Prospective, Multi-center, Single-arm Study of the Shockwave Medical Peripheral Intravascular Lithotripsy (IVL) System for Treatment of Calcified Peripheral Arterial Disease (PAD) in Below-the-Knee (BTK) Arteries

(Disrupt PAD BTK II)

Protocol Number: CP 65007

Protocol Date: 08/22/2023

Revision: C

Study Device: Shockwave Medical Peripheral Intravascular Lithotripsy System

Study Sponsor Name and Address: Shockwave Medical, Inc.
5403 Betsy Ross Drive
Santa Clara, CA 95054
USA

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1.0 INVESTIGATOR SIGNATURE PAGE

Study Title: Prospective, Multi-center, Single-arm Study of the Shockwave Medical Peripheral Intravascular Lithotripsy (IVL) System for Treatment of Calcified Peripheral Arterial Disease (PAD) in Below-the-Knee (BTK) Arteries (Disrupt PAD BTK II)

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Protocol Revision Date: 22 August 2023

Study Sponsor: Shockwave Medical, Inc.
5403 Betsy Ross Drive
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USA

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 outlined protocol requirements, all attachments, and applicable local and United States Food and Drug Administration regulations. This investigation will be conducted in accordance with the ethical principles as noted in the Declaration of Helsinki, the requirements of EU Medical Device Regulation (EU MDR) 2017/745, the ISO 14155:2020 Good Clinical Practices, and applicable IRB/EC requirements.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

2.0 STUDY SUMMARY

Study Title	Prospective, Multi-center, Single-arm Study of the Shockwave Medical Peripheral Intravascular Lithotripsy (IVL) System for Treatment of Calcified Peripheral Arterial Disease (PAD) in Below-the-Knee (BTK) Arteries (Disrupt PAD BTK II)
Study Objective	To assess the continued safety and effectiveness of the Shockwave Medical Peripheral IVL System for the treatment of calcified, stenotic BTK arteries.
Study Device(s)	Shockwave Medical Peripheral IVL System
Manufacturer	Shockwave Medical, Inc.
Indications for Use	The Shockwave Medical IVL 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.
Study Design	Post-market, prospective, multi-center, single-arm study
Enrollment	Up to 250 subjects at up to 40 global sites
Subject Population	Subjects with moderate to severe calcified peripheral artery disease below the knee presenting with Rutherford Category (RC) 3 to 5 with the RC 3 cohort capped at 20% of total enrollment. Up to two (2) target lesions allowed for each subject.
Study Duration / Follow-Up Period	Study subjects will be followed through discharge, 30 days, 6, 12, & 24 months. Duplex Ultrasound (DUS) assessments required at 6 and 12 months. Total anticipated study duration approximately 48 months.
Primary Safety Endpoint	Major Adverse Limb Events (MALE) or Post-Operative Death (POD) at 30 days defined as a composite of: • all-cause death • above-ankle amputation of the index limb • major reintervention (new bypass graft, jump/interposition graft revision, or thrombectomy/thrombolysis) of the index limb involving a BTK artery

Primary Effectiveness Endpoint	• Procedure Success defined as ≤50% residual stenosis for all treated target lesions without serious angiographic complications (flow-limiting dissection, perforation, distal embolization, or acute vessel closure) as assessed by the angiographic core lab at the final timepoint.

Secondary Endpoints:	• Serious angiographic complications (flow-limiting dissection, perforation, distal embolization, or acute vessel closure) as assessed by the angiographic core lab
	• Lesion Success defined as final residual stenosis ≤50% in the target lesion without serious angiographic complications as assessed by the angiographic core lab
	• Primary Patency at 6 and 12 months (assessed for subject and lesion) defined as the absence of both total occlusion (100% diameter stenosis as assessed by DUS core lab) in all of the target lesions in a flow pathway, as well as any CEC adjudicated Clinically-Driven Target Lesion Revascularization (CD-TLR)
	• Clinically-Driven Target Lesion Revascularization (CD-TLR), CEC adjudicated, at 30 days, 6, 12, & 24 months
	• Major Adverse Events (MAE), CEC adjudicated at 30 days defined as a composite of:
	  ○ 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
	• Quality of Life (QoL) assessed by VascuQoL questionnaire at 30 days, 6, 12, & 24 months, reported as change from baseline
	• Ankle-brachial index (ABI) or toe-brachial index (TBI) at 30 days, 6, 12, & 24 months, reported as change from baseline
	• Major Target Limb Amputation, CEC adjudicated, at 30 days, 6, 12, & 24 months
	• Rutherford Category at 30 days, 6, 12, & 24 months, reported as change from baseline

