AGENT IDE

A Prospective, Randomized (2:1), Multicenter Trial to Assess the Safety and Effectiveness of the Agent™ Paclitaxel Coated PTCA Balloon Catheter for the Treatment of Subjects with In-Stent Restenosis (ISR)

S2358

CLINICAL INVESTIGATION PLAN

IDE#: G200100

National Clinical Trial (NCT) #: NCT04647253

Sponsored By

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Vendors/Labs	A list of vendors/laboratories involved in the trial is maintained by the sponsor.

Original Release: 27 March 2020

Current Version: 14 April 2023

Revision Version	Protocol Date	Template number and version	Protocol Section Modified	Summary of Changes	Justification for Modification
A	27 March 2020	90702637 Rev/Ver AL	N/A	N/A	Initial Release
B	02 October 2020	90702637 Rev/Ver AN	Section 6, 7 8, 9, 10, 11 and 18	Section 6: lesion length to be treated 26 mm Section 7: maximum number of subjects that can cross over from Agent to POBA arm Section 8: Inclusion criteria: lesion length 26 mm; Exclusion criteria: recent COVID patients Section 9: Subject withdrawal language updated Section 10: Preferred cardiac enzyme is CK-MB; antiplatelet therapy updated Section 11: Additional sub-group analysis added Section 18: Additional risk added	Updated protocol per FDA design recommendations
C	09 December 2020	90702637 Rev/Ver AO	Section 7, 8, 10, 11, 19 and 23	Section 7: increase number of subjects, add stratification by center and stent layer and clarify personnel blinding. Update to study schematic. Section 8: Update Inclusion/ Exclusion criteria. Section 10: Update Antiplatelet therapy. Section 11: Update statistical considerations. Section 19: Add Serious Health Threat definition.	Updated protocol per Steering Committee recommendations and updated BSC template.

Revision Version	Protocol Date	Template number and version	Protocol Section Modified	Summary of Changes	Justification for Modification
				Section 23: Add Study Registration language.	
D	01 October 2021	90702637 Rev/Ver AP		Version D of protocol not implemented	NA
E	25 March 2022	90702637 Rev/Ver AP		Version E of protocol not implemented	NA
F	25 October 2022	90702637 Rev/Ver AQ		Clarify the adaptive design with formal interim analysis. Update safety reporting section to align with current protocol template.	Clarifying the adaptive design and statistical method per FDA recommendation.
G	14 April 2023	90702637 Rev/Ver AQ	Section 2,6,11 and 25	Clarifying the analysis of MI to include the peri-procedural MI (PPMI) according to the SCAI definition and spontaneous MI according to the 4th Universal MI definition. Correct definition of technical success	Clarify the analysis of cardiac enzyme data and MI per FDA recommendation.

2. Protocol Synopsis

<table>
<tr><th colspan="2">AGENT IDE Study (S2358)
A Prospective, Randomized (2:1), Multicenter Trial to Assess the Safety and Effectiveness of the Agent™ Paclitaxel Coated PTCA Balloon Catheter for the Treatment of Subjects with In-Stent Restenosis (ISR)</th></tr>
<tr><td>Study Objective(s)</td><td>To assess the safety and effectiveness of the Agent™ Paclitaxel Coated PTCA Balloon Catheter compared to balloon angioplasty (POBA) in patients with in-stent restenosis (ISR) of a previously treated lesion of up to 26 mm in length (by visual estimate) in a native coronary artery 2.0 mm to 4.0 mm in diameter.</td></tr>
<tr><td>Planned Indication(s) for Use</td><td>The Agent™ Paclitaxel Coated balloon catheter is indicated for percutaneous transluminal coronary angioplasty (PTCA) in coronary arteries 2.0 mm to 4.0 mm in diameter and up to 26mm in length, for the purpose of improving myocardial perfusion to treat in-stent restenosis (ISR).</td></tr>
<tr><td>Test Device</td><td>Agent™ Paclitaxel Coated PTCA Balloon Catheter (Agent Drug Coated Balloon or Agent DCB).</td></tr>
<tr><td>Device Sizes</td><td>AGENT™ devices with a balloon length between 12 mm and 30 mm and diameters between 2.00 and 4.00 mm will be used in this study according to the following size matrix:
<table>
<tr><th rowspan="2">Balloon Diameter (mm)</th><th colspan="3">Balloon Length (mm)</th></tr>
<tr><th>12</th><th>20</th><th>30</th></tr>
<tr><td>2.00</td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>2.50</td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>3.00</td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>3.50</td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>4.00</td><td>X</td><td>X</td><td>X</td></tr>
</table></td></tr>
<tr><td>Control Device</td><td>Commercially available, PTCA Dilation Catheter</td></tr>
<tr><td>Study Design</td><td>A prospective, multi-center, 2:1 randomized (AGENT to POBA), controlled, single-blind, superiority trial.</td></tr>
<tr><td>Planned Number of Subjects</td><td>At least 480 subjects and up to a maximum of 600 subjects will be enrolled in the trial.</td></tr>
</table>

AGENT IDE Study (S2358) A Prospective, Randomized (2:1), Multicenter Trial to Assess the Safety and Effectiveness of the Agent™ Paclitaxel Coated PTCA Balloon Catheter for the Treatment of Subjects with In-Stent Restenosis (ISR)	
Planned Number of Investigational Sites	Up to 40 sites in the United States
Primary Endpoint	The primary endpoint is the 12-month Target Lesion Failure (TLF) rate, 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. The MI events include the Peri-Procedural MI (PPMI) according to the SCAI MI definition and the spontaneous MI according to the 4th Universal MI definition.
Additional Endpoints	Clinical endpoints measured in-hospital and at 30 days, 6 months, 12 months, then annually through 5 years. • Target lesion revascularization (TLR) rate, Target lesion failure (TLF) rate (primary endpoint at 12 months), Target vessel revascularization (TVR) rate • Target vessel failure (TVF) rate • MI (Q-wave and non–Q-wave) rate (PPMI per the SCAI definition and spontaneous MI per 4th Universal definition) • Cardiac death rate, • Non-cardiac death rate • All-cause death rate • Stent thrombosis rates (per Academic Research Consortium [ARC] definitions) Periprocedural endpoint: • Clinical procedural success rate • Technical success rate Change in Quality of Life: • Functional status of general health-related quality of life measured by changes in EQ-5D scores at hospital discharge, 12 months, 24 months and 36 months.
Method of Assigning Patients to Treatment	After successful pre-treatment of the lesion and confirmation that inclusion/exclusion criteria have been met, subjects will be randomized (2:1) to receive either the test device or a control device. A subject will be considered enrolled at the time of randomization.

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Follow-up Schedule	Clinical follow-up: in hospital, 30 days, 6 months, 12 months, then annually through 5 years post index procedure. The study will be considered complete with regard to the primary endpoint after all subjects have completed the 12-month follow-up period. Subjects who are enrolled but who do not receive a study/ control device will be followed through 12 months only.
Study Duration	Enrolled subjects will be followed for 5 years following the index procedure.
Antiplatelet Therapy	It is required that subjects receive a minimum of 1-month dual antiplatelet therapy. Antiplatelet monotherapy should be continued for the duration of the study.
Clinical Inclusion Criteria	CI1. Subject must be at least 18 years of age CI2. Subject (or legal guardian) understands the trial requirements and the treatment procedures, and provides written informed consent before any trial-specific tests or procedures are performed CI3. Subject is eligible for percutaneous coronary intervention (PCI) CI4. Subject is willing to comply with all protocol-required follow-up evaluation CI5. Women of child-bearing potential must agree to use a reliable method of contraception from the time of screening through 12 months after the index procedure
Angiographic Inclusion Criteria (visual estimate)	AI1. In-stent restenosis in a lesion previously treated with either a drug-eluting stent or bare metal stent, located in a native coronary artery with a visually estimated reference vessel diameter (RVD) > 2.0 mm and ≤ 4.0 mm. AI2. Target lesion length must be < 26 mm (by visual estimate) and must be covered by only one balloon. AI3. Target lesion must have visually estimated stenosis > 50% and < 100% in symptomatic patients (>70% and <100% in asymptomatic patients) prior to lesion pre-dilation. AI4. Target lesion must be successfully pre-dilated.

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	Note: Successful predilation/pretreatment refers to dilation with a balloon catheter of appropriate length and diameter, or pretreatment with directional or rotational coronary atherectomy, laser or cutting/scoring balloon with no greater than 50% residual stenosis and no dissection greater than National Heart, Lung, Blood Institute (NHLBI) type C. Thrombolysis in Myocardial Infarction (TIMI) grade flow in the target lesion must be >2 AI5. If a non-target lesion is treated, it must be treated first and must be deemed a success. ***Note:*** Successful treatment of a non-target lesion is defined as a residual stenosis of ≤ 30% in 2 near-orthogonal projections with TIMI 3 flow, as visually assessed by the physician, without the occurrence of prolonged chest pain or ECG changes consistent with MI.
Clinical Exclusion Criteria	CE1. Subject has other serious medical illness (e.g. cancer, congestive heart failure) that may reduce life expectancy to less than 24 months. CE2. Subject has current problems with substance abuse (e.g. alcohol, cocaine, heroin, etc.). CE3. Subject has planned procedure that may cause non-compliance with the protocol or confound data interpretation. CE4. Subject is participating in another investigational drug or device clinical study that has not reached its primary endpoint. CE5. Subject intends to participate in another investigational drug or device clinical study within 12 months after the index procedure. CE6. Woman who is pregnant or nursing. (A pregnancy test must be performed within 7 days prior to the index procedure, except for women who definitely do not have child-bearing potential.) CE7. Left ventricular ejection fraction known to be < 25%. CE8. Subject had PCI or other coronary interventions within the last 30 days. CE9. Planned PCI or CABG after the index procedure. CE10. STEMI or QWMI <72h prior to the index procedure. CE11. Cardiogenic shock (SBP < 80 mmHg requiring inotropes, IABP or fluid support).

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	CE12. Known allergies against paclitaxel or other components of the used medical devices. CE13. Known hypersensitivity or contraindication for contrast dye that in the opinion of the investigator cannot be adequately pre-medicated. CE14. Intolerance to antiplatelet drugs, anticoagulants required for procedure. CE15. Platelet count < 100k/mm3 (risk of bleeding) or > 700k/mm3. CE16. Subject with renal insufficiency (creatinine ≥2.0 mg/dl) or failure (dialysis dependent). CE17. Subject has suspected or proven COVID-19 at present or within the past 4 weeks with resolution of symptoms.
Angiographic Exclusion Criteria (visual estimate)	AE1. Target lesion is located within a bifurcation with planned treatment of side branch vessel. AE2. Target lesion is located within a saphenous vein or arterial graft. AE3. Thrombus present in the target vessel. AE4. > 50% stenosis of an additional lesion proximal or clinically significant distal (>2.0mm RVD) to the target lesion. AE5. Patient with unprotected left main coronary artery disease. (>50% diameter stenosis)
Multiple Interventions During Index Procedure	Up to 2 native coronary artery lesions in 2 major epicardial vessels may be treated. Subjects may have 1 target lesion, or 1 target lesion and 1 non-target lesion (in non-target vessel) treated. One lesion must meet the angiographic criteria for a target lesion as described above and is appropriate to be treated with study / control device. A maximum of 1 non-target lesion in 1 non-target vessel may be treated during the index procedure with a commercially available device. The non-target lesion must be treated during the index procedure prior to the treatment of the target lesion and deemed an angiographic success.
Statistical Methods	

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Primary Statistical Hypothesis	The primary endpoint of Target Lesion Failure at 12 months for the Agent DCB arm is superior to that for the POBA arm.
Statistical Test Method	A z-test with unpooled variance for the difference of two proportions will be used to test the hypothesis of superiority of DCB over POBA in the 12-month clinical endpoint: H_0: $TLF_{DCB} \geq TLF_{POBA}$ H_1: $TLF_{DCB} < TLF_{POBA}$ where TLF_{DCB} and TLF_{POBA} are the TLF through 12 months for the DCB and POBA arms respectively. The primary analysis set for the primary endpoint is the Intent to treat analysis set. This endpoint will also be analyzed for the per protocol analysis set.
Sample Size Parameters	The sample size calculation for the primary endpoint is based on the following assumptions: • Expected TLF_{DCB} = 10.6 % (based on meta-analysis of historical trials and including an adjustment to account for the oculo-stenotic reflex) • Expected TLF_{POBA} = 21.2% (based on meta-analysis of historical trials and including an adjustment to account for the oculo-stenotic reflex) • Test significance level (α) = 2.5% (1-sided) • Power = 85% • Randomization ratio = 2 DCB: 1 POBA • Number of evaluable subjects per arm= 310 DCB + 155 POBA • Expected attrition rate = 3% • Total planned enrollment = 480 subjects, 320 in DCB and 160 in POBA • The sample size re-estimation will be performed on the planned formal interim analysis by the Independent DMC Statisticians. The final sample size may be increased up to a maximum of 600 subjects which is based on the observed conditional power of the interim analysis. Details of this adaptive approach are pre-specified in the statistical analysis plan (SAP).

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Success Criteria for the Primary Endpoint	The final analysis with the sample size derived from the sample size re-estimation strategy will be conducted on subjects with 1 year data. If the *P* value from the z-test with unpooled variance for the difference of two proportions is less than 0.025 (1-sided) and the event rate in the DCB group is less than the rate in the POBA group in the final analysis, the primary endpoint for the DCB will be concluded to be statistically significantly lower than that for the POBA. This corresponds to the one-sided 97.5% upper confidence bound on the difference between treatment groups (DCB minus POBA) for the observed rate of the primary endpoint being less than zero.

3. Table of Contents

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4. Introduction

4.1. *Background*

The Agent IDE trial is designed to assess the safety and effectiveness of the Agent™ Paclitaxel Coated PTCA Balloon Catheter compared to balloon angioplasty (POBA) in patients with in-stent restenosis of a previously treated lesion of up to 26 mm in length (by visual estimate) in a native coronary artery 2.0 mm to 4.0 mm in diameter. Additional angiographic and clinical data was collected outside of the US in the AGENT ISR study to support future FDA approval.

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.

Restenosis, the renarrowing of a blood vessel that had become narrowed and received treatment, is a common adverse event of endovascular procedures such as angioplasty and stenting. Management of in-stent restenosis (ISR) following implantation of a coronary stent is clinically challenging. Currently available therapeutic options include drug-coated balloons (DCB) coated with an antiproliferative drug paclitaxel that inhibits the proliferation of neointimal smooth muscle cells, thereby reducing the rate of restenosis.[1] Data from numerous clinical trials and registries have demonstrated the use of drug coated balloons (DCB) as a safe and effective treatment for ISR.[2] The German consensus group recommends DCB treatment not only for ISR, but also for de-novo lesions in small coronary arteries and bifurcation lesions.[3] Similarly, the Guidance on Myocardial Revascularization released by the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) recommends DCB treatment as an alternative option to treat ISR.[4]

Agent DCB is a paclitaxel-coated Percutaneous Transluminal Coronary Angioplasty (PTCA) device based on the well characterized and commercially available Emerge™ PTCA Dilatation Catheter (Boston Scientific Corporation, Massachusetts, United States). Collaborative efforts between Boston Scientific and Hemoteq AG (Wuerselen, Germany) resulted in the development of a low-dose formulation of paclitaxel (2 $\mu m/mm^2$) blended with the inactive excipient Acetyl Tributyl Citrate (ATBC). This paclitaxel coating, once delivered to the arterial tissue, is thought to maintain the luminal diameter by reducing neointimal proliferation and the onset of restenosis. The Agent device incorporates a number of features designed to allow a reduced paclitaxel dose density (2 $\mu m/mm^2$) as compared to

the majority of currently marketed products, such as SeQuent Please DCB (3 µm/mm^2) (B. Braun Interventional Systems Inc.). In preclinical studies, the Agent DCB demonstrated comparable tissue drug absorption, clinical safety and vascular response outcomes to 3 µm/mm^2 formulations of CE-marked DCB platforms, while reducing systemic drug exposure. The Agent ISR study compared a reduced drug coating formulation with the SeQuent Please DCB. Agent proved non-inferior to SeQuent Please for in-stent late loss at 6 months. Death and MI were similar between groups at 12 months; the rate of stent thrombosis (ST) was numerically lower with Agent (no ST events reported in the Agent arm out to 12M) but did not reach significance.

Data from this AGENT IDE study will characterize the clinical safety and efficacy of drug coated balloon compared with conventional balloon angioplasty for treatment of coronary in-stent restenosis.

4.2. *Clinical Background*

Data from a prospective European randomized trial, AGENT ISR, to demonstrate safety and performance of the Agent Paclitaxel-Coated PTCA Balloon Catheter when compared to the SeQuent Please Paclitaxel-Releasing Coronary Balloon Catheter in the treatment of in-stent restenosis is provided below. A summary of the ISAR-DESIRE 3A clinical trial is also provided. This clinical data in combination with other preclinical and clinical data supports the safety and performance of Agent for the treatment of patients with ISR.

