SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Intravascular Lithotripsy System
Device Trade Name:	Shockwave Intravascular Lithotripsy (IVL) System with Shockwave C^2 Coronary Intravascular Lithotripsy (IVL) Catheter
Device Procode:	QMG
Applicant's Name and Address:	Shockwave Medical, Inc. 5403 Betsy Ross Drive Santa Clara, CA, USA
Date(s) of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P200039
Date of FDA Notice of Approval:	February 12, 2021
Breakthrough Device:	Granted breakthrough device status on August 19, 2019 because the device and the proposed indication for use meet the criteria to be granted designation as a Breakthrough Device.

II. INDICATIONS FOR USE

The Shockwave Intravascular Lithotripsy (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.

III. CONTRAINDICATIONS

Shockwave Intravascular Lithotripsy (IVL) System with Shockwave C^2 Coronary IVL Catheter is contraindicated for the following:

- This device is not intended for stent delivery.
- This device is not intended for use in carotid or cerebrovascular arteries.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Shockwave Intravascular Lithotripsy (IVL) System with Shockwave C^2 Coronary IVL Catheter labeling.

V. DEVICE DESCRIPTION

The Shockwave Intravascular Lithotripsy (IVL) System consists of the Shockwave C^2 Coronary IVL Catheter, the IVL Generator, the IVL Connector Cable, and its accessories. The Shockwave C^2 Coronary IVL Catheter is used exclusively with these other components. The IVL Connector Cable is a remote actuator which connects the IVL Generator to the IVL Catheter and is used to activate the lithotripsy therapy from the IVL Generator. **Figure 1** shows the Shockwave IVL System that includes the Shockwave C^2 IVL Catheter, IVL Generator and IVL Connector Cable.

Figure 1: Shockwave IVL System with the Shockwave C^2 Coronary IVL Catheter

These system components are described in detail below.

A. Shockwave C^2 Coronary IVL Catheter

The Shockwave C^2 Coronary IVL Catheter is a proprietary lithotripsy device delivered through the coronary arterial system of the heart to the site of an otherwise difficult to treat calcified stenosis, including calcified stenoses that are anticipated to exhibit resistance to full balloon dilatation or subsequent uniform coronary stent expansion. The IVL Catheter contains integrated lithotripsy emitters for the localized delivery of acoustic pressure pulse therapy. The lithotripsy technology generates acoustic pressure pulses within the target treatment site, disrupting calcium within the lesion allowing subsequent dilatation of a coronary artery stenosis using low balloon pressure. The system consists of the IVL Catheter, IVL Connector Cable and IVL Generator. The Shockwave C^2 Coronary IVL Catheter is available in four (4) sizes: 2.5x12mm, 3.0x12mm, 3.5x12mm, and 4.0x12mm. The Shockwave C^2 Coronary IVL Catheter is compatible with a 6F guiding catheter and extensions, has a working length of 138cm, and shaft depth markers

at the proximal end. The catheter is coated with hydrophilic coating up to 22.75 cm from the distal tip to reduce friction during device delivery.

Refer to **Figure 2** below for Shockwave C^2 Coronary IVL Catheter components.

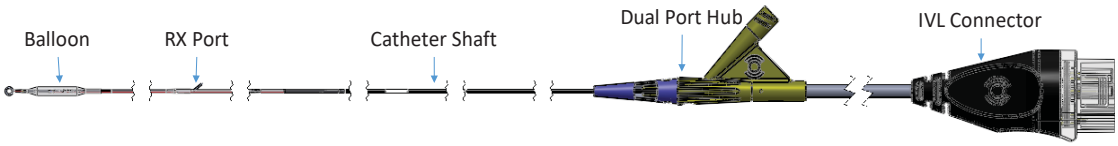

Figure 2: Shockwave C^2 Coronary IVL Catheter

The catheter shaft contains an inflation lumen, a guidewire lumen, and the lithotripsy emitters. The inflation lumen is used for inflation and deflation of the balloon with 50/50 saline/contrast medium. The guidewire lumen enables the use of a 0.014" guidewire to facilitate advancement of the catheter to and through the target stenosis. The system is designed as "Rapid Exchange" (Rx), so a 190cm - 300cm length guidewire is indicated. The emitters are positioned along the length of the balloon working length for delivery of lithotripsy therapy. The balloon is located near the distal tip of the catheter. Two (2) radiopaque marker bands within the balloon denote the working length of the balloon to aid in positioning of the balloon during treatment. The balloon is designed to provide an expandable segment of known length and diameter at a specific pressure. The proximal hub has two (2) ports: one for inflation/deflation of the balloon, and one for the connection to the IVL Connector Cable.

The Shockwave C^2 Coronary 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.

B. IVL Generator and IVL Connector Cable

The IVL Generator and Connector Cable are used with a Shockwave Medical IVL Catheter to deliver localized, lithotripsy-enhanced, dilatation of severely calcified, stenotic arteries. The IVL Generator, IVL Connector Cable, and IVL Catheters are designed to communicate during catheter preparation and patient treatment. This feature allows automatic setting of pulse parameters unique to each catheter type such as catheter pulse life.

The Shockwave Medical IVL Generator and IVL Connector Cable are intended for use with Shockwave Medical IVL Catheters only.

The IVL Generator is provided non-sterile and is reusable. The IVL Generator is shipped with the following items:

- IV Pole mounts for IVL Generator and Charger
- Charger Module
- IVL Connector Cable
- AC Mains Cable

- Operator's Manual

The product is provided as an assembly including the IVL Generator, IVL Pole Mount, and Charger, as shown in **Figure 3** below.

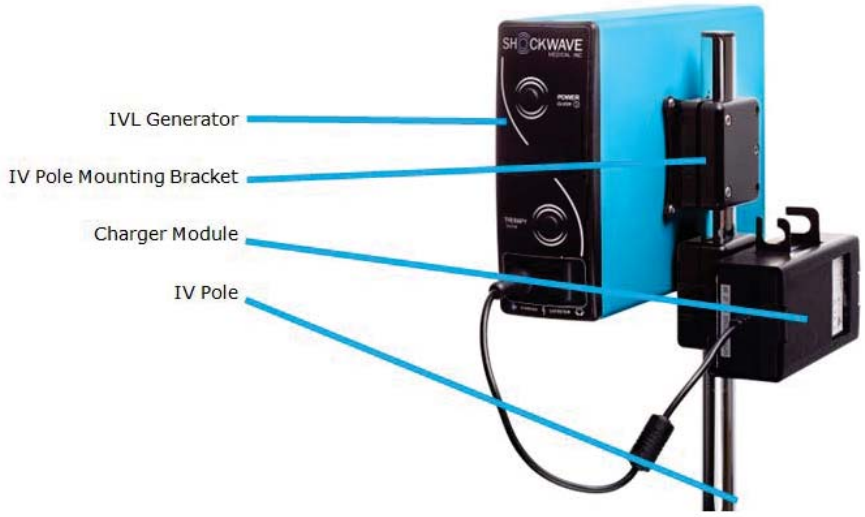

Figure 3: IVL Generator (mounted on IV Pole, not supplied)

The IVL Generator is supplied with a non-sterile and reusable IVL Connector Cable. The IVL Connector Cable is used with any appropriately sized sterile sleeve.

The IVL Connector Cable is a remote actuator that connects the IVL Generator to the Shockwave C^2 Coronary IVL Catheter and is used to activate lithotripsy energy from the IVL Generator to the balloon. The IVL Connector Cable is shown below in **Figure 4**.

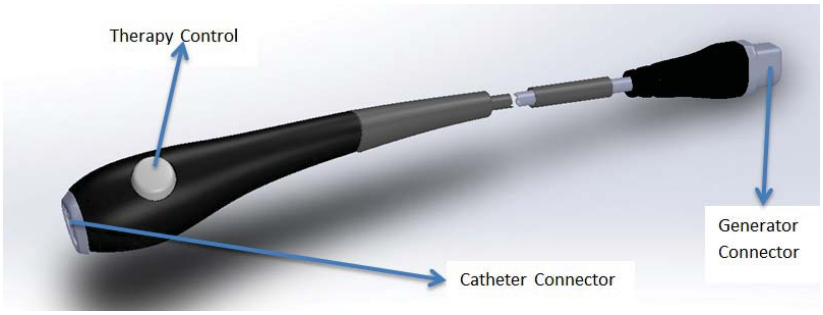

Figure 4: IVL Connector Cable

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for vessel preparation of calcified lesions prior to coronary stent implantation, including rotational or orbital atherectomy, high pressure balloon angioplasty, and cutting or scoring balloon angioplasty. Each alternative has its own advantages and disadvantages. Patients should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The Shockwave IVL System with the original Shockwave C^2 Coronary IVL Catheter is available for commercial distribution in the countries listed in **Table 1**. The modified Shockwave C^2 Coronary IVL Catheter studied under IDE G180146, which has a slight increase in the balloon double wall thickness, is not marketed for commercial distribution in any geography to date. The Shockwave Intravascular Lithotripsy (IVL) System with Shockwave C^2 Coronary IVL Catheter has not been withdrawn from any country for reasons relating to device safety and effectiveness.

Table 1: Commercial Availability of the Shockwave IVL System with Shockwave C^2 Coronary IVL Catheter

Bahrain	Israel	Qatar
Chile	Kingdom of Saudi Arabia (KSA)	Serbia
European Union	Lebanon	South Africa
Hong Kong	New Zealand	Turkey
India	Oman	UAE

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device.

- Abrupt vessel closure
- Allergic reaction to contrast medium, anticoagulant and/or antithrombotic therapy
- Aneurysm
- Arrhythmia
- Arteriovenous fistula
- Bleeding complications
- Cardiac tamponade or pericardial effusion
- Cardiopulmonary arrest
- Cerebrovascular accident (CVA)
- Coronary artery/vessel occlusion, perforation, rupture or dissection
- Coronary artery spasm
- Death
- Emboli (air, tissue, thrombus or atherosclerotic emboli)
- Emergency or non-emergency coronary artery bypass surgery
- Emergency or non-emergency percutaneous coronary intervention
- Entry site complications
- Fracture of the guide wire or failure/malfunction of any component of the device that may or may not lead to device embolism, dissection, serious injury or surgical

intervention

- Hematoma at the vascular access site(s)
- Hemorrhage
- Hypertension/ Hypotension
- Infection/sepsis/fever
- Myocardial Infarction
- Myocardial Ischemia or unstable angina
- Pain
- Peripheral Ischemia
- Pseudoaneurysm
- Renal failure/insufficiency
- Restenosis of the treated coronary artery leading to revascularization
- Shock/pulmonary edema
- Slow flow, no reflow, or abrupt closure of coronary artery
- Stroke
- Thrombus
- Vessel closure, abrupt
- Vessel injury requiring surgical repair
- Vessel dissection, perforation, rupture, or spasm

In addition, patients may be exposed to other risks associated with coronary interventional procedures, including risks from conscious sedation and local anesthetic, the radiographic contrast agents used during angiography, the drugs given to manage the subject during the procedure, and the radiation exposure from fluoroscopy.