	• Number of existing, new, and recurrent wounds at 30 days, 6, 12, & 24 months • Number of healed wounds at 30 days, 6, 12, & 24 months • Number of non-healed wounds by category (improving, stagnant, worsening) at 30 days, 6, 12, & 24 months
IVUS Sub-study	• Up to 50 subjects; IVUS required at baseline, immediately post-IVL, and end of procedure
Study Inclusion Criteria	**General Inclusion Criteria** 1. Age of subject is ≥ 18. 2. Subject is able and willing to comply with all assessments in the study. 3. Subject or subject's legal representative has been informed of the nature of the study, agrees to participate, and has signed the approved consent form. 4. Rutherford Category 3, 4, or 5 in the target limb. 5. Estimated life expectancy >1 year. **Angiographic Inclusion Criteria** 6. Up to 2 below-the-knee target lesion(s) in native vessels in one or both limbs. 7. Target lesion from the distal segment (P3) of the popliteal artery to the ankle joint. 8. Target lesion reference vessel diameter (RVD) between 2.0mm and 4.0mm by investigator visual estimate. 9. Target lesion with ≥70% stenosis by investigator visual estimate. 10. Target lesion length is ≤200mm by investigator visual estimate. Target lesion can be all or part of the 200mm treated zone. 11. Distal reconstitution of at least one pedal vessel (<50% stenosis) (desert foot excluded) in the target limb. 12. Evidence of at least moderate calcification at the target lesion site by angiography/IVUS OR non-dilatable lesion indicating presence of calcium. Must meet <u>one</u> of the following:

	a. Angiography requires fluoroscopic evidence of calcification on parallel sides of the vessel and extending > 50% the length of the lesion. b. IVUS requires presence of ≥270 degrees of calcium over the course of at least 10mm. c. Non-dilatable lesion requires attempted treatment with PTA during the index procedure with residual stenosis > 50% and no serious angiographic complications.
Study Exclusion Criteria	**General Exclusion Criteria** 1. Rutherford Category 0, 1, 2 or 6 (target limb). 2. Subjects with osteomyelitis or deep soft tissue infection are excluded unless infection can be treated with an individual toe ray amputation or transmetatarsal amputation (TMA) in the target limb in the opinion of the investigator.. 3. History of endovascular or surgical procedure on the target limb within the last 30 days, or planned within 30 days of the index procedure with the exception of toe amputation. 4. Subject in whom antiplatelet or anticoagulant therapy is contraindicated. 5. Subject has known allergy to contrast agents or medications used to perform endovascular intervention that cannot be adequately pre-treated. 6. Subject has known allergy to urethane, nylon, or silicone. 7. Myocardial infarction within 30 days prior to enrollment. 8. History of stroke within 60 days prior to enrollment. 9. Subject has acute or chronic renal disease with eGFR <30 ml/min/1.73m^2 (using CKD-EPI formula), unless on renal replacement therapy. 10. Subject is pregnant or nursing. 11. Subject is participating in another research study involving an investigational agent (pharmaceutical, biologic, or medical device) that has not reached the primary endpoint. 12. 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. 13. Covid-19 diagnosis within 30 days. 14. The planned use of cutting/scoring balloons, re-entry or atherectomy devices in target lesions during the index procedure. 15. Planned major amputation (of either leg). 16. Acute limb ischemia (of either leg). 17. Occlusion of all the inframalleolar outflow arteries/vessels (i.e., desert foot) in the target limb. 18. Subject has an anticipated life span of less than one (1) year. 19. Subject already enrolled into this study. **Angiographic Exclusion Criteria** 20. Failure to treat clinically significant inflow lesions in the ipsilateral iliac, femoral, or popliteal arteries with ≤30% residual stenosis, and no serious angiographic complications (e.g., embolism). 21. Failure to successfully treat significant *non-target* infra-popliteal lesions prior to treatment of *target* lesion(s). Successful treatment is defined as obtaining ≤50% residual stenosis with no serious angiographic complications (e.g., embolism). 22. Treatment of vessels below the ankle joint. 23. Failed pre-dilatation in *target* lesion during index procedure with angiographic evidence of serious angiographic complications. 24. Target lesion includes in-stent restenosis. 25. Evidence of aneurysm or thrombus in target vessel. 26. No calcium or mild calcium in the target lesion. 27. Target lesion within native or synthetic vessel grafts. 28. 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.
Study Statistical Methods	• Intent-to-Treat (ITT) analysis with pre-defined subgroups (e.g., renal failure)