4.2.1. AGENT ISR Prospective Randomized Trial

The AGENT ISR clinical study was a prospective, multicenter, 1:1 randomized, non-inferiority study conducted at 11 sites in Germany and France. The study's objective was to determine safety and performance of Agent Paclitaxel-Coated PTCA Balloon Catheter compared to the SeQuent Please Paclitaxel-Releasing Coronary Balloon Catheter for the treatment of patients with in-stent restenosis of the previously treated lesion. The trial enrolled 125 patients with enrollment completed on May 11, 2016; 6-month and 12-month interim results and clinical endpoints through 3 years of follow-up are available. The primary endpoint of this study was in-stent late lumen loss (LLL) at 6 months post procedure as measured by quantitative coronary angiography and is powered to test for non-inferiority of the Agent balloon to the SeQuent Please balloon. Clinical endpoints measured in-hospital, at 30 days, and then at 6 months, 1 year, 2 years and 3 years include:

- TLR rate
- TVR rate
- All death rate
- Cardiac death rate
- Non-cardiac death rate
- MI rate
- Composite of all death and MI
- QWMI rate and NQWMI rate
- Stent thrombosis rate
- TLF rate
- TVF rate

The primary statistical hypothesis was met as in-stent late loss was non-inferior in the Agent DCB group compared to the SeQuent Please DCB. Agent DCB was non-inferior to SeQuent Please DCB as the two-sided upper 95% confidence bound for the difference in 6-month late lumen loss is <0.20 (pre-defined non-inferiority margin). The 6-month results with regards to primary endpoint are provided in **Table 4.2-1.**

Table 4.2-1: 6 Month Results – In Stent Late Lumen Loss

Agent (N=51)	Sequent Please (N=49)	Difference [95% CI]	Noninferiority Margin	$P_{noninferior}$
0.397 ± 0.43	0.393 ± 0.536	0.004 [-0.189, 0.196]	0.2	0.046

Reference: Hamm et al, 2019[5]

Numbers are mean± standard deviation
**Measured by an independent, blinded core laboratory*
Noninferiority test from a 2-sided Student's t-test comparing the difference between Agent and SeQuent Please to the noninferiority margin

Additional clinical endpoints through 3 years of follow-up are shown in Table 4.2-2. The data demonstrated comparable outcomes between Agent and SeQuent Please between 1-3 years. Three-year rates of TLF and TLR were not significantly different in Agent versus SeQuent Please arms (TLF: 18.5% versus 16.7%, P=0.98 and TLR: 12.3% versus 15.0%, P= 0.86. There was no ST in the Agent arm, and 5 patients in the SeQuent Please arm experienced stent thrombosis through 3 years.

Table 4.2-2: Clinical Endpoints through 3 Years

Events	Agent	SeQuent Please	*P* value
30 days			
Death and MI	0.0% (0/65)	1.7% (1/60)	0.97
Death	0.0% (0/65)	0.0% (0/60)	1.00
Cardiac Death	0.0% (0/65)	0.0% (0/60)	1.00
Non-Cardiac Death	0.0% (0/65)	0.0% (0/60)	1.00
MI	0.0% (0/65)	1.7% (1/60)	0.97
Q-wave MI	0.0% (0/65)	0.0% (0/60)	1.00
Non-Q-wave MI	0.0% (0/65)	1.7% (1/60)	0.97
TLR	0.0% (0/65)	1.7% (1/60)	0.97
TVR	0.0% (0/65)	1.7% (1/60)	0.97
TLF	0.0% (0/65)	1.7% (1/60)	0.97
TVF	0.0% (0/65)	1.7% (1/60)	0.97
Stent Thrombosis	0.0% (0/65)	1.7% (1/60)	0.97
6 months			
Death and MI	3.1% (2/65)	3.3% (2/60)	1.00
Death	1.5% (1/65)	1.7% (1/60)	1.00
Cardiac Death	1.5% (1/65)	1.7% (1/60)	1.00
Non-Cardiac Death	0.0% (0/65)	0.0% (0/60)	1.00

Events	Agent	SeQuent Please	*P* value
MI	1.5% (1/65)	1.7% (1/60)	1.00
Q-wave MI	0.0% (0/65)	0.0% (0/60)	1.00
Non-Q-wave MI	1.5% (1/65)	1.7% (1/60)	1.00
TLR	3.1% (2/65)	5.0% (3/60)	0.93
TVR	4.6% (3/65)	5.0% (3/60)	1.00
TLF	6.2% (4/65)	6.7% (4/60)	0.90
TVF	7.7% (5/65)	6.7% (4/60)	1.00
Stent Thrombosis	0.0% (0/65)	1.7% (1/60)	0.97
1-year			
Death and MI	6.2% (4/65)	5.0% (3/60)	1.00
Death	3.1% (2/65)	1.7% (1/60)	1.00
Cardiac Death	3.1% (2/65)	1.7% (1/60)	1.00
Non-Cardiac Death	0.0% (0/65)	0% (0/60)	1.00
MI	4.6% (3/65)	3.3% (2/60)	1.00
Q-wave MI	0.0% (0/65)	0.0% (0/60)	1.00
Non-Q-wave MI	4.6% (3/65)	3.3% (2/60)	1.00
TLR	7.7% (5/65)	10.0% (6/60)	0.89
TVR	10.8% (7/65)	11.7% (7/60)	1.00
TLF	10.8% (7/65)	11.7% (7/60)	1.00
TVF	13.8% (9/65)	13.3% (8/60)	1.00
Stent Thrombosis	0.0% (0/65)	3.3% (2/60)	0.44
2 years			
Death and MI	9.2% (6/65)	10% (6/60)	1.00
Death	6.2% (4/65)	3.3% (2/60)	0.75
Cardiac Death	4.6% (3/65)	3.3% (2/60)	1.00
Non-Cardiac Death	1.5% (1/65)	0% (0/60)	1.00
MI	6.2% (4/65)	6.7% (4/60)	1.00
Q-wave MI	1.5% (1/65)	0% (0/60)	1.00
Non-Q-wave MI	6.2% (4/65)	6.7% (4/60)	1.00
TLR	10.8% (7/65)	15.0% (9/60)	0.66
TVR	13.8% (9/65)	16.7% (10/60)	0.85
TLF	13.8% (9/65)	16.7% (10/60)	0.85
TVF	16.9% (11/65)	18.3% (11/60)	1.00
Stent Thrombosis	0% (0/65)	6.7% (4/60)	0.11
3-year			
Death and MI	16.9% (11/65)	13.3% (8/60)	0.76
Death	13.8% (9/65)	5.0% (3/60)	0.17
Cardiac Death	7.7% (5/65)	3.3% (2/60)	0.50
Non-Cardiac Death	6.2% (4/65)	1.7% (1/60)	0.41
MI	6.2% (4/65)	8.3% (5/60)	0.90
Q-wave MI	1.5% (1/65)	0% (0/60)	1.00
Non-Q-wave MI	6.2% (4/65)	8.3% (5/60)	0.90
TLR	12.3% (8/65)	15% (9/60)	0.86

Events	Agent	SeQuent Please	*P* value
TVR	16.9% (11/65)	16.7% (10/60)	1.00
TLF	18.5% (12/65)	16.7% (10/60)	0.98
TVF	21.5% (14/65)	18.3% (11/60)	0.82
Stent Thrombosis	0% (0/65)	8.3% (5/60)	0.06

Numbers are % (count/sample size)
P values are from K-S test for interval-scaled variables and the χ^2 or K-W test for other variables
Abbreviation MI=myocardial infarction; TLR=target lesion revascularization (by definition TLR is also a TVR); TVR=target vessel revascularization; TLF=target lesion failure (defined as composite of cardiac death, MI and TLR)

In conclusion, this study met its primary objective by demonstrating non-inferiority of the Agent DCB to SeQuent Please with respect to the 6-month angiographic endpoint of in-stent LLL (0.046). Clinical events rates were comparable in both groups through 3 years of follow-up. Importantly, no stent thrombosis was reported in the Agent group through 3 years.

The ISAR-DESIRE 3A trial was a prospective, multicenter, non-randomized, single arm study of Agent DCB with comparison against an historical control group (SeQuent Please DCB) from the ISAR-DESIRE 3 trial for the treatment of subjects with a coronary restenosis after implantation of limus-analogue drug-eluting stents (DES). The trial enrolled 125 patients. The primary endpoint was In-segment percent diameter stenosis (%DS) collected during follow-up angiography at 6-8 months post index procedure. The Agent DCB was shown to be non-inferior to the SeQuent Please DCB for the primary endpoint (In-segment percent diameter stenosis). The %DS for the Agent DCB group was 38.9±17.5% and the %DS for the SeQuent Please DCB group was 38.0±21.5% (*P*=0.0056). TLR in the Agent DCB group and SeQuent Please DCB group at 1 year was 20.6% and 22.1%, respectively (*P*=0.80). All-cause mortality in the Agent DCB group and SeQuent Please DCB group at 1 year post index procedure was 0.8% and 2.2%, respectively (*P*=0.39). The incidence of events did not differ between the Agent DCB and SeQuent Please DCB groups.[5]

Agent paclitaxel-coated balloon was granted a CE mark in July 2014 and is currently marketed in Europe and other regions with indications for percutaneous transluminal coronary angioplasty (PTCA) for treatment of in-stent restenosis (ISR) and de novo small vessel disease.

4.3. *Study Rationale*

Drug Coated Balloon technology can be an alternative therapy available for US cardiologists to treat patients with in-stent restenosis in coronary vessels. As noted in section 4.2 clinical data are available from the randomized trial with the Agent product, AGENT ISR. The data from this RCT coupled with data from this randomized IDE study are expected to provide adequate evidence supporting the safety and efficacy for the Agent DCB product for use in the US. While the control arm in the AGENT ISR study is another DCB that is not approved in the United States, the control DCB has been shown to be superior to POBA which is an accepted therapy for ISR in the United States. The direct superiority of Agent over POBA is the hypothesis that will be proven in this randomized IDE study. POBA is a widely used

treatment for ISR, as the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention (Levine, et al), section 6.3.4 recommends use of POBA to treat focal restenosis after DES implantation.

A 12-month primary endpoint will be evaluated as this is after the drug has been shown to have left the adventitia, given the release kinetics.

5. Device Description

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). The balloon catheter platform is based on the commercially available BSC Emerge™ PTCA balloon catheter system (K130391). The Agent balloon catheter is designed to inhibit vascular restenosis by delivering drug to diseased arterial tissue.

The catheter has a drug coating formulation consisting of paclitaxel (active pharmaceutical ingredient) at 2 µg/mm^2, and ATBC excipient (inactive ingredient).

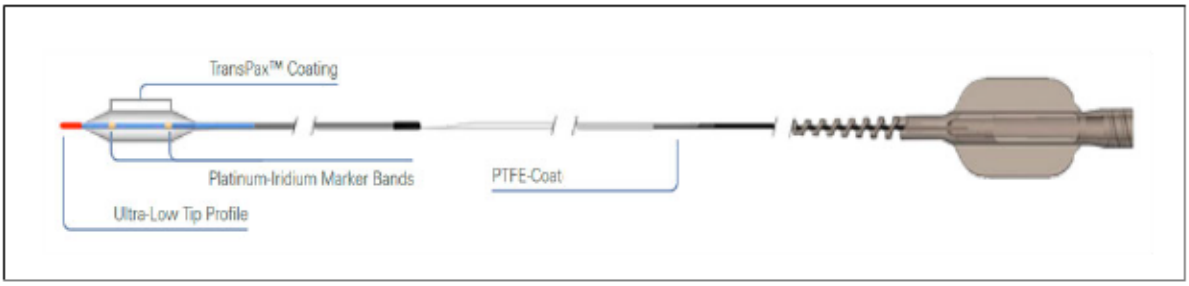
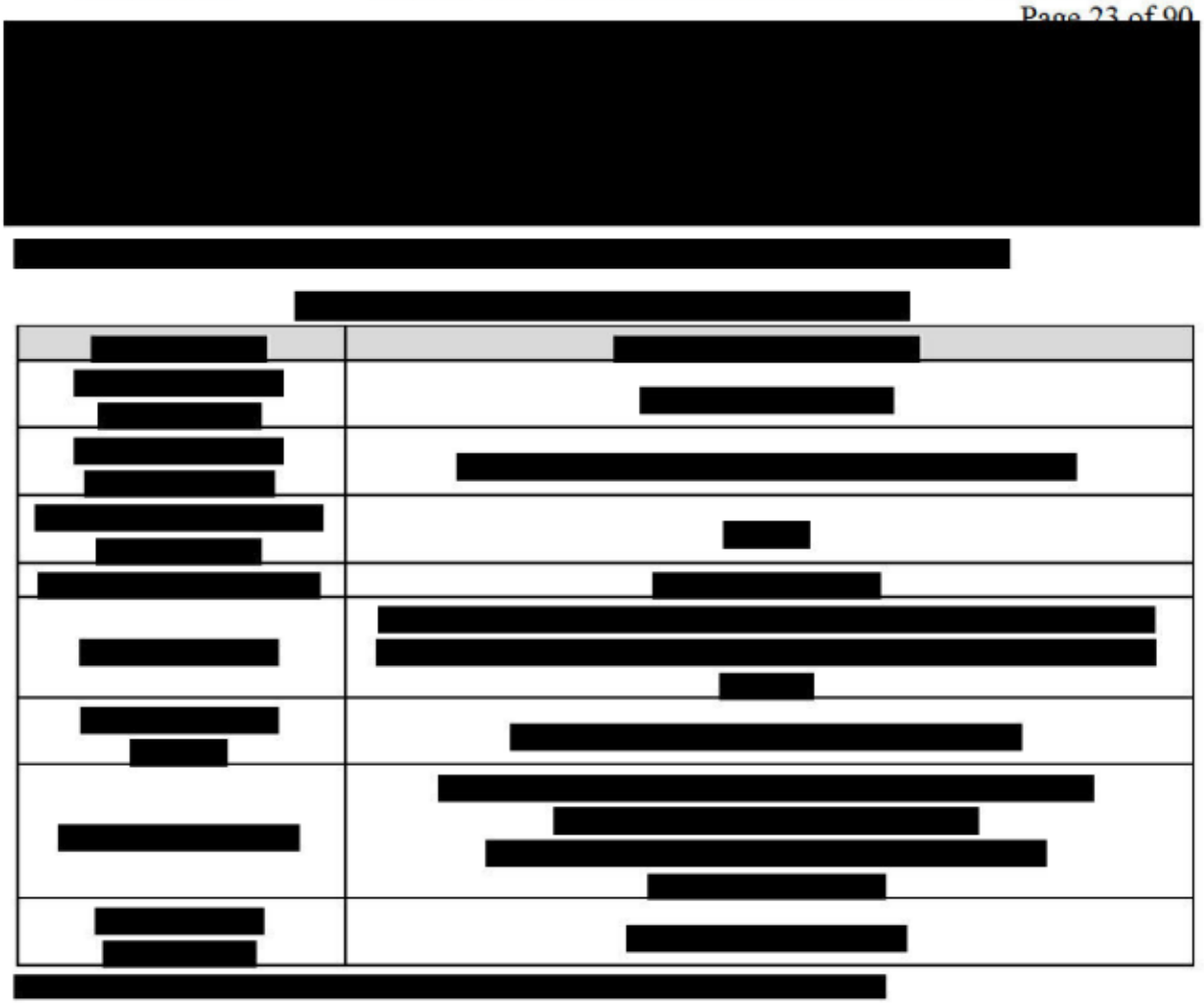


Figure 5-1: Agent Monorail Paclitaxel-Coated PTCA Balloon Catheter

5.1. *Device Component Description*

The device component of Agent is the Emerge Monorail PTCA balloon catheter system. Agent and Emerge are highly similar to the predicate device, Apex PTCA balloon catheter (Boston Scientific Corporation).

[redacted]



The clinical product matrix will include a subset of the proposed product matrix as identified in Table 5.1-2. The balloon lengths and diameters, which will be included in the clinical study, were chosen to bracket the entire product matrix intended for commercialization in the US.

Table 5.1-2: Agent IDE Matrix

Balloon Diameter (mm)	Balloon Length (mm)		
	12	20	30
2.00	X	X	X
2.50	X	X	X
3.00	X	X	X
3.50	X	X	X
4.00	X	X	X

5.2. *Drug Component Description and Coating Formulation*

The balloon coating consists of paclitaxel (PTx) and the excipient, Acetyl-Tri-n-Butyl 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.[7,8] The chemical structure of paclitaxel is provided in Figure 5-2.

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.[8] Paclitaxel has been shown to inhibit proliferation and migration of smooth muscle cells, effectively suppressing neointimal hyperplasia after vessel injury.[8-10] [redacted]

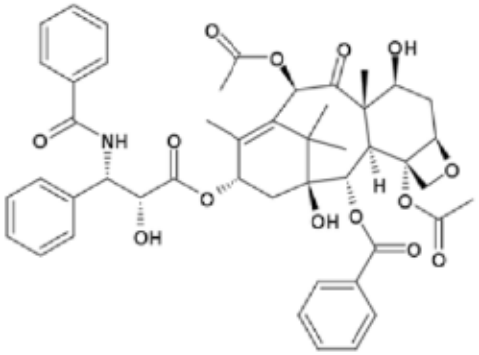


Figure 5-2: Chemical structure of paclitaxel

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 5-3.

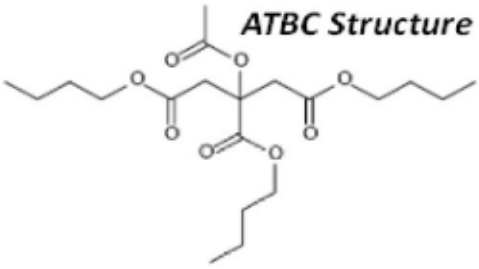


Figure 5-3: Chemical Structure of Acetyltributyl Citrate (ATBC)

[redacted]

[redacted]

[redacted]	[redacted]			
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

5.3. *Pharmacodynamics*

The drug substance coating aims to support the function of the balloon (widening of narrowed vessels) by counteracting balloon induced neointimal hyperproliferation, which as response to injury caused by the intervention may result in restenosis of the dilated vessel lumen.

For this purpose, paclitaxel was selected. By coating the drug substance on the balloon surface used to dilate the stenotic artery an exclusively local effect is achieved. The drug is transferred to the dilated segment when the balloon is inflated. Effective local drug substance concentrations are achieved with very low systemic exposure (reducing the probability of potential systemic side effects).

These properties of paclitaxel have demonstrated usefulness in the treatment of atherosclerotic artery diseases as demonstrated by the excellent clinical results with drug-eluting stents (DES). After implantation of a paclitaxel-coated stent, the drug substance inhibits vascular smooth muscle migration and proliferation, subsequent to endothelial injury by percutaneous transluminal angioplasty with the therapeutic goal to prevent in-stent restenosis.