Risks identified as related to the device and its use:

- Allergic/immunologic reaction to the catheter material(s) or coating
- Device malfunction, failure, or balloon loss of pressure leading to device embolism, dissection, serious injury or surgical intervention
- Atrial or ventricular extrasystole
- Atrial or ventricular capture

These risks are similar to other commercially available devices with similar indications for use and are reported in the published literature.

For specific adverse events that occurred in the clinical study, please see Section X below.

IX. SUMMARY OF NONCLINICAL STUDIES

A. Laboratory Studies

1. Biocompatibility

Biocompatibility of the Shockwave IVL System materials was evaluated based on device contact and duration in accordance with ISO 10993-1 and FDA Guidance, Use of International Standard ISO 10993-1, "Biological Evaluation of Medical Devices Part 1: Evaluation and testing within a risk management process," Attachment A, (guidance issued June 16, 2016). The IVL Generator and IVL Connector Cable are non-patient contacting and provided non-sterile; therefore, biocompatibility testing was not required for these components.

The Shockwave C^2 Coronary IVL Catheter is classified as an externally communicating blood contact limited exposure device (<24 hours). A summary of the required biocompatibility testing for the device and results can be found in **Table 2**.

Table 2: Summary of Biocompatibility Testing

Test Performed	Test Description	Purpose	Results
Cytotoxicity	MEM Elution Using L-929 Fibroblast Cells ISO 10993-5 ISO 10993-12	To evaluate whether an extract of the test article could cause cytotoxicity using the L929 mouse fibroblast cell culture.	**Pass, non-cytotoxic**
Sensitization	ISO Guinea Pig Maximization Sensitization Test ISO 10993-10 ISO 10993-12	To evaluate the allergenic potential or sensitizing capacity of the test article in guinea pigs.	**Pass, non-sensitizing**
Irritation or Intracutaneous Reactivity	ISO Intracutaneous Reactivity Test ISO 10993-10 ISO 10993-12	To evaluate local dermal irritation effects of leachables following intracutaneous injections into rabbits.	**Pass, non-irritant**
Systemic Toxicity (acute)	ISO Acute Systemic Injection Test (2 Extracts) ISO 10993-11 ISO 10993-12	To evaluate acute systemic toxicity of leachables extracted from the test article following a single intravenous or intraperitoneal injection in mice.	**Pass, non-toxic**

Test Performed	Test Description	Purpose	Results
	Materials Mediated Rabbit Pyrogen ISO 10993-11 ISO 10993-12	To determine if a saline extract of the test article causes a febrile response in rabbits.	**Pass, non-pyrogenic**
Hemocompatibility	ISO 10993-4 - Complement Activation SC5b-9 with supplied comparison ISO 10993-4 ISO 10993-12	To measure the compliment activating potential of the test article in human plasma.	**Pass, Not a complement activator**
	ISO 10993-4 - Hemolysis Test (ASTM F756) Extract and Direct Contact Methods ISO 10993-4 ISO 10993-12 ASTM Guideline F619-14 ASTM Guideline F756-13	To determine the ability of a test article or its extract, to destroy red blood cells with the subsequent release of the hemoglobin.	**Pass, non-hemolytic**
Thrombogenicity	Thromboresistance Evaluation conducted during Chronic GLP Animal Study ISO 10993-4 ISO 10993-12	To evaluate the potential of the test article to cause thrombus formation when placed in the vasculature of swine.	**Pass, Non-thrombogenic**
Material Characterization and Toxicology Risk Assessment	Extractables ISO 10993-18 ISO 10993-17 ISO 10993-12	To assess the extractables profile of the submitted test article.	**Compounds consistent with manufacturing materials, and amounts do not raise toxicity concerns.**

2. **Bench Testing**

Engineering bench testing of the Shockwave IVL System with Shockwave C^2 Coronary IVL Catheter was conducted to verify the design outputs meet the design requirements and to confirm the safety and performance of the product from a non-clinical testing perspective.

Shockwave C^2 Coronary IVL Catheter

Bench testing to assess the safety and effectiveness of Shockwave C^2 Coronary IVL Catheter was conducted in accordance with FDA Guidance Class II Special Controls Guidance Document for Certain Percutaneous Transluminal Coronary Angioplasty (PTCA) Catheters.

Table 3 includes the tests performed, the objective of the tests, the acceptance criteria, and the result of the test.

Table 3: Summary of Functional Testing Performed on the Shockwave C^2 Coronary IVL Catheter

Test	Test Summary/Purpose	Acceptance Criteria	Results
Visual Inspection	Verify there is no damage to the balloon and catheter after removal of the protective sheath.	The catheter and balloon shall be free of damage after removal of balloon protective sheath.	**PASSED**
Inflation port compatibility	Determine if the inflation port in the luer connector meets the functional requirements.	Inflation ports shall meet requirements for a luer fitting.	**PASSED**
Guidewire Compatibility	Determine the system compatibility with 0.014" guide wire.	The system shall be compatible with 0.014" guide wires.	**PASSED**
Guide Catheter Compatibility	Ensure the catheter components and seals have a max profile that can be inserted through a 6F Catheter without excessive force.	The system shall be compatible with 6F Guide Catheters.	**PASSED**
Nominal Balloon Diameter	Verify the balloon diameter is within the target diameter when inflated to nominal pressure.	The balloon diameter at nominal pressure shall be within a clinically acceptable range.	**PASSED**
Balloon Working Length	Verify the balloon working length at nominal pressure.	The balloon working length at nominal pressure shall be nominally 12 mm.	**PASSED**
Balloon Compliance	Verify the balloon has acceptable diameter growth from nominal.	The balloon diameter at 10 ATM shall be within a clinically acceptable range	**PASSED**

Test	Test Summary/Purpose	Acceptance Criteria	Results
		compared to nominal.	
Inflation Time	Verify the time it takes to inflate the system to nominal pressure.	Inflation time to nominal pressure shall support hemodynamic flow.	**PASSED**
Deflation Time	Verify the time it takes to deflate the system from nominal pressure.	Deflation time from RBP (10 ATM) shall not disrupt hemodynamic flow.	**PASSED**
Rated Burst Pressure (RBP)	Verify the minimum system rated burst pressure of the balloon and catheter.	Min RBP (for shaft, seals and balloon) shall be 10 ATM.	**PASSED**
Fatigue (Multiple Inflations)	Verify the catheter can withstand multiple inflations without failure.	The catheter shall be durable enough to withstand 20 inflation/deflation cycles up to RBP of 10 ATM.	**PASSED**
Crossing Profile	Verify the balloon folded diameter.	The crossing profile for each balloon (shall be within the range $\leq$ 0.044" and $\leq$ 0.047".	**PASSED**
Distal Tip Profile	Determine the distal/tip maximum outer diameter.	Max tip entry OD shall be consistent with a crossing profile of $\leq$ 0.047".	**PASSED**
Distal Tip Length	Determine the distal tip length of the catheter.	The distal tip length shall be nominally 4.0 mm.	**PASSED**
Tip Durability	Verify the distal tip maintains its integrity after simulated use.	The distal tip shall not excessively deform (i.e., split or excessive fold / crease) or break when tracking across a tight lesion.	**PASSED**
Coating Length	Verify the hydrophilic coating length on the catheter.	The tolerance interval for coating length shall be nominally 22.75 cm.	**PASSED**
Coating Lubricity	Verify the frictional force of the catheter.	Catheter shaft friction shall have a pull force of $\leq$150 grams.	**PASSED**

Test	Test Summary/Purpose	Acceptance Criteria	Results
Coating Uniformity	Verify the integrity / uniformity of the hydrophilic coating on the catheter after simulated use.	Coverage surface area shall allow for a frictional force of ≤150 grams.	**PASSED**
Particulate Evaluation	Characterize the generated particles sizes and counts.	Particulate generation shall be ≤6000, ≤600, and ≤60 for 10 µm, 25 µm, and 50 µm, respectively.	**PASSED**
Marker Band Spacing	Verify the spacing between the distal and proximal marker bands on the catheter.	The spacing between the balloon marker bands shall be nominally 12 mm.	**PASSED**
Marker Band Alignment	Verify the distal marker band alignment to the distal balloon shoulder.	The balloon distal marker band shall align to the distal shoulder of the balloon.	**PASSED**
Catheter Working Length	Verify the working length of the catheter.	Working length of the catheter shall be nominally 138 cm.	**PASSED**
Catheter Tip to Rx Port Length	Verify the guide wire lumen length of the catheter.	The location of the Rx port shall be sufficient to prevent loss of the guide wire.	**PASSED**
Length from Rx Port to Hypotube Bond	Verify the length of the Rx port to the hypotube bond.	The length from the Rx port to hypotube bond shall allow for acceptable flexibility.	**PASSED**
Catheter Shaft Marking Length	Verify the shaft marking lengths.	The marks on the catheter shaft shall allow for anatomical positioning	**PASSED**
Kink Resistance / Flexibility	Verify the flexibility / kink resistance of the different shafts /sections of the catheter.	Catheter shall not kink when tracking through tortuous anatomy.	**PASSED**

