Study Title: Prospective, Multicenter, Single-Arm Study of the SWM-1234 in Calcified Coronary Arteries (Disrupt CAD IV Study-Japan)

NCT Number: NCT 04151628

Protocol Date: June 19, 2019

Study Title:	Prospective, Multicenter, Single-Arm Study of the SWM-1234 in Calcified Coronary Arteries (Disrupt CAD IV Study - Japan)
Study Objective:	The objective of this study is to assess the safety and effectiveness of SWM-1234 to treat de novo, calcified, stenotic, coronary lesions prior to stenting.
Study Design:	Prospective, multicenter, single-arm study
Number of sites/ Sample Size	The study will be conducted at up to 8 sites in Japan. It is anticipated that up to 64 subjects will be enrolled in the SWM-1234 study, in addition to 8 roll-in subjects (1 per study site).
Subject Population:	The study will enroll subjects with *de novo*, calcified coronary artery lesions presenting with stable, unstable or silent ischemia that are suitable for percutaneous coronary intervention (PCI). All potential subjects must complete the consent process prior to undergoing any trial specific procedures and evaluations.
Study Duration / Follow-Up Period:	Enrollment duration: approximately 7 months Study duration: approximately 3 years Subjects will be followed through discharge, 30 days, 6, 12 and 24 months
OCT/OFDI Sub-study	An Optical Coherence Tomography (OCT) / Optical frequency domain imaging (OFDI) sub-study will be conducted on all subjects. The objective is to further understand the mechanism of action of SWM-1234 for the treatment of *de novo*, calcified, stenotic, coronary lesions prior to stenting. OCT or OFDI imaging will be completed at three time-points during the index procedure.
Primary Safety Endpoint:	Safety will be assessed by freedom from major adverse cardiac events (MACE) within 30 days of the index procedure. MACE is defined as: • Cardiac death; or • Myocardial Infarction (MI) defined as CK-MB level > 3 times the upper limit of lab normal (ULN) value with or without new pathologic Q wave at discharge (periprocedural MI) and using the Fourth Universal Definition of Myocardial Infarction beyond discharge (spontaneous MI); or • Target Vessel Revascularization (TVR) defined as revascularization at the target vessel (inclusive of the target lesion) after the completion of the index procedure
Primary Effectiveness Endpoint:	Procedural Success defined as stent delivery with a residual stenosis <50% (core laboratory assessed) and without in-hospital MACE.

Secondary Endpoints:	• Device Crossing Success is defined as the ability to deliver the SWM-1234 catheter across the target lesion, and delivery of lithotripsy without serious angiographic complications immediately after treatment. • Angiographic Success defined as stent delivery with <50% residual stenosis and without serious angiographic complications. • Procedural Success defined as stent delivery with a residual stenosis ≤30% (core laboratory assessed) and without in-hospital MACE. • Angiographic Success defined as stent delivery with ≤30% residual stenosis and without serious angiographic complications. • Serious angiographic complications defined as severe dissection (Type D to F), perforation, abrupt closure, and persistent slow flow or persistent no reflow. • MACE at 6, 12 and 24 months. • Target lesion failure (TLF) defined as cardiac death, target vessel myocardial infarction (Q wave and non-Q wave), or ischemia-driven target lesion revascularization (ID-TLR) by percutaneous or surgical methods at 30 days, 6, 12 and 24 months. • At each time period: All death, cardiac death, MI, TV-MI, procedural and nonprocedural MI, ID-TVR, ID-TLR, ID-non-TLR ID-non-TVR, all revascularizations (ID and non-ID), and stent thrombosis (ARC definite, probable, definite or probable). • Sensitivity analyses will be reported for MI using the Fourth Universal definition of MI and the Society for Cardiovascular Angiography and Interventions (SCAI) definitions at 30 days, 6, 12 and 24 months.
Inclusion Criteria:	1. Subject is ≥18 years of age 2. Subjects with native coronary artery disease (including stable or unstable angina and silent ischemia) suitable for PCI 3. For patients with unstable ischemic heart disease, biomarkers (troponin or CK-MB) must be less than or equal to the upper limit of lab normal within 12 hours prior to the procedure (note: if both labs are drawn, both must be normal). 4. For patients with stable ischemic heart disease, biomarkers may be drawn prior to the procedure or at the time of the procedure from the side port of the sheath. a. If drawn prior to the procedure, biomarkers (troponin or CK-MB) must be less than or equal to the upper limit of lab normal within 12 hours of the procedure (note: if both labs are drawn, both must be normal).

   b. If biomarkers are drawn at the time of the procedure from the side port of the sheath prior to any intervention, biomarker results do not need to be analyzed prior to enrollment

