Study Title: Equity in Modifying Plaque Of WomEn with UndeRtreated Calcified Coronary Artery Disease (EMPOWER CAD)

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Study Device: Shockwave Medical Coronary Intravascular Lithotripsy System

Study Sponsor Name and Address: Shockwave Medical, Inc.
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1. Study Summary

Study Title	Equity in Modifying Plaque Of WomEn with UndeRtreated Calcified Coronary Artery Disease (EMPOWER CAD)
Study Objective	To generate real-world clinical evidence associated with coronary IVL in a population of female subjects with calcified coronary artery disease.
Study Device(s), commercially available	Shockwave Medical Coronary IVL System
Manufacturer	Shockwave Medical, Inc.
Intended Use	The Shockwave Coronary IVL System is intended to treat calcified stenoses, including calcified stenoses that are anticipated to exhibit resistance to full balloon dilatation or subsequent uniform coronary stent expansion.
Study Design	Post-market, prospective, multi-center, single-arm observational study
Enrollment	Up to 400 subjects at up to 50 global sites in the US, UK and Europe
Subject Population	Female subjects referred for percutaneous coronary intervention (PCI) with coronary IVL and stenting per standard of care.
Study Duration / Follow-Up Period	Subjects will have clinical follow-up prior to discharge from the index procedure and at 30 days, 1, 2 and 3 years. Follow-up will be via telephone contact (or optional clinic visit).
Primary Safety Endpoint	Target lesion failure (TLF) at 30 days defined as a composite of cardiac death, myocardial infarction (per SCAI definition for peri-procedural MI; per 4th Universal Definition for spontaneous MI beyond discharge) attributable to target vessel (TV-MI), or ischemia-driven target lesion revascularization (ID-TLR).
Primary Effectiveness Endpoint	Procedural Success defined as stent delivery with a residual in-stent stenosis ≤30% in all target lesions (core laboratory assessed) and without in-hospital TLF (CEC adjudicated).

Secondary Endpoints:	• Angiographic Success defined as stent delivery with ≤30% residual stenosis and without serious angiographic complications. • Procedural Success defined as stent delivery with a residual stenosis <50% in all target lesions (core laboratory assessed) and without in-hospital TLF. • Angiographic Success defined as stent delivery with < 50% 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. • TLF at 1, 2 and 3 years. • Major Adverse Cardiac Events (MACE) defined as a composite of cardiac death, myocardial infarction (per SCAI definition for peri-procedural MI; per 4th Universal Definition for spontaneous MI beyond discharge), and target vessel revascularization at 30 days, 1, 2 and 3 years. • At each time period: All death, cardiac death, MI, TV-MI, procedural and nonprocedural MI, ID-TVR, ID-TLR, ID-non-TLR, ID-non-TVR, all revascularizations (ID and non-ID), and stent thrombosis (ARC definite, probable, definite or probable). • MI rates and all composite endpoints (TLF, MACE) will also be reported using the 4th Universal Definition for peri-procedural and spontaneous MI at all timepoints. • Angina symptoms assessed as a change from baseline (at each time period) by Seattle Angina Questionnaire (SAQ-7). • Quality of life assessed by EQ-5D-5L as a change from baseline (at each time period). • Quality of life assessed by Generalized Anxiety Disorder Questionnaire (GAD-7) as a change from baseline (at each time period).
Optical Coherence Tomography (OCT) Sub-study	Up to 200 consecutive subjects who consent to participate in the OCT sub study will undergo OCT assessment at baseline, immediately post-IVL /or post-adjunctive device, and end of procedure (after stent implantation / post-dilatation). The OCT sub study will be performed at pre-selected qualified sites.
Study Inclusion Criteria	1. The subject is a non-pregnant female ≥18 years of age 2. The subject meets indications for PCI and stent 3. The subject is scheduled to undergo PCI with coronary IVL and stenting per standard of care for non-stented lesion 4. The subject is willing to comply with protocol-specified follow-up evaluations 5. The subject, or legally authorized representative, has been