Test	Test Summary/Purpose	Acceptance Criteria	Results
Distal / Tip & Proximal Balloon Bond Tensile Strength	Verify the tensile strength of the catheter's balloon distal/tip and proximal bonds.	The tensile force required to break the catheter's bonds shall be within a sufficient range to prevent component separation.	**PASSED**
Catheter Bonds Strength	Verify the tensile strength of all catheter bonds	The tensile force required to break the catheter's bonds shall be within a sufficient range to prevent component separation.	**PASSED**
Catheter Torsional Strength	Verify the ability of the catheter to withstand torsional force during simulated use.	Catheter shall withstand torsional rotation.	**PASSED**
Emitters and Marker Band Integrity	Verify the marker bands and emitters remain in position and free of damage after pre-conditioning and simulated use.	Emitters and marker bands are functional upon insertion treatment and retraction.	**PASSED**
System Leakage	Verify the catheter is free of leakage during use.	The system shall be free of leakage after simulated use in a coronary bench top model and after lithotripsy treatment.	**PASSED**
System Burst	Verify the catheter's burst pressure.	Catheter sub-assembly shall not rupture during test. Catheters shall not rupture or leak.	**PASSED**
Temperature Rise Test	Verify the temperature on the balloon exterior during lithotripsy treatment.	Temperature rise sufficient in that it would not cause tissue damage during use.	**PASSED**
Catheter Connector Extension Length	Verify the connector extension length.	The connector length shall be adequate to connect with accessory devices.	**PASSED**
Sonic Output	Verify the average mechanical energy generated by the emitters.	The sonic energy shall be sufficient to crack vascular calcium.	**PASSED**

Test	Test Summary/Purpose	Acceptance Criteria	Results
Emitter Spacing and Alignment	Verify the distance between the emitters and between the emitter and distal marker band after simulated use of the catheter.	The spacing between emitters and distal marker band shall be within a range to allow for sufficient sonic output.	**PASSED**
Maximum Total Pulse Cycling	Verify the catheter can pulse up to a minimum of 80 pulses without failure.	Product shall deliver a minimum of 80 pulses without failure.	**PASSED**
External Surface	Verify the catheter is free of extraneous matter prior to use.	The catheter external surface shall be free of extraneous matter.	**PASSED**

IVL Generator and Connector Cable

Testing was conducted on the IVL System (IVL Generator, IVL Connector Cable, charging power supply, and IVL Catheter) according to harmonized test standards for active medical devices and to software validation requirements, following uniquely-designed test protocols for the device. In addition, the IVL Generator and Connector Cable met international certification requirements using CB scheme by Underwriters Laboratories (UL), Shockwave Medical's test laboratory for safety in compliance ANSI AAMI ES60601-1:2005/(R)2012 and A1:2012, C1:2009/(R)2012 and A2:2010/(R)2012 (Consolidated Text) Medical electrical equipment - Part 1: General requirements for basic safety and essential performance (IEC 60601-1:2005, MOD), and IEC 60601-1-6 Edition 3.1 2013-10 Medical electrical equipment - Part 1-6: General requirements for basic safety and essential performance - Collateral standard: Usability. The IVL System is intended for use in a professional healthcare environment and was certified for electrical safety by UL to IEC 60601-1-2 Edition 4.0 2014-02 Medical electrical equipment - Part 1-2: General requirements for basic safety and essential performance - Collateral Standard: Electromagnetic disturbances - Requirements and tests.

Software Testing
The software for the IVL Generator was verified/validated and documented according to the FDA guidance document "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices."

B. Animal Studies

Shockwave Medical conducted one (1) acute and one (1) chronic swine animal study with the Shockwave Intravascular Lithotripsy (IVL) System Shockwave C^2 Coronary IVL Catheter according to Good Laboratory Practice (GLP) requirements 21 CFR 58 to evaluate the safety of the Shockwave IVL System. The objective of these studies was to

assess the safety of mechanical energy applied during IVL followed by stenting, compared to balloon angioplasty alone followed by stenting. The IVL Test group addressed the clinical use case of potential treatment overlap when two separate IVL balloons are used.

In regard to outcomes, there was no mortality, significant morbidity, or adverse events noted during the experimental procedures or in life observation period of either study. Some notable pathology observations in the acute study included epicardial hemorrhage with fat necrosis overlying almost all of the test article treated arteries on gross examination as well as histopathology, which was absent in the balloon angioplasty controls. Prominent epicardial fat swelling was also noted on the surface of all of the hearts in the subacute study, although it is not clear whether the findings were associated with the test or control treated arteries, or both. Vascular wall inflammation and mean diameter stenosis was moderate and similar among groups in both studies, and in-stent lumen narrowing <50% was observed by the operator in all stented arteries at terminal angiography. It was hypothesized that outcomes were potentially related to excessive mechanical overstretch, treatment of non-diseased, non-calcified vessels, and/or limitations of the animal model.

Given the limitations of the animal model, mitigation for these observations were addressed in the clinical study by evaluating angiographic and intravascular imaging outcomes during the procedure, adjudicated in-hospital outcomes, and adjudicated 30-day clinical outcomes on the first 30 pivotal subjects enrolled. These clinical data supported the continued evaluation of the Shockwave IVL device in the full pivotal clinical study under IDE G180146.

All Good Laboratory Practice (GLP) study objectives were met. Procedural observations, angiographic findings, and the histopathological results of the GLP studies demonstrate that IVL can be safely delivered in conjunction with the clinical standard of care (stenting). No significant difference between the IVL test and balloon angioplasty control groups was observed in the studies.

The studies support the conclusion that there are no safety concerns associated with the use of the Shockwave IVL System.

C. Additional Studies

1. Sterilization

The Shockwave C^2 Coronary IVL Catheter is sterilized using validated electron beam irradiation (e-beam) sterilization process per method VDmax25 that provides a sterility assurance level (SAL) of 10^{-6}. The Shockwave C2 Coronary IVL Catheter is a sterile, single use medical device and is not intended for reuse or re-sterilization. Validation and annual revalidation are completed based on the standards in ISO 11135-1:2015 Sterilization of health care products-Radiation-Part 1: Requirements for development, validation, and routine control of a sterilization process for medical

devices. The IVL Generator, IVL Connector Cable and accessories are provided non-sterile.

2. **Shelf Life**

A shelf life of 2 years has been established for the Shockwave C2 Coronary IVL Catheter based on product and package shelf life testing. The Shockwave C2 Coronary IVL Catheter was tested following accelerated aging to an equivalent of 2 years per an approved shelf life protocol. Testing demonstrated the Shockwave C2 Coronary IVL Catheter met the established acceptance criteria.

The IVL Generator and Connector Cable are re-usable durable medical equipment. The battery life of the IVL Generator and Connector Cable was designed and validated to provide a useful life of 3 years or more based on actual usage.

3. **Packaging**

The Shockwave C2 Coronary IVL Catheters are single use, disposable, sterile devices. Catheter packaging was designed and validated to ensure the sterility and integrity of individually packaged and sealed devices. Each device is individually packaged in a catheter hoop with a hoop connector on a Backer Card and placed into a peelable pouch labeled with the size of the balloon catheter. The sealed pouch is then packaged in a shelf carton and is secured with a tamperproof seal on the shelf carton.

The IVL Generator and Connector Cable are re-usable medical equipment and are provided non-sterile. The IVL Generator and Connector Cable are placed in a durable liner along with an appropriate power cord(s), AC power adaptor, and mounting accessories in a shipper. Packaging validation was conducted in accordance with ISTA 2A requirements. The IVL Connector Cable can also be provided separately as a replacement component.

X. SUMMARY OF PRIMARY CLINICAL STUDY

Shockwave Medical, Inc. performed a clinical study to establish a reasonable assurance of safety and effectiveness of the Shockwave Coronary Lithotripsy System (IVL) for the treatment of severely calcified, stenotic *de novo* coronary lesions prior to stenting in the US and in France, Germany, and the United Kingdom under IDE# G180146. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

Patients were treated between January 9, 2019 and March 27, 2020. The database for this PMA reflected data collected through June 28, 2020 and included 431 enrolled patients (47 roll-in, 384 pivotal) patients. There were 47 investigational sites (38 US and 9 OUS).

The Disrupt CAD III study was a prospective, multicenter, single-arm, global clinical study.

Study Endpoints were evaluated by three (3) external groups:

- Independent Angiographic Core Lab: An independent core laboratory provided an unbiased assessment of all imaging utilized in the endpoint assessments. All imaging was performed in accordance with the core laboratory's recommended protocol which was provided to the sites.
- Independent Clinical Events Committee (CEC): CEC served as a forum for review and adjudication of all major adverse cardiac events (MACE).
- Independent Data Safety Monitoring Board (DSMB): DSMB reviewed safety data on a regular basis and monitored the continuing validity and scientific merit of the trial.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the Disrupt CAD III study was limited to patients who met the following 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 index 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, 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 (LVEF) >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

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

Patients were <u>not</u> permitted to enroll in the Disrupt CAD III Study if they met any of the following exclusion criteria:

1. Any comorbidity or condition which may reduce compliance with the protocol, including follow-up visits
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
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. 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
27. Definite or possible thrombus (by angiography or intravascular imaging) in the target vessel
28. Evidence of aneurysm in target vessel within 10 mm of the target lesion
29. Target lesion is an ostial location (LAD, LCX, or RCA, within 5 mm of ostium)

or an unprotected left main lesion
30. Target lesion is a bifurcation with ostial diameter stenosis ≥30%
31. Second lesion with >50% stenosis in the same target vessel as the target lesion including its side branches
32. Target lesion is located in a native vessel that can only be reached by going through a saphenous vein or arterial bypass graft
33. Previous stent within the target vessel implanted within the last year
34. Previous stent within 10 mm of the target lesion regardless of the timing of its implantation
35. Angiographic evidence of a dissection in the target vessel at baseline or after guidewire passage

2. Follow-up Schedule

All patients were scheduled for follow-up examinations at 30 days and 6, 12, and 24 months post-procedure.

Table 4 summarizes the evaluations and assessments performed pre- and post-operatively.