	• Designed to assess exact 95% confidence interval (CI) for primary endpoints; no formal hypothesis testing
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3.0 INTRODUCTION

3.1 Background

3.1.1 Peripheral Arterial Disease

Peripheral arterial disease (PAD) is one of the most common indications of atherosclerotic disease and impacts more than 200 million people globally [1]. PAD is caused by the accumulation of plaque in the arteries that do not supply the brain or the heart. Although it can involve the renal arteries and/or the arteries of the neck or arms, PAD normally develops in the lower extremities. The reduced blood flow may lead to pain, tissue loss and eventual foot/leg amputation or death. Risk factors for PAD include advanced age, smoking, hypertension, diabetes, and concomitant cardiovascular disease [1]. Calcified PAD is associated with coronary artery disease, diabetes and chronic kidney disease [2].

Early diagnosis and treatment of PAD reduces an individual's risk of cardio- or cerebrovascular disease morbidity and mortality [3]. Percutaneous endovascular therapies are being increasingly employed as the primary revascularization treatment for PAD, including calcified occlusions [4-6]. Endovascular therapies include percutaneous angioplasty (PTA), nitinol stents, directional and rotational atherectomy, laser atherectomy, drug-eluting stents (DES) and drug-coated balloons (DCB) [6].

Infrapopliteal atherosclerosis is a multilevel disease affecting below-the-knee (BTK) arteries and is often associated with critical limb ischemia (CLI). CLI represents the most severe form of PAD and is characterized by ischemic rest pain and/or nonhealing ulcers [7]. BTK lesions are often technically challenging to treat due to long length, small vessel diameter, poor outflow, and severe calcification [8]. Vessel wall calcification is more severe in BTK lesions compared to more proximal lesions, with medial calcification being most prevalent in the infrapopliteal segment. Due to the severity and unequal distribution of calcium in infrapopliteal lesions, vessel wall expansion can occur in a non-uniform manner increasing the risk for severe dissection with high pressure balloon dilatation [8]. Procedural success for infrapopliteal lesions has improved; however, recoil, dissections, and restenosis remain limitations of infrapopliteal endovascular procedures [9].

3.1.2 Intravascular Lithotripsy

Intravascular lithotripsy is a balloon-based calcium modification treatment modality that uses acoustic pressure waves to modify vessel wall calcium. Peripheral IVL is designed to improve vessel wall compliance to optimize acute gain while minimizing acute vessel injury. The safety and effectiveness of IVL has been reported in several clinical studies in moderate to severe calcified PAD across multiple vessel beds [10-18], including the Disrupt PAD BTK study and the Disrupt PAD III Observational Study (OS), which evaluated peripheral IVL in BTK lesions.

The DISRUPT BTK study enrolled 20 patients with moderate to severe calcified infrapopliteal lesions with 30-day follow-up [13]. After treatment with IVL using the first generation M^5 catheter, all patients achieved a residual stenosis < 50%. There was only one type B dissection,

and a total of two (2) stents were placed. These initial promising results supported the use of IVL to maximize luminal gain while minimizing dissections when treating severely calcified infrapopliteal lesions.