5. Left ventricular ejection fraction >25% within 6 months (note: in the case of multiple assessments of LVEF, the measurement closest to enrollment will be used for this criteria; may be assessed at time of index procedure)
6. Subject or legally authorized representative, signs a written Informed Consent form to participate in the study, prior to any study-mandated procedures
7. Lesions in non-target vessels requiring PCI may be treated either:
   a. >30 days prior to the study procedure if the procedure was unsuccessful or complicated; or
   b. >24 hours prior to the study procedure if the procedure was successful and uncomplicated (defined as a final lesion angiographic diameter stenosis <30% and TIMI 3 flow (visually assessed) for all non-target lesions and vessels without perforation, cardiac arrest or need for defibrillation or cardioversion or hypotension/heart failure requiring mechanical or intravenous hemodynamic support or intubation, and with no post-procedure biomarker elevation >normal; or
   c. >30 days after the study procedure

Angiographic Inclusion Criteria

8. The target lesion must be a *de novo* coronary lesion that has not been previously treated with any interventional procedure
9. Single *de novo* target lesion stenosis of protected LMCA, or LAD, RCA or LCX (or of their branches) with:
   a. Stenosis of ≥70% and <100% or
   b. Stenosis ≥50% and <70% (visually assessed) with evidence of ischemia via positive stress test, or fractional flow reserve value ≤0.80, or iFR <0.90 or IVUS or OCT minimum lumen area ≤4.0 mm²
10. The target vessel reference diameter must be ≥2.5 mm and ≤4.0 mm
11. The lesion length must not exceed 40 mm
12. The target vessel must have TIMI flow 3 at baseline (visually assessed; may be assessed after pre-dilatation)

	13. Evidence of calcification at the lesion site by, a) angiography, with fluoroscopic radio-opacities noted without cardiac motion prior to contrast injection involving both sides of the arterial wall in at least one location and total length of calcium of at least 15 mm and extending partially into the target lesion, OR by b) IVUS or OCT, with presence of ≥270 degrees of calcium on at least 1 cross section 14. Ability to pass a 0.014" guide wire across the lesion
Exclusion Criteria:	1. Any comorbidity or condition which may reduce compliance with this protocol, including follow-up visits 2. Subject is a member of a vulnerable population including individuals with mental disability, persons in nursing homes, children, impoverished persons, persons in emergency situations, homeless persons, nomads, refugees, and those incapable of giving informed consent. 3. Subject is participating in another research study involving an investigational agent (pharmaceutical, biologic, or medical device) that has not reached the primary endpoint 4. Subject is pregnant or nursing (a negative pregnancy test is required for women of child-bearing potential within 7 days prior to enrollment) 5. Unable to tolerate dual antiplatelet therapy (i.e., aspirin, and either clopidogrel, prasugrel, or ticagrelor) for at least 6 months (for patients not on oral anticoagulation) 6. Subject has an allergy to imaging contrast media which cannot be adequately pre-medicated 7. Subject experienced an acute MI (STEMI or non-STEMI) within 30 days prior to index procedure, defined as a clinical syndrome consistent with an acute coronary syndrome with troponin or CK-MB greater than 1 times the local laboratory's upper limit of normal 8. New York Heart Association (NYHA) class III or IV heart failure 9. Renal failure with serum creatinine >2.5 mg/dL or chronic dialysis 10. History of a stroke or transient ischemic attack (TIA) within 6 months, or any prior intracranial hemorrhage or permanent neurologic deficit 11. Active peptic ulcer or upper gastrointestinal (GI) bleeding within 6 months

12. Untreated pre-procedural hemoglobin <10 g/dL or intention to refuse blood transfusions if one should become necessary
13. Coagulopathy, including but not limited to platelet count <100,000 or International Normalized ratio (INR) > 1.7 (INR is only required in subjects who have taken warfarin within 2 weeks of enrollment)
14. Subject has a hypercoagulable disorder such as polycythemia vera, platelet count >750,000 or other disorders
15. Uncontrolled diabetes defined as a HbA1c ≥10%
16. Subject has an active systemic infection on the day of the index procedure with either fever, leukocytosis or requiring intravenous antibiotics
17. Subjects in cardiogenic shock or with clinical evidence of left-sided heart failure (S3 gallop, pulmonary rales, oliguria, or hypoxemia)
18. Uncontrolled severe hypertension (systolic BP >180 mm Hg or diastolic BP >110 mm Hg)
19. Subjects with a life expectancy of less than 1 year
20. Non-coronary interventional or surgical structural heart procedures (e.g., TAVR, MitraClip, LAA or PFO occlusion, etc.) within 30 days prior to the index procedure
21. Planned non-coronary interventional or surgical structural heart procedures (e.g., TAVR, MitraClip, LAA or PFO occlusion, etc.) within 30 days after the index procedure
22. Subject refusing or not a candidate for emergency coronary artery bypass grafting (CABG) surgery
23. Planned use of atherectomy, scoring or cutting balloon, or any investigational device other than lithotripsy
24. Unprotected left main diameter stenosis >30%
25. Target vessel is excessively tortuous defined as the presence of two or more bends >90º or three or more bends >75º
26. Definite or possible thrombus (by angiography or intravascular imaging) in the target vessel
27. Evidence of aneurysm in target vessel within 10 mm of the target lesion
28. Target lesion is an ostial location (LAD, LCX, or RCA, within 5 mm of ostium) or an unprotected left main lesion
29. Target lesion is a bifurcation with ostial diameter stenosis ≥30%

