Study Title: New Enrollment Post Approval Registry for the Shockwave Intravascular Lithotripsy (IVL) System with Shockwave C2 Coronary Intravascular Lithotripsy (IVL) Catheter (Disrupt CAD III PAS Study)

NCT Number: NCT05021757

Protocol Date: May 4, 2021

Revision: B

Investigational Plan/Study/Protocol Number:	Disrupt CAD III PAS Study – CP 64647
Study Title:	New Enrollment Post Approval Registry for the Shockwave Intravascular Lithotripsy (IVL) System with Shockwave C^2 Coronary IVL Catheter
Study Objective:	The objective of this Post Approval Registry is to better understand the utilization, safety, and effectiveness of the Shockwave Coronary IVL System in a ”real-world” setting.
Study Devices:	Shockwave IVL System with Shockwave C^2 Coronary IVL Catheter
Indications for Use:	The Shockwave IVL System with Shockwave C^2 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, observational, single-arm post-approval study using data collected in the National Cardiovascular Data Registry (NCDR®) CathPCI Registry®.
Enrollment/ Number of Sites:	Approximately 1000 patients in the CathPCI Registry® (including a minimum of 30 patients with permanent pacemakers [PPM] or implantable cardioverter defibrillators [ICDs]) will be enrolled.
Subject Population:	Patients with severely calcified, stenotic de novo coronary artery lesions presenting with stable, unstable, or silent ischemia that are suitable for percutaneous coronary intervention (PCI) and with clinical characteristics similar to the Disrupt CAD III IDE study (IDE G180146).
Study Duration / Follow-Up Period:	Subjects will be followed through discharge. A minimum of 150 patients will be followed 30 days post-procedure.
Safety Endpoints:	Mortality and procedure-related adverse events IVL-specific data reporting • IVL-related ventricular arrhythmia • IVL balloon loss of pressure and related serious dissections • Safety of IVL in patients with PPM/ICD
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. Left ventricular ejection fraction >25% within 6 months 4. The target lesion must be a de novo coronary lesion that has not been previously treated with any interventional procedure 5. LAD, RCA or LCX (or of their branches) with: • Stenosis of ≥70% and <100% or

	• Stenosis ≥50% and <99% (visually assessed) with evidence of ischemia via positive stress test, or fractional flow reserve (FFR) value ≤0.80, or iFR <0.90 or IVUS or OCT minimum lumen area ≤4.0 mm² 6. The lesion length must not exceed 40 mm 7. The target vessel must have TIMI flow 3 at baseline (visually assessed; may be assessed after pre-dilatation) 8. Evidence of calcification at the lesion site by 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
Exclusion Criteria:	1. Subject experienced an acute MI (STEMI or non-STEMI) within 30 days prior to index procedure 2. New York Heart Association (NYHA) class III or IV heart failure 3. Renal failure with serum creatinine >2.5 mg/dL or chronic dialysis 4. Subjects in cardiogenic shock or with clinical evidence of acute heart failure 5. Target lesion is located in a native vessel that can only be reached by going through a saphenous vein or arterial bypass graft 6. Previous stent within target lesion (in-stent restenosis)
Statistical Methods:	Interim results and final results will be analyzed using descriptive statistics; there is no formal hypothesis testing for the PAS.
Sponsor:	Shockwave Medical, Inc. 5403 Betsy Ross Drive Santa Clara, CA 95054 USA

1.0 INTRODUCTION/BACKGROUND

1.1 Disrupt CAD III IDE Study

The objective of the Disrupt CAD III investigational device exemption (IDE) study was to assess the safety and effectiveness of the Shockwave Intravascular Lithotripsy (IVL) System with Shockwave C^2 Coronary Intravascular Lithotripsy (IVL) Catheter, hereafter referenced as the Shockwave Coronary IVL System, to treat de novo, calcified, stenotic, coronary lesions prior to stenting against objective performance goals.

A total of 431 subjects (47 roll-in, 384 pivotal) were enrolled from 47 centers in the United States, France, Germany and the UK. Enrollment began in January 2019 and was completed in March 2020. The primary safety endpoint was freedom from major adverse cardiac events (MACE) through 30 days and the primary effectiveness endpoint of Procedural Success (defined as stent delivery with a residual stenosis < 50% without in-hospital MACE) was evaluated at discharge. The Pivotal Analysis Set (n=384) was the primary analysis cohort used to assess the primary safety and effectiveness endpoints.

The study met its primary safety endpoint. The observed freedom from 30-day MACE was 92.2% (353/383) and the lower bound of the one-sided 95% confidence interval was 89.9%, greater than the performance goal of 84.4%. As such, the null hypothesis was rejected, and the primary safety endpoint was met ($p<0.0001$). The study also met its primary effectiveness endpoint. The observed rate of Procedural Success was 92.4% (355/384) and the lower bound of the one-sided 95% confidence interval was 90.2%, greater than the performance goal of 83.4%. As such, the null hypothesis was rejected, and the primary effectiveness endpoint was met ($p<0.0001$).

