Prospective Multi-Center, Randomized Post-Market Study (PMS) of the Shockwave Medical, Inc. Intravascular Lithotripsy System in Peripheral Arteries

NCT02923193

October 10, 2019

Randomized study of the Shockwave Medical Peripheral Lithoplasty® System used in combination with DCB versus standard balloon angioplasty used in combination with DCB to treat moderate and severely calcified femoropopliteal arteries (Disrupt PAD III).

Disrupt PAD III

Protocol Number: CP 60892

Protocol Date: October 10, 2019

Revision: F

Study Devices: Shockwave Medical Peripheral Lithoplasty System and Medtronic IN.PACT DCB

Sponsor Name and Address: Shockwave Medical, Inc.
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Santa Clara, CA 95054
USA

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1.0 INVESTIGATOR SIGNATURE PAGE

Study Title: Randomized study of the Shockwave Medical Peripheral Lithoplasty® System used in combination with DCB versus standard balloon angioplasty used in combination with DCB to treat moderate and severely calcified femoropopliteal arteries (Disrupt PAD III).

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Principal Investigator Acknowledgement Signature

I have received and reviewed this version of the above noted study protocol and will conduct the study in accordance with the investigator requirements.

Investigator's Name (print)	Site Number
Investigator's Signature	Date

2.0 STUDY SUMMARY

Study Title:	Randomized study of the Shockwave Medical Peripheral Lithoplasty® System used in combination with DCB versus standard balloon angioplasty used in combination with DCB to treat moderate and severely calcified femoropopliteal arteries (Disrupt PAD III).
Study Objective:	The objective of the randomized study is to assess the safety and effectiveness of Lithoplasty treatment used in combination with DCB versus standard balloon angioplasty used in combination with DCB to treat moderate and severely calcified femoropopliteal arteries. In addition to the randomized study, an observational study (OS) of subjects who do not meet the inclusion/exclusion criteria for the randomized study will be conducted. The objective of the observational study is to assess the real-world acute performance of the Shockwave Medical Peripheral Lithoplasty System in the treatment of calcified, stenotic, peripheral arteries. Once enrollment in the randomized portion of the study is complete, subjects may continue to be enrolled in the observational study provided they meet OS eligibility criteria.
Study Devices:	Shockwave Medical Peripheral Lithoplasty System and Medtronic IN.PACT DCB.
Indications for Use:	**Indications for Use Outside the United States:** The Shockwave Medical Peripheral Lithoplasty® System is indicated for lithotripsy-enhanced, low-pressure balloon dilatation of calcified, stenotic peripheral arteries in patients who are candidates for percutaneous therapy. The IN.PACT Admiral DCB is indicated for percutaneous transluminal angioplasty (PTA) in patients with obstructive disease of peripheral arteries, including patients with in-stent restenosis (ISR) and arteriovenous (AV) access to help maintain hemodialysis access in patients with end-stage renal disease. Note: While the IN.PACT Admiral DCB is indicated for use in patients with end-stage renal disease who require arteriovenous (AV) access to help maintain hemodialysis access, and in patients with in-stent restenosis, such patients are not being studied in this protocol. **US Indications for Use:** The Shockwave Medical Lithoplasty System is intended for lithotripsy

	enhanced balloon dilatation of lesions, including calcified lesions, in the peripheral vasculature, including the iliac, femoral, ilio-femoral, popliteal, infra-popliteal, and renal arteries. Not for use in the coronary or cerebral vasculature. The IN.PACT Admiral paclitaxel-coated PTA balloon catheter is indicated for percutaneous transluminal angioplasty, after appropriate vessel preparation, of de novo, restenotic, or in-stent restenotic lesions with lengths up to 180 mm in superficial femoral or popliteal arteries with reference vessel diameters of 4-7 mm.
Study Design:	The Disrupt PAD III is a prospective, multi-center, single blind, randomized (1:1) study of Lithoplasty treatment used in combination with DCB versus standard balloon angioplasty used in combination with DCB to treat moderate and severely calcified femoropopliteal arteries. The observational study is a prospective, multi-center, single arm observational study for subjects who do not meet the inclusion/exclusion criteria of the randomized study or for subjects who are recruited after enrollment in the randomized portion of the study is complete.
Enrollment:	Up to 400 subjects at up to 60 sites in Europe, the United States and New Zealand will be enrolled in the randomized study. A maximum of 1500 subjects at the same 60 sites will be enrolled in the observational study with a minimum of 200 subjects treated with the S4 Lithoplasty catheter.
Subject Population:	Subjects with moderate and severely calcified femoropopliteal artery disease presenting with Rutherford Category 2 to 4 of the target limb in the randomized study. Real-world claudicant or critical limb ischemia (CLI) population in the observational study.
Study Duration / Follow-Up Period:	Approximately 36 months of enrollment for the randomized study at up to 60 global sites. Randomized study subjects will be followed through discharge, 30 days, and 6, 12 and 24 months. Duplex Ultrasound (DUS) assessments will be completed at 12 and 24 months. Observational study subjects will be followed through hospital discharge.
Randomized Study Primary Effectiveness Endpoint:	Procedural success is defined as residual stenosis $\leq$30% without flow-limiting dissection (≥ grade D) prior to DCB or stenting by angiographic core lab.
Randomized Study Powered Secondary	Primary patency at 12 months defined as freedom from clinically-driven target lesion revascularization (TLR) and freedom from restenosis

Effectiveness Endpoint:	determined by duplex ultrasound or angiogram ≥50% stenosis. As pre-specified, acute PTA failure requiring a stent at any time during the index procedure will be counted as a loss of primary patency.
Randomized Study Secondary Endpoints:	• Major Adverse Event (MAE) at 30 days, 6, 12 and 24 months defined as: – Need for emergency surgical revascularization of target limb – Unplanned target limb major amputation (above the ankle) – Symptomatic thrombus or distal emboli that require surgical, mechanical or pharmacologic means to improve flow and extend hospitalization – Perforations that require an intervention, including bail-out stenting • Primary patency at 24 months. • Clinically-driven TLR at 30 days, 6, 12 and 24 months. • Ankle-brachial index (ABI) at 30 days, 6, 12 and 24 months reported as change from baseline • Rutherford Category at 30 days, 6, 12, and 24 months reported as change from baseline. • Quality of Life assessed by EQ-5D questionnaire at 30 days, 6, 12 and 24 months reported as change from baseline. • Walking capacity assessed by the Walking Impairment Questionnaire (WIQ) at 30 days and at 6, 12 and 24 months reported as change from baseline
Randomized Study Inclusion Criteria:	**General Inclusion Criteria** 1. Subject is able and willing to comply with all assessments in the study. 2. Subject or subject's legal representative have been informed of the nature of the study, agrees to participate and has signed the approved consent form. 3. Age of subject is ≥ 18. 4. Rutherford Clinical Category 2, 3, or 4 of the target limb. 5. Estimated life expectancy >1 year. 6. Subject is a suitable candidate for angiography and endovascular intervention in the opinion of the investigator or per hospital guideline. 7. Subject is intended to undergo treatment with Lithoplasty followed by DCB, or DCB with standard balloon pre-dilatation. **Angiographic Inclusion Criteria** 8. Target lesion that is located in a native, de novo superficial femoral artery (SFA) or popliteal artery (popliteal artery extends to and

	ends proximal to the ostium of the anterior tibial artery). 9. Target lesion reference vessel diameter is between 4.0mm and 7.0mm by visual estimate. 10. Target lesion is ≥70% stenosis by investigator via visual estimate. 11. Target lesion length is ≤180mm for lesions 70-99% stenosed. Target lesion can be all or part of the 180mm treated zone. 12. Chronic total occlusion, lesion length is ≤100mm of the total ≤180 mm target lesion. 13. Subject has at least one patent tibial vessel on the target leg with runoff to the foot, defined as no stenosis >50%. 14. Calcification is at least moderate defined as presence of fluoroscopic evidence of calcification: 1) on parallel sides of the vessel and 2) extending > 50% the length of the lesion if lesion is ≥50mm in length; or extending for minimum of 20mm if lesion is <50mm in length.
Randomized Study Exclusion Criteria:	**General Exclusion Criteria** 1. Rutherford Clinical Category 0, 1, 5 and 6. 2. Subject has active infection requiring antibiotic therapy. 3. Planned target limb major amputation (above the ankle). 4. History of prior endovascular or surgical procedure on the index limb within the past 30 days or planned within 30 days of the index procedure. 5. Subject has a known coagulopathy or has bleeding diatheses, thrombocytopenia with platelet count less than 100,000/microliter. 6. Subject in whom antiplatelet or anticoagulant therapy is contraindicated. 7. Subject has known allergy to contrast agents or medications used to perform endovascular intervention that cannot be adequately pre-treated. 8. Subject has known allergy to urethane, nylon, or silicone. 9. Myocardial infarction within 60 days prior to enrollment. 10. History of stroke within 60 days prior to enrollment. 11. History of thrombolytic therapy within two weeks of enrollment. 12. Subject has acute or chronic renal disease defined as serum creatinine of >2.5 mg/dL or >220 umol/L, or on dialysis. 13. Subject is pregnant or nursing.

14. Subject is participating in another research study involving an investigational agent (pharmaceutical, biologic, or medical device) that has not reached the primary endpoint.
15. Subject has other medical, social or psychological problems that, in the opinion of the investigator, preclude them from receiving this treatment, and the procedures and evaluations pre- and post-treatment.
16. The use of specialty balloons, re-entry or atherectomy devices.

Angiographic Exclusion Criteria

17. In-stent restenosis within 10mm of the target zone.
18. Lesions within 10mm of the ostium of the SFA or within 10mm of the ostium of the anterior tibial artery.
19. Evidence of aneurysm or thrombus in target vessel.
20. No calcium or mild calcium in the target lesion.
21. Target lesion within native or synthetic vessel grafts.
22. Subject has significant stenosis (>50% stenosis) or occlusion of inflow tract before target treatment zone (e.g. iliac or common femoral) not successfully treated.
23. Subject requires treatment of a peripheral lesion on the ipsilateral limb distal to target site at the time of the index procedure.
24. Failure to successfully cross the guidewire across the target lesion; successful crossing defined as tip of the guidewire distal to the target lesion in the absence of flow limiting dissections or perforations.

Subjects who do not meet the inclusion/exclusion criteria for the randomized study may satisfy the eligibility criteria for the observational study.

Randomized Study Statistical Methods:	The randomized study is powered to show that the Shockwave Medical Peripheral Lithoplasty System is superior to standard balloon angioplasty, both in the primary effectiveness endpoint of Procedural Success, and in the powered secondary effectiveness endpoint of Primary Patency. Procedural Success will be assessed on a per-subject basis. The objective of the study is to show that the Procedural Success Rate for the Lithoplasty treatment arm is greater than the Procedural Success Rate for the PTA treatment arm. The objective is met when the resulting Fisher's Exact test is statistically significant using a one-sided $\alpha = 0.025$ level of statistical significance. Primary Patency at 12 months will be assessed on a per-subject basis. If the primary effectiveness objective is met, then the powered secondary effectiveness endpoint will be tested. The objective of the study is to show that the Primary Patency Rate for Lithoplasty followed by DCB treatment arm is greater than the Primary Patency Rate for the PTA followed by DCB treatment arm. The objective is met when the resulting Fisher's Exact test is statistically significant using a one-sided $\alpha = 0.025$ level of statistical significance. The selected baseline variables will be compared between the Lithoplasty followed by DCB versus PTA followed by DCB treatment arms. Additionally, statistical analyses will be performed for primary and powered secondary effectiveness endpoints based on selected subgroups that will be defined in the statistical analysis plan. *Primary Analysis Set:* The primary analysis set will be the Intent-to-Treat (ITT) population. The ITT population includes all randomized subjects, which is the point of subject enrollment. *Secondary Analysis Set:* The secondary analysis set will be the Per-Protocol (PP) population. The PP population includes all subjects who received the correct randomized treatment assignment and had no pre-specified inclusion and exclusion violation(s).
Observational Study Primary Effectiveness Endpoint:	Procedural success is defined as final residual stenosis $\leq$30% without flow-limiting dissection (≥ grade D) by angiographic core lab.
Observational Study Inclusion Criteria:	1. Subjects intended to be treated with the Shockwave Medical Peripheral Lithoplasty® System for de-novo or restenotic lesions of the

	femoral, ilio-femoral, popliteal, and infra-popliteal arteries. 2. Subjects presenting with claudication or CLI by Rutherford Clinical Category 2,3,4,5, or 6 of the target limb. 3. Age of subject is ≥ 18. 4. Subject or subject's legal representative have been informed of the nature of the study, agrees to participate, and has signed the approved study consent form. 5. Calcification is at least moderate, defined as presence of fluoroscopic evidence of calcification: 1) on parallel sides of the vessel and 2) extending > 50% the length of the lesion if lesion is ≥50mm in length; or extending for minimum of 20mm if lesion is <50mm in length.
Observational Study Exclusion Criteria:	1. Subjects with any medical condition that would make him/her an inappropriate candidate for treatment with Shockwave Medical Peripheral Lithoplasty® System as per Instructions for Use (IFU) or investigator's opinion. 2. Subject is already enrolled in other investigational (interventional) studies that would interfere with study endpoints.
Observational Study Statistical Methods:	Descriptive statistics will be reported for the observational study.
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3.0 INTRODUCTION

3.1 Background

Peripheral arterial disease (PAD) is a chronic occlusive arterial disease caused by plaque buildup in the arterial lumen, which leads to diminished blood flow. Disability and mortality associated with PAD has increased over the last 20 years and is no longer limited to the elderly population and now includes young adults.[1] Globally, 202 million people were living with PAD in 2010.[2] The femoropopliteal artery is the most common location for occlusive disease and lower extremity PAD is the third leading cause of atherosclerotic cardiovascular morbidity behind cardiovascular disease and stroke.[1] Approximately 15-30% of people with lower extremity PAD will progress from intermittent claudication (IC) to critical limb ischemia (CLI)[3, 4] and will require some type of percutaneous endovascular or surgical procedure to achieve revascularization.

