Statistical Analysis Plan

AGENT IDE Study (S2358)

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

Revision History

Original Release: Feb 04, 2021

Current Version: April 5, 2023

Revision History

Document Revision Number	Template Number and Version	Section	Change	Reason for Change
A	90702621 Rev/Ver AE	N/A	N/A	Initial Release
B	90702621 Rev/Ver AE	3.1.2, 5.2, 5.3, 5.4, 5.5 and 5.6	Interim analysis, Sample size re-estimation, sensitivity analysis, subgroup analysis and poolability analysis	Per FDA questions
C	90702621 Rev/Ver AE	1-3.1 and 4.1-5.6	Addition of a non-randomized, single-arm registry cohort of subjects with target lesion > 26 mm and ≤ 36 mm to be treated with two Agent drug coated balloons.	Reflect the protocol amendment to change the study objective and planned indication for use to allow treatment of lesions up to 36 mm in length

Revision History (continued)

Document Revision Number	Template Number and Version	Section	Change	Reason for Change
D	90702621 Rev/Ver AE	1-3.1, 4.1-5.6, and Appendix A	Removal of a non-randomized, single-arm registry cohort of subjects with target lesion > 26 mm and ≤ 36 mm to be treated with two Agent drug coated balloons. Clarifying the adaptive design with formal interim analysis based on the first 40% with 1-year data for the sample size re-estimation strategy. The one-sided chi-square test for the primary endpoint with the intent of using the unpooled variance for the difference of 2 proportions in the protocol is clarified as the z-test with unpooled variance for the difference of two proportions to test the primary endpoint hypothesis. Revising the simulation output from EAST using the rho family alpha spending function of 50 and the calculation of Conditional Power and N re-estimation by using the Chen, DeMets and Lan adaptive method. Adding the analysis convention of eligible cross-over patients from POBA to AGENT DCB in the per-protocol analysis population.	Convert back to the original study objective with planned indication for use to allow treatment of lesions up to 26 mm in length Due to the fast enrollment, the study will enroll 600 subjects and the planned interim analysis with the sample size re-estimation strategy for PMA submission will be based on the first 40% subjects with complete 1-year data. The equivalence of the z-test with unpooled variance for the difference of two proportions to the chi-square test with the intent of using unpooled variance for two proportions is clarified. The interim alpha is set to zero as the interim analysis is solely for sample size re-estimation and the unweighted z-test with unpooled variance for the difference of two proportions will be used for the hypothesis testing. For crossover patients, they are considered to experience a study primary endpoint and are censored at the time of crossover for the analysis of other clinical endpoint in the per-protocol analysis population; events with onset dates on or after the time of crossover will be summarized separately.
E	90702621 Rev/Ver AE	Protocol Summary, 3.1, 3.1.4, 3.2, 5.4, and 7.4	Clarifying the analysis of the MI to include the peri-procedural MI (PPMI) according to the SCAI definition and spontaneous MI according to the 4th Universal MI definition. Correcting the definition of technical success	To address the heterogeneity of the Upper Limit of Normal (ULN) for Troponin I and T, the unified ULNs are applied to determine the cardiac enzyme elevation for PPMI regardless of the site reported ULNs in the database per FDA recommendation.

TABLE OF CONTENTS

1 PROTOCOL SUMMARY

<table>
<tr><td>Study Objective(s)</td><td>To assess the safety and effectiveness of the Agent™ Paclitaxel Coated PTCA Balloon Catheter compared to balloon angioplasty (POBA) in patients with in-stent restenosis (ISR) of a previously treated lesion of up to 26 mm in length (by visual estimate) in a native coronary artery 2.0 mm to 4.0 mm in diameter.</td></tr>
<tr><td>Planned Indication(s) for Use</td><td>The Agent™ Paclitaxel Coated balloon catheter is indicated for percutaneous transluminal coronary angioplasty (PTCA) in coronary arteries 2.0 mm to 4.0 mm in diameter and up to 26 mm in length, for the purpose of improving myocardial perfusion to treat in-stent restenosis (ISR).</td></tr>
<tr><td>Test Device</td><td>Agent™ Paclitaxel Coated PTCA Balloon Catheter (Agent Drug Coated Balloon or Agent DCB)</td></tr>
<tr><td>Device Sizes</td><td>AGENT™ devices with a balloon length between 12 mm and 30 mm and diameters between 2.00 and 4.00 mm will be used in this study according to the following size matrix:
<table>
<tr><th rowspan="2">Balloon Diameter (mm)</th><th colspan="3">Balloon Length (mm)</th></tr>
<tr><th>12</th><th>20</th><th>30</th></tr>
<tr><td>2.00</td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>2.50</td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>3.00</td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>3.50</td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>4.00</td><td>X</td><td>X</td><td>X</td></tr>
</table></td></tr>
<tr><td>Control Device</td><td>Commercially available, PTCA Dilation Catheter</td></tr>
<tr><td>Study Design</td><td>A prospective multi-center, 2;1 randomized (AGENT to POBA), controlled, single-blind, superiority trial.</td></tr>
<tr><td>Planned Number of Subjects</td><td>At least 480 subjects and up to a maximum of 600 subjects will be enrolled in the trial.</td></tr>
<tr><td>Planned Number of Sites/ Countries</td><td>Up to 40 sites in the United States</td></tr>
<tr><td>Primary Endpoint</td><td>The primary endpoint is the 12-month Target Lesion Failure (TLF) rate, defined as any ischemia-driven revascularization of the target lesion (TLR), myocardial infarction (MI, Q-wave and non–Q-wave)</td></tr>
</table>