Table 4: Schedule of Events and Evaluations

Assessment	Screening/ Baseline[1] (Day -14 to Day 0)	Enrollment/ Procedure (Day 0)	12-24 hours post-procedure, or at discharge[2]	Discharge	30 Days (±7 days)	6, 12, 24 Months (±30 days)
Informed Consent	X					
Medical History	X					
Physical Examination/Vital Signs	X					
New York Heart Association (NYHA) Classification	X					
Canadian Cardiovascular Society (CCS) Angina Classification	X				X	X
Laboratory Assessments	Platelet count, creatinine, hemoglobin	CK-MB (required if drawn from the sheath)[3], troponin[4]	CK-MB[3], troponin, creatinine, hemoglobin			

Assessment	Screening/ Baseline[1] (Day -14 to Day 0)	Enrollment/ Procedure (Day 0)	12-24 hours post-procedure, or at discharge[2]	Discharge	30 Days (±7 days)	6, 12, 24 Months (±30 days)
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 imaging		X[7]				
Sub-study: PPM/ICD Device Interrogation		X[8]	X			
Sub-study: Hemodynamics		X[9]				
Medication use	X	X		X	X	X
Adverse Event Assessment		X		X	X	X

1. Screening/Baseline data collection may occur any time within 14 days of the procedure
2. Laboratory assessments and ECG should be collected 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.

7. For subjects that have consented to the OCT sub-study
8. For subjects that have consented to the PPM/ICD sub-study
9. For subjects that have consented to the hemodynamics sub-study

The key timepoints are shown below in the tables summarizing safety and effectiveness.

3. Clinical Endpoints

Primary Safety Endpoint
The primary safety endpoint was freedom from major adverse cardiac events (MACE) within 30 days of the index 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 (TVR) defined as revascularization at the target vessel (inclusive of the target lesion) after the completion of the index procedure.

The primary safety endpoint was pre-specified to be compared to a performance goal (PG) of 84.4% at a one-sided alpha level of 0.05. The pre-specified null and alternative hypotheses are as follows:

$$H_0: \pi_S \leq 84.4\%$$
$$H_A: \pi_S > 84.4\%$$

where π_S is the true 30-day MACE free rate.

Primary Effectiveness Endpoint
The primary effectiveness endpoint was Procedural Success defined as stent delivery with a residual stenosis <50% (angiographic core laboratory assessed) and without in-hospital MACE. The primary effectiveness endpoint was planned to be compared to a PG of 83.4% at a one-sided alpha level of 0.05. The pre-specified null and alternative hypotheses are as follows:

$$H_0: \pi_E \leq 83.4\%$$
$$H_A: \pi_E > 83.4\%$$

where π_E is the procedure success rate.

The primary safety and effectiveness endpoints are evaluated based on comparisons to pre-specified performance goals derived from relevant published reports including the ORBIT II trial which studied a similar population [1].

The overall sample size for Disrupt CAD III was driven by the primary safety endpoint. The endpoint was met if the one-sided lower 95% confidence limit was greater than the PG. Assuming a true 30-day MACE free rate of 89.6%, an attrition rate of 5%, a sample size of 392 patients (minimum 372 patients) was required to achieve approximately 90% power to meet the endpoint based on a performance goal of 84.4% at a one-sided α-level of 0.05. For the primary effectiveness endpoint, the expected procedure success rate was 88.9%, and with 5% attrition, a sample size of 360 patients provides at least 90% power to meet the primary effectiveness endpoint. While 392 patients were planned to be enrolled, only 384 patients were enrolled due to enrollment issues associated with the COVID-19 pandemic. However, this still met the minimum required sample sizes, as described above.

Secondary Endpoints

Secondary endpoints evaluated in the Disrupt CAD III study included:

- 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, 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 [2] and the Society for Cardiovascular Angiography and Interventions (SCAI) [3] definitions at 30 days, 6, 12 and 24 months.

B. Accountability of PMA Cohort

At the time of database lock, of 384 patients enrolled in the PMA study 99.7% (383/384) are available for analysis at the primary endpoint timepoint, the 30-day post-operative visit.

Follow up compliance through the 30-day follow-up visit is presented in **Table 5** below.

Table 5: Subject Disposition through 30 Days

Disposition Category	Total
Signed Informed Consent	749
Screen Failure	318
Enrolled	431
Analysis Sets	
Roll-in (RI) Population[1]	47
Pivotal Analysis (PA) Set[2]	384
Pivotal Analysis (PA) Set	
Discontinued	0.3% (1/384)
Lost to follow-up	0.3% (1/384)
Withdrawn consent	0.0% (0/384)
Investigator's decision	0.0% (0/384)
Death	0.5% (2/384)

1. The first subject enrolled at each site was considered a roll-in and was not included in the pivotal cohort. All subsequent enrolled subjects at a given site were included in the Pivotal Analysis Set.
2. The Pivotal Analysis Set includes all pivotal subjects and is the cohort used for hypothesis testing of the primary safety and effectiveness endpoints. Roll-ins are excluded.

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a pivotal study performed in the US. **Table 6** summarizes the pivotal subject demographics. The mean age of all subjects enrolled in the pivotal cohort was 71.2 ± 8.6 years, ranging from 43 to 95 years. The majority of subjects (76.6%, 294/384) were male and predominantly white (82.8%, 318/384). Mean body mass index (BMI) in the pivotal cohort was 29.2 ± 5.0 kg/m^2.

Table 6: Subject Demographics for Disrupt CAD III Subjects (Pivotal Analysis Set)

Parameter	Pivotal (N=384)
Age (years)	
N	384
Mean ± Std Dev	71.2 ± 8.6
Median (Q1,Q3)	71.0 (66.0, 77.0)

Parameter	Pivotal (N=384)
Min, Max	43.0, 95.0
Gender % (n/N)	
Male	76.6% (294/384)
Female	23.4% (90/384)
Geography % (n/N)	
United States	87.2% (335/384)
Europe	12.8% (49/384)
Race % (n/N)	
White	82.8% (318/384)
Black and African American	3.1% (12/384)
Asian	3.4% (13/384)
American Indian or Alaska Native	0.5% (2/384)
Native Hawaiian or Other Pacific Islander	0.3% (1/384)
Not Specified	9.9% (38/384)
Ethnicity % (n/N)	
Hispanic or Latino	4.2% (16/384)
Not Hispanic or Latino	85.9% (330/384)
Not Specified	9.9% (38/384)
Body Mass Index (kg/m^2)	
N	384
Mean ± Std Dev	29.2 ± 5.0
Median (Q1,Q3)	28.3 (25.9, 32.3)
Min, Max	18.8, 52.6
Std Dev= Standard deviation; Q1 = First quartile; Q3 = Third quartile	

Table 7 summarizes the medical history of the pivotal subjects. Diabetes was reported in 40.1% (154/384) of the pivotal subjects enrolled. The majority of pivotal subjects suffered from hypertension (89.1%, 342/384) and hyperlipidemia (89.1%, 342/384), 46.9% (180/384) had prior percutaneous coronary interventions, 9.4% (36/384) had prior coronary artery bypass graft (CABG), 18.0% (69/384) had a history of myocardial infarction, and 12.0% (46/384) had renal insufficiency. Former smokers were reported in 43.0% (165/384) of subjects, while 12.2% (47/384) were current smokers.

Table 7: Medical History (Pivotal Analysis Set)

Parameter	Pivotal (N=384)
Diabetes Mellitus	40.1% (154/384)
Type	
Type I	1.0% (4/384)
Type II	39.1% (150/384)
Treatment	
Medically Treated	35.5% (136/383)
Insulin (with or without oral meds)	14.1% (54/383)
Oral Meds (with or without insulin)	29.8% (114/383)
Insulin Plus Oral Meds	8.4% (32/383)
Insulin Alone	5.7% (22/383)
Oral Meds Alone	21.4% (82/383)
Diet	4.4% (17/383)
Hyperlipidemia	89.1% (342/384)
Hypertension	89.1% (342/384)
Prior Stroke or TIA	7.6% (29/384)
Stroke	5.5% (21/384)
TIA	3.9% (15/384)
Myocardial Infarction	18.0% (69/384)
Prior Coronary Intervention[1]	46.9% (180/384)
Prior CABG	9.4% (36/384)
Prior Non-coronary Interventional or Surgical Heart Procedure	3.1% (12/384)
Aortic Valve Replacement	1.8% (7/384)
Transcatheter	0.3% (1/384)
Surgical	1.6% (6/384)
Other	1.6% (6/384)
Peripheral Vascular Disease	13.0% (50/384)
Congestive Heart Failure	12.2% (47/384)
Arrhythmia	20.6% (79/384)
Ventricular	4.2% (16/384)
Atrial	15.1% (58/384)
Ventricular and Atrial	1.3% (5/384)
Pacemaker	4.7% (18/384)
ICD/CRT-D	1.6% (6/384)
COPD	9.4% (36/384)

Parameter	Pivotal (N=384)
Active Peptic Ulcer or Upper Gastrointestinal Bleeding	0.3% (1/384)
Smoking/tobacco use	55.2% (212/384)
Current/recent (within last 3 months)	12.2% (47/384)
Former (stopped > 3 months)	43.0% (165/384)
Renal insufficiency[2]	12.0% (46/384)

TIA = transient ischemic attack; CABG = coronary artery bypass graft; ICD = implantable cardioverter defibrillator; CRT-D = cardiac resynchronization therapy

1. Percutaneous transluminal coronary angioplasty (PTCA), drug-eluting stent (DES) or atherectomy procedures.
2. An increase in serum creatinine of ≥1.0 mg/dl over previous value requiring medical treatment but which does not require dialysis to resolve.

Pre-procedure angiographic characteristics as assessed by the core lab for the pivotal subjects are presented in **Table 8**. The left anterior descending artery (LAD) was the most common target vessel (56.5%, 217/384)), with a baseline reference vessel diameter (RVD) of 3.03 ± 0.47 mm and minimal lumen diameter (MLD) of 1.06 ± 0.36 mm. Percent diameter stenosis (DS) on quantitative coronary angiography was 65.1 ± 10.8% with a lesion length of 26.09 ± 11.68 mm. Severe calcification was present in 100.0% of the lesions with a calcified length of 47.85 ± 18.81 mm. Side branch involvement was noted in 29.9% (115/384) of subjects (denoted as bifurcation/trifurcation).