The presence and extent of calcification adds to the complexity of treating these lesions.[5, 6] The risk factors most strongly associated with vascular calcification are advanced age, diabetes mellitus, chronic kidney disease and hypertension.[7] A recent study noted those above 70 years of age had vascular calcium present in at least one vascular bed, and two-thirds had calcium in all arterial beds.[8] Angiography has been shown to underestimate the degree of vascular calcium, which is concerning since it is primarily used to determine the appropriate percutaneous strategy for the treatment of PAD.[9] Calcification increases the risk of vascular complications following treatment with angioplasty or stenting including dissections, perforation, distal embolization, TLR and binary restenosis.[10, 11, 12, 13, 14]

Traditional interventional therapies for PAD have ongoing complications including acute procedure failure and long-term restenosis. Acute procedural failure is the result of incomplete vessel expansion with ongoing high-grade stenosis, or flow-limiting dissections, both of which occur in those presenting with greater complexity and degree of vascular calcification. Bail-out stenting with a metallic implant is required in these situations to ensure vessel patency.

Lithoplasty is a balloon-based technology that targets calcification to “normalize” vessel compliance prior to low pressure dilatation. Lithoplasty is designed to optimize acute gain while minimizing acute vessel injury and reducing bail-out stenting. In a recent presentation of pooled 30-day results of the DISRUPT PAD program, Lithoplasty demonstrated compelling effectiveness and safety results in the treatment of moderately and severely calcified vessels with minimal vessel injury, and only one stent implanted in 95 subjects. Acute effectiveness results showed high procedural success across all types of lesions and a large acute gain of 3.0mm after the procedure.[15]

In the chronic phase, target lesion restenosis leads to recurrence of claudication symptoms and may result in repeated revascularizations, sometimes requiring surgical bypass to maintain durable patency in the lower extremity.[16],[17] The advent of biologic therapies with anti-proliferative drugs has resulted in a paradigm shift in the treatment of PAD. Drug-coated balloons (DCB) have gained acceptance as a method to deliver biologic therapies with the anti-proliferative drug paclitaxel to combat restenosis. Recent pivotal studies with DCBs in lesions up to 15-18cm have shown positive 12 month patency results and a lower need for implants[18],[19] though they have excluded severe calcium. All-comers DCB studies have enrolled longer lesions without severe calcium and have shown an ongoing favorable benefit, though the need for stent implantation reaches 40% in longer lesions.[20] A recent single-center experience suggests severe calcium acts as a barrier to DCBs and results in a dramatic reduction in 12 month patency for those with circumferential and long calcium. [21]

Although considerable progress has been made over the last decade, the search continues for the optimal treatment strategy in calcified, stenotic PAD that delivers durable patency results. The combination of peripheral Lithoplasty to treat calcification and reduce the need for stents, in conjunction with a DCB to reduce restenosis in the long term is an attractive therapeutic option for patients with PAD. The objectives of the Disrupt PAD III randomized study are to identify if combination therapy results in improved acute gain and less need for stents, as well as an improved long term patency when compared to DCB with standard balloon pre-dilatation. The objective of the observational study is to assess the real-world acute performance of the Shockwave Medical Peripheral Lithoplasty® in the treatment of calcified, stenotic, peripheral arteries.

3.2 Study Device Description

The study devices being evaluated in the randomized study are the Shockwave Medical Peripheral Lithoplasty® System (referred to as the Lithoplasty System throughout the remainder of this document), and the Medtronic IN.PACT Drug Coated Balloon (DCB).

The treatment arm of the randomized study will be treated using Lithoplasty and DCB, and the control arm will be treated using percutaneous transluminal angioplasty (PTA) and DCB. A description of the Lithoplasty System is followed by a description of the IN.PACT DCB in the sections below.

Refer to each manufacturer's instructions for use (IFU) provided with these commercially available devices for a complete product description.

3.2.1 Shockwave Medical Lithoplasty System

The Shockwave Medical Lithoplasty System is a proprietary balloon catheter system designed to enhance percutaneous transluminal angioplasty by enabling delivery of the calcium disrupting capability of lithotripsy prior to balloon dilatation at low pressures. The Lithoplasty System consists of a Lithoplasty balloon catheter with five integrated pairs of lithotripsy emitters, a Lithoplasty Generator, Connector Cable, and related accessories and replacement components.

The Lithoplasty Catheter is delivered through the peripheral arterial system of the lower extremities to the site of an otherwise difficult to treat, calcified stenosis. The balloon is inflated at a lower than nominal pressure and the lithotripsy emitters are energized thereby generating pulsatile mechanical energy within the balloon at the target treatment site, disrupting calcium within the lesion, and allowing subsequent dilation of a peripheral artery stenosis using low balloon pressure.

The balloon is available in 8 sizes: 3.5 mm, 4.0 mm, 4.5 mm, 5.0 mm, 5.5 mm, 6.0 mm, 6.5 mm, and 7.0 mm diameter and 60 mm length. The OTW catheter has a working length of 110 cm and is compatible with 300 cm length, 0.014" guide wires. The catheter is compatible with 6 or 7Fr introducer sheaths depending on balloon size. The catheter tri-lumen hub contains an inflation lumen, a guidewire lumen, and the Lithoplasty connector. The inflation lumen is used for inflation of the balloon with 50/50 saline/contrast medium. A Connector Cable is a remote actuator that connects the Lithoplasty Generator to the Lithoplasty Catheter and is used to activate energy delivery from the Lithoplasty Generator.

The Shockwave S^4 Intravascular Lithoplasty Catheter is a line extension and was specifically designed to treat calcified below-the-knee (BTK) calcium. Currently, it is available for use in the PAD III Observational Study Arm only.

The catheters are available in two sizes of 3.5 mm and 4.0 mm in a 40 mm length and are compatible with the Shockwave Lithoplasty generator and connector cable. The catheters are 0.014" guidewire and 5F sheath compatible with a 135 cm working length.

The Lithoplasty Catheter is supplied sterile via e-beam sterilization. It is intended for single use only and is not intended for reuse or re-sterilization. The Connector Cable and Lithoplasty Generator are non-sterile, reusable medical devices.

3.2.2 IN.PACT Admiral DCB

The IN.PACT Admiral DCB is an over-the-wire (OTW) balloon catheter with a drug-coated balloon at the distal tip. The drug component, referred to as the FreePac™ drug coating, consists of the drug paclitaxel and the excipient urea. The device component physically dilates the vessel lumen by PTA, and the drug is intended to reduce the proliferative response that is associated with restenosis.

PTA Catheter Component

The IN.PACT Admiral DCB is available in balloon lengths ranging from 20 mm to 120 mm, balloon diameters ranging from 4.0 mm to 7.0 mm, and in catheter effective lengths of 80 cm and 130 cm. The IN.PACT Admiral DCB is compatible with 0.035" guidewires. Devices are compatible with 5F (for the 4.0 mm balloon diameter), 6F (for the 5.0-6.0 mm balloon diameters), and 7F (for the 7.0 mm balloon diameter) introducer sheaths.

The IN.PACT Admiral DCB is coated with the FreePac™ coating solution, which is a proprietary coating with a nominal drug dose density of 3.5 µg of paclitaxel per mm2 of the expanded balloon surface. The FreePac™ coating contains a hydrophilic excipient (urea) which facilitates the release and transfer of the active pharmaceutical ingredient (paclitaxel) into the arterial vessel wall. Additionally, the FreePac™ solution contains two solvents, tetrahydrofuran (THF) and pyrogen-free water, which are used during the FreePac™ formulation process but evaporate off the balloon surface after the FreePac™ coating is applied.

3.3 Observational Study Device

Subjects in the observational study will undergo treatment using the Shockwave Medical Lithoplasty System. Adjunctive procedures including PTA, DCB or stenting may be performed per physician discretion.

3.4 Indication for Use

3.4.1 Indications for Use Outside the United States

The Shockwave Medical Lithoplasty System is indicated for lithotripsy-enhanced, low-pressure balloon dilatation of calcified, stenotic peripheral arteries in patients who are candidates for percutaneous therapy.

The IN.PACT Admiral is indicated for percutaneous transluminal angioplasty (PTA) in patients with obstructive disease of peripheral arteries, including patients with in-stent restenosis (ISR) and arteriovenous (AV) access to help maintain hemodialysis access in patients with end-stage renal disease.

Note: While the IN.PACT Admiral DCB is indicated for use in patients with end-stage renal disease who require arteriovenous (AV) access to help maintain hemodialysis access, and in patients with in-stent restenosis, such patients are not being studied in this protocol.

3.4.2 US Indications for Use

The Shockwave Medical Lithoplasty System is intended for lithotripsy enhanced balloon dilatation of lesions, including calcified lesions, in the peripheral vasculature, including the iliac, femoral, ilio-femoral, popliteal, infra-popliteal, and renal arteries. Not for use in the coronary or cerebral vasculature.

The IN.PACT Admiral paclitaxel-coated PTA balloon catheter is indicated for percutaneous transluminal angioplasty, after appropriate vessel preparation, of de novo, restenotic, or in-stent restenotic lesions with lengths up to 180 mm in superficial femoral or popliteal arteries with reference vessel diameters of 4-7 mm.

4.0 STUDY OBJECTIVES

The objective of the randomized study is to assess the safety and effectiveness of Lithoplasty treatment used in combination with DCB versus standard balloon angioplasty used in combination with DCB to treat moderate and severely calcified femoropopliteal arteries.

Specific objectives will be to assess the impact on:

1. Procedural success of the vessel treatment prior to DCB or stenting
2. Provisional stent rate
3. Primary patency at 12 months

Subjects who do not meet the randomized study inclusion and exclusion criteria, but meet the inclusion and exclusion criteria for the observational study may be enrolled in the observational study. The objective of the observational study is to assess the real-world acute performance of the Shockwave Medical Lithoplasty System in the treatment of calcified, stenotic, peripheral arteries.

4.1 Randomized Study Primary Endpoint

Primary Effectiveness Endpoint:

Procedural success is defined as residual stenosis ≤30% without flow-limiting dissection (≥ grade D) prior to DCB or stenting by angiographic core lab.

4.2 Randomized Study Secondary Endpoints

Powered Secondary Effectiveness Endpoint:

Primary patency at 12 months defined as freedom from clinically-driven target lesion revascularization (TLR) and freedom from restenosis determined by duplex ultrasound or angiogram ≥50% stenosis. As pre-specified, acute PTA failure requiring a stent at any time during the index procedure will be counted as a loss of primary patency.

Other Secondary Endpoints:

Safety:

- MAE at 30 days, 6, 12 and 24 months defined as:
  - Need for emergency surgical revascularization of target limb
  - Unplanned target limb major amputation (above the ankle)
  - Symptomatic thrombus or distal emboli that require surgical, mechanical or pharmacologic means to improve flow and extend hospitalization

– Perforations that require an intervention, including bail-out stenting

Patency:
- Primary patency at 24 months.
- Clinically-driven TLR at 30 days, 6, 12 and 24 months.

Clinical:

- Ankle-brachial index ABI at 30 days, 6, 12 and 24 months reported as change from baseline
- Rutherford Category at 30 days, 6, 12 and 24 months reported as change from baseline.
- Quality of Life assessed by EQ-5D questionnaire at 30 days, 6, 12 and 24 months reported as change from baseline.
- Walking capacity assessed by the Walking Impairment Questionnaire (WIQ) at 30 days and at 6, 12 and 24 months reported as change from baseline

4.3 Observational Study Primary Endpoint

Primary Effectiveness Endpoint:

Procedural success is defined as final residual stenosis $\leq$30% without flow-limiting dissection (≥ grade D) by angiographic core lab.

5.0 STUDY DESIGN

This protocol includes a prospective, multi-center, single blind, randomized (1:1) study of Lithoplasty System treatment used in combination with DCB versus standard balloon angioplasty used in combination with DCB to treat moderate and severely calcified femoropopliteal arteries. Subjects who do not meet the randomized study inclusion and exclusion criteria, but who meet the observational study inclusion/exclusion criteria may be enrolled in that study. The observational study is a prospective, multi-center, single arm observational study.

5.1 Study Rationale

Both Lithoplasty and the IN.PACT DCB can be used individually, or in combination to treat patients with calcified, stenotic femoropopliteal arteries. As noted in the introductory section, although considerable progress has been made over the last decade, the search continues for the optimal treatment strategy in calcified, stenotic PAD that delivers durable patency results. The combination of peripheral Lithoplasty to treat calcification and reduce the need for stents, in conjunction with a DCB to reduce restenosis in the long term is an attractive therapeutic option for patients with PAD that is available to physicians. The objectives of the Disrupt PAD III randomized study are to identify if this combination therapy results in improved acute gain and less need for stents, as well as an improved long-term patency when compared to DCB with standard balloon pre-dilatation.

The objective of the observational study is to assess outcomes of real-world claudicant or CLI patients who do not meet the inclusion and exclusion criteria for the randomized study, but who are candidates for Lithoplasty System treatment.

5.2 Location

Up to sixty (60) global sites will participate in the study. Study sites will be located in Europe, the United States, and New Zealand.

5.3 Number of Subjects

A maximum of 400 subjects at up to 60 sites with moderate or severely calcified femoropopliteal artery disease presenting with Rutherford Category 2 to 4 will be enrolled in the randomized study. Each site will be allowed to enroll a maximum of 15% (60 subjects) of the total study enrollment.

A maximum of 1500 subjects will be enrolled in the observational study at the same 60 sites, with a minimum of 200 subjects treated with the S4 Lithoplasty catheter.

