Study Title: Prospective, Multicenter, Single-Arm, Global IDE Study of the Shockwave Coronary Intravascular Lithotripsy (IVL) System with the Shockwave $C^2$ Coronary IVL Catheter in Calcified Coronary Arteries (Disrupt CAD III Study)

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| Investigational Plan/Study/Protocol Number: | Disrupt CAD III Study – CP 61982 |
| Study Title: | Prospective, Multicenter, Single-Arm, Global IDE Study of the Shockwave Coronary Intravascular Lithotripsy (IVL) System with the Shockwave $C^2$ Coronary IVL Catheter in Calcified Coronary Arteries (Disrupt CAD III 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 to treat *de novo,* calcified, stenotic, coronary lesions prior to stenting. |
| Study Devices: | Shockwave Coronary Intravascular Lithotripsy (IVL) System |
| IDE Indications for Use: | The Shockwave Coronary IVL System is indicated for lithotripsy-enabled, low-pressure dilatation of *de novo*, calcified, stenotic, coronary arteries prior to stenting. |
| Study Design: | Prospective, multicenter, single-arm, global IDE study to evaluate the safety and effectiveness of the Shockwave Coronary IVL System in *de novo,* calcified, stenotic, coronary arteries prior to stenting. Disrupt CAD III is being conducted as a staged pivotal study.<br><br>Following FDA approval of the Shockwave Coronary IVL System, this protocol will transition to a Continued Follow-up Study (CFS). The Disrupt CAD III CFS will evaluate long-term safety and effectiveness for subjects enrolled in the pivotal cohort of the Disrupt CAD III IDE study through two years. There are no new enrollments in the Disrupt CAD III CFS. |
| Enrollment/ Number of Sites: | Approximately 392 subjects will be enrolled at 50 global sites. A minimum of 50% of the total enrollment will come from the United States. |
| 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 18 months<br>Study duration: approximately 4 years<br>Subjects will be followed through discharge, 30 days, 6, 12 and 24 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:<br>• Cardiac death; or<br>• 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 |

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| | • 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 IVL catheter across the target lesion, and delivery of lithotripsy without serious angiographic complications immediately after IVL.<br>• Angiographic Success defined as stent delivery with <50% residual stenosis and without serious angiographic complications.<br>• Procedural Success defined as stent delivery with a residual stenosis ≤30% (core laboratory assessed) and without in-hospital MACE.<br>• Angiographic Success defined as stent delivery with ≤30% residual stenosis and without serious angiographic complications.<br>• Serious angiographic complications defined as severe dissection (Type D to F), perforation, abrupt closure, and persistent slow flow or persistent no reflow.<br>• MACE at 6, 12 and 24 months.<br>• 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.<br>• 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).<br>• 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<br>2. Subjects with native coronary artery disease (including stable or unstable angina and silent ischemia) suitable for PCI<br>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).<br>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 (note: CK-MB is required if drawn from the sheath).

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

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| | 10. The target vessel reference diameter must be ≥2.5 mm and ≤4.0 mm<br>11. The lesion length must not exceed 40 mm<br>12. The target vessel must have TIMI flow 3 at baseline (visually assessed; may be assessed after pre-dilatation)<br>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<br>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<br>2. Subject is a member of a vulnerable population as defined in 21 CFR 56.111, 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. Vulnerable populations also may include members of a group with a hierarchical structure such as university students, subordinate hospital and laboratory personnel, employees of the Sponsor, members of the armed forces, and persons kept in detention<br>3. Subject is participating in another research study involving an investigational agent (pharmaceutical, biologic, or medical device) that has not reached the primary endpoint<br>4. Subject is pregnant or nursing (a negative pregnancy test is required for women of child-bearing potential within 7 days prior to enrollment)<br>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)<br>6. Subject has an allergy to imaging contrast media which cannot be adequately pre-medicated<br>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<br>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. High SYNTAX Score (≥33) if assessed as standard of care, unless the local heart team has met and recommends PCI is the most appropriate treatment for the patient
25. Unprotected left main diameter stenosis >30%
26. Target vessel is excessively tortuous defined as the presence of two or more bends >90º or three or more bends >75º

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| | 27. Definite or possible thrombus (by angiography or intravascular imaging) in the target vessel<br>28. Evidence of aneurysm in target vessel within 10 mm of the target lesion<br>29. Target lesion is an ostial location (LAD, LCX, or RCA, within 5 mm of ostium) or an unprotected left main lesion<br>30. Target lesion is a bifurcation with ostial diameter stenosis ≥30%<br>31. Second lesion with >50% stenosis in the same target vessel as the target lesion including its side branches<br>32. Target lesion is located in a native vessel that can only be reached by going through a saphenous vein or arterial bypass graft<br>33. Previous stent within the target vessel implanted within the last year<br>34. Previous stent within 10 mm of the target lesion regardless of the timing of its implantation<br>35. Angiographic evidence of a dissection in the target vessel at baseline or after guidewire passage |
| Statistical Methods: | The primary safety and effectiveness endpoints are based on a comparison to pre-specified performance goals (PG) based on relevant published reports, and previously used in the ORBIT II study with a similar population.<br><br><u>Primary Safety Endpoint:</u><br>Safety will be assessed by freedom from major adverse cardiac events (MACE) within 30 days of the index procedure.<br>Statistical Hypothesis:<br>• $H_0$: $\pi_S \leq PG$<br>• $H_A$: $\pi_S > PG$<br>• $\pi_S$ = 30-day freedom from MACE<br>• PG = Performance Goal for 30-day freedom from MACE of 84.4%<br>• Expected 30-day freedom from MACE = 89.6%<br>• Statistical significance: one-sided $\alpha = 0.05$<br>• Statistical power = 90%<br>• Sample size = 392 subjects adjusting for 5% lost to follow up |

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| | Primary Effectiveness Endpoint:<br>Procedural Success defined as stent delivery with a residual stenosis <50% and without in-hospital MACE.<br>Statistical Hypothesis:<br>• $H_0$: $\pi_e \leq PG$<br>• $H_A$: $\pi_e > PG$<br>• $\pi_e$ = Procedure success<br>• PG = Performance Goal for procedure success of 83.4%<br>• Expected 30-day Procedure Success = 88.9%<br>• Statistical significance: one-sided $\alpha = 0.05$<br>• Statistical power = 90%<br>• Sample size = 360 subjects adjusting for 5% lost to follow-up<br><br>The study will have 81% power to meet both the safety and effectiveness endpoints.<br><br>The overall sample size is based on the primary safety endpoint. Assuming a true 30-day MACE free rate of 89.6%, a relative risk (RR) of 1.5 and an attrition rate of 5%, an evaluable sample size of 392 subjects is required to achieve approximately 90% power to reject the null hypothesis for the primary safety endpoint that the true 30-day MACE free rate is at least 84.4% at a one-sided α-level of 0.05. This corresponds to 372 evaluable subjects at 30 days. |
| Sponsor: | Shockwave Medical, Inc.<br>5403 Betsy Ross Drive<br>Santa Clara, CA 95054<br>USA |