	related to the target vessel, or cardiac death. The MI events include the Peri-Procedural MI (PPMI) according to the SCAI MI definition and the spontaneous MI according to the 4th Universal MI definition.
Additional Endpoints	Clinical endpoints measured in-hospital and at 30 days, 6 months, 12 months, then annually through 5 years. • Target lesion revascularization (TLR) rate, Target lesion failure (TLF) rate (primary endpoint at 12 months), Target vessel revascularization (TVR) rate • Target vessel failure (TVF) rate • MI (Q-wave and non–Q-wave) rate (PPMI per the SCAI definition and spontaneous MI per 4th Universal definition) • Cardiac death rate, • Non-cardiac death rate • All-cause death rate • Stent thrombosis rates (per Academic Research Consortium [ARC] definitions) Periprocedural endpoint: • Clinical procedural success rate • Technical success rate Change in Quality of Life: • Functional status of general health-related quality of life measured by changes in EQ-5D scores at hospital discharge, 12 months, 24 months and 36 months.
Method of Assigning Subjects to Treatment	After successful pre-treatment of the lesion and confirmation that inclusion/exclusion criteria have been met, subjects will be randomized (2:1) to receive either the test device or a control device. A subject will be considered enrolled at the time of randomization.
Follow-up Schedule	Clinical follow-up: in hospital, 30 days, 6 months, 12 months, then annually through 5 years post index procedure. The study will be considered complete with regard to the primary endpoint after all subjects have completed the 12-month follow-up period. Subjects who are enrolled but who do not receive a study/ control device will be followed through 12 months only.
Study Duration	Enrolled subjects will be followed for 5 years following the index procedure.
Antiplatelet Therapy	It is required that subjects receive a minimum of 1-month of dual antiplatelet therapy. Antiplatelet monotherapy should be continued for the duration of the study.

Statistical Methods	
Primary Statistical Hypothesis	The primary endpoint of Target Lesion Failure at 12 months for the Agent DCB arm is superior to that for the POBA arm.
Statistical Test Method	A z-test with unpooled variance for the difference of two proportions will be used to test the hypothesis of superiority of DCB over POBA in the 12-month clinical endpoint: H_0: $TLF_{DCB} \geq TLF_{POBA}$ H_1: $TLF_{DCB} < TLF_{POBA}$ where TLF_{DCB} and TLF_{POBA} are the TLF through 12 months for the DCB and POBA arms respectively. The primary analysis set for the primary endpoint is the Intent to treat analysis set. This endpoint will also be analyzed for the per protocol analysis set.
Sample Size Parameters	The sample size calculation for the primary endpoint is based on the following assumptions: • Expected TLF_{DCB} = 10.6 % (based on meta-analysis of historical trials and including an adjustment to account for the occulo-stenotic reflex) • Expected TLF_{POBA} = 21.2% (based on meta-analysis of historical trials and including an adjustment to account for the occulo-stenotic reflex) • Test significance level (α) = 2.5% (1-sided) • Power = 85% • Randomization ratio = 2 DCB: 1 POBA • Number of evaluable subjects per arm= 310 DCB + 155 POBA • Expected attrition rate = 3% • Total planned enrollment = 480 subjects, 320 in DCB and 160 in POBA The sample size re-estimation will be performed on the planned formal interim analysis by the Independent DMC Statisticians. The final sample size may be increased up to a maximum of 600 randomized subjects which is based on the observed conditional power of the interim analysis. Details of this adaptive approach are pre-specified in section 5.2-5.3.
Success Criteria for the Primary Endpoint	The final analysis with the sample size derived from the sample size re-estimation strategy will be conducted on subjects with 1 year data. If the *P* value from the z-test with unpooled variance for the difference of two proportions is less than 0.025 (1-sided) and the

	event rate in the DCB group is less than the rate in the POBA group in the final analysis, the primary endpoint for the DCB will be concluded to be statistically significantly lower than that for the POBA. This corresponds to the one-sided 97.5% upper confidence bound on the difference between treatment groups (DCB minus POBA) for the observed rate of the primary endpoint being less than zero.

2 INTRODUCTION

This statistical analysis plan addresses the planned analyses for the AGENT Clinical Trial based on the clinical study protocol (92294616). Specified analyses may be used for scientific presentations and/or manuscripts, and regulatory submissions. The primary analysis will be based on the data through 12 months post-procedure.

3 ENDPOINT ANALYSIS

3.1 Primary Endpoint

The primary endpoint is the 12-month Target Lesion Failure (TLF) rate, defined as any ischemia-driven revascularization of the target lesion (TLR), myocardial infarction (MI, Q-wave and non–Q-wave) related to the target vessel, or cardiac death. The MI events include the PPMI according to the SCAI MI definition and the spontaneous MI according to the 4th Universal MI definition.