5.4 Clinical Study Duration

Enrollment in the randomized study is anticipated to last approximately 36 months. Subject follow-up intervals are at hospital discharge, at 30 days, and at 6, 12 and 24 months post-procedure. DUS assessments will occur at 12 and 24 months.

Enrollment during the course of the observational study is anticipated to last approximately 36 months. Subjects in the observational study will be followed through hospital discharge.

6.0 STUDY PROCEDURES

6.1 Screening

All patients presenting to the institution with known femoropopliteal disease requiring an interventional procedure will be evaluated for eligibility and participation in the randomized study. A member of the participating site's study team will perform an initial evaluation of the potential participant's medical history and previously performed examinations to assess for initial eligibility. Pre-procedure imaging (DUS, angiogram, CTA, MRA) is recommended, but not mandatory if within institution's standard-of-care to confirm stenosis and calcification ahead of procedural angiography.

Potential subjects will be screened for eligibility in the randomized study. Written informed consent will be obtained prior to any study-specific requirements. A potential subject will be informed of the elements of both the randomized and observational clinical studies including, risks, potential benefits and required follow-up procedures prior to obtaining the potential subject's informed consent. No study-specific requirements will be performed prior to obtaining informed consent.

Subjects who meet the inclusion/exclusion criteria for the randomized study will undergo an angiogram. At the time of the angiogram, the subject will be randomized if they meet the randomized study angiographic inclusion and exclusion criteria, and a guidewire is successfully passed through the target lesion. A subject is considered an angiographic screen failure for the randomized study if they do not meet angiographic eligibility.

If the subject does not meet the inclusion/exclusion criteria for the randomized study or presents with calcified stenosis in the iliac, common femoral or below-the-knee, and meets the inclusion/exclusion criteria for the observational study, the subject may be enrolled in the observational study. Once enrollment in the randomized portion of the study is complete, subjects may continue to be enrolled in the observational study provided they meet OS eligibility criteria.

6.2 Subject Selection

Subjects who meet all general and angiographic inclusion criteria and no general and angiographic exclusion criteria of the randomized study will be eligible for enrollment in the randomized study. Subjects who do not meet the randomized inclusion and exclusion criteria (or subjects recruited after enrollment in the randomized portion of the study is complete), but meet inclusion and exclusion criteria of the observational study will be eligible for enrollment in the observational study.

6.2.1 Randomized Study General Inclusion Criteria

1. Subject is able and willing to comply with all assessments in the study.
2. Subject or subject's legal representative have been informed of the nature of the study, agrees to participate and has signed the approved consent form.
3. Age of subject is $\geq$ 18.
4. Rutherford Clinical Category 2, 3, or 4 of the target limb.
5. Estimated life expectancy >1 year.
6. Subject is a suitable candidate for angiography and endovascular intervention in the opinion of the investigator or per hospital guideline.
7. Subject is intended to undergo treatment with Lithoplasty followed by DCB or DCB with standard balloon pre-dilatation.

6.2.2 Randomized Study Angiographic Inclusion Criteria

8. Target lesion that is located in a native, de novo superficial femoral artery (SFA) or popliteal artery (popliteal artery extends to and ends proximal to the ostium of the anterior tibial artery).
9. Target lesion reference vessel diameter is between 4.0mm and 7.0mm by visual estimate.
10. Target lesion is ≥70% stenosis by investigator via visual estimate.
11. Target lesion length is ≤180mm for lesions 70-99% stenosed. Target lesion can be all or part of the 180mm treated zone.
12. Chronic total occlusion, lesion length is ≤100mm of the total ≤180 mm target lesion.
13. Subject has at least one patent tibial vessel on the target leg with runoff to the foot, defined as no stenosis >50%.
14. Calcification is at least moderate defined as presence of fluoroscopic evidence of calcification: 1) on parallel sides of the vessel and 2) extending > 50% the length of the lesion if lesion is ≥50mm in length; or extending for minimum of 20mm if lesion is <50mm in length.

6.2.3 Randomized Study General Exclusion Criteria

1. Rutherford Clinical Category 0, 1, 5 and 6.
2. Subject has active infection requiring antibiotic therapy.
3. Planned target limb major amputation (above the ankle).

4. History of prior endovascular or surgical procedure on the index limb within the past 30 days or planned within 30 days of the index procedure.
5. Subject has a known coagulopathy or has bleeding diatheses, thrombocytopenia with platelet count less than 100,000/microliter.
6. Subject in whom antiplatelet or anticoagulant therapy is contraindicated.
7. Subject has known allergy to contrast agents or medications used to perform endovascular intervention that cannot be adequately pre-treated.
8. Subject has known allergy to urethane, nylon, or silicone.
9. Myocardial infarction within 60 days prior to enrollment.
10. History of stroke within 60 days prior to enrollment.
11. History of thrombolytic therapy within two weeks of enrollment.
12. Subject has acute or chronic renal disease defined as serum creatinine of >2.5 mg/dL or >220 umol/L, or on dialysis.
13. Subject is pregnant or nursing.
14. Subject is participating in another research study involving an investigational agent (pharmaceutical, biologic, or medical device) that has not reached the primary endpoint.
15. Subject has other medical, social or psychological problems that, in the opinion of the investigator, preclude them from receiving this treatment, and the procedures and evaluations pre- and post-treatment.
16. The use of specialty balloons, re-entry or atherectomy devices.

6.2.4 Randomized Study Angiographic Exclusion Criteria

17. In-stent restenosis within 10mm of the target zone.
18. Lesions within 10mm of the ostium of the SFA or within 10mm of the ostium of the anterior tibial artery.
19. Evidence of aneurysm or thrombus in target vessel.
20. No calcium or mild calcium in the target lesion.
21. Target lesion within native or synthetic vessel grafts.
22. Subject has significant stenosis (>50% stenosis) or occlusion of inflow tract before target treatment zone (e.g. iliac or common femoral) not successfully treated.
23. Subject requires treatment of a peripheral lesion on the ipsilateral limb distal to target site at the time of the index procedure.

24. Failure to successfully cross the guidewire across the target lesion; successful crossing defined as tip of the guidewire distal to the target lesion in the absence of flow limiting dissections or perforations.

6.2.5 Observational Study Inclusion Criteria

1. Subjects intended to be treated with Shockwave Medical Lithoplasty for de-novo or restenotic lesions of the femoral, ilio-femoral, popliteal, and infra-popliteal arteries.
2. Subjects presenting with claudication or CLI by Rutherford Clinical Category 2,3,4,5, or 6 of the target limb.
3. Age of subject is $\geq$ 18.
4. Subject or subject's legal representative have been informed of the nature of the study, agrees to participate and has signed the approved consent form.
5. Calcification is at least moderate defined as presence of fluoroscopic evidence of calcification: 1) on parallel sides of the vessel and 2) extending > 50% the length of the lesion if lesion is ≥50mm in length; or extending for minimum of 20mm if lesion is <50mm in length.

6.2.6 Observational Study Exclusion Criteria

1. Subjects with any medical condition that would make him/her an inappropriate candidate for treatment with Shockwave Lithoplasty as per Instructions for Use (IFU) or investigator's opinion.
2. Subject already enrolled in other investigational (interventional) studies that would interfere with study endpoints.

6.3 Informed Consent

Prior to undergoing any study specific tests or procedures, the subject (or their *legally* authorized representative) must sign and date the site's current Ethics Committee (EC) or Institutional Review Board (IRB) and Shockwave Medical approved informed consent form in order to be eligible for study participation. The informed consent must contain all elements required by ISO 14155:2011 and be in compliance with the ethical principles of the Declaration of Helsinki.

The potential subject will be informed of the elements of both the randomized and observational clinical studies including, risks, potential benefits and required follow-up procedures prior to obtaining the potential subject's informed consent.

6.3.1 Process for Obtaining Informed Consent

The process for obtaining informed consent is outlined below:

- The Investigator or his/her authorized designee conducts the informed consent process,
- All aspects of the clinical study that are relevant to the subject's decision to participate will be included in the consent form,
- Investigators will avoid any coercion or undue improper influence on, or inducement of, the subject to participate,
- The consent process shall not waive or appear to waive the subject's legal rights,
- The consent must use native non-technical language that is understandable to the subject,
- The Investigator, or designee will provide ample time for the subject to read and understand the informed consent form and to consider participation in the clinical investigation,
- The consent must include personally dated signatures of the subject and the Investigator, or an authorized designee responsible for conducting the informed consent process, and/or all signatures required by the reviewing EC/IRB,
- The Investigator, or designee, will provide the subject with a copy of the signed and dated informed consent form and any other written information,

6.3.2 Subjects Needing Legally Authorized Representative

Informed consent may be given by a legally authorized representative only if a subject is unable to make the decision to participate in a clinical study. In such cases, the subject shall also be informed about the clinical study within his/her ability to understand.

6.3.3 Subjects Unable to Read or Write

Informed consent shall be obtained through a supervised oral process if a subject or legally authorized representative is unable to read or write if allowed by the EC/IRB. An independent witness shall be present throughout the process. The written informed consent form and any other information shall be explained to the prospective subject or his/her legally authorized representative and, whenever possible, either shall sign and personally date the informed consent form. The witness also signs and personally dates the informed consent form attesting that the information was accurately explained and that informed consent was freely given.

6.3.4 Addition of New Information

Shockwave Medical will revise the written informed consent form whenever new information becomes available that may be relevant to the subject's confirmed participation in the study. The revised information will be sent to the investigator for approval by the EC/IRB. After approval by the EC/IRB, a copy of this information must be provided to the participating subjects, and the informed consent process as described above needs to be repeated.

6.4 Schedule of Events and Evaluations

Table 1 lists the schedule of events and evaluations required for the randomized study. Table 2 lists the schedule of events and evaluations required for the observational study.

Table 1. Randomized Study Schedule of Events

Assessment	Screening/ Baseline[1]	Enrollment and Procedure	Discharge[3]	30 Days (+/- 7D)	6 Months (+/- 30D)	12 Months (+/- 30D)	24 Months (+/- 30D)	Pre Target Limb Revasc[5]
Informed Consent[2]	X							
Medical History	X							
Physical Examination	X		X	X	X	X	X	X
Laboratory Assessments: Chemistry and CBC	X							
Urine pregnancy test if female[1]	X							
Walking Impairment Questionnaire	X			X	X	X	X	X
EQ-5D	X			X	X	X	X	X
Ankle Brachial Index (ABI)[1]	X			X	X	X	X	X
Rutherford Category (RC)	X			X	X	X	X	X
Angiographic Lesion Assessment		X						X
Duplex Ultrasound	R[4]					X	X	

Assessment	Screening/ Baseline[1]	Enrollment and Procedure	Discharge[3]	30 Days (+/- 7D)	6 Months (+/- 30D)	12 Months (+/- 30D)	24 Months (+/- 30D)	Pre Target Limb Revasc[5]
Medication regimen per protocol	X		X	X	X	X	X	
Adverse Event Assessment		X	X	X	X	X	X	X

[1] Evaluations may be done up to 30 days before the procedure with the exception of pregnancy test, which must be completed within 7 days of treatment procedure and ABI, which may be completed within 60 days of the procedure.
[2] Consent to be obtained within 30 days prior to treatment procedure.
[3] Examinations are to be completed within 12-24 hours post-procedure or prior to discharge, whichever comes first.
[4] Pre-procedure imaging (DUS, angiogram, CTA, MRA) is recommended, but not mandatory if within Institution's standard-of-care to confirm stenosis and calcification ahead of angiography.
[5] Evaluations will be completed prior to a target limb revascularization to assess symptoms and functional status.

Table 2. Observational Study Schedule of Events

Assessment	Screening/ Baseline[1]	Enrollment and Procedure	Discharge[3]
Informed Consent[2]	X		
Medical History	X		
Physical Examination			X
Ankle Brachial Index (ABI)[1]	X		
Rutherford Category (RC)	X		
Angiographic Lesion Assessment		X	
Duplex Ultrasound	R[4]		
Medication regimen per protocol			X
Adverse Event Assessment		X	X

[1] Evaluations may be done up to 30 days before the procedure with the exception of ABI, which may be completed within 60 days of the procedure.
[2] Consent to be obtained within 30 days prior to treatment procedure.
[3] Examinations are to be completed within 12-24 hours post-procedure or prior to discharge, whichever comes first.
[4] Pre-procedure imaging (DUS, angiogram, CTA, MRA) is recommended, but not mandatory if within Institution's standard-of-care to confirm stenosis and calcification ahead of angiography.

6.5 Medications

It is recommended to administer anticoagulation and antiplatelet medications according to existing 2011 ESC and 2011 ACC/AHA guidelines for treatment of peripheral arterial disease as noted in Table 3 below.

Table 3. Anticoagulation / Antiplatelet Medications

Medication	Pre-procedure	During Procedure	Post-procedure
Aspirin	Loading dose of up to 500 mg required, if not on chronic single-agent antiplatelet therapy.	N/A	Minimum of 75 mg/QD for a minimum of 30 days.
Clopidogrel	Loading dose of 300-600 mg required, if not on chronic single-agent antiplatelet therapy or 75 mg times three days prior to treatment.	N/A	75 mg/QD for a minimum of 30 days.
Heparin	N/A	Per hospital standard of care	N/A
Prasugrel*	Loading dose of 60 mg required, if not on chronic single-agent antiplatelet therapy or 10 mg times three days prior to treatment.	N/A	10 mg/QD for 30 days.
Ticagrelor*	Loading dose of 180 mg required, if not on chronic antiplatelet therapy.	N/A	90 mg/BID for a minimum of 30 days.