	informed of the nature of the study, agrees to its provisions, and has provided written informed consent, approved by the appropriate Institutional Review Board (IRB) or Ethics Committee (EC)
Study Exclusion Criteria	1. Subjects with known mental or physical illness or known history of substance abuse that may cause non-compliance with the protocol, confound the data interpretation, or is associated with a life expectancy of less than one year 2. Subjects presenting with cardiogenic shock at the time of the index procedure 3. Serious angiographic complication in the target vessel prior to treatment with coronary IVL including severe dissection (Type D to F), perforation, abrupt closure, persistent slow-flow or persistent no reflow 4. Subject unable to tolerate anticoagulation/antiplatelet therapy per guidelines 5. Subject is enrolled in any study of an investigational device or drug that may interfere with study results
Study Statistical Methods	• Intent-to-Treat (ITT) analysis with pre-defined subgroups • Designed to assess exact 95% confidence interval (CI) for primary endpoints; no formal hypothesis testing
Study Sponsor/Study Management	Shockwave Medical, Inc. 5403 Betsy Ross Drive Santa Clara, CA 95054 USA Contact: Randee Randoll Title: Director, Clinical Affairs Telephone (direct): 408.550.2626 Email: rrandoll@shockwavemedical.com
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1.0 INTRODUCTION/BACKGROUND

1.1 Calcified Coronary Lesions

Coronary artery calcification (CAC) is common especially in the elderly population and those with more advanced disease. Approximately 38% and 73% of all lesions display calcification as detected by angiography and intravascular ultrasound (IVUS), respectively [1]. As IVUS is not routinely used as a diagnostic modality, coronary calcification is most likely underestimated [2].

Conventional percutaneous coronary intervention (PCI) to treat calcified lesions has a greater risk of stent underexpansion and malapposition, both of which are associated with adverse clinical outcomes [3]. To facilitate stent placement and optimize stent expansion in calcified lesions, adjunctive plaque-modifying devices are often used including atherectomy (rotational, orbital, laser) and cutting/scoring balloons [4]. Despite advances in interventional equipment and techniques, effective treatment for patients with advanced coronary calcification remains a challenge. Compared to non-calcified lesions, calcified coronary lesions are associated with a higher incidence of major adverse cardiac events (MACE), especially, the rate of non–Q-wave myocardial infarction (MI) [5]. Calcified lesions are associated with a high frequency of restenosis, target lesion revascularization (TLR), vessel dissection during PCI, failure to deliver a stent, balloon ruptures and undilatable lesions [2]. In a study of pooled data from 6,855 patients, the presence of calcification was associated with an increase in the rate of ischemic events at 1 year, especially within the first 30 days, reflecting the negative impact of calcification during stent implantation resulting in an increase in acute and subacute stent failure [6].

Women with moderate-to-severe lesion calcium are particularly vulnerable to poor outcomes. In a dedicated DES registry of 6371 female patients, of which 1622 (25.5%) had moderate/severe calcium, outcomes at 3 years were significantly worse with a reported 38% higher mortality, a 48% higher rate of death or myocardial infarction (MI), and a 56% higher rate of death, MI, or target lesion revascularization (TLR) compared with treatment of mildly or noncalcified lesions [7]. Plaque modification with atherectomy improves lesion compliance, allowing optimal stent expansion, but is associated with increased periprocedural complications including coronary dissections, perforation, and higher rates of periprocedural MI [2, 8, 9]. The procedural risks of atherectomy are accentuated in women who have rates of serious flow-limiting coronary dissections and cardiac tamponade that are 4- to 5-fold higher than men treated with rotational atherectomy, leading to 2-fold higher rates of in-hospital major adverse cardiac events (MACE) [10]. Similar results have been reported with orbital atherectomy [11]. Acute procedural complications in women may limit the use of atherectomy to optimize DES expansion (one of the strongest predictors of subsequent stent thrombosis and restenosis) [12, 13] and likely contribute to the poor outcomes reported in the longer term.

1.2 Coronary Intravascular Lithotripsy

Lithotripsy is a technology originally designed to fragment renal calcifications by pulsing them with high-power acoustic shock waves [14]. The design concept of the Shockwave Coronary IVL System is to use the same core lithotripsy technology, albeit at energy levels that are orders of magnitude lower in intensity and number [15]. The Shockwave Coronary IVL catheter is based on conventional balloon catheter concepts; however, the balloon is inflated at a lower than nominal pressure and the lithotripsy emitters are energized thereby generating pulsatile mechanical energy within the balloon at the target treatment site, disrupting calcium within the

lesion, and allowing subsequent dilatation of coronary artery stenosis using low balloon pressure.