Table 8: Pre-Procedural Angiography (Core Lab) (Pivotal Analysis Set)

Parameter	Pivotal (N=384)
Target Lesion Vessel, % (n/N)	
LAD	56.5% (217/384)
RCA	29.2% (112/384)
Circumflex	12.8% (49/384)
Left Main	1.6% (6/384)
Bypass graft	0.0% (0/384)
Lesion Length (mm)	
N	381
Mean ± Std Dev	26.09 ± 11.68
Median (Q1, Q3)	24.92 (16.74, 33.71)
Min, Max	3.93, 74.57
> 27 mm	44.1% (168/381)
RVD[1] (mm)	
N	381

Parameter	Pivotal (N=384)
Mean ± Std Dev	3.03 ± 0.47
Median (Q1, Q3)	3.00 (2.68, 3.33)
Min, Max	1.99, 4.68
<2.25 mm	1.6% (6/381)
MLD (mm)	
N	381
Mean ± Std Dev	1.06 ± 0.36
Median (Q1, Q3)	1.08 (0.83, 1.31)
Min, Max	0.10, 2.16
% Diameter Stenosis (DS)[1]	
N	381
Mean ± Std Dev	65.1 ± 10.8
Median (Q1, Q3)	63.3 (56.3, 72.5)
Min, Max	50.0, 96.7
Eccentric[2], % (n/N)	3.1% (12/384)
Calcification, % (n/N)	100.0% (384/384)
None or Mild	0.0% (0/384)
Moderate	0.0% (0/384)
Severe	100.0% (384/384)
Calcification Length (mm)	
N	384
Mean ± Std Dev	47.85 ± 18.81
Median (Q1, Q3)	43.84 (32.89, 60.45)
Min, Max	15.40, 106.94
Bifurcation/Trifurcation, % (n/N)	29.9% (115/384)

LAD = left anterior descending coronary artery; RCA = right coronary artery; RVD = reference vessel diameter; MLD = minimal lumen diameter; Std Dev = standard deviation; Q1 = first quartile; Q3 = third quartile

1. Interpolated
2. Eccentric is defined as a vessel that has only one of its luminal edges compromised by more than 25%.

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the pivotal analysis cohort of 383 pivotal patients available for the 30-day evaluation. The key safety outcomes for this study are

presented below in **Table 9**.

As shown, the observed 30-day MACE free rate was 92.2% 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 that the 30-day MACE free rate was at most 84.4% was rejected, and the primary safety endpoint was met (p<0.0001).

Table 9: Primary Safety Endpoint (Pivotal Analysis Set)

Primary Safety Endpoint	% (n/N) [95% Lower Confidence Interval][1]	Hypothesis	*P* value[2]	Conclusion
Freedom from MACE within 30 days post-procedure[3]	92.2% (353/383)[4] [89.9%]	H_0: $\pi_s \leq$ 84.4% H_A: $\pi_s >$ 84.4%	<0.0001	Performance Goal Met

1. 95% lower confidence interval is calculated based on a one-sided asymptotic Wald (normal approximation-based) confidence interval for a binomial proportion. The standard error is calculated from the sample proportion.
2. P-value is calculated based on a one-sided asymptotic Wald (normal approximation-based) test for a binomial proportion at a 0.05 level of significance. The standard error is calculated from the sample proportion.
3. All MACE were adjudicated by an independent CEC. If full data were not available, the event was adjudicated based on the clinical judgement of the independent CEC. Missing data were not imputed and a sensitivity analysis was performed to assess endpoint robustness.
4. One subject was excluded from the primary safety endpoint analysis due to insufficient follow-up (< 23 days).

Components of the composite primary safety endpoint are shown in **Table 10**. The majority of 30-day events (27 of 30, 90.0%) occurred in the peri-procedural period as indicated by the in-hospital MACE rate of 7.0% (27/384).

Table 10: Primary Safety Endpoint Components (Pivotal Analysis Set)

Cumulative MACE Rates	In-Hospital N=384	30-Day Follow-up N=383[1]
MACE[2,3]	7.0% (27/384)	7.8% (30/383)
Cardiac Death	0.3% (1/384)	0.5% (2/383)
Non-Q-wave MI[4]	5.7% (22/384)	6.0% (23/383)
Q-wave MI	1.0% (4/384)	1.6% (6/383)
Target Vessel Revascularization	0.5% (2/384)	1.6% (6/383)

Cumulative MACE Rates	In-Hospital N=384	30-Day Follow-up N=383[1]

1. One subject was excluded from the primary safety endpoint analysis due to insufficient follow-up (< 23 days).
2. All MACE were adjudicated by an independent CEC. If full data were not available, the event was adjudicated based on the clinical judgement of the independent CEC. Missing data were not imputed and a sensitivity analysis was performed to assess endpoint robustness.
3. Some subjects failed >1 component of the MACE criteria; therefore, the categories are not mutually exclusive.
4. Myocardial Infarction (MI) is 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).

Adverse effects that occurred in the IDE clinical study:

All device and procedure related Serious Adverse Events (SAE) through 30 days are summarized in **Table 11**, categorized by MedDRA code and stratified by device and procedure relatedness. No unanticipated adverse device effects (UADEs) occurred. In the pivotal cohort, 2.1% (8/384) of subjects experienced a device-related SAE and 6.8% (26/384) experienced a procedure-related SAE. The most common device-related SAE was dissection (0.8%, 3/384); others included elevated cardiac biomarker, angina, MI, perforation, ischemia and hypotension.

Table 11: Summary of SAEs through 30 Days (Pivotal Analysis Set)

	Device-Related[1]		Procedure-Related[2]	
System Organ Class / Preferred Term	**Subjects % (n/N)**	**Events N**	**Subjects % (n/N)**	**Events N**
Total Patients with Serious Adverse Events	**2.1% (8/384)**	**8**	**6.8% (26/384)**	**38**
Blood and lymphatic system disorders	**0.0% (0/384)**	**0**	**0.3% (1/384)**	**1**
Anaemia	0.0% (0/384)	0	0.0% (0/384)	0
Haemorrhagic anaemia	0.0% (0/384)	0	0.3% (1/384)	1
Iron deficiency anaemia	0.0% (0/384)	0	0.0% (0/384)	0
Cardiac disorders	**1.8% (7/384)**	**7**	**5.5% (21/384)**	**25**
Coronary artery dissection	0.8% (3/384)	3	2.9% (11/384)	11
Myocardial infarction	0.3% (1/384)	1	1.8% (7/384)	7
Arrhythmia	0.0% (0/384)	0	0.5% (2/384)	2
Angina pectoris	0.3% (1/384)	1	0.5% (2/384)	2
Cardiac arrest	0.0% (0/384)	0	0.0% (0/384)	0
Cardiac failure congestive	0.0% (0/384)	0	0.0% (0/384)	0

	Device-Related[1]		Procedure-Related[2]	
System Organ Class / Preferred Term	**Subjects % (n/N)**	**Events N**	**Subjects % (n/N)**	**Events N**
Coronary artery disease	0.0% (0/384)	0	0.0% (0/384)	0
Coronary artery occlusion	0.0% (0/384)	0	0.0% (0/384)	0
Coronary artery perforation	0.3% (1/384)	1	0.3% (1/384)	1
Coronary artery thrombosis	0.0% (0/384)	0	0.3% (1/384)	1
Left ventricular failure	0.0% (0/384)	0	0.0% (0/384)	0
Myocardial ischaemia	0.3% (1/384)	1	0.3% (1/384)	1
Congenital, familial and genetic disorders	**0.0% (0/384)**	**0**	**0.3% (1/384)**	**1**
Congenital coronary artery malformation	0.0% (0/384)	0	0.3% (1/384)	1
Gastrointestinal disorders	**0.0% (0/384)**	**0**	**0.0% (0/384)**	**0**
Enterocolitis haemorrhagic	0.0% (0/384)	0	0.0% (0/384)	0
Intestinal ischaemia	0.0% (0/384)	0	0.0% (0/384)	0
General disorders and administration site conditions	**0.0% (0/384)**	**0**	**0.0% (0/384)**	**0**
Non-cardiac chest pain	0.0% (0/384)	0	0.0% (0/384)	0
Pain	0.0% (0/384)	0	0.0% (0/384)	0
Pyrexia	0.0% (0/384)	0	0.0% (0/384)	0
Hepatobiliary disorders	**0.0% (0/384)**	**0**	**0.3% (1/384)**	**1**
Hepatic failure	0.0% (0/384)	0	0.3% (1/384)	1
Infections and infestations	**0.0% (0/384)**	**0**	**0.0% (0/384)**	**0**
Sepsis	0.0% (0/384)	0	0.0% (0/384)	0
Diverticulitis	0.0% (0/384)	0	0.0% (0/384)	0
Injury, poisoning and procedural complications	**0.0% (0/384)**	**0**	**0.3% (1/384)**	**1**
Facial bones fracture	0.0% (0/384)	0	0.0% (0/384)	0
Head injury	0.0% (0/384)	0	0.0% (0/384)	0
Skin wound	0.0% (0/384)	0	0.0% (0/384)	0
Vascular access site haematoma	0.0% (0/384)	0	0.3% (1/384)	1
Investigations	**0.0% (0/384)**	**0**	**0.5% (2/384)**	**2**
Myocardial necrosis marker increased (elevated cardiac biomarker)	0.0% (0/384)	0	0.5% (2/384)	2
Metabolism and nutrition disorders	**0.0% (0/384)**	**0**	**0.0% (0/384)**	**0**
Hyponatraemia	0.0% (0/384)	0	0.0% (0/384)	0

	Device-Related[1]		Procedure-Related[2]	
System Organ Class / Preferred Term	**Subjects % (n/N)**	**Events N**	**Subjects % (n/N)**	**Events N**
Musculoskeletal and connective tissue disorders	**0.0% (0/384)**	**0**	**0.0% (0/384)**	**0**
Pain in extremity	0.0% (0/384)	0	0.0% (0/384)	0
Psoriatic arthropathy	0.0% (0/384)	0	0.0% (0/384)	0
Spinal osteoarthritis	0.0% (0/384)	0	0.0% (0/384)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0.0% (0/384)**	**0**	**0.0% (0/384)**	**0**
Bladder cancer	0.0% (0/384)	0	0.0% (0/384)	0
Hepatocellular carcinoma	0.0% (0/384)	0	0.0% (0/384)	0
Nervous system disorders	**0.0% (0/384)**	**0**	**0.3% (1/384)**	**1**
Cerebrovascular accident	0.0% (0/384)	0	0.3% (1/384)	1
Dizziness	0.0% (0/384)	0	0.0% (0/384)	0
Seizure	0.0% (0/384)	0	0.0% (0/384)	0
Renal and urinary disorders	**0.0% (0/384)**	**0**	**0.3% (1/384)**	**1**
Acute kidney injury	0.0% (0/384)	0	0.0% (0/384)	0
Renal failure	0.0% (0/384)	0	0.3% (1/384)	1
Respiratory, thoracic and mediastinal disorders	**0.0% (0/384)**	**0**	**0.3% (1/384)**	**1**
Respiratory failure	0.0% (0/384)	0	0.3% (1/384)	1
Vascular disorders	**0.3% (1/384)**	**1**	**1.0% (4/384)**	**4**
Hypertension	0.0% (0/384)	0	0.0% (0/384)	0
Hypotension	0.3% (1/384)	1	0.5% (2/384)	2
Shock	0.0% (0/384)	0	0.3% (1/384)	1
Peripheral ischaemia	0.0% (0/384)	0	0.3% (1/384)	1

Note: A subject experiencing multiple occurrences of an adverse event was counted, at most, once per system organ class and preferred term. Adverse events are coded using MedDRA version 21.1.

