SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Drug-eluting percutaneous transluminal coronary angioplasty catheter
Device Trade Name:	AGENT™ Paclitaxel-Coated Balloon Catheter
Device Procode:	OOB
Applicant's Name and Address	Boston Scientific Corporation One Scimed Place Maple Grove, MN 55311
Date(s) of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P230035
Date of FDA Notice of Approval:	February 29, 2024
Breakthrough Device:	Granted breakthrough device status on January 22, 2021 because the combination product and proposed indication for use met the criteria outlined in FDA Guidance Document "Breakthrough Devices Program."

II. INDICATIONS FOR USE

The AGENT™ Paclitaxel-Coated Balloon Catheter is intended to be used after appropriate vessel preparation in adult patients undergoing percutaneous coronary intervention (PCI) in coronary arteries 2.0 mm to 4.0 mm in diameter and lesions up to 26 mm in length for the purpose of improving myocardial perfusion when treating in-stent restenosis (ISR).

III. CONTRAINDICATIONS

Use of the AGENT™ Drug-Coated Balloon Catheter is contraindicated in the following:

- Use in the supra-aortic/cerebrovascular arteries.
- Unprotected native left main coronary artery disease.
- Coronary artery spasm in the absence of a significant stenosis.
- Patients with known hypersensitivity to paclitaxel (or structurally-related compounds).
- Patients who cannot receive recommended antiplatelet and/or anticoagulant therapy.
- Pregnant or breast-feeding women or women who are intending to become pregnant, or men intending to father children.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the AGENT™ Paclitaxel-Coated Balloon Catheter labeling.

V. DEVICE DESCRIPTION

The AGENT™ Paclitaxel-Coated Balloon Catheter (hereafter referred to as AGENT Drug-Coated Balloon (DCB), AGENT Balloon Catheter, or AGENT DCB) is a monorail, semi-compliant percutaneous coronary intervention (PCI) catheter; the balloon portion of the device is coated with a TransPax™ coating (paclitaxel as the active pharmaceutical ingredient and acetyl tributyl citrate (ATBC) as the excipient). The AGENT Drug-Coated Balloon, see **Figure 1**, is designed to inhibit restenosis by delivering drug to the diseased arterial tissue. The distal section of the catheter is dual lumen and coaxial.

The outer lumen is used for inflation of the balloon to conform to the vessel wall, and the inner lumen permits the use of guidewires ≤0.014 in (0.36 mm) to facilitate advancement of the catheter. The proximal section of the catheter is a single-lumen, stainless steel hypotube with a single luer port hub for inflation/deflation of the balloon during drug delivery. The semi-compliant balloon is designed to provide an inflatable segment of known diameter and length at recommended pressures. The balloon is available in diameters of 2.0-4.0 mm and in lengths of 12-30 mm. A balloon protector is placed over the drug-coated balloon to maintain a low profile and to protect the balloon and drug coating. A mandrel is placed into the inner lumen to protect the patency of the catheter during storage. The catheter tip is tapered to facilitate advancement of the catheter to the treatment area and through the stenosis. The shaft is coated with a hydrophilic coating (ZGlide™), which is present from the guidewire port to just proximal to the balloon. The

effective length of the catheter is 144 cm. Marks on the proximal portion of the catheter shaft indicate the exit of the balloon catheter tip out of the guide catheter (one mark at 90 cm and two marks at 100 cm). Two radiopaque marker bands, in conjunction with fluoroscopy, aid in positioning the AGENT Drug-Coated Balloon.

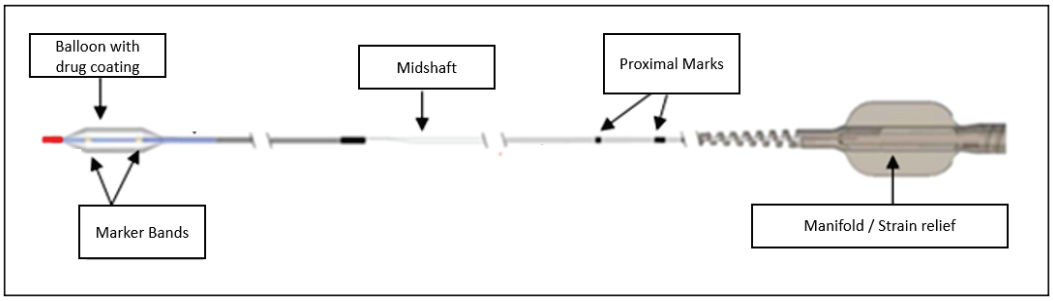

Figure 1: AGENT Paclitaxel-Coated Balloon Catheter

The AGENT DCB's catheter is identical to the cleared Emerge™ PTCA Balloon Catheter System (K163174). The coating used on the AGENT DCB's balloon, including its drug dose density, is the identical TransPax drug coating as used on the Ranger™ DCB (P190019).

Mechanism of Action

AGENT DCB provides mechanical expansion of a diseased vessel (primary mode of action) while transferring a pharmacological agent (i.e., paclitaxel) to inhibit neointimal proliferation of the vessel wall.

DRUG COATING DESCRIPTION

The drug coating for the AGENT balloon catheter consists of paclitaxel (the active pharmaceutical ingredient) and acetyl tributyl citrate (the inactive ingredient).

Drug Substance – Paclitaxel (PTx)

The active pharmaceutical ingredient in the proprietary AGENT balloon coating is paclitaxel [CAS no. 33069-62-4]. Paclitaxel as an active substance is well described in scientific literature and is used in both medicinal products (drug products) and combination products (device/drug products). The principal mechanism by which paclitaxel inhibits neointimal growth is through the stabilization of microtubules by preventing depolymerization during the final G2/M phase of cell division.

The chemical name of paclitaxel is: Benzenepropanoic acid, β -(benzoylamino) - α - hydroxy -, 6, 12b – bis (acetyloxy) - 12-(benzoyloxy) - 2a,3,4,4a,5,6,9,10,11,12,12a,12b-

dodecahydro-4,11- dihydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11 methano-1H-cyclodeca[3,4]benz[1,2-b]oxet-9-yl ester, [2aR-[2aα,4β,4aβ,6β,9α (αR*,βS*), 11α,12α,12aα,12bα]].

Paclitaxel is a diterpenoid with a characteristic taxane skeleton of 20 carbon atoms, a molecular weight of 853.91 g/mol and a molecular formula of $C_{47}H_{51}NO_{14}$ (**Figure 2**). It is highly lipophilic and insoluble in water, but freely soluble in polar solvents such as methanol, ethanol, chloroform, ethyl acetate and dimethyl sulfoxide.

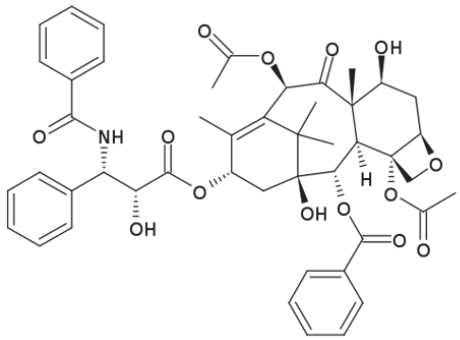

Figure 2: Paclitaxel Chemical Structure

Excipient – Acetyl Tributyl Citrate

The inactive ingredient in the AGENT DCB coating is acetyl tributyl citrate (ATBC), which constitutes 20% of the coating formulation by weight. ATBC has no pharmacological effect and serves as an excipient in the DCB coating, designed to enhance coating integrity and facilitate drug coating transfer to the treated lesion vessel.

ATBC is a carboxylic acid ester with a molecular weight of 402.48 g/mol. It is a colorless, slightly viscous, liquid. ATBC is an excipient used for various commercially available products, including oral tablets (up to 18 mg per tablet / capsule) and in aqueous pharmaceutical coatings, controlled release systems, transdermal patches, and drug coated balloons for peripheral indications (e.g., BSC's Ranger™ device). The chemical structure of acetyl tributyl citrate is shown in **Figure 3**.

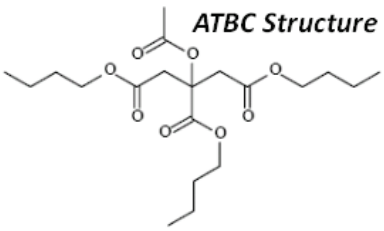

Figure 3: ATBC Chemical Structure

DRUG DOSE

The nominal drug dose density on the AGENT DCB is 2 µg/mm² of cylindrical balloon surface. The target drug content for every balloon size is defined by the product of the calculated cylindrical balloon surface area (A) and the nominal drug dose density, as shown in the following equation:

Target Drug Content 2 µg/mm²) x A (mm²)

AGENT balloons have diameters ranging from 2.00 mm to 4.00 mm and lengths of 12 mm to 30 mm. An overview of the AGENT DCB product matrix, including their respective total drug amount, is provided in **Table 1**.

Table 1: Nominal Drug Content Per Balloon Size

Diameter (mm)	Drug Dose by Balloon Length			
	12 mm	**15 mm**	**20 mm**	**30 mm**
2.00	165 µg	204 µg	272 µg	406 µg
2.25	177 µg	219 µg	291 µg	435 µg
2.50	196 µg	243 µg	322 µg	482 µg
2.75	216 µg	266 µg	354 µg	529 µg
3.00	235 µg	290 µg	386 µg	577 µg
3.50	274 µg	338 µg	449 µg	672 µg
4.00	312 µg	386 µg	513 µg	767 µg

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternative therapeutic options for treatment of coronary in-stent restenosis, including:

- Medical therapy and risk factor modification (e.g., diet, exercise, smoking cessation)
- Coronary artery bypass graft (CABG) surgery
- Vascular brachytherapy
- Plain old balloon angioplasty (POBA; i.e., angioplasty with a balloon with no drug coating)
- Additional stent

Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The AGENT Drug-Coated Balloon has been commercially available for distribution in the European Union (EU) since receiving CE Mark in July 2014. Since that time, the AGENT device has been commercially available in the countries identified in **Table 2**. During this time, the device has not been withdrawn from marketing for any reason related to its safety or effectiveness.

Table 2: List of Approved Countries

Afghanistan	Algeria	Andorra	Antigua and Barbuda
Argentina	Armenia	Aruba	Australia
Austria	Azerbaijan	Bahamas	Bahrain
Barbados	Belgium	Belize	Bermuda
Bonaire Saba	Bosnia-Herzegovina	Brunei	Bulgaria
Cambodia	Cayman Islands	Chile	Colombia
Costa Rica	Croatia	Curacao	Cyprus
Czech Republic	Denmark	Dominican Republic	Dutch Antilles
Ecuador	Egypt	El Salvador	Estonia
Finland	France	Georgia	Germany
Great Britain	Greece	Guatemala	Guyana
Haiti	Honduras	Hong Kong	Hungary
Iceland	India	Indonesia	Iraq
Ireland	Israel	Italy	Jamacia
Japan	Jordan	Kenya	Kosovo
Kuwait	Kyrgyzstan	Latvia	Lebanon
Libya	Liechtenstein	Lithuania	Luxembourg
Macau	Macedonia	Malaysia	Malta
Martinique	Mauritius	Mexico	Moldova
Mongolia	Montenegro	Morocco	Myanmar
Namibia	Nepal	Netherlands	New Zealand
Norway	Oman	Panama	Pakistan
Paraguay	Peru	Philippines	Poland
Portugal	Qatar	Romania	Russia
Saudi Arabia	Singapore	Saint Maarten	Slovakia
Slovenia	South Africa	South Korea	Spain
Sudan	Suriname	Sweden	Switzerland
Taiwan	Tajikistan	Thailand	Trinidad and Tobago

Tunisia	Turkey	Turkmenistan	United Arab Emirates
Uruguay	Uzbekistan	Vietnam	Palestine
Yemen			

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the AGENT DCB or the angioplasty procedure.

- Additional, possibly surgical, intervention
- Allergy (drug coating and its components, device, medications, contrast)
- Arrhythmia including conduction system disorder
- Bleeding (including hemorrhage or hematoma possibly requiring transfusion or additional intervention)
- Cerebrovascular accident (stroke) / transient ischemic attack (TIA)
- Death
- Embolism (tissue, plaque, thrombus, device, drug coating)
- Fever/inflammation
- Hemodynamic instability
- Hypotension/hypertension (shock)
- Kidney injury/failure
- Myocardial ischemia/infarction
- Organ insufficiency/failure (heart, liver, lungs)
- Pain (anginal, non-anginal)
- Pericardial effusion/cardiac tamponade
- Radiation injury
- Sepsis/infection
- Slow flow/no reflow
- Vessel injury (spasm, dissection, perforation, rupture, arteriovenous fistula, aneurysm)
- Vessel occlusion (abrupt closure, slow flow / no reflow, thrombosis, restenosis)

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

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

IX. SUMMARY OF NONCLINICAL STUDIES

A. LABORATORY STUDIES

A series of non-clinical laboratory studies related to the product were performed to evaluate the device, including: biocompatibility studies, bench testing, coating characterization testing, chemistry, manufacturing and controls (CMC) testing, sterilization testing, packaging/shelf life testing, and Good Laboratory Practice (GLP) animal studies. A summary for each of the evaluations is provided below.

i. Biocompatibility

Biocompatibility testing of the AGENT Paclitaxel-Coated Balloon Catheter (AGENT DCB) was conducted in accordance with ISO 10993-1 *Biological Evaluation of Medical Devices – Part 1: Evaluation and Testing within a Risk Management Process, FDA Guidance – Use of International Standard ISO 10993-1 – Guidances for Industry and Food and Drug Administration Staff*. Testing was completed separately on three separate test articles:

1) the final, drug-coated AGENT balloon catheter,

2) the bare (no drug or excipient) AGENT balloon catheters, and

3) on the isolated AGENT Drug-Coated Balloon only (with no catheter).

