SHOCKWAVE MEDICAL INC	Disrupt CAD II Protocol Synopsis
	NCT03328949

Study Title: Prospective Multi-Center, Single Arm Post-Market Study (PMS) of the Shockwave Medical, Inc. Coronary Lithoplasty® System in Coronary Arteries (Disrupt CAD II)

NCT Number: 03328949

Date: October 18, 2019

SHOCKWAVE MEDICAL INC	Disrupt CAD II Protocol Synopsis
	NCT03328949

Investigational Plan/Study/Protocol Number:	Disrupt CAD II Study - CP 61774
Study Title:	Prospective Multi-Center, Single Arm Post-Market Study (PMS) of the Shockwave Medical, Inc. Coronary Lithoplasty® System in Coronary Arteries
Study Objective:	The objective of the study is to assess the safety and performance of the Shockwave Medical, Inc. Coronary Lithoplasty® System to treat calcified, stenotic, de novo coronary lesions prior to stenting in a real-world post-market study.
Study Device:	Coronary Intravascular Lithotripsy (IVL) (previously referred to as Lithoplasty®) System by Shockwave Medical, Inc.
Indications for Use:	The Shockwave Medical Coronary IVL System is indicated for lithotripsy-enhanced, low-pressure balloon dilatation of calcified, stenotic de novo coronary arteries prior to stenting.
Study Design:	Prospective, multi-center, single arm post market study to evaluate the real-world safety and performance of the Coronary IVL System for lithotripsy-enhanced, low-pressure balloon dilatation of calcified, stenotic de novo coronary arteries prior to stenting.
Enrollment/ Number of Sites:	Maximum of 120 subjects at up to 15 sites in Europe.
Subject Population:	Patients ≥18 years of age scheduled for a coronary stent procedure who have angiographic evidence of significant calcified stenosis of the left main coronary artery (LMCA), left anterior descending artery (LAD), right coronary artery (RCA), or left circumflex (LCX).
Study Duration/ Follow-Up Period:	Approximately 8 to 10 months of enrollment at 15 European sites. Subjects will be followed through discharge and at 30 days by phone follow-up.
Primary Safety Endpoint:	In-hospital major adverse cardiac events (MACE)
Secondary Endpoints:	Performance will be assessed by the ability of the Lithoplasty System to produce acceptable residual stenosis (<50%) after stenting with no evidence of in-hospital MACE. Each patient that achieves both of these requirements will be considered a "clinical success", and the rate of clinical success among subjects will be evaluated. Angiographic success defined as success in facilitating stent delivery with <50% residual stenosis and without serious angiographic complications. Serious angiographic

	complications are defined as severe dissection (Type D to F), perforation, abrupt closure, and persistent slow flow or persistent no reflow. Cardiac death at 30 days.
Inclusion Criteria:	1. Patient is ≥ 18 years of age 2. Troponin must be less than or equal to the upper limit of lab normal value within 24 hours prior to the procedure OR if troponin is elevated, concomitant CK must be normal. 3. The target vessel must have a TIMI flow 3 at baseline 4. Patients with significant (≥ 50% diameter stenosis) native coronary artery disease including stable or unstable angina and silent ischemia, suitable for PCI 5. Ability to tolerate dual antiplatelet agent (i.e. aspirin, clopidogrel, prasugrel, or ticagrelor for 1 year and single antiplatelet therapy for life 6. Single lesion stenosis of protected LMCA, or LAD, RCA or LCX artery ≥50% in a reference vessel of 2.5 mm - 4.0 mm diameter and ≤ 32 mm length 7. Presence of calcification within the lesion on both sides of the vessel as assessed by angiography 8. Planned treatment of single lesion in one vessel 9. Ability to pass a 0.014" guide wire across the lesion 10. Patient, or authorized representative, signs a written Informed Consent form to participate in the study, prior to any study-mandated procedures 11. Patient is able and willing to comply with all assessments in the study
Exclusion Criteria:	1. Concomitant use of Atherectomy, specialty balloon, or investigational coronary devices 2. Prior PCI procedure within the last 30 days of the index procedure 3. Patient has planned cardiovascular interventions within 30 days post index procedure 4. Second lesion with ≥50% stenosis in the same target vessel 5. Left ventricular ejection fraction < 40% 6. Patient refusing or not a candidate for emergency coronary artery bypass grafting (CABG) surgery 7. Uncontrolled severe hypertension (systolic BP >180 mm Hg or diastolic BP >110 mm Hg) 8. Severe renal failure with serum creatinine >2.5 mg/dL, unless on chronic dialysis 9. Untreated pre-procedural hemoglobin <10 g/dL

