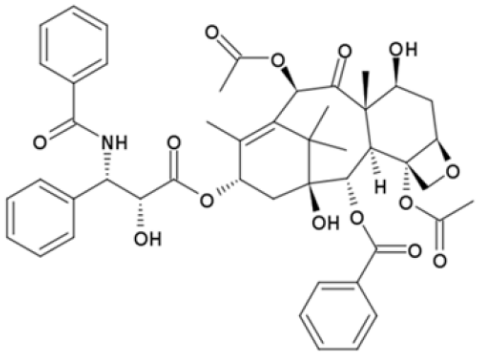

Figure 5.2-1: Chemical Structure of Paclitaxel

The coating utilizes the inactive ingredient Acetyl-Tri-n-Butyl Citrate (ATBC) as an excipient to facilitate the release and transfer of paclitaxel into the arterial wall. ATBC is a carboxylic acid ester with a molecular weight of 402.48 g/mol. ATBC is a colorless, slightly viscous liquid with very faint sweet herbaceous odor. The chemical structure of ATBC is provided in Figure 5.2-2.

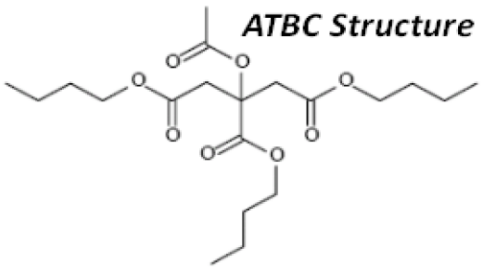

Figure 5.2-2: Chemical Structure of Acetyltributyl Citrate (ATBC)

[redacted]

5.4. Labeling of Investigational Device

The Directions for Use (DFU) for the Agent DCB will be included in the Manual of Operations. The Agent DCB is labeled on the front, back and bottom spine of the outer carton, and on the inside sterile pouch. The labeling will include the following information in Japanese or in English.

In Japanese:

- Identification number
- Sponsor name and address
- Storage condition
- Exclusively for Clinical Investigations

In English:

- Lot number
- Serial number
- Balloon dimensions (balloon diameter and length in mm)
- Expiration (use by) date

[redacted]

5.8. Control Device

SeQuent® Please Drug Eluting Balloon Catheter is the control device for the SV trial. The balloon size utilization is determined by the research investigator. And it should be used according to the localstandard care.

SeQuent Please paclitaxel-coated balloon has a drug formulation consisting of paclitaxel (the active pharmaceutical ingredoent) and an iopromide (the inactive ingredient). The resulting drug dose density (total weight of drug per unit of balloon surface area) on the coated balloon is 3 μg/mm^2. SeQuent Please paclitaxel-coated balloon has been approved in Japan and indicated for percutaneous transluminal coronary angioplasty (PTCA) in the in-stent restenosis (ISR) and de novo small vessel disease (<3.00 mm in diameter).

Note: A center may use the SeQuent® Please Neo Drug Eluting Balloon Catheter if it is approved and commercially available.

[redacted]

[redacted]

6. Trial Objectives and Endpoints

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.

6.1. Primary Safety Endpoint

The primary endpoint assesses 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.

6.2. Additional Endpoints

[redacted]

- TLR rate
- TLF rate
- TVR rate
- 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 EQ5D scores [redacted]

[redacted]

- Percent diameter stenosis (%DS)
- Late lumen loss
- Binary restenosis rate
- Minimum lumen diamete

[redacted]

- Technical success rate
- Clinical procedural success rate

Criteria is defined as below.

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.

7. Study Design

The clinical trial for SV trial is a prospective, multicenter, 2:1 randomized (Agent DCB to SeQuent Please DCB), controlled, single-blind, non-inferiority trial. Primary objective is to evaluate the safety and effectiveness of the Agent DCB for the treatment of Japanese subjects with a small vessel de novo native atherosclerotic coronary artery lesion.

ISR substudy is a prospective, multicenter, single-arm, open trial. Primary objective is to evaluate the safety and effectiveness of the Agent DCB for the treatment of Japanese subjects with an In stent restenosis coronary artery lesion.

7.1. Scale and Duration

150 subjects will be randomized/enrolled to support a 2:1 randomization in this SV trial and 30 subjects will be enrolled in this ISR substudy. The trial is to be conducted in Japan [redacted]