Multiple test articles were used in order to ensure that any potential effects of the drug coating component on biocompatibility could be differentiated from any potential effects of the device component.

The results of the biocompatibility studies conducted are summarized in **Table 3**.

Table 3: Summary of Biocompatibility Testing

Test Name	Applicable ISO Standard(s)	Test Article			Result(s)
		1	2	3	
Cytotoxicity Study Using the ISO Elution Method	ISO 10993-5	√	√	√	Non-cytotoxic
Cytotoxicity Study Using the Direct Contact Method	ISO 10993-5			√	Non-cytotoxic
ISO Guinea Pig Maximization Sensitization Test	ISO 10993-10	√	√	√	Non-sensitizer
ISO Intracutaneous Reactivity Study in Rabbits	ISO 10993-10	√	√	√	Non-irritant
ISO Acute Systemic Toxicity Study in Mice	ISO 10993-11	√	√	√	Non-toxic
USP Rabbit Pyrogen Study, Materials Mediated	ISO 10993-11	√	√	√	Non-pyrogenic
ASTM Hemolysis Study – Direct Method	ISO 10993-4	√	√	√	Non-hemolytic
ASTM Hemolysis Study – Extract	ISO 10993-4	√	√	√	Non-hemolytic
Partial Thromboplastin Time	ISO 10993-4	√			Met requirements
Platelet and Leukocyte Count	ISO 10993-4	√			Met requirements
Complement Activation (SC5b-9 Assay)	ISO 10993-4	√	√	√	Not a complement activator

This biocompatibility assessment concluded the AGENT DCB demonstrated acceptable biological risk under its intended use.

The Thrombogenicity, Implantation, and Sub-chronic/Chronic Toxicity endpoints, per ISO 10993-4, -6, and -11, respectively, were leveraged from the GLP animal

safety study using the final AGENT drug coated balloon catheter. The outcomes related to these endpoints were found to be acceptable.

Chemical characterization per ISO 10993-18 (Exhaustive Extraction and Analysis by GC/MS, LC/MS, ICP/MS) and associated toxicological risk assessments were performed. These studies supported the acceptable biological risk for the AGENT DCB for endpoints of Sub-chronic/Chronic Toxicity, Genotoxicity, and Carcinogenicity.

ii. Bench Testing

A summary of the in vitro engineering studies to support the AGENT Paclitaxel-Coated Balloon Catheter is provided in **Table 4**. All testing was completed in accordance with national and international standards and FDA guidance documents, as applicable, to support the approved indication.

Table 4: Summary of Bench Testing

Test	Testing Objective	Acceptance Criteria	Test Results
Dimensional and Functional Attributes	Demonstrate accurate dimensions, including crossing profile, effective length, balloon length, and guidewire compatibility, on the product label and compatible with accessory devices.	Compatible with labeled dimensions	Pass
Rated Burst Pressure	To ensure catheter/ balloon burst pressures are above the labeled pressure range.	>14 atm (2.0-3.0 mm) and >12 atm (3.5-4 mm)	Pass
Balloon Compliance	Measure the balloon to supply accurate compliance chart.	Characterize for development of the balloon compliance curve	Acceptable Outcomes
Balloon Inflation and Deflation Time	To ensure balloon can inflate and deflate to achieve labeled balloon diameter without delays to procedure.	Characterize inflation time; ≤60 s deflation	Acceptable outcomes; Pass
Balloon Fatigue	Repeat inflations to ensure freedom from leakage and damage on multiple inflations.	Must be able to withstand 10 repeat inflations	Pass
Tensile Strength	To ensure all bonds present on the balloon catheter withstands certain tensile forces without fractures.	≥1.3-22.2N, depending on bond	Pass
Flexibility and Shaft Kink	Catheter is wrapped around challenging radii mandrels till kink and confirmed catheter can perform as intended wire movement or inflation/deflation.	Characterize	Acceptable Outcomes
Torque Strength	To ensure catheter withstands rotational	Characterize	Acceptable

	forces without fractures.		Outcomes
Balloon Preparation, Delivery, and Retraction	Assures that the catheter can advance to the target lesion, deploy, and withdraw without any damage.	The device can be prepared, tracked, deployed, and retracted with no damage	Pass
Radiopacity	To ensure radiopaque markerbands are visible under fluoroscopy to aid in the placement of the balloon.	Must be visible	Pass
Hydrophilic coating integrity	To show that the hydrophilic coating remains largely intact after simulated use	Characterize	Acceptable Outcomes

iii. Coating Characterization Testing

Analytical and characterization testing was performed to evaluate characteristics of the AGENT DCB drug coating. A summary of the test and test description is located within **Table 5**.

Table 5: Summary of AGENT DCB Coating Characterization

Test	Description	Test Results
Particulate Quantitation (Simulated Use)	Characterize the total counts and sizes of particulates generated from AGENT DCB in simulated use conditions	Acceptable Outcomes
Particulate Identity and Crystallinity Characterization	Characterize chemical identification and crystallinity of particulates	Acceptable Outcomes
Drug Coating Thickness	Characterize coating thickness of the balloon at multiple locations along the length and circumference of the balloon	Acceptable Outcomes
Drug Coating Circumferential Uniformity	Measure the uniformity of drug content of multiple circumferential segments of finished AGENT DCB	Acceptable Outcomes
Drug Coating Longitudinal Uniformity	Measure the uniformity of drug content of multiple longitudinal segments, depending on balloon length, of finished AGENT DCB	Acceptable Outcomes
Drug Coating Durability	Durability and any performance impact to durability, is manifested in an assessment of drug content. Cohesion and adhesion of the coating is assessed in the measurement of drug content after the following steps: 1. Insertion through a guide catheter 2.Track through simulated anatomy	Acceptable Outcomes
Drug Coating Crystallinity Characterization	Characterize degree of crystallinity of the drug coating	Acceptable Outcomes
Drug Coating Integrity	Characterize drug coating Integrity including quantification of coated area after the	Acceptable Outcomes

	following steps: 1. Insertion through a guide catheter 2.Track through simulated anatomy	

iv. Chemistry, Manufacturing and Controls (CMC) Testing

The established requirements for ongoing AGENT DCB release batch and stability testing are summarized in **Table 6**.

Table 6: AGENT DCB CMC Testing Requirements

Test	Description	Acceptance Criteria
Appearance	Packaging securement and appearance of the balloon coating appearance is evaluated by visual inspection	Must meet visual standard
Drug Identity	The identity of the drug substance, paclitaxel, is confirmed by HPLC analysis and its UV spectrum	Identity must be confirmed
Drug Content Assay	Paclitaxel content is quantified by high performance liquid chromatography (HPLC) to ensure product contains the labeled dose	Drug content mean value should be 90.0 – 110.0% of label claim
Drug Content Uniformity	Paclitaxel content is quantified by HPLC to ensure individual devices contain the labeled dose	USP <905>
Drug Degradants and Impurities	The levels of drug degradants and impurities are quantified by HPLC to ensure they remain within acceptable levels	ICH Q3B(R2)
Residual Acetone Content	The residual acetone from the manufacturing process is quantified by gas chromatography – flame ionization detector (GC-FID) to ensure it remains within acceptable levels	Residual acetone levels must be within limits
Drug Release	The released paclitaxel is quantified by HPLC to ensure it is within limits	The drug release at multiple timepoints must be within limits.
Device Sterility	The sterility of the single-use device is evaluated per USP <71>	USP <71>
Endotoxins	Endotoxin levels are evaluated per AAMI ST72 to ensure they are within established safety guidelines	AAMI ST72
Particulates	Device particulate matter is evaluated using light obscuration particle counting procedures documented in USP <788>.	Particulate sizes and counts must be within limits

v. Sterilization

The AGENT Paclitaxel-Coated Balloon Catheter device is sterilized using the BSC2000-2 100% ethylene oxide (EO) sterilization cycle. The BSC2000-2 cycle is an all-in-one process, a type of dynamic sterilization cycle in which conditioning and aeration as well as sterilization occur in the sterilizer chamber. This cycle is validated and controlled in accordance with ISO 11135:2014 (Sterilization of Health Care Products - Ethylene Oxide - Requirements for Development, Validation and Routine Control of Sterilization Process for Medical Devices) to provide a Sterility Assurance Level (SAL) of at least 10^{-6}.

The amount of bacterial endotoxin was verified to be within the ANSI/AAMI ST72 specification limit.

vi. Packaging

Packaging verification testing was performed to demonstrate that the AGENT DCB packaging can withstand the hazards of distribution and the environment, and that the sterility of the device is maintained throughout the labeled shelf life. Package integrity testing included a visual assessment, bubble leak testing, and seal strength testing. Testing was conducted at baseline, aged, challenge sterilization, and distribution conditions.

vii. Shelf Life

Shelf-life studies evaluating the effects of aging on the mechanical properties of the catheter, packaging, and the stability of the drug were conducted to establish a shelf life/expiration date for the AGENT DCB product. The data generated support a 24-month shelf life for the AGENT DCB device and the product is labeled accordingly.

B. ANIMAL STUDIES

The following *in vivo* animal testing was conducted in a porcine coronary artery model to evaluate the safety of the AGENT DCB. Two animal studies were conducted in accordance with 21 CFR 58 (Good Laboratory Practices) and one animal study was not conducted in accordance with 21 CFR 58.

- One GLP pharmacokinetic (PK) study was completed evaluating drug content in blood (time points from 0.5 hours to 14 days), treated coronary arterial tissue, and downstream myocardium/organ specimens (time points from 1 hours to 144 days) in a naive, non-ISR coronary artery swine model.

- One non-GLP PK study was completed evaluating drug content in blood (time points from 0.5 hours to 28 days), treated coronary arterial tissue, and downstream myocardium/organ specimens (time points from 1 to 28 days) in an in-stent restenosis coronary artery swine model.
- One GLP safety and safety margin study was completed (time points from 4 to 180 days) providing evidence of drug delivery, tissue response, and safety in a non-injured coronary artery swine model.

In addition to the principal endpoints noted for each study, all animals were carefully evaluated for general health (i.e., vital signs, behavior, nutritional condition, gait, etc.) and clinical responses to treatment.

A list and description of the animal studies conducted is presented in **Table 7**.

Table 7: Summary of Animal Safety, Safety Margin, and PK Studies

Study ID	Number & Animal Type	Local Drug Dose	Balloon Size	Time Points	Major Endpoints	Endpoints Met
GLP Pharmacokinetics (19-020G)	n=18 Domestic Swine	1x	3.0 & 3.5 x 15 mm	Tissue 1 hour, 1/7/14/28/ 60/90/144 days Blood Baseline, 10/30 minutes, 1/8/12/16 hours, 1/3/7/14 days	Quantitative Angiography; Clinical Health; Arterial, Non-Target Tissue, and Blood Levels	Yes
Non-GLP Pharmacokinetics ISR Model (19-026N)	n=3 Domestic Swine	1x	3.0 & 3.5 x 15 mm	Tissue 1/7/28 days Blood Baseline, 10/30 minutes, 1/8/12/16 hours, 1/3/7/14/28 days	Quantitative Angiography; Clinical Health; Arterial, Non- Target Tissue, and Blood Levels; Acute Performance	Yes
GLP Safety, Safety Margin, and Vascular Response (18-095G)	n=24 Domestic Swine	1x, 3x	3.0 & 3.5 x 20 mm	4/30/90/180 days	Quantitative Angiography; Clinical Safety; Histology; Morphometric and Morphologic Analysis	Yes

The preclinical studies conducted demonstrate and confirm the safety of the AGENT DCB. The GLP safety evaluation study (18-095G) of the AGENT DCB demonstrated favorable safety parameters as defined by the following:

- Successful delivery of the device to the target treatment location without major procedural or device related complications, such as acute thrombosis, major bleeding, or flow-limiting dissection.
- No morbidity or mortality device-related complications during the treatment procedures and in-life phases of the experiments.
- No major angiographic differences observed between test and control treatment groups. No major vessel abnormalities were reported. Angiographic flow and stenosis were similar across treatment arms (1X, 3X, and Uncoated Balloon).
- The histological morphometric assessments of the treated iliofemoral arteries were generally comparable across treatment arms (1X, 3X, and Uncoated Balloon) including external elastic lamina, internal elastic lamina, lumen, medial, and neointimal areas, neointimal thickness and percent stenosis. There were no incidences of thrombotic occlusion or aneurysmal formation out to 180 days.
- Comparable histological indicators of vessel wall healing such as: injury, inflammation, and fibrosis with the test articles (1X, 3X) when compared to control tissue sections. The extent of endothelial coverage as determined by light microscopy in tissue sections were comparable between arms with endothelization nearly complete by 30 days and no abnormal findings on any endothelial surface.
- Downstream non-target tissues, including myocardium and organs, showed no clinically relevant evidence of adverse effects such as embolization-associated ischemia, thrombosis, or systemic organ toxicity.
- Acute performance data demonstrated acceptable clinical safety (including no thrombus formation) and device performance.