5.4. *Pharmacokinetics*

Agent DCBs have been studied regarding pharmacokinetic characteristics, i.e. resulting drug tissue levels, in a porcine animal model. Drug delivery to the vessel wall and absorption into the arterial tissue leading to measurable PTx concentrations is essential to the clinical effectiveness of Agent. The pharmacokinetic profile for Agent was compared to Pantera Lux and SeQuent Please coronary DCB devices (EU commercial devices). Studies IMTR 20111245 and 09-107N evaluated drug delivery for Agent, Pantera Lux and Sequent Please

in coronary arteries. The results of PK studies IMTR20111245 and 09-107N support the local and systemic safety of Agent and are on file at BSC.

5.5. *Device Labeling*

The Directions for Use (DFU) will be included in the AGENT IDE study Manual of Operations. The study devices are labeled on the front, and side of the outer carton and on the inside sterile pouch. Packaging will include peelable, self-adhesive labels for each unit of product shipped. The labeling will include the following information:

- Product Name
- Catalog Number and Universal Part Number (UPN)
- Global Trade Item Number (GTIN)
- Lot number
- Balloon dimensions (balloon diameter and balloon length in mm)
- Expiration (use by) date

The following statements appear on the AGENT study device product labeling for clinical US distribution.

Caution: Investigational Device. Limited by United States law to investigational use. Exclusively for Clinical Investigations

6. Study Objectives and Endpoints

To assess the safety and effectiveness of the Agent™ Paclitaxel Coated PTCA Balloon Catheter compared to balloon angioplasty (POBA) in patients with in-stent restenosis of a previously treated lesion of up to 26 mm in length (by visual estimate) in a native coronary artery 2.0 mm to 4.0 mm in diameter.

6.1. *Primary Endpoint*

The primary endpoint is the 12-month Target Lesion Failure (TLF) rate, 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. The MI events include the PPMI according to the SCAI MI definition and the spontaneous MI according to the 4th Universal MI definition.

6.2. *Additional Endpoints*

Clinical endpoints measured in-hospital and at 30 days, 6 months, 12 months, then annually through 5 years.

- Target lesion revascularization (TLR) rate, Target lesion failure (TLF) rate (primary endpoint at 12 months), Target vessel revascularization (TVR) rate
- Target vessel failure (TVF) rate

- MI (Q-wave and non–Q-wave) rate (PPMI per the SCAI definition and spontaneous MI per 4th Universal definition)
- Cardiac death rate
- Non-cardiac death rate
- All-cause death rate
- Stent thrombosis rates (per Academic Research Consortium [ARC] definitions)

Periprocedural endpoint:

- Clinical procedural success rate
- Technical success rate

Change in Quality of Life:

- Functional status of general health-related quality of life measured by changes in EQ-5D scores at hospital discharge, 12 months, 24 months and 36 months

7. Study Design

The AGENT IDE clinical trial is a prospective, multi-center, 2:1 randomized (AGENT to POBA), controlled, single-blind, superiority trial to assess the safety and effectiveness of the AGENT DCB in patients with in-stent restenosis.

7.1. *Scale and Duration*

The AGENT Study will be conducted at up to 40 sites in the United States with planned initial enrollment of at least 480 subjects. An interim analysis for the sample size re-estimation will be performed on the 1-year data from the first 40% (192) randomized subjects of the initial enrollment of 480 patients. The final sample size may be increased up to a maximum of 600 subjects enrolled in the trial.

All subjects will be screened according to the protocol inclusion and exclusion criteria. Subjects meeting all inclusion criteria and no exclusion criteria will be randomized in a 2:1 allocation to either AGENT DCB or POBA, respectively.

Clinical follow-up will be required at the following time points: in hospital, 30 days, 6 months, 12 months, and annually through 5 years post index procedure.

A schematic of the AGENT IDE trial design is shown in the diagram below in Figure 7-1.

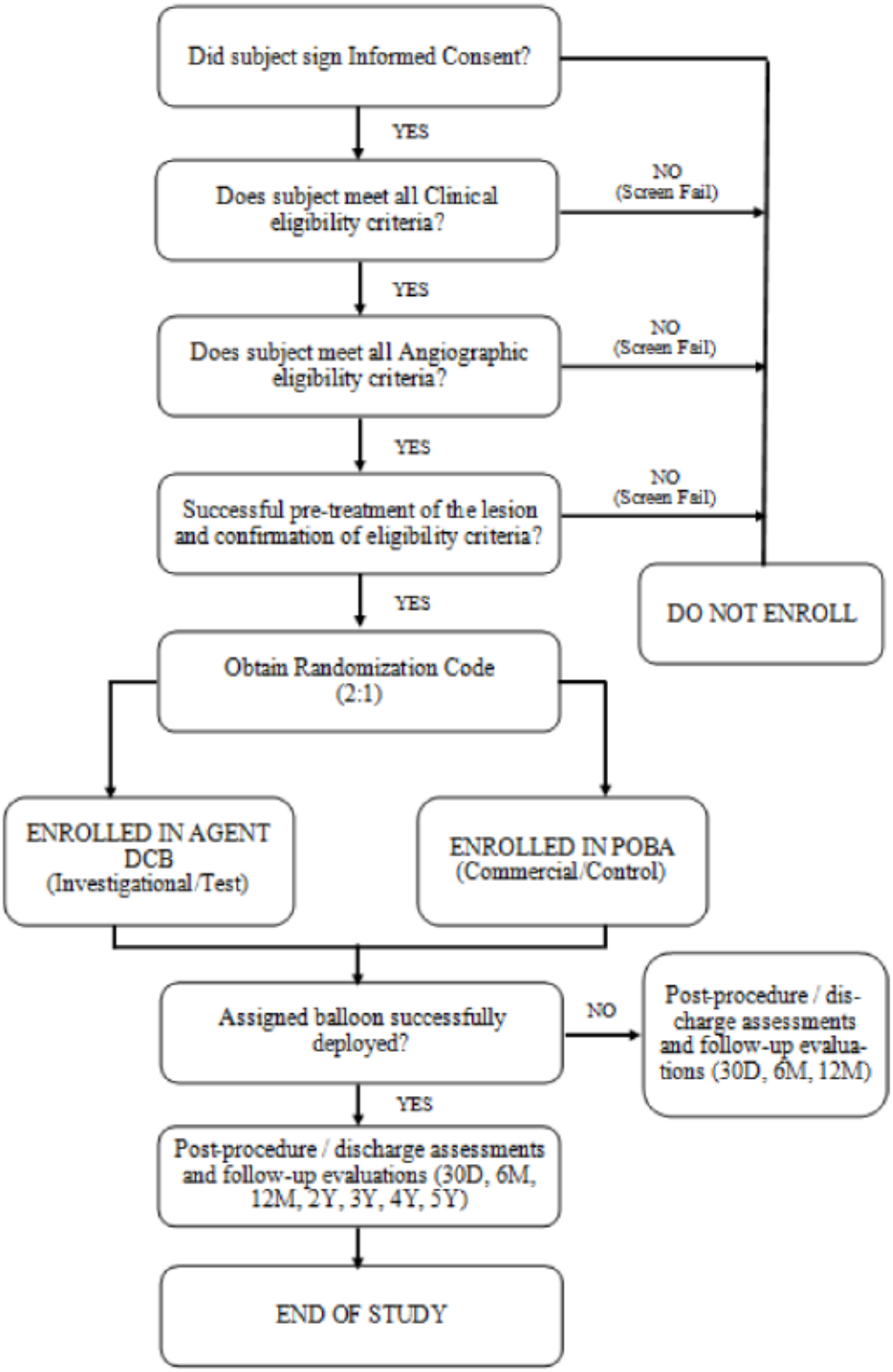


Figure 7-1: AGENT IDE Study Design

7.2. *Treatment Assignment*

Once the subject has met all clinical inclusion and no clinical exclusion criteria, the subject should be considered eligible to be enrolled in the trial. If the subject is found to meet exclusion criteria during the angiographic eligibility assessment, the subject will be considered a screen failure. If the subject is found to meet the inclusion criteria during the angiographic phase of the procedure, the subject will be considered eligible to be enrolled.

Eligible subjects in this trial will be randomized in a 2:1 allocation to either AGENT™ or POBA and stratified by center and single versus multiple stent layer restenosis. After successful pre-treatment of the lesion and confirmation that inclusion/ exclusion criteria have been met, subjects will be randomized (2:1) to receive either the test device or a control device. A subject will be considered enrolled at the time of randomization. All randomized subjects will be assigned unique identification numbers. Medidata Rave EDC system will be used to assign subjects to the treatment groups/device. Instructions on randomization and the Medidata Rave EDC system are provided in the Manual of Operations

If a subject is randomized to POBA and presents during follow-up with symptomatic and angiographically severe restenosis (meets criteria for ischemia-driven revascularization) within 12 months of enrollment, the subject will be eligible to cross over and receive an Agent device. The Agent DCB is an investigational device and must be deployed by study personnel (investigator or sub-investigator) at the participating site. There will be a maximum of 30 subjects in the study that will be allowed to cross over and be treated with the Agent DCB after initial POBA treatment. Use of the Agent DCB during the index procedure or as part of a planned, staged procedure is not permitted in patients randomized to the POBA arm under any circumstances. Crossover procedures will be monitored to ensure required clinical and angiographic criteria are met.

AGENT is a single blind trial. Subjects will be blinded to treatment assigned and treatment received. All subjects must remain blinded through study completion. Packaging of the investigational control and test devices are different, therefore the Investigator performing the procedure will not be blinded to the assigned treatment arm or resulting treatment. Study site personnel will be trained not to disclose the treatment assignment to the subject to minimize the potential unblinding of the subject. When possible, the site personnel conducting clinical follow-up will be blinded to a subject's treatment assignment. Core Laboratory personnel and the Clinical Events Committee (CEC) will be blinded to a subject's treatment assignment during the trial. The Biostatistician will remain blinded until the analysis of results. Instructions regarding the unblinding of a subject for a medical emergency can be found in the Manual of Operations (MOP).

7.2.1. Target and Non-target Lesions

A target lesion is the lesion selected by the Investigator for treatment with the study/control device (AGENT™ or POBA). It is expected that only a single balloon catheter will be used to treat the target lesion, and the balloon should only be inflated once. Repeat inflation of the DCB at the treatment site should be limited to emergency/ bail-out situations, e.g. to treat vessel perforations of flow-limiting dissections when exchange for an uncoated balloon is deemed inappropriate due to safety considerations. The target lesion includes the arterial

segment treated with the study/control device plus the arterial segment 5 mm proximal and 5 mm distal to the treatment site. The target lesion must meet all the angiographic selection criteria.

Up to 2 native coronary artery lesions in 2 major epicardial vessels may be treated. One lesion must meet the angiographic criteria described above and is appropriate to be treated with an AGENT™ drug coated balloon. A maximum of 1 non-target lesion in 1 non-target vessel may be treated with a commercially available device during the index procedure. The non-target lesion must be treated during the index procedure prior to the treatment of the target lesion and deemed an angiographic success prior to the treatment of the target lesion.

Note: Successful treatment of a non-target lesion is defined as a residual stenosis of ≤ 30% in 2 near-orthogonal projections with TIMI 3 flow, as visually assessed by the physician, without the occurrence of prolonged chest pain or ECG changes consistent with MI.

Note: Multiple focal stenoses will be considered as a single lesion if they can be completely treated with 1 study/ control device.

Predilation/pretreatment of the target lesion is required in this trial. If the target lesion is not successfully predilated/pretreated, the subject should not be enrolled. If a non-target lesion is to be treated, it must be treated first and must be deemed an angiographic success. Following the successful treatment of the non-target lesion, predilation of the target lesion may then be performed.

Note: Successful predilation/pretreatment refers to dilation with a balloon catheter of appropriate length and diameter, or pretreatment with directional or rotational coronary atherectomy, laser or cutting/scoring balloon with no greater than 50% residual stenosis and no dissection greater than National Heart, Lung, Blood Institute (NHLBI) type C. Thrombolysis in Myocardial Infarction (TIMI) grade flow in the target lesion must be >2

7.3. *Justification for the Study Design*

The AGENT IDE trial will evaluate the safety and effectiveness of the Agent™ Paclitaxel Coated PTCA Balloon Catheter compared to balloon angioplasty (POBA) in patients with in-stent restenosis of a previously treated lesion of up to 26 mm in length (by visual estimate) in a native coronary artery 2.0 mm to 4.0 mm in diameter.

POBA is a widely used treatment for ISR, as the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention (Levine, et al), section 6.3.4 recommends use of POBA to treat focal restenosis after DES implantation, and thus BSC feels this is the appropriate control for this trial.

The AGENT IDE trial will implement limited exclusion criteria so that a broad range of subject and lesion complexities are studied in the trial. Ongoing dynamic data safety monitoring will be performed throughout the trial to minimize subject risk. All enrolled subjects receiving the study balloon will be followed for 5 years post index procedure.

8. Subject Selection

8.1. *Study Population and Eligibility*

Clinical and angiographic inclusion and exclusion criteria for the AGENT IDE trial are included in Table 8.2-1 and Table 8.3-1 respectively. Prior to enrollment in the trial, a subject should meet all of the clinical and angiographic inclusion criteria and none of the clinical or 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 Table 8.3-1) is met.

Table 8.2-1: Inclusion Criteria

Clinical Inclusion Criteria	CI1. Subject must be at least 18 years of age CI2. Subject (or legal guardian) understands the trial requirements and the treatment procedures, and provides written informed consent before any trial-specific tests or procedures are performed CI3. Subject is eligible for percutaneous coronary intervention (PCI) CI4. Subject is willing to comply with all protocol-required follow-up evaluation CI5. Women of child-bearing potential must agree to use a reliable method of contraception from the time of screening through 12 months after the index procedure
Angiographic Inclusion Criteria (visual estimate)	AI1. In-stent restenosis in a lesion previously treated with either a drug-eluting stent or bare metal stent, located in a native coronary artery with a visually estimated reference vessel diameter (RVD) > 2.0 mm and ≤ 4.0 mm. AI2. Target lesion length must be < 26 mm (by visual estimate) and must be covered by only one balloon. AI3. Target lesion must have visually estimated stenosis > 50% and < 100% in symptomatic patients (>70% and <100% in asymptomatic patients) prior to lesion pre-dilation. AI4. Target lesion must be successfully pre-dilated. ***Note***: Successful predilation/pretreatment refers to dilation with a balloon catheter of appropriate length and diameter, or pretreatment with directional or rotational coronary atherectomy, laser or cutting/scoring balloon with no greater than 50% residual stenosis and no dissection greater than National Heart, Lung, Blood Institute (NHLBI) type C. Thrombolysis in Myocardial Infarction (TIMI) grade flow in the target lesion must be >2 AI5. If a non-target lesion is treated, it must be treated first and must be deemed a success. ***Note:*** Successful treatment of a non-target lesion is defined as a residual stenosis of ≤ 30% in 2 near-orthogonal projections with TIMI 3 flow, as visually assessed by the physician, without the occurrence of prolonged chest pain or ECG changes consistent with MI.

8.3. *Exclusion Criteria*

Table 8.3-1: Exclusion Criteria

Clinical Exclusion Criteria	CE1. Subject has other serious medical illness (e.g. cancer, congestive heart failure) that may reduce life expectancy to less than 24 months. CE2. Subject has current problems with substance abuse (e.g. alcohol, cocaine, heroin, etc.). CE3. Subject has planned procedure that may cause non-compliance with the protocol or confound data interpretation. CE4. Subject is participating in another investigational drug or device clinical study that has not reached its primary endpoint. CE5. Subject intends to participate in another investigational drug or device clinical study within 12 months after the index procedure. CE6. Woman who is pregnant or nursing. (A pregnancy test must be performed within 7 days prior to the index procedure, except for women who definitely do not have child-bearing potential.) CE7. Left ventricular ejection fraction known to be < 25%. CE8. Patient had PCI or other coronary interventions within the last 30 days. CE9. Planned PCI or CABG after the index procedure. CE10. STEMI or QWMI <72h prior to the index procedure. CE11. Cardiogenic shock (SBP < 80 mmHg requiring inotropes, IABP or fluid support). CE12. Known allergies against paclitaxel or other components of the used medical devices. CE13. Known hypersensitivity or contraindication for contrast dye that in the opinion of the investigator cannot be adequately pre-medicated. CE14. Intolerance to antiplatelet drugs, anticoagulants required for procedure. CE15. Platelet count < 100k/mm3 (risk of bleeding) or > 700k/mm3. CE16. Subject with renal insufficiency (creatinine ≥2.0 mg/dl) or failure (dialysis dependent). CE17. Subject has suspected or proven COVID-19 at present or within the past 4 weeks with resolution of symptoms.
Angiographic Exclusion Criteria (visual estimate)	AE1. Target lesion is located within a bifurcation with planned treatment of side branch vessel. AE2. Target lesion is located within a saphenous vein or arterial graft. AE3. Thrombus present in the target vessel AE4. > 50% stenosis of an additional lesion proximal or clinically significant distal (> 2.0 mm RVD) to the target lesion. AE5. Subject with unprotected left main coronary artery disease. (>50% diameter stenosis)

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

9. Subject Accountability

9.1. *Point of Enrollment*

Once the subject has signed the IRB approved study informed consent form (ICF) and has met all clinical inclusion and no clinical exclusion criteria, the subject should be considered eligible to be enrolled in the trial. If the subject is found to meet exclusion criteria during the angiographic eligibility assessment, the subject will be considered a screen failure and should not be enrolled/randomized or receive an investigational device, nor should the subject be followed post procedure per protocol. If the subject is found to meet the inclusion criteria during the angiographic phase of the procedure, the subject will be considered eligible to be enrolled/ randomized. The Medidata Rave EDC system will be used to assign subjects to treatment group (study/control) device. Subjects will be considered enrolled after they have been successfully randomized (i.e. when a treatment assignment is received by the investigative site).