	30. Second lesion with >50% stenosis in the same target vessel as the target lesion including its side branches 31. Target lesion is located in a native vessel that can only be reached by going through a saphenous vein or arterial bypass graft 32. Previous stent within the target vessel implanted within the last year 33. Previous stent within 10 mm of the target lesion regardless of the timing of its implantation 34. Angiographic evidence of a dissection in the target vessel at baseline or after guidewire passage
Statistical Methods:	An Investigational Device Exemption (IDE G180146) study called Disrupt CAD III will enroll 392 subjects at 50 US and European sites. The Disrupt CAD III population is intended to support the US FDA approval. The primary safety and effectiveness endpoints in this CAD IV study will be compared to a similar set of subjects from the CAD III study using a propensity-score matched analysis. To maximize power and take advantage of the larger CAD III study, 1:5 matching will be done. Primary Safety Endpoint: Safety will be assessed by freedom from major adverse cardiac events (MACE) within 30 days of the index procedure. Statistical Hypothesis: • H_0: πS CAD IV ≤ πS CAD III - δ • H_A: πS CAD IV > πS CAD III - δ • $\pi_{S\ CAD\ IV}$ = 30-day freedom from MACE in CAD IV • $\pi_{S\ CAD\ III}$ = 30-day freedom from MACE in CAD III • δ = Margin of non-inferiority, 9.36% • Expected 30-day freedom from MACE in CAD IV = 89.6% • Expected 30-day freedom from MACE in CAD III = 89.6% • Statistical significance: one-sided α = 0.1 • 1:5 matching (CAD IV: CAD III) Based on the above assumptions 60 evaluable CAD IV subjects will be needed to achieve a statistical power of 72%. To account for a possible 5% attrition rate, 64 subjects will be enrolled. Primary Effectiveness Endpoint:

	Procedural Success defined as stent delivery with a residual stenosis <50% and without in-hospital MACE. Statistical Hypothesis: • H_0: $\pi_{e\ CAD\ IV} \leq \pi e$ CAD III - δ • H_A: $\pi_{e\ CAD\ IV} > \pi e$ CAD III - δ • $\pi_{e\ CAD\ IV}$ = Procedure success rate in CAD IV • $\pi_{e\ CAD\ III}$ = Procedure success rate in CAD III • δ = Margin of non-inferiority, 10.0% • Expected 30-day Procedure Success in CAD IV = 88.9% • Expected 30-day Procedure Success in CAD III = 88.9% • Statistical significance: one-sided α = 0.1 • 1:5 matching (CAD IV: CAD III) Based on the above assumptions 60 evaluable CAD IV subjects will be needed to achieve a statistical power of 75%. To account for a possible 5% attrition rate, 64 subjects will be enrolled.
Sponsor:	Shockwave Medical, Inc. 5403 Betsy Ross Drive Santa Clara, CA 95054 USA

1.0 INTRODUCTION/BACKGROUND

1.1 Calcified Coronary Lesions

Calcified coronary lesions are associated with advanced age, diabetes and chronic kidney disease.(1) Approximately 38% and 73% of all lesions display calcification as detected by angiography and intravascular ultrasound (IVUS), respectively. As IVUS is not routinely used as a diagnostic modality, coronary calcification is most likely underestimated.(2)

Coronary artery calcification impacts interventional outcomes by adversely affecting stent delivery(3), damaging the drug-eluting polymer(4) and impairing stent expansion and apposition.(5) Current therapies used to overcome these limitations include high-pressure balloon dilation and atherectomy. However, balloon angioplasty is limited in its ability to modify calcific plaque. Dilatation in eccentric calcium may be biased by the guidewire towards the non-calcified segments of the artery; in concentric calcium, the pressure-generated force may be insufficient for calcium fracture and vessel expansion.