3.1.1 Hypotheses

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

$$H_0: TLF_{DCB} \geq TLF_{POBA}$$
$$H_1: TLF_{DCB} < TLF_{POBA}$$

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

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

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

3.1.2 Sample Size

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

- Expected mean TLF_{DCB} = 10.6% (based on meta-analysis of historical trials and including an adjustment to account for the occulo-stenotic reflex)
- Expected mean TLF_{POBA} = 21.2% (based on meta-analysis of historical trials and including an adjustment to account for the occulo-stenotic reflex)
- Test significance level (α) = 2.5% (1-sided)
- Power* = 85%
- Randomization ratio = 2 DCB: 1 POBA
- Number of evaluable subjects per arm = 310 (DCB) and 155 (POBA)

- Expected attrition rate = 3%
- Total planned enrollment = 480 subjects, 320 in DCB and 160 in POBA
- An adaptive group sequential design with one planned formal interim analysis as described in section 5.3 for sample size re-estimation will be conducted on 1-year data from the first 40% (192) randomized subjects of the planned initial enrollment of 480 subjects. Details of this adaptive approach are pre-specified in section 5.2-5.3.

* the power is the overall study power for the sample size re-estimation.

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

3.1.3 Statistical Methods

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

The corresponding z-statistic with the unpooled variance for the difference of 2 proportions for the superiority testing of DCB over POBA with respect to the primary endpoint is:

$$\mathrm{z} = \frac{p_1 - p_2}{sqrt[\frac{p_1(1-p_1)}{n_1} + \frac{p_2(1-p_2)}{n_2}]}$$

where p_1 and p_2 are the proportions of subjects with TLF for the AGENT DCB and POBA groups with the corresponding n_1 and n_2 sample sizes, respectively.

The corresponding 97.5% upper confidence bound is

$$(p_1 - p_2) + z(0.975) * \ sqrt[\frac{p_1(1-p_1)}{n_1} + \frac{p_2(1-p_2)}{n_2}].$$

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

The statistical approach uses an adaptive group sequential design with one planned formal interim analysis as described in section 5.2-5.3 for sample size re-estimation will be conducted on the first 40% (192) of the randomized subjects for the primary endpoint.

The sample size re-estimation will be performed based on the interim data and the final sample size for the primary endpoint analysis may be increased up to a maximum of 600 subjects. A final primary endpoint analysis with the alpha of 0.025 will be performed on the final sample size from the sample size re-estimation strategy recommended from the DMC; in this scenario, the Original PMA will be filed using the sample size as recommended by the DMC following the sample size re-estimation strategy.

A secondary analysis of the primary endpoint inclusive of the 12-month visit window with the corresponding components will be performed. The descriptive statistics for the number of days of 12-month visit from procedure will be summarized. Any discrepancy of the secondary analysis compared to the primary analysis of the primary endpoint will be identified.

3.1.4 Analysis of MI Events

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

For the PPMI according to the SCAI MI definition, the unified Upper Limit of Normal (ULN) of 0.045 ng/mL for Troponin I and the unified ULN of 0.022 ng/mL for Troponin T will be applied to determine the cardiac enzyme elevation (in terms of multiple times relative to the ULN) regardless of the site reported ULNs in the database. This is an agreed approach with the FDA to address the heterogeneity of the various ULNs from all local laboratories in the AGENT IDE study, in which the traditional and high sensitivity assay types were used but the assay type was not captured in the database.

The following convention of the cardiac enzyme assays will be applied to determine the cardiac enzyme elevation according to the SCAI MI definition for PPMI:

1) If only Total CK is available and no other enzyme data are available, Total CK < ULN implies no cardiac enzyme elevation. Note: if Total CK > ULN, other enzyme data should be available.
2) If CK-MB is available, CK-MB is used to determine cardiac enzyme elevation.
3) If no CK-MB is available, Troponin I is used to determine cardiac enzyme elevation.
4) If no CK-MB and no Troponin I are available, Troponin T is used to determine cardiac enzyme elevation.

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

Patients with no clinical signs or symptoms of MI and with normal CK but no other enzyme data available post-procedure are not considered to have had an MI.

For patients with missing baseline enzyme data, normal baseline is assumed. For patients with missing post-procedure cardiac enzyme data, enzyme elevation is considered missing. For patients with only one post-procedure cardiac enzyme data, enzyme elevation will be derived based on one value and is not considered missing, though it is considered a protocol derivation. For patients with 2 or 3 post-procedure cardiac enzyme data, enzyme elevation will be derived based on the peak of the available data.

3.2 Additional Endpoints

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

- Target lesion revascularization (TLR) rate, Target lesion failure (TLF) rate (primary endpoint at 12 months), Target vessel revascularization (TVR) rate
- Target vessel failure (TVF) rate
- MI (Q-wave and non–Q-wave) rate (PPMI per the SCAI definition and spontaneous MI per 4th Universal definition)
- Cardiac death rate
- Non-cardiac death rate
- All-cause death rate
- Stent thrombosis rates (per Academic Research Consortium [ARC] definitions)

Periprocedural endpoint:

- Technical success rate
- Clinical procedural success rate

Change in Quality of Life:

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

4 GENERAL STATISTICAL METHODS

4.1 Analysis Sets

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

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

If a subject is randomized to POBA at enrollment and requires revascularization of the target lesion within 12 months of enrollment of this study, the investigator will have the option to treat the lesion with Agent (crossover procedure, which will be considered a study endpoint event). For eligible patients who crossover from POBA to AGENT DCB, they are considered to have experienced a study endpoint event of TLR and are censored at the time of crossover for the analysis of other clinical endpoints in the per-protocol

analyses. In addition, events with onset dates on or after the time of crossover treatment will be summarized separately. These events will be included in the intent to treat analyses.