The preclinical pharmacokinetic studies (19-020G and 19-026N) demonstrated effective drug delivery and uptake into the arterial tissues at the therapeutic dose density (2.0 $\mu g/mm^2$) with no evidence of drug toxicity demonstrated as follows:

- Arterial paclitaxel concentrations were highest at the early time points, notably at day 1 post-procedure, and decreased to low but detectable levels through 144 days in the GLP de novo PK study. Pharmacokinetic parameters of arterial tissue demonstrated a C_{max} of 162.8 ng/mg (19-020G model).
- Blood paclitaxel concentrations reached their maximum at the earliest time points, within hours post-device deployment, followed by a rapid elimination profile,

reaching levels below quantification by 3 days post-procedure in the GLP de novo PK study.

- Paclitaxel was detected at low levels in distal tissues and organs, including the distal myocardium, sub-adjacent myocardium, and lungs, out to 90 days. Detectable levels out to 14 days were also present in the spleen and liver. The presence of paclitaxel in major organs or muscles was not associated with any clinically relevant adverse clinical reactions. Systemic concentrations in non-target tissues exhibited much lower paclitaxel concentrations relative to the treated arteries at the earlier time points and further decreased to non-detectable or almost non-detectable levels over 144 days. Results indicate limited systemic and non-target tissue drug exposure to paclitaxel with treatment using AGENT DCB.
- The PK profiles of AGENT DCB in treated vessel, blood, and downstream tissues and organs were similar between the *de novo* and in-stent restenosis animal models. Based on this data, the *de novo* model was found to be sufficient to represent and predict the paclitaxel PK profiles and arterial concentrations in an in-stent restenosis model.

Pharmacokinetic data demonstrated localization of paclitaxel with limited systemic and non-target tissue exposure. Histopathology data demonstrated an acceptable drug dose and embolic load safety margin for the intended therapeutic dose of 2.0 μg/mm^2 and range of allowable balloon sizes.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study, AGENT IDE Study, to establish a reasonable assurance of safety and effectiveness of the AGENT Paclitaxel-Coated Balloon Catheter 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. The study was conducted in the US under IDE # G200100. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. STUDY DESIGN

Patients were treated between May 2021 and August 2022. The database for this PMA reflected data collected through October 18, 2023 and included 600 patients. There were 40 investigational sites, all in the United States (US).

The AGENT IDE clinical study was a prospective, multicenter, 2:1 randomized (AGENT DCB to "plain old balloon angioplasty" (POBA)), controlled, single-blind,

superiority trial to assess the safety and effectiveness of the AGENT DCB as compared to POBA in patients with ISR.

The AGENT IDE Study used an adaptive group-sequential design with an initial planned enrollment of 480 patients, and one formal interim analysis on the 1-year data after randomization of the first 90% of subjects, with the expectation that the first 40% of randomized patients would have 1-year follow up at that time. The interim analysis was prespecified to be performed by the Data Monitoring Committee (DMC) for potential sample size re-estimation of up to 600 patients. Due to rapid enrollment in the trial, no subjects had completed 1-year follow-up for the interim analysis at the time of the planned interim analysis; therefore, the DMC recommended to continue enrollment to the maximum of 600 patients. To determine final sample size for the primary endpoint analysis, the sponsor and FDA agreed the DMC would perform an interim analysis on the first 40% of patients (n=192) with 1-year data when those data were available using the prespecified adaptive design strategy. Based on this interim analysis, the DMC's recommendation was to evaluate the primary endpoint on the first 480 patients, which was consistent with the initial planned sample for the trial.

The primary endpoint of 1-year target lesion failure (TLF) was analyzed based on the primary endpoint cohort (N=480). The primary endpoint analysis was also performed on the total enrollment cohort (N=600). Results for both are presented within this SSED. All other data, including the additional clinical endpoints presented below, are based on the total enrollment cohort (N=600).

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the AGENT IDE Study was limited to patients who met the following clinical and angiographic inclusion criteria (**Table 8**):

Table 8: 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	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.

estimate)	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.

Patients were <u>not</u> permitted to enroll in the AGENT IDE Study if they met any of the following exclusion criteria (**Table 9**):

Table 91: 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).

2. Follow-up Schedule

All patients were scheduled to return for follow-up examinations at hospital discharge, 30 days, 6 months, 1 year, and then annually between 2 and 5 years post-procedure. Adverse events and complications were recorded at all visits. Patients who were enrolled but who did not receive treatment were to be followed through 12 months only.

Pre-procedure, patients were assessed for quality of life (using the EQ-5D questionnaire), medical history, angina, cardiac enzymes, cardiac rhythm (using ECG), kidney function (using serum creatinine), use of antiplatelet medications, and complete blood count including platelets. Post-procedure, the objective parameters measured during the study included quality of life, angina, cardiac enzymes (pre-discharge only), cardiac rhythm, and use of antiplatelet medications. Adverse events and clinical endpoints were recorded at all visits. The schedule of pre-procedure and post-procedure evaluations is included in **Table 10** below.

Table 10: AGENT IDE Study Follow-up 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.

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

The key timepoints are shown below in the tables summarizing safety and effectiveness.

3. Clinical Endpoints

The primary endpoint, which included components for both safety and effectiveness, is the 1-year rate of target lesion failure (TLF) defined as a composite of:

- Any ischemia-driven target lesion revascularization (TLR).
- Myocardial infarction (MI; Q-wave and non–Q-wave) related to the target vessel.
- Cardiac death.

Myocardial infarction included both peri-procedural MI and spontaneous MI. Peri-procedural MI (within 48 hours of the index procedure) was defined per the SCAI definition**Error! Bookmark not defined.** and spontaneous MI (more than 48 hours after the index procedure) per 4th Universal definition**Error! Bookmark not defined.**.

As agreed upon with FDA prior to unblinding, in order to account for potential heterogeneity in outcomes related to the use of multiple enzymes and ULNs, a unified ULN for cTn-I (ULN = 0.045 ng/ml) and a unified ULN for cTn-T (ULN = 0.022 ng/ml) were used to identify potential PPMI events.

With regards to safety, additional endpoints were measured, including all cause death, cardiac death, MI, and stent thrombosis per Academic Research Consortium (ARC) definitions.

With regards to effectiveness, additional endpoints included clinical procedural success rate, technical success rate, target lesion revascularization (TLR), target vessel revascularization (TVR), and change in quality of life.

With regard to success/failure criteria, the study was considered a success if the AGENT DCB was shown to be superior to the POBA control for the primary endpoint of TLF at one year.

A z-test with unpooled variance for the difference of two proportions was to be used to test the hypothesis of superiority of the AGENT 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 rates through 12 months for the DCB and POBA arms, respectively.

The primary analysis set for the primary endpoint was the intent to treat (ITT) analysis set.

B. Accountability of Full Cohort

At the time of database lock, of 600 patients enrolled in the PMA study, 95.8% (389/406) of AGENT DCB and 95.9% (186/194) of POBA subjects were eligible for analysis at the completion of the primary endpoint, the 12 month post-procedure visit (**Table 11**). **Figure 4** shows the AGENT IDE Study randomization and enrollment process and follow-up schedule.

Table 11: AGENT IDE Subject Disposition Table, ITT (N=600)

Patient Disposition	POBA	AGENT	Total
Intent-to-Treat Analysis Set	194	406	600
Death ≤395 days with no 12-month clinical follow-up performed	8	17	25
Eligible for 12-month clinical follow-up[a]	95.9% (186/194)	95.8% (389/406)	95.8% (575/600)
12-month clinical follow-up performed[b]	94.6% (176/186)	95.9% (373/389)	95.5% (549/575)
Office visit	135	275	410
Telephone contact	41	98	139
12-month clinical follow-up not performed	10	16	26
Prematurely discontinued	3	7	10

Patient Disposition	POBA	AGENT	Total
Patient withdrew consent	2	7	9
Lost to follow-up	0	0	0
Investigator discretion	1	0	1
Missed 12-month visit; no later follow-up visit performed	7	9	16
12-month clinical follow-up or death[c]	94.8% (184/194)	96.1% (390/406)	95.7% (574/600)

Numbers are counts of subjects or % (Count/Sample Size).
a. Subjects who died prior to completion of follow-up window and prior to completing a 12-month clinical follow-up visit are considered censored and are excluded from calculation of proportion of subjects who completed clinical follow-up visit.
b. Based on subjects eligible for 12-month clinical follow-up (excludes subjects who died within 395 days with no 12-month follow-up).
c. Includes subjects who have died in both the numerator and the denominator; based on Intent-to-Treat analysis set.

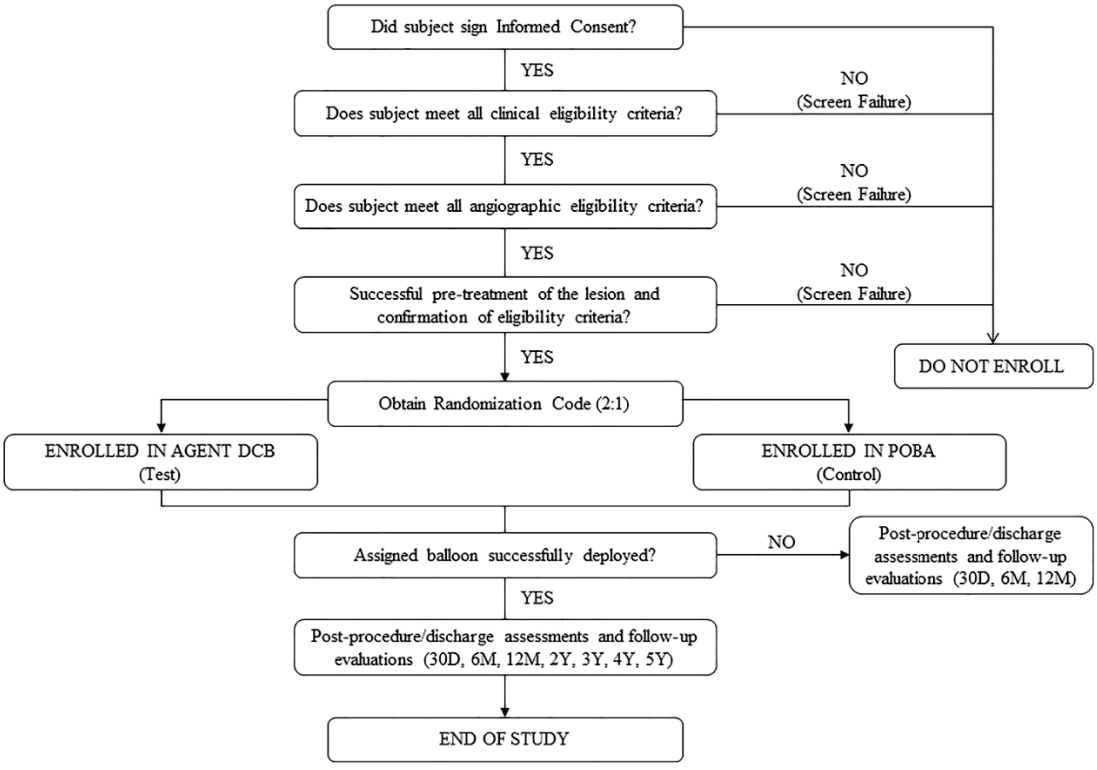

Figure 4: AGENT IDE Study Enrollment and Randomization Process and Follow-up Schedule

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for an interventional cardiovascular study performed in the US. **Table 12** presents demographics for the ITT analysis set. AGENT and POBA treatment arms were well-balanced with no significant differences in any demographic parameters. Combining both treatment arms, patient mean age was 68.3 years, 26.2% of patients were female, and 75.3% of patients were white.

Given lower enrollment of racial and ethnic minorities and female patients as compared to the general coronary artery disease population in the US, a post approval surveillance study will be initiated for an all-comers patient population with specific focus and analyses for these underrepresented groups. See **Section XIV** below for details on the post-approval surveillance study.