Rotational and orbital atherectomy selectively ablate superficial calcium increasing stent deliverability but have limited impact on deep calcium that limits vessel expansion during stent implantation.(5,6) In addition, rates of peri-procedural complications including perforation, slow flow and peri-procedural myocardial infarction (MI) are still significantly higher with atherectomy than balloon-based therapies.(7,8,9,10,11)

Abdel-Waheb et al. reported a 1.7% perforation rate following treatment with rotablator plus drug-eluting stent (DES). At nine months, rotational atherectomy (RA) had similar rates of binary restenosis, target lesion revascularization (TLR), stent thrombosis and

[1] Lee M et al. The impact and pathophysiologic consequences of coronary artery calcium deposition in percutaneous coronary interventions. J Invasive Cardiol 2016; 28(4): 160-167.
[2] Bhatt P, Parikh P, Patel A, et al. Orbital atherectomy system in treating calcified coronary lesions: 3-Year follow-up in first human use study (ORBIT I trial). Cardiovasc Revasc Med 2014: 15:204-208.
[3] Mori S, Yasuda S, Kataoka Y, Morii I, Kawamura A, Miyazaki S. Significant association of coronary artery calcification in stent delivery route with restenosis after sirolimus-eluting stent implantation. Circ J 2009; 73:1856-63.
[4] Wiemer M, Butz T, Schmidt W, Schmitz KP, Horstkotte D, Langer C. Scanning electron microscopic analysis of different drug eluting stents after failed implantation: from nearly undamaged to major damaged polymers. Catheter Cardiovasc Interv 2010:75: 905-911.
[5] Kini AS, Vengrenyuk Y, Pena J, et al. Optical coherence tomography assessment of the mechanistic effects of rotational and orbital atherectomy in severely calcified coronary lesions. Catheter Cardiovasc Interv 2015;86:1024-32.
[6] Karimi Galougahi K, Shlofmitz RA, Ben-Yehuda O, et al. Guiding Light: Insights Into Atherectomy by Optical Coherence Tomography. JACC Cardiovasc Interv 2016;9:2362-3.
[7] Abdel-Wahab M, Richardt G, Joachim Buttner H, et al. High-speed rotational atherectomy before paclitaxel-eluting stent implantation in complex calcified coronary lesions: the randomized ROTAXUS (Rotational Atherectomy Prior to Taxus Stent Treatment for Complex Native Coronary Artery Disease) trial. JACC Cardiovasc Interv 2013;6:10-19.
[8] Iwasaki K, Samukawa M, Furukawa H. Comparison of the effects of nicorandil versus verapamil on the incidence of slow flow/no reflow during rotational atherectomy. Am J Cardiol 2006;98:1354-6.
[9] Matsuo H, Watanabe S, Watanabe T, et al. Prevention of no-reflow/slow-flow phenomenon during rotational atherectomy—a prospective randomized study comparing intracoronary continuous infusion of verapamil and nicorandil. Am Heart J 2007;154:994.e1-6.
[10] Sakakura K, Ako J, Wada H, et al. Beta-blocker use is not associated with slow flow during rotational atherectomy. J Invasive Cardiol 2012;24:379-84.
[11] Sakakura K, Ako J, Wada H, et al. Comparison of frequency of complications with on-label versus off-label use of rotational atherectomy. Am J Cardiol 2012;110:498-501.

MACE, despite a higher procedural acute gain over percutaneous transluminal coronary angioplasty PTCA. (7) Chambers et al. reported the 30-day orbital atherectomy (OA) results from the ORBIT II Study. Orbital atherectomy procedural success, defined as less than 50% residual stenosis after stenting and no in-hospital MACE, was 88.9%. In addition, percent residual stenosis following stenting was low at 5.8%. Angiographic complications included severe dissection and abrupt closure of 3.4% and 1.8%, respectively, while in-hospital non-Q wave MIs occurred in 8.6% of the subjects.[(12)]

1.2 Coronary Intravascular Lithotripsy

The completed Disrupt CAD I Study conducted by Shockwave Medical Inc. reported the safety and performance of coronary intravascular lithotripsy (IVL) in vessel preparation for *de novo*, calcified, stenotic, coronary lesions prior to stent implantation in 60 subjects followed for six months. Successful delivery of the IVL catheter was achieved in 59 (98.5%) subjects with reduction in residual stenosis to less than 50% in all 60 (100%) subjects. The angiographic luminal acute gain following stent implantation was 1.7 mm and residual stenosis was 13.3%. Freedom from MACE was present in 57 (95%) subjects due to 3 (5%) non-Q wave MI at 30 days. At 6 months, freedom from MACE was present in 54 of 59 (91.5%) subjects due to 2 additional patients suffering cardiac death. Results of the optical coherence tomography (OCT) sub-study (n=31) identified modification with fracture as a major mechanism of action of IVL in vivo and demonstrated effectiveness in the achievement of significant acute area gain and enabled stent apposition and expansion.[(13)]