4.2 Control of Systematic Error/Bias

Patients will be randomly assigned to treatment groups and patients will remain blinded to treatment throughout the course of the study.

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

4.3 Number of Subjects per Investigative Site

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

5 ADDITIONAL DATA ANALYSES

5.1 Other Endpoints/Measurements

The Kaplan-Meier product-limit method will be used to estimate event or event-free rates for time-to-event outcomes, and treatment groups will be compared using log-rank and Wilcoxon tests.

5.2 Interim Analyses

One planned formal interim analysis as described in section 5.3 for sample size re-estimation will be conducted on the first 40% (192) randomized subjects with 1-year data. The purpose of the interim analysis is solely for sample size re-estimation.

5.3 Sample Size Re-Estimation

5.3.1 Unfavorable, Promising and Favorable Zones

The sample space of the possible interim outcome is partitioned into three zones: unfavorable, promising, and favorable. The sample size increase will only be performed if the conditional power at the interim look lies in the promising zone. The conditional power (CP), defined as the probability of obtaining a positive outcome at the end of the trial, given the data already observed, is used to define the promising zone. In this study, the unfavorable zone, promising zone and favorable zone are defined as the observed

conditional power at interim analysis being less than minimum conditional power[#] (CP_{min} = 0.46), in the interval [CP_{min}, CP_{target}: 0.85] and being greater than the CP_{target}: 0.85, respectively. **Table 1** presents the three zones.

Table 1 Promising Zone by Conditional Power (CP)[#]

Zones	Conditional Power
Unfavorable	<0.46
Promising	0.46 - 0.85
Favorable	>0.85

[#]Cyrus R. Mehta and Stuart J. Pocock, Adaptive increase in sample size when interim results are promising: A practical guide with examples, *Statist. Med.* ***2011,*** 30 3267–3284

5.3.2 Conditional power and adaptive sample size re-estimation

The treatment effect estimate obtained at the interim analysis will be used to recompute the sample size needed to reach the CP_{target} of 0.85 at the study end. The sample size increase will be limited to a Nmax of 600 and the calculation is performed by using the Chen, DeMets and Lan (CDL) method.

The sample size re-estimation is based on the maximum allowed sample size (Nmax=582 with 3% attrition up to 600) and the observed conditional power at interim analysis. The sample size re-estimation using conditional power[#] at interim analysis will be calculated using EAST*. **Figure** 1 illustrates the sample size re-estimation, the numbers on the top right of the figure show the sample size (SS) and the conditional power (CP). For example, when the conditional power (CP) is 0.761, the sample size is 582. **Table 2** presents the selected sample size re-estimation for different conditional powers observed at interim analysis and **Figure 1** presents the screenshot from EAST for the sample size re-estimation.

**EAST® 6.5 Software, Cytel, Inc. 2018.*

Table 2 Sample size re-estimation by conditional power[#]

Conditional Power	Evaluable Sample Size	Enrolled Sample Size (including 3% attrition)
<0.46 (unfavorable zone)	465	480
0.46-0.761	582	600
0.80	533	549
0.84	479	494
≥0.85 (favorable zone)	465	480

[#]Cyrus R. Mehta and Stuart J. Pocock, Adaptive increase in sample size when interim results are promising: A practical guide with examples, *Statist. Med.* ***2011,*** 30 3267–3284

Figure 1 Sample size re-estimation by zone and conditional power.

