Study Title: Prospective, Multicenter, Single-Arm IDE Study of the Shockwave Coronary Intravascular Lithotripsy (IVL) System with the Shockwave C2+ 2Hz Coronary IVL Catheter in Calcified Coronary Arteries (Disrupt CAD Duo Study)

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Shockwave Disrupt CAD Duo Study Synopsis

Investigational Plan/ Study/Protocol Number:	Disrupt CAD Duo Study - CP-68277
Study Title	Prospective, Multicenter, Single-Arm IDE Study of the Shockwave Coronary Intravascular Lithotripsy (IVL) System with the Shockwave C^{2+} 2Hz Coronary IVL Catheter in Calcified Coronary Arteries (Disrupt CAD Duo Study).
Study Objective	The objective of this investigational device exemption (IDE) study is to assess the safety and effectiveness of the Shockwave Coronary Intravascular Lithotripsy (IVL) System with the Shockwave C^{2+} 2Hz Coronary IVL Catheter to treat *de novo*, calcified, stenotic, coronary lesions prior to stenting.
Study Device	Shockwave C^{2+} 2Hz Coronary IVL Catheter with Shockwave Intravascular Lithotripsy (IVL) System
Manufacturer	Shockwave Medical, Inc.
Investigational Indication for Use	The Shockwave Coronary Intravascular Lithotripsy (IVL) System with the Shockwave C^{2+} 2Hz Coronary IVL Catheter is indicated for lithotripsy-enabled, low-pressure balloon dilatation of severely calcified, stenotic *de novo* coronary arteries prior to stenting.
Study Design	Prospective, multicenter, single-arm, IDE study. It is a confirmatory study designed to assess non-inferiority of the primary safety and effectiveness endpoints to a propensity-matched cohort from the Disrupt CAD III IDE study.
Enrollment/ Number of Sites	Up to 145 subjects (138 evaluable) will be enrolled at up to 20 US sites. Each site will be allowed to enroll a maximum of 15% (22 subjects) of the total study enrollment.
Subject Population	Subjects with de novo, calcified coronary artery lesions presenting with stable, unstable, or silent ischemia that are suitable for percutaneous coronary intervention (PCI).
Study Duration/ Follow-Up Period	Enrollment duration: approximately 10-12 months Study duration: approximately 2 years. Subjects will be followed through discharge, 30 days, 6, and 12 months
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) (using the SCAI definition for peri-procedural MI; using the 4th Universal Definition for spontaneous MI beyond discharge); 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 ≤30 % (core laboratory assessed) and without in-hospital MACE.
Secondary Endpoints	• Device Crossing Success is 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 <50% (core laboratory assessed) and without in-hospital MACE. • Angiographic Success defined as stent delivery with ≤30% residual stenosis and withouserious 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, and 12 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 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). • MI at each time period using alternative definitions for peri-procedural MI (Fourth Universal Definition and CK-MB > 3x ULN).
Optical Coherence Tomography (OCT) Sub-study	An OCT Sub-study will be conducted on up to 60 subjects at sites that routinely perform OCT imaging as standard of care, and OCT images will be analyzed by an independent core laboratory. OCT imaging will be completed at three time-points during the index procedure.
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 subjects with unstable ischemic heart disease, biomarkers (CK-MB and troponin) must be less than or equal to the upper limit of the laboratory normal within 12 hours prior to the procedure (note: both must be normal) 4. For subjects 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 (CK-MB and troponin) must be less than or equal to the upper limit of the laboratory normal within 12 hours of the procedure (note: both must be normal)

	b. If 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 criterion; 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. Non-target lesions 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 mm^2 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 participating in another research study involving an investigational

	agent (pharmaceutical, biologic, or medical device) that has not reached the primary endpoint 3. Subject is pregnant or nursing (a negative pregnancy test is required for women of child- bearing potential within 7 days prior to enrollment) 4. Unable to tolerate antiplatelet/anticoagulation therapy per society guidelines 5. Subject has an allergy to imaging contrast media which cannot be adequately pre- medicated 6. 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 greater than 1 times the local laboratory's upper limit of normal 7. New York Heart Association (NYHA) class III or IV heart failure 8. Subject has acute or chronic renal disease with eGFR <30 ml/min/1.73m^2 (using CKD-EPI formula) 9. History of a stroke or transient ischemic attack (TIA) within 60 days, or any prior intracranial hemorrhage or permanent neurologic deficit 10. Active peptic ulcer or upper gastrointestinal (GI) bleeding within 3 months 11. Untreated pre-procedural hemoglobin <10 g/dL or intention to refuse blood transfusions if one should become necessary 12. 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) 13. Subject has a hypercoagulable disorder such as polycythemia vera, platelet count >750,000 or other related blood disorders 14. Subject has an active systemic infection on the day of the index procedure with either fever, leukocytosis or requiring intravenous antibiotics 15. Subjects with clinical evidence of cardiogenic shock 16. Uncontrolled severe hypertension (systolic BP >180 mm Hg or diastolic BP >110 mm Hg) 17. Subjects with a life expectancy of less than 1 year 18. 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 19. 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 20. Subject refusing or not a candidate for emergency coronary artery bypass grafting (CABG) surgery 21. Planned use of atherectomy, scoring or cutting balloon, or any investigational device other than lithotripsy Angiographic Exclusion Criteria 22. Unprotected left main diameter stenosis >30% 23. Definite or possible thrombus (by angiography or intravascular imaging) in the target vessel 24. Evidence of aneurysm in target vessel within 10 mm of the target lesion