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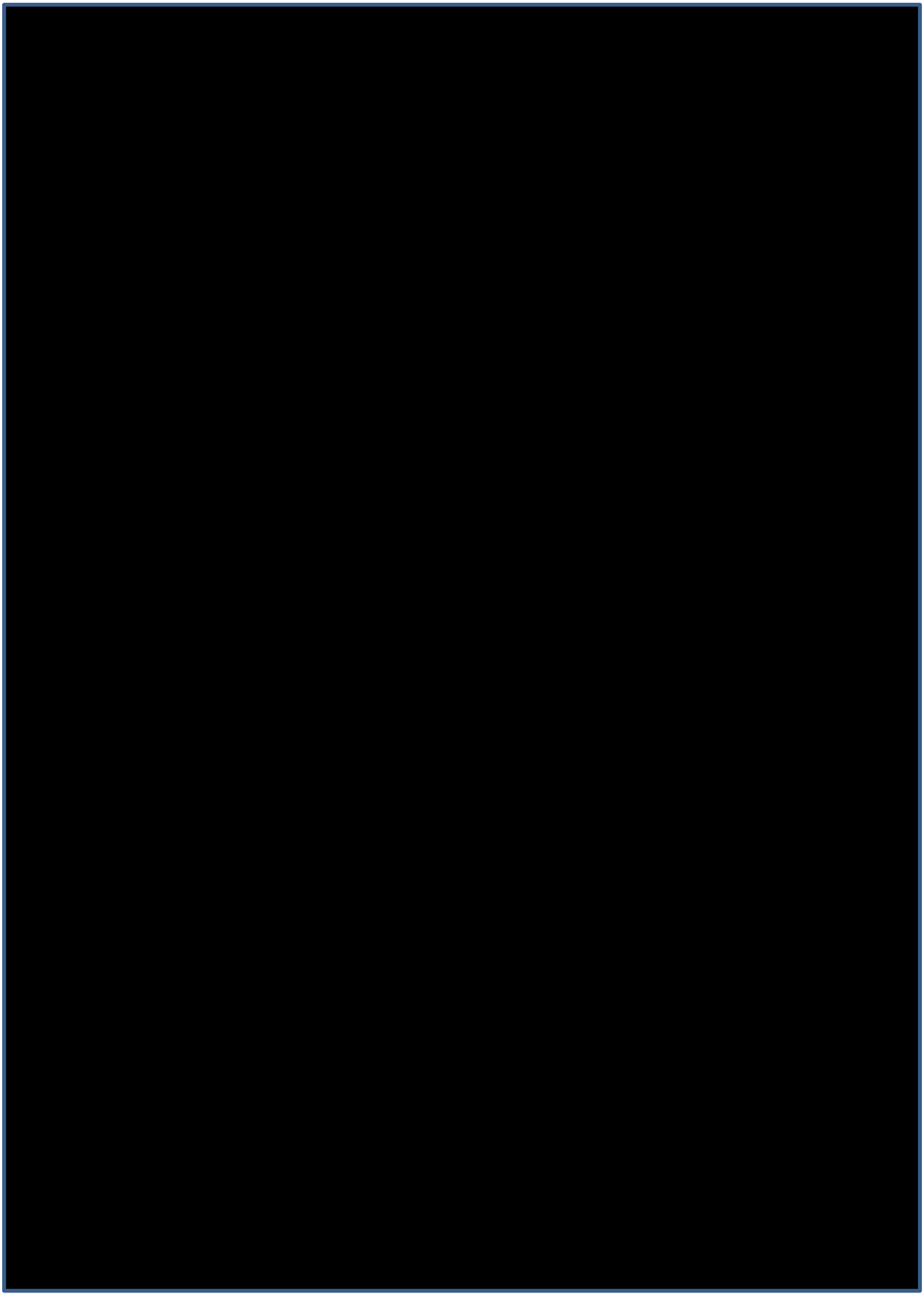

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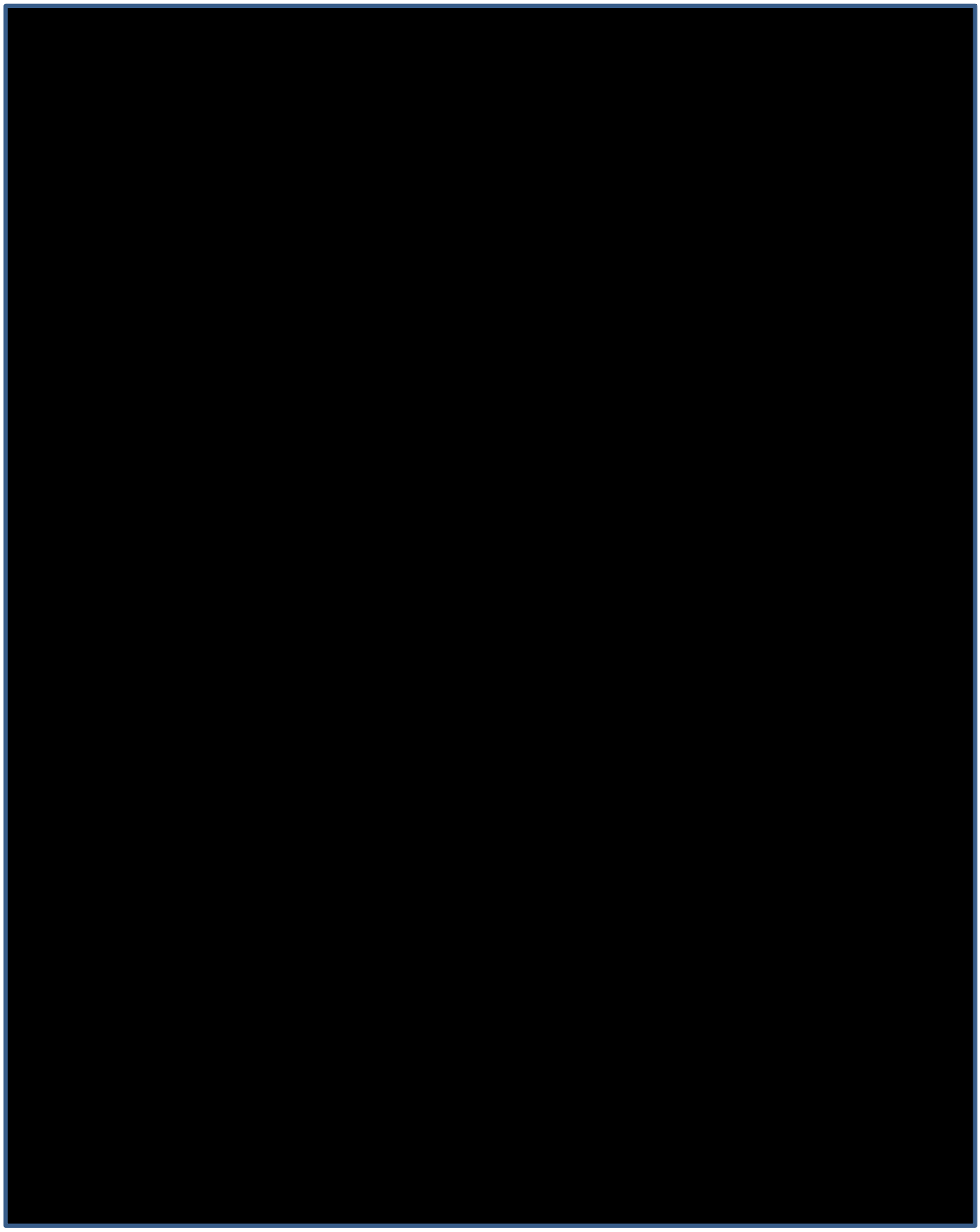