Table 12: Demographics, ITT (N=600)

Demographics	POBA N=194	AGENT N=406	*P*-value
Age (years)	67.90 ± 9.68 (194)	68.42 ± 9.79 (406)	0.54
≥ 75	28.4% (55/194)	26.8% (109/406)	0.70
Sex			
Female	27.3% (53/194)	25.6% (104/406)	0.66
Male	72.7% (141/194)	74.4% (302/406)	0.66
Race[†]			
American Indian or Alaska Native	0.5% (1/194)	0.0% (0/406)	0.32
Asian	3.1% (6/194)	2.2% (9/406)	0.58
Black or African American	5.2% (10/194)	7.9% (32/406)	0.22
Native Hawaiian or Other Pacific Islander	0.5% (1/194)	0.2% (1/406)	0.54
White	76.3% (148/194)	74.9% (304/406)	0.71
Other	1.5% (3/194)	3.9% (16/406)	0.12
Not Disclosed	9.3% (18/194)	5.7% (23/406)	0.10
Ethnicity[†]			
Hispanic or Latino	4.6% (9/194)	6.4% (26/406)	0.39

Numbers are presented as % (count/sample size) or mean ± standard deviation (n).
P-values are 2-sided and from Student's t Test for continuous variables and the Chi-square or Fisher's Exact (*) Test for discrete variables. The p values have not been adjusted for multiplicity.

Demographics	POBA N=194	AGENT N=406	*P*-value
†A subject may be identified in multiple ethnicity and race categories.			

Tables 13 and 14 show the baseline clinical characteristics and cardiac history of the patient population. Approximately 50% of patients had diabetes, 50% had a history of MI, and 37% presented with unstable angina or recent MI. In general, baseline clinical characteristics were comparable between the Agent DCB and POBA control groups.

Table 132: Baseline Clinical Characteristics, ITT (N=600)

Baseline Characteristic	POBA N=194	AGENT N=406	*P*-value
Physical Assessment			
Height (cm)	171.98 ± 9.83 (191)	172.12 ± 10.55 (396)	0.88
Weight (kg)	89.65 ± 21.67 (193)	89.07 ± 18.48 (404)	0.74
Body Mass Index‡ (kg/m^2)	30.10 ± 5.85 (191)	30.01 ± 5.53 (396)	0.86
Medical History			
Smoking, Ever	57.7% (112/194)	57.6% (234/406)	0.98
Current	9.8% (19/194)	10.3% (42/406)	0.83
Previous	47.9% (93/194)	47.3% (192/406)	0.88
Smoking History Unknown	0.0% (0/194)	1.7% (7/406)	0.10
Diabetes Mellitus	50.0% (97/194)	51.0% (206/404)	0.82
Medically Treated	46.4% (90/194)	44.3% (179/404)	0.63
Insulin or Other Injectables	25.3% (49/194)	23.0% (93/404)	0.55
Hyperlipidemia	94.8% (184/194)	94.6% (382/404)	0.88
Hypertension	95.9% (186/194)	94.6% (383/405)	0.49
Bleeding Disorder	2.6% (5/193)	2.3% (9/399)	0.78
Peripheral Vascular Disease	16.1% (31/192)	19.5% (78/401)	0.33
Chronic Obstructive Pulmonary Disease	10.3% (20/194)	9.7% (39/403)	0.81
History of Stroke or TIA	9.8% (19/194)	14.2% (57/402)	0.13
History of Renal Disease	16.6% (32/193)	18.4% (74/402)	0.59
Prior COVID-19 Infection	13.3% (23/173)	13.0% (49/376)	0.93
COVID-19 Vaccination	84.7% (138/163)	87.2% (287/329)	0.43
Numbers are presented as % (count/sample size) or mean ± standard deviation (n).			

Baseline Characteristic	POBA N=194	AGENT N=406	*P*-value
P-values are 2-sided and from Student's t Test for continuous variables and the Chi-square or Fisher's Exact (*) Test for discrete variables. The p values have not been adjusted for multiplicity. *‡The body mass index is the weight in kilograms divided by the square of the height in meters.* *Abbreviation: ITT=intent-to-treat; TIA=transient ischemic attack*			

Table 143: Cardiac History and Baseline Status, ITT (N=600)

Cardiac History	POBA N=194	AGENT N=406	*P*-value
Family History of CAD	99.5% (193/194)	99.8% (405/406)	0.54
Prior MI	50.0% (95/190)	49.7% (198/398)	0.95
Prior CABG	28.6% (55/192)	30.8% (124/403)	0.60
History of Heart Failure	21.4% (41/192)	22.9% (92/401)	0.66
NYHA Classification			0.56
I – No Symptoms	3.6% (7/192)	2.0% (8/401)	0.27
II – Mild Symptoms	7.3% (14/192)	8.0% (32/401)	0.77
III – Limited Activity	5.2% (10/192)	4.7% (19/401)	0.80
IV – Severe Limitations	0.0% (0/192)	0.0% (0/401)	Undef
Unknown	5.2% (10/192)	8.2% (33/401)	0.18
History of Arrhythmia	18.2% (35/192)	21.9% (88/401)	0.30
Indication for Procedure			
Recent MI	6.2% (12/194)	5.2% (21/406)	0.61
Unstable angina	31.4% (61/194)	31.5% (128/406)	0.98
Stable angina	51.5% (100/194)	55.4% (225/406)	0.37
Silent ischemia	2.6% (5/194)	1.7% (7/406)	0.54
Other indication	8.2% (16/194)	6.2% (25/406)	0.34
LVEF Measurement (%)	54.23 ± 9.89 (189)	54.05 ± 10.56 (393)	0.84
History of Multivessel Disease	78.4% (149/190)	79.3% (317/400)	0.82
History of Left Main Disease	20.7% (39/188)	22.6% (89/394)	0.62

Numbers are presented as % (count/sample size) or mean ± standard deviation (n).
P-Values are 2-sided and from Student's t Test for continuous variables and the Chi-square or Fisher's Exact (*) Test for discrete variables. The p values have not been adjusted for multiplicity.
The Mantel-Haenszel (MH) tests use non-missing data and exclude the 'Unknown' category. For NYHA classification, the MH test is performed on all subjects with congestive heart failure.
Note: Recent MI is defined as MIs that occurred within 2 weeks prior to the index procedure. Patients with STEMI fewer than 72 hours prior were excluded.

Cardiac History	POBA N=194	AGENT N=406	*P*-value
Abbreviation: CABG=coronary angiography bypass graft; CAD=coronary artery disease; CCS=Canadian Cardiovascular Society; ITT=intent-to-treat; LVEF=left ventricular ejection fraction; NYHA=New York Heart Association; MI=myocardial infarction; Undef=undefined.			

Table 15 presents baseline lesion characteristics as determined by core laboratory quantitative coronary angiography (QCA). Most characteristics were similar between arms, including the presence of multiple-layer in-stent restenosis (AGENT 43.3% versus POBA 42.3%), mean reference vessel diameter (2.7 ± 0.5 mm in both arms), and lesion length (AGENT 12.8 ± 6.3 mm vs. POBA 11.8 ± 6.6 mm). Some differences are noted for various lesion characteristics, including certain ISR patterns and ulceration, but the sample sizes are low and these differences were not likely to influence the outcome of the study.

Table 15: Baseline Target Lesion Characteristics as Determined by the Angiographic Core Laboratory, ITT (N=600)

Target Lesion Characteristic	POBA N=194 Lesions, N=194 Subjects	AGENT N=407 Lesions, N=406 Subjects	*P*-value
Single Stent Layer†	57.7% (112/194)	56.7% (230/406)	0.80
Multiple Stent Layer†	42.3% (82/194)	43.3% (176/406)	0.80
Target Lesion Vessel			
LAD	35.6% (69/194)	34.7% (141/406)	0.84
LCx	24.2% (47/194)	24.1% (98/406)	0.98
RCA	35.6% (69/194)	38.4% (156/406)	0.49
LM	4.6% (9/194)	2.7% (11/406)	0.22
Lesion Location			
Proximal	32.0% (62/194)	31.5% (128/406)	0.92
Mid	40.2% (78/194)	44.1% (179/406)	0.37
Distal	12.4% (24/194)	11.1% (45/406)	0.64
Ostial	15.5% (30/194)	13.3% (54/406)	0.48
Minimal Lumen Diameter (mm)	0.92 ± 0.40 (191)	0.95 ± 0.36 (405)	0.35
Mean Lumen Diameter (mm)	2.27 ± 0.58 (189)	2.31 ± 0.50 (399)	0.39
% Diameter Stenosis (mm)	66.41 ± 12.76 (191)	64.98 ± 12.05 (405)	0.19
Mehran ISR Pattern			
1A (articulation)	0.0% (0/189)	0.0% (0/403)	Undef
1B (margin)	1.1% (2/189)	1.0% (4/403)	1.00

Target Lesion Characteristic	POBA N=194 Lesions, N=194 Subjects	AGENT N=407 Lesions, N=406 Subjects	*P*-value
1C (focal)	44.4% (84/189)	36.7% (148/403)	0.07
1D (multifocal)	1.1% (2/189)	0.7% (3/403)	0.66
2 (intrastent)	47.1% (89/189)	57.1% (230/403)	0.02
3 (proliferative)	4.8% (9/189)	4.0% (16/403)	0.66
4 (total occlusion)	1.6% (3/189)	0.5% (2/403)	0.33
Tortuosity, Any	0.0% (0/192)	0.7% (3/405)	0.55
Moderate	0.0% (0/192)	0.7% (3/405)	0.55
Severe	0.0% (0/192)	0.0% (0/405)	Undef
Calcification, Any	12.5% (13/104)	12.6% (28/222)	0.98
Moderate	2.9% (3/104)	5.0% (11/222)	0.56
Severe	9.6% (10/104)	7.7% (17/222)	0.55
Ulceration	1.5% (3/194)	0.0% (0/406)	0.03
Aneurysm	0.5% (1/194)	0.0% (0/406)	0.32
Pre-Procedure TIMI Flow			
0	3.1% (6/192)	2.0% (8/405)	0.39
1	1.6% (3/192)	0.5% (2/405)	0.33
2	4.2% (8/192)	5.2% (21/405)	0.59
3	91.1% (175/192)	92.3% (374/405)	0.61
Lesion Preparation (Pretreatment) †			
Target lesion successfully dilated	100% (194/194)	99.5% (405/407)	1.00

Numbers are presented as % (count/sample size) or mean ± standard deviation (n).
P-values are two-sided and from Student's t Test for continuous variables and Chi-square or Fisher's Exact (*) Test for discrete variables. The p values have not been adjusted for multiplicity.
†Site-reported values.
Abbreviations: ITT=intent-to-treat, MLD=minimum lumen diameter; TIMI= Thrombolysis In Myocardial Infarction; LAD=left anterior descending; LCx=left circumfex; LMCA=left main coronary artery; NA=not applicable; RCA=right coronary artery; Undef=undefined

Table 16 presents procedural characteristics. AGENT and POBA treatment groups were well-balanced with no significant differences in procedural characteristics. Mean procedure time was 55.2 minutes, 87.2 % of patients had only the target lesion treated and 12.8% had both target plus one non-target lesion treated. Only one study device was allowed for the AGENT DCB arm, hence the slight difference in number of study devices used (3.6% of subjects in the POBA arm had 2 study devices used). Similarly, one target lesion was allowable in the study, though one patient had 2 target lesions treated, which was considered a protocol deviation. The use of cutting balloons was similar in lesions treated with AGENT DCB as compared to lesions treated

with POBA (25.1% vs. 23.7%). Intravascular imaging was performed in approximately 74% of patients during the procedure.

Table 16: Procedural Characteristics, ITT (N=600)

Measure	POBA N=194 Lesions, N=194 Subjects	AGENT N=407† Lesions, N=406 Subjects	*P*-value
Urgency of intervention			
Elective	90.2% (175/194)	89.7% (364/406)	0.83
Urgent / Emergent	9.8% (19/194)	10.3% (42/406)	0.83
Procedure Time (min)	53.15 ± 27.06 (193)	56.19 ± 29.81 (402)	0.23
Target Lesions Treated by Subject	1.00 ± 0.00 (194)	1.00 ± 0.05 (406)	0.49
1 Target Lesion Treated	100% (194/194)	99.8% (405/406)	1.00*
2 Target Lesions Treated	0.0% (0/194)	0.2% (1/406)†	1.00*
Study Device (POBA or AGENT) Usage by Subject in Target Lesion			
0 Study Devices	0.0% (0/194)	0.2% (1/406)‡	1.00*
1 Study Device	95.4% (185/194)	99.8% (405/406)	0.0002*
2 Study Devices	3.6% (7/194)	0.0% (0/406)	0.0003*
3 Study Devices	1.0% (2/194)	0.0% (0/406)	0.10*
Subjects with Only Target Lesion Treated	86.6% (168/194)	87.4% (355/406)	0.77
Subjects with Both Target & Non-Target Lesions Treated	13.4% (26/194)	12.6% (51/406)	0.77
Cutting Balloon Use	23.7% (46/194)	25.1% (102/407)	0.72
Intravascular Imaging During Procedure	76.8% (149/194)	72.4% (294/406)	0.25
Post-Procedure			
Hospital Length of Stay (days)	0.72 ± 1.75 (194)	0.59 ± 0.93 (406)	0.24

Numbers are presented as % (count/sample size) or mean ± standard deviation (n).
P-values are two-sided and from Student's t Test for continuous variables and the Chi-square or Fisher's Exact (*) Test for discrete variables. The p values have not been adjusted for multiplicity
†One patient in the DCB arm had two target lesions treated with DCB that was counted as a protocol deviation.
‡Study balloon rupture in the DCB arm causing perforation. This was counted as a device deficiency

Use of dual antiplatelet therapy (DAPT; aspirin plus a $P2Y_{12}$ inhibitor) pre-procedure, at hospital discharge, 30-day, 6-month, and 1-year follow-up time points is shown in **Table 17.** The percentage of subjects on DAPT was similar between the two treatment groups at each time point.