The Shockwave Coronary IVL System has been evaluated as an adjunct to coronary stenting in severely calcified lesions in the four Disrupt CAD studies: Disrupt CAD I-IV [16-19]. These individual single-arm, prospective, multicenter, nonrandomized studies demonstrated high rates of device and procedural success as well as excellent early angiographic and clinical outcomes, providing evidence for device performance and safety as well as insights into the mechanism(s) of calcium modification.

A patient-level pooled analysis was completed for the Disrupt CAD I-IV studies which showed the very low rates of serious angiographic complications in the pooled analysis are consistent with the IVL mechanism of action which involves circumferential and longitudinal multiplane calcium fracture in situ without the generation of atheroembolic debris and/or significant heat energy [20]. In severely calcified lesions, IVL improves vessel compliance, mitigating the need for aggressive high-pressure balloon dilatation prior to stent delivery, with its associated potential for barotrauma and severe dissection. This unique mechanism of action is reflected by the significant improvements observed by quantitative coronary angiography in minimal luminal diameter (MLD) and percentage diameter stenosis after IVL alone despite an average peak IVL balloon pressure of only 6 atm [15].

An additional analysis was performed on the patient-level pooled data from the Disrupt CAD I-IV studies to evaluate sex-based outcomes of severely calcified coronary lesions treated with IVL lesion preparation before stent implantation [21]. Results showed that IVL-facilitated DES implantation was safe and effective independent of patient sex and was associated with infrequent angiographic complications, without evidence of excess acute angiographic or clinical complications in women [21].

1.3 Study Rationale

The pooled Disrupt CAD I-IV analysis represents the largest series evaluating sex-based outcomes with coronary IVL and included data from 144 women. The EMPOWER CAD study is designed to expand upon this clinical foundation by prospectively enrolling up to 400 female patients and addressing some of the limitations of the pooled analysis [21]. Specifically, EMPOWER CAD is an all-comers study which will enroll a broader population including patients with acute coronary syndromes and those with more complex lesions that were excluded from the CAD I-IV studies including ostial, unprotected left main, length >40 mm, and those lesions with moderate calcium. The EMPOWER CAD study will also provide longer-term outcomes up to three years. Lastly, by generating real-world clinical evidence associated with coronary IVL in a population of female patients with calcified coronary artery disease, the EMPOWER CAD study aims to directly address the underrepresentation of women in cardiovascular clinical trials [22].

2.0 Study Device Description

2.1 Shockwave Coronary IVL System

The commercially available Shockwave Coronary IVL System consists of an IVL Catheter that is used exclusively with the IVL Generator, IVL Connector Cable and its accessories. 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, refer to Figure 1. Representative Shockwave IVL System.

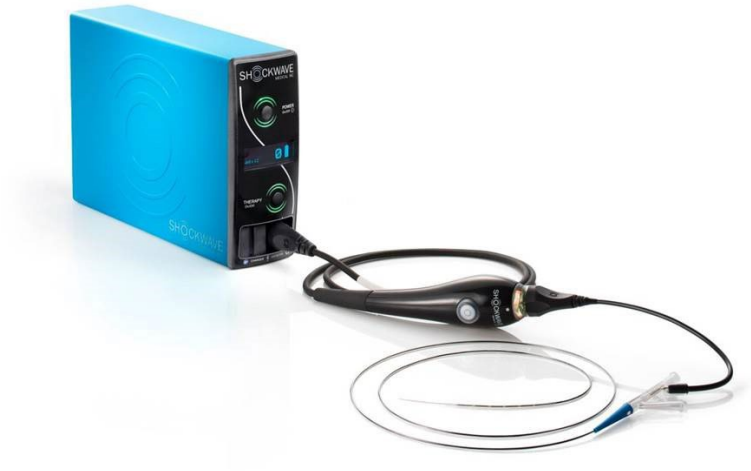

Figure 1. Representative Shockwave IVL System

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2.4 Indications for Use

The Shockwave Coronary IVL System (study devices) utilized during the conduct of this study will be commercially available. Refer to the associated IFUs for each country's approved device indication.

3.0 STATISTICAL CONSIDERATIONS

3.1 General Statistical Methods

Descriptive statistics will be provided in this clinical study. Analyses will be conducted at pre-specified time points including 30 days, 1, 2 and 3 years.