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.

While trial withdrawal is discouraged, subjects may choose to withdraw from the trial at any time, with or without reason and without prejudice to further treatment. Withdrawn subjects will not undergo any additional trial follow-up, nor will they be replaced (the justified sample size considers an estimated allowance for attrition). The reason for withdrawal will be recorded (if given) in all cases of withdrawal. If a subject decides to withdraw, he/she will be asked to participate in a limited capacity allowing his/her medical status to be followed by telephone contact, medical chart review, or by other agreed upon method. If the subject decides not to continue participation in a limited capacity, data that have already been collected on withdrawn subjects will be retained and used for analysis, but no new data will be collected after withdrawal. The Investigator may discontinue a subject from participation in the trial if the Investigator feels that the subject can no longer fully comply with the requirements of the trial or if any of the trial procedures are deemed potentially harmful to the subject.

9.3. *Lost to Follow-Up*

A subject will be considered lost to follow-up after the subject misses 2 consecutive annual follow-up visits. A minimum of 3 attempts (i.e. 2 phone calls followed by a certified letter, or other traceable letter, if necessary) should be made to contact the subject for each missed follow-up visit and this information documented in the source.

Missed or late visits will be recorded as Protocol Deviations.

9.4. *End-of-Study Definition*

The study will be considered complete with regard to the primary endpoint after all patients have completed the 12-month follow-up period. A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit shown in the Data Collection Schedule (Table 10.1-1). The end of the study is defined as completion of the last patient last visit as shown in the Data Collection Schedule.

9.5. *Enrollment Controls*

The AGENT IDE trial will implement a formal Enrollment Communication Plan. The plan will outline the specific activities and responsibilities of BSC employees and representatives, and nature and timing of communications to Investigators as enrollment draws to a close. The objective of the plan is to minimize the risk of enrollment beyond the protocol-specified enrollment cap of up to 600 subjects.

10. Study Methods

10.1. *Data Collection*

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

Table 10.1-1: Data Collection Schedule

Procedure/Assessment	Baseline/ Screening[a]	Procedure	Postprocedure/ Discharge	Follow-up Visits				
				30 Days (± 7 Days)[c] Telephone Interview or Office Visit	6 Months (± 30 Days)[c] Telephone Interview or Office Visit	12 Months (± 30 Days)[c] Office Visit	2 year, 3 year (± 30 Days)[c] Office Visit	4 year, 5 Year (± 30 Days)[c] Telephone Interview or Office Visit
Informed consent process, including informed consent signature date[b]	X							
EQ-5D Questionnaire	X		X			X	X	
Demographics, including age, gender, and race and ethnicity (unless restricted by local laws)	X							
Medical history, including diabetes mellitus status[d]	X							
Angina assessment	X		X	X	X	X	X	X
Cardiac enzymes[e,f]	X		X					
12-lead ECG	X		X			X		
Serum creatinine/ CBC and platelets	X							
Antithrombotic medications		X						
Antiplatelet medications	X	X	X	X	X	X	X	X
PCI procedure information for target lesion	X							
Procedural, target lesion, non-target lesion (if applicable) predilation, postdilation (if applicable), and study device information		X						
Angiography		X						
AE and ADE assessment		X	X	X	X	X		
SAE, SADE, UADE, USADE, all CEC events and device deficiency assessment[g]		X	X	X	X	X	X	X

a: Baseline/ Screening assessments must take place ≤ 14 Days before procedure unless otherwise noted.

Procedure/Assessment	Baseline/ Screening[a]	Procedure	Postprocedure/ Discharge	Follow-up Visits				
				30 Days (± 7 Days)[c] Telephone Interview or Office Visit	6 Months (± 30 Days)[c] Telephone Interview or Office Visit	12 Months (± 30 Days)[c] Office Visit	2 year, 3 year (± 30 Days)[c] Office Visit	4 year, 5 Year (± 30 Days)[c] Telephone Interview or Office Visit

b: If the study Informed Consent Form is modified during the course of the trial, study subjects will be re-consented, if necessary

c: All follow-up dates will be calculated from the date of the index procedure. The protocol-required follow-ups may be performed via telephone interview and/ or an office visit within the applicable follow-up window as noted in the protocol. Beyond the 12-month follow-up, follow-up will be limited to the Safety Population (e.g., those study subjects who received a study/control device). Subjects who are enrolled but who do not receive a study / control device will be followed for 12 months only.

d: Height and weight should be documented in the eCRF if available in the subject medical record

e: Preprocedure cardiac enzymes can be drawn from the sheath at the time of sheath insertion. If cardiac enzymes are drawn preprocedure, the two results drawn closest to the procedure time should be recorded in the eCRF.

f: Two cardiac enzyme draws must be obtained at intervals per standard of care within 24 hours after the index procedure. The first draw should be performed 6-12 hours postprocedure and the second draw should be performed 18-24 hours postprocedure. If the subject is discharged prior to 18 hours postprocedure, the second draw should be obtained at the time of discharge (it is recommended that in these cases the second draw occur no earlier than 16 hours postprocedure).

g: SAEs, SADEs, UADEs, , CEC events, and device deficiencies will be monitored and reported to BSC from the time of enrollment through the 12-month follow-up for all subjects enrolled (regardless of whether a study/ control device was received) and beyond the 12-month follow-up through the 5-year follow-up for the Safety Population (e.g., those study subjects who received a study/ control device). AEs and ADEs will only be collected through the 12-month follow up.

Abbreviations: AE = Adverse event, ADE=adverse device effect; BSC=Boston Scientific Corporation; PCI=percutaneous coronary intervention; SADE=serious adverse device effect; SAE=serious adverse events; UADE=unanticipated adverse device effect

10.2. *Study Candidate Screening*

Study personnel will maintain documentation of subjects who fail to meet the AGENT IDE trial eligibility criteria, including the reason for screen failure.

10.3. *Informed Consent*

Before any study specific tests or procedures are performed, subjects who meet eligibility criteria will be asked to sign the IRB/IEC approved study ICF. Subjects must be given ample time to review the ICF and have questions answered before signing.

Study personnel should explain to the subject that even if the subject agrees to participate in the trial and signs the ICF, cardiac catheterization may demonstrate that the subject is not a suitable candidate for the trial.

Refer to section 9.1 for definition of point of enrollment.

10.4. *Baseline / Screening*

The following data must be collected and must take place ≤ 14 Days before procedure unless otherwise noted:

- Confirmation of clinical eligibility criteria
- Demographics including age, gender, and race and ethnicity (unless restricted by local laws)
- Medical history (general medical, cardiac, neurological, renal and peripheral history), including but not limited to, the following:
  - Diabetes mellitus status
  - Current angina status
  - Height and Weight (if available)
- Laboratory tests
  - Serum creatinine
  - Complete blood count (CBC) with platelets
- Current antiplatelet medications
- 12-lead electrocardiogram (ECG)
- Target lesion: previous PCI procedure, vessel treated, site treated, and type of procedure performed
- Cardiac Enzymes (see Note [1,2])
- EQ-5D Questionnaire

Note[1]: Preprocedure cardiac enzymes can be drawn from the sheath at the time of sheath insertion.

Note[2]: While CK-MB is the preferred cardiac enzyme, it is recommended that the same type of cardiac enzymes be analyzed prior to the index procedure and postprocedure for a given index hospitalization (i.e., not switching from CK-MB to troponin or vice versa).

10.5. *Required Concomitant Medications*

Protocol-required concomitant medications must be reported in the electronic case report form (eCRF) from the time of baseline through the 5-year follow-up. Information pertaining to the use of antiplatelet medications including dose changes, medication interruptions, and medication cessation, must be documented. Additional concomitant medications may be prescribed at the discretion of the treating physician according to standard of care.

10.5.1. Loading Dose (P2Y12 inhibitor)

- For subjects who have been taking a P2Y12 inhibitor for ≥ 72 hours at the time of the index procedure, a loading dose is not required.
- For subjects who have not been taking a P2Y12 inhibitor for ≥ 72 hours at the time of the index procedure, a loading dose is recommended. It is recommended that the loading dose be administered prior to the index procedure or not more than 2 hours after the index procedure. The following loading doses are recommended:
  - Clopidogrel: A peri-procedural loading dose of ≥ 300 mg is recommended.
  - Prasugrel: A peri-procedural loading dose of 60 mg is recommended.
  - Ticagrelor: A peri-procedural loading dose of 180 mg is recommended.

10.5.2. Loading Dose (Aspirin)

- For subjects who have been taking aspirin daily for ≥ 72 hours at the time of the index procedure, a loading dose is not required.
- For subjects who have not been taking aspirin daily for ≥ 72 hours at the time of the index procedure, a loading dose of aspirin is recommended prior to the index procedure. The dosage of the loading dose is at the discretion of the Investigator. It is recommended that the loading dose be administered prior to the index procedure.

10.5.3. In the Cardiac Catheterization Laboratory

The subject must be treated with heparin or an alternative antithrombotic (such as bivalirudin or enoxaparin) during the interventional portion of the procedure. If heparin is used, maintenance of an activated clotting time (ACT) >250 seconds throughout the interventional portion of the procedure is recommended. If enoxaparin or bivalirudin is used for procedural anticoagulation, monitoring of the anticoagulation level should be performed according to local laboratory practice.

Note: Platelet glycoprotein IIA/IIIB inhibitors such as Abciximab, eptifibatide, and tirofiban may be used at the discretion of the Investigator.

To eliminate coronary artery spasm that would interfere with accurate measurement of lumen obstruction due to plaque alone, intracoronary nitroglycerin (NTG) or isosorbide dinitrate

(ISDN) should be administered prior to the baseline angiogram. A dose of 100-200 µg of intracoronary NTG is preferred; however, alternative doses of 50 µg may be administered at the Investigator's discretion when deemed clinically necessary. Alternatively, if ISDN is administered, an oral dose of 2-3 mg is recommended.

10.5.4. Postprocedure

The treatment described in this section is applicable to subjects who receive a study/control device in a target vessel. Subjects who are enrolled but who do not receive a study/control device should be treated per standard of care and followed per protocol.

It is required that subjects receive a minimum of 1-month dual anti-platelet therapy. Antiplatelet monotherapy should be continued for the duration of the study.

10.5.4.1. Optimal medical therapy

In addition to dual antiplatelet therapy, it is recommended that subjects be treated with optimal medical therapy (including statins and beta blockers) to improve outcomes.

10.6. *Cardiac Catheterization*

10.6.1. Index Procedure

The start of the index procedure is defined as the time of sheath insertion. If a previously placed sheath is used (i.e., from a separate diagnostic procedure), index procedure start time is defined as the time of guide catheter insertion into sheath for the interventional procedure.

During cardiac catheterization, the following procedures and assessments must be completed.

- Angiography is to be performed according to the Angiographic Core Laboratory procedure guidelines.
- Confirm angiographic eligibility criteria of lesion(s).
- Pre-dilate/pretreat the target lesion and non-target lesion (if applicable). Confirmation of pre-dilation success with IVUS is strongly recommended.
- If the subject is randomized to receive study treatment, then inflate Agent DCB catheter per IFU.
- If the subject is randomized to the control group an additional inflation of at least 6 atm for 30 sec should follow if only a single pre-dilation inflation is necessary.
- Confirmation of all target lesion final angiographic assessment by IVUS is strongly recommended.

  Note: *IVUS imaging performed should be sent to the sponsor.*

10.7. *End of the Index Procedure*

The end of the index procedure is defined as the time the guiding catheter was removed (post final angiography). The introducer(s) sheaths should be removed as per standard local practice. The following procedures must be completed:

- Document procedural, target lesion, non-target lesion (if applicable), pre-dilation, post-dilation (if applicable), and study/control device information on the appropriate eCRFs.
- Record antithrombotic medications
- Complete AE assessment and collect source documents as described in Section 19
- Finalize angiographic procedure film and related required documentation to submit to the Core Laboratory per instructions set in the Manual of Operations.

10.8. *Postprocedure/ Discharge*

The subject may be discharged from the hospital when clinically stable at the Investigator's discretion but preferably not less than 18 hours after the index procedure. The following assessments must be completed post index procedure.

- Angina assessment
- Cardiac enzymes
  Two cardiac enzyme draws must be obtained at intervals per standard of care within 24 hours after the index procedure. The first draw should be performed 6-12 hours postprocedure and the second draw should be performed 18-24 hours postprocedure.

  Note: If the subject is discharged prior to 18 hours postprocedure, the second draw should be obtained at the time of discharge (it is recommended that in these cases the second draw occur no earlier than 16 hours postprocedure).
- Record antiplatelet medications
- 12 lead ECG
- EQ-5D Questionnaire
- Complete AE assessment and collect source documents as described in Section 19

It is important that trial site personnel review the trial requirements with the subject to maximize compliance with the follow-up schedule and required medication regimen. It is also important that trial site personnel instruct subjects to return for follow-up assessments according to the trial event schedule in Section 10. Study staff should establish a date for the follow-up telephone call with the subject and if possible, schedule the visit at the time of hospital discharge.

10.9. *Angiography*

All subjects will undergo angiographic assessment during the index procedure per standard of care. Subjects requiring reintervention for the target vessel during the 5-year follow-up period will undergo angiographic assessment at the time of reintervention as standard of care. Angiographic data and images collected during the index procedure and during any reinterventions of a target vessel during the 5-year follow-up period must be forwarded to the

Angiographic Core Laboratory for analysis. Angiograms performed at a non-investigational site should also be sent to the Core Laboratory.

Angiograms will be centrally assessed for qualitative and quantitative analysis by the Angiographic Core Laboratory. In addition, the Angiographic Core Laboratory will assess the quality of the recordings and adherence to the acquisition guidelines provide selected quality control feedback if necessary.

10.10. *Follow-Up*

All enrolled subjects who receive a study/control device, AGENT™ or POBA, will be evaluated through hospital discharge and at 30 days, 6 months, 12 months, then annually through 5 years post index procedure. Subjects who are enrolled but who do not receive a study/control device will be followed for 12 months only.

All protocol-required follow-up assessments must be conducted with direct contact with the subjects either in person or by telephone interview. At the time of each protocol required follow-up, study site personnel should answer any study related questions the subject may have in addition to completing the required protocol assessments. In the absence of cardiac symptoms, routine follow-up, cardiac procedures, and tests are left to the discretion of the Investigator.

During the 5-year follow-up period, if the subject experiences an event, it must be assessed and documented as described in Section 19. If the subject experiences new or recurrent cardiac symptoms during the trial, a more detailed evaluation (including repeat angiography) may be performed at the discretion of the Investigator and treating physicians.

If the subject undergoes repeat catheterization, the circumstances and outcome of the event must be assessed and documented as described in Section 19. If the repeat catheterization results in reintervention of the target vessel(s), angiographic data and images must be sent to the Angiographic Core Laboratory.

Subjects requiring reintervention should be treated according to the Investigator's discretion and standard of care. These subjects should receive an approved, commercially available treatment (if appropriate). Prior to initiating an angiogram, the results of the subjects' clinical status and functional testing should be documented. Prior to conducting the angiogram, indication(s) for the angiogram must be documented.

10.10.1. 30-Day Follow-up (30±7 Days)

All enrolled subjects must be evaluated 30 days after the index procedure. The follow-up assessment may be performed via telephone interview with the subject or during an office visit. During the 30-day follow-up, the following assessments must be completed.

- Angina assessment
- AE assessment and source document collection as described in Section 19
- Current antiplatelet medications (P2Y12 inhibitor and aspirin). Information pertaining to dose changes, medication interruptions, and medication cessation must be documented.

10.10.2. 6-Month Follow-up (180±30 Days)

All enrolled subjects must be evaluated 6 months after the index procedure. The follow-up assessment may be performed via telephone interview with the subject or during an office visit. During the 6-month follow-up, the following assessments must be completed.

- Angina assessment
- AE assessment and source document collection as described in Section 19
- Current antiplatelet medications (P2Y12 inhibitor and aspirin). Information pertaining to dose changes, medication interruptions, and medication cessation must be documented.

10.10.3. 12-Month Follow up (±30 Days)

All enrolled subjects must be evaluated 12 months after the index procedure. The follow-up assessment must be performed with the subject during an office visit. During the 12-month follow-up, the following assessments must be completed.

- Angina assessment
- 12-month ECG
- EQ-5D Questionnaire
- AE assessment and source document collection as described in Section 19
- Current antiplatelet medications (P2Y12 inhibitor and aspirin). Information pertaining to dose changes, medication interruptions, and medication cessation must be documented.

10.10.4. 2 year and 3 year Follow up (±30 Days)

All enrolled subjects must be evaluated at 2 years and 3 years after the index procedure. The follow-up assessment must be performed with the subject during an office visit. During the 2 year and 3-year follow-up, the following assessments must be completed.

- Angina assessment
- EQ-5D Questionnaire
- AE assessment and source document collection as described in Section 19
- Current antiplatelet medications (P2Y12 inhibitor and aspirin). Information pertaining to dose changes, medication interruptions, and medication cessation must be documented.

10.10.5. 4 and 5-Year Follow-up (±30 Days)

All enrolled subjects must be at evaluated 4 and 5 years after the index procedure. The follow-up assessment may be performed via telephone interview with the subject or during an office visit. During the annual follow-up, the following assessments must be completed.

- Angina assessment
- AE assessment and source document collection as described in Section 19
- Current antiplatelet medications (P2Y12 inhibitor and aspirin). Information pertaining to dose changes, medication interruptions, and medication cessation must be documented.

10.11. *Source Documents*

It is preferable that original source documents, when available, are maintained at the investigative center. In lieu of original source documents, certified copies are required to be maintained. A certified copy is a copy (irrespective of the type of media used) of the original record that has been verified (i.e., by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original. Source documentation includes but is not limited to those items noted in Table 10.11-1.