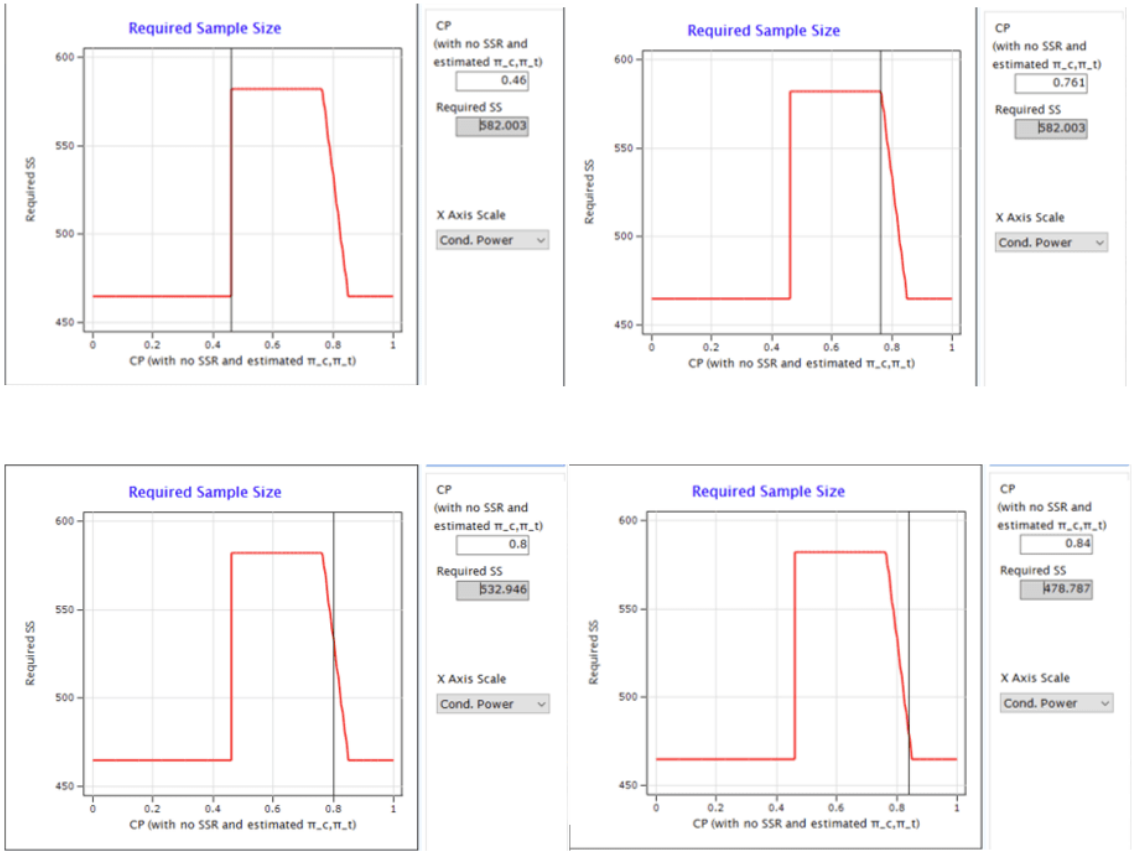


Table 3 presents the summary of the sample size re-estimation from EAST (refer to appendix A section a – screenshot from EAST); the target CP is 85% and minimum CP is 46%. The overall simulated study power is 85.0% which is based on unpooled variance.

Zone:	Simulation Rejecting H_0		Average Sample Size
	Counts	%	
Unfavorable	14560/25095	58.0%	465
Promising	20490/22663	90.4%	561
Favorable	49916/52242	95.5%	465
Efficacy	0/0	0%	0
Average study power	84966/100000	85.0%	487
# of Interim Look	Sample Size	Boundaries for Efficacy	Stopping for Efficacy
1 (40%)	186	0.000	0/100000 (0%)
2 (100%)	465	0.025	84966/100000 (85.0%)
Total			84966/100000 (85.0%)

Note: simulation with 100,000 runs using a random seed of 123456789.
Note: The rho family alpha spending function of 50 is used to set the interim alpha of 0% in this simulation study using the EAST software.

5.3.3 Type I error of the sample size re-estimation

The simulation for the type I error is conducted in the EAST software (refer to Appendix A section b – screenshot from EAST), the simulation results show that the simulated type I error of 2.23% which is less than 2.5% to reject the H_0. The results of simulation are based on 100,000 times of the trial cases with the same expected rate of 21.2% for control group and test group, only 2232 cases rejected the H_0. The simulation is based on the unpooled variance.

Table 4 presents the summary of the simulation for type I error; the simulation shows that the power is 2.23% to reject the hypothesis H_0 for the sample size re-estimation with maximum evaluable 582 subjects. Therefore, the simulated type I error is maintained at the 2.5% significance level.

Table 4 Summary of simulation for type I error of sample size re-estimation

Zone:	Simulation Rejecting H_0		Average Sample Size
	Counts	%	
Unfavorable	781/88654	0.9%	465
Promising	641/7925	8.1%	569
Favorable	810/3421	23.7%	465
Efficacy	0/0	0%	0
Average study power	2232/100000	2.23%	473
# of Interim Look	Sample Size	Boundaries for Efficacy	Stopping for Efficacy
1 (40%)	186	0.000	0/100000 (0%)
2 (100%)	465	0.025	2232/100000 (2.23%)
Total			2232/100000 (2.23%)

Note: Simulation with 100,000 runs using a random seed of 123456789.
Note: The rho family alpha spending function of 50 is used to set the interim alpha of 0% in this simulation study using the EAST software.

5.4 Sensitivity Analysis

A sensitivity analysis (tipping-point analysis) will be performed to assess the impact of subjects with inadequate follow-up, i.e., missing data, on the primary endpoint and to assess the robustness of the conclusion of the primary analysis. The tipping point analysis will include all subjects who have no TLF events and were excluded from the primary analysis based on the sufficient follow-up rule in section 7.6.

The sensitivity analysis for the rates of MI using other conventional MI definitions, such as the ARC-2 and the 4th Universal Definition of MI will be performed.

An analysis will be performed to summarize the pre- and post-cardiac biomarkers by treatment group and by magnitude of elevation above the upper limit of normal (ULN). For Troponin I and Troponin T, the unified ULNs will be used in the elevation analysis regardless of the site reported ULNs in the database as described in section 3.1.4.

An additional sensitivity analysis for the primary endpoint will be performed by censoring at the death date for those COVID-19 related deaths, if the COVID-19 related mortality rate is high. The COVID-19 related adverse events will be summarized.

5.5 Subgroup Analyses

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

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

The treatment effect by these pre-specified subgroups with respect to the primary endpoint with their corresponding treatment by subgroup interactions will be conducted using logistic regression model and the interaction will be tested at a 0.15 alpha level.

5.6 Justification of Pooling

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

5.7 Multivariable Analyses

Univariate and multivariate analyses will be performed to assess the effect of potential predictors on the primary endpoint of 12-month TLF using logistic regression. Analyses may also be performed for pre-specified clinical endpoints as needed. Linear regression

will be used for continuous outcomes and Cox proportional hazards regression may be used to assess the effects of possible predictors in a time-to-event manner.