Categorical variables will be summarized by the number of observations available, frequency, and percentage. Unless otherwise noted, missing data will be excluded from the denominator. Comparisons will utilize a Chi-square test, or Fisher's exact test when 20% or more of expected cell frequencies are less than 5. Clinical outcomes analyzed at 30 days will be evaluated as categorical (binary) data. McNemar's chi-square may be used to assess within-subject changes in a bivariate response variable. Exact confidence intervals will be generated for estimates of proportions.

Continuous variables will be summarized by the mean, standard deviation, median, minimum, and maximum. Within-subject changes will be analyzed parametrically using the Paired t-test if the differences are normally distributed, or non-parametrically using the Sign-Rank Test if the differences are not normally distributed. Asymptotic confidence intervals will be generated for estimates of means.

[redacted]

3.2 Primary Endpoints

[redacted]

3.2.1 Primary Safety Endpoint

The primary safety endpoint is freedom from Target Lesion Failure (TLF) at 30 days, defined as a composite of:

- Cardiac death, or
- Myocardial Infarction (per SCAI definition for peri-procedural MI; per 4th Universal Definition for spontaneous MI beyond discharge) attributable to target vessel (TV-MI), or
- Ischemia-driven target lesion revascularization (ID-TLR)

3.2.2 Primary Effectiveness Endpoint

The primary effectiveness endpoint is Procedural Success defined as stent delivery with a residual in-stent stenosis ≤30% in all target lesions (core laboratory assessed) and without in-hospital TLF (CEC adjudicated).

3.3 Sample Size Determination

The sample size was calculated based on the precision of the exact 2-sided 95% confidence interval (CI) of the primary effectiveness endpoint, using Disrupt CAD III female subgroup results as a reference [18].[redacted]

The calculation of the EMPOWER CAD sample size was based on a procedural success estimate of 90.0%. Combined with a desired precision of +/- 3.1% and an alpha of 0.05 (95% CI), a sample size of 360 was selected to provide a probability width ("power") of 0.8. Assuming a lost-to-follow-up rate of 10%, up to 400 subjects will be enrolled.

The EMPOWER CAD study will enroll a broader population relative to the prior pooled analysis from CAD I-IV; as such, point estimates from this real-world population may be used as reference for future studies.

3.4 Population Analysis

The primary analysis population will be the Intent-to-Treat (ITT) cohort which includes all enrolled subjects.

3.5 Handling of Dropout of Missing Data

No imputation of or adjustments for missing data will be performed for the primary analyses. All available data will be presented. For time to event analyses, subjects who do not experience the event in question will be censored at their last known follow-up.

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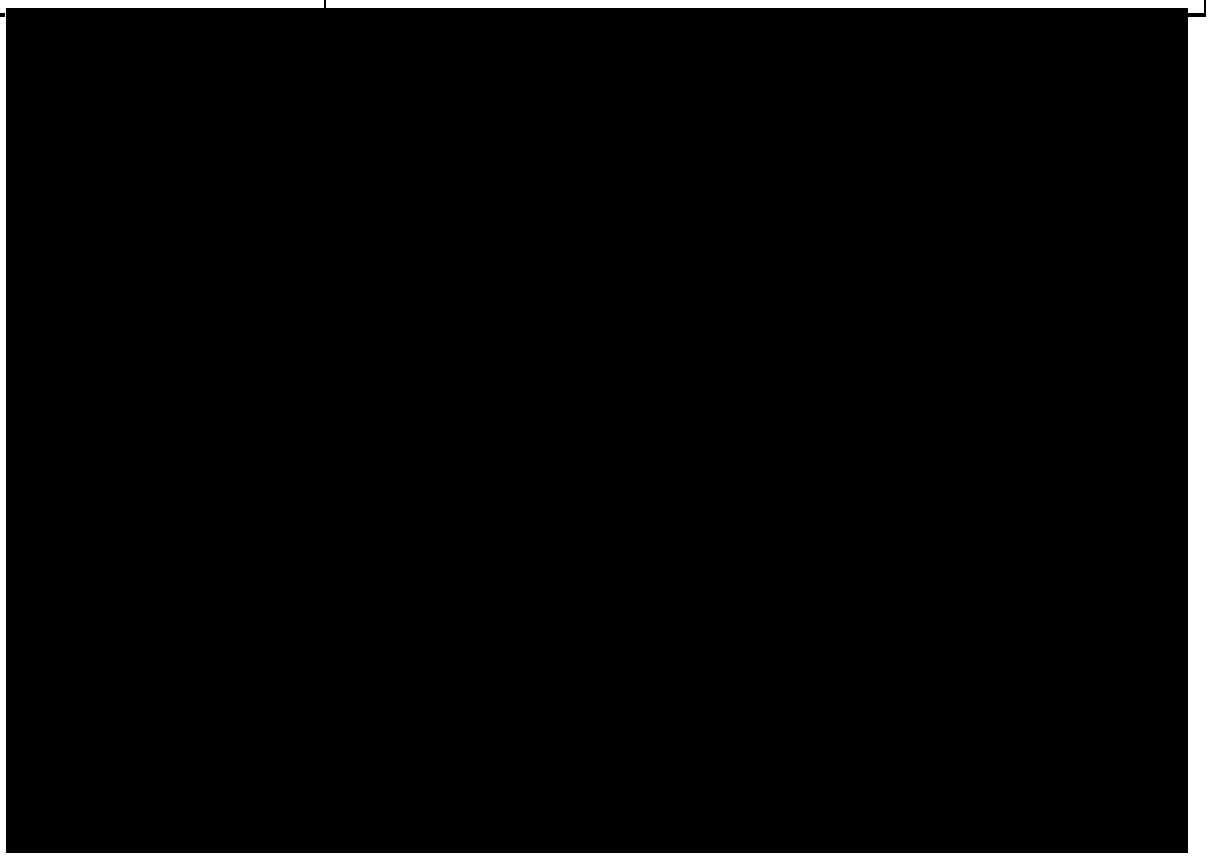