The Disrupt CAD II study was a post-market clinical follow-up trial designed to evaluate the safety and performance of the Shockwave Coronary Intravascular Lithotripsy System using real world data. The study was conducted at 15 sites in Europe with up to 120 subjects. Subjects were followed for 30 days post procedure and the primary safety endpoint was in-hospital major adverse cardiac events (MACE). Enrollment in the Disrupt CAD II study started in May 2018.

1.3 Study Rationale

Disrupt CAD IV is a single arm study enrolling Japanese subjects with similar inclusion and exclusion criteria to the Disrupt CAD III IDE study. The primary safety and effectiveness endpoints in CAD IV will be compared to a similar set of subjects from the CAD III study using a propensity-score matched analysis. To maximize power and take advantage of the larger CAD III study, 1:5 matching will be done. Non-inferiority of CAD IV primary safety and effectiveness endpoints to CAD III will be assessed. The rationale for this global IDE study is to assess the safety and effectiveness of the Shockwave Coronary IVL System with up to 24 months of follow-up.

[12] Chambers J, Feldman R, et al. Pivotal Trial to Evaluate the Safety and Efficacy of the Orbital Atherectomy System in Treating De Novo, Severely Calcified Coronary Lesions (ORBIT II). J Am Coll Cardiol Intv 2014; 7: 510-518.
[13] Ali ZA, Brinton TJ, Hill JM, Maehara A, Matsumura M, Karimi Galougahi K, Illindala U, Götberg M, Whitbourn R, Van Mieghem N, Meredith IT, Di Mario C, Fajadet J. Optical Coherence Tomography Characterization of Coronary Lithoplasty for Treatment of Calcified Lesions: First Description. JACC Cardiovasc Imaging. 2017 Aug;10(8):897-906.

2.0 Study Device Description

The study device being evaluated is SWM-1234.

2.1 Study Device System

SWM-1234 is a proprietary catheter system designed to enhance stent outcomes by enabling delivery of the calcium disrupting capability of lithotripsy prior to balloon dilatation at low pressures. The system consists of an IVL Catheter with two lithotripsy emitters enclosed within an integrated balloon, an IVL Generator, IVL Connector Cable, and related accessories.
The IVL Catheter consists of a standard PTCA catheter with two lithotripsy emitters incorporated into the 12 mm balloon section of the catheter. The balloon is inflated at a lower than nominal pressure and the lithotripsy emitters are energized thereby generating pulsatile sonic pressure waves within the balloon at the target treatment site, disrupting calcium within the lesion, and allowing subsequent dilation of a coronary artery stenosis using low balloon pressure prior to stenting.

The C^2 IVL Catheter is available in 4 sizes: 2.5 mm, 3.0 mm, 3.5 mm, and 4.0 mm diameter, and are all 12 mm length. The Rapid Exchange (Rx) Catheter has a working length of 138 cm and is compatible with 190 or 300 cm length 0.014" guidewires. The IVL Catheter has compatibility with guide catheters as specified in the Instructions for Use (IFU). The IVL Catheter dual-lumen hub contains an inflation lumen, and the Catheter Connector. The inflation port is used for inflation of the balloon with 50/50 saline/contrast medium, as is standard practice with standard PTCA balloons. The Catheter Connector port facilitates connection to the Connector Cable.
The IVL Generator is used to support all sizes of IVL Catheters and the software can detect the different IVL Catheter types and sizes through a unique PCB incorporated inside the IVL Catheter. The IVL Connector Cable connects the IVL Generator to the IVL Catheter and includes a remote actuator used to activate the energy delivery from the IVL Generator to the IVL Catheter. The IVL Catheter is used exclusively with the Shockwave IVL Generator and IVL Connector Cable.

The IVL Catheter is supplied sterile via e-beam sterilization. It is intended for single use only and is not intended for reuse or re-sterilization. The IVL Generator and IVL Connector Cable are non-sterile and reusable.

2.2 Indication for Use

The SWM-1234 is an investigational device that is not currently commercially available in Japan.