Table 17: Dual Antiplatelet Medication Usage Through 1 Year, ITT (N=600)

Medication	POBA N=194	AGENT N=406	*P*-value
DAPT (Aspirin and one of Clopidogrel, Ticlopidine, Prasugrel or Ticagrelor)			

Medication	POBA N=194	AGENT N=406	*P*-value
Prior Regimen or Loading Dose	77.8% (151/194)	73.4% (298/406)	0.24
Discharge	95.4% (185/194)	95.8% (389/406)	0.80
30 Days	90.5% (172/190)	91.3% (365/400)	0.77
6 Months	83.2% (158/190)	85.7% (335/391)	0.43
12 Months	77.8% (137/176)	79.6% (297/373)	0.63

Numbers are % (count/sample size). P-values are from two-sided from Chi-square test. The p values have not been adjusted for multiplicity

D. SAFETY AND EFFECTIVENESS RESULTS

The primary analysis of safety and effectiveness was based on the ITT cohort of the initial 480 patients available for the 12-month evaluation of target lesion failure.

The study primary endpoint was met. AGENT DCB was superior to POBA as the one-sided upper 97.5% confidence bound for the difference in 1-year TLF was less than zero in the ITT population. Specifically, 18.2% subjects treated with AGENT and 29.3% of the POBA treated subjects in the ITT population experienced TLF by 1 year. Per-protocol analysis was also performed, and the result was identical. **Table 18** shows the primary endpoint of 1-year TLF for the primary endpoint analysis cohort (N=480).

Table 18: Primary Endpoint Results, N=480

12-Month TLF	POBA N=159	AGENT N=321	Difference [95% CI]	One-sided 97.5% UCB	One-sided *P*-value for superiority
ITT	29.3% (44/150)	18.2% (55/302)	-11.1% [-19.6%, -2.6%]	-2.6%	0.0051

Primary Endpoint Analysis: Full Cohort (N=600): 12-Month TLF

The primary endpoint analysis was also performed on the total enrollment cohort (N=600) after that data became available. As shown in **Table 19,** the rate of 1-year TLF was 18.2% in patients treated with AGENT and 29.0% of patients treated with POBA in the ITT population. These data demonstrate very similar outcomes to the initial 480-patient analysis presented above. Per-protocol analysis was also performed, and the result was again identical.

Table 19: Primary Endpoint Results, Full Cohort (N=600)

12-Month TLF	POBA N=194	AGENT N=406	Difference [95% CI]	One-sided 97.5% UCB
ITT	29.0% (54/186)	18.2% (71/390)	-10.8% [-18.4%, -3.3%]	-3.3%

Time-to-event event curves (Kaplan-Meier analysis) to 1 year for target lesion failure are shown below in **Figure 5** for the full 600 patient cohort. The estimated event rate was 17.9 % for AGENT and 28.6% for POBA.

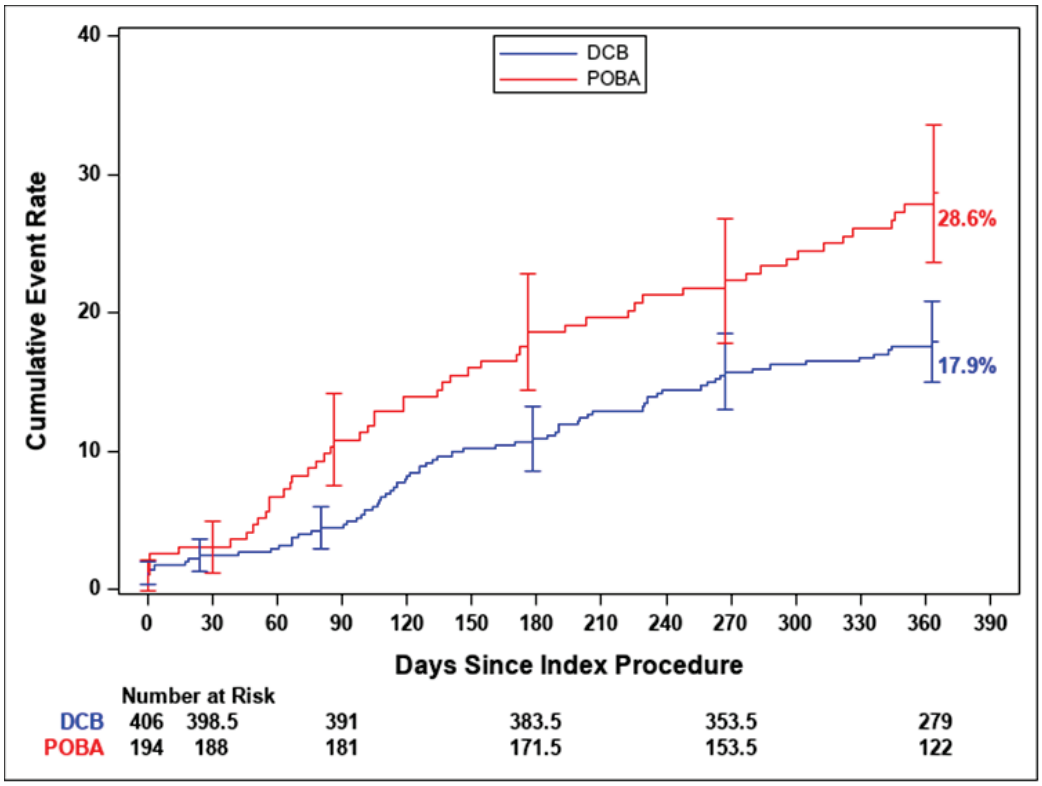

Figure 5: Kaplan-Meier Event Curve for TLF to 12 Months, N=600

Values are presented as cumulative event rate ± 1.5 standard error

1. Safety Results

The analysis of safety was based on the ITT cohort of 582 patients available for the 12-month evaluation. The key safety outcomes for this study are presented below in **Table 20**. Adverse effects are reported in **Table 21.**

Safety endpoints adjudicated by the CEC included death (all-cause and cardiac death), MI, and ISR stent thrombosis. Rates of death were comparable across treatment groups. Rates of MI at 12 months numerically favored the AGENT DCB over POBA (7.4% AGENT vs 12.2% POBA). None of the subjects in the AGENT arm experienced definite/probable ISR stent thrombosis compared to 6 subjects in the POBA arm (0.0% versus 3.2%). **Table 20** below presents a summary of the safety-related endpoints adjudicated by the CEC at all currently available timepoints.

Table 20: Summary of CEC-Adjudicated Safety Endpoints (N=600)

Event	POBA (N=194)	DCB (N=406)
In-Hospital Safety Events		
Death	0.0% (0/194)	0.0% (0/406)
MI	2.6% (5/194)	1.5% (6/406)
ARC ISR Stent Thrombosis Related to Target Lesion	0% (0/194)	0.0% (0/406)
Events to 30 Days		
Death	0.0% (0/194)	0.5% (2/406)
Cardiac Death	0.0% (0/194)	0.2% (1/406)
Non-Cardiac Death	0.0% (0/194)	0.2% (1/406)
MI	2.6% (5/194)	2.0% (8/406)
ARC ISR Stent Thrombosis Related to Target Lesion	0% (0/194)	0.0% (0/406)
Events to 6 Months		
Death	0.5% (1/194)	1.7% (7/404)
Cardiac Death	0.5% (1/194)	1.5% (6/404)
Non-Cardiac Death	0.0% (0/194)	0.2% (1/404)
MI	8.2% (16/194)	4.2% (17/404)
ARC ISR Stent Thrombosis Related to Target Lesion	2.1% (4/194)	0.0% (0/404)
Events to 12 Months		
Death	3.7% (7/189)	4.1% (16/393)
Cardiac Death	1.6% (3/189)	2.8% (11/393)
Non-Cardiac Death	2.1% (4/189)	1.3% (5/393)
MI	12.2% (23/189)	7.4% (29/393)
ARC ISR Stent Thrombosis Related to Target Lesion	3.7% (7/189)	0.3% (1/393)

*Rates presented include definite, probable, and possible stent thrombosis events

There were a total of 623 serious adverse events reported in 226 patients in the AGENT DCB group, compared to a total of 306 serious adverse events reported in 113 patients in the POBA control group through 12 months of follow up. The frequency and nature of adverse events observed in the AGENT DCB group were similar to those observed for the POBA control group.

When evaluating all adverse events, including non-serious adverse events, a numerical increase was observed for Acute Kidney Injury in the DCB arm as compared to POBA (6.7% vs 3.1%). However, most observations were non-serious, the event rates in both arms were low compared to known rates of acute kidney injury after PCI procedures, and the observed difference was likely due to chance.

Serious adverse events that occurred in the AGENT IDE Study with an event rate >1% are presented in **Table 21.** A serious adverse event either resulted in death, was life-threatening, required inpatient hospitalization or caused prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, or required intervention to prevent permanent impairment of damage. Adverse events were reported by sites and coded using MedDRA preferred terms. Only categories of adverse events occurring at a rate of >1% in either treatment group are reported. Thus, the listed events may not add up to the total amount in each group or overall.

Table 21: Serious Adverse Events Through 1 Year with Event Rate >1% (N=600)

Serious Adverse Event			POBA (N=194 Subjects)		DCB (N=406 Subjects)	
MedDRA System Organ Class	**MedDRA High-Level Group Term**	**MedDRA Preferred Term**	**Events (n)**	**Percent of Subjects with Event (n/N)**	**Events (n)**	**Percent of Subjects with Event (n/N)**
Total	**Total**	**Total**	**306**	**58.2% (113/194)**	**623**	**55.7% (226/406)**
Cardiac disorders	**Total**	**Total**	**132**	**38.7% (75/194)**	**238**	**35.0% (142/406)**
	Coronary artery disorders	**Total**	**98**	**33.0% (64/194)**	**153**	**28.8% (117/406)**
		Angina unstable	36	12.9% (25/194)	43	8.6% (35/406)
		Angina pectoris	28	11.9% (23/194)	43	9.9% (40/406)
		Acute myocardial infarction	16	7.2% (14/194)	25	5.2% (21/406)
		Coronary artery disease	12	5.7% (11/194)	21	5.2% (21/406)
		Myocardial infarction	2	1.0% (2/194)	7	1.7% (7/406)
		Acute coronary syndrome	2	1.0% (2/194)	5	1.2% (5/406)
	Heart failures	**Total**	**20**	**7.7% (15/194)**	**35**	**5.9% (24/406)**
		Cardiac failure	2	1.0% (2/194)	17	2.5% (10/406)
		Cardiac failure congestive	10	4.1% (8/194)	8	1.7% (7/406)
		Cardiac failure acute	4	2.1% (4/194)	3	0.7% (3/406)
		Left ventricular failure	2	1.0% (2/194)	3	0.7% (3/406)
	Cardiac arrhythmias	**Total**	**9**	**4.6% (9/194)**	**39**	**6.4% (26/406)**
		Atrial fibrillation	5	2.6% (5/194)	16	3.4% (14/406)
	Cardiac valve disorders	**Total**	**2**	**1.0% (2/194)**	**4**	**1.0% (4/406)**