* Prasugrel or Ticagrelor as an alternative to clopidogrel is appropriate for existing management of acute coronary syndrome (ACS). Follow 2014 ESC myocardial revascularization guidelines: 2014 ESC/EACTS Guidelines on myocardial revascularization European Heart Journal (2014) 35, 2541–2619 doi:10.1093/eurheartj/ehu278

6.6 Baseline Assessments

Baseline assessments for subjects in the randomized study and the observational study must be completed within 30 days of the procedure with the exception of ABI, which can be completed within 60 days of the procedure and a pregnancy test, which must be done within 7 days of procedure. Informed consent must be obtained prior to any study-specific evaluations not considered standard of care needed to assess eligibility. Subjects on warfarin or direct thrombin inhibitors should be followed per institutional standard of care by the physician.

Baseline assessments for the randomized study include:

- Medical history

- Physical examination
  - Vital signs
  - Height and weight
  - Ankle-brachial index
  - Rutherford Category
- Laboratory assessments
- Urine pregnancy test if female of child-bearing age
- Anticoagulation and antiplatelet medications
- EQ-5D and WIQ questionnaires

Baseline assessments for the observational study include:

- Medical History
- Ankle Brachial Index (ABI)
- Rutherford Category (RC)

6.7 Index Procedure

6.7.1 Angiographic Eligibility

A radiopaque ruler will be placed directly on the subject's leg under the sterile drapes. The end of the ruler is placed at the tibial tubercle. The ruler will serve as a location marker for the target lesion being treated the index procedure, and as a reference point for follow-up examinations including follow-up duplex evaluations.

Angiography will be performed per the guidelines established by the core lab, including an assessment of the target lesion and distal run-off. All randomized study angiographic inclusion and exclusion criteria in Table 4 must be met prior to the decision to randomize. The subject can then be randomized, after a guidewire is successfully passed through the target lesion. The subject is considered an angiographic screen failure for enrollment in the randomized study if they do not meet angiographic eligibility. The subject may be enrolled in the observational study.

Table 4. Angiographic Eligibility Assessment

Inclusion Criteria	Exclusion Criteria
Target lesion that is located in a native, de novo superficial femoral artery (SFA) or popliteal artery (popliteal artery extends to and ends proximal to the ostium of the anterior tibial artery).	In-stent restenosis within 10mm of the target zone.
Target lesion reference vessel diameter	Lesions within 10mm of the ostium of the

Inclusion Criteria	Exclusion Criteria
is between 4.0mm and 7.0mm by visual estimate.	SFA or within 10mm of the ostium of the anterior tibial artery.
Target lesion is ≥70% stenosis by investigator via visual estimate.	Evidence of aneurysm or thrombus in target vessel.
Target lesion length is ≤180mm for lesions 70-99% stenosed. Target lesion can be all or part of the 180mm treated zone.	No calcium or mild calcium in the target lesion.
Chronic total occlusion, lesion length is ≤100mm of the total ≤180 mm target lesion.	Target lesion within native or synthetic vessel grafts.
Subject has at least one patent tibial vessel on the target leg with runoff to the foot, defined as no stenosis >50%.	Subject has significant stenosis (>50% stenosis) or occlusion of inflow tract before target treatment zone (e.g. iliac or common femoral) not successfully treated.
Calcification is at least moderate defined as presence of fluoroscopic evidence of calcification: 1) on parallel sides of the vessel and 2) extending > 50% the length of the lesion if lesion is ≥50mm in length; or extending for minimum of 20mm if lesion is <50mm in length.	Subject requires treatment of a peripheral lesion on the ipsilateral limb distal to target site at the time of the index procedure.
	Failure to successfully cross the guidewire across the target lesion; successful crossing defined as tip of the guidewire distal to the target lesion in the absence of flow limiting dissections or perforations.

6.7.2 Randomized Study Randomization and Enrollment

The subject will be enrolled in the randomized study after they have signed the study informed consent, and all general and angiographic eligibility criteria have been confirmed, including successful wire crossing.

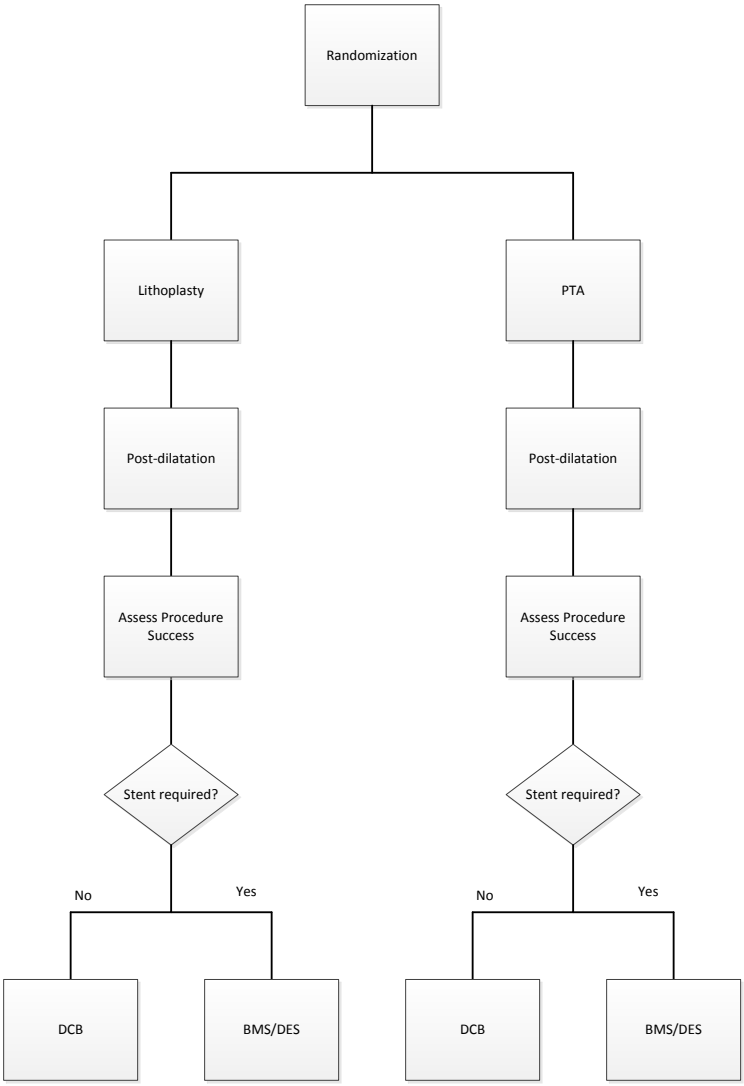
Eligible subjects in the randomized study will be randomized in a 1:1 fashion to one of the two treatment arms:

1. Lithoplasty System followed by DCB *or*
2. Standard balloon angioplasty followed by DCB

Randomization will be accomplished using Interactive Voice Response System (IVRS) or an online website. Refer to the IVRS randomization instructions on how to randomize subjects. Confirmation of randomization assignment will be provided to the site after randomization occurs, and must be maintained in the study binders.

Enrollment is defined at the point of randomization. All randomized subjects will be included in the intent to treat analysis. In the event the subject is not treated or treated according to the wrong treatment arm, they will be analyzed according to the treatment arm in which they were randomized and followed per protocol.

Figure 1. Randomized Study flow diagram



6.7.3 Randomized Study Blinding

The randomized study is a single blind study. The randomized study subjects will remain blinded through completion of the 12-month follow-up visit for the powered secondary effectiveness endpoint. The independent Core Labs and the Clinical Events Committee (CEC) will be blinded to the treatment assignment throughout the 24-month study duration.

Site staff, including investigators and research coordinators, will not be blinded to treatment assignment due to visual differences in the devices in each treatment arm. Shockwave Medical employees and CROs whose responsibilities require knowledge of treatment assignment to perform their respective roles will not be blinded. These individuals include data management, study monitors, safety, and regulatory

staff. Unblinded employees within Shockwave Medical and at the clinical sites will receive training to ensure maintenance of the study blinding.

6.7.4 Randomized Study Treatment Arm Procedure

Lithoplasty treatment

A full description of the procedure is detailed in the Instructions for Use (IFU). The appropriate sized Lithoplasty balloon catheter should be selected per the IFU. Once the Lithoplasty balloon is placed in the target lesion area, the balloon should be inflated to 4 ATM and Lithoplasty treatment delivered for the pre-programmed time of 30 seconds to deliver 30 pulses. Note that the generator is programmed to force a minimum pause time of 10 seconds following every 30 pulses delivered. Following the Lithoplasty, inflate the balloon to the reference size using the balloon compliance chart (refer to IFU) and record lesion response on fluoroscopy. Deflate the balloon and wait 30 seconds to re-establish blood flow. Repeat the steps above to complete a minimum single treatment with 60 pulses. Additional treatments can be performed if deemed necessary.

If additional lesion area needs to be treated, follow the treatment steps as identified above and per the IFU. The catheter can be advanced to the next treatment area. Confirm the balloon catheter is of the appropriate size for the next treatment area.

If the operator is unable to pass the Lithoplasty balloon through the lesion, a standard PTA balloon, up to 3.0mm, may be used prior to treatment with the Lithoplasty Balloon. All efforts should be made to pass the Lithoplasty balloon prior to use of a standard PTA balloon.

Post-dilatation with a semi or non-compliant PTA balloon catheter should be completed when post-Lithoplasty results in one of the following below. The physician should use a 1:1 balloon catheter to artery ratio and may dilate for up to three minutes.

- Residual stenosis >30% by visual estimate, or
- Presence of a flow-limiting (≥Grade D) dissection, and
- Trans-lesional gradient >10 mm Hg is observed.

Procedural Success

Following Lithoplasty and any post-dilatation, an angiographic cine will be obtained to assess procedural success of the vessel treatment prior to DCB or stenting. Follow the angiographic core lab procedures to complete angiography showing the target lesion with reproducible landmarks for follow-up evaluation and assessment.

Provisional stenting should be performed with a bare or drug-eluting stent after primary treatment or post-dilatation balloon inflations are determined not to be successful. In order to ensure consistency between treatment arms, a provisional stent should be placed for an acute PTA failure defined as:

- Residual stenosis ≥50% by visual estimate, or
- Un-resolved flow-limiting (≥Grade D) dissection, and
- Trans-lesional gradient >10 mm Hg is observed.

The angiographic core lab will confirm correct use of a stent based on the criteria above for subjects that receive a provisional stent. As pre-specified, an acute PTA failure requiring a stent at any time during the index procedure will be counted as a loss of primary patency.

DCB (Drug-coated balloon) treatment

Investigators should follow the Medtronic IN.PACT IFU for instructions on the DCB procedure. No additional pre-dilatation will be required after the Lithoplasty procedure and before treatment with a DCB. Ensure the entire vessel segment dilated with a Lithoplasty catheter is covered by a DCB to prevent geographic miss.

Follow procedures to maximize optimal balloon angioplasty results in the IN.PACT IFU including a prolonged inflation of the DCB.

Final angiogram

Follow the angiographic core lab procedures to complete final angiography showing the target lesion with reproducible landmarks for follow-up evaluation and assessment. In addition, a final distal run-off with imaging to the foot shall be performed to assess for procedural complications, including distal embolization and thrombus.

6.7.5 Randomized Study Control Arm Procedure

PTA treatment

PTA treatment can be completed with any commercially available semi or non-compliant PTA balloon catheters. No specialty balloons including scoring or cutting balloons are permitted. Investigators should follow the manufacturer's instructions for use to size the reference vessel to the manufacturer's compliance chart. If additional lesion area needs to be treated, follow the treatment steps as identified above and per the IFU. The catheter can be advanced to the next treatment area. Confirm the balloon catheter is of the appropriate size for the next treatment area.

To ensure consistency between the treatment and control arms, dilatation should be done for one minute per treatment area.

Post-dilatation with a semi or non-compliant PTA balloon catheter should be completed when post-PTA results in one of the following below. The physician should use a 1:1 balloon catheter to artery ratio and may dilate for up to three minutes.

- Residual stenosis >30% by visual estimate, or
- Presence of a flow-limiting (≥Grade D) dissection, and

- Trans-lesional gradient >10 mm Hg is observed.

Procedural Success

Following PTA dilatation and any post-dilatation, an angiographic cine will be obtained to assess procedural success of the vessel treatment prior to DCB or stenting. Follow the angiographic core lab procedures to complete angiography showing the target lesion with reproducible landmarks for follow-up evaluation and assessment.

Provisional stenting should be performed with a bare or drug-eluting stent after primary treatment or post-dilatation balloon inflations are determined not to be successful. In order to ensure consistency between treatment arms, a provisional stent should be placed for an acute PTA failure defined as:

- Residual stenosis ≥50% by visual estimate, or
- Un-resolved flow-limiting (≥Grade D) dissection, and
- Trans-lesional gradient >10 mm Hg is observed.

The angiographic core lab will confirm correct use of a stent based on the criteria above for subjects that receive a provisional stent. As pre-specified, an acute PTA failure requiring a stent will be counted as a loss of primary patency.

Drug-coated balloon treatment

Investigators should follow the Medtronic IN.PACT IFU for instructions on the DCB procedure. Ensure the entire vessel segment dilated with PTA balloon catheter is covered by a DCB to prevent geographic miss.

Follow procedures to maximize optimal balloon angioplasty results in the IN.PACT IFU including a prolonged inflation of the DCB.

Final angiogram

Follow the angiographic core lab procedures to complete a final angiographic cine showing the target lesion with reproducible landmarks for follow-up evaluation and assessment. In addition, a final distal run-off with imaging to the foot shall be performed to assess for procedural complications, including distal embolization and thrombus.

6.7.6 Observational Study Procedure

For subjects enrolled in the observational study, Lithoplasty treatment should be administered as indicated in section 6.7.4 and in accordance with the procedure details in the IFU. Adjunctive procedures including PTA, DCB or stenting may be performed per physician discretion.