	25. Target lesion is located in a native vessel that can only be reached by going through a saphenous vein or arterial bypass graft 26. Previous stent within 5 mm of the target lesion regardless of the timing of its implantation 27. Angiographic evidence of a dissection or perforation in the target vessel at baseline or after guidewire passage
Statistical Methods	The primary safety and effectiveness endpoints in the Disrupt CAD Duo study will be compared to a similar set of subjects from the Disrupt CAD III study using a propensity-score matched analysis and a non-inferiority design. **Primary Safety Endpoint** In the Disrupt CAD III study, freedom from 30-day MACE was 96.3% (369/383) using the SCAI definition for peri-procedural MI. The null and alternative hypotheses for the primary safety endpoint are as follows: $H_0: \Pi_{S,C2+} \leq \Pi_{S,CAD\ III} - \delta_S$ $H_A: \Pi_{S,C2+} > \Pi_{S,CAD\ III} - \delta_S$ where $\Pi_{S,C2+}$ is the true 30-day freedom from MACE rate in the Disrupt CAD Duo study, $\Pi_{S,CAD\ III}$ is the true 30-day freedom from MACE rate in the propensity-matched Disrupt CAD III cohort (using the SCAI definition for peri-procedural MI), and δ_S is the pre-specified margin of non-inferiority. The assumptions for the sample size calculations are listed below. • Expected 30-day freedom from MACE rate for the Disrupt CAD Duo study ($\Pi_{S,C2+}$) = 96.3% • Expected 30-day freedom from MACE rate in Disrupt CAD III propensity-matched cohort (using the SCAI definition for peri-procedural MI) ($\Pi_{S,CAD\ III}$) = 96.3% • Margin of non-inferiority (δ_S) = 7% • One-sided statistical significance level (α) = 0.05 • Two-sample Farrington-Manning non-inferiority test of binomial proportions • 1:2 propensity score matching (Disrupt CAD Duo:Disrupt CAD III) Based on the above assumptions, a sample size of 138 evaluable subjects provides a statistical power of 90.0% for safety. Up to 145 subjects may be enrolled to account for attrition. **Primary Effectiveness Endpoint** In the Disrupt CAD III study, Procedural Success was 96.4% (370/384) (defined as ≤ 30% final residual stenosis with no in hospital MACE using the SCAI definition for peri-procedural MI). The null and alternative hypotheses for the primary effectiveness endpoint are as follows: $H_0: \Pi_{E,C2+} \leq \Pi_{E,CAD\ III} - \delta_E$ $H_A: \Pi_{E,C2+} > \Pi_{E,CAD\ III} - \delta_E$

	where $\Pi_{E,C2+}$ is the true Procedural Success rate in the Disrupt CAD Duo study, $\Pi_{E,CAD\ III}$ is the true Procedural Success rate in the propensity-matched Disrupt CAD III cohort (using the SCAI definition for peri-procedural MI and ≤ 30% final residual stenosis), and δ_E is the pre-specified margin of non-inferiority. The assumptions for the sample size calculations are listed below. • Expected Procedural Success rate for the Disrupt CAD Duo study ($\Pi_{E,C2+}$) = 96.4% • Expected Procedural Success rate in Disrupt CAD III propensity-matched cohort (using the SCAI definition for peri-procedural MI) ($\Pi_{E,CAD\ III}$) = 96.4% • Margin of non-inferiority (δ_E) = 7% • One-sided statistical significance level (α) = 0.05 • Two-sample Farrington-Manning non-inferiority test of binomial proportions • 1:2 propensity score matching (Disrupt CAD Duo:Disrupt CAD III) Based on the above assumptions, a sample size of 138 evaluable subjects provides a statistical power of 90.0% for effectiveness. Up to 145 subjects may be enrolled to account for attrition. The study will be deemed a success if both the primary safety and effectiveness endpoints are met.
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