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7.5. Justification for the Trial Design

The AGENT Japan SV trial will evaluate the safety and effectiveness of the Agent DCB for the treatment of subjects with a small vessel de novo native coronary artery lesion compared with the SeQuent Please DCB. The SeQuent Please DCB was chosen as the control device because it is the commercially available DCB approved in Japan at the moment of planning this trial for treatment of small vessel de novo native coronary artery lesion. As reported in Section 5.8., the test and control DCB deliver the same drug, paclitaxel. Coronary artery disease patients with ISR will be considered as part of the ISR substudy. The ISR substudy will evaluate the safety and effectiveness of the Agent DCB for the treatment of subjects with an ISR coronary artery lesion.

[redacted]

8. Subject Selection

8.1. Trial Population and Eligibility

Clinical and angiographic inclusion and exclusion criteria are included in Table 8.2-1 and Table 8.3-1. Prior to enrollment, a subject must meet all of the clinical and angiographic inclusion criteria and none of the clinical and angiographic exclusion criteria.

8.2. Inclusion Criteria

Subjects who meet all of the following criteria (see Table 8.2-1) may be given consideration for inclusion in this clinical investigation, provided no exclusion criterion (see Section 8.3) is met.

Table 8.2-1: Inclusion Criteria

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 applys for ***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(s). - 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.)*.

8.3. Exclusion Criteria

Subjects who meet any one of the following criteria (see Table 8.3-1) cannot be included in this study or will be excluded from this clinical study.

Table 8.3-1: Exclusion Criteria

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.

9. Subject Accountability

9.1. Point of Enrollment

Subjects must sign and date the institutional review board (IRB)-approved trial-specific informed consent form (ICF) prior to the completion of any trial-related procedure(s).

The subject must satisfy all clinical inclusion and none of the clinical exclusion prior to the intervention.

[redacted]

9.2. Withdrawal

All subjects enrolled in the clinical study (including those withdrawn from the clinical study) shall be accounted for and documented. If a subject withdraws from the clinical investigation, the reason(s) shall be reported. If such withdrawal is due to problems related to investigational device safety or performance, the

investigator shall ask for the subject's permission to follow his/her status/condition outside of the clinical study.

Subjects may withdraw from the trial at any time by notifying the trial investigator. The investigator may also terminate a subject's participation in the trial (ie, if the subject routinely fails to complete required trial procedures or if the investigator believes it is in the subject's best interest).

[redacted]

9.4. End-of-Study Definition

The trial will be considered complete (with regards to the primary endpoint) after all enrolled subjects have completed the 6 months follow-up visit, are withdrawn prior to 6 months follow-up visit, have died, or the last 6 months follow-up visit window is closed.