Introduction of the Shockwave S^4 IVL catheter allowed for expanded treatment of BTK lesions due to a smaller crossing profile and balloon diameters relative to the M^5 catheter. Adams et al recently analyzed a cohort of patients from the PAD III Observational Study (OS) with calcified BTK disease treated with the S^4 IVL catheter [10]. A total of 101 patients with 114 calcified infrapopliteal arteries were enrolled at 15 sites and were followed through discharge. This study included a challenging patient and lesion cohort with 69% of patients presenting with CLI and 35% with chronic total occlusion (CTO) lesions. The continued safety and effectiveness of peripheral IVL was demonstrated as 99% of lesions achieved a residual stenosis < 50% with no occurrences of serious angiographic complications at the end of the procedure, regardless of BTK lesion location. Notably, acute results in this "real world" setting with complex lesions were consistent with prior outcomes reported in other peripheral IVL studies [10].

3.2 Study Rationale

In an effort to continually improve IVL therapy, the Disrupt PAD BTK II study is being conducted to assess the continued safety, effectiveness and optimal clinical use of the Shockwave Medical Peripheral IVL System for the treatment of calcified, stenotic BTK arteries. Relative to the previous Disrupt BTK study, the BTK II study includes longer lesions and has long-term follow-up. Relative to the PAD III OS cohort, this study limits use of adjunctive therapy like atherectomy which can confound results.

The Disrupt PAD BTK II study also includes a treatment algorithm designed to standardize IVL treatment of BTK lesions with the goal of optimizing outcomes. Based on a recently proposed algorithm for balloon angioplasty [8], the IVL treatment strategy includes assessment of calcification, optimal balloon sizing, comprehensive IVL treatment along the full length of the target lesion, and assessment of post-IVL residual stenosis. Lastly, this study includes an IVUS Sub-study.

4.0 STUDY DEVICE / TEST ARTICLE DESCRIPTION

4.1 Peripheral IVL System

The Shockwave Peripheral IVL 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 application of lithotripsy mechanical pulse waves alters the structure of an occlusive vascular deposit (stenosis) prior to low-pressure balloon dilatation of the stenosis and facilitates the passage of blood.

The IVL System consists of a balloon catheter with integrated lithotripsy emitters, an IVL Generator, Connector Cable, and related accessories and replacement components (Figure 1). The Shockwave IVL System is built on traditional balloon angioplasty catheter technology, rendering it inherently familiar and easy to use for interventional cardiologists, interventional radiologists, and vascular surgeons. Accordingly, the device should be used only by physicians who are familiar with interventional vascular procedures and who have read and understood the device instructions for use. Refer to the Instructions for Use (IFU) for product descriptions.

The IVL System components do not contain any medicinal substances, blood derivatives or materials derived from animal or human tissue. The balloon materials (PEBAX for M^5 and M^{5+} IVL catheters and Nylon for the S^4 IVL catheter) will come in contact with tissues or body fluids.

There are specific Instructions For Use (IFU) and labelling for the United States (US) and for Outside of the US (OUS).

Figure 1. Shockwave Peripheral IVL System

4.2 Peripheral IVL Catheters

The Shockwave Peripheral IVL Catheters (models M^5, M^{5+} and S^4) are available in multiple balloon sizes ranging from 2.5mm to 8.0mm in diameter, and 40 or 60mm lengths, depending on the model. The catheters have a working length of 110cm to 135cm and are compatible with 300cm length, 0.014" guidewires. The Shockwave IVL Catheter is compatible with 5 to 7F introducer sheaths, depending on the balloon size and catheter model. The catheter kits include a sterile sleeve for the connector cable.

For all catheter types, energy is delivered from the IVL Generator through the Connector Cable to the pulse emitters located inside the balloon in the IVL Catheter. The IVL Generator software can detect the different catheter sizes through a unique PCB installed inside the catheter connector. The IVL Generator and Connector Cable are used exclusively with the IVL Catheters. The IVL Connector Cable is a remote actuator that connects the IVL Generator to the IVL Catheter and is used to activate energy delivery from the IVL Generator. During use, it is covered by a sterile drape. The IVL Generator and Connector Cable are supplied non-sterile and are reusable. The IVL Catheter is supplied sterile via E-beam sterilization. It is intended for single use only and is not intended for reuse or re-sterilization.