For each outcome, predictors will be listed in ascending order of *P* value. Univariate analyses will be performed overall as well as separately for each treatment group. For the multivariate analyses, only coefficients in the final model, i.e., with *P* values less than 0.1 will be listed.

The following variables will be analyzed as possible predictors of 12-Month TLF:

Treatment	Group (POBA=0, AGENT=1)
Demographics	Sex, age
Baseline Characteristics	Previous CABG, previous PCI, hyperlipidemia, previous MI, peripheral vascular disease, angina class 3/4, arrhythmia, previous TIA or CVA, renal disease, medically treated diabetes, hypertension, current smoking at baseline, LVEF
Angiographic Lesion Characteristics	Coronary artery location (LAD), lesion length, calcification, thrombus, moderate/severe vessel tortuosity, lesion angulation, aneurysmal appearance
Quantitative Angiographic Variables	RVD, Pre-procedure MLD
Peri-Procedural Variables	GIIb/IIIa inhibitor use

5.8 Other Analyses

5.8.1 Baseline Characteristics

Baseline data will be summarized by treatment group. Subject demographics, clinical history, risk factors, and pre-procedure lesion characteristics will be summarized using descriptive statistics (e.g., mean, standard deviation, n, minimum, maximum) for continuous variables and frequency tables for discrete variables.

Treatment groups will be compared with a Chi-square test or a Fisher exact test for discrete variables and a Student t-test for continuous variables. Treatment differences between AGENT and POBA and 95% confidence intervals of the differences will be presented. Procedural characteristics will be summarized similarly.

5.8.2 Post-procedure Endpoints

Post-procedure information will be collected at regularly scheduled follow-up examinations as detailed in the clinical trial schedule in the protocol and will be summarized using descriptive statistics for continuous variables (e.g., mean, standard deviation, n, minimum, maximum) and frequency tables or proportions for discrete variables.

Treatments will be compared with a Chi-square test or a Fisher exact test for discrete variables and a Student t-test for continuous variables. Treatment differences between AGENT and POBA and 95% confidence intervals of the differences will be presented.

5.8.3 Subject Disposition

Subject disposition (e.g., number completing the study, number lost-to-follow-up, etc.) will be summarized with frequency tables and percentages by treatment group.

5.9 Long-Term Follow-up Analyses

Survival analysis using Kaplan-Meier estimates incorporating the censored data (event-free up to the last known follow-up date) will be performed at 1 year, 2 years, 3 years, 4 years, and 5 years. For long term safety analyses (after 1 year), results for time-to-first event variables will be of primary interest.

Binary rate analysis will also be performed. The analyses performed on the 2-year endpoints (event cut-off of 730 days, 700 days necessary follow-up, and also reporting 366-730 day rates), will be repeated for reporting results for year 3 (event cut-off of 1095 days, 1065 days necessary follow-up, and also reporting 731-1095 day rates), year 4 (event cut-off of 1460 days, 1430 days necessary follow-up, and also reporting 1096-1460 day rates), and year 5 (event cut-off of 1855 days, 1795 days necessary follow-up, and also reporting 1461-1855 day rates) with the time point cut-offs changing as per the visit schedule and windows as defined in the protocol.

5.10 Changes to Planned Analyses

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

6 VALIDATION

The Global Clinical WI (BSC: 90702587): Clinical Data Reporting Validation will apply to all clinical data reports being generated per this document.

7 PROGRAMMING CONSIDERATIONS

7.1 Statistical Software

Sample sizes were calculated using EAST® 6.5 Software, a commercial software program. All statistical analyses will be done using The SAS System Version 9.2 software or above (Copyright © 2000 SAS Institute Inc., SAS Campus Drive, Cary, North Carolina 27513, USA. All rights reserved.).

7.2 Format of Output

Results of analysis will be output programmatically to Microsoft Office® Word documents from SAS with no manual intervention. All output for the final statistical report will be in the form of a Word document containing tables, figures, graphs, and listings, as appropriate.

7.3 Methods for Handling Missing Data

All subjects who are enrolled will be eligible for evaluation, regardless of the treatment that ensues. Handling of dropouts and missing data will depend on their frequency and the nature of the outcome measure. Adjustments for missing outcomes data will be performed if deemed necessary to eliminate or minimize bias and will be described completely. Statistical models that account for censored data will be employed in appropriate circumstances, e.g., for time-to-event outcomes. Outlier values will be evaluated and values determined to be invalid will be queried. All data will be included in the analysis unless judged to be invalid.

When calculating rates of adverse events, missing and partial dates will be handled as shown in the table below.

Partial Date	Action Taken
Entire adverse event onset date is missing	The procedure date will be used for the onset date.
The month and the day of the month are missing but the year is available	January 1st will be used for the month and day of the onset date. However, if the imputed date falls before the procedure date, then the procedure date will be used for the onset date.
Day is missing, but the month and year are available	The 1st will be used as the day of the onset date. However, if the imputed date falls before the procedure date, then the procedure date will be used for the onset date.

7.4 Rules and Definitions

Binary event rates (proportions) will be calculated on a per subject basis except technical success.

The number of subjects included in the TLF rates (overall and individual components) will be based on subjects who have adequate follow-up (see Section 7.6) and/or have experienced any component of TLF.

The number of subjects included in the other clinical events and ST rates will be based on subjects who have adequate (see Section 7.7) follow-up and/or have experienced the event or ST, respectively.