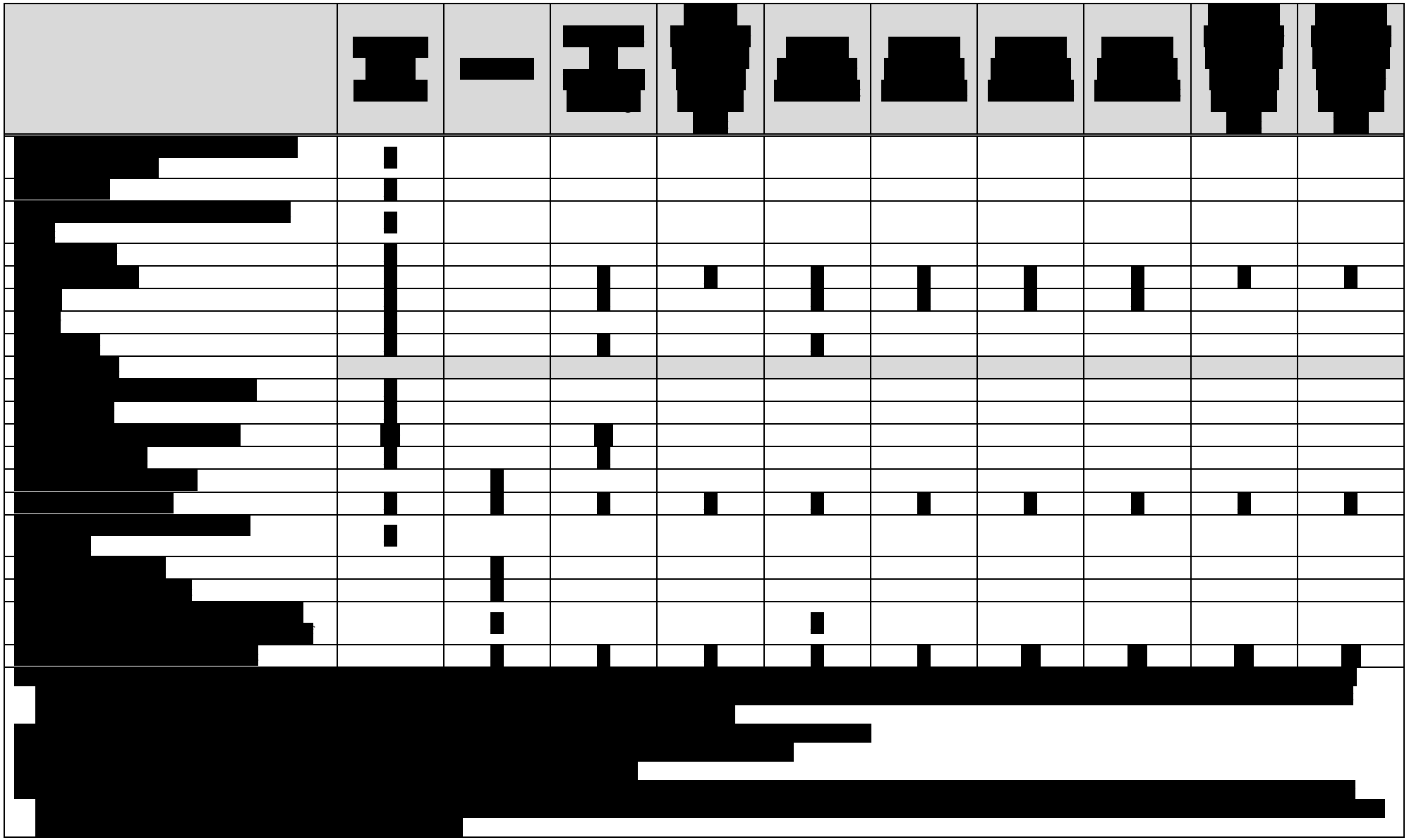
[redacted]

10. Trial Methods

10.1. Data Collection

The data collection schedule is shown in Table 10.1-1.

[redacted]



10.2. Trial Candidate Screening

A screening log will be maintained by each investigational center to document selected information about potential subjects who fail to meet the AGENT Japan SV trial eligibility criteria for enrollment including the reason for screen failure.

10.2.1. Strategies for Recruitment and Retention

Subjects may be recruited through the investigator's practice, referring physicians and/or the use of recruitment tools. Potential subjects may be identified through an investigational center's database query (chart reviews) or as new or existing patients attend clinic visits. Any information disseminated to potential subjects (eg, advertisements, pamphlets, posters) must be reviewed by the investigational center's IRB prior to use.

[redacted]

10.3. Informed Consent

The subject must sign and date the ICF prior to any trial- required testing or procedures.

Prior to signing the ICF the investigator, or qualified designee, will explain to each potential subject the purpose and nature of the trial, procedures, expected trial duration, available alternative therapies, the benefits and risks involved with trial participation.

Trial personnel should explain to the subject that even if the subject agrees to participate in the trial and signs the ICF, the angiography assessment may demonstrate that the subject is not a suitable candidate for the trial. Refer to Section 9.1. Point of Enrollment.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

11. Statistical Considerations

This section describes statistical approaches of this study. More details will be described in a separate statistical analysis plan.

11.1. Endpoints for SV study

11.1.1. Primary Endpoint

The primary endpoint in this trial is the TLF rate for SV study 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. [redacted]

[redacted]

11.2. Endpoints for ISR substudy

11.2.1. Primary Endpoint

The primary endpoint in this trial is the TLF rate for ISR substudy 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. [redacted]

11.3. General Statistical Methods

11.3.1. Analysis Sets

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

[redacted]

11.3.2. Control of Systematic Error/Bias

Selection of subjects will be made from the investigator's usual patient load. All patients meeting the eligibility criteria and having signed the ICF will be eligible for enrollment in the study. [redacted]

[redacted]

11.4. Data Analyses

Descriptive statistics 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]

11.4.2. Interim Analyses

No formal interim analyses are planned.

[redacted]

11.4.4. Justification of Pooling

Not appreciable.

11.4.5. Multivariable Analyses

To explore predicted covariates for primary parameters, univariate and multivariate analyses to be performed (if applicable logistic model for binary variable, cox regression for time-to-event data). Details will be described in the Statistical Analysis Plan.

11.4.6. Other Analyses

Handling of 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. Additional information may be found in the Statistical Analysis Plan.

11.4.7. Changes to Planned Analyses

Any changes to the planned statistical analyses made prior to performing the interim and full primary analyses (i.e. unblinding) will be documented in an amended 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 trial report along with a reason for the deviation.

12. Data Management

12.1. Data Collection, Processing, and Review

Subject data will be recorded in a limited access secure electronic data capture (EDC) system.

The clinical database will reside on a production server hosted by Medidata EDC System. All changes made to the clinical data will be captured in an electronic audit trail and available for review by sponsor or its representative. The associated Rave software and database have been designed to meet regulatory compliance for deployment as part of a validated system compliant with laws and regulations applicable to the conduct of clinical trials pertaining to the use of electronic records and signatures. Database backups are performed regularly.