Procedural success and final angiogram

Angiographic cines will be obtained to assess procedural success of the vessel treatment post-Lithoplasty and following any adjunctive procedures, if performed. In

addition, a final distal run-off with imaging to the foot shall be performed to assess for procedural complications, including distal embolization and thrombus.

6.8 Follow-Up

6.8.1 Discharge or Within 12-24 Hours Post Procedure

The following assessments and procedures will be performed within **12-24 hours** post procedure or prior to hospital discharge, whichever occurs first **for subjects in the randomized and observational study:**

- Follow up visit assessments including:
  - Physical examination
  - Target review of symptoms
- Adverse event assessment
- Anticoagulation and antiplatelet medications

6.8.2 30-Day Follow-Up

The following evaluations will be scheduled for **30 days** (+/-7 days) post procedure for subjects in the ***randomized study only***:

- Follow-up visit assessments including:
  - Physical examination
  - Rutherford Category
  - ABI (at rest or after exercise; keep consistent with screening)
  - Target review of symptoms
- EQ-5D and WIQ questionnaires
- Adverse event assessment
- Anticoagulation and antiplatelet medications

6.8.3 6-Month Follow-Up

The following evaluations will be scheduled for **6 months** [**180 days** (+/-30 days)] post procedure for subjects in the ***randomized study only***:

- Follow-up visit assessments including:
  - Physical Examination
  - Rutherford Category
  - ABI (at rest or after exercise; keep consistent with screening)
  - Target review of symptoms
- EQ-5D and WIQ questionnaires
- Adverse event assessment
- Anticoagulation and antiplatelet medications

6.8.4 12-Month Follow-Up

The following evaluations will be scheduled for **12 months** [**365 days** (+/- 30 days)] post procedure for subjects in the ***randomized study only***:

- Follow-up visit assessments including:
  - Physical Examination
  - Rutherford Category
  - ABI (at rest or after exercise; keep consistent with screening)
  - Target review of symptoms
- EQ-5D and WIQ questionnaires
- Duplex ultrasound
- Adverse event assessment
- Anticoagulation and antiplatelet medications

6.8.5 24-Month Follow-Up

The following evaluations will be scheduled for **24 months** [**730 days** (+/- 30 days)] post procedure for subjects in the ***randomized study only***:

- Follow-up visit assessments including:
  - Physical Examination
  - Rutherford Category
  - ABI (at rest or after exercise; keep consistent with screening)
  - Target review of symptoms
- EQ-5D and WIQ questionnaires
- Duplex ultrasound
- Adverse event assessment
- Anticoagulation and antiplatelet medications

6.8.6 Prior to target limb revascularization

The following evaluations will be completed prior to any target limb revascularization to assess symptoms and functional status prior to revascularization.

  - Physical Examination
  - Rutherford Category
  - ABI (at rest or after exercise; keep consistent with screening)
  - Target review of symptoms
- EQ-5D and WIQ questionnaires
- Angiographic Lesion Assessment

6.8.7 Prospective Health Economic Sub-Study

A prospective health economic sub-study will be conducted at the US study sites for both the Randomized and the Observational study. For the Randomized study costs for the index procedure and costs related to PAD treatment of the target limb will be collected through 24 months of follow-up for both treatment arms. Subjects enrolled in the Observational study will have the cost of their index procedure collected. The objective is to understand the cost effectiveness of these two approaches on peripheral artery revascularization.

6.9 Subject Withdrawal

A study subject has the right to discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. A subject that has withdrawn from the study will be treated according to standard of medical care and will not be replaced.

7.0 BENEFITS AND RISKS

7.1 Benefits

There are no guaranteed benefits from participation in the study. The randomized study will provide safety and effectiveness data of Lithoplasty treatment used in combination with DCB versus DCB with standard balloon pre-dilatation to treat moderate and severely calcified femoropopliteal arteries. The observational study will provide outcomes data for the real-world claudicant or CLI populations. These clinical results may inform physicians in determining the optimal treatment strategy for this patient population.

7.2 Risks

For detailed information on the risks of the devices used in the study procedure, including a complete list of warnings, precautions and potential adverse events, please refer to the Instructions for Use for the Lithoplasty System and the IN.PACT DCB provided with the products. It is important to ensure that the IFU referred to represents the generation of both of the devices used in the study procedure.

7.3 Mitigation of Risks

As with any endovascular procedure, appropriate safety precautions will be followed. Risks of observed or theoretical adverse events have been mitigated through the Instructions for Use, physician training, and patient selection in the study protocol.

All efforts will be made to minimize these risks by:

- Site selection
- Ensuring compliance to the protocol and IFU
- Study Monitoring
- Safety processes – protocol adverse event reporting requirements, CEC oversight, and safety reporting to regulatory authorities including Vigilance reporting/US Medical Device Reporting, if required
- Risk management process

8.0 STATISTICAL CONSIDERATIONS

8.1 Introduction

The randomized study is a prospective, multi-center, single blind, randomized (1:1) study of Lithoplasty treatment used in combination with DCB versus standard balloon angioplasty used in combination with DCB to treat moderate and severely calcified femoropopliteal arteries.

A maximum of 400 subjects will be enrolled at up to 60 sites located in Europe, the United States and New Zealand.

The objective of the study is to assess the safety and effectiveness of Lithoplasty treatment used in combination with DCB versus standard balloon angioplasty used in combination with DCB to treat moderate and severely calcified femoropopliteal arteries.

Specific objectives will be to assess the impact on:

1. Procedural success of the vessel treatment prior to DCB or stenting
2. Provisional stent rate
3. Primary patency at 12 months

The observational study will assess baseline, procedural, and hospital discharge outcomes of Lithoplasty used in the treatment of subjects with calcified, stenotic, peripheral arteries.

8.2 Sample Size Justification

The randomized study is powered to show that the Shockwave Medical Peripheral Lithoplasty System is superior to standard balloon angioplasty, both in the primary effectiveness endpoint of Procedural Success, and in the powered secondary effectiveness endpoint of Primary Patency.

For the primary effectiveness endpoint of Procedural Success, assume the following:

Statistical Hypothesis: H_0: $\pi_{Treatment} \leq \pi_{Control}$ vs H_1: $\pi_{Treatment} > \pi_{Control}$, where $\pi_{Treatment}$ is the Procedural Success Rate for the Lithoplasty Treatment arm, and $\pi_{Control}$ is the Procedural Success Rate for the PTA Treatment arm.

Statistical Test: Fisher's Exact test

Statistical Significance: one-sided $\alpha = 0.025$

Statistical Power: $1 - \beta = 0.80$

Expected Success Rates: $\pi_{Treatment} = 0.85$ and $\pi_{Control} = 0.62$

Minimum Sample Size: n = 130 subjects, 65 per treatment arm

For the powered secondary effectiveness endpoint of Primary Patency at 12-Months, assume the following:

Statistical Hypothesis: H_0: $\pi_{Treatment} \leq \pi_{Control}$ vs H_1: $\pi_{Treatment} > \pi_{Control}$, where $\pi_{Treatment}$ is the Primary Patency Rate for the Lithoplasty followed by DCB Treatment arm, and $\pi_{Control}$ is the Primary Patency Rate for the PTA followed by DCB Treatment arm.

Statistical Test: Fisher's Exact test

Statistical Significance: one-sided $\alpha = 0.025$

Statistical Power: $1 - \beta = 0.85$

Expected Success Rates: $\pi_{Treatment} = 0.78$ and $\pi_{Control} = 0.61$

Minimum Sample Size: n = 284 subjects, 142 per treatment arm

The sample size requirements for the powered secondary effectiveness endpoint exceed those for the primary effectiveness endpoint. As a result, the powered secondary effectiveness endpoint will be used to calculate the minimum required sample size for the study. Assuming that roughly 15% of the subjects will be lost-to-follow-up, a total of 334 subjects (167 per treatment arm) is required for the powered secondary endpoint. In total, up to 400 subjects may be enrolled.

The observational study will include a maximum of 1500 subjects. Data collection for these subjects will include evaluations at baseline, procedural and hospital discharge intervals only.

8.3 Randomized Study Primary Endpoint – Procedural Success

Procedural success is defined as residual stenosis ≤30% without flow-limiting dissection (≥ grade D) prior to DCB or stenting by angiographic core lab.
Procedural Success will be assessed on a per-subject basis.

The objective of the study is to show that the Procedural Success Rate for the Lithoplasty treatment arm is greater than the Procedural Success Rate for the PTA treatment arm. The objective is met when the resulting Fisher's Exact test is statistically significant using a one-sided $\alpha = 0.025$ level of statistical significance.

8.4 Randomized Study Powered Secondary Effectiveness Endpoint – Primary Patency

The powered secondary effectiveness endpoint for the randomized study is Primary Patency at 12 months defined as freedom from clinically-driven target lesion revascularization (TLR) and freedom from restenosis determined by duplex ultrasound or angiogram >50% stenosis.

Primary Patency will be assessed on a per-subject basis.

If the primary effectiveness objective is met, then the powered secondary effectiveness endpoint will be tested. The objective of the study is to show that the Primary Patency Rate for the Lithoplasty followed by DCB treatment arm is greater than the Primary Patency Rate for the PTA followed by DCB treatment arm. The objective is met when the resulting Fisher's Exact test is statistically significant using a one-sided $\alpha = 0.025$ level of statistical significance.

8.5 Randomized Study Analysis of Baseline, Secondary Endpoints and Subgroups

Baseline variables will be compared between the Lithoplasty followed by DCB versus DCB with standard balloon pre-dilatation treatment arms.

Descriptive statistics for the secondary endpoints will be provided. Analyses will be provided at pre-specified time points including 30 day, 6, 12 or 24 months. In the event of a target limb or vessel revascularization, the data immediately prior to the revascularization will be applied for Rutherford Category, ABI, WIQ and EQ-5D secondary endpoints.

Additionally, statistical analyses will be performed for primary and powered secondary effectiveness endpoints based on selected subgroups that will be defined in the statistical analysis plan.

8.6 Randomized Study Secondary Endpoints:

Other randomized study secondary endpoints include the following:

Safety:

- MAE at 30 days, 6, 12 and 24 months defined as:
  - Need for emergency surgical revascularization of target limb
  - Unplanned target limb major amputation (above the ankle)
  - Symptomatic thrombus or distal emboli that require surgical, mechanical or pharmacologic means to improve flow and extend hospitalization

– Perforations that require an intervention, including bail-out stenting

Patency:
- Primary patency at 12 months.
- Clinically-driven TLR at 30 days, 6, 12 and 24 months.

Clinical:

- Ankle-brachial index ABI at 30 days, 6, 12 and 24 months reported as change from baseline
- Rutherford Category at 30 days, 6, 12 and 24 months reported as change from baseline.
- Quality of Life assessed by EQ-5D questionnaire at 30 days, 6, 12 and 24 months reported as change from baseline.
- Walking capacity assessed by the Walking Impairment Questionnaire (WIQ) at 30 days and at 6, 12 and 24 months reported as change from baseline

8.7 Randomized Study Analysis Set

8.7.1 Primary Analysis Set:

The primary analysis set for the randomized study will be the Intent-to-Treat (ITT) population. The ITT population includes all randomized subjects, which is the point of subject enrollment.

8.7.2 Secondary Analysis Set:

The secondary analysis set for the randomized study will be the Per-Protocol (PP) population. The PP population includes all subjects who received the correct randomized treatment assignment and had no pre-specified inclusion and exclusion violation(s).

9.0 ADVERSE EVENTS

Standard definitions and reporting requirements for reportable adverse events for the randomized and observational study are provided below.

9.1 Adverse Event Definitions

9.1.1 Adverse Event (AE):

Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the study medical device.

This definition includes events related to the investigational medical device or the comparator. This definition includes events related to the procedures involved.

9.1.2 Serious Adverse Event (SAE):

An adverse event that

a) led to death

b) led to a serious deterioration in the health of a subject that either resulted in

1) a life-threatening illness or injury, or

2) a permanent impairment of a body structure or a body function, or

3) in-patient or prolonged hospitalization, or

4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to body structure or a body function

c) led to fetal distress, fetal death or a congenital abnormality or birth defect.

Planned hospitalization for a pre-existing condition, or a procedure required by the study protocol without serious deterioration in health, is not considered a serious adverse event.

9.1.3 Adverse Device Effect (ADE):

An adverse device effect is defined as any untoward adverse event related to the use of an investigational or study medical device.

This definition includes adverse events resulting from insufficient or inadequate Instructions for Use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.

This definition includes any event resulting from use error or from intentional misuse of the investigational or study medical device.

9.1.4 Serious Adverse Device Effect (SADE):

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

9.1.5 Unanticipated Serious Adverse Device Effect (USADE)

Serious adverse device effect, which by its nature, incidence, severity or outcome has not been identified in the current version of the Instructions for Use or Risk Management Report.

To further clarify, an Anticipated SADE (ASADE) is considered an effect which by its nature, incidence, severity or outcome has been previously identified in the Instructions for Use or Risk Management Report.

9.2 Adverse Event Device Relatedness

Based on clinical judgment, the Investigator must provide a determination of the relationship between the use of the medical device (including the medical procedure) and the occurrence of each adverse event according to the following categories:

• Causal Relationship (Definite) – The adverse event is clearly related to the study device: the event has a temporal relationship to the study device, follows a known pattern of response, or is otherwise logically related to the study device, and no alternative cause is present.

• Probable – The adverse event is likely related to the study device: the event has a temporal relationship to the study device, follows a known or suspected pattern of response, or is otherwise logically related to the study device, but an alternative cause may be present.

• Possible – The adverse event is unlikely related to the study device: the event does not follow a clear temporal relationship to the study device or does not follow a known pattern of response, or is otherwise possibly to be due to the subject's clinical state or other modes of therapy.