1. Includes events reported with device relatedness as possible, probable or definite.
2. Includes events reported with procedure relatedness as possible, probable or definite.

Angiographic complications for the pivotal cohort are summarized in **Table 12**. Angiographic complications were assessed by the core lab at several time points during the procedure including: pre-IVL, immediately following IVL (post-IVL), following final pre-dilation after IVL but before stent placement (if applicable), immediately following stent placement (post-stent), and after final OCT/IVUS (if applicable).

In the pivotal cohort (n=384), 12 subjects (3.1%) experienced a serious angiographic complication at any time, nine (9) subjects (2.6%, 9/341) experienced a serious angiographic complication immediately following IVL, and two (2) (0.5%, 2/384) had an ongoing serious angiographic complication at the end of procedure.

Table 12: Angiographic Complications (Core Lab) (Pivotal Analysis Set)

	Pre-IVL	Post-IVL	After Final Pre-Dil Before Stent	Post-Stent	Post OCT-IVUS	Final[1]	Anytime
Any Serious Angiographic Complication[2]	0.0% (0/384)	2.6% (9/341)	1.6% (1/64)	0.8% (3/357)	0.0% (0/122)	0.5% (2/384)	3.1% (12/384)
Any Dissection	0.0% (0/384)	17.6% (60/341)	6.3% (4/64)	2.2% (8/357)	0.0% (0/122)	2.3% (9/384)	18.0% (69/384)
Dissection[3]							
A	0.0% (0/384)	0.3% (1/341)	0.0% (0/64)	0.0% (0/357)	0.0% (0/122)	0.3% (1/384)	0.5% (2/384)
B	0.0% (0/384)	10.6% (36/341)	3.1% (2/64)	2.2% (8/357)	0.0% (0/122)	1.6% (6/384)	12.2% (47/384)
C	0.0% (0/384)	4.7% (16/341)	1.6% (1/64)	0.0% (0/357)	0.0% (0/122)	0.3% (1/384)	4.4% (17/384)
Severe Dissection (Type D to F)							
D	0.0% (0/384)	1.5% (5/341)	0.0% (0/64)	0.0% (0/357)	0.0% (0/122)	0.0% (0/384)	1.3% (5/384)
E	0.0% (0/384)	0.6% (2/341)	0.0% (0/64)	0.0% (0/357)	0.0% (0/122)	0.0% (0/384)	0.5% (2/384)
F	0.0% (0/384)	0.0% (0/341)	1.6% (1/64)	0.0% (0/357)	0.0% (0/122)	0.3% (1/384)	0.3% (1/384)
Perforation[4]							
Any	0.0% (0/384)	0.0% (0/341)	0.0% (0/64)	0.6% (2/357)	0.0% (0/122)	0.3% (1/384)	0.5% (2/384)
I	0.0% (0/384)	0.0% (0/341)	0.0% (0/64)	0.0% (0/357)	0.0% (0/122)	0.0% (0/384)	0.0% (0/384)
II	0.0% (0/384)	0.0% (0/341)	0.0% (0/64)	0.3% (1/357)	0.0% (0/122)	0.3% (1/384)	0.3% (1/384)

	Pre-IVL	Post-IVL	After Final Pre-Dil Before Stent	Post-Stent	Post OCT-IVUS	Final[1]	Anytime
III	0.0% (0/384)	0.0% (0/341)	0.0% (0/64)	0.3% (1/357)	0.0% (0/122)	0.0% (0/384)	0.3% (1/384)
Abrupt Closure	0.0% (0/384)	0.0% (0/341)	1.6% (1/64)	0.0% (0/357)	0.0% (0/122)	0.3% (1/384)	0.3% (1/384)
Slow Flow	0.0% (0/384)	0.6% (2/341)	0.0% (0/64)	0.3% (1/357)	0.0% (0/122)	0.0% (0/384)	0.8% (3/384)
No Reflow	0.0% (0/384)	0.0% (0/341)	0.0% (0/64)	0.0% (0/357)	0.0% (0/122)	0.0% (0/384)	0.0% (0/384)

1. The final image is the one chosen by the analyst based on optimal projection, image quality, etc. from the post-procedural images obtained after all devices have been removed and the procedure has been completed.
2. Serious angiographic complications include severe dissection (Type D to F), perforation, abrupt closure, persistent slow flow and no flow.
3. Dissections were categorized per the NHLBI classification system.
4. Perforations were categorized per the Ellis classification for coronary perforation.

To date, follow-up is ongoing for the 6-month and 12-month time points. In compliance with the SAP, survival analysis techniques were used to analyze time to event variables that occurred later than 30 days of follow-up. For 6 and 12 months, MACE rates are presented as Kaplan-Meier (KM) estimated event rates with the number of subjects. The incidence of MACE, a composite of cardiac death, MI, and TVR, in longer-term follow-up through 12 months is shown in **Table 13.** The MACE rate (by KM estimate) at 6 and 12 months was 10.3% (39 total subjects) and 15.1% (49 total subjects), respectively. Of the MACE events that occurred beyond 30 days, none were adjudicated by the CEC as being probably or definitely device-related.

Table 13: Longer-term Major Adverse Cardiac Events (MACE) rates (CEC-Adjudicated)

Cumulative MACE Rates	6 Months	12 Months
Number of Subjects with Completed Follow-up Visits	370	201
MACE[1,2]	10.3% (39)	15.1% (49)
Cardiac Death	0.8% (3)	1.3% (4)
Non-Q-wave MI[3]	7.7% (29)	8.9% (32)
Q-wave MI	1.6% (6)	1.6% (6)
Target Vessel Revascularization	2.9% (11)	7.0% (19)

Cumulative MACE Rates	6 Months	12 Months
Note: 6- and 12-month MACE rates are presented as Kaplan-Meier estimated event rates with the number of events. 1. All MACE were adjudicated by an independent CEC. If full data were not available, the event was adjudicated based on the clinical judgement of the independent CEC. Missing data were not imputed and a sensitivity analysis was performed to assess endpoint robustness. 2. Some subjects failed >1 component of the MACE criteria; therefore, the categories are not mutually exclusive. 3. Myocardial Infarction (MI) is 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).		

2. Effectiveness Results

The analysis of effectiveness was based on the 384 evaluable patients at the 30-day timepoint. Key effectiveness outcomes are presented in **Table 14**.

The observed rate of Procedural Success was 92.4% 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 that the procedural success rate was at most 83.4% was rejected and the primary effectiveness endpoint was met (p<0.0001).

Table 14: Primary Effectiveness Endpoint (Pivotal Analysis Set)

Primary Effectiveness Endpoint	% (n/N) [95% Lower Confidence Interval][1]	Hypothesis	*P* value[2]	Conclusion
Procedural Success[3]	92.4% (355/384) [90.2%]	H_0: $\pi_s \leq$ 83.4% H_A: $\pi_s >$ 83.4%	<0.0001	Performance Goal Met

1. 95% lower confidence interval is calculated based on a one-sided asymptotic Wald (normal approximation-based) confidence interval for a binomial proportion. The standard error is calculated from the sample proportion.
2. P-value is calculated based on a one-sided asymptotic Wald (normal approximation-based) test for a binomial proportion at a 0.05 level of significance. The standard error is calculated from the sample proportion.
3. Procedural Success defined as stent delivery with a residual in-stent stenosis <50% (core laboratory assessed) and without in-hospital MACE (CEC adjudicated).

Components of the composite primary effectiveness endpoint are shown in **Table 15**. There were 27 subjects who experienced an in-hospital MACE. Three (3) subjects did not receive a stent; two (2) were IVL Device Delivery Failures that did not receive any percutaneous or surgical treatment on the day of the index procedure, and one subject had failed stent delivery after successful IVL. All subjects who received a stent had <50% residual in-stent stenosis per core lab analysis.

Table 15: Primary Effectiveness Endpoint Components (Pivotal Analysis Set)

Primary Effectiveness Endpoint: Procedural Success	% (n/N)
Procedural Success[1,2]	92.4% (355/384)
Stent Delivered[3]	99.2% (381/384)
< 50% Residual In-Stent Stenosis	100.0% (381/381)
Without In-Hospital MACE	93.0% (357/384)

1. Procedural Success defined as stent delivery with a residual in-stent stenosis <50% (core laboratory assessed) and without in-hospital MACE (CEC adjudicated).
2. Some subjects failed >1 component of the Procedural Success criteria; therefore, the categories are not mutually exclusive.
3. Three (3) subjects did not receive a stent; two (2) were IVL Device Delivery Failures that did not receive any therapy on the day of the index procedure, and one subject had failed stent delivery after successful IVL.

A summary of post-IVL and post-stent angiography as determined by the Core Lab for pivotal subjects is provided in **Table 16**.

Table 16: Post-IVL and Post-Stent Angiography (Core Lab) (Pivotal Analysis Set)

Parameter	Pivotal (N=384)	
	Post-IVL	Post-Stent (In-Stent)
MLD (mm), Mean ± Std Dev (N)	1.87 ± 0.48 (341)	2.74 ± 0.43 (381)
% Diameter Stenosis, Mean ± StdDev (N)	37.2 ± 13.5 (341)	11.9 ± 7.1 (381)
Acute Gain (mm), Mean ± Std Dev (N)	0.82 ± 0.48 (339)	1.68 ± 0.46 (378)

MLD = minimal lumen diameter; Std Dev = standard deviation

Target Lesion Revascularization (TLR) was 0.3% in-hospital and 1.3% at 30 days. At 6 and 12 months, Kaplan-Meier (KM) estimates are 2.4% and 4.8%, respectively.