The investigator is responsible for the accuracy, completeness and timeliness of the data submitted and must review all data for accuracy and provides his/her electronic signature on the appropriate electronic case report forms (eCRFs) in compliance with local regulations. A written signature on printouts of the eCRFs must also be provided if required by local regulation. Changes to data previously submitted to the sponsor require a new electronic signature by the investigator acknowledging and approving the changes.

Visual and/or electronic data review will be performed to identify possible data discrepancies. Manual and/or automatic queries will be created in the Medidata EDC system and will be issued to the site for appropriate response. Site staff will be responsible for resolving all queries in the database.

12.2. Data and Record Retention

The Principal Investigator or his/her desginee and Investigational site will maintain all essential trial documents and source documents, in original format, that support the data collected on study patients in compliance with GCP guidances. Documents must be retained for at least 3 years after the last approval of marketing application or the formal discontinuation of the clinical investigation of the device, whichever is longer.

When these documents no longer need to be maintained, it is BSJ's responsibility to inform the Investigator and Site. The Investigator and Site will take measures to ensure that these essential documents are not accidentally damaged or destroyed. If for any reason the Investigator and Site withdraw responsibility for maintaining these

essential documents, custody must be transferred to an individual who will assume responsibility. BSJ must receive written notification of this custodial change.

[redacted]

13. Deviations

A trial deviation occurs when the investigator or the investigationali center personnel did not conduct the clinical trial according to the clinical protocol, clinical study agreement, or applicable laws and regulations.

An Investigator must not make any changes or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency. An investigator shall notify the sponsor and the reviewing IRB of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency, and those deviations which affect the scientific integrity of the clinical investigation. Such notice shall be given as soon as possible, but no later than 5 working days after the emergency occurred.

[redacted]

All deviations from the investigational plan, with the reason for the deviation and the date of occurrence, must be documented and reported to the sponsor using EDC system. Investigational centers will also be required to report deviations to the IRB, per local guidelines and government regulations.

Deviations will be reviewed and evaluated on an ongoing basis and, as necessary, appropriate corrective and preventive actions (including IRB and regulatory authority notification, site re-training, or site discontinuation/termination) will be put into place by the sponsor.

14. Device Accountability

The investigational devices shall be securely maintained, controlled, and used only in this clinical trial. The Medidata RAVE EDC will be used to track subjects and the device management vendor, Cenduit LLC, will track device allocations throughout the trial enrollment.

The sponsor's device management vendor shall keep records to document the physical location of all investigational devices from shipment of investigational devices from BSJ or designated facility/equipment to the investigation sites until return or disposal. Records shall be kept by the device management vendor, [redacted], to document the physical location and conditions of storage of all investigational devices.

[redacted]

[redacted]

15. Compliance

15.1. Statement of Compliance

The AGENT Japan SV clinical trial will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and that are consistent with Good Clinical Practices (GCP), Order for Enforcement of the Pharmaceutical and Medical Device Law, regulatory requirements and this protocol. The study shall not begin until the required approval from the IRB and/or favorable opinion from regulatory authority has been obtained, if appropriate. Also, the study shall not begin prior to issuance of the site Authorization to Enroll, as provided by BSJ. Any additional requirements imposed by the IRB or regulatory authority shall be followed, if appropriate.

15.2. Investigator Responsibilities

The Principal Investigator of an investigational site is responsible for ensuring that the study is conducted in accordance with the Clinical Study Agreement, the clinical investigational plan, GCP, ethical principles that have their origins in the Declaration of Helsinki, any conditions of approval imposed by the reviewing IRB, and Pharmaceutical and Medical Device Law, Regulatory authority, whichever affords the greater protection to the subject.

The Principal Investigator's responsibilities include, but are not limited to, the following.

- Prior to beginning the study, sign the Clinical Study Agreement and comply with the Investigator responsibilities as described in such Agreement.
- Prior to beginning the study, sign the Protocol Signature page documenting his/her agreement to conduct the study in accordance with the protocol.
- Provide his/her qualifications and experience to assume responsibility for the proper conduct of the study and that of key members of the site team through up-to-date curriculum vitae or other relevant documentation.
- Make no changes in or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency; document and explain any deviation from the approved protocol that occurred during the course of the clinical investigation.
- Create and maintain source documents throughout the clinical study and ensure their availability with direct access during monitoring visits or audits; ensure that all clinical-investigation-related records are retained per requirements.
- Ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.
- Record, report, and assess (seriousness and relationship to the device/procedure) every adverse event as applicable per the protocol and observed device deficiency.
- Report to sponsor, per the protocol requirements, all serious adverse events (SAEs) and device deficiencies that could have led to a serious adverse device effect (SADE) and potential unanticipated serious adverse device effect (USADE) or unanticipated adverse device effect (UADE)
- Report to the IRB and regulatory authorities any SAEs and device deficiencies that could have led to a SADE and potential/USADE or UADE, if required by applicable laws or regulations or this protocol or by the IRB, and supply Boston Scientific (or delegate) with any additional requested information related to the safety reporting of a particular event