Table 10.11-1: Source Documentation Requirements

Requirement	Disposition
Printed, optical, or electronic document containing source data. Examples may include but are not limited to: hospital records, laboratory notes, device accountability records, photographic negatives, radiographs, records kept at the investigation center, at the laboratories and at the medico-technical departments involved in the clinical investigation	Retain at center.

Note: Please see section 25.2 for definitions of "source data' and "source document"

10.12. *Angio core lab documentation*

This study requires an angiographic core laboratory. Appropriate certifications and documentation records are required to be maintained at the site for laboratory and/or vendors.

11. Statistical Considerations

11.1. *Endpoints*

11.1.1. Primary Endpoint

The primary endpoint of Target Lesion Failure at 12 months for the Agent DCB arm is superior to that for the POBA arm.

11.1.1.1. Hypotheses

A z-test with unpooled variance for the difference of two proportions will be used to test the hypothesis of superiority of DCB over POBA in the 12-month clinical endpoint:

H_0: $TLF_{DCB} \geq TLF_{POBA}$

H_1: $TLF_{DCB} < TLF_{POBA}$

where TLF_{DCB} and TLF_{POBA} are the TLF through 12 months for the DCB and POBA arms respectively.

The primary analysis set for the primary endpoint is the Intent to treat analysis set. This endpoint will also be analyzed for the per protocol analysis set.

A z-test with unpooled variance for the difference of two proportions will be used to test the one-sided hypothesis of superiority between the rates of the two treatment groups. If the *P* value from the z-test is < 0.025 (1-sided) and the event rate of the DCB group is less than the rate of the POBA group, the rate of TLF for the DCB group will be concluded to be superior to that of the POBA. This corresponds to the one-sided 97.5% upper confidence bound on the difference between treatment groups (DCB minus POBA) for the observed rate of the primary endpoint being less than zero.

11.1.1.2. Sample Size

The sample size calculation for the primary endpoint is based on the following assumptions:

- Expected mean TLF_{DCB} = 10.6% (based on meta-analysis of historical trials and including an adjustment to account for the oculo-stenotic reflex)
- Expected mean TLF_{POBA} = 21.2% (based on meta-analysis of historical trials and including an adjustment to account for the oculo-stenotic reflex)
- Test significance level (α) = 2.5% (1-sided)
- Power = 85%
- Randomization ratio = 2 DCB: 1 POBA
- Number of evaluable subjects per arm = 310 (DCB) and 155 (POBA)
- Expected attrition rate = 3%
- Total planned enrollment = 480 subjects, 320 in DCB and 160 in POBA
- An adaptive group sequential design with one formal interim analysis for the primary endpoint sample size re-estimation will be conducted on 1-year data from the first 40% (N=192) randomized subjects of the planned initial enrollment of 480 subjects. Details of this adaptive approach are pre-specified in the statistical analysis plan (SAP).

A final analysis for the PMA submission will be conducted on the number of randomized subjects (at least 480 but up to 600 subjects) recommended by the independent DMC based on the sample size re-estimation strategy at the interim analysis. If the pre-specified interim analysis indicates that the study should be stopped at 480 subjects, then only the first 480 subjects will be considered for the primary endpoint analysis of the study in the PMA filing. If the pre-specified interim analysis indicates the study enrollment will be less than 600, the primary endpoint of all 600 enrolled subjects will also be presented.

11.1.1.3 Additional Endpoints

Clinical endpoints measured in hospital and at 30 days, 6 months, 12 months, then annually through 5 years. Additional clinical endpoints include:

- Target lesion revascularization (TLR) rate, Target lesion failure (TLF) rate (primary endpoint at 12 months), Target vessel revascularization (TVR) rate
- Target vessel failure (TVF) rate
- MI (Q-wave and non–Q-wave) rate (PPMI per the SCAI definition and spontaneous MI per the 4th Universal definition)
- Cardiac death rate

- Non-cardiac death rate
- All-cause death rate
- Stent thrombosis rates (per Academic Research Consortium [ARC] definitions)

Periprocedural endpoint:

- Technical success rate
- Clinical procedural success rate

Change in Quality of Life:

- Functional status of general health-related quality of life measured by changes in EQ-5D scores at hospital discharge, 12 months, 24 months and 36 months

11.2. *General Statistical Methods*

11.2.1. Analysis Sets

All primary and additional endpoints will be analyzed both on an intent-to-treat basis and on a per-protocol basis. For intent-to-treat analyses, all subjects who sign the IRB/IEC-approved study ICF and are enrolled in the study will be included in the analysis according to their randomized treatment, regardless of whether or not a study Agent™ Paclitaxel Coated PTCA Balloon Catheter or a control balloon angioplasty (POBA) was used.

For per-protocol analyses, only subjects who had the assigned study/control device (AGENT™ DCB or POBA) received in the target coronary artery at the index procedure will be included in the analysis. For subjects in the RCT with a target lesion, a study/control device must be used to treat the target lesion for the patient to be included in the per-protocol analysis set.

For eligible patients who crossover from POBA to AGENT DCB, they are considered to have experienced a study endpoint event of TLR and are censored at the time of crossover for the analysis of other clinical endpoints in the per-protocol analyses. In addition, events with onset dates on or after the time of crossover treatment will be summarized separately. These events will be included in the ITT analyses.

11.2.2. Control of Systematic Error/Bias

Subjects in the RCT will be randomly assigned to treatment groups and patients will remain blinded to treatment throughout the course of the study. Selection of subjects will be made from the Investigator's usual patient load. All subjects meeting the eligibility criteria and having signed the ICF will be eligible for enrollment in the study. In determining subject eligibility for the study, the Investigator's assessment of angiographic parameters before device placement will be used. However, to control for interobserver variability among sites, an Angiographic Core Laboratory will determine the angiographic results to be used in the data analyses. An independent CEC composed of expert cardiologists will adjudicate all reported events of death, MI, TVR and Stent Thrombosis.

11.2.3. Number of Subjects per Investigative Site

A computer-generated list of random treatment allocations (i.e., a randomization schedule) will be used to assign subjects to treatment in a 2:1 ratio of DCB to POBA. Randomization will be stratified by center and single vs. multiple stent layer restenosis. Each site will enroll no more than 20% of subjects of the total sample size.

11.3. *Data Analyses*

Baseline and outcome variables will be summarized using descriptive statistics for continuous variables (mean, standard deviation, number of observations, minimum and maximum) and discrete variables (percentage and count/sample). See Section 11.1 for a discussion on analysis of the primary endpoint and additional measurements.

11.3.1. Analysis of MI Events

The composite endpoint of TLF is comprised of cardiac death, MI related to the target vessel, and target lesion revascularization. The MI events include the PPMI according to the SCAI MI definition within 48 hours of the index procedure and the spontaneous MI according to the 4th Universal MI definition after 48 hours of the index procedure.

For the PPMI according to the SCAI MI definition, the unified Upper Limit of Normal (ULN) of 0.045 ng/mL for Troponin I and the unified ULN of 0.022 ng/mL for Troponin T will be applied to determine the cardiac enzyme elevation (in terms of multiple times relative to the ULN). This is an agreed approach with the FDA to address the heterogeneity of the various ULNs from all local laboratories in the AGENT IDE study.

All CEC reportable PPMI events using the unified ULNs of Troponin I and T to determine the cardiac enzyme elevation according to the SCAI MI definition will be adjudicated by CEC.

11.3.2. Other Endpoints/Measurements

Other measurements not driven by statistical hypotheses are listed in Section 11.1.1.3.

11.3.3. Interim Analyses

One planned formal interim analysis as described in the Statistical Analysis Plan for sample size re-estimation will be conducted on the first 40% (N=192) randomized subjects with 1-year follow up. The purpose of the interim analysis is to determine the sample size for the primary analysis for the PMA submission.

11.3.4. Subgroup Analyses

Primary and pre-specified additional endpoints will be summarized and treatment groups will be compared for the following subgroups of randomized subjects.

- Gender (male and female)

- Age (< 75 and ≥ 75 years)
- Diabetic Status
- Small Vessel vs Larger Vessel (RVD < 2.75 and ≥ 2.75 mm)
- One stent layer restenosis and Multiple stent layer restenosis (recurrent restenosis)
- Target lesion only and Target lesion plus 1 non-target lesion treated
- BMS and DES Restenosis.
- CTO and non-CTO

No adjustments for multiple comparisons will be made.

11.3.5. Justification of Pooling

Analyses for the primary endpoint will be presented using data pooled across institutions. An assessment of the poolability of subjects across centers will be made using logistic regression with clinical center as a fixed effect and a generalized linear mixed model with a clinical center as a random effect. The dependent variable is the primary endpoint of 12-month TLF, the independent variables are treatment, clinical center, and the corresponding treatment by clinical center interaction which are the fixed effects in the logistic regression model. A second mixed linear regression model using the clinical center as a random effect in the random effect logistic regression model will also be performed by using proc glimmix in SAS. If the *P* values for clinical center by treatment interaction in the two models are ≥0.15, it can be concluded that the treatment effect is not different across the centers and the data can be pooled. In the analysis to justify pooling across centers, the centers with fewer than 6 subjects enrolled in the study will be removed from the analysis.

11.3.6. Multivariable Analyses

Univariate and multivariate analyses will be performed to assess the effect of potential predictors on the primary endpoint as described in the Statistical Analysis Plan.

11.3.7. Changes to Planned Analyses

Any changes to the planned statistical analyses made prior to performing the analyses 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 study report along with a reason for the deviation.

12. Quality of Life

The QOL instruments used for the trial will be the EQ-5D for general health.

The EQ-5D is a descriptive system of health-related quality of life states consisting of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) each of which can take one of five responses. The responses record five levels of severity (no

problems/slight problems/moderate problems/severe problems/extreme problems) within a particular EQ-5D dimension.

13. Data Management

13.1. *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 the 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 studies pertaining to the use of electronic records and signatures. Database backups are performed regularly.

The Investigator 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.

All access to the clinical database will be changed to "Read only" after all data is either "Hard Locked" or "Entry Locked". Once acceptance of the final report or finalization of publications (as applicable) is received, final database storage and archiving activities can begin. Once all of the closeout activities are completed a request to IT is submitted to have the "Database Locked" or Decommissioned and all database access revoked.

13.2. *Data Retention*

The Principal Investigator or his/her designee or Investigational site will maintain all essential study documents and source documentation that support the data collected on the study subjects in compliance with applicable regulatory requirements.

The Principal Investigator or his/her designee will take measures to prevent accidental or premature destruction of these documents. If for any reason the Principal Investigator or his/her designee withdraws responsibility for maintaining these essential documents, custody must be transferred to an individual who will assume responsibility and BSC must receive written notification of this custodial change. Sites are required to inform Boston Scientific in writing where paper or electronic files are maintained in case files are stored off site and are not readily available.

13.3. *Core Laboratories*

The AGENT IDE trial will use an Angiographic Core Laboratory for analysis of angiography data. Results from the angiographic Core Laboratory will be entered or uploaded into the EDC system and will only be available to BSC.

All subjects will undergo angiographic assessment during the index procedure. Angiographic follow-up is not required; however, subjects requiring reintervention for the target vessel during the 5-year follow-up period will undergo angiographic assessment at the time of reintervention as standard of care.

Angiographic data, images (including IVUS and OCT), and technician's worksheets collected during the index procedure and during reinterventions for the target vessel(s) during the 5-year follow-up period (if applicable) must be forwarded to the Angiographic Core Laboratory for analysis. Angiographic data and images for reintervention for vessels not treated during the study index procedure should not be sent to the Angiographic Core Laboratory.

14. Protocol Deviations

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/EC/REB, and the regulatory authority if applicable 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, or per prevailing local requirements, if sooner than 5 working days.

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. Sites may also be required to report deviations to the IRB/EC/REB, 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 but not limited to, IRB/FDA notification, site re-training, or site discontinuation/termination) will be put into place by the sponsor.

The sponsor will not approve protocol waivers.

15. Device Accountability for Products Labelled Investigational

The investigational devices shall be securely maintained, controlled, and used only in this clinical study. Additionally, study personnel must follow the instructions related to the storage of the test device as noted in the corresponding clinical DFU. An electronic interactive response technology (IRT) will be used for investigational device management and accountability during the study.

For investigational-labelled items, the Principal Investigator or an authorized designee shall do the following:

- Securely maintain and control access to these items to ensure they are used only in this clinical study and only per the protocol.
- Ensure the storage environment for these items is appropriate for maintaining conditions per the items' labeling (e.g. temperature, humidity, etc., as applicable)
- Return remaining items upon Sponsor request and in the condition in which they were provided, reasonable wear and tear excepted

The sponsor or designee shall keep records to document the physical location of all investigational devices from shipment of investigational devices from BSC or designated facility to the investigation sites until return or disposal. The IRT will be used to document reception of the investigational device at a center.

Records shall be kept by authorized site study personnel to document the physical location and conditions of storage of all investigational devices. Sites must not dispose of any investigational devices for any reason at the site unless instructed to do so by BSC. Any investigational device that is disposed of at the site must be documented appropriately. Sites must document the reasons for any discrepancy noted in device accountability.

The principal investigator or an authorized designee shall keep records documenting the receipt, use, return and disposal of the investigational devices, which shall include the following:

- Name(s) of person(s) who received, used, returned, or disposed of each item
- Date of receipt at the site
- Identification of each investigational device (unique identifier or lot number/batch number/serial number)
- Expiry date, as applicable
- Date of use
- Subject identification
- Date of return and quantity of all investigational devices of unused, expired, or malfunctioning investigational devices, if applicable.

Once the Investigator and site are notified in writing by BSC that subject enrollment is complete, all unused investigational devices must be returned to BSC or its designee.

15.1. *Device Accountability for the Control Device*

Appropriate information on the control device size will be collected.

16. Compliance

16.1. *Statement of Compliance*

This clinical investigation is financed by the study sponsor. Before the investigational site can be "Authorized to Enroll," the investigational site must enter into a Clinical Study Agreement with the sponsor that details the financing of the study as well as the rights and obligations of the investigational site and the investigator.

This study will be conducted in accordance with ISO 14155 Clinical Investigation of Medical Devices for Human Subjects- GCP, or the relevant parts of the ICH Guidelines for GCP, ethical principles that have their origins in the Declaration of Helsinki, and applicable individual country laws and regulations. The study shall not begin until the required approval/favorable opinion from the IRB and/or 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 the sponsor. Any additional requirements imposed by the IRB/EC/REB or regulatory authority shall be followed, if appropriate.

16.2. *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 investigation plan, ISO 14155, ethical principles that have their origins in the Declaration of Helsinki, any conditions of approval imposed by the reviewing IRB/EC/REB, and prevailing local and/or country laws and/or regulations, 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.
- 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 and disclose potential conflicts of interest, including financial, that may interfere with the conduct of the clinical study or interpretation of results.
- 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 reportable events.
- Report to the IRB/EC/REB 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/EC/REB, and supply BSC with any additional requested information related to the safety reporting of a particular event.
- Maintain the device accountability records and control of the device, ensuring that the investigational device is used only by authorized/designated users and in accordance with this protocol and instructions 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/EC/REB when performing auditing activities.
- Ensure that informed consent is obtained in accordance with applicable laws, this protocol and local IRB/EC/REB 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.
- As applicable, provide the subject with necessary instructions on proper use, handling, storage, and return of the investigational device when it is used/operated by the subject.
- 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.
- Attempt to enroll patients representative of the sites overall patient population.

All investigators will provide their qualifications and experience to assume responsibility for their delegated tasks through up-to-date curriculum vitae or other relevant documentation and disclose potential conflicts of interest, including financial, that may interfere with the conduct of the clinical study or interpretation of results.

16.2.1. 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, ensuring research team members are competent to perform the tasks they have been delegated and have adequate supervision of those to whom tasks are delegated. Where there is a sub-investigator at a site, the sub-investigator should not be delegated the primary supervisory responsibility for the site. The Principal Investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

16.3. *Institutional Review Board/ Ethics Committee*

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

A copy of the written IRB/EC/REB and/or competent authority (CA) approval of the protocol (or permission to conduct the study) and ICF, must be received by the sponsor 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/EC/REB before the changes are implemented to the study. All changes to the ICF will be IRB/EC/REB 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/EC/REB approval and renewals will be obtained throughout the duration of the study as required by applicable local/country laws or regulations or IRB/EC/REB requirements. Copies of the study reports and the IRB/EC/REB continuance of approval must be provided to the sponsor.

16.4. *Sponsor Responsibilities*

All information and data sent to BSC concerning subjects or their participation in this study will be considered confidential by BSC and will be kept confidential in accordance with all applicable laws and regulations. Only authorized BSC personnel and/or a BSC 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 BSC 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 devices, 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.

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.

16.5. *Insurance*

Where required by local/country regulation, proof and type of insurance coverage, by BSC for subjects in the study will be obtained.

17. Monitoring

Monitoring will be performed during the study to assess continued compliance with the protocol and applicable regulations. In addition, the clinical research monitor verifies that study records are adequately maintained, that data are reported in a satisfactory manner with respect to timeliness, adequacy, and accuracy, and that the Principal Investigator continues to have sufficient staff and facilities to conduct the study safely and effectively. The Principal Investigator/institution guarantees direct access to original source documents, either in electronic or paper form, by BSC personnel, their designees, and appropriate regulatory authorities.

The sponsor will put a plan in place to document the specific monitoring requirements.