Additional secondary endpoints were evaluated, but did not identify any new safety issues and showed similar results to the other endpoints presented.

Device Malfunctions

Table 17 provides details on the catheter malfunctions related to balloon rupture/loss of pressure, stratified by catheter design. The modified Shockwave C2 IVL catheter included a slight increase in the balloon double wall thickness (DWT) in order to reduce the potential for loss of pressure. Because multiple IVL catheters were used in some cases, rates are shown by subject and by catheter.

In the safety set (n=431), a total of 527 catheters were used: 342 catheters (64.9%) with the original design and 185 (35.1%) with the modified design. The rate of balloon rupture/loss of pressure in the original catheter group was 9.4% (32/342) versus 5.9% (11/185) in the modified design group.

Table 17: IVL Catheter Malfunctions (Safety Set)

	Original Catheter Design*		Modified Catheter Design*	
Catheter Malfunction/Deficiency	**Subjects (n=276) % (n/N)**	**Catheters (n=342) % (n/N)**	**Subjects (n=159) % (n/N)**	**Catheters (n=185) % (n/N)**
Balloon rupture/loss of pressure	10.5% (29/276)	9.4% (32/342)	6.3% (10/159)	5.9% (11/185)
Prior to IVL	0.4% (1/276)	0.3% (1/342)	0.6% (1/159)	0.5% (1/185)
During the IVL treatment	4.3% (12/276)	3.8% (13/342)	3.8% (6/159)	3.8% (7/185)
During the post-IVL low pressure balloon dilatation	5.8% (16/276)	4.7% (16/342)	1.9% (3/159)	1.6% (3/185)
Other: Blood noted in balloon	0.7% (2/276)	0.6% (2/342)	0.0% (0/159)	0.0% (0/185)

*Four (4) subjects underwent procedures using both types of catheters and are included in both categories.

A post-hoc sub-group analysis was conducted to evaluate the association between balloon loss of pressure and post-IVL angiographic adverse events and 30-day MACE in the safety set of Disrupt CAD III (n=431). Results are shown in **Table 18.** Please note that the reported rates in the balloon loss of pressure group shown in Table 2 are influenced by the low denominator (n=39).

Table 18: Angiographic Complications in Subjects with and without Balloon Loss of Pressure (Safety Set)

	Loss of Pressure	**No Loss of Pressure**	**P-value[1]**
30-Day MACE[2]	7.7% (3/39)	8.2% (32/391)	1.0000
Post-IVL Angiographic Complications (ACL-assessed)[3]			
Dissection	29.7% (11/37)	16.2% (56/345)	0.0650
Grade A-C	24.3% (9/37)	14.5% (50/345)	0.1471

	Loss of Pressure	No Loss of Pressure	P-value[1]
Grade D-F	5.4% (2/37)	1.7% (6/345)	0.1763
Perforation	0.0% (0/37)	0.0% (0/345)	1.0000
Abrupt closure	0.0% (0/37)	0.0% (0/345)	1.0000
Slow flow	2.7% (1/37)	0.3% (1/345)	0.1846
No reflow	0.0% (0/37)	0.0% (0/345)	1.0000

MACE = major adverse cardiac events; ACL = angiographic core lab
1. P-value is calculated based on a two-sided Fisher exact test at a 0.05 level of significance.
2. A total of 430 subjects in the safety set were evaluated for 30-day MACE; one subject (105-009) was excluded due to insufficient follow-up.
3. A total of 382 subjects in the safety set had post-IVL images available for analysis.

Results show no significant difference in 30-day MACE or post-IVL angiographic complications (core lab assessed) between subjects with and without balloon loss of pressure. The overall rate of dissections was numerically higher in the loss of pressure group but was not statistically significant (p=0.0650). In patients with balloon loss of pressure, the majority of the dissections identified by the core lab were low grade (A-C).

FDA believes that these data support the reasonable assurance of device safety and effectiveness but will continue to monitor this occurrence in a larger patient cohort through a post approval registry study (see details below).

3. Subgroup Analyses
The following preoperative characteristics were evaluated for potential association with outcomes: age >75, prior CABG, gender, site geography, RVD < 2.25 mm, lesion length > 27 mm, bifurcated lesions, diabetics, and renal insufficiency.

Freedom from 30-day MACE was observed in 92.8% (272/293) males and 90.0% (81/90) females. No evidence of heterogeneity regarding the primary safety endpoint was observed between gender groups. The procedural success rate for males was 93.2% (274/294) and for females 90.0% (81/90). Similarly, no evidence of heterogeneity regarding the primary effectiveness endpoint was observed between gender groups.

4. Pediatric Extrapolation
In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included

218 investigators of which none were full-time or part-time employees of the sponsor and four (4) of the investigators had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: None of the investigators
- Significant payment of other sorts: two (2) of the investigators (one investigator had both significant payments of other sorts and equity)
- Proprietary interest in the product tested held by the investigator: None of the investigators
- Significant equity interest held by investigator in sponsor of covered study: three (3) of the investigators (one investigator had both equity and significant payments of other sorts)

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

The Disrupt CAD III study includes three (3) sub-studies:

Optical Coherence Tomography (OCT) sub-study
The objective of the OCT sub-study was to further understand the mechanism of action of intravascular lithotripsy for the treatment of severely calcified, stenotic *de novo* coronary lesions prior to stenting in up to 100 subjects.

A total of 180 subjects consented for potential participation in the OCT sub-study. Of these, 109 subjects underwent OCT with images submitted to the core lab, and 100 had image sets suitable for analysis (including availability of at least one post-IVL or post-stent image). Results are summarized in **Table 19**.

The Disrupt CAD III OCT sub-study provides safety and effectiveness data confirming the impact of coronary IVL on the vascular response to therapy. Vascular trauma as assessed by intra-medial hematoma following IVL was minimal. The OCT data provide further evidence of calcium fracture as the underlying mechanism of action for coronary IVL. OCT imaging after coronary IVL in severely calcified vessels demonstrated calcium fractures in two-thirds of lesions which resulted in increased vessel compliance and facilitated an increase in minimum stent area and favorable stent expansion.

Table 19: OCT Sub-Study Results

OCT Parameter	N=100
Pre-procedure, n	**97**
Minimal lumen area, mm^2	2.2 ± 0.8
Lumen area stenosis, %	72.4 ± 11.6
Lesion length, mm	31.6 ± 10.2
Calcium angle at max calcium site, degrees	292.5 ± 76.5
Post-IVL, n	**92**
Acute area gain, mm^2	1.4 ± 1.1
Calcium fracture, %	67.4
Intra-medial hematoma in lesion, %	6.1
Max angle of intra-medial hematoma, °	107.2 ± 51.4
Length of intra-medial hematoma, mm	8.3 ± 4.3
Post-stent, n	**98**
Min stent area, mm^2	6.5 ± 2.1
Stent expansion at max calcium site, %	101.7 ± 28.9
Values are % or mean ± SD	

Hemodynamic sub-study

The Disrupt CAD III Hemodynamic sub-study was designed to evaluate the effect of IVL on hemodynamics during the index procedure in a minimum of 20 subjects.

Table 20 summarizes the hemodynamic data for those subjects with IVL-induced capture (n=171; 41.1%) and those without (n=245; 58.9%). Pre-procedure heart rate (HR) was lower in the group with IVL-induced capture (65.9 ± 11.4 vs 69.0 ± 11.9 bpm, p=0.0094) and a higher percentage of subjects had HR ≤ 60 bpm (37.4% vs 20.8%, p=0.0002) in that group. There were no instances of sustained ventricular arrhythmias in the group with IVL-induced capture, and there was no difference in the magnitude of BP drop between the two groups.

Table 20: Hemodynamic Effects of IVL-Induced Capture During Index Procedure

Parameter	Subjects without IVL-induced capture (n=245)	Subjects with IVL-induced capture (n=171)	p-value
Pre-Procedure Heart Rate (bpm)	69.0 ± 11.9	65.9 ± 11.4	0.0094
Heart Rate ≤ 60 bpm	20.8% (51/245)	37.4% (64/171)	0.0002
Drop in Systolic BP during IVL Procedure	24.5% (58/237)	40.5% (66/163)	0.0007
Clinically Significant Drop in Systolic BP[1]	3.4% (2/58)[2,3]	1.5% (1/66)[4]	0.5988

Parameter	Subjects without IVL-induced capture (n=245)	Subjects with IVL-induced capture (n=171)	p-value
Magnitude of Systolic BP Drop	23.5 ± 15.0	18.9 ± 14.2	0.0670
Sustained Ventricular Arrhythmia During or After IVL Procedure	0.4% (1/245)[2]	0% (0/171)	1.0000

1. Clinical significance determined by the investigator.
2. One subject experienced a drop in BP (23 mmHg) secondary to ventricular tachycardia which occurred during pre-dilatation prior to IVL and the procedure continued without further complication.
3. One subject experienced a drop in BP (50 mmHg) following two unsuccessful attempts to deliver a stent post-IVL, loss of guidewire position, difficulty placing a new guidewire, and subsequent PTCA.
4. One subject experienced a drop in BP (36 mmHg) after becoming transiently bradycardic and hypotensive following IVL; after treatment, the procedure continued without further complication.

IVL-induced capture is a recognized risk identified in the current Instructions for Use (IFU). Previously published reports along with data from Disrupt CAD III suggest the phenomenon is more likely to occur in patients with a lower heart rate (< 60 bpm). Those with IVL-induced capture had a prompt return of the normal rhythm and blood pressure once the IVL therapy was completed. Based on the totality of information available (Disrupt CAD I, II, III and published reports to date), the likelihood that IVL-induced capture may lead to a clinically significant arrythmia is low.

Permanent Pacemaker (PPM) and Implantable Cardioverter Defibrillator (ICD) sub-study

The Disrupt CAD III PPM/ICD sub-study was designed to evaluate the safety and impact of IVL on implantable pacemaker and defibrillator devices in a minimum of 20 subjects. Of the seven (7) subjects who consented to have the device interrogated for the sub-study, pre-procedure and post-procedure interrogation reports were available for five (5) subjects. Sites reported no impact on device settings, sensing or pacing functions and no triggered ICD shocks were reported.