In some cases, the adverse event may not be adequately assessed because information is insufficient or contradictory and/or the data cannot be verified or supplemented. Maximum effort will be made to define and categorize the event and avoid these situations. If relatedness remains uncertain, then classify the event as "possible".

• Unlikely – The adverse event can be reasonably explained by another cause and/or the relationship with the use of the device seems not relevant, but additional information may be obtained.

• Not Related – The adverse event is clearly not related to the study device: the event has no temporal or other relationship to the administration of the investigational device follows no known or suspected pattern of response, and an alternative cause is present.

9.3 Device Deficiencies

9.3.1 Definitions

Device Deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance (includes malfunctions, use errors, and inadequate labeling).

NOTE: Device deficiencies include malfunctions, use errors, and inadequate labeling.

Device Malfunction is a failure of the study medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or study protocol.

9.3.2 Reporting

All device deficiencies and malfunctions will be documented on the case report form, reported to the Shockwave Medical Clinical Study manager within 48 hours after the designated study site personnel first learns of the event, and reported to the EC/IRB (if required) within the EC/IRB required timeframe.

If a deficiency or malfunction meets the definition of a product complaint (any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device after it is released for distribution), a Shockwave Medical Complaint Form will be completed by a Shockwave Medical Clinical or Quality representative and entered into the company's complaint log. The Shockwave Medical Quality representative is responsible for assessing the need for and submitting any eMDR and/or Vigilance reports, if required.

Additionally, any IN.PACT DCB device deficiency or malfunction should be reported to that device's manufacturer.

9.4 Adverse Event Reporting Requirements

9.4.1 AE Reporting Requirements

All AE information will be collected from enrollment through 24 months post-procedure for subjects in the randomized study. For subjects in the observational study, AEs will be collected through hospital discharge.

AEs should be reported in the subject's medical records and on the study adverse event case report forms (CRF). Data reported should include date of onset, treatment, resolution, and an assessment of both seriousness and relationship to the study device. AEs will be followed until the event has resolved.

Any AEs that meet EC/IRB reporting requirements must also be reported to the EC/IRB per the institution's policy.

9.4.2 SAE Reporting Requirements

Any AE meeting any of the criteria for an SAE occurring at any time during the study must be reported to the Shockwave Medical Clinical Study Manager **within 48 hours** after the designated study site personnel first learns of the event. The SAE must also be reported to the EC/IRB per the institution's policy for reporting SAEs. SAEs should be reported in the subject's medical records and on the adverse event case report forms (CRF). Data reported should include date of onset, treatment, resolution, and an assessment of relationship to the study device. SAEs will be followed until the event has resolved (in the case of permanent impairment, the event will be followed until it stabilizes and the overall clinical outcome has been ascertained).

The Investigator must adhere to the following criteria in the case of serious adverse events:

- The Investigator or Co-Investigator must sign the Adverse Event Form(s).
- It is the responsibility of the Investigator to inform their EC/IRB of serious adverse events as required by their EC/IRB procedures. The Investigator should forward a copy of this report to the Sponsor and file in the site regulatory binder.

9.4.3 ADE Reporting Requirements

All ADE information (including ADEs and SADEs) will be collected from enrollment through 24 months post procedure for the randomized study, and through hospital discharge for the observational study. ADEs will be recorded in the subject's medical records and on the adverse event case report forms (CRF). Each ADE must be evaluated to determine if the event meets the definition of serious adverse device effects. ADEs should be reported in the subject's medical records and on the adverse event case report forms (CRF). Data reported should include date of onset, treatment,

resolution, and an assessment of both seriousness and relationship to the study device. ADEs will be followed until the event has resolved (in the case of permanent impairment, the event will be followed until it stabilizes and the overall clinical outcome has been ascertained).

9.4.4 SADE Reporting Requirements

All ADEs will be evaluated by the Shockwave Medical Clinical Study Manager to determine if the ADE meets the definition of a SADE. All SAEs must be reported within 48 hours after the designated study site personnel first learns of the event. All SAEs and SADEs should be reported to the EC/IRB in accordance with their requirements.

9.4.5 AE and Device Deficiency Reporting Time Frames

Table 5 summarizes the time sensitive reporting requirements for adverse events and device deficiencies. The Shockwave Medical Clinical Study Manager is the Sponsor contact person for these reporting requirements.

Table 5. Investigator Responsibilities for Submitting Clinical Events to Sponsor

Type of Event	Process
Device deficiencies (including malfunctions)	Submit within 48 hours after the designated study site personnel first learns of the event and to the EC/IRB (if required) within the EC/IRB required timeframe.
Serious adverse events (SAE, SADE, USADE)	Submit within 48 hours after the designated study site personnel first learns of the event and to the EC/IRB within the EC/IRB required timeframe.
Adverse events (AE, ADE)	Submit to Shockwave Medical as soon as possible after Investigator has become aware of the event, and to the EC/IRB (if required) within the EC/IRB required timeframe.

10.0 Investigator Responsibilities

The role of the principal investigator is to implement and manage the conduct of the clinical study at their site, as well as ensure data integrity and the rights, safety and well-being of the participating subjects.

10.1 EC/IRB Approval

The Investigator must obtain EC/IRB approval to conduct the study prior to screening any potential subjects, and comply with annual continuing approval requirements. All correspondence with the EC/IRB should be maintained in the site's study files.

10.2 Informed Consent

The Investigator is responsible for ensuring that all applicable local, national, Declaration of Helsinki, and ISO 14155:2011 requirements for all devices in the study are met when completing the informed consent process. It is the responsibility of the Investigator to ensure written informed consent from each subject, or the legally authorized representative of the subject, is obtained prior to the initiation of any study-related procedures. The Investigator must comply with the requirements specified in protocol Section 6.3.

10.3 Protocol Compliance and Delegation of Authority

The investigator shall conduct the clinical study in compliance with this study protocol, and ensure that an adequate study site team and facilities exist and are maintained and documented during the duration of the clinical study. The Investigator must maintain a Delegation of Authority Form of appropriately qualified persons to whom the Investigator has delegated significant study related duties.

10.4 Medical Care of Subjects

The investigator shall

- Provide adequate medical care to a subject during and after a subject's participation in the clinical study in the case of adverse events, as described in the informed consent,
- Inform the subject of the nature and possible cause of any adverse events experienced,
- Inform the subject of any new significant findings occurring during the clinical study, including the need for additional medical care that may be required,
- Provide the subject with well-defined procedures for possible emergency situations related to the clinical study, and make the necessary arrangements for emergency treatment,

- Ensure that clinical records are clearly marked to indicate that the subject is enrolled in a particular clinical study,
- Inform, with the subject's approval or when required by national regulations, the subject's personal physician about the subject's participation in the clinical study, and
- Make all reasonable efforts to ascertain the reason(s) for a subject's premature withdrawal from the clinical study while fully respecting the subject's rights.

10.5 Safety Reporting

The investigator must comply with the safety reporting requirements specified in protocol Section 9.

10.6 Protocol Amendment(s)

The investigator or clinical site staff will not make any modifications to this protocol or the Informed Consent form without prior written approval from the Sponsor. Sponsor and Investigator will agree to all amendments made to the protocol or the Informed Consent form. If protocol changes affect the scientific soundness of the clinical investigation, or affect the health, welfare, safety and rights of patients, Investigator and/or Sponsor will obtain written approval by the Investigator's EC/IRB, before implementing changes. All amendments must then be submitted to the local EC/IRB, as appropriate for approval.

10.7 Records Retention

All study records and documentation must be maintained by the investigator and are subject to inspection and copying, and must be retained for a period of two (2) years after the study is completed or terminated. The Shockwave Medical Clinical Research Department should be contacted if the Investigator plans to leave the study site. An Investigator may withdraw responsibility to maintain records for the time required by the study protocol by transferring custody to another qualified person willing to accept responsibility for them.

11.0 Sponsor Responsibilities

As the study Sponsor, Shockwave Medical is responsible for the overall conduct and quality of the study. Shockwave Medical will ensure that qualified monitors and designated personnel are monitoring the study according to the pre-determined monitoring plan and that the Informed Consent process is followed per the study site's requirements. The sponsor is responsible for the classification and reporting of adverse events and ongoing safety evaluation of the clinical study.

11.1 Selection and Training of Study Sites

Investigators will be qualified by education, training and experience to assume responsibility for the proper conduct of the clinical investigation. Investigators must disclose potential conflicts of interest, including financial, that may interfere with the conduct of the clinical investigation or interpretation of results.

Shockwave Medical and/or its designees are responsible for the training of appropriate clinical site personnel, including the Investigator, Sub-Investigator(s), and Research Coordinator(s). Initial training will be conducted by Shockwave Medical or its designees and will be on-going as required.

An individual Training Record must be signed and dated by both Shockwave Medical and/or its designee conducting the training, and each member of the research team that attended the training session before any study activity is performed. Original signed training records must be submitted to Shockwave Medical and a copy of each training record retained in the study Regulatory Binder.

11.2 Monitoring of Study Sites

Clinical data from the randomized controlled study will be monitored. Data from the observational study will be collected via the electronic data capture system, but will not be monitored by the Sponsor or Sponsor designee.

11.2.1 Randomized Study Monitoring Methods

Monitoring functions will be conducted by Shockwave Medical and/or its designated CRO. Specific monitoring requirements are detailed in the study specific Monitoring Plan maintained in the Shockwave Medical and CRO clinical study project files.

All monitoring activities shall be documented in a written report to the sponsor. Corrective action will be taken to resolve any issues of noncompliance. If Shockwave Medical finds that an Investigator is not complying with the executed Investigator Agreement, the study protocol, the applicable laws and regulations, or the requirements of the reviewing EC/IRB, prompt action will be taken to secure compliance. Shockwave Medical will reserve the right to suspend or terminate the participation of the Investigator or the study site.

11.2.2 Randomized Study Monitoring Visits

Scheduled monitoring visits to the clinical study site may occur at the following times: prior to the start of the study, interim visits throughout the clinical study as required (annually at a minimum), and upon completion of the clinical study. For interim site visits 100% of source documents must be made available to the monitors. Sites that enroll rapidly may be visited more frequently at Shockwave Medical's discretion. A final Close-Out Visit will be conducted upon completion of the entire clinical study or at the time a site is terminated.

11.3 Study Deviations

A study deviation is defined as an instance(s) of failure to follow, intentionally or unintentionally, the requirements of the study protocol, applicable laws or regulations, or the Investigator Agreement. No deviation from the protocol will be implemented by an Investigator without the prior review and approval by Shockwave Medical. Such approval will be documented in writing and maintained in the study files. The Investigator must document and notify Shockwave Medical of any deviation from the study protocol as soon as possible. Requests for deviations, and reports of deviations, if the deviation affects the subject's rights, safety and well-being, or the scientific integrity of the clinical investigation will be reported to the EC/IRB, as required by their procedures.

Major deviations include those that involve the primary endpoint, the informed consent process and the inclusion/exclusion criteria of the study, or any deviation that involves or leads to a serious adverse event in a study participant.

Under certain circumstances, deviations from the study protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the Sponsor and the EC/IRB. Such deviations shall be documented in writing, and reported to the Sponsor and the EC/IRB as soon as possible, and no later than 5 working days.

Subject specific deviations will be reported on the Protocol Deviation Case Report form. Investigators will also adhere to procedures for reporting study deviations to their EC/IRB in accordance with their requirements. Deviations from clinical protocol will be reviewed and evaluated by Shockwave Medical on an ongoing basis and, as necessary, appropriate corrective actions put into place.

11.4 Device Use Information

Confirmation that all participating sites will have an available inventory of the study devices will be obtained by Shockwave Medical prior to study start. Devices will be stored and dispensed as per the participating institutions' procedures. Device identifiers for both the Lithoplasty device and the Admiral IN.PACT DCB will be recorded on case report forms.

11.5 Study/Site Suspension or Early Termination

The sponsor may suspend or prematurely terminate the study at either an individual site or the entire clinical study for significant and documented reasons. A principal investigator, EC/IRB, or regulatory authority may suspend or prematurely terminate participation in a clinical study at the sites for which they are responsible.

If suspicion of an unacceptable risk to subjects arises during the clinical study, or when so instructed by the EC/IRB or regulatory authorities, the sponsor shall suspend the clinical study while the risk is assessed. The sponsor shall terminate the clinical study if an unacceptable risk is confirmed.

Shockwave Medical shall consider terminating or suspending the participation of a particular study site or investigator in the clinical study if monitoring or auditing identifies serious or repeated deviations on the part of an investigator. If suspension or premature termination occurs, the terminating party shall justify its decision in writing and promptly inform the other parties with whom they are in direct communication. The principal investigator and sponsor shall keep each other informed of any communication received from the EC/IRB or any regulatory authority.

If, for any reason, Shockwave Medical suspends or prematurely terminates the study at an individual site, the sponsor shall inform the EC/IRB. If the suspension or premature termination was in the interest of safety, the sponsor shall inform all other principal investigators.

If suspension or premature termination occurs, Shockwave Medical will remain responsible for providing resources to fulfill the obligations from the study protocol and existing agreements for follow up of the subjects enrolled in the clinical study, and the principal investigator or authorized designee shall promptly inform the enrolled subjects at his/her site, if appropriate.

Routine close-out activities shall be conducted to ensure that the principal investigator's records are complete, all documents needed for the sponsor's files are retrieved, remaining clinical study materials are disposed of, previously identified issues have been resolved and all parties are notified.

Resumption of a Study after Temporary Suspension:

When the sponsor completes an analysis of the reason(s) for the suspension, implements the necessary corrective actions, and decides to lift the temporary suspension, the sponsor shall inform the principal investigators, the EC/IRB, and provide them with the relevant data supporting this decision. Concurrence shall be obtained from the EC/IRB before the clinical study resumes. If subjects have been informed of the suspension, the principal investigator or authorized designee shall inform them of the reasons for resumption.