Serious Adverse Event			POBA (N=194 Subjects)		DCB (N=406 Subjects)	
MedDRA System Organ Class	**MedDRA High-Level Group Term**	**MedDRA Preferred Term**	**Events (n)**	**Percent of Subjects with Event (n/N)**	**Events (n)**	**Percent of Subjects with Event (n/N)**
	Myocardial disorders	**Total**	**2**	**1.0% (2/194)**	**4**	**1.0% (4/406)**
		Cardiomyopathy	2	1.0% (2/194)	0	0.0% (0/406)
Infections and infestations	**Total**	**Total**	**20**	**7.7% (15/194)**	**50**	**10.1% (41/406)**
	Infections - pathogen unspecified	**Total**	**13**	**4.6% (9/194)**	**36**	**7.4% (30/406)**
		Pneumonia	5	2.6% (5/194)	10	2.2% (9/406)
		Urinary tract infection	2	1.0% (2/194)	3	0.7% (3/406)
	Viral infectious disorders	**Total**	**5**	**2.6% (5/194)**	**6**	**1.5% (6/406)**
		COVID-19	2	1.0% (2/194)	3	0.7% (3/406)
		COVID-19 pneumonia	2	1.0% (2/194)	2	0.5% (2/406)
	Bacterial infectious disorders	**Total**	**2**	**1.0% (2/194)**	**8**	**2.0% (8/406)**
		Cellulitis	2	1.0% (2/194)	3	0.7% (3/406)
General disorders and administration site conditions	**Total**	**Total**	**19**	**8.2% (16/194)**	**38**	**8.1% (33/406)**
	General system disorders NEC	**Total**	**11**	**4.1% (8/194)**	**24**	**5.7% (23/406)**
		Non-cardiac chest pain	5	2.6% (5/194)	11	2.7% (11/406)
		Chest pain	4	1.5% (3/194)	5	1.2% (5/406)
	Complications associated with device	**Total**	**5**	**2.6% (5/194)**	**6**	**1.5% (6/406)**
		Vascular stent stenosis	3	1.5% (3/194)	5	1.2% (5/406)
		Vascular stent thrombosis	2	1.0% (2/194)	0	0.0% (0/406)
	Administration site reactions	**Total**	**2**	**1.0% (2/194)**	**5**	**1.2% (5/406)**
Vascular disorders	**Total**	**Total**	**19**	**8.2% (16/194)**	**28**	**6.2% (25/406)**
	Decreased and nonspecific blood pressure disorders and shock	**Total**	**4**	**2.1% (4/194)**	**12**	**3.0% (12/406)**
		Hypotension	3	1.5% (3/194)	8	2.0% (8/406)
	Arteriosclerosis, stenosis, vascular insufficiency and necrosis	**Total**	**5**	**2.6% (5/194)**	**8**	**1.5% (6/406)**
		Aortic stenosis	2	1.0% (2/194)	2	0.5% (2/406)
		Peripheral arterial occlusive disease	2	1.0% (2/194)	1	0.2% (1/406)
	Vascular hypertensive disorders	**Total**	**5**	**2.6% (5/194)**	**4**	**1.0% (4/406)**
		Hypertension	4	2.1% (4/194)	3	0.7% (3/406)
	Vascular haemorrhagic disorders	**Total**	**3**	**1.5% (3/194)**	**0**	**0.0% (0/406)**
		Haematoma	3	1.5% (3/194)	0	0.0% (0/406)
Respiratory, thoracic and mediastinal disorders	**Total**	**Total**	**23**	**8.2% (16/194)**	**45**	**5.9% (24/406)**
	Respiratory disorders NEC	**Total**	**9**	**4.1% (8/194)**	**21**	**3.4% (14/406)**
		Acute respiratory failure	3	1.5% (3/194)	8	1.0% (4/406)
		Dyspnoea	3	1.5% (3/194)	6	1.5% (6/406)
	Bronchial disorders (excl neoplasms)	**Total**	**6**	**3.1% (6/194)**	**12**	**1.5% (6/406)**
		Chronic obstructive	4	2.1% (4/194)	10	1.2% (5/406)

Serious Adverse Event			POBA (N=194 Subjects)		DCB (N=406 Subjects)	
MedDRA System Organ Class	**MedDRA High-Level Group Term**	**MedDRA Preferred Term**	**Events (n)**	**Percent of Subjects with Event (n/N)**	**Events (n)**	**Percent of Subjects with Event (n/N)**
		pulmonary disease				
	Lower respiratory tract disorders (excl obstruction and infection)	**Total**	**2**	**1.0% (2/194)**	**6**	**1.5% (6/406)**
		Pulmonary oedema	2	1.0% (2/194)	2	0.5% (2/406)
	Pulmonary vascular disorders	**Total**	**3**	**1.5% (3/194)**	**1**	**0.2% (1/406)**
		Pulmonary embolism	2	1.0% (2/194)	0	0.0% (0/406)
	Pleural disorders	**Total**	**2**	**1.0% (2/194)**	**3**	**0.7% (3/406)**
		Pleural effusion	2	1.0% (2/194)	2	0.5% (2/406)
Nervous system disorders	**Total**	**Total**	**21**	**7.7% (15/194)**	**29**	**6.4% (26/406)**
	Neurological disorders NEC	**Total**	**7**	**3.6% (7/194)**	**11**	**2.7% (11/406)**
		Syncope	2	1.0% (2/194)	3	0.7% (3/406)
		Presyncope	2	1.0% (2/194)	1	0.2% (1/406)
	Central nervous system vascular disorders	**Total**	**8**	**3.6% (7/194)**	**6**	**1.5% (6/406)**
		Cerebrovascular accident	4	2.1% (4/194)	2	0.5% (2/406)
Injury, poisoning and procedural complications	**Total**	**Total**	**15**	**6.7% (13/194)**	**30**	**5.9% (24/406)**
	Procedural related injuries and complications NEC	**Total**	**7**	**3.6% (7/194)**	**11**	**2.2% (9/406)**
		Plaque shift	2	1.0% (2/194)	3	0.7% (3/406)
		Vascular pseudoaneurysm	2	1.0% (2/194)	0	0.0% (0/406)
	Injuries NEC	**Total**	**4**	**2.1% (4/194)**	**13**	**3.0% (12/406)**
		Fall	2	1.0% (2/194)	3	0.7% (3/406)
	Bone and joint injuries	**Total**	**4**	**2.1% (4/194)**	**5**	**0.7% (3/406)**
		Humerus fracture	2	1.0% (2/194)	0	0.0% (0/406)
Gastrointestinal disorders	**Total**	**Total**	**12**	**5.2% (10/194)**	**38**	**5.4% (22/406)**
	Gastrointestinal haemorrhages NEC	**Total**	**0**	**0.0% (0/194)**	**9**	**1.7% (7/406)**
	Gastrointestinal signs and symptoms	**Total**	**2**	**0.5% (1/194)**	**8**	**1.2% (5/406)**
	Gastrointestinal stenosis and obstruction	**Total**	**2**	**1.0% (2/194)**	**5**	**0.7% (3/406)**
	Dental and gingival conditions	**Total**	**2**	**1.0% (2/194)**	**3**	**0.7% (3/406)**
		Dental caries	2	1.0% (2/194)	2	0.5% (2/406)
	Abdominal hernias and other abdominal wall conditions	**Total**	**2**	**1.0% (2/194)**	**2**	**0.5% (2/406)**
	Diverticular disorders	**Total**	**2**	**1.0% (2/194)**	**0**	**0.0% (0/406)**
Renal and urinary disorders	**Total**	**Total**	**6**	**3.1% (6/194)**	**27**	**5.4% (22/406)**
	Renal disorders (excl nephropathies)	**Total**	**3**	**1.5% (3/194)**	**15**	**3.0% (12/406)**
		Acute kidney injury	3	1.5% (3/194)	12	2.5% (10/406)
		Total	**2**	**1.0% (2/194)**	**6**	**1.5% (6/406)**

Serious Adverse Event			POBA (N=194 Subjects)		DCB (N=406 Subjects)	
MedDRA System Organ Class	**MedDRA High-Level Group Term**	**MedDRA Preferred Term**	**Events (n)**	**Percent of Subjects with Event (n/N)**	**Events (n)**	**Percent of Subjects with Event (n/N)**
	Urinary tract signs and symptoms	Urinary retention	0	0.0% (0/194)	5	1.2% (5/406)
Metabolism and nutrition disorders	**Total**	**Total**	**11**	**4.1% (8/194)**	**23**	**3.7% (15/406)**
	Glucose metabolism disorders (incl diabetes mellitus)	**Total**	**5**	**2.6% (5/194)**	**6**	**1.5% (6/406)**
		Hyperglycaemia	5	2.6% (5/194)	3	0.7% (3/406)
	Electrolyte and fluid balance conditions	**Total**	**3**	**1.0% (2/194)**	**6**	**1.2% (5/406)**
		Hypokalaemia	2	1.0% (2/194)	1	0.2% (1/406)
	Acid-base disorders	**Total**	**3**	**1.0% (2/194)**	**3**	**0.7% (3/406)**
Blood and lymphatic system disorders	**Total**	**Total**	**7**	**3.6% (7/194)**	**16**	**3.7% (15/406)**
	Anaemias nonhaemolytic and marrow depression	**Total**	**5**	**2.6% (5/194)**	**11**	**2.7% (11/406)**
		Anaemia	5	2.6% (5/194)	7	1.7% (7/406)
	Platelet disorders	**Total**	**2**	**1.0% (2/194)**	**1**	**0.2% (1/406)**
		Heparin-induced thrombocytopenia	2	1.0% (2/194)	0	0.0% (0/406)
Musculoskeletal and connective tissue disorders	**Total**	**Total**	**5**	**2.6% (5/194)**	**13**	**3.0% (12/406)**
	Joint disorders	**Total**	**2**	**1.0% (2/194)**	**7**	**1.5% (6/406)**
	Musculoskeletal and connective tissue deformities (incl intervertebral disc disorders)	**Total**	**2**	**1.0% (2/194)**	**2**	**0.5% (2/406)**
		Cervical spinal stenosis	2	1.0% (2/194)	0	0.0% (0/406)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**Total**	**Total**	**4**	**2.1% (4/194)**	**11**	**2.5% (10/406)**
	Gastrointestinal neoplasms malignant and unspecified	**Total**	**2**	**1.0% (2/194)**	**1**	**0.2% (1/406)**
Investigations	**Total**	**Total**	**3**	**1.5% (3/194)**	**13**	**2.0% (8/406)**
	Microbiology and serology investigations	**Total**	**2**	**1.0% (2/194)**	**3**	**0.7% (3/406)**
		SARS-CoV-2 test positive	2	1.0% (2/194)	3	0.7% (3/406)
Eye disorders	**Total**	**Total**	**1**	**0.5% (1/194)**	**7**	**1.5% (6/406)**
Skin and subcutaneous tissue disorders	**Total**	**Total**	**2**	**1.0% (2/194)**	**3**	**0.7% (3/406)**
Immune system disorders	**Total**	**Total**	**2**	**1.0% (2/194)**	**0**	**0.0% (0/406)**
	Allergic conditions	**Total**	**2**	**1.0% (2/194)**	**0**	**0.0% (0/406)**
		Hypersensitivity	2	1.0% (2/194)	0	0.0% (0/406)
Other	**Total**	**Total**	**4**	**2.1% (4/194)**	**14**	**3.2% (13/406)**

"Events" numbers are total episodes of each type of event among all patients.
"Percent of Subjects with Event" numbers are percent of patients who experienced one or more episodes of the event.
"Events" numbers for "TOTAL" are the sum of the individual event category totals.
"Percent of Subjects with Event" numbers for "TOTAL" is the percent of patients who experienced an adverse event.
Only events with rate >1% in either arm are included and listed by preferred term; thus, the sum of events that are included in each category may not equal the total.

Device Deficiencies: During the procedure, 3 study devices were reported as having deficiencies. One balloon had a material rupture (burst) during inflation, one could not cross the lesion despite pre-dilatation, and one device was reported as having a deficiency of "Other" (investigator decision to remove an undeployed DCB and insert a new DCB with a guideliner for delivery). The balloon that burst led to a serious adverse event of vessel perforation. Balloon rupture is a known potential failure mode for all PTCA catheters, and this single event does not raise concerns related to the AGENT DCB design.

2. Effectiveness Results

The primary analysis of effectiveness, which was a component of the primary endpoint, was based on the ITT cohort of 582 evaluable patients at the 12-month time point as described above. Additional effectiveness outcomes, including components of the primary endpoints as well as procedural endpoints, are presented in **Table 22.**

Clinical procedural success was analyzed per patient and defined as 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, without the occurrence of in-hospital MI, target vessel revascularization, or cardiac death. Technical success was analyzed per lesion and defined as 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. Acute success rates were comparable in both groups and as expected in this in-stent restenosis population.

The rate of target lesion revascularization (TLR) at 12 months was 13.0% versus 24.3% in the AGENT and POBA arms, respectively. This difference in revascularization rates appears to demonstrate the drug coating's ability to lower, although not eliminate, the recurrence of in-stent restenosis.