In Disrupt CAD III, 27 patients were analyzed, using a combination of procedural heart rhythm/hemodynamics and PPM/ICD device interrogation. The pre-procedure heart rate in the PPM/ICD sub-group was similar to the full study population (68.9 ± 13.3 vs 67.8 ± 11.8 bpm, respectively). IVL-induced capture was noted more frequently in the PPM/ICD group compared to all enrolled subjects (59.3% vs 41.1%). The proportion of PPM/ICD subjects with a transient drop in systolic blood pressure during the IVL procedure was similar to the incidence in the full safety set (37.0% vs 31.0%, respectively); the magnitude of the drop was likewise comparable (18.4 ± 18.9 vs 21.1 ± 14.7 mmHg). There were no instances of clinically significant drop in blood pressure or sustained ventricular arrhythmia in the

PPM/ICD group. There were no reports of shocks triggered by IVL in those with an ICD. Sites reported no impact on device settings, sensing or pacing functions and no triggered ICD shocks were reported.

Furthermore, in a pooled safety set analysis of patients enrolled in Disrupt CAD I, II, II and IV which includes 42 data on 42 patients with PPM/ICDs, there were no PPM/ICD-related events and no hemodynamic adverse events, as noted in **Table 21** below. Three (3) subjects enrolled in Disrupt CAD III (7.1%, 3/42) with a PPM/ICD experienced an arrhythmia > 30 days following the index procedure; however, none were related to the study device (IVL) or the index procedure.

Table 21: Summary of PPM/ICD Events (CAD I-IV Pooled Safety Set)

	CAD I[1]	CAD II[2]	CAD III[3]	CAD IV[4]	Pooled
Prior PPM/ICD	**11.7% (7/60)**	**5.8% (7/120)**	**6.3% (27/431)**	**1.4% (1/72)**	**6.1% (42/683)**
AEs Relevant to Potential PPM/ICD Interaction	**0.0% (0/7)**	**0.0% (0/7)**	**11.1% (3/27)**	**0.0% (0/1)**	**7.1% (3/42)**
PPM/ICD Events[5]	0.0% (0/7)	0.0% (0/7)	0.0% (0/27)	0.0% (0/1)	0.0% (0/42)
Arrhythmia	0.0% (0/7)	0.0% (0/7)	11.1% (3/27)[6]	0.0% (0/1)	7.1% (3/42)
Hemodynamic Events[7]	0.0% (0/7)	0.0% (0/7)	0.0% (0/27)	0.0% (0/1)	0.0% (0/42)
IVL-related AEs Relevant to Potential PPM/ICD Interaction	**0.0% (0/7)**	**0.0% (0/7)**	**0.0% (0/27)**	**0.0% (0/1)**	**0.0% (0/42)**
Adverse pacing/ICD[5]	0.0% (0/7)	0.0% (0/7)	0.0% (0/27)	0.0% (0/1)	0.0% (0/42)
Arrhythmia	0.0% (0/7)	0.0% (0/7)	0.0% (0/27)	0.0% (0/1)	0.0% (0/42)
Hemodynamic events[7]	0.0% (0/60)	0.0% (0/7)	0.0% (0/27)	0.0% (0/1)	0.0% (0/42)

1. CAD I includes all AEs reported during the study follow-up period (180 days).
2. CAD II includes all AEs reported during the study follow-up period (30 days).
3. CAD III includes all AEs reported as of June 28, 2020 during the study follow-up period (24 months); follow-up is ongoing.
4. CAD IV includes all AEs reported as of August 6, 2020 during the study follow-up period (24 months); follow-up is ongoing.
5. Inappropriate ICD shock, transient pacing inhibition
6. All 3 subjects had medical history of arrhythmia; no events were device-related and all occurred > 30 days after index procedure.
7. Hypotension, cardiogenic shock, hemodynamic instability

In addition, a literature review of 66 independent publications with coronary IVL was completed to assess the association of PPM/ICD adverse events and coronary IVL.

Publications included case reports/series, single-center and multi-center studies. Only three (3) publications reported prior PPM/ICD in the study results; no adverse events were associated with prior PPM/ICD in these publications [4-6].

Based on the totality of the data, the likelihood for adverse interaction between IVL treatment and implanted PPM/ICD devices is low. FDA believes that these data support reasonable assurance of safety and effectiveness in this patient population, though this occurrence will continue to be monitored in a larger patient cohort through a post approval registry study (see details below).

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory System Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The study 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 ($p<0.0001$). These results support the effectiveness of the Shockwave IVL System with Shockwave C^2 Coronary IVL Catheter for the treatment of severely calcified, stenotic *de novo* coronary lesions prior to stenting.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory, animal studies, as well as data collected in clinical studies, conducted to support PMA approval as described above. 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 ($p<0.0001$). These results support the safety of the Shockwave IVL System with Shockwave C^2 Coronary IVL Catheter for the treatment of severely calcified, stenotic *de novo* coronary lesions prior to stenting.

C. Benefit-Risk Determination

The probable benefits and probable risks of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. The Disrupt CAD III Study met the study success criteria by meeting both the primary safety and effectiveness endpoints. The study evidence supports the reliability of the device and

demonstrates the probable benefits to health for its intended uses, patients, and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks.

Additional factors to be considered in determining probable risks and benefits for the Shockwave Intravascular Lithotripsy (IVL) System with Shockwave C^2 Coronary IVL Catheter device included:

i. The clinical study was well designed and conducted. The clinical study provided adequate follow-up (30 days) to evaluate safety and effectiveness, with separate analyses conducted to assess the impact of missing data.
ii. The device is intended for the treatment of severely calcified, stenotic *de novo* coronary lesions prior to stenting. The results adequately support general use in the identified population.
iii. The frequency and types of the adverse events reported throughout the pivotal clinical study are in alignment with what might be expected in the studied patient population and therapeutic area. No unanticipated adverse device effects were reported in the study.

l. Patient Perspectives

This submission either did not include specific information on patient perspectives or the information did not serve as part of the basis of the decision to approve or deny the PMA for this device.

In conclusion, given the available information above, the data support that for the treatment of severely calcified, stenotic *de novo* coronary lesions prior to stenting, the probable benefits outweigh the probable risks.

D. Overall Conclusions

The data in the PMA application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. Given all of the available data, it is reasonable to conclude that the benefits of the use of the device for the target population outweigh the risk of illness or injury when used as indicated in accordance with the labeling and Instructions for Use (IFU).

XIV. CDRH DECISION

CDRH issued an approval order on February 12, 2021. The final conditions of approval cited in the approval order are described below.

1. *Shockwave IVL System with Shockwave C^2 Coronary IVL Catheter New Enrollment Post Approval Registry*: This new enrollment registry assessment is a prospective, multicenter, single-arm post-approval registry to further evaluate the Shockwave Intravascular Lithotripsy (IVL) System with the Shockwave C^2 Coronary IVL Catheter in severely calcified, stenotic *de novo* coronary arteries prior to stenting. The purpose of the

study is to better understand the utilization, safety, and effectiveness of Shockwave Medical Coronary IVL in a real-world setting.

The study will collect data on the following outcomes: rate of 1) IVL-related ventricular arrhythmias, 2) IVL balloon loss of pressure and related serious dissections, and 3) safety of IVL in patients with prior permanent pacemakers and implantable cardioverter defibrillators (PPM/ICD).

Approximately 1000 patients (including a minimum of 30 PPM/ICD patients) with clinical characteristics similar to IDE G180146 will be enrolled and followed through discharge. A minimum of 150 patients will be followed 30 days post-procedure.

Interim results and final results will be analyzed using descriptive statistics. Six (6) month interim summaries and/or registry status will be submitted for the first two (2) years and then annually thereafter, out to 3 years (or earlier if data collection, including a minimum of thirty (30) PPM/ICD patients, has been completed).

2. *DISRUPT CAD III Continued Follow-Up Study*: This study will evaluate the long-term safety and effectiveness of the Shockwave Coronary Lithotripsy System in 384 subjects from the premarket study (DISRUPT CAD III trial). The DISRUPT CAD III trial was designed as a prospective, multicenter, single arm trial. Subjects will be followed annually through 2 years post-procedure.

   The primary safety endpoint is freedom from major adverse cardiac events (MACE) at 12 and 24 months, reported descriptively.

   The endpoints to be assessed through 2 years post-procedure are rate of: (1) target lesion failure (TLF) and (2) all death, cardiac death, MI, TV-MI, 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) at 6, 12 and 24 months.

   Robust independent adjudication of events (i.e., Clinical Events Committee) will be maintained throughout the Continued Follow-Up Study, unmodified from the pivotal portion of the study. DISRUPT CAD III updates will be provided annually until all subjects have completed the 2-year follow-up visit, are discontinued prior to the 2-year follow-up visit, have died, or the 2-year follow-up window has closed.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

XVI. REFERENCES

1. Chambers, J.W., 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). JACC Cardiovasc Interv, 2014. 7(5): p. 510-8.
2. Thygesen, K., et al., Fourth Universal Definition of Myocardial Infarction (2018). J Am Coll Cardiol, 2018. 72(18): p. 2231-2264.
3. Moussa, I.D., et al., Consideration of a new definition of clinically relevant myocardial infarction after coronary revascularization: an expert consensus document from the Society for Cardiovascular Angiography and Interventions (SCAI). Catheter Cardiovasc Interv, 2014. 83(1): p. 27-36. Chambers, J.W., 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). JACC Cardiovasc Interv, 2014. 7(5): p. 510-8.
4. Wilson, S.J., et al., Incidence of "shocktopics" and asynchronous cardiac pacing in patients undergoing coronary intravascular lithotripsy. EuroIntervention, 2020. 15(16): p. 1429-1435.
5. Boeder, N.F., et al., First-in-man lithoplasty of a LIMA bypass with ECMO support in a last-remaining-vessel. Cardiovasc Revasc Med, 2020.
6. Hill, J.M., et al., Intravascular Lithotripsy for Treatment of Severely Calcified Coronary Artery Disease: The Disrupt CAD III Study. J Am Coll Cardiol, 2020. 76(22): p. 2635-46.