4.2.1 Shockwave M^5 IVL Catheter

The Shockwave M^5 IVL Catheters are available in multiple balloon sizes ranging from 3.5mm to 7.0mm diameter and 60mm length. The Over-the-Wire (OTW) catheters have a working length of 110cm and are compatible with 300cm length, 0.014" guidewires. The Shockwave M^5 IVL Catheter is compatible with 6 or 7F introducer sheaths depending on balloon size. There is no coating on the Shockwave M^5 IVL Catheters. The M^5 catheter has 5 emitters and can deliver a maximum of 300 lithotripsy pulses per catheter at a rate of 1 pulse per second (1 Hz).

4.2.2 Shockwave M^{5+} IVL Catheter

The Shockwave M^{5+} IVL Catheter is a line extension of the Shockwave M^5. It has the same balloon sizes as the Shockwave M^5 with the addition of an 8.0mm balloon. The treatment frequency of the Shockwave M^{5+} was increased from 1 pulse/sec to 2 pulses/sec (1 Hz to 2 Hz). The catheter working length was extended to 135cm and is still compatible with 300cm length, 0.014" guidewires. All other characteristics are the same as the Shockwave M^5 catheter.

4.2.3 Shockwave S^4 IVL Catheter

The Shockwave S^4 IVL Catheters are available in balloon sizes of 40mm in length and diameter sizes: 2.5mm, 3.0mm, 3.5mm and 4.0mm diameter. The OTW catheters have a working length of 135cm and are compatible with 300cm length, 0.014" guidewires. The Shockwave S^4 IVL Catheter is compatible with 5F introducer sheaths. There is a hydrophilic coating on the S^4 IVL Catheters. The S^4 catheter has 4 emitters and can deliver a maximum of 160 lithotripsy pulses per catheter at a rate of 1 pulse per second (1 Hz).

4.2.4 Generator and Connector Cable

The Shockwave IVL Generator (Model 825D) and Connector Cable are provided as a kit. The catalog number for the kit is IVLGCCD.

4.3 Indication for Use

The Shockwave Peripheral IVL System with all IVL catheter models (M^5, M^{5+} and S^4) is cleared by the FDA and is CE marked.

4.3.1 United States

The Shockwave Medical M^5, M^{5+}, and S^4 Peripheral Intravascular Lithotripsy Systems are 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.

4.3.2 Outside of the US (excluding Australia)

The Shockwave Medical M^5 and Shockwave Medical S^4 Peripheral Intravascular Lithotripsy Systems are indicated for lithotripsy-enhanced, low-pressure balloon dilatation of calcified, stenotic peripheral arteries in patients who are candidates for percutaneous therapy.

The Shockwave Medical M^{5+} Peripheral Intravascular Lithotripsy System is indicated for lithotripsy-enhanced, low-pressure balloon dilatation of lesions, including calcified lesions, in the peripheral vasculature, including the iliac, femoral, ilio-femoral, popliteal, infra-popliteal, and renal arteries. This device is not intended for use in coronary, carotid, or cerebrovascular arteries.

5.0 STUDY OBJECTIVES

The objective of this study is to assess the continued safety and effectiveness of the Shockwave Medical Peripheral IVL System for the treatment of calcified, stenotic BTK arteries.

5.1 Primary Endpoint(s)

5.1.1 Primary Safety Endpoint

The primary safety endpoint is Major Adverse Limb Events (MALE) or Post-Operative Death (POD) at 30 days defined as a composite of:

- all-cause death
- above-ankle amputation of the index limb
- major reintervention (new bypass graft, jump/interposition graft revision, or thrombectomy/thrombolysis) of the index limb involving a BTK artery

5.1.2 Primary Effectiveness Endpoint

The primary effectiveness endpoint is Procedure Success defined as ≤50% residual stenosis for all treated target lesions without serious angiographic complications (flow-limiting dissection, perforation, distal embolization, or acute vessel closure) as assessed by the angiographic core lab at the final timepoint.