Table 22: Summary of Effectiveness Outcomes

Endpoint	POBA (N=194)	DCB (N=406)
Acute Success		
Clinical Procedural Success	88.7% (172/194)	92.1% (374/406)
Technical Success	89.7% (174/194)	93.4% (380/407)
In-Hospital Revascularization Events		
Target Vessel Revascularization (TVR)	1.0% (2/194)	0.0% (0/406)

Endpoint	POBA (N=194)	DCB (N=406)
Target Lesion Revascularization (TLR)	1.0% (2/194)	0.0% (0/406)
Revascularization Events to 30 Days		
TVR	2.1% (4/194)	0.7% (3/406)
TLR	1.5% (3/194)	0.5% (2/404)
Revascularization Events to 6 Months		
TVR	17.0% (33/194)	7.9% (32/404)
TLR	15.5% (30/194)	7.7% (31/404)
Revascularization Events to 12 Months		
TVR	25.9% (49/189)	14.2% (56/393)
TLR	24.3% (46/189)	13.0% (51/393)

Quality of Life: Functional status of general health-related quality of life was measured by changes in the EQ-5D scores. EQ-5D is a descriptive system of health-related quality of life states consisting of 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression), each of which can capture one of five responses. The responses record 5 levels of severity (no problems/slight problems/moderate problems/severe problems/extreme problems) within a particular EQ-5D dimension. There were no significant differences between the AGENT and POBA arms with regards to the quality-of-life scores from baseline to 12 months. One year after the procedure, patients treated with AGENT DCB reported an approximate 5% increase in health-related quality of life, while patients treated with POBA reported an approximate 3% increase.

3. Subgroup Analyses

The following preoperative characteristics were evaluated for potential association with outcomes: sex (male and female), age (<75 and ≥ 75 years , diabetic status, small vessel vs larger vessel (RVD <2.75 mm and ≥2.75 mm), one stent layer restenosis vs multiple stent layer restenosis (recurrent restenosis), target lesion only vs target lesion plus 1 non-target lesion treated, BMS vs DES restenosis, and chronic total occlusion (CTO) vs non-CTO. The AGENT IDE was not designed or powered to study safety or effectiveness of the AGENT DCB versus POBA in these pre-specified subgroups, so these analyses are considered hypothesis-generating. The primary endpoint results for these subgroups are included in **Table 23** below.

These subgroup analyses mostly showed that the primary endpoints outcomes were similar within the various subgroups, including sex and vessel diameter. While no interaction was seen, the treatment effect with the AGENT DCB was numerically greater in older patients, non-diabetics, and in patients with existing multiple stent layers. A significant interaction was noted in patients with target lesion treatment only vs a target lesion plus 1 non-target lesion, where the AGENT DCB had a significantly lower rate of TLF for target lesion treatment only (30.7% POBA vs 17.4% AGENT DCB) as compared to both target and non-target lesion treatment, where the AGENT DCB had a numerically higher TLF rate (15.4% POBA vs 22.4% AGENT DCB). It is important to note that the sample size was small (only n=77 subjects total had both a target and non-target lesion treatment), and this analysis was not powered.

Table 23: Primary Endpoint Results for Various Subgroups, Intent-to-Treat (N=600)

TLF at 12 Months	POBA (N=194)	DCB (N=406)	Relative Risk [95% CI]	Difference [95% CI]	P-value	Interaction P-value
Female (N=157)	(N=53)	(N=104)				0.9067
	23.5% (12/51)	13.9% (14/101)	0.59 [0.29, 1.18]	-9.7% [-23.1%, 3.8%]	0.1350	
Male (N=443)	(N=141)	(N=302)				
	30.4% (42/138)	19.5% (57/292)	0.64 [0.46, 0.90]	-10.9% [-19.8%, -2.0%]	0.0121	
Age <75 years (N=436)	(N=139)	(N=297)				0.3223
	27.6% (37/134)	19.2% (55/286)	0.70 [0.48, 1.00]	-8.4% [-17.2%, 0.5%]	0.0529	
Age ≥75 years (N=164)	(N=55)	(N=109)				
	30.9% (17/55)	15.0% (16/107)	0.48 [0.27, 0.88]	-16.0% [-29.9%, -2.0%]	0.0169	
Diabetics (N=269)	(N=90)	(N=179)				0.3619
	29.5% (26/88)	22.1% (38/172)	0.75 [0.49, 1.15]	-7.5% [-18.8%, 3.9%]	0.1868	
Non-Diabetics (N=329)	(N=104)	(N=225)				
	27.7% (28/101)	15.1% (33/219)	0.54 [0.35, 0.85]	-12.7% [-22.6%, -2.7%]	0.0074	
Small Vessel (RVD< 2.75 mm)[∞] (N=332)	(N=101)	(N=231)				0.9095
	28.1% (27/96)	17.3% (39/225)	0.62 [0.40, 0.95]	-10.8% [-21.1%, -0.5%]	0.0285	
Large Vessel (RVD ≥ 2.75 mm)[∞] (N=265)	(N=91)	(N=174)				
	29.7% (27/91)	19.2% (32/167)	0.65 [0.41, 1.01]	-10.5% [-21.6%, 0.6%]	0.0548	
Single Stent Layer[¥] (N=341)	(N=112)	(N=229)				0.5010
	20.2% (22/109)	13.6% (30/220)	0.68 [0.41, 1.11]	-6.5% [-15.3%, 2.2%]	0.1255	
Multiple Stent Layer[¥] (N=258)	(N=82)	(N=176)				
	40.0% (32/80)	23.8% (41/172)	0.60 [0.41, 0.87]	-16.2% [-28.6%, -3.7%]	0.0085	
Target Lesion Treatment Only[+] (N=523)	(N=168)	(N=355)				0.0763
	30.7% (50/163)	17.4% (60/344)	0.57 [0.41, 0.79]	-13.2% [-21.4%, -5.1%]	0.0007	

TLF at 12 Months	POBA (N=194)	DCB (N=406)	Relative Risk [95% CI]	Difference [95% CI]	P-value	Interaction P-value
Both Target and Non-Target Lesion Treatment[+] (N=77)	(N=26)	(N=51)				
	15.4% (4/26)	22.4% (11/49)	1.46 [0.52, 4.13]	7.1% [-11.1%, 25.2%]	0.4667	
History of DES Treatment Only[£] (N=527)[T]	(N=171)	(N=356)				0.9735
	29.9% (50/167)	18.7% (64/343)	0.62 [0.45, 0.86]	-11.3% [-19.4%, -3.2%]	0.0041	
History of Both DES and BMS Treatment[£] (N=19)	(N=6)	(N=13)				
	60.0% (3/5)	38.5% (5/13)	0.64 [0.24, 1.73]	-21.5% [N/A]	0.6078*	
History of BMS Treatment Only[£] (N=38)	(N=9)	(N=29)				
	0.0% (0/9)	6.9% (2/29)	Undef [Undef, Undef]	6.9% [N/A]	1.0000*	
Total Occlusion (N=14)	(N=5)	(N=9)				0.5815
	20.0% (1/5)	22.2% (2/9)	1.11 [0.13, 9.42]	2.2% [N/A]	1.0000*	
Non-Total Occlusion (N=582)	(N=186)	(N=396)				
	29.3% (53/181)	18.0% (69/383)	0.62 [0.45, 0.84]	-11.3% [-18.9%, -3.6%]	0.0024	

'P-value' tests the difference between treatments for each subgroup from the chi-square test.
'Interaction P-Value' tests the treatment by subgroup interaction from logistic regression. An interaction p-value of 0.15 was considered a significant interaction.
[*]Diabetic subgroup includes diabetic subjects requiring medical treatment (oral or injection) for control of blood glucose levels.
[**]Non-diabetics subgroup includes diabetic subjects treated with diet only or subjects without diabetics.
[∞]RVD is based on angio core lab data.
[¥]Refers to subjects with single stent layer restenosis treatment or subjects with multiple stent layer restenosis treatment.
[+]Refers to subjects with Target Lesion Treatment Only or subjects with Both Target and Non Target Lesion Treatment.
[£]Refers to subjects with history of DES treatment only, BMS treatment only or with both DES/BMS treatment.

Subgroups for race and ethnicity were not pre-specified but evaluated post hoc. The primary endpoint results for these subgroups are included in **Table 24** below.

Table 24: Primary Endpoint Results for Race and Ethnicity Subgroups, Intent-to-Treat (N=600)

Endpoints	POBA (N=194)	DCB (N=406)	Relative Risk [95% CI]	Difference [95% CI]
Asian (N=15)				
TLF	16.7% (1/6)	11.1% (1/9)	0.67 [0.05, 8.73]	-5.6% [-41.8%, 30.6%]
Cardiac Death	0.0% (0/6)	0.0% (0/9)	Undef [Undef, Undef]	0.0% [NA, NA]

Endpoints	POBA (N=194)	DCB (N=406)	Relative Risk [95% CI]	Difference [95% CI]
MI related to the TV	16.7% (1/6)	0.0% (0/9)	0.00 [Undef, Undef]	-16.7% [-46.5%, 13.2%]
TLR	16.7% (1/6)	11.1% (1/9)	0.67 [0.05, 8.73]	-5.6% [-41.8%, 30.6%]
Black or African American (N=42)				
TLF	33.3% (3/9)	23.3% (7/30)	0.70 [0.23, 2.16]	-10.0% [-44.3%, 24.3%]
Cardiac Death	0.0% (0/9)	3.3% (1/30)	Undef [Undef, Undef]	3.3% [-3.1%, 9.8%]
MI related to the TV	11.1% (1/9)	10.0% (3/30)	0.90 [0.11, 7.63]	-1.1% [-24.3%, 22.1%]
TLR	33.3% (3/9)	16.7% (5/30)	0.50 [0.15, 1.70]	-16.7% [-50.2%, 16.9%]
White (N=452)				
TLF	28.8% (42/146)	18.9% (56/296)	0.66 [0.46, 0.93]	-9.8% [-18.4%, -1.3%]
Cardiac Death	2.1% (3/146)	3.4% (10/296)	1.64 [0.46, 5.88]	1.3% [-1.8%, 4.4%]
MI related to the TV	11.0% (16/146)	5.4% (16/296)	0.49 [0.25, 0.96]	-5.6% [-11.2%, 0.1%]
TLR	23.3% (34/146)	13.5% (40/296)	0.58 [0.38, 0.88]	-9.8% [-17.7%, -1.9%]
Hispanic or Latino (N=35)				
TLF	33.3% (3/9)	8.3% (2/24)	0.25 [0.05, 1.26]	-25.0% [-57.7%, 7.7%]
Cardiac Death	0.0% (0/9)	0.0% (0/24)	Undef [Undef, Undef]	0.0% [NA, NA]
MI related to the TV	22.2% (2/9)	0.0% (0/24)	0.00 [Undef, Undef]	-22.2% [-49.4%, 4.9%]
TLR	22.2% (2/9)	8.3% (2/24)	0.38 [0.06, 2.28]	-13.9% [-43.2%, 15.4%]
Other (N=19)				
TLF	0.0% (0/2)	20.0% (3/15)	Undef [Undef, Undef]	20.0% [-0.2%, 40.2%]
Cardiac Death	0.0% (0/2)	0.0% (0/15)	Undef [Undef, Undef]	0.0% [NA, NA]
MI related to the TV	0.0% (0/2)	13.3% (2/15)	Undef [Undef, Undef]	13.3% [-3.9%, 30.5%]
TLR	0.0% (0/2)	13.3% (2/15)	Undef [Undef, Undef]	13.3% [-3.9%, 30.5%]

4. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

5. Clinical Pharmacokinetics

A human pharmacokinetic (PK) sub-study was not conducted for the AGENT DCB. Since pre-clinical PK data suggested that the drug was present at low levels in the blood and cleared rapidly, the possible systemic drug exposure of the AGENT DCB in humans based on the intended use is expected to be low with limited safety concerns. Therefore, it was determined that human PK data was not needed to mitigate any risks due to the systemic exposure of the drug from the AGENT DCB.

6. Long Term Data:

Study follow up is ongoing and many of the trial subjects have yet to complete their 2-year follow up. All available 2-year data, which accounted for approximately 1/3 of patients (199/600), including the primary endpoints, its components, and all-cause mortality, were evaluated. The outcomes are trending in the same manner as the primary endpoint data at 1 year. Based on available data, the rate of all-cause mortality is similar between study arms.

E. FINANCIAL DISCLOSURE

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 218 investigators of which none were full-time or part-time employees of the sponsor and 4 had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0
- Significant payment of other sorts: 4
- Proprietary interest in the product tested held by the investigator: 0
- Significant equity interest held by investigator in sponsor of covered study: 0

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

The AGENT Japan study was considered supplementary data to support the safety and effectiveness of the AGENT DCB, especially in subjects with small ISR vessels. This trial enrolled AGENT DCB subjects that had a mean reference vessel diameter (RVD) of 2.22±0.36 mm in the SV study and 2.59±0.50 mm in the ISR substudy.

The AGENT Japan Small Vessel (SV) Study was a prospective, multicenter, 2:1 randomized controlled (AGENT DCB to SeQuent Please DCB), single-blind, noninferiority trial. The ISR Substudy was a prospective, non-randomized, multicenter, single-arm, open-label trial. AGENT Japan SV study enrolled 150 patients at 14 sites in

Japan and a total of 30 ISR patients were enrolled and treated with the AGENT DCB at 9 sites in Japan.