- Maintain the control of the device, ensuring that the investigational device is used only by authorized/designated users and in accordance with this protocol and instructions/directions for use.
- Allow the sponsor to perform monitoring and auditing activities, and be accessible to the clinical research monitor or auditor and respond to questions during monitoring visits or audit(s).
- Allow and support regulatory authorities and the IRB when performing auditing activities.
- Ensure that informed consent is obtained in accordance with applicable laws, this protocol and local IRB requirements.
- Provide adequate medical care to a subject during and after a subject's participation in a clinical study in the case of adverse events, as described in the Informed Consent Form (ICF).
- Inform the subject of the nature and possible cause of any adverse events experienced.
- Inform the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required.
- Provide the subject with well-defined procedures for possible emergency situations related to the clinical study, and make the necessary arrangements for emergency treatment, including decoding procedures for blinded/masked clinical investigations, as needed
- Ensure that clinical medical records are clearly marked to indicate that the subject is enrolled in this clinical study.
- Ensure that, if appropriate, subjects enrolled in the clinical investigation are provided with some means of showing their participation in the clinical investigation, together with identification and compliance information for concomitant treatment measures (contact address and telephone numbers shall be provided).
- Inform, with the subject's approval or when required by national regulations, the subject's personal physician about the subject's participation in the clinical investigation.
- Make all reasonable efforts to ascertain the reason(s) for a subject's premature withdrawal from clinical investigation while fully respecting the subject's rights.
- Ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation.

15.2.1. Delegation of Responsibility

When specific tasks are delegated by an investigator, including but not limited to conducting the informed consent process, the Principal Investigator is responsible for providing appropriate training, are competent to perform the tasks they have been delegated and adequate supervision of those to whom tasks are delegated. Where there is a sub investigator at a center, the sub investigator should not be delegated the primary supervisory responsibility for the investigational site. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

15.3. Institutional Review Board

The investigational site will obtain the written and dated approval/favorable opinion of the IRB for the clinical investigation before recruiting subjects and implementing all subsequent amendments, if required.

A copy of the written IRB approval of the protocol (or permission to conduct the study) and ICF, must be received by the sponsor (or designee) before recruitment of subjects into the study and shipment of investigational product/equipment. Prior approval must also be obtained for other materials related to subject recruitment or which will be provided to the subject.

Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the ICF will be IRB approved; a determination will be made regarding whether a new ICF needs to be obtained from participants who provided consent, using a previously approved ICF. Annual IRB approval and renewals will be obtained throughout the duration of the study as required by IRB requirements. Copies of the study reports and the IRB continuance of approval must be provided to the sponsor (or designee).

15.4. Sponsor Responsibilities

The clinical trial organization in Japan, including investigational sites in Japan, is provided as an attachment to the protocol.

All information and data sent to Boston Scientific (or delegate) concerning subjects or their participation in this study will be considered confidential by Boston Scientific and will be kept confidential. Only authorized Boston Scientific personnel and/or a Boston Scientific representative including, but not limited to Contract Research Organization (CRO), will have access to this information. Authorized regulatory personnel have the right to inspect and copy all records pertinent to this study. Study data collected during this study may be used by Boston Scientific for the purposes of this study, publication, and to support future research and/or other business purposes, such as overseeing and improving the performance of its device, new medical research and proposals for developing new medical products and procedures. All data used in the analysis and reporting of this study or shared with a third-party researcher will be without identifiable reference to specific subjects.

Boston Scientific will keep subjects' identifiable health information confidential in accordance with all applicable laws and regulations. Boston Scientific may use subjects' health information to conduct this research, as well as for additional purposes, such as overseeing and improving the performance of its device, new medical research and proposals for developing new medical products or procedures, and other business purposes. Information received during the study will not be used to market to subjects; subject names will not be placed on any mailing lists or sold to anyone for marketing purposes.

Note: BSJ may utilize a contract research organization (CRO) or other contractors to act as its representative for carrying out designated tasks. Responsibilities for these entities are defined in the applicable contracts or agreements. Contact information for the CROs is provided as an attachment to the protocol or in the study Manual of Operations (MOP).

[redacted]

15.5. Reimbursement and Compensation

Subject Reimbursement: Travel and other expenses incurred by subjects as a result of participation in the study will be reimbursed in accordance with pertinent Regulations and per the investigational sites.

Compensation for Subject's Health Injury: BSJ will stipulate an insurance policy to cover potential health injury for study subjects. If any study related health injury occurs and a site is held responsible for its compensation, BSJ will assume the responsibility, except in the case those damages are incurred due to intentional misconduct or negligence at the site.

16. Monitoring

Monitoring will be performed to assess continued compliance with the protocol and applicable regulations. The monitoring plan contains the strategy for frequency of monitoring visits and source data verification to be completed for the trial.

The monitor verifies that trial records are adequately maintained, that data are reported in a satisfactory manner with respect to timeliness, adequacy, and accuracy, and that the investigator continues to have sufficient staff and facilities to conduct the trial safely and effectively. The investigator/institution guarantees direct access to original source documents (ie, paper and electronic hospital charts, appointment books, laboratory records) by Boston Scientific personnel, their designees, and applicable regulatory authorities.

The trial may also be subject to a quality assurance audit by Boston Scientific or its designees, as well as inspection by appropriate regulatory authorities. It is important that the principal investigator and relevant trial personnel are available during on-site monitoring visits or audits and that sufficient time is devoted to the process.

[redacted]

[redacted]

17.3. Risks associated with Participation in the Clinical Trial

There may be additional risks linked to the procedure, and follow-up testing which are unforeseen at this time. All testing planned for the follow-up period is standard of care.

[redacted]

17.5. Risk Minimization Actions

Additional risks may exist. Risks can be minimized through compliance with this protocol, performing procedures in the appropriate hospital environment, adherence to subject selection criteria, close monitoring of the subject's physiologic status during research procedures and/or follow-ups and by promptly supplying Boston Scientific with all pertinent information required by this protocol.