5.2 Secondary Endpoints

- Serious angiographic complications (flow-limiting dissection, perforation, distal embolization, or acute vessel closure) as assessed by the angiographic core lab
- Lesion Success defined as final residual stenosis ≤50% in the target lesion without serious angiographic complications as assessed by the angiographic core lab
- Primary Patency at 6 and 12 months as assessed by both subject and lesion level defined as the absence of both total occlusion (100% diameter stenosis as assessed by DUS core lab) in all of the target lesions in a flow pathway, as well as any CEC adjudicated Clinically-Driven Target Lesion Revascularization (CD-TLR)
- Clinically-Driven Target Lesion Revascularization (CD-TLR), CEC adjudicated, at 30 days, 6, 12, & 24 months
- Major Adverse Events (MAE), CEC adjudicated, at 30 days defined as a composite of:
    - 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

- Quality of Life (QoL) assessed by VascuQoL questionnaire at 30 days, 6, 12, & 24 months, reported as change from baseline
- Major Target Limb Amputation, CEC adjudicated, at 30 days, 6, 12, & 24 months
- Ankle-brachial index (ABI) or toe-brachial index (TBI) at 30 days, 6, 12, & 24 months, reported as change from baseline
- Rutherford Category at 30 days, 6, 12, & 24 months, reported as change from baseline
- Number of existing, new, and recurrent wounds at 30 days, 6, 12, & 24 months
- Number of healed wounds at 30 days, 6, 12, & 24 months
- Number of non-healed wounds by category (improving, stagnant, worsening) at 30 days, 6, 12, & 24 months

5.3 Exploratory Endpoints

- Exploratory endpoints will be defined in the Statistical Analysis Plan (SAP).

6.0 STUDY DESIGN

The Disrupt PAD BTK II study is a post-market, prospective, multi-center, single-arm study of the Shockwave Peripheral IVL System to treat calcified peripheral arteries. There is no control arm as all Peripheral IVL catheters evaluated in this clinical study have received market approval. Adjunctive therapy usage is limited to minimize bias in regard to study results. Use of adjunctive therapy like cutting/scoring balloons, re-entry or atherectomy devices in target lesions is therefore not allowed.

6.1 Regulatory Status

Per ISO 14155:2020, the PAD BTK II study is a post-market clinical investigation defined as a study carried out following market approval of a medical device, intended to answer specific questions relating to effectiveness or safety of a medical device when used in accordance with its approved labeling.

6.2 Clinical Development Stage

Per ISO 14155:2020, the medical devices being used in the PAD BTK II study are in the post-market stage which includes additional confirmatory clinical investigations to establish effectiveness of the medical device in a broader population of users and subjects in comparison to previous studies. Also included are observational clinical investigations for better understanding of device safety, such as rare adverse events and long-term outcomes.

6.3 Type of Clinical Investigation Design

Per ISO 14155:2020, the PAD BTK II study is considered to be an observational clinical investigation defined as a study that draws inferences about the possible effect of an intervention on subjects, but does not require the investigator to assign subjects into intervention groups or to collect data variables beyond those available throughout the course of normal clinical practice and burden to the subject. See Sections 7.6 through 7.8 for information on data collection requirements and assessment of burden to the subject.

6.4 Description of Clinical Investigation

Per ISO 14155:2020, the PAD BTK II study is considered to be a post-market clinical investigation as it is intended to answer specific questions relating to effectiveness or safety of a medical device when used in accordance with its approved labelling.

6.5 Burden to Subjects

Per ISO 14155:2020, the PAD BTK II study is considered to be a non-interventional clinical investigation. No additional invasive or burdensome diagnostic or monitoring procedures are applied to the subjects and epidemiological methods are used for the analysis of collected data.

Subjects are not assigned to an intervention group and the majority of data collection requirements fall within the course of normal clinical practice including physical exam, ABI/TBI, Rutherford Category assessment, and duplex ultrasound. The VascuQol questionnaire may not be standard of care at all centers; however, the assessment is non-invasive, introduces no additional risk, and is not considered to be an additional burden to the subject.