The primary objective of the AGENT Japan study was to determine the safety and effectiveness of the AGENT DCB compared to B. Braun's SeQuent® Please Paclitaxel-Releasing Coronary Balloon Catheter for the treatment of Japanese patients with a small de novo native atherosclerotic coronary artery lesion or ISR of a previously treated lesion (ISR substudy). This study is relevant as it was performed using AGENT devices identical to the proposed AGENT US devices in terms of design and intended use.

The primary endpoint was the 6-month TLF rate, defined as any ischemia-driven TLR, MI (Q-wave and non–Q-wave) related to the target vessel, or cardiac death. Additional clinical endpoints included TLR, TLF, TVR, all cause death, MI (Q-wave and non-Q-wave), and ST (per Academic Research Consortium definitions). Angiographic parameters measured by angiography at 6 months post-procedure (in-lesion/in-stent and in-segment) included % diameter stenosis (% DS), binary restenosis, minimum lumen diameter (MLD), and late lumen loss. Periprocedural endpoints included the rates of clinical procedural success and technical success. Quality of life (evaluated at hospital discharge, 6-months, 1-year, 2 years, and 3 years post-procedure) was measured by changes in EQ-5D scores.

The primary endpoint results for the AGENT Japan SV Study are included in **Table 25** below.

Table 25: Primary Endpoint Results for the AGENT Japan SV Study

	SeQuent Please (N=49)	Agent DCB (N=101)	Difference [95% CI]	One-sided 97.5% Farrington-Manning Upper Confidence Bound	Non-Inferiority Margin (Delta)	One-Sided P-Value
6-Month TLF * (Intent-to-Treat)	0.0% (0/49)	3.0% (3/101)	3.0% [NA]	9.57%	13.2%	0.0012

P-value is from the Farrington-Manning test and is based on the standard normal distribution.
A two-group Farrington-Manning test is used to test the one-sided hypothesis of non-inferiority in proportions.
If the P-value from the one-sided Farrington-Manning test is <0.025, Agent DCB is concluded to be non-inferior to SeQuent Please DCB.
TLF is defined as any ischemia driven revascularization of the target lesion TLR), myocardial infarction (MI, Q-wave and non–Q-wave) related to the target vessel, or cardiac death.

The primary endpoint results for the AGENT Japan ISR Substudy are included in **Table 26** below.

Table 26: Primary Endpoint Results for the AGENT Japan ISR Substudy

	Agent (N=30 Subjects)	95% Confidence Interval	One-sided 97.5% asymptotic upper confidence bound	Performance Goal	1-Sided P-Value
6-Month TLF *	3.3% (1/30)	[0.0%, 9.8%]	9.8%	15.1%	<.0001

	Agent (N=30 Subjects)	95% Confidence Interval	One-sided 97.5% asymptotic upper confidence bound	Performance Goal	1-Sided P-Value
(Intent-to-Treat)					

1-sided P-Value is based on the Exact Method.
95% Confidence Interval is based on 2-Sided Asymptotic method.
TLF is defined as any ischemia driven revascularization of the target lesion (TLR), myocardial infarction (MI, Q-wave and non–Q-wave) related to the target vessel, or cardiac death.

While this study has limitations, it is consistent with the results from the primary clinical study.

Panel Meeting Recommendation and FDA's Post-Panel Action

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory System Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. EFFECTIVENESS CONCLUSIONS

The AGENT IDE Study was a prospective, multi-center, randomized controlled trial comparing the AGENT DCB with POBA for the treatment of coronary ISR. The AGENT IDE Study met its primary endpoint, including effectiveness components, demonstrating superiority to POBA with TLF rates of 18.2% and 29.3%, respectively ($p = 0.0051$) in the primary ITT analysis set. This difference was largely driven by a lower rate of ischemia-driven TLR and target vessel-related MI in patients treated with AGENT compared to POBA. As such, the null hypothesis was rejected, and the primary endpoint was met. Additional effectiveness endpoints such as procedural and technical success demonstrated the AGENT DCB's acceptable acute performance. These results support the effectiveness of the AGENT DCB for percutaneous coronary intervention (PCI) in coronary arteries 2.0 mm to 4.0 mm in diameter and lesions up to 26 mm in length for the purpose of improving myocardial perfusion when treating in-stent restenosis (ISR).

B. SAFETY CONCLUSIONS

The risks of the AGENT Paclitaxel-Coated Balloon Catheter are based on the results obtained from biocompatibility testing, *in vivo* pre-clinical safety, safety margin, and

pharmacokinetics testing, *in vitro* engineering testing, coating characterization, chemistry, manufacturing and controls information, sterilization testing, stability testing, as well as data collected in the clinical study conducted to support PMA approval as described above. These tests revealed the following information:

- The biocompatibility, *in vivo* pharmacokinetics, and *in vivo* animal safety testing conducted demonstrate that the acute and chronic *in vivo* performance characteristics of the product provide reasonable assurance of safety and acceptability for clinical use.
- The *in vitro* engineering testing conducted demonstrated that the performance characteristics met the product specifications. The coating characterization testing adequately depicted the important attributes of AGENT's drug coating. The chemistry, manufacturing, and controls information ensures that only product meeting specifications will be released.
- The test results obtained from the sterilization testing demonstrated that the product can be adequately sterilized and is acceptable for commercial use.
- The functional shelf life and drug stability testing demonstrated that the product can be labeled with a shelf life of 24 months.
- The clinical testing conducted demonstrated that the product provides a reasonable assurance of safety when used as indicated in accordance with the Instructions for Use. In the IDE study, adverse event rates, including mortality, observed with use of Agent DCB to treat coronary ISR lesions were comparable to the control arm and were in line with expectations.

C. BENEFIT-RISK DETERMINATION

The probable benefits of the device are based on data collected in a clinical study conducted to support PMA approval as described above. Patients treated with the AGENT DCB experienced fewer revascularization events and MI events compared with patients treated with POBA. Compared with using balloon angioplasty to treat coronary ISR lesions, approximately 9 patients would need to be treated with the AGENT DCB to prevent one incidence of target lesion failure at 1 year. Based on the primary endpoint of this trial, almost 1 in 3 patients (29.3%) treated with POBA experienced a TLF event at 12 months compared to approximately 1 in 5 patients (18.2%) treated with the AGENT DCB. Preliminary two-year data suggests a similar benefit.

The probable risks of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. The risks of using the

AGENT DCB to treat in-stent restenosis appear to be very similar to the risks of using POBA and the risks of PCI for in-stent restenosis in general. No unanticipated adverse device effects were reported in the study. The AGENT IDE Study supports the safe use of one DCB device per patient. The safety of using multiple devices in one procedure has not been established.

Additional factors considered in determining probable risks and benefits included:

1) The clinical study was a high quality randomized, controlled trial, with a prespecified statistical analysis plan. Any uncertainty related to the primary endpoint is therefore low.

2) Alternative treatments are available, but patients with in-stent restenosis are at high risk for recurrence regardless of treatment. The results of the AGENT IDE Study demonstrate more favorable outcomes compared to POBA.

3) The clinical study provided adequate follow-up (on all subjects to 12 months) to evaluate safety and effectiveness.

4) Longer term follow-up (up to 24 months) was provided, as available, prior to the PMA approval. Longer term data showed similar trends as seen for the primary endpoint results. The preliminary/incomplete results indicated that long term mortality was comparable between the test arm as compared to the control arm.

5) Patient risk is minimized by limiting the use to operators who have the necessary training to use the device safely and effectively. This includes appropriate lesion selection, adequate lesion preparation and adherence to the recommended periprocedural medication regimens.

6) No other coronary drug coated balloons have been approved for use in the US. However, drug coated balloons have been approved for the coronary vasculature for numerous years as well as for use in the peripheral vasculature. Peripheral DCBs have been shown to have benefits over POBA, including reduction in need for repeat revascularization.

7) FDA has determined that there are no known safety concerns related to paclitaxel coated products. A previous signal of potentially increased late mortality for peripheral paclitaxel coated products was determined to not be supported after review of the totality of the available data and analyses.

1. Patient Perspective:

   Patient perspectives considered during the review included an assessment of general health-related quality of life as measured by changes in EQ-5D scores.

There were no significant differences between the AGENT and POBA arms with regards to the quality-of-life scores from baseline to 12 months.

In conclusion, given the available information above, the data support that for the treatment of coronary ISR the probable benefits outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. The clinical study results of the AGENT DCB showed favorable outcomes compared to POBA for the treatment of coronary ISR. Given all of the available data, it is reasonable to conclude that the benefits of the use of the device for the target population outweigh the risk of illness or injury when used as indicated in accordance with the labeling and Instructions for Use (IFU).

XIII. CDRH Decision

CDRH issued an approval order on February 29, 2024. The final conditions of approval cited in the approval order are described below:

1. Long-term drug stability studies will be completed on three total finished product batches representing the commercial process each year, evaluating one lot of the largest-longest device size, one lot of an intermediate size, and one lot of the shortest-smallest device size manufactured during that time period. All batches for these studies will be stored at Long Term Conditions of 25°C ± 2°C/60% RH ± 5%, per ICH Q1A(R2). Testing for all studies will occur at 0, 6, 12, 18, and 24 months, per detailed instruction in document 97105846. Be advised that failure to comply with any post-approval requirement, including test protocol, sampling size, sampling plan, and acceptance criteria, constitutes grounds for FDA withdrawal of approval of the PMA in accordance with 21 CFR 814.82(c) and 814.46(a)(2).

2. As you have proposed in your November 21, 2023 interactive response for the CMC module, further process development studies will be completed to support the current coating process, specifications, and process capability, which should be evaluated using all finished product testing. For the additional requested studies, in order to ensure that the commercial manufacturing process is capable of consistently delivering quality product across all proposed operating conditions, product should be manufactured at the extremes of solution concentration and full lot release testing should be provided to support these process parameters. If these parameters are not supported based on the added testing, you should further tighten your in-process specification. The full validation protocols, acceptance criteria, study outcomes, and supportive development and qualification studies should be submitted in a future PMA report. If any changes to your coating process are warranted (e.g., in process

coating specification), then you should submit a PMA supplement to request this change.

3. *AGENT Post-Approval Surveillance Analysis:* This surveillance will be carried out to assess the real-world safety and effectiveness of the AGENT Paclitaxel-Coated Balloon Catheter (AGENT DCB), including in patient populations underrepresented in the AGENT IDE pivotal trial (i.e., women and underrepresented racial and ethnic groups). It will involve all consecutive patients treated within the first 2 years following device approval who are entered into the American College of Cardiology (ACC) CathPCI Registry®, including approximately 30,000 patients through discharge and 10,000 patients through 2 years. Data from the CathPCI Registry will be linked to data from the Centers for Medicare and Medicaid Services (CMS) database to obtain data through 2 years. Endpoints include in-hospital adverse events, and all-cause death, myocardial infarction, and revascularization through 2 years. Comparative outcomes in women and underrepresented racial and ethnic groups with in-stent restenosis will be specifically evaluated.

4. *The AGENT IDE Continued Follow-Up Study:* This study will evaluate the long-term safety and effectiveness of the AGENT DCB in 600 subjects from the premarket study (The AGENT IDE Study). The AGENT IDE Study was designed as a global, multicenter, single blind, randomized (2:1 AGENT DCB to POBA) trial. Subjects will be followed annually through 5 years post-procedure, and all efforts must be made to minimize the amount of missing long-term data (a minimum of 75% of subjects should be evaluable for the primary endpoint at 3 years, and a minimum of 90% of subjects should have a documented mortality status at 5 years).

   The primary endpoint is the 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.

   The endpoints to be assessed through 5 years post-procedure are rate of: (1) serious adverse events (SAE), (2) death (including cardiac, non-cardiac, and all-cause), (3) MI (Q-wave and non-Q-wave) rate (PPMI per the SCAI definition and spontaneous MI per 4th Universal Definition), (4) stent/vessel thrombosis rates, (5) target lesion failure (TLF) rate, (6) target lesion revascularization (TLR) rate, (7) target vessel revascularization (TVF) rate, and (8) changes in Quality of Life (as measured by changes in EQ-5D score; through 3 years only).

The applicant's manufacturing facilities have been found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

Directions for Use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

XV. REFERENCES

1. Moussa ID, Klein LW, Shah B, et al. Consideration of a New Definition of Clinically Relevant Myocardial Infarction After Coronary Revascularization: An Expert Consensus Document From the Society for Cardiovascular Angiography and Interventions (SCAI). *Journal of the American College of Cardiology.* 2013;62(17):1563-1570.

2. Thygesen Kristian, Alpert Joseph S., Jaffe Allan S., et al. Fourth Universal Definition of Myocardial Infarction (2018). *Journal of the American College of Cardiology.* 2018;72(18):2231-2264

3. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation* 2007;115:2344–51