5.0 Index Procedure

5.1 Coronary Intravascular Lithotripsy Procedure

A full description of the IVL procedure is detailed in the Instructions for Use (IFU) including appropriate balloon sizing. Note that there are specific IFUs and labelling provided for the United States (US) and for Outside of the US (OUS). An appropriately-sized IVL catheter should be selected per the IFU.

The recommended procedural steps outlined below represent an "IVL first" approach; adjunctive devices may be used if there are challenges after first attempting to cross with the IVL catheter [redacted] Any departures from this algorithm will not be considered protocol deviations; information on all devices used in the procedure (including the order in which they were used) will be captured. Angiographic images captured during the procedure will be sent to the core lab for analysis.

- If multiple lesions are to be treated, it is recommended that non-target lesions be preferentially treated first.
- If a serious angiographic complication occurs in a target or non-target vessel prior to insertion of the IVL catheter, the subject should be treated per standard of care; however, they should not be enrolled in the study.
- If the Investigator is able to pass a guidewire but is unable to pass the IVL catheter across the target lesion, an adjunctive tool (balloon, atherectomy, cutting/scoring balloon) may be used prior to re-insertion of the IVL Catheter. The lesion will then be treated per the IFU with the IVL Catheter.

  Note: Pre-dilatation may be performed using standard techniques based on physician discretion.

- The subject is considered enrolled once the IVL Catheter has been inserted into the access artery.
- Once the IVL catheter is placed in the target lesion area, the balloon should be inflated to 4 atm and IVL treatment delivered for the pre-programmed time of 10 seconds to deliver 10 pulses.