6.6 Site Selection

Up to 40 global sites will participate in the study.

6.7 Number of Subjects

Up to 250 subjects with moderate to severe calcified peripheral artery disease below the knee presenting with Rutherford Category (RC) 3 to 5 will be enrolled. The RC 3 will be capped at 20% of total enrollment. If a subject has a target lesion in each limb and one of the limbs is RC 3, this subject will count toward the Rutherford Category 3 cap. Up to two (2) target lesions allowed for each subject. Each site will be allowed to enroll up to 15% (37 subjects) of total study enrollment.

6.8 Clinical Study Duration

Enrollment is anticipated to last approximately 24 months. Study subjects will be followed through hospital discharge, 30 days, and 6-, 12-, and 24-months post-procedure. Duplex ultrasound (DUS) assessments will be completed at 6 and 12 months. Total anticipated study duration is 48 months.

6.9 IVUS Sub-study

Up to 50 subjects will be enrolled in an optional IVUS Sub-study. All study centers with intravascular ultrasound (IVUS) imaging capability will have the opportunity to participate in the Sub-study. A separate IVUS protocol will be provided to participating study centers.

7.0 STUDY PROCEDURES

7.1 Screening

Patients presenting to the institution with known infrapopliteal disease requiring an interventional procedure will be evaluated for eligibility and participation in the clinical 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) should be performed according to the institution's standard of care.

Potential subjects will be screened for eligibility. Written informed consent will be obtained prior to any study-specific requirements. A potential subject will be informed of the elements of the clinical study including risks, potential benefits, and required follow-up procedures prior to obtaining the potential subject's informed consent.

7.2 Subject Selection

Subjects who meet the clinical inclusion/exclusion criteria will undergo an angiogram performed according to the institution's standard of care. If all angiographic eligibility criteria are met, the subject is considered to be enrolled once the peripheral IVL catheter has been inserted over a 0.014" guidewire that crossed the target lesion. A subject is considered an angiographic screen failure if they do not meet angiographic eligibility criteria. Subjects who screen fail will be documented as such in the electronic data capture (EDC) system.

7.2.1 Inclusion Criteria

Subjects are required to meet all of the following inclusion criteria in order to be enrolled in the clinical study. For lesion characteristics, each target lesion must meet eligibility. The subject would, at the investigator's discretion, receive the treatment required per Study Protocol which also may be per standard of care (SOC).

General Inclusion Criteria

1. Age of subject is ≥ 18.
2. Subject is able and willing to comply with all assessments in the study.
3. Subject or subject's legal representative has been informed of the nature of the study, agrees to participate, and has signed the approved consent form.
4. Rutherford Category 3, 4, or 5 in the target limb.
5. Estimated life expectancy >1 year.

Angiographic Inclusion Criteria

6. Up to 2 below-the-knee target lesion(s) in native vessels in one or both limbs.
7. Target lesion from the distal segment (P3) of the popliteal artery to the ankle joint.

8. Target lesion reference vessel diameter (RVD) between 2.0mm and 4.0mm by investigator visual estimate.
9. Target lesion with ≥70% stenosis by investigator visual estimate.
10. Target lesion length is ≤200mm by investigator visual estimate. Target lesion can be all or part of the 200mm treated zone.
11. Distal reconstitution of at least one pedal vessel (<50% stenosis) (desert foot excluded) in the target limb.
12. Evidence of at least moderate calcification at the target lesion site by angiography/IVUS OR non-dilatable lesion indicating presence of calcium. Must meet one of the following:
    a. Angiography requires fluoroscopic evidence of calcification on parallel sides of the vessel and extending >50% the length of the lesion.:
    b. IVUS requires presence of ≥270 degrees of calcium over the course of at least 10mm.
    c. Non-dilatable lesion requires attempted treatment with PTA during the index procedure with residual stenosis >50% and no serious angiographic complications.