For baseline categorical variables, “unknown” responses and missing values will not be counted in rate denominators.

The date of last follow-up will be the latest of the following dates for each subject: date of a major event with CEC adjudication, index procedure date, discharge date, and scheduled follow-up visit date.

Days to (event or last known status) = (event or status) date minus procedure date.

Length of hospital stay = discharge date minus procedure date.

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

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

In-hospital event rates are calculated as the proportion of subjects who experience the specified event from index procedure through day of discharge out of all subjects enrolled.

Out-of-hospital event rates are calculated as the proportion of subjects who experience the specified event from the day after discharge through the number of days as specified out of all subjects who were discharged following index procedure and have adequate follow-up or have experienced the event as specified.

7.5 Summarization of Site-Reported Serious and Non-Serious Adverse Events

Site-reported subject-based event rates will be calculated at various time points based on all events reported by the site regardless of whether or not they are ultimately adjudicated to be (or lead to) a death, MI, TVR, Stroke or ST.

7.6 Calculation of 12-Month TLF Rates

7.6.1 Valid Data Sources

- CEC forms.
- Follow-up case report forms (CRFs) – used in determining length of follow-up.

7.6.2 Valid Data Points

- Date of event.
- Date of last follow-up as defined in Section 7.4.

7.6.3 Assumptions

- Presence of a valid data point implies knowledge of subject's event status up through that data point (i.e., that date). More specifically, a subject is assumed to be event-free up to the first event or up to the latest non-event data point.
- TVR, MI, ST, and adverse event CRFs are not valid data sources.

7.6.4 Approach

- Subject experiences 1st event ≤ 365 days post-procedure, regardless of latest clinical follow-up
  Subject counts in both the denominator and numerator.

- Subject is event-free with date of last follow-up ≥335 days post-procedure
  Subject counts in denominator, does not count in numerator.

- Subject is event-free with date of last follow-up < 335 days post-procedure
  Subject does not count in both the denominator and numerator, i.e., subject is excluded from the calculation.

- Subject experiences 1st event > 365 days post-procedure, regardless of latest clinical follow-up
  Subject counts in denominator, does not count in numerator.
  Specifically, this subject is known (assumed) to be event-free up to the occurrence of the first adjudicated event (which occurred >365 days post-procedure).

7.7 Calculation of Other Event Rates

The calculation method from Section 7.6 will be extended to other endpoints and time points (e.g., 2 years) with the appropriate modifications to the numbers of days. For example, for 2 years, the event must have occurred within 730 days of procedure and the valid data point must be ≥700 days (early portion of window for the 2-year visit).

The following are the maximum days to event and number of days post-procedure that are considered to be adequate follow-up:

Follow-up Visit	Maximum Days to Event*	Days for Adequate Follow-up**
30 Days	30	23
6 Months	180	150
12 Months	365	335
2 Years	730	700
3 Years	1095	1065
4 Years	1460	1430
5 Years	1855	1795

* - this is the target date for the follow-up visit except for the 5-year visit where this is the end of the visit window
** - this is the start of the visit window

The all death/TVR/MI rates (overall and individual components) and TVF will be calculated based on the subjects who have adequate follow-up and/or have experienced any components of all death/TVR/MI.

All event rates will be calculated relative to the date of procedure (i.e., post-procedure).

Bibliography

1. Cyrus R. Mehta and Stuart J. Pocock, Adaptive increase in sample size when interim results are promising: A practical guide with examples, *Statist. Med.* ***2011,*** 30 3267–3284

8 APPENDIX A

a. Parameters of Sample Size Re-Estimation (Screenshot from EAST).

Test Parameters	
Simulation ID	CDLSim2
Design Type	Superiority
Number of Looks	2
Test Type	1-Sided
Sample Size (n)	465
Variance	Unpooled Estimate
Avg. Power at Termination	0.85
Response Generation Parameters	
Prop. under Control (π_c)	0.212
Prop. under Treatment (π_t)	0.106
$\delta = \pi_t - \pi_c$	-0.106
Sample Size Re-estimation Parameters	
Method of Adaptation	Chen-DeMets-Lan
Adapt At Look No.	1
Max. Sample Size if Adapt	
Multiplier	1.252
Total #	582
Target CP	0.85
Use Wald Stat. if CP >=	0.46
Promising Zone Scale	Cond. Power
Min. CP	0.46
Max. CP	0.85
CP Computation Based on	Estimated (π_c, π_t)
Simulation Control Parameters	
Starting Seed	Fixed
Number of Simulations	100000

Zone-wise Averages

Zone	Simulations Rejecting H0		Simulations Not Rejecting H0		Total Simulations		Average Sample Size
	Count	Row %	Count	Row %	Count	Column %	
Futility	0	0.000%	0	0.000%	0	0.000%	0
Unfavorable	14560	58.020%	10535	41.980%	25095	25.095%	465
Promising	20490	90.412%	2173	9.588%	22663	22.663%	561.042
Favorable	49916	95.548%	2326	4.452%	52242	52.242%	465
Efficacy	0	0.000%	0	0.000%	0	0.000%	0
All Trials	84966	84.966%	15034	15.034%	100000	100.000%	486.766