	10. Coagulopathy manifested by platelet count <100,000 or International Normalized ratio (INR) >1.7 (INR is only required in patients who have taken warfarin within 2 weeks of enrollment) 11. Patients in cardiogenic shock 12. Acute myocardial infarction (MI) within the past one (1) month, and/or signs of active myocardial ischemia at the time of enrollment including elevated Troponin-I or T (with concomitant elevation of CK), ischemic ECG changes or chest pain 13. History of a stroke or transient ischemic attack (TIA) within 3 months 14. NYHA class III or IV heart failure 15. Active peptic ulcer or upper gastrointestinal (GI) bleeding within 6 months 16. Patients with a life expectancy of less than 1 year 17. Target vessel < 2.4 mm in diameter 18. Target lesion > 32 mm in length 19. Chronic Total Occlusion (CTO) 20. Previous stent procedure within 5 mm of target lesion 21. Angiographic evidence of a target lesion severe dissection prior to Coronary Lithoplasty treatment 22. Unprotected Left Main diameter stenosis ≥ 50% 23. Visible thrombus (by angiography) at target lesion site 24. Target lesion is located in a native vessel distal to anastomosis with a saphenous vein graft or LIMA/RIMA bypass 25. Patient has active systemic infection 26. Patient has connective tissue disease (e.g., Marfan's syndrome) 27. Patient has a hypercoagulable disorder 28. Uncontrolled insulin dependent diabetes 29. Patient has allergy to imaging contrast media for which they cannot be pre-medicated 30. Evidence of aneurysm in target vessel 31. Patient is pregnant or nursing
Sponsor:	Shockwave Medical, Inc. 5403 Betsy Ross Drive Santa Clara, CA 95054 United States of America

1 INTRODUCTION

1.1 Background

Challenges in Treating Calcified Plaque

Calcified coronary lesions are associated with age, diabetes and chronic kidney disease.[1] Approximately 38% and 73% of all coronary artery 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] Calcification adversely impacts interventional outcomes by complicating device delivery[3], damaging the drug-eluting polymer[4] and impairing stent expansion and apposition[5].

Current Therapies

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, and in concentric calcium may be of insufficient pressure-generated force to lead to 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, 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 9 months, rotational atherectomy (RA) had similar rates of binary restenosis, target lesion revascularization (TLR), stent thrombosis and MACE, despite a higher procedural acute gain over PTCA. Chambers et al reported the 30-day orbital atherectomy (OA) results from the ORBIT II Study. OA 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%, and in-hospital non-Q wave MI's occurred in 8.6% of the subjects.[12]

Shockwave Medical Coronary Intravascular Lithotripsy (IVL)

Intravascular Lithotripsy (IVL) is a technique based on lithotripsy, an established treatment strategy for renal calculi, in which multiple lithotripsy emitters mounted on a traditional balloon catheter platform create diffusive pulsatile mechanical energy to disrupt calcium within the vessel wall at low inflation pressures. The completed Disrupt CAD I Study reported the safety and performance of coronary IVL in vessel preparation for calcified, stenotic, *de novo* coronary lesions prior to stent implantation.

Disrupt CAD I Study

Successful delivery of the IVL balloon 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 subjects suffering cardiac death. Results of the optical coherence tomography (OCT) sub-study identified modification with fracture as a major mechanism of action of IVL in vivo and demonstrated efficacy in the achievement of significant acute area gain and favorable stent expansion.[13]

As a result of the CAD I study meeting its primary and secondary endpoints and being able to demonstrate a strong safety profile throughout the study, the coronary IVL system received CE marking in Europe on 18 April 2017.

1.2 Rationale for Disrupt CAD II Study

The Disrupt CAD II post-market surveillance study was initiated in May 2018 to evaluate the real-world safety and performance of the Coronary IVL System and to ensure that pre-market study outcomes from CAD I were generalizable to a broader population with a larger number of physician users.

2 STUDY DEVICE DESCRIPTION

The Coronary Lithoplasty System is a proprietary balloon catheter system designed to enhance PTCA by enabling delivery of the calcium disrupting capability of lithotripsy prior to balloon dilatation at low pressures. The Coronary Lithoplasty System consists of a Lithoplasty Balloon Catheter with two integrated pairs of lithotripsy emitters, a Lithoplasty Generator, Connector Cable, and related accessories.

The Lithoplasty 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 mechanical energy 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 Lithoplasty Catheters are available in 7 sizes: 2.5 mm, 2.75mm, 3.0 mm, 3.25 mm, 3.5mm, 3.75 mm, and 4.0 mm diameter and 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 Lithoplasty Catheter has compatibility with guide catheters as specified in the Instructions for Use (IFU). The Lithoplasty 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 Lithoplasty Generator design is used to support all sizes of Lithoplasty Catheters and the software can detect the different Lithoplasty Catheter types and sizes through a unique PCB incorporated inside the Lithoplasty Catheter. The Connector Cable connects the Generator to the Lithoplasty Catheter and includes a remote actuator used to activate the energy delivery from the Generator to the Lithoplasty Catheter. The Lithoplasty Catheter is used exclusively with the Shockwave Medical Lithoplasty Generator and Connector Cable.

The Lithoplasty 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 Lithoplasty Generator and Connector Cable are non-sterile and reusable.

3 STATISTICAL CONSIDERATIONS

3.1 Statistical Methods

3.1.1 Sample Size Justification

The primary objective of the study is to confirm if the true primary endpoint rate meets the upper bound of the 95% confidence interval.