11.6 Study Completion

The study is considered completed after all subjects have undergone all of their protocol required follow-up visits, all CRFs have been submitted, all queries have been resolved, all action items have been closed, and all site payments have been made. All unused study materials will be collected and returned to Shockwave Medical or appropriately discarded as per instruction. After study closure, a final study report will be completed, even if the clinical study was terminated prematurely.

11.7 Audits / Inspections

Shockwave Medical initiated audits or EC/IRB initiated inspections at the study sites may occur during the course of, or after completion of the study. Access to all study records, including source documents, for inspection and duplication may be requested.

11.8 Publication Policies

Publications based on the results of the study will follow the process outlined in the Investigator Agreement. During the course of, or at the conclusion of the study, a multi-center manuscript may be prepared for publication in a reputable peer-reviewed scientific journal. The publication of the results from any single site experience within the study is not allowed until the preparation and publication of the multi-center results has occurred. Exceptions to this rule require the prior approval of Shockwave Medical.

After publication of the multi-center manuscript, a single site may publish the results of its subjects after first complying with the requirements in the Investigator Agreement. Any proposed publications must be submitted to Shockwave Medical for review and comment at least forty-five (45) days in advance of submitting such proposed publications to a publisher or other third party. If no response is received from Shockwave Medical within thirty (30) days of the date submitted, the Investigator may proceed with publication as long as all work and research on the clinical study has been completed.

This study is registered with www.clinicaltrials.gov (Identifier NCT02923193).

11.9 Data Management

Shockwave Medical and Data Management designees will oversee and/or perform all data management functions. Data management functions include database development, system maintenance, user training, data queries, and report generation. The principal investigator and/or study staff is responsible for the accuracy and completeness of all study data recorded.

11.9.1 Case Report Forms

All required data for this study will be collected via web-based electronic data capture (EDC) system and entered in electronic Case Report Forms (eCRFs).

A unique study identifier will be assigned to each study subject. All information recorded on the eCRFs about the subject will be recorded using the study identifier. The database will contain only the study identifier to identify the subject. The code with patient name and study number will be maintained in a secured location.

11.9.2 Transmission of Data

For electronic CRFs:

Required data will be recorded on the appropriate electronic Case Report Forms at the time of or as soon as possible after the subject visit. The eCRFs and any requested supporting source documents must be sent to Shockwave Medical and/or retrieved from the investigator during monitoring visits.

11.9.3 Data Queries

Any data discrepancies identified during data review or a monitoring visit will be queried by Shockwave Medical or its designee and must be resolved by the investigational site staff and investigator in a timely manner.

Data audits may be performed for quality assurance of data handling. Any discrepancies will be queried by Shockwave Medical or its designee and must be resolved by the investigational site staff and investigator in a timely manner, particularly during those times data is being prepared for CEC safety reviews and reports required by the regulatory authorities.

11.9.4 Sponsor Data Retention

Shockwave Medical will retain all study data received for a period of two (2) years after the investigation is completed or terminated, or, two (2) years after the records are no longer required to support the application to market the device (whichever date is later), or longer if required by applicable local regulations.

12.0 STUDY COMMITTEES

12.1 Clinical Events Committee (CEC)

To meet the ethical responsibilities and standards for research subjects, an independent Clinical Events Committee shall serve as forum for adjudication of any major adverse events (MAEs) and target lesion/vessel revascularizations (TLR/TVR) in the randomized study. In order to enhance objectivity and reduce the potential for bias, the CEC shall be independent of the Sponsor as well as the investigational sites/investigators. Observational study AEs will not be adjudicated by the CEC.

The CEC is made up of clinicians (interventional and non-interventional) with pertinent expertise who are not participants in the study and who do not have any other real or potential conflicts of interest. The CEC is charged with the development of specific criteria used for the categorization of adverse events and clinical endpoints in the study. Criteria will be established for selected complications and clinical events.

At the onset of the study, the CEC will establish explicit rules outlining the minimum amount of data required and the algorithm followed in order to classify an event. The methodology for performing these responsibilities shall be developed and outlined in the CEC Charter. Operational provisions shall be established to minimize potential bias (i.e., CEC members shall be blinded to the clinical site to the extent possible during adverse event review and adjudication). In the case of an MAE with associated imaging, the CEC may review imaging assessments to assess the reported event.

13.0 ETHICAL and REGULATORY CONSIDERATIONS

13.1 Role of Shockwave Medical

As the Sponsor of this clinical study, Shockwave Medical has the overall responsibility for conduct of the study, including assurance that the study will be conducted according to the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil October 2013), applicable EC/IRB requirements, as well as any ISO 14155:2011 and/or national requirements. In this study, Shockwave Medical will have certain direct responsibilities and may delegate other responsibilities to qualified consultants and/or contract research organizations.

The study will be conducted in Europe, the United States and New Zealand. Shockwave Medical will comply with all applicable safety reporting requirements.

This protocol and any amendments will be submitted to each site's EC/IRB for formal approval of the study. All subjects considered for this study will be provided a consent form describing this study and providing sufficient information for them to make an informed decision about their participation.

13.2 Subject Confidentiality

Subject confidentiality will be maintained throughout the clinical study. A unique subject identification code will be assigned and used to allow identification of all data reported for each subject.

Study data may be made available to third parties, e.g., in the case of an audit, provided the data are treated confidentially and that the subject's privacy is guaranteed. The identity of a subject will never be disclosed in the event that study data are published.

14.0 Definitions and List of Abbreviations

14.1 Study Definitions

Access Site Hemorrhage: Bleeding from the access site which requires transfusion, hospitalization (either admission or extended stay), or further treatment for management. Hemorrhage, without frank bleeding, needing ≥1 unit RBCs will be considered a serious adverse event.

Access Site Infection: Culture-proven wound infection or presumptive treatment with antibiotics for clinically diagnosed wound infection.

Acute Renal Failure: Acute post-operative renal insufficiency resulting in one or more of the following: (a) increase of >1.0 mg/dl in serum creatinine from most recent prior measured level, and current measured absolute value is >2.0 mg/dl; (b) a new requirement for dialysis.

Acute PTA failure:

- Residual stenosis ≥50% by visual estimate,
- or un-resolved flow-limiting (≥Grade D) dissection, and
- Trans-lesional gradient >10 mm Hg is observed.

Adverse Device Effect (ADE): An adverse event related to the use of the medical device. This definition includes any event resulting from insufficiencies or inadequacies in the instructions for use or the deployment of the device. This definition includes any event that is a result of a user error.
NOTE 1: This definition includes adverse events resulting from insufficient or inadequate Instructions for Use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. This definition includes any event resulting from insufficiencies or inadequacies in the Instructions for Use or the deployment of the device or any event that is a result of user error.
NOTE 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

Adverse Event (AE): An adverse event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational device/procedure.

Air Embolism: An inadvertent introduction of air or gas to the vasculature that requires medical treatment.

Allergic Reaction: An allergic reaction characterized by rash, nausea, vomiting, upper respiratory congestion, urticaria, shortness-of-breath, vasovagal reaction, or general cardiovascular collapse (anaphylaxis).

Amputation (major): Any requirement for amputation above the ankle or higher.

Amputation (minor): Any requirement for amputation below the ankle.

Amputation, Unplanned: An amputation associated with the target limb that occurs between the index procedure and 30 days that was not previously planned as part of the overall treatment strategy.

Anemia: Decrease from baseline in red blood cells, hemoglobin, or total blood volume that is associated with hemodynamic changes or requires transfusion, or a drop in hematocrit to below 30%. Any documented anemic event requiring ≥2 units PRBCs will be considered an SAE.

Angina: A tight or heavy feeling in the chest, discomfort which spreads from the chest to the arm, back, neck, jaw, or stomach, numbness or tingling in the shoulders, arms or wrists, shortness of breath, and nausea relieved by rest or nitroglycerine.

Angina, unstable: Chest pain that increases in frequency, intensity, or duration, which occurs at rest, or which is new in onset. Unstable angina is a syndrome that is intermediate between stable angina and myocardial infarction: it is characterized by an accelerating or "crescendo" pattern of chest pain that lasts longer than stable angina, occurs at rest or with less exertion than stable angina, or is less responsive to medication. Unstable angina and myocardial infarction are considered acute coronary syndromes.

Ankle / Brachial Index (ABI): The ratio of systolic blood pressure measured at the ankle to systolic blood pressure measured at the brachial artery.

Arterial Occlusion / Thrombosis at Puncture Site: Angiographic or ultrasonographic evidence of occlusion at the puncture site limiting antegrade flow to the distal limb.

Arterial Perforation/Rupture/Puncture of an Arterial Wall: Classified as follows:
Angiographic perforation: Perforation detected by the clinical site at any point during the procedure.

Clinical perforation: Perforation requiring additional treatment (including efforts to seal the perforation), or resulting in significant extravasation of blood from the site, abrupt closure, limb ischemia or death.

Arterial Pseudoaneurysm: Disruption of arterial wall confirmed by imaging study and requiring intervention.

Arteriovenous Fistula (AVF): An abnormal passage or communication between an artery and a vein which may be due to the percutaneous introduction of ancillary devices (e.g., needles, catheters, guide wires) confirmed by imaging studies.

Atypical Chest Pain: Located under the sternum, left chest, abdomen, back, or arm and is fleeting or sharp. It is unrelated to exercise, not relieved by rest or the administration of nitroglycerin.

Bacteremia: Presence of viable bacteria in the circulating blood. May be associated with clinical signs/symptoms such as fever. Must be confirmed by having one positive blood culture and no subsequent negative cultures.

Bleeding Complication (Major): Bleeding resulting in ≥3 g/dl decrease in hemoglobin (if hemoglobin level not available, a decrease in hematocrit of ≥ 10%), or necessitating transfusion of >1 unit of PRBC's /whole blood, or necessitates surgery/endoscopic intervention.

Access site: Bleeding from the arteriotomy site which requires transfusion, hospitalization (either admission or extended stay), or further treatment for management.

Calcification Classification: Calcification must be: 1) on parallel sides of the vessel and 2) extending >50% the length of the lesion if lesion is ≥50mm in length; or extending for minimum of 20mm if lesion is <50mm in length.

CAPA: Corrective and Preventative Action.

Cardiac Arrhythmia: Electrical disruption of the heart rhythm requiring specific medication, defibrillation, or pacemaker insertion to address condition.

Cardiogenic Shock: Subject presents with SBP <80 mm Hg for more than 30 minutes unresponsive to fluids or requiring intravenous vasopressor agent or an intra-aortic balloon pump (IABP).

Cardiovascular Death: All cardiovascular cause mortality.

Cerebral Vascular Accident (CVA): See Stroke.

Closure, Abrupt: Occurrence of new (during the index procedure), persistent slow, reduced, or loss of flow within the target vessel that requires intervention other than the index or adjunct treatment. Abrupt closure may also be referred to as acute occlusion if there is a total loss of flow.

Closure, Subacute: Target lesion site occlusion that occurs after the index procedure is completed (e.g., the subject has left the treatment area) and within 30 days of procedure.

Congestive Heart Failure: Documentation of one of the following: a) paroxysmal nocturnal dyspnea (PND), b) dyspnea on exertion (DOE) due to heart failure, c) elevated PCW with associated SOB or x-ray consistent with congestion. May be related to fluid overload in the presence of underlying cardiovascular disease.

Contrast-Induced Nephropathy: Associated with contrast agent resulting in >25% increase in serum creatinine or an absolute value of >0.5 mg/dl.

Contrast Media Reaction: An allergic reaction, immediate or delayed, associated with the intravascular administration of contrast media that results in symptoms (e.g., itching, hives) or physiologic changes requiring treatment (e.g., anaphylactic reaction) or death.

Critical Limb Ischemia: Clinical manifestation of peripheral arterial disease characterized by Rutherford Clinical Scale Category of 2-6. (For the purposes of this study, only subjects with Rutherford Clinical Scale Category of 2, 3, and 4, are eligible for enrollment).

Death: (divided into 2 categories)

Cardiac death is death due to any of the following:

1. Acute myocardial infarction.
2. Cardiac perforation/pericardial tamponade.
3. Arrhythmia or conduction abnormality.
4. Stroke within 30 days of the procedure or stroke suspected of being related to the procedure
5. Death due to complication of the procedure, including bleeding, vascular repair, transfusion reaction, or bypass surgery.
6. Any death for which a cardiac cause cannot be excluded.

Non-cardiac death is a death not due to cardiac causes (as defined immediately above).

De novo: A segment of artery that has not previously been treated with angioplasty or stenting.

Deep Vein Thrombosis (DVT): Thrombosis of a deep vein, as confirmed by imaging study or direct visualization.

Device Deficiency: is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance (includes malfunctions, use errors, and inadequate labeling).

Device Malfunction: A malfunction of a device is an unexpected change to the device that is contradictory to the Instructions for Use and may or may not affect device performance.

Dissection: Disruption of an arterial wall resulting in separation of the intimal layer. May or may not be flow limiting.

Dissection Classifications (National Heart, Lung and Blood Institute – NHLBI)

Type A: Small radiolucent area within the lumen of the vessel disappearing with the passage of the contrast material.

Type B: Appearance of contrast medium parallel to the lumen of the vessel disappearing within a few cardiac cycles.

Type C: Dissection protruding outside the lumen of the vessel persisting after passage of the contrast material.

Type D: Spiral shaped filling defect with our without delayed run-off of the contrast material in the antegrade flow.

Type E: Persistent luminal filling defect with delayed run-off of the contrast material in the distal lumen.

Type F: Filling defect accompanied by total coronary occlusion.

Disseminated Intravascular Coagulation (DIC): A syndrome arising as a complication of many different serious and life-threatening illnesses. In its acute form it is a hemorrhagic disorder, characterized by multiple ecchymoses, mucosal bleeding, and depletion of platelets and clotting factors. Chronic DIC is more subtle and involves thromboembolism accompanied by evidence of activation of the coagulation system.