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

18. Potential Risks and Benefits

18.1. *Anticipated Adverse Events*

Potential AEs (in alphabetical order) include, but are not limited to the following:

- Allergic reaction (device, contrast medium, medications)

- Arrhythmias and conduction disturbances
- Cardiac tamponade /pericardial effusion
- Death
- Embolization (air, device, plaque, thrombus, etc.)
- Hematoma / pseudoaneurysm/arteriovenous fistula
- Heart Failure / volume overload
- Hemodynamic instability / cardiogenic shock/ hypo-or hypertension
- Hemorrhage
- Myocardial ischemia / infarction
- Percutaneous or surgical re-intervention
- Respiratory insufficiency
- Sepsis / infection
- Slow flow/ no reflow/ vascular thrombosis
- Vasovagal reactions
- Vessel injury (dissection, perforation, rupture)
- Vessel spasm /occlusion

Potential adverse events not captured above, that have been associated with administration of paclitaxel at systemic doses, include, but are not limited to, the following:

- Allergic/immunologic reaction to drug (paclitaxel or structurally-related compounds)
- Alopecia
- Anemia
- Blood product transfusion
- Gastrointestinal symptoms
- Hematologic dyscrasia (including leukopenia, neutropenia, thrombocytopenia)
- Abnormal liver enzymes
- Histologic changes in vessel wall, including inflammation, cellular damage or necrosis
- Myalgia/Arthralgia
- Peripheral neuropathy

There may be other potential adverse events that are unforeseen at this time. Apart from hypersensitivity reactions (allergic/immunologic reactions), the likelihood of paclitaxel-related adverse events with Agent use is low due to the low doses used on the balloon when compared to the systemic chemotherapeutic doses these adverse events are associated with.

18.2. *Anticipated Adverse Device Effects*

The anticipated adverse device effects (ADE) have been identified and are listed in section 18.1.

18.3. ***Risks Associated with the Study Device(s)***

The Agent DCB study device features a reduced paclitaxel dose density (2 µg/mm²) as compared to most currently marketed DCB products, including SeQuent Please DCB (3 µg/mm²). This coating composition is expected to reduce systemic drug exposure and may improve the device´s safety profile as judged from preclinical data [32].

Meta-analyses of randomized controlled trials of paclitaxel-coated balloons and paclitaxel-eluting stents used to treat peripheral arterial disease in the femoropopliteal arteries have identified an increased risk of late mortality at 2 years and beyond. The magnitude and mechanism for the increased risk in mortality is currently unclear. The analyses also demonstrated reduced revascularization rates with the drug-containing products. Inadequate information is available to evaluate the potential mortality risk associated with the use of paclitaxel-coated devices for the treatment of other diseases/conditions. However, similar, more recent meta analyses for devices used in coronary vasculature did not find any mortality signal for paclitaxel drug-coated balloons with data out 3 years.

Most patients to be enrolled in this study usually have been referred for either endovascular treatment or diagnostic imaging before a treatment decision can be made. In all cases the treating physician(s) shall consider and discuss alternative treatments with each individual patient before initiating screening and enrollment into this study. Hence, once endovascular treatment within this study has been identified as feasible and desired mode of treatment, assignment to either of the two study arms will lead to treatment with a state-of-the-art device with a beneficial risk benefit profile. In general, treatment in this study will follow the routine course of coronary vascular procedures.

Patients treated with Agent are subject to the same risks shared by all patients undergoing PCI treatment. The risks associated with Agent are described and analyzed in HTQ's Risk Analysis (RSK 110919 179a) compliant with ISO 14971:2012; and include:

- Allergic reaction
- Embolism
- Infection,
- Myocardial infarction (MI)
- Necrosis
- Restenosis of treated segment
- Thrombosis
- Vessel trauma (dissection /perforation
- Exposure to harmful material
- Prolonged procedure
- Toxicity
- Additional intervention required
- Vessel Occlusion / Acute recoil
- Stroke/TIA
- Vessel spasm/vasospasm

These harms could potentially lead to death. The Risk Analysis did not identify any residual risks above the predefined acceptance criteria after implementation of the required mitigations.

18.4. *Risks associated with Participation in the Clinical Study*

In addition to the aforementioned risks associated with the PCI and the use of paclitaxel, use of dual antiplatelet therapy increases the risk of bleeding. There may be additional risks linked to drug coated balloon therapy which are unforeseen at this time

18.5. *Risk Minimization Actions*

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

18.6. *Anticipated Benefits*

Contemporary interventional cardiology literature reports numerous potential advantages of non-stent-based local drug delivery via DCB.

When compared with uncoated balloon angioplasty, DCB is anticipated to have the same advantages as DES over BMS. Antiproliferative drug delivery directly to the target lesion is expected to reduce vascular smooth muscle proliferation and consequently the rate of restenosis.

Drug delivery via DCB could also allow more homogenous drug transfer to the diseased vessel wall as opposed to the areas directly contacted by a coated stent strut. The enhanced uniformity of delivery could also enhance drug efficacy. Drug concentrations in the vessel wall with DCB are highest just after balloon injury, when the neointimal process is the most vigorous. After drug absorption to quell the restenotic process, the absence of drug, polymer and metal used in coronary stents could facilitate earlier re-endothelialization, potentially reducing the risk of late and very late thrombosis.

Obviating the need for an additional layer of metal to treat a restenotic lesion may be particularly beneficial when treating small vessels. Another advantage of DCB over DES is the reduced duration of DAPT required with DCB that could possibly result in a reduced rate of medication-related bleeding complications. Additionally, the absence of a metal structure allows conformation to the original arterial anatomy; a critical consideration when treating small vessel and bifurcation lesions. The absence of a permanent prosthesis also reduces the potential for complications during future endovascular procedures (should they be required).

18.7. *Risk to Benefit Rationale*

Reported benefits associated with the use of DCB include 1) homogenous, local drug delivery; 2) avoidance of permanent bioprosthesis or foreign material implant; 3) repeatability of the intervention; 4) respect of the original anatomy and 5) the benefits of a lower restenosis rate when compared with uncoated balloon/stent therapy.

Drug delivery with a balloon instead of a stent allows more homogenous drug transfer to the vessel wall, as opposed to, the limited area directly contacted by stent struts. Efficient drug delivery will reduce vascular smooth muscle cell proliferation (restenosis), while allowing earlier healing of the endothelial layer. The absence of permanent bioprosthesis or implant may also make future revascularization efforts less complicated.

Comparison of data from AGENT IDE with existing clinical data, will contribute to an understanding of the performance and safety of DCB in patients with coronary ISR.

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. Evaluation of the risks and benefits that are expected to be associated with use of the Agent DCB demonstrate that when used under the conditions intended, the benefits associated with use of Agent DCB should outweigh the risks.

19. Safety Reporting

19.1. *Reportable Events by investigational site to Boston Scientific*

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

- All Serious Adverse Events (SAE)
- All CEC events inclusive of death, MI*, TVR and stent thrombosis
- All Adverse Events (through 12 months)
- All Adverse Device Effects (ADE) (through 12 months)
- All Investigational Device Deficiencies
- Unanticipated Adverse Device Effects
- New findings/updates in relation to already reported events

If pre-procedure cardiac enzymes were not drawn, but the event otherwise meets the protocol definition of MI, the event should be reported as an MI for CEC adjudication.

When possible, the medical diagnosis should be reported as the Event Term instead of individual symptoms.

If it is unclear whether or not an event fits one of the above categories, or if the event cannot be isolated from the device or procedure, it should be submitted as an adverse event and/or device deficiency.

Any reportable, experienced by the study subject after informed consent and once considered enrolled in the study (as defined in study subject classification section), whether prior to, during or subsequent to the study procedure, must be recorded in the eCRF.

Underlying diseases and chronic conditions are not reported as AEs unless there is an increase in severity or frequency during the course of the investigation. Death should not be recorded as an AE but should only be reflected as an outcome of one (1) specific SAE (Table 19.2-1 Table 19.2-1: Safety Definitions for AE definitions).

Refer to Section 18 for the known risks associated with the study device(s).

In-patient hospitalization is defined as the subjects being admitted to the hospital, with the following exceptions.

- A hospitalization that is uncomplicated and elective/planned (i.e., planned prior to enrollment) does not have to be reported as an SAE.
- If complications or events occur during an elective/planned (i.e., planned prior to enrollment) hospitalization after enrollment, the complications and event AEs must be reported if they meet the protocol-specified definitions. However, the original elective/planned hospitalization(s) itself should not be reported as an SAE.

19.2. *Definitions and Classification*

Adverse event definitions are provided in Table 19.2-1. Administrative edits were made on the safety definitions from applicable regulations and guidance including (but not limited to) 21 CFR Part 812, ISO 14155 and EU MDR 2017/745/MDCG 2020-10/1 Guidance on Safety Reporting in Clinical Investigations for clarification purposes.

Table 19.2-1: Safety Definitions

Term	Definition
Adverse Event (AE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the investigational medical device and whether anticipated or unanticipated. **NOTE 1**: This includes events related to the investigational medical device or comparator. **NOTE 2**: This definition includes events related to the procedures involved. **NOTE 3**: For users or other persons, this definition is restricted to events related to the investigational medical device.
Adverse Device Effect (ADE)	Adverse event related to the use of an investigational medical device

Table 19.2-1: Safety Definitions

Term	Definition
Ref: ISO 14155 *Ref: MDCG 2020-10/1*	**NOTE 1**: This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device. **NOTE 2**: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device. **NOTE 3**: This includes 'comparator' if the comparator is a medical device.
Serious Adverse Event (SAE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	Adverse event that led to any of the following: a) death, b) serious deterioration in the health of the subject, users or other persons as defined by either: 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, including chronic diseases, or 3) in-patient hospitalization or prolongation of existing hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function c) fetal distress, fetal death, or a congenital abnormality or birth defect including physical or mental impairment **NOTE 1:** Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without a serious deterioration in health, is not considered a serious adverse event.
Serious Adverse Device Effect (SADE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated Adverse Device Effect (UADE) *Ref: 21 CFR Part 812*	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.
Serious Health Threat *Ref: ISO 14155*	Signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in subjects, users or other persons, and that requires prompt remedial action for other subjects, users or other persons. Note 1: This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.

Table 19.2-1: Safety Definitions

Term	Definition
Device Deficiency *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	An inadequacy of a medical device related to its identity, quality, durability, reliability, usability, safety or performance. **NOTE 1**: Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling. **NOTE 2**: This definition includes device deficiencies related to the investigational medical device [or the comparator].
The following definitions will be used for defining hospitalization or prolongation of hospitalization for SAE classification purposes:	
Hospitalizations	Hospitalization does not include: • emergency room visit that does not result in in-patient admission Note: although an emergency room visit does not itself meet the definition for hospitalization, it may meet other serious criteria (e.g. medical or surgical intervention to prevent permanent impairment or damage) • elective and pre-planned treatment/surgery for a pre-existing condition that is documented in the subject's record at the time of consent/enrollment • admission for social reasons and/or respite care in the absence of any deterioration in the subject's general condition (e.g. subject is homeless, caregiver relief) pre-planned, protocol-specified admission related to the clinical study (e.g. procedure required by protocol)
Prolongation of hospitalization	In-patient admission to the hospital that is prolonged beyond the expected standard duration for the condition under treatment. Note: new adverse events occurring during the hospitalization are evaluated to determine if they prolonged hospitalization or meet another SAE criteria.

19.3. *Relationship to Study Device(s)and/or Study Procedure*

The Investigator must assess the relationship of the reportable AE to the study device(s) and/ or study procedure. See criteria in Table 19.3-1.

Table 19.3-1: Criteria for Assessing Relationship of Study Device(s) or Procedure to Adverse Event

Classification	Description
Not Related *Ref: MDCG 2020-10/1*	Relationship to the device, comparator or procedures can be excluded when: - the event has no temporal relationship with the use of the investigational device or the procedures related to the use of the investigational device;

Table 19.3-1: Criteria for Assessing Relationship of Study Device(s) or Procedure to Adverse Event

Classification	Description
	- the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; - the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event; - the event involves a body-site or an organ that cannot be affected by the device or procedure; - the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors); - the event does not depend on a false result given by the investigational device used for diagnosis, when applicable; - In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.
Possibly Related *Ref: MDCG 2020-10/1*	The relationship with the use of the investigational device or comparator, or the relationship with procedures is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.
Probably Related *Ref: MDCG 2020-10/1*	The relationship with the use of the investigational device or, comparator, or the relationship with procedures seems relevant and/or the event cannot be reasonably explained by another cause.
Causal Relationship *Ref: MDCG 2020-10/1*	The serious event is associated with the investigational device or comparator or with procedures beyond reasonable doubt when: - the event is a known side effect of the product category the device belongs to or of similar devices and procedures; - the event has a temporal relationship with investigational device use/application or procedures; - the event involves a body-site or organ that -the investigational device or procedures are applied to;-the investigational device or procedures have an effect on; - the serious event follows a known response pattern to the medical device (if the response pattern is previously known); - the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible); - other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out; - harm to the subject is due to error in use; - the event depends on a false result given by the investigational device used for diagnosis, when applicable;

Table 19.3-1: Criteria for Assessing Relationship of Study Device(s) or Procedure to Adverse Event

Classification	Description
	- In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

19.4. *Investigator Reporting Requirements*

The communication requirements for reporting to BSC are as shown in Table 19.4-1.

Table 19.4-1: Investigator Reporting Requirements

Event Classification	Communication Method	Communication Timeline pre-market studies (21 CFR Part 812, MDCG 2020-10/1)
Unanticipated Adverse Device Effect / Unanticipated Serious Adverse Device Effect	Complete AE eCRF page with all available new and updated information.	• Within 1 business day of first becoming aware of the event. • Terminating at the end of the study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• At request of sponsor.
Serious Adverse Event	Complete AE eCRF page with all available new and updated information.	• Immediately, but not later than 3 calendar days of first becoming aware of the event or as per local/regional regulations. • Reporting required through the end of the study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• Upon request of sponsor
Serious Adverse Device Effects	Complete AE eCRF page with all available new and updated information.	• Immediately, but not later than 3 calendar days of first becoming aware of the event or as per local/regional regulations. • Reporting required through the end of the study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• When documentation is available • Upon sponsor request.
Device Deficiencies (including but not limited to malfunctions, use errors and inadequacy in information supplied by the	Complete Device Deficiencies CRF with all available new and updated information.	• Immediately, but not later than 3 calendar days of first becoming aware of the event. • Reporting required through the end of the study

Table 19.4-1: Investigator Reporting Requirements

Event Classification	Communication Method	Communication Timeline pre-market studies (21 CFR Part 812, MDCG 2020-10/1)
manufacturer, including labeling) Note: Any Device Deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, circumstances had been less fortunate is considered a reportable event.	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• At request of sponsor
Adverse Event including Adverse Device Effects	Complete AE eCRF page, which contains such information as date of AE, treatment of AE resolution, assessment of seriousness and relationship to the device.	• In a timely manner but not later than 10 business days after becoming aware of the information • At sponsor request • AEs and ADEs will only be collected through 12 month follow up
	Provide all relevant source documentation (de-identified/pseudonymized) for reported event.	

* Please note that pre-market studies are clinical studies with investigational devices or with medical devices that bear the regulatory approval and are not being used for the same approved indications.

19.5. *Device Deficiencies*

All AGENT DCB device deficiencies will be collected and 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 MOP. 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.

Device deficiencies (including but not limited to failures, malfunctions, and product nonconformities) are not adverse events; they should be reported on the appropriate eCRF per the study CRF Completion Guidelines. If an adverse event results from a device failure or malfunction, the AE should be recorded as an adverse event on the appropriate eCRF if it meets the protocol-specified definition of a reportable event.

Any Device Deficiency that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate is considered a reportable event.

19.6. ***Reporting to Regulatory Authorities / IRBs / ECs / REBs/ Investigators***

BSC is responsible for reporting adverse event information to all participating Principal Investigators, IRBs/ECs/REBs and regulatory authorities, as applicable.

The Principal Investigator is responsible for informing the IRB/EC/REB, and regulatory authorities of UADEs and SAEs as required by local/regional regulations.

20. Informed Consent

Subject participation in this clinical study is voluntary. Written Informed Consent is required from each subject or his/her legally authorized representative. 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 principles of the Declaration of Helsinki, ISO 14155, any applicable national regulations, and local Ethics Committee and/or Regulatory authority, as applicable. The ICF must be accepted by BSC or its delegate (e.g. CRO) and approved by the site's IRB/EC/REB, or central IRB, if applicable.

Boston Scientific 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/EC/REB. Any modification requires acceptance from BSC prior to use of the form. The ICF must be in a language understandable to the subject and if needed, BSC will assist the site in obtaining a written consent translation. Translated consent forms must also have IRB/EC/REB approval prior to their use. 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,
- use native language that is non-technical and understandable to the subject or his/her legal representative,
- 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 or legal representative competent 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.

Failure to obtain subject consent will be reported by BSC to the applicable regulatory authority according to their requirements (e.g., FDA requirement is within 5 working days of learning of such an event). Any violations of the informed consent process must be reported as deviations to the sponsor and local regulatory authorities (e.g. IRB/EC/REB), as appropriate.

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/EC/REB. The new version of the ICF must be approved by the IRB/EC/REB. Acceptance by Boston Scientific is required if changes to the revised ICF are requested by the site's IRB/EC/REB. The IRB/EC/REB will determine the subject population to be re-consented.

21. Committees

21.1. *Safety Monitoring Process*

To promote early detection of safety issues, BSC processes will provide accelerated evaluation of safety events. Success of this program requires dynamic collection of unmonitored data as soon as the event is reported. This is expedited through BSC's Global Safety Office, which is responsible for coordinating the collection of information for the subject dossier from the sites and Angiographic Core Laboratory. During regularly scheduled monitoring visits, the clinical research monitors will support the dynamic reporting process through their review of source document information.

21.2. *Clinical Events Committee (CEC)*

The Clinical Events Committee (CEC) is an independent group of individuals with pertinent expertise who review and adjudicate important clinical endpoints and relevant AEs reported by study Investigators.

The CEC will review a safety event dossier, which may include copies of subject source documents provided by study sites, for all reported cases of stent thrombosis, TVR, MI (Q-wave and non–Q-wave), and death.