Key assumptions:

- One-sided alpha = 0.05
- True rate of 7.7%
- Upper bound of 95% confidence interval = 13%
- Sample size = 120 subjects
- Maximum number of events with 120 subjects = 9

3.1.2 Analysis Populations

The primary analysis dataset was the Intent-To-Treat (ITT) population which included all enrolled subjects.

The secondary analysis set was the Per-Protocol (PP) population which included subjects with no pre-specified inclusion or exclusion violations.

No imputation of or adjustments for missing data were performed for the primary or secondary analyses.

3.1.3 Primary Endpoint Analysis

The primary safety endpoint was the frequency of in-hospital major adverse cardiac events (MACE). MACE was defined as the following:

- Cardiac death
- MI - defined as a CK-MB level > 3 times the upper limit of lab normal (ULN) value with or without new pathologic Q wave
- TVR - defined as revascularization at the target vessel (inclusive of the target lesion) after the completion of the index procedure

Number and proportions of subjects with any type of MACE were reported. No formal hypothesis testing was performed; however, 95% confidence intervals were provided for the primary safety endpoint.

3.1.4 Secondary Endpoint Analyses

Clinical Success: The number and proportion of subjects achieving clinical success were defined by subjects achieving both of the following requirements:

- Ability of the Coronary Lithotripsy System to produce acceptable residual stenosis (<50%) after stenting
- No evidence of in-hospital MACE

Angiographic Success: The number and proportion of subjects achieving angiographic success were defined as success in facilitating stent delivery with <50% residual stenosis 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.

Cardiac Death: The number and proportion of subjects who experience cardiac death within 30 days of the lithotripsy procedure.

The lower 95% CI limit for clinical success and 2-sided 95% CI limit for angiographic success and cardiac death rate within 30 days of the lithotripsy procedure were reported.

3.2 Study Assessments

3.2.1 Schedule of Events

Table 1 summarizes the schedule of events and assessments for study subjects required by protocol Revision C.

Table 1. Schedule of Events

Assessment	*Screening/ Baseline (Day -14 to Day 0)*	*Enrollment and Procedure (Day 0)*	*Post Treatment*	*Discharge*	*30 Days (+/- 7D)*[3]
Informed Consent	X				
Medical History	X				
Physical Examination	X			X	
NYHA Classification	X				
Canadian Cardiovascular Society (CCS) Angina Classification	X				
Laboratory Assessments	CK, Platelets, Creatinine, Hemoglobin, BUN	Troponin[2]		Troponin, CK, CK-MB, Creatinine, Hemoglobin	
Urine pregnancy test, if female of childbearing potential within 7 days of procedure	X				
LVEF	X[1]				
ECG	X			X	
Coagulation Studies: PT/PTT INR	X				
Angiographic Lesion Assessment		X	X		
Medication regimen per protocol	X			X	X
Adverse Event Assessment		X	X	X	X

[1] Screening/baseline LVEF results must be within 90 days of procedure

[2] Troponin to be collected and analyzed within 24 hours prior to procedure

[3] Telephone Follow-Up

3.2.2 Shockwave Medical Coronary IVL Procedure

A full description of the procedure is detailed in the Instructions for Use (IFU). The appropriately sized IVL balloon catheter was selected per the IFU. Once the IVL balloon was placed in the target lesion area, the balloon was inflated to 4 ATM and IVL treatment delivered for the pre-programmed time of 10 seconds to deliver 10 pulses. Note that the generator was programmed to force a minimum pause time of 10 seconds following every 10 pulses delivered. Following the IVL treatment, the balloon was inflated to the reference size using the balloon compliance chart (refer to IFU) and the lesion response was recorded on fluoroscopy. The balloon was deflated and the physician waited 30 seconds to re-establish blood flow. The steps above were repeated to complete a minimum single treatment with 20 pulses. If additional lesion areas needed to be treated, the treatment steps as identified above and per the IFU were repeated. The pulse maximum for each catheter was 80 pulses. If more pulses were needed, an additional catheter was used.

If the Investigator was able to pass a guidewire but was unable to pass the IVL balloon catheter across the lesion, then an adjunctive tool (i.e. 1.5 mm PTCA balloon, Guide Liner guide extension catheter, or buddy wire) was used prior to re-insertion of the IVL Coronary Balloon. The eligible lesion was then treated directly per the IFU with the IVL device.

The residual stenosis was assessed by the physician following the IVL procedure. The IVL procedure was considered successful if the residual stenosis was <50% by visual estimate, as determined by the Investigator, prior to stent placement. If the residual stenosis was >50%, a non-compliant balloon was used to dilate the lesion prior to stenting. This information was recorded in the case report form.

The stent was delivered using a standard approach. If needed, the stent was post-dilated using PTCA balloons. Following delivery of the coronary stent, angiography was performed to determine the final residual stenosis.

Use of intravascular imaging, including optical coherence tomography (OCT), was allowed per standard of care as clinically needed.

4 LIST OF REFERENCES

[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;75:905-11.

[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;6:10-9.

[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.

[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 Cariol Intv 2014; 7: 510-8.

[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.