Dizziness: Imprecise term commonly used to describe various symptoms such as faintness, giddiness, imbalance, lightheadedness, unsteadiness, or vertigo.

Drug Reactions: An unwanted or harmful side effect experienced following the administration of a drug or combination of drugs and is suspected to be related to the drug.

Embolization, Distal: Any distal emboli confirmed by imaging considered to be related to the Shockwave Lithoplasty®-treated lesion.

Embolization, Symptomatic: Clinical signs or symptoms of distal emboli detected in the treated limb distal to the treated lesion after the index procedure **or** noted angiographically and requiring mechanical or pharmacologic means to improve flow. This includes new abrupt occlusions or filling defects.

Femoropopliteal DVT: defined as DVT involvement limited to the superficial femoral or popliteal veins, with or without distal (e.g., toward foot) DVT involvement, based on duplex ultrasound exam.

Fever: A temperature 38°C (>101.4° F) not related to a culture positive infection.

General Discomfort: Physical or psychosocial signs or symptoms commonly associated with hospitalization that are investigated and determined to require minor (i.e., aspirin, non-narcotic medication) or no treatment.

Hematoma: Collection of blood (or its degradation products) which exceeds 5 cm in diameter, requires treatment, or prolongs hospitalization.

Hemorrhage: Any bleeding which results in a drop in hematocrit from pre-procedure level which is associated with hemodynamic compromise or which results in a hematocrit of ≤30%, or blood loss that requires transfusion.

Hypertension: Systolic BP >140 mmHg, or diastolic >90 mmHg requiring specific medical therapy.

Iliofemoral DVT: Defined as DVT involvement of the common or external iliac veins or the common femoral vein, with or without distal (e.g., toward foot) DVT involvement, based on duplex ultrasound exam.

Infection, access site: Infection at the vascular access site, documented by lab culture or clinical evidence requiring medical treatment (irrigation, debridement, antibiotics, etc.) to resolve.

Infection, sepsis: Culture-proven infections or presumptive treatment with antibiotics for clinically diagnosed infection.

Infection, systemic: Systemic infection documented by positive lab culture or clinical evidence, requiring medical treatment to treat and resolve.

Intracranial Hemorrhage: Includes all bleeding within the cranium either subarachnoid, intra-parenchymal, or intracerebral.

Limb Ischemia: Deficient supply of oxygenated blood to the tissues in the limbs that is due to obstruction of the inflow of arterial blood characterized by pain and/or discoloration of the limb.

Lithoplasty: Shockwave Medical's proprietary balloon angioplasty catheter including lithotripsy technology that creates pulsatile mechanical energy for disrupting calcified vascular plaque.

Lithotripsy: A medical procedure for disrupting calculus in the body.

Luminal Patency: Post-procedure residual stenosis <50% as determined by investigator visual assessment or quantitative analysis of the end of procedure angiogram.

Major Adverse Event (MAE): For the purposes of this study, the definition of Major Adverse Event(s) includes:

- Need for emergency surgical revascularization of target limb
- Unplanned target limb major amputation (above the ankle)
- Symptomatic thrombus or distal emboli that require surgical, mechanical or pharmacologic means to improve flow and extend hospitalization
- Perforations that require an intervention, including bail-out stenting

Myocardial Infarction (MI): Evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia.

Perforation: Puncture of an arterial wall.

Pneumonia: Diagnosed by one of the following: Positive cultures of sputum, blood, pleural fluid, emphysema fluid, transtracheal fluid or transthoracic fluid; consistent with the diagnosis and clinical findings of pneumonia. Should include chest x-ray diagnostic of pulmonary infiltrates.

Procedural Success for randomized study: Procedural success is defined as residual stenosis ≤30% without flow-limiting dissection (≥ grade D) prior to DCB or stenting by angiographic core lab.

Procedural Success for observational study: Procedural success is defined as final residual stenosis ≤30% without flow-limiting dissection (≥ grade D) by angiographic core lab.

Pseudoaneurysm: Disruption of the arterial wall characterized by an out-pouching or pocket with swirling, flowing blood outside of the confines of the arterial lumen.

Recurrent Occlusion: Occlusion (i.e., total obstruction of vessel lumen) after a successful canalization.

Recurrent Thrombosis: Thrombosis (i.e., sub-total obstruction of vessel lumen) following successful treatment.

Renal failure (Acute): Acute post-operative renal insufficiency resulting in one or more of the following: (a) increase of >1.0 mg/dl in serum creatinine from most recent prior measured level, and current measured absolute value is >2.0 mg/dl; (b) a new requirement for dialysis.

Renal Insufficiency: An increase in serum creatinine of ≥1.0 mg/dl over previous value requiring medical treatment but which does not require dialysis to resolve.

Respiratory Failure: New onset of respiratory insufficiency that requires placement of endotracheal tube and/or pneumothorax with or without chest tube.

Respiratory Insufficiency: Deterioration of subject's respiratory efforts that require supportive or medical treatment.

Retroperitoneal bleed: Bleeding into the back of the abdomen from a vascular access or puncture site.

Restenosis: Reoccurrence of narrowing or blockage or target lesion.

Rutherford Clinical Category Scale: Clinical scale identifying three grades of claudication and three grades of critical limb ischemia ranging from rest pain alone to minor and major tissue loss. (ACC/AHA PAD Practice Guidelines – Hirsch et al. 2005)

Grade	Category	Clinical Description
	0	Asymptomatic
I	1	Mild claudication
	2	Moderate claudication
	3	Severe claudication
II	4	Ischemic rest pain
	5	Minor tissue loss
III	6	Ulceration or gangrene

Septicemia: One positive blood culture AND clinical evidence for infection (e.g., fever, elevated WBC count, hypotension, need for increased inotropic support, end organ dysfunction, coagulopathy/ DIC [disseminated intravascular coagulation], need for increased ventilator support, etc.).

Serious Adverse Device Effect (SADE): A serious adverse device effect is defined as an adverse device effect that results in any of the consequences characteristics of a serious adverse event or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune.

Serious Adverse Event (SAE): A serious adverse event (SAE) is defined an adverse event that:

- led to death,
- led to a serious deterioration in the health of the subject, that either resulted in:
    - a life-threatening illness or injury, or
    - resulted in a permanent impairment of a body structure or a body function, or
    - required in-patient hospitalization or prolongation of existing hospitalization, or
    - resulted in medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to body structure or a body function, or,
    - led to fetal distress, fetal death or a congenital abnormality or birth defect.

NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the investigational plan without serious deterioration in health, is not considered a serious adverse event.

Stroke: any neurological deficit lasting 24 hours or longer, or lasting less than 24 hours with a brain imaging study showing infarction consistent with deficit. May be further categorized as:

- Ischemic Stroke: neurologic deficit meeting the study definition for Stroke that is attributed to thromboembolic event. □
- Hemorrhagic Stroke: neurologic deficit meeting the study definition for Stroke that is attributed to bleeding into brain tissue, epidural, subdural, or subarachnoid space; or a combination of these sites.

Target Lesion Revascularization, Clinically-driven (TLR): Any revascularization (endovascular or surgical) within the target femoropopliteal vessel due to symptoms or drop of ABI >20% or >0.15 when compared to the 30-day ABI and associated with an angiographic lesion >50% at the target lesion site.

Target Vessel Revascularization, Clinically-driven (TVR), non-TLR: Any revascularization (endovascular or surgical) within the target femoropopliteal vessel due to symptoms or drop of ABI >20% or >0.15 when compared to the post-procedure baseline ABI and associated with an angiographic lesion >50% in the target vessel.

Total Occlusion A 100% stenotic lesion as documented by angiographic absence of flow.

Thrombocytopenia: A persistent decrease in the number of blood platelets to subnormal levels.

Thrombus: Blood clot that obstructs a blood vessel.

Transient Ischemic Attack (TIA): Focal neurologic abnormalities of sudden onset and brief duration (i.e., lasting less than 24 hours and, if an imaging study is performed, shows no evidence of infarction).

Toe / Brachial Index (TBI): The ratio of systolic blood pressure measured at the toe to systolic blood pressure measured at the brachial artery.

Unanticipated Adverse Device Effect (UADE): An Unanticipated Adverse Device Effect (UADE) is defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by or associated with the device, if that adverse effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the protocol or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Unanticipated Serious Adverse Device Effect (USADE): A serious adverse device effect that has not been expected to occur with the device or during the course of the study procedures and has not otherwise been identified as a possible risk in the clinical investigations.

Unstable Angina: Angina which increases in frequency, intensity, or duration, which occurs at rest, or which is new in onset. Unstable angina is a syndrome that is intermediate between stable angina and myocardial infarction: it is characterized by an accelerating or "crescendo" pattern of chest pain that lasts longer than stable angina, occurs at rest or with less exertion than stable angina, or is less responsive to medication. Unstable angina and myocardial infarction are considered acute coronary syndromes.

Vascular Occlusion / Thrombosis at Puncture Site: Angiographic or ultrasonographic evidence of occlusion at the puncture site limiting flow to the limb.

Vasovagal Reaction: Reflex stimulation of the vagus nerve causing slowing of the heartbeat, decreased blood pressure, etc. and requires treatment consisting of any of the following: (a) >1 liter of IV fluids; (b) postural changes; (c) pacing intervention; or (d) administration of atropine.

14.2 List of Abbreviations

ABI	Ankle brachial index
ADE	Adverse Device Effect
AE	Adverse Event
CEC	Clinical Events Committee
CLI	Critical Limb Ischemia
CRF	Case Report Form
CTO	Chronic total occlusion
DCB	Drug Coated Balloon
DUS	Duplex Ultrasound
EC	Ethics Committee
IFU	Instructions for use

ISR	In Stent Restenosis
ITT	Intent-to-Treat
IRB	Institutional Review Board
MAE	Major adverse event
OTW	Over the wire
PAD	Peripheral artery disease
PP	Per Protocol
PTA	Percutaneous transluminal angioplasty
SADE	Serious Adverse Device Effect
SAE	Serious adverse event
SFA	Superficial femoral artery
TLR	Target Lesion Revascularization
TVR	Target Vessel Revascularization

15.0 Revision History

Revision	Release Date	DCO #	Reason for Revision	Doc Owner
A	9/8/2016	16624	Initial release.	G. Sahyun
B	12/16/16	16995	1. Change in procedural flow impacting the assessment of primary effectiveness endpoint. 2. Addition of interim analysis increasing sample size.	G. Sahyun

Revision	Release Date	DCO #	Reason for Revision	Doc Owner
C	8/15/17	17749	1. General administrative changes and corrections throughout document. 2. Addition of observational study. 3. Change the number of sites. 4. Ensure alignment of MAE definition throughout document. 5. Remove lower limit of target lesion length for angiographic inclusion criteria #11. 6. Add clarification to angiographic inclusion criteria #12. 7. Add definition to angiographic inclusion criteria #14 for calcification based on lesion length. 8. Update general exclusion criteria #12 to be more specific. 9. Change angiographic inclusion criteria #17 to be more specific. 10. Change angiographic inclusion criteria #18. 11. Add clarification to angiographic criteria #24. 12. Update statistical method for analysis of randomized study arm only. 13. Change minimum sample size for analysis. 14. Remove language that discusses commercial availability. 15. Add instructions to screening procedures and subject selection for the different study arms. 16. Define observational study inclusion and exclusion criteria. 17. Update schedule of events for discharge to match study endpoints. 18. Add schedule of events for observational study. 19. Update Anticoagulation /Antiplatelet Medications for consistency. 20. Update Angiographic Eligibility Assessment table to be consistent with body of the protocol. 21. Update instructions for Lithoplasty procedure to be consistent with IFU. 22. Correct control arm procedures. 23. Remove specific device sizing instruction. 24. Add observational study procedure guidance. 25. Update reporting requirements to include observational study. 26. Include reference to observational study for CEC. 27. Change TLR definition to align with CEC charter. 28. Change TVR definition to align with CEC charter.	P. Phattanagosai

Revision	Release Date	DCO #	Reason for Revision	Doc Owner
D	4/2/2018	18447	1. Increase total number of sites from 50 to 60. 2. Increase sample size in randomized portion of the trial from 334 to 400. 3. Update sample size justification. 4. Increase sample size in observational portion of the trial from 250 to 500. 5. Clarified that enrollment in the observational portion of the trial may continue after enrollment in the randomized portion of the trial has been complete.	P. Phattanagosai
E	11/29/2018	19140	1. Increase sample size in observational portion of the trial from 500 to 1000 2. Update study primary endpoint throughout the document. Add requirement of post-treatment residual stenosis of ≤30% without flow-limiting dissection (≥ grade D) prior to DCB or stenting by angiographic core lab.	B. Greschner
F	10/10/2019	20009	1. General administrative changes and corrections throughout document. 2. Increase sample size in observational study from 1000 to 1500. Specify that a minimum of 200 subjects will be treated with the S4 Lithoplasty catheter. 3. Update study duration for both randomized and observational study to 36 months throughout document. 4. Clarify verbiage for Primary Endpoint for Observational Study to include time point for evaluation by angiographic core lab throughout document. 5. Introduce S4 Lithoplasty catheter. 6. Update Schedule of Events and section 6.8.6 for randomized study with assessments required prior to pre-target limb revascularization. Widen ABI window to 60 days and update section 6.6. 7. Remove SOC assessments, Walking Impairment Questionnaire and EQ-5D from Schedule of Events for observational study. Widen ABI window to 60 days and update section 6.6. 8. Correct post-dilatation requirements to >30% residual stenosis throughout document. 9. Open up Health Economics sub-study to subjects enrolled in observational study. 10. Remove requirement for conducting at least 50 cases using the second generation generator.	B. Greschner

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