Committee membership will include practitioners of cardiology and cardiovascular interventional therapy, as well as other experts with the necessary therapeutic and subject matter expertise to adjudicate the event categories outlined above. Responsibilities, qualifications, membership, and committee procedures are outlined in the CEC charter.

21.3. *Steering Committee*

A Steering Committee consisting of Sponsor Clinical Management and the Study Coordinating PI will be convened. Responsibilities may include oversight of the overall conduct of the study which may 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 Steering Committee may request participation of Agent IDE Investigators on the Committee.

21.4. *Data Monitoring Committee (DMC)*

The Data Monitoring Committee (DMC) is responsible for the oversight review of all AEs. The DMC will include leading experts in cardiology, cardiovascular interventional therapy, and biostatistics who are not participating in the trial and who have no affiliation with BSC. During the course of the trial, the DMC will review accumulating safety data to monitor the incidence of CEC events and other trends that would warrant modification or termination of the trial. Responsibilities, qualifications, membership, and committee procedures are outlined in the DMC Charter.

Data will be supplied to and reviewed by the DMC. Any DMC recommendations for study modification or termination because of concerns over subject safety or issues relating to data monitoring or quality control will be submitted in writing to the Executive Committee for consideration and final decision. However, if the DMC at any time determines that a potentially serious risk exists to subjects in this trial, the DMC chairman will immediately notify both BSC and the Principal Investigator.

22. Suspension or Termination

22.1 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/ECs/REBs, and regulatory authorities, as applicable, will be notified in writing in the event of study termination.

22.1.1 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.

22.2 Termination of Study Participation by the Investigator or Withdrawal of IRB/ EC /REB Approval

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

22.3. 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/EC/REB 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/EC/REB terminates participation in the study, participating investigators, associated IRBs/ECs/REBs, 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.

22.4 Criteria for Suspending/Terminating a Study Site

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, if enrollment is significantly slower than expected, 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 study devices and testing equipment, as applicable, will be returned to BSC unless this action would jeopardize the rights, safety or well-being of the subjects. The IRB/EC/REB and regulatory authorities, as applicable, will be notified. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

23. Study Registration and Results

23.1. *Study Registration*

To comply with applicable laws and regulations, the study will be registered on a publicly accessible database.

23.2. *Clinical Investigation Report*

Study results will be made available in accordance with the legal requirements and the recognized ethical principles, in accordance with the Boston Scientific Policy. A Clinical Investigation Report will be made available to all investigators, IRB/EC/REB and regulatory authorities, as applicable in accordance with the Boston Scientific Policy and local requirements. As applicable an abbreviated Clinical Investigation Report will be made available on a publicly accessible database.

23.3. *Publication Policy*

BSC requires disclosure of its involvement as a sponsor or financial supporter in any publication or presentation relating to a BSC study or its results. BSC will submit study results for publication (regardless of study outcome) following the conclusion or termination of the study. Boston Scientific adheres to the Contributorship Criteria set forth in the Uniform Requirements of the International Committee of Medical Journal Editors (ICMJE; http://www.icmje.org). In order to ensure the public disclosure of study results in a timely manner, while maintaining an unbiased presentation of study outcomes, BSC personnel may assist authors and investigators in publication preparation provided the following guidelines are followed:

- All authorship and contributorship requirements as described above must be followed.
- BSC involvement in the publication preparation and the BSC Publication Policy should be discussed with the Coordinating Principal Investigator(s) and/or Executive/Steering Committee at the onset of the project.
- The First and Senior authors are the primary drivers of decisions regarding publication content, review, approval, and submission.

The data, analytic methods, and study materials for this clinical trial may be made available to other researchers in accordance with the Boston Scientific Data Sharing Policy (https://www.bostonscientific.com/).

24. Bibliography

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25. Abbreviations and Definitions

25.1. *Abbreviations*

Abbreviations are shown in Table 25.1-1.

Table 25.1-1: Abbreviations

Abbreviation/Acronym	Term
ACC	American College of Cardiology
ACT	activated clotting time
ADE	adverse device effect
AE	adverse event
AHA	American Heart Association

Table 25.1-1: Abbreviations

Abbreviation/Acronym	Term
ATBC	Acetyl Tributyl Citrate
ATM	atmosphere
ARC	Academic Research Consortium
BSC	Boston Scientific Corporation
BMS	bare metal stent
CABG	coronary artery bypass graft
CBC	complete blood count
CEC	Clinical Events Committee
CK	creatine kinase
CK-MB	creatine kinase-myoglobin band, a fraction of creatine kinase
CRO	Contract research organization
eCRF	electronic case report form
CVA	cerebrovascular accident
DES	drug-eluting stent
DFU	Directions for Use
DMC	Data Monitoring Committee
ECG	electrocardiogram
EDC	electronic data capture
ESC	European Society of Cardiology
FDA	Food and Drug Administration
FHU	First Human Use
FFR	fractional flow reserve
GCP	Good Clinical Practices
GI	gastrointestinal
GUSTO	Global Strategies for Opening Occluded Coronary Arteries
IABP	intra-aortic balloon pump
IC	Intercontinental
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDE	Investigational Device Exemption
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISDN	isosorbide dinitrate
ISO	International Standards Organization

Table 25.1-1: Abbreviations

Abbreviation/Acronym	Term
ISR	In stent restenosis
ITT	intention to treat
LAD	left anterior descending coronary artery
LBBB	left bundle branch block
LCX	left circumflex coronary artery
MACE	major adverse cardiac event
MI	myocardial infarction
MLD	minimum lumen diameter
NHLBI	National Heart, Lung, and Blood Institute
NTG	Nitroglycerin
OUS	Outside the United States
PCI	percutaneous coronary intervention
PG	Performance Goal
PK	pharmacokinetics
POBA	Plain Old Balloon Angioplasty
PTCA	Percutaneous transluminal coronary angioplasty
QCA	quantitative coronary angiography
RCA	right coronary artery
RVD	reference vessel diameter
SADE	serious adverse device effect
SAE	serious adverse event
SCAI	Society for Cardiovascular Angiography and Interventions
STEMI	ST elevation myocardial infarction
TIA	transient ischemic attack
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
ULN	upper limit of normal
URL	upper reference limit
US	United States
WBC	white blood cell

Table 25.1-1: Abbreviations

Abbreviation/Acronym	Term

25.2. ***Definitions***

Terms are defined below.

ABRUPT CLOSURE

Abrupt closure is the occurrence of new severely reduced flow (TIMI grade 0 or 1) within the target vessel that persists and requires bailout, including emergency surgery, or results in MI or death. Abrupt closure requires proven association with a mechanical dissection of the treatment site or instrumented vessel, coronary thrombus, or severe spasm. Abrupt closure does not connote "no reflow" due to microvascular flow limitation in which the epicardial artery is patent but has reduced flow. Abrupt closure also does not connote transient closure with reduced flow in which the assigned treatment reversed the closure.

Sub-abrupt closure is an abrupt closure that occurs after the target procedure is completed and the subject has left the catheterization laboratory and before hospital discharge.

Threatened abrupt closure is a grade B dissection and ≥50% diameter stenosis or any dissection of grade C or higher.

ADVERSE DEVICE EFFECT (*Ref: ISO 14155 and MEDDEV 2.7/3)*

Adverse event related to the use of an investigational medical device

> NOTE 1: This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device.
>
> NOTE 2: This definition includes any event resulting from use error or intentional abnormal use of the investigational medical device.

ADVERSE EVENT (*Ref: ISO 14155 and MEDDEV 2.7/3*)

Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, whether or not related to the investigational medical device.

NOTE 1: This includes events related to the investigational medical device or comparator.

NOTE 2: This definition includes events related to the procedures involved.

NOTE 3: For users or other persons, this definition is restricted to events related to the investigational medical device.

ADVERSE EVENT RELATIONSHIP TERMS

Adverse Event Relationship terms are detailed in section 20.3-1.

ANGIOGRAPHIC SUCCESS

Angiographic success is a mean lesion diameter stenosis < 50% (< 30% for stents) in 2 near-orthogonal projections with TIMI 3flow, as visually assessed by the physician, without the occurrence of prolonged chest pain or ECG changes consistent with MI

ANNUAL FOLLOW-UPS

Annual follow-ups are those that occur annually through 2 years after the index procedure. The timing of annual follow-ups is calculated based on one calendar year equaling 365 days. The follow-up window is 30 days. Therefore, the 1-year and 2-year follow-ups should occur 365±30 days and 730±30 days after the index procedure, respectively.

ANTICIPATED EVENT

Event that is previously identified in the Protocol, ICF, or DFU.

ARRHYTHMIA

An arrhythmia is any variation from the normal rhythm of the heart, including sinus arrhythmia, premature beats, heart block, atrial or ventricular fibrillation, atrial or ventricular flutter, and atrial or ventricular tachycardia.

ARTERIOVENOUS FISTULA

An arteriovenous fistula is an abnormal passage or communication between an artery and a vein. It may result from injury or it may occur as a congenital abnormality.

BAILOUT

- Bailout typically refers to a persistent dissection but can also include a vessel complication at the ostium or along the course of the major coronary artery used to access the target lesion.
- The decision of whether to treat in a bailout situation is at the discretion of the interventionalist.

BIFURCATION LESION

A bifurcation lesion is a lesion associated with the area where a branch vessel >2.0 mm in diameter by visual estimate originates.

BINARY RESTENOSIS

Binary restenosis is a diameter stenosis >50% at the previously treated lesion site, including the originally treated area and the adjacent proximal and distal QCA analysis segment.

BLEEDING CLASSIFICATIONS (*Ref: GUSTO*)

- Severe or life-threatening: Either intracranial hemorrhage or bleeding that causes hemodynamic compromise and requires intervention
- Moderate: Bleeding that requires blood transfusion but does not result in hemodynamic compromise

- Mild: Bleeding that does not meet criteria for either severe or moderate bleeding

BRAUNWALD CLASSIFICATION OF UNSTABLE ANGINA

Severity

- Class I: New onset, severe or accelerated angina. Subjects with angina of less than 2 months duration, severe or occurring 3 or more times per day, or angina that is distinctly more frequent and precipitated by distinctly less exertion; no pain at rest in the last 2 months.
- Class II: Angina at rest, subacute. Subjects with 1 or more episodes of angina at rest during the preceding month, but not within the preceding 48 hours.
- Class III: Angina at rest, acute. Subjects with 1 or more episodes of angina at rest within the preceding 48 hours.

Clinical Circumstances

- Class A: Secondary unstable angina. A clearly identified condition extrinsic to the coronary vascular bed that has intensified myocardial ischemia (e.g., anemia, fever, infection, hypotension, tachyarrhythmia, thyrotoxicosis, and hypoxemia secondary to respiratory failure).
- Class B: Primary unstable angina.
- Class C: Postinfarction unstable angina (within 2 weeks of documented MI).

CANADIAN CARDIOVASCULAR SOCIETY CLASSIFICATION

- Class 1: Ordinary physical activity does not cause angina, such as walking and climbing stairs. Angina with strenuous or rapid or prolonged exertion at work or recreation.
- Class 2: Slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in cold, or in wind, or under emotional stress, or any only during the first hours after awakening. Walking more than 2 blocks on the level and climbing more than 1 flight of ordinary stairs at a normal pace and in normal conditions.
- Class 3: Marked limitations of ordinary physical activity. Walking 1 to 2 blocks on the level and climbing 1 flight of stairs in normal conditions and at a normal pace.
- Class 4: Inability to carry on any physical activity without discomfort; angina syndrome may be present at rest.

CARDIAC TAMPONADE

Cardiac tamponade is an acute compression of the heart due to effusion of the fluid into the pericardium, or the collection of blood in the pericardium, from rupture of the heart or penetrating trauma.

CARDIOGENIC SHOCK

Cardiogenic shock is a clinical state of hypoperfusion characterized by a systolic blood pressure <80 mmHg and/or a central filling pressure >20 mmHg, or a cardiac index

<1.8 liters/min/m^2 where there is evidence of insufficient end organ profusion. Shock is also considered present if intravenous inotropes and/or intra-aortic balloon pump (IABP) are needed to maintain a systolic blood pressure >80 mmHg and a cardiac index >1.8 liters/minute/m^2.

CREATINE KINASE-MYOGLOBIN BAND

Creatine kinase-myoglobin band (CK-MB) is an isoenzyme of creatine kinase (CK) with a distinct molecular structure specific as an indicator of myocardial cell injury. It is used to evaluate possible causes of chest pain, to detect and diagnose acute MI and re-infarction, and to monitor the severity of myocardial ischemia.

CLINICAL EVENTS COMMITTEE

A CEC is an independent group of individuals with pertinent expertise that review and adjudicate important endpoints and relevant AEs reported by study investigators.

CLINICAL EVENTS COMMITTEE EVENT

The CEC will adjudicate all reported cases of stent thrombosis, TVR, MI (Q-wave and non–Q-wave), and death (to ensure appropriate classification of death as cardiac or non-cardiac). A case adjudicated by the CEC is considered to be a CEC event.

CLINICAL PROCEDURAL SUCCESS

Clinical procedural success is postprocedure diameter stenosis <30% in 2 near-orthogonal projections with TIMI 3 flow in the target lesion, as visually assessed by the physician, without the occurrence of in-hospital MI, TVR, or cardiac death.

COMPLICATION (ANGIOGRAPHIC OR CLINICAL)

A complication (angiographic or clinical) is an undesirable clinical event that results in death, injury, or invasive intervention. Complications may include, but are not limited to, perforation, occlusion, intimal flap, dissection, loss of side branch, distal embolization, non-fatal MI, elevated CK Total, prolonged angina, hypotension, hematoma, arrhythmias, etc. Complications may or may not be related to the investigational device.

CONGESTIVE HEART FAILURE

Congestive heart failure is an inadequacy of the heart such that it fails to maintain adequate circulation of blood, so that congestion and edema develop in the tissues. Clinical syndrome is characterized by shortness of breath, non-pitting edema, enlargement of the liver, engorged neck veins, and pulmonary rales.

CORONARY ANEURYSM

A coronary aneurysm is a pathologic dilation of a segment of a blood vessel involving all three layers of the vessel wall ≥1.5× the RVD.

CORONARY ARTERY SPASM

Coronary artery spasm, or coronary vasospasm, is a spasm of a coronary artery, resulting in a decrease in lumen diameter. It may occur distal to the treatment site and is generally reversed with intracoronary administration of NTG or with adjunct balloon dilation.

DEATH

Death is categorized as cardiac or non-cardiac.

Cardiac death is defined as death due to any of the following.

- Acute MI
- Cardiac perforation/pericardial tamponade
- Arrhythmia or conduction abnormality
- CVA through hospital discharge or CVA suspected of being related to the procedure
- Death due to complication of the procedure, including bleeding, vascular repair, transfusion reaction, or bypass surgery
- Any death in which a cardiac cause cannot be excluded

Non-cardiac death is defined as a death not due to cardiac causes as defined above.

DEVICE DEFICIENCY (*Ref: ISO 14155 and MEDDEV 2.7/3*)

A inadequacy of an investigational medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer.

DISSECTION, NHLBI CLASSIFICATION

- Type A: Small radiolucent area within the lumen of the vessel disappearing with the passage of the contrast material
- Type B: Appearance of contrast medium parallel to the lumen of the vessel disappearing within a few cardiac cycles
- Type C: Dissection protruding outside the lumen of the vessel persisting after passage of the contrast material
- Type D: Spiral shaped filling defect with or without delayed run-off of the contrast material in the antegrade flow
- Type E: Persistent luminal filling defect with delayed run-off of the contrast material in the distal lumen
- Type F: Filling defect accompanied by total coronary occlusion

DIABETES MELLITUS

Subjects will be categorized as having diabetes mellitus if medical treatment (oral or injection) is required for control of blood glucose levels.

DISTAL EMBOLIZATION

Distal embolization is migration of a filling defect or thrombus to distally occlude the target vessel or one of its branches.

EMERGENCY BYPASS SURGERY

Emergency bypass surgery is CABG surgery performed on an urgent or emergent basis for severe vessel dissection or closure, or treatment failure resulting in new ischemia.

EPICARDIAL VESSEL

Epicardial vessels include the LAD and its branches, the LCX and its branches, and the RCA and its branches.

EQ-5D™

A standardized instrument developed by the EuroQol Group as a measure of health-related quality of life. The descriptive system of health-related quality of life states consist of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) each of which can take one of five responses. The responses record five levels of severity (no problems/slight problems/moderate problems/severe problems/extreme problems) within a particular EQ-5D dimension

HYPERTENSION

Hypertension is persistently high arterial blood pressure. Various criteria for its threshold have been suggested, ranging from 140 mmHg systolic and 90 mmHg diastolic to as high as 220 mmHg systolic and 110 mmHg diastolic. Hypertension may have no known cause or be associated with other primary diseases.

HYPOTENSION

Sustained hypotension is a systolic blood pressure less than 80 mmHg lasting more than 30 minutes or requiring intervention (e.g., pacing, IABP, intravenous vasopressors, to sustain systolic blood pressure). This excludes transient hypotension or vagal reactions, which are self-limited or readily reversible.

INDEX PROCEDURE START TIME

Index procedure start time is defined as the time of sheath insertion. If a previously placed sheath is used (i.e., from an earlier diagnostic procedure), index procedure start time is defined as the time of guide catheter insertion into sheath for the interventional procedure.

INDEX PROCEDURE END TIME

Index procedure end time is defined as the time the guide catheter is removed after the final angiography.

INTIMAL FLAP

An extrusion of tissue extending from the arterial surface into the lumen (0 = absent; 1 = present).

LEFT MAIN DISEASE

Left main disease is a significant lesion in the left main coronary artery of at least 50% diameter stenosis. A protected left main artery means the vessels supplied by the diseased left main (usually the LAD and CX) are supplied by a functioning graft, either venous or arterial, connected to any of the branches of the left coronary artery. A stent in the left main coronary artery does not in itself constitute a protected left main.