The SWM-1234 is indicated to facilitate coronary intervention by removal of calcified de novo coronary artery lesions

3.0 STATISTICAL CONSIDERATIONS

3.1 Evaluation of Primary Endpoints

CAD IV will be single arm study enrolling Japanese subjects with similar inclusion and exclusion criteria to the Disrupt CAD III IDE study. The primary safety and effectiveness endpoints in CAD IV will be compared to a similar set of subjects from the CAD III study using a propensity-score matched analysis. To maximize power and take advantage of the larger CAD III study, 1:5 matching will be done.

Primary Safety Endpoint:

Safety will be assessed by freedom from major adverse cardiac events (MACE) within 30 days of the procedure. MACE is defined as the composite occurrence of:

- Cardiac death; or
- Myocardial Infarction (MI)- defined as CK-MB level > 3 times the upper limit of lab normal (ULN) value with or without new pathologic Q wave at discharge (periprocedural MI) and using the Fourth Universal Definition of Myocardial Infarction beyond discharge (spontaneous MI); or
- Target vessel revascularization-defined as revascularization at the target vessel (inclusive of the target lesion) after the completion of the index procedure

For the primary safety endpoint, the non-inferiority of CAD IV freedom from MACE to CAD III freedom from MACE within 30 days of the procedure will be assessed. Specifically, the null and alternative hypotheses are listed below.

Statistical Hypothesis:

- H_0: $\pi_{S\ CAD\ IV} \leq \pi_{S\ CAD\ III} - \delta$
- H_A: $\pi_{S\ CAD\ IV} > \pi_{S\ CAD\ III} - \delta$
- $\pi_{S\ CAD\ IV}$ = 30-day freedom from MACE in CAD IV
- $\pi_{S\ CAD\ III}$ = 30-day freedom from MACE in CAD III
- δ = Margin of non-inferiority, 9.36%
- Expected 30-day freedom from MACE in CAD IV = 89.6%
- Expected 30-day freedom from MACE in CAD III = 89.6%
- Statistical significance: one-sided α = 0.1
- 1:5 matching (CAD IV : CAD III)
- Based on the above assumptions 60 evaluable CAD IV subjects will be needed to achieve a statistical power of 72%. To account for a possible 5% attrition rate, 64 subjects will be enrolled.

Primary Effectiveness Endpoint:
Procedural Success defined as stent delivery with a residual stenosis <50% (by angiographic core laboratory analysis) and without in-hospital MACE.
For the primary effectiveness endpoint, the non-inferiority of CAD IV procedural success to CAD III procedural success will be assessed. For the primary effectiveness endpoint, the null and alternative hypotheses are listed below.

Statistical Hypothesis:
- H_0: $\pi_{e\ CAD\ IV} \leq \pi_{e\ CAD\ III} - \delta$
- H_A: $\pi_{e\ CAD\ IV} > \pi_{e\ CAD\ III} - \delta$
- $\pi_{e\ CAD\ IV}$ = Procedure success rate in CAD IV
- $\pi_{e\ CAD\ III}$ = Procedure success rate in CAD III
- δ = Margin of non-inferiority, 10.0%
- Expected 30-day Procedure Success in CAD IV = 88.9%
- Expected 30-day Procedure Success in CAD III = 88.9%
- Statistical significance: one-sided $\alpha = 0.1$
- 1:5 matching (CAD IV: CAD III)
- Based on the above assumptions 60 evaluable CAD IV subjects will be needed to achieve a statistical power of 75%. To account for a possible 5% attrition rate, 64 subjects will be enrolled.

3.2 Populations for Analyses

The primary analysis dataset for all study outcomes will be the intent-to-treat (ITT) population wherein data from all enrolled subjects will be analyzed.

Study outcomes will also be analyzed using a per-protocol (PP) population. The PP population includes all subjects who had no pre-specified inclusion and exclusion violations and were treated with IVL therapy.

3.3 Analysis Strategy

3.3.1 General Approach

Continuous variables will be summarized using the mean, standard deviation (SD), median, first and third quartiles, minimum, and maximum. Categorical data will be summarized as a frequency and percentage. The number of events, Kaplan-Meier estimated event rates, and log-rank test will summarize time to event data greater than 30 days.

3.3.2 Analysis of Primary Endpoints

For the primary safety endpoint analysis, the non-inferiority of CAD IV freedom from MACE rate at 30 days to CAD III freedom from MACE rate at 30 days will be assessed using the

Farrington-Manning test of non-inferiority for two binomial proportions with a non-inferiority margin of δ = 9.36% at the 0.1 level of significance (one-sided).
Propensity score matching will identify a covariate-unbiased population of subjects between the CAD IV and CAD III populations. To maximize power and take advantage of the larger CAD III study, 1:5 matching will be done.
A logistic regression will be used to model the likelihood of study enrollment in CAD IV versus CAD III as a function of the baseline characteristics. The covariates are chosen a priori based on their suspected relationship to MACE, possible relationship to study, and the ability to obtain comparable values from the two trials. The full list of baseline characteristics is present below.