On February 12, 2021, the Shockwave Coronary IVL System was granted FDA approval. As part of the FDA Conditions of Approval, Shockwave Medical is conducting a Post Approval Registry leveraging the ACC NCDR® CathPCI Registry®. Established registries like the CathPCI Registry® are an efficient way to collect objective clinical endpoint data on large, real-world populations from a broad spectrum of institutions.

1.2 NCDR® CathPCI Registry®

Developed in 1997 by the American College of Cardiology (ACC), the NCDR® was created as an exploration into strategies for improving cardiovascular care through the use and application of clinical data. Today, the NCDR® is a reputable and dependable quality improvement resource that continues to evolve to meet the demands of the changing health care environment.

Currently, the NCDR® suite of cardiovascular data registries covers several clinical areas including acute myocardial infarction (MI) treatment, diagnostic cardiac catheterization and percutaneous coronary intervention (PCI), and transcatheter valve therapy procedures.

The CathPCI Registry® assesses the characteristics, treatments and outcomes of cardiac disease patients who receive diagnostic catheterization and/or PCI procedures. The tool captures the data that measure adherence to ACC/AHA clinical practice guideline recommendations, procedure performance standards and appropriate use criteria (AUC) for coronary revascularization. Over 1700 institutions currently participate in the CathPCI Registry®, representing over 95% of US centers performing PCI procedures. Data on over 750,000 patients undergoing PCI are collected annually. The CathPCI Registry® is approved as non-exempt human subject research under 45 CFR 46 Subpart A with a waiver of informed consent.

1.3 Study Rationale

The Coronary IVL New Enrollment Post Approval Registry is being conducted to better understand the utilization, safety, and effectiveness of the Shockwave Coronary IVL System in a ”real-world” setting following FDA approval.

2.0 DATA COLLECTION AND ANALYSIS

2.1 Data Collection Forms

Hospitals enter information from PCI procedures using an online form based on the CathPCI Registry® Data Collection Form. All data in the registry is site-reported; there is no independent adjudication of adverse events or core lab assessment of angiographic characteristics.

The CathPCI Registry® data collection form will be used for this study and captures information on each PCI case including:

- Demographics
- History and Risk Factors
- Pre-Procedure information (diagnostics, medications)
- Procedural details
    - Concomitant procedures
    - Target lesion characteristics (site-reported)
    - Devices used
    - Post-intervention stenosis (site-reported)
- Intra and post-procedure adverse events
- Discharge information
- Follow-up information at 30 days (adverse events, medications) (for sites that have opted in to report data beyond discharge)

Observational information on IVL-specific data will be collected on a separate IVL Addendum developed by ACC to support the PAS. The IVL Addendum form captures procedural information including:

- Ventricular arrhythmias during IVL pulses
- IVL balloon loss pressure or burst/rupture
- Serious dissections related to IVL burst/rupture
- Inappropriate ICD shocks during delivery of IVL pulses
- Adverse interactions between IVL and the PPM

2.2 Data Processing

The ACC will provide quarterly reports to Shockwave on procedures in the CathPCI Registry® where a Shockwave C^2 Coronary IVL catheter was used. The reports will include all fields contained in the Data Collection form and all fields in the IVL Addendum.

Shockwave will filter the data to identify patients with clinical characteristics similar to the population studied in the Disrupt CAD III study using the eligibility criteria outlined above.

2.3 Data Integrity

To ensure the validity of this dataset, the registries within the NCDR® employ a multipronged approach to ensure that high quality data are captured by the participating facilities as follows: (1) National audit program, (2) data quality checks and system alerts, (3) trained data capture personnel, (4) data capture software rules, and (5) data dictionary development.

1. National Audit Program

   Each registry within the NCDR® has a data audit conducted annually. Facilities are randomly selected for participation in the audit, which compares the medical record data provided to the auditor by the facility against the data collected in the registry.

2. Data Quality Checks and System Alerts

   Patient data are entered directly and securely to the registries through a web-based data collection tool. The Data Quality Check function provides real-time alerts that identify out-of-range errors and incomplete data so that participants may return to the relevant fields and correct/complete them.

   Prior to any large-scale analysis of any registry data, a number of additional range and logic checks will be conducted to ensure data completeness and validity.

3. Trained Data Collection Personnel

   Facilities participating in the NCDR® may employ varied personnel for data capture and entry. Physicians provide clinical and programmatic oversight and each facility has an assigned Registry Site Manager (RSM) to oversee data collection and registry reporting.

4. Data Capture Software Rules

   The NCDR® provides participating facilities a web-based tool to capture patient data that conforms to clinical and technical specifications for core elements, definitions, coding, editing, transmission, and encryption protocols. The rigor of these technical specifications explicitly impacts the quality of data captured by employing a series of rules that create a uniform platform for data to be collected across multiple facilities.

5. Data Dictionary Development

   The selection of registry data elements are based on input from clinical experts, regulatory agencies, and industry. These evidence-based elements are intended to measure clinical practice and patient outcomes for each patient, as well as identify patterns of clinical care and facilitate risk judgment.

2.4 Statistical Analysis

Interim results and final results will be analyzed using descriptive statistics; there is no formal hypothesis testing for the PAS. The sample size of 1000 is sufficient to accommodate approximately 30 PPM/ICD patients.