Promising Zone defined as 0.46 <= CP < 0.85

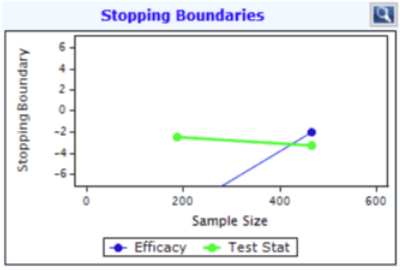
Average Sample Size

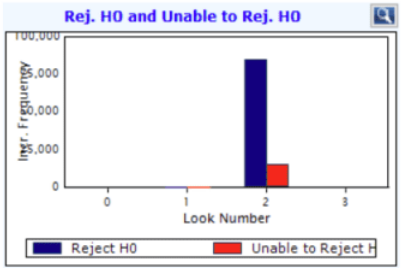
Look #	Average Sample Size (n)
1	186
2	486.766
Average	486.766

Simulation Boundaries and Incremental Boundary Crossing Probabilities

Look #	Sample Size (n)	Boundaries	Stopping For	Total Simulations	
		Efficacy	Efficacy	Count	%
1	186	-9.624	0	0	0.000%
2	465	-1.96	84966	100000	100.000%
Total			84966	100000	
%			84.966%		

Look #	Look Position	H0+	H0-	H1+	H1-	Latest Simula... Test St...	Average Sample Size	Incr. # Unable to Reject H0	Incr. # Rejecting H0	Total Simulation Count (I...	Total Simulation % (Incr.)
1	186.000		-9.624			-2.414	186.000	0	0	0	0
2	465.000		-1.960			-3.218	486.766	15034	84966	100000	100
						Total	486.766	15034.000	84966.000	100000	100
						%		15.034	84.966		





Number of Trials Completed = 100000
Simulation Seed = 123456789
Elapsed Time = 00:00:03
Close

Note: The rho family spending function of 50 is used to set the interim alpha of 0% in this simulation study using EAST software.

b. Assessment of Type I Error for Sample Size Re-Estimation (Screenshot from EAST).

Test Parameters	
Simulation ID	CDLSim3
Design Type	Superiority
Number of Looks	2
Test Type	1-Sided
Sample Size (n)	465
Variance	Unpooled Estimate
Avg. Power at Termination	0.022
Response Generation Parameters	
Prop. under Control (π_c)	0.212
Prop. under Treatment (π_t)	0.212
$\delta = \pi_t - \pi_c$	0
Sample Size Re-estimation Parameters	
Method of Adaptation	Chen-DeMets-Lan
Adapt At Look No.	1
Max. Sample Size if Adapt	
Multiplier	1.252
Total #	582
Target CP	0.85
Use Wald Stat. if CP >=	0.46
Promising Zone Scale	Cond. Power
Min. CP	0.46
Max. CP	0.85
CP Computation Based on	Estimated (π_c, π_t)
Simulation Control Parameters	
Starting Seed	Fixed
Number of Simulations	100000

Zone-wise Averages

Zone	Simulations Rejecting H0		Simulations Not Rejecting H0		Total Simulations		Average Sample Size
	Count	Row %	Count	Row %	Count	Column %	
Futility	0	0.000%	0	0.000%	0	0.000%	0
Unfavorable	781	0.881%	87873	99.119%	88654	88.654%	465
Promising	641	8.088%	7284	91.912%	7925	7.925%	569.32
Favorable	810	23.677%	2611	76.323%	3421	3.421%	465
Efficacy	0	0.000%	0	0.000%	0	0.000%	0
All Trials	2232	2.232%	97768	97.768%	100000	100.000%	473.267
Promising Zone defined as 0.46 <= CP < 0.85							

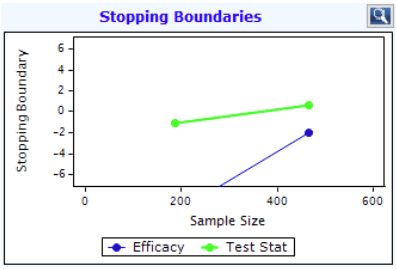
Average Sample Size

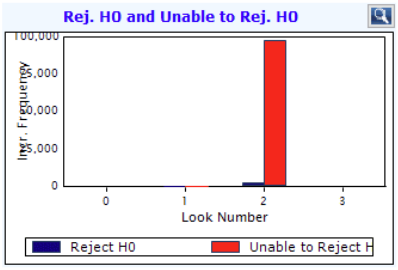
Look #	Average Sample Size (n)
1	186
2	473.267
Average	473.267

Simulation Boundaries and Incremental Boundary Crossing Probabilities

Look #	Sample Size (n)	Boundaries	Stopping For	Total Simulations	
		Efficacy	Efficacy	Count	%
1	186	-9.624	0	0	0.000%
2	465	-1.96	2232	100000	100.000%
Total			2232	100000	
%			2.232%		

Look #	Look Position	H0+	H0-	H1+	H1-	Latest Simula... Test St...	Average Sample Size	Incr. # Unable to Reject H0	Incr. # Rejecting H0	Total Simulation Count (I...	Total Simulation % (Incr.)
1	186.000		-9.624			-1.121	186.000	0	0	0	0
2	465.000		-1.960			0.621	473.267	97768	2232	100000	100
						Total	473.267	97768.000	2232.000	100000	100
						%		97.768	2.232		





Number of Trials Completed = 100000
Simulation Seed = 123456789
Elapsed Time = 00:00:03

Close

Note: The rho family spending function of 50 is used to set the interim alpha of 0% in this simulation study using EAST software.