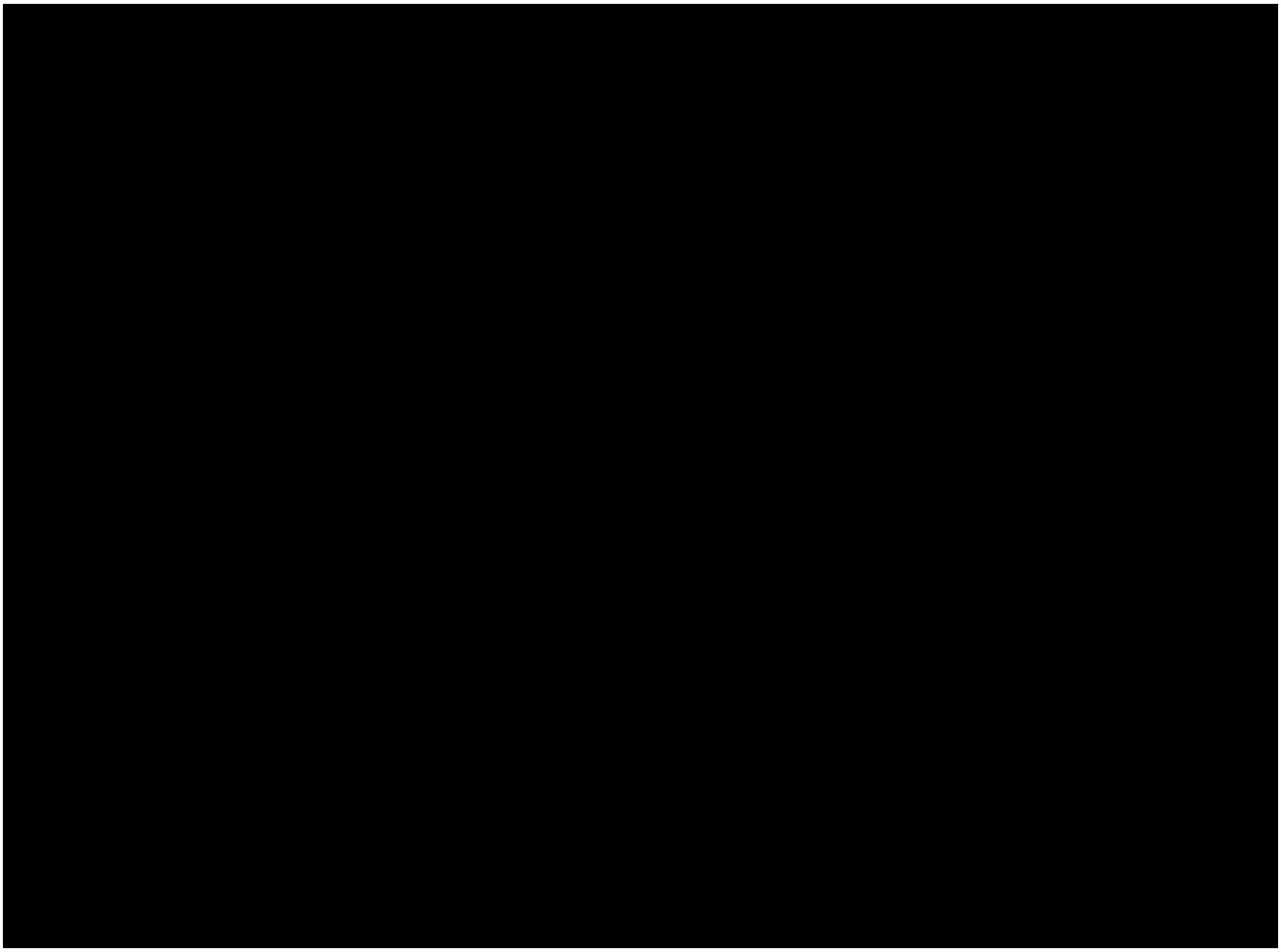
  Note: The IVL Generator is programmed to force a minimum pause time of 10 seconds following every 10 pulses delivered.

- Following IVL, inflate the balloon to the reference size using the balloon compliance chart (refer to IFU) and record lesion response on fluoroscopy.
- Deflate the balloon to re-establish blood flow.
- Repeat prior steps for additional treatment cycles until the lesion has been sufficiently dilated or the catheter is re-positioned.

If additional lesion area needs to be treated, follow the treatment steps identified above and per the IFU to ensure appropriate overlap between segments [redacted]

Note: The maximum number of pulses to treat a single arterial segment is 80 pulses and therefore 160 pulses in an overlap segment. Additional catheters may be used when necessary.

- The residual stenosis will be assessed by the physician following the IVL procedure. The IVL procedure is considered successful when the residual stenosis allows for adequate balloon expansion by visual estimate, as determined by the Investigator prior to stent placement. Consider additional IVL pulses if needed to optimize residual stenosis.
- If the residual stenosis is sub-optimal following IVL, a balloon or other adjunctive device (atherectomy, cutting/scoring balloon) must be used to dilate the lesion prior to stenting. This information will be recorded in the case report form.
- Post-IVL angiography should be performed after IVL pulses have been delivered and prior to stent delivery.
- The stent will then be delivered using a standard approach.
- Following stent implantation, post-dilatation with a non-compliant balloon with inflation pressure ≥16 atm is strongly recommended.
- Following delivery of the coronary stent and post-dilatation, angiography will be performed to determine the final residual stenosis for assessment of the primary effectiveness endpoint.



5.2 Optical Coherence Tomography (OCT) Sub-study

For subjects enrolled in the OCT Sub-study, OCT images must be assessed at baseline, immediately post-IVL (or post-adjunctive therapy), and end of procedure.

6.0 References

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