• Age (at enrollment)

• Gender (male vs female)

• Site geography (US vs outside of US)

• Diabetes mellitus (medically treated)

• Prior CABG

• Estimated glomerular filtration rate (eGFR)

• Reference vessel diameter (angiographic core lab assessed)

• Lesion length (angiographic core lab assessed)

• Bifurcated lesions (angiographic core lab assessed)

Every CAD IV patient will be matched with up to 5 of the closest CAD III patients based on the absolute difference in propensity scores. Unmatched patients will be excluded from the primary analysis. Finally, the proportion of freedom from MACE at 30-days along with the corresponding exact 95% CIs will be presented for the CAD IV group and the matched CAD III group. Farrington-Manning one-sided p-value and lower bound of the one-sided 90% CI of the difference in proportion between matched CAD III and CAD IV groups will be presented.
Similar to the primary safety endpoint, for the primary effectiveness endpoint analysis, the non-inferiority of CAD IV procedure success to CAD III procedure success will be assessed using the Farrington-Manning test of non-inferiority for two binomial proportions with a non-inferiority margin of δ = 10.0% at the 0.1 level of significance (one-sided). Comparison between the two studies will be performed on the same set of propensity-score matched subjects as in the primary safety analysis.

In addition to the analysis of primary endpoints, all comprehensive Disrupt CAD IV results will be reported to assess CAD IV as a standalone study as well.

3.4 Analysis of Secondary Endpoints

Secondary endpoints will be presented as descriptive statistics. A description of each endpoint is summarized in this section.

• Device Crossing Success defined as the ability to deliver the IVL catheter across the target lesion, and delivery of lithotripsy without serious angiographic complications immediately after IVL

• Angiographic Success defined as stent delivery with <50% residual stenosis and without serious angiographic complications

• Procedural Success defined as stent delivery with a residual stenosis <30% (core laboratory assessed) and without in-hospital MACE

• Angiographic Success defined as stent delivery with <30% residual stenosis and without serious angiographic complications

• Serious angiographic complications defined as severe dissection (Type D to F), perforation, abrupt closure, and persistent slow flow or persistent no reflow

• MACE at 6, 12 and 24 months

• Target lesion failure (TLF) defined as cardiac death, target vessel myocardial infarction (Q wave and non-Q wave), or ischemia-driven target lesion revascularization (ID-TLR) by percutaneous or surgical methods at 30 days, 6, 12 and 24 months

• At each time period: All death, cardiac death, MI, TV-MI, procedural and nonprocedural MI, ID-TVR, ID-TLR, ID-non-TLR TVR, ID-non-TVR, all revascularizations (ID and non-ID), and stent thrombosis (ARC definite, probable, definite or probable)

• Sensitivity analyses will be reported for MI using the Fourth Universal Definition of MI and the Society for Cardiovascular Angiography and Interventions (SCAI) definitions at 30 days, 6, 12 and 24 months

4.0 Schedule of Evaluations

Table 1 lists the schedule of evaluations required for this study.

Table 1: Schedule of Evaluations

Assessment	Screening/ Baseline[1] (Day -14 to Day 0)	Enrollment / Procedure (Day 0)	12-24 hours post-procedure, or at discharge[2]	30 Days (±7 days)	6, 12, 24 Months (±30 days)
Informed Consent	X				
Medical History	X				
Physical Examination/Vital Signs	X				
NYHA Classification	X				
Canadian Cardiovascular Society (CCS) Angina Classification	X			X	X
Laboratory Assessments	Platelet count, creatinine, hemoglobin	CK-MB[3], troponin[4]	CK-MB[3], troponin, creatinine, hemoglobin		
Urine/serum pregnancy test is required for women of child-bearing potential within 7 days prior to enrollment	X				
LVEF (within 6-months of procedure)	X[5]				
12-lead ECG	X		X		
Coagulation Studies: PT/PTT and INR (only required for patients who have taken warfarin within two weeks of enrollment)	X				
Angiography		X		X[6]	X[6]
Sub-study: OCT/OFDI imaging		X			
Medication use	X	X	X	X	X
Adverse Event Assessment		X	X	X	X

[1] Screening/Baseline data collection can occur any time within 14 days of the procedure
[2] Laboratory assessments may be drawn at 12-24 hours post-procedure or at discharge, whichever is earlier, but at least 6 hours post procedure in patients with early discharge.
[3] For centers unable to perform the CK-MB assessment on-site, a blood sample must be drawn and sent to the central lab
[4] Patients presenting with stable angina may have biomarkers drawn from the side port of the sheath at the time of the procedure and the results do not need to be analyzed prior to enrollment.
[5] LVEF may be assessed during the baseline cardiac catheterization, prior to enrollment.
[6] If a revascularization procedure occurs during the follow-up period (planned or unplanned), angiographic images must be submitted to the core lab.