17.6. Anticipated Benefits

Potential anticipated benefits include the effective treatment of a small vessel de novo coronary artery lesion or in-stent restenosis with improvement in the symptoms of disease. However, the Agent DCB is a test device and these potential benefits may or may not actually be present.

17.7. Risk to Benefit Rationale

The Agent DCB is expected to be suitable for its intended purpose. There are no unacceptable residual risks/intolerable risks and all applicable risks have been addressed through the provision of appropriate directions for use (DFU) and Kiki-Gaiyosho. The Agent DCB is expected to have an acceptable adverse event profile when used under the conditions intended; the benefits associated with the use of the Agent DCB are expected to outweigh the risks.

18. Safety Reporting

18.1. Reportable Events by investigational center to Boston Scientific

It is the responsibility of the investigator to assess and report to BSJ any event which occurs in any of following categories:

- All Serious Adverse Events (SAE)
- All Investigational Device Deficiencies
- Unanticipated Serious Adverse Device Effects (USADE)/ Unanticipated Adverse Device Effects (UADE)
- Adverse Device Effect (ADE)/ Serious Adverse Device Effect (SADE)

- New findings/updates in relation to already reported events
- All other adverse events

[redacted]

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18.5. Boston Scientific Device Deficiencies

All Boston Scientific device deficiencies including Agent DCB deficiencies (including but not limited to failures, malfunctions, use errors, product nonconformities, and inadequacy in the information supplied by the manufacturer) will be documented and reported to BSC. If possible, the device(s) should be returned to BSC for analysis. Instructions for returning the investigational device(s) will be provided in the Manual of Operations. If it is not possible to return the device, the investigator should document why the device was not returned and the final disposition of the device. Device failures and malfunctions should also be documented in the subject's medical record.

[redacted]

18.6. Reporting to Regulatory Authorities / IRBs / Investigators

BSJ will report to regulatory agency and notify all PIs and head of the investigational sites if any significant safety information was received. Additionally, information which implies possible influence to patient's safety and the conduct of the study will also notified to all PIs and the head of the investigational sites.

19. Informed Consent

Subject participation in this clinical study is voluntary. Informed Consent is required from each subject. The Investigator is responsible for ensuring that Informed Consent is obtained prior to the use of any investigational devices, study-required procedures and/or testing, or data collection.

The obtaining and documentation of Informed Consent must be in accordance with the ethical principles that have their origins in the Declaration of Helsinki and that are consistent with Good Clinical Practices (GCP), Pharmaceutical Affairs Law, regulatory authority and this protocol. The ICF must be accepted by BSJ or its delegate (e.g. CRO), and approved by the site's IRB, or central IRB, if applicable.

BSJ will provide a study-specific template of the ICF to investigators participating in this study. The ICF template may be modified to meet the requirements of the investigative site's IRB. Any modification requires acceptance from BSJ prior to use of the form. The ICF must be in a language understandable to the subject and if needed. Privacy language shall be included in the body of the form or as a separate form as applicable.

The process of obtaining Informed Consent shall at a minimum include the following steps, as well as any other steps required by applicable laws, rules, regulations and guidelines:

- be conducted by the Principal Investigator or designee authorized to conduct the process,
- include a description of all aspects of the clinical study that are relevant to the subject's decision to participate throughout the clinical study,
- avoid any coercion of or undue influence of subjects to participate,
- not waive or appear to waive subject's legal rights,
- will use native language that is non-technical and understandable to the subject,
- provide ample time for the subject to consider participation and ask questions if necessary,
- ensure important new information is provided to new and existing subjects throughout the clinical study.

The ICF shall always be signed and personally dated by the subject to sign the ICF under the applicable laws, rules, regulations and guidelines and by the investigator and/or an authorized designee responsible for conducting the informed consent process. If a legal representative signs, the subject shall be asked to provide informed consent for continued participation as soon as his/her medical condition allows. The original signed ICF will be retained by the site and a copy of the signed and dated document and any other written information must be given to the person signing the form. Informed Consent signature can be replaced by printed name and seals of appropriate individuals.

If new information becomes available that can significantly affect a subject's future health and medical care, that information shall be provided to the affected subject(s) in written form via a revised ICF or, in some situations, enrolled subjects may be requested to sign and date an addendum to the ICF. In addition to new significant information during the course of a study, other situations may necessitate revision of the ICF, such as if there are amendments to the applicable laws, protocol, a change in Principal Investigator, administrative changes, or following annual review by the IRB. The new version of the ICF must be approved by the IRB. Acceptance by Boston Scientific Japan K.K. is required if changes to the revised ICF are requested by the site's IRB. The IRB will determine the subject population to be re-consented.

Study personnel should explain to the subject that even if the subject agrees to participate in the trial and signs the ICF, catheterization may demonstrate that the subject is not a suitable candidate for the trial. A Screening Log will be maintained by the investigational site to document select information about candidates who fail to meet the trial eligibility criteria, including, but not limited to, the reason for screen failure.

20. Committees

20.1. Executive Committee

An Executive Committee composed of Boson Scientific Clinical Management and selected Coordinating Principal Investigator(s) will be convened. This committee will be responsible for the overall conduct of the study which will include protocol development, study progress, subject safety, overall data quality and integrity, and timely dissemination of study results through appropriate scientific sessions and publications. As appropriate the Executive Committee may request participation of AGENT Japan SV trial Investigators on the committee.

20.2. Safety Monitoring Process

To promote early detection of safety issues, the clinical events committee will provide evaluations of safety events. Success of this program requires dynamic collection of unmonitored data as soon as the event is reported. This is expedited through the Boston Scientific safety group (or designee), which is responsible for coordinating the collection of information for the subject dossier from Medidata Rave EDC database that is entered by the centers and core laboratories. During regularly scheduled monitoring activities, clinical research monitors will support the dynamic reporting process through their review of source document and other data information.

20.3. Clinical Events Committee

The clinical events committee (CEC) is an independent group of individuals with no affiliation with Boston Scientific. Committee membership will include practitioners of cardiovascular intervention therapy, as well as other experts with the necessary therapeutic and subject matter expertise to review and adjudicate the following endpoints and major adverse events reported by the trial investigators:

[redacted]

21. Suspension or Termination

21.1. Premature Termination of the Study

Boston Scientific reserves the right to terminate the study at any stage but intends to exercise this right only for valid scientific or business reasons and reasons related to protection of subjects. Investigators, associated IRBs, and regulatory authorities, as applicable, will be notified in writing in the event of study termination.

21.1.1. Criteria for Premature Termination of the Study

Possible reasons for premature study termination include, but are not limited to, the following.

- The occurrence of unanticipated adverse device effects that present a significant or unreasonable risk to subjects enrolled in the study.
- An enrollment rate far below expectation that prejudices the conclusion of the study.
- A decision on the part of Boston Scientific to suspend or discontinue development of the device.

21.2. Termination of Study Participation by the Investigator or Withdrawal of IRB Approval

Any investigator, or associated IRB may discontinue participation in the study or withdraw approval of the study, respectively, with suitable written notice to Boston Scientific. Investigators, associated IRBs, and regulatory authorities, as applicable, will be notified in writing in the event of these occurrences.

21.3. Requirements for Documentation and Subject Follow-up

In the event of premature study termination a written statement as to why the premature termination has occurred will be provided to all participating sites by Boston Scientific. The IRB and regulatory authorities, as applicable, will be notified. Detailed information on how enrolled subjects will be managed thereafter will be provided.

In the event an IRB terminates participation in the study, participating investigators, associated IRBs, and regulatory authorities, as applicable, will be notified in writing. Detailed information on how enrolled subjects will be managed thereafter will be provided by Boston Scientific.

In the event a Principal Investigator terminates participation in the study, study responsibility will be transferred to another investigator, if possible. In the event there are no opportunities to transfer Principal Investigator responsibility; detailed information on how enrolled subjects will be managed thereafter will be provided by Boston Scientific.

The Principal Investigator or his/her designee must return all study-related documents and investigational product to Boston Scientific, unless this action would jeopardize the rights, safety, or welfare of the subjects.

21.4. Criteria for Suspending/Terminating a Study Center

Boston Scientific reserves the right to stop the inclusion of subjects at a study site at any time after the study initiation visit if no subjects have been enrolled for a period beyond 3 months after site initiation, or if the site has multiple or severe protocol violations/noncompliance without justification and/or fails to follow remedial actions.

In the event of termination of site participation, all investigational and testing equipment, as applicable, will be returned to Boston Scientific unless this action would jeopardize the rights, safety or well-being of the subjects. The IRB and regulatory authorities, as applicable, will be notified. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

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22. Publication Policy

BSJ requires disclosure of its involvement as a sponsor or financial supporter in any publication or presentation relating to a BSJ study or its results. BSJ will submit study results for publication (regardless of study outcome) in a timely manner. Boston Scientific Corporation follows authorship principals as set forth in the Uniform Requirements of the International Committee of Medical Journal Editors (ICMJE; http://www.icmje.org). [redacted]

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24. Abbreviations and Definitions

24.1. Abbreviations

Abbreviations are shown in Table 24.1-1.

Table 24.1-1: Abbreviations

Abbreviation/Acronym	Term
ACC	American College of Cardiology
ACT	Activated Clotting Time
ADE	Adverse Device Effect
AE	Adverse Event
AHA	American Heart Association
BSC	Boston Scientific Corporation
BSJ	Boston Scientific Japan
BMS	Bare Metal Stent
CABG	Coronary Artery Bypass Graft
CEC	Clinical Events Committee
CK	Creatine Kinase
CRO	Contract Research Organization
eCRF	electronic Case Report Form
DAPT	Dual Antiplatelet Therapy
DCB	Drug-Coated Balloon
DES	Drug-Eluting Stent
ECG	Electrocardiogram
EDC	Electronic Data Capture
GCP	Good Clinical Practices
HCP	Health Care Professional
ICF	Informed Consent Form
IRB	Institutional Review Board
ISO	International Standards Organization
ISR	In-Stent Restenosis
IVUS	Intravascular ultrasound
LL	Late Loss
MACE	Major Adverse Cardiac Event
NHLBI	National Heart, Lung, and Blood Institute
MLD	Minimum lumen diameter
PCI	Percutaneous Coronary Intervention
POBA	Plain Old Balloon Angioplasty

Abbreviation/Acronym	Term
PTCA	Percutaneous Transluminal Coronary Angioplasty
QCA	Quantitative Coronary Angiography
QOL	Quolity of life
RVD	Reference Vessel Diameter
SADE	Serious Adverse Device effect
SAE	Serious Adverse Event
SV	Small Vessel
TIMI	Thrombolysis in Myocardial Infarction
TLF	Target Lesion Failure
TLR	Target Lesion Revascularization
TVF	Target Vessel Failure
TVR	Target Vessel Revascularization
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect

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