7.2.2 Exclusion Criteria

Subjects who meet any of the following exclusion criteria may not be enrolled in the study:

General Exclusion Criteria

1. Rutherford Clinical Category 0, 1, 2, and 6 (target limb).
2. Subjects with osteomyelitis or deep soft tissue infection are excluded unless infection can be treated with an individual toe ray amputation or transmetatarsal amputation (TMA) in the target limb in the opinion of the investigator.
3. History of endovascular or surgical procedure on the target limb within the last 30 days, or planned within 30 days of the index procedure with the exception of toe amputation(s).
4. Subject in whom antiplatelet or anticoagulant therapy is contraindicated.
5. Subject has known allergy to contrast agents or medications used to perform endovascular intervention that cannot be adequately pre-treated.
6. Subject has known allergy to urethane, nylon, or silicone.
7. Myocardial infarction within 30 days prior to enrollment.
8. History of stroke within 60 days prior to enrollment.

9. Subject has acute or chronic renal disease with eGFR <30 ml/min/1.73m^2 (using CKD-EPI formula), unless on renal replacement therapy.
10. Subject is pregnant or nursing.
11. Subject is participating in another research study involving an investigational agent (pharmaceutical, biologic, or medical device) that has not reached the primary endpoint.
12. 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.
13. Covid-19 diagnosis within 30 days.
14. The planned use of cutting/scoring balloons, re-entry or atherectomy devices in target lesions during the index procedure.
15. Planned major amputation (of either leg).
16. Acute limb ischemia (of either leg).
17. Occlusion of all the inframalleolar outflow arteries/vessels (i.e., desert foot) in the target limb.
18. Subject has an anticipated life span of less than one (1) year.
19. Subject already enrolled into this study.

Angiographic Exclusion Criteria

20. Failure to treat clinically significant inflow lesions in the ipsilateral iliac, femoral, or popliteal arteries with ≤30% residual stenosis, and no serious angiographic complications (e.g., embolism).
21. Failure to successfully treat significant *non-target* infra-popliteal lesions prior to treatment of *target* lesion(s). Successful treatment is defined as obtaining ≤50% residual stenosis with no serious angiographic complications (e.g., embolism).
22. Treatment of vessels below the ankle joint.
23. Failed pre-dilatation in *target* lesion during index procedure with angiographic evidence of serious angiographic complications.
24. Target lesion includes in-stent restenosis.
25. Evidence of aneurysm or thrombus in target vessel.
26. No calcium or mild calcium in the target lesion.
27. Target lesion within native or synthetic vessel grafts.

28. 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.

7.3 Informed Consent

Prior to undergoing any study-specific tests or procedures, the subject or their legally designated representative must sign and date the site's current and approved Institutional Review Board (IRB)/ Ethics Committee (EC) informed consent form (ICF) in order to be eligible for study participation. The informed consent must contain all elements required by 21 CFR Part 50, EU MDR 2017/745 Article 63, and ISO 14155:2020 and comply with the ethical principles of the Declaration of Helsinki.

7.3.1 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 IRB/EC
- The Investigator or designee will provide the subject with a copy of the signed and dated informed consent form and any other written information

7.3.2 Subjects Needing Legally Designated Representative

Informed consent may be given by a legally designated 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.

Please follow the local IRB/EC guidelines on this process.

7.3.3 Subjects Unable to Read or Write

Informed consent shall be obtained through a supervised oral process if a subject or legally designated representative is unable to read or write, if allowed by the IRB/EC. 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 designated 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.

7.3.4 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 clinical study. The revised information will be sent to the Investigator for approval by the IRB/EC. After approval by the IRB/EC, a copy of this information must be provided to the participating subjects, and the informed consent process as described above needs to be repeated.

Please follow the local IRB/EC guidelines on the process of re-consenting subjects.

7.4 Schedule of Events and Evaluations

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

Table 1. Schedule of Events and Evaluations

Assessment	Screening / Baseline	Enrollment and Procedure	Discharge[4]	30 Days (±7 days)	6 Months (180±30 days)	12 Months (365±30 days)	24 Months (730±30 days)	TLR
Eligibility	√							
Informed Consent [1]	√							
Medical History	√							
Physical Exam	√			√	√	√