5.0 Index Procedure

5.1 Coronary Intravascular Lithotripsy Procedure

A full description of the procedure is detailed in the Instructions for Use (IFU). The appropriate sized SWM-1234 catheter should be selected per the IFU. A summary of the procedural steps is provided below. Angiographic images captured during the procedure will be sent to the core lab for analysis.

- If the Investigator is able to pass a guidewire but is unable to pass the IVL Catheter across the lesion, an adjunctive tool (e.g., a GuideLiner or comparable guide extension catheter, +/- a buddy wire or buddy balloon) should be used prior to re-insertion of the IVL Catheter. The lesion will then be treated per the IFU with the IVL Catheter. If the IVL catheter will still not cross the lesion, the lesion may be pre-dilated with a 1.5 mm or occasionally 2.0 mm PTCA balloon, after which the IVL catheter should be re-inserted.

  Note: *The subject is considered enrolled once the IVL Catheter has been inserted over a 0.014" guidewire which had previously passed across the study lesion.*

- If the Investigator is not able to cross the lesion with the IVL Catheter after exhausting adjunctive tools, this will be defined as a Device Delivery failure. Any further treatment will be done per standard care without the use of IVL. In the case of Device Delivery Failure, the patient is considered enrolled; as such, the subject should be followed per the Schedule of Evaluations and will be included in the intent-to-treat analysis.

  Note: *To avoid Device Delivery Failures, the adjunctive tools noted above may be used before the IVL catheter is initially inserted.*

  Note: *Use of IVL is not permitted if non-conventional PTCA treatments, including atherectomy, laser or cutting/scoring balloons, were previously used to treat the lesion.*

- Once the IVL catheter is placed in the target lesion area, the balloon should be inflated to 4 atm and IVL treatment delivered for the pre-programmed time of 10 seconds to deliver 10 pulses.

  Note: *The IVL Generator is programmed to force a minimum pause time of 10 seconds following every 10 pulses delivered.*

- Following IVL, inflate the balloon to the reference size using the balloon compliance chart (refer to IFU) and record lesion response on fluoroscopy.
- Deflate the balloon to re-establish blood flow.
- Repeat the steps above to complete a minimum single treatment with 20 pulses.

- If additional lesion area needs to be treated, follow the treatment steps identified above and per the IFU to ensure appropriate overlap between segments.

Note: *The pulse maximum for each catheter is 80 pulses. If more pulses are needed, an additional catheter must be used. The maximum number of pulses to treat a single arterial segment is 80 pulses and therefore 160 pulses in an overlap segment.*

- The residual stenosis will be assessed by the physician following the IVL procedure. The IVL procedure is considered successful when the residual stenosis is <50%, by visual estimate, as determined by the Investigator prior to stent placement.
- If the residual stenosis is >50% following IVL, a non-compliant balloon must be used to dilate the lesion prior to stenting. This information will be recorded in the case report form.
- The stent will then be delivered using a standard approach.
- Following stent implantation, post-dilatation with a non-compliant balloon with inflation pressure >=16 atm is mandatory.
- Following delivery of the coronary stent and post-dilatation, angiography will be performed to determine the final residual stenosis for assessment of the primary effectiveness endpoint.
- In addition, all subjects will be evaluated for life-threatening arrhythmias during the study. Baseline heart rhythm including the presence of baseline ectopy will be assessed. An assessment of ectopy and blood pressure in temporal association with IVL pulses will be recorded during the IVL procedure including any sustained ventricular tachycardia or fibrillation.

5.2 Optical Coherence Tomography (OCT) Sub-study

An OCT/Optical Frequency Domain Imaging (OFDI) sub-study will be conducted on all subjects. The objective is to further understand the mechanism of action ofSWM-1234 for the treatment of *de novo,* calcified, stenotic, coronary lesions prior to stenting. OCT or OFDI imaging will be completed at three time points: 1) pre-procedure, 2) immediately post-IVL treatment and 3) at the end of procedure following angiography. All OCT/OFDI images will be analyzed at the OCT core laboratory. OFDI or OCT may be used.