LESION CHARACTERISTICS (ACC/AHA CLASSIFICATION)

- Type A lesions: Minimally complex, length <10 mm, concentric, readily accessible, non-angulated segment (<45°), smooth contour, little or no calcification, less than totally occlusive, not ostial in location, no major side branch involvement, and an absence of thrombus.
- Type B lesions: Moderately complex, tubular (length 10 to 20 mm), eccentric, moderate tortuosity of proximal segment, moderately angulated segment (>45°, <90°), irregular contour, moderate or heavy calcification, total occlusions <3 months old, ostial in location, bifurcation lesions requiring double guidewire, and some thrombus present.
- Type C lesions: Severely complex, diffuse (length ≥20 mm), excessive tortuosity of proximal segment, extremely angulated segments >90°, total occlusions >3 months old and/or bridging collaterals, inability to protect major side branches, and degenerated vein grafts with friable lesions.

LESION LENGTH

Lesion length is measured as distance from the proximal to the distal shoulder in the view that demonstrates the stenosis in its most elongated projection. Lesion length is classified as discrete (<10 mm), tubular (10-20 mm), or diffuse (>20 mm).

LESION LOCATION

Lesion location is the location of the lesion according to the specific coronary artery (i.e., left main, LAD, LCX, or RCA) or bypass graft, and is specified as proximal, mid, or distal. A standard map will be provided to be used for location descriptions.

Note: In the Agent IDE trial, the ramus will be considered to be a branch of the LCX for purposes of determining eligibility and for determining TVR.

LEUKOPENIA

Leukopenia is a leukocyte count of $<3.0 \times 10^9$/liter for more than 3 days.

MALFUNCTION

A malfunction is a failure of the device to meet performance specifications or otherwise perform as intended.

MULTI-VESSEL DISEASE

Multi-vessel disease refers to the presence of >50% diameter stenosis as measured by caliper method or QCA on-line in 2 or 3 major epicardial coronary vessels or bypassed branches.

MYOCARDIAL INFARCTION

In the AGENT IDE trial, MI will be adjudicated according to the SCAI, 4th Universal and ARC-2 Myocardial Infarction definitions. MI endpoint events will be analyzed based on the SCAI definition for peri-procedural MI and 4th Universal definition for spontaneous MI.

(1) SCAI MI Definition:

In patients with normal baseline CK-MB:

The peak CK-MB measured within 48 hours of the procedure rises to _10x the local laboratory ULN, or to _5x ULN with new pathologic Q-waves in _2 contiguous leads or new persistent LBBB, OR in the absence of CK-MB measurements and a normal baseline cTn, a cTn (I or T) level measured within 48 hours of the PCI rises to _70x the local laboratory ULN, or _35x ULN with new pathologic Q-waves in _2 contiguous leads or new persistent LBBB.

In patients with elevated baseline CK-MB (or cTn) in whom the biomarker levels are stable or falling:

The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above from the most recent pre-procedure level.

In patients with elevated CK-MB (or cTn) in whom the biomarker levels have not been shown to be stable or falling:

The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above plus new ST-segment elevation or depression plus signs consistent with a clinically relevant MI, such as new onset or worsening heart failure or sustained hypotension.

(2) The 4th Universal MI Definition:

Acute MI (types 1, 2 and 3 MI):

The term acute myocardial infarction should be used when there is acute myocardial injury with clinical evidence of acute myocardial ischemia and with detection of a rise and/or fall of cardiac troponin (cTn) values with at least one value above the 99th percentile upper reference limit (URL) AND at least one of the following:

- Symptoms of myocardial ischemia
- New ischemic ECG changes
- Development of pathological Q waves
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology
- Identification of a coronary thrombus by angiography or autopsy (not for types 2 or 3 MIs)

Post-mortem demonstration of acute athero-thrombosis in the artery supplying the infarcted myocardium meets criteria for type 1 MI.

Evidence of an imbalance between myocardial oxygen supply and demand unrelated to acute athero-thrombosis meets criteria for type 2 MI.

Myocardial Infarction resulting in death when biomarker values are unavailable (type 3 MI):

Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes before cTn values become available or abnormal, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarkers could be identified, or MI was detected by an autopsy examination.

Percutaneous Coronary Intervention-Related Myocardial Infarction (type 4a MI) and Coronary Artery Bypass Grafting-Related Myocardial Infarction (type 5 MI):

Percutaneous coronary intervention (PCI) related MI ≤48 hours after the index procedure is arbitrarily defined by an elevation of cTn values >5 times for type 4a MI and >10 times for type 5 MI of the 99th percentile URL in patients with normal baseline values. Patients with elevated preprocedural cTn values, in whom the preprocedural cTn level are stable (≤20% variation) or falling, must meet the criteria for a >5- or >10-fold increase and manifest a change from the baseline value of >20%.

AND

One of the following:

- New ischemic ECG changes (this criterion is related to type 4a MI only)
- Development of new pathological Q waves
- Angiographic findings consistent with a procedural flow-limiting complication such as coronary dissection, occlusion of a major epicardial artery or graft, side-branch occlusion-thrombus, disruption of collateral flow or distal embolization
- Imaging evidence of loss of viable myocardium that is presumed to be new and, in a pattern consistent with an ischemic etiology

Isolated development of new pathological Q waves meets the type 4a MI or type 5 MI criteria with either revascularization procedure if cTn values are elevated and rising but less than the pre-specified thresholds for PCI and CABG.

Other types of 4 MI include type 4b MI stent thrombosis and type 4c MI restenosis that both meet type 1 MI criteria.

Post-mortem demonstration of a procedure-related thrombus meets the type 4a MI criteria or type 4b MI criteria if associated with a stent.

Criteria for prior or silent/unrecognized myocardial infarction:

Any one of the following criteria meets the diagnosis for prior or silent/unrecognized MI:

- Abnormal Q waves with or without symptoms in the absence of non-ischemic causes
- Imaging evidence of loss of viable myocardium in a pattern consistent with ischemic etiology
- Patho-anatomical findings of a prior MI

(3) ARC-2 MI Definition

Spontaneous MI:

ARC-2 endorses the classification of spontaneous MI and MI related to complications of the study device (types 1, 2, 3, 4b, and 4c) proposed by the 2012 universal definition of MI. Suspected spontaneous MI triggers, for which a biomarker rise is documented without clear evidence of a type 1 or 2 MI, should be adjudicated and reported as "myocardial injury not meeting MI criteria"

Periprocedural Myocardial Infarction Percutaneous Coronary Intervention and Coronary Artery Bypass Grafting (Within 48 Hours)

Absolute rise in cardiac troponin (from baseline) ≥35 times the 99th percentile URL

AND

One or more of the following:

- New significant Q waves or equivalent
- Flow-limiting angiographic complications
- New "substantial" loss of myocardium on imaging

NON-TARGET LESION

A non-target lesion is any lesion treated during the index procedure which is not a target lesion. A maximum of 1 non-target lesion in 1 non-target vessel may be treated with a commercial treatment (e.g., stent, balloon angioplasty, excluding brachytherapy) during the index procedure.

PERFORATION

Perforations are classified as follows:

- Angiographic perforation: Perforation detected by clinical site or Angiographic Core Laboratory at any point during the procedure.
- Clinical perforation: Perforation requiring additional treatment, including efforts to seal the perforation or pericardial drainage, or resulting in significant pericardial effusion, abrupt closure, MI, or death.
- Pericardial hemorrhage/tamponade: Perforation causing tamponade.

POBA

Mechanical balloon expansion of a coronary stenosis without stent implantation or drug delivery

PROLONGED ANGINA PECTORIS

Prolonged angina pectoris is angina lasting longer than 1 hour.

PSEUDOANEURYSM

A pseudoaneurysm is an encapsulated hematoma in communication with an artery. It is often difficult to distinguish from an expanding hematoma at the site of arterial puncture.

REFERENCE VESSEL DIAMETER (RVD)

Reference diameter of the normal artery segment is an angiographic measurement of the artery proximal and/or distal to the lesion intended for intervention. This is also referred to as "reference vessel diameter" (RVD).

REPEAT INTERVENTION

Repeat intervention is a PCI or CABG performed after the index procedure ends The repeat intervention should be performed to improve blood flow.

RESTENOSED LESION

A restenosed lesion is a previously treated lesion that again has a stenosis.

RESTENOSIS

See Binary Restenosis.

SERIOUS ADVERSE DEVICE EFFECT (*Ref: ISO 14155 and MEDDEV 2.7/3*)

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

SERIOUS ADVERSE EVENT (*Ref: ISO 14155 and MEDDEV 2.7/3*)

Adverse event that:

a) Led to death,

- b) Led to serious deterioration in the health of the subject as defined by either:
  1) a life-threatening illness or injury, or
  2) a permanent impairment of a body structure or a body function, or
  3) in-patient hospitalization or prolongation of existing hospitalization , or
  4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
- c) Led to fetal distress, fetal death, or a congenital abnormality or birth defect.

NOTE 1: Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without a serious deterioration in health, is not considered a serious adverse event.

SOURCE DATA

All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in the source documents (original records or certified copies) (ICH E6 (1.51 and 1.52))

SOURCE DOCUMENTS

Original documents, data, and records (ICH E6 (1.51 and 1.52))

STENT THROMBOSIS (*Ref: Academic Research Consortium Definition*) [11]

Stent thrombosis is the acute occlusion or stenosis of an intravascular stent caused by in situ thrombosis. Stent thrombosis should be reported as a cumulative value at the different time points and with the different separate time points. Time 0 is defined as the time point after the guide catheter has been removed and the patient left the catheterization lab.

Timing:

- Acute stent thrombosis*: 0-24 hours after stent implantation
- Subacute stent thrombosis*: >24 hours to 30 days after stent implantation
- Late stent thrombosis: >30 days to 1 year after stent implantation
- Very late stent thrombosis: >1 year after stent implantation

* Acute/subacute can also be replaced by early stent thrombosis. Early stent thrombosis is 0-30 days.

Stent thrombosis may be defined as:

- Confirmed/definite
- Probable
- Possible

Confirmed/Definite (is considered *either* angiographic confirmed or pathologic confirmed)

Angiographic confirmed stent thrombosis is considered to have occurred if:

- TIMI flow is:

TIMI flow grade 0 with occlusion originating in the stent or in the segment 5 mm proximal or distal to the stent region in the presence of thrombus*

TIMI flow grade 1, 2 or 3 originating in the stent or in the segment 5 mm proximal or distal to the stent region in the presence of a thrombus*

AND at least one of the following criteria, up to 48 hours, has been fulfilled:

- New onset of ischemic symptoms at rest (typical chest pain with duration >20 minutes)
- New ischemic ECG changes suggestive of acute ischemia
- Typical rise and fall in cardiac biomarkers (>2× ULN of CK)

The incidental angiographic documentation of stent occlusion in the absence of clinical syndromes is not considered a confirmed stent thrombosis (silent thrombosis).

* Intracoronary thrombus

Non-occlusive thrombus: Spheroid, ovoid or irregular non-calcified filling defect or lucency surrounded by contrast material (on 3 sides of within a coronary stenosis) seen in multiple projections, or persistence of contrast material within the lumen, or a visible embolization of intraluminal material downstream.

Occlusive thrombus: A TIMI 0 or TIMI 1 intra-stent or proximal to a stent up to the most adjacent proximal side branch or main branch (if originating from the side branch).

Probable

Clinical definition of probable stent thrombosis is considered to have occurred in the following cases:

- Any unexplained death within the first 30 days
- Irrespective of the time after the index procedure and MI in the absence of any obvious cause which is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis

Possible

Clinical definition of possible stent thrombosis is considered to have occurred with any unexplained death beyond 30 days.

STROKE/CEREBROVASCULAR ACCIDENT

An acute symptomatic episode of neurological dysfunction attributed to a vascular cause lasting more than 24 hours or lasting 24 hours or less with a brain imaging study or autopsy showing infarction.

Classification:

- Ischemic Stroke: An acute symptomatic episode of focal cerebral, spinal, or retinal dysfunction caused by an infarction of central nervous system tissue.
- Hemorrhagic Stroke: An acute symptomatic episode of focal or global cerebral or spinal dysfunction caused by a nontraumatic intraparenchymal, intraventricular, or subarachnoid hemorrhage.
- Undetermined Stroke: A stroke with insufficient information to allow categorization as ischemic or hemorrhagic.

An event that lasts < 24 hours may be adjudicated as a stroke if the following treatments were used:

- Pharmacologic, i. e., thrombolytic drug administration, or
- Non-pharmacologic, i.e., neurointerventional procedure (*e.g.,* intracranial angioplasty)

SUCCESSFUL PREDILATION/PRETREATMENT

Successful predilation/pretreatment refers to dilation with a balloon catheter of appropriate length and diameter, or pretreatment with directional or rotational coronary atherectomy, laser or cutting/scoring balloon with no greater than 50% residual stenosis and no dissection greater than NHLBI type C.

TARGET LESION

The target lesion is the lesion selected by the Investigator for treatment with a study device. The target lesion analysis segment includes the arterial segment treated with the study stent

plus the arterial segment 5 mm proximal and 5 mm distal to the treatment site. The target lesion should meet the angiographic selection criteria.

TARGET LESION FAILURE

Target lesion failure is any ischemia-driven revascularization of the target lesion, MI (Q-wave and non–Q-wave) related to the target vessel, or (cardiac) death. For the purposes of this protocol, if it cannot be determined with certainty whether the MI was related to the target vessel, it will be considered a TLF.

TARGET LESION REVASCULARIZATION

Target lesion revascularization is any ischemia-driven repeat percutaneous intervention, to improve blood flow, of the successfully treated target lesion or bypass surgery of the target vessel with a graft distally to the successfully treated target lesion. A TLR will be considered ischemia-driven if the target lesion diameter stenosis is ≥50% by QCA and there is presence of clinical or functional ischemia which cannot be explained by other coronary or graft lesions. Clinical or functional ischemia is any of the following:

- The subject has a positive functional study corresponding to the area served by the target lesion.
- The subject has ischemic ECG changes at rest in a distribution consistent with the target vessel.
- The subject has ischemic symptoms referable to the target lesion.

A TLR will be considered as ischemia-driven if the lesion diameter stenosis is ≥70% by QCA even in the absence of clinical or functional ischemia.

TARGET VESSEL

The target vessel is any coronary vessel (e.g., left main coronary artery, LAD, LCX, or RCA) containing a target lesion. Side branches of a target vessel such as the LAD are also considered part of the target vessel.

TARGET VESSEL FAILURE

Target vessel failure is any ischemia-driven revascularization of the target vessel, MI (Q-wave and non–Q-wave) related to the target vessel or cardiac death. For the purposes of this protocol, if it cannot be determined with certainty whether the MI or death was related to the target vessel, it will be considered a TVF.

TARGET VESSEL REVASCULARIZATION

Target vessel revascularization is defined as a TLR (see definition above) or a TVR remote (see definition below).

TARGET VESSEL REVASCULARIZATION REMOTE

Target vessel revascularization remote is any ischemia-driven repeat percutaneous intervention, to improve blood flow, or bypass surgery of not previously existing lesions diameter stenosis ≥50% by QCA in the target vessel, excluding the target lesion. A TVR will be considered ischemia-driven if the target vessel diameter stenosis is ≥50% by QCA and any of the following are present:

- The subject has a positive functional study corresponding to the area served by the target vessel.
- The subject has ischemic ECG changes at rest in a distribution consistent with the target vessel.
- The subject has ischemic symptoms referable to the target vessel.

A TVR will also be considered as ischemia-driven if the lesion diameter stenosis is ≥70% even in the absence of clinical or functional ischemia.

TECHNICAL SUCCESS

Technical success is successful crossing and dilation of the lesion, without balloon rupture, and post-procedure diameter stenosis of <30% in 2 near-orthogonal projections with TIMI 3 flow in the target lesion, as visually assessed by the physician.

TECHNICIAN WORKSHEET

A Technician Worksheet is a record for listing the filming sequence and angulations of x-ray equipment, details of inflations, and description of lesion(s).

THROMBUS (ANGIOGRAPHIC)

Thrombus (angiographic) is discrete, mobile intraluminal filling with defined borders with/without associated contrast straining, classified as either absent or present.

THROMBOLYSIS IN MYOCARDIAL INFARCTION CLASSIFICATION

- TIMI 0: No anterograde flow beyond the point of occlusion.
- TIMI 1: Contrast passes the point of obstruction but hangs up and fails to opacify the entire distal coronary bed during the duration of the angiographic filming sequence.
- TIMI 2: Contrast opacifies the entire coronary bed distal to the stenosis but the rate of entry and/or clearance is slower than in the comparable areas not perfused by the dilated vessel. Specifically, anterograde filling of contrast with complete filling of the artery and its major and minor branches after more than 3 full cardiac cycles. Alternatively, delayed contrast washout in the target lesion territory may occur, compared with comparable areas of myocardium not perfused by the target lesion.
- TIMI 3: Complete perfusion. Specifically, anterograde flow of contrast with complete filling of the artery and its major and minor branches within 3 full cardiac cycles. Contrast also clears from the arterial segment within 3 full cardiac cycles.

TOTAL OCCLUSION

A total occlusion is a lesion with no flow (i.e., TIMI flow 0). A total occlusion is considered chronic if the vessel has been closed for > 3 months.

TRANSIENT ISCHEMIC ATTACK

A TIA is a focal ischemic neurological deficit of abrupt onset and of presumed vascular etiology that resolves completely within 24 hours of onset.

UNANTICIPATED ADVERSE DEVICE EFFECT (*Ref: 21CFR Part 812*)

Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously

identified in nature, severity, or degree of incidence in the protocol or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

UNANTICIPATED SERIOUS ADVERSE DEVICE EFFECT (*Ref: ISO 14155 and MEDDEV 2.7/3*)

Serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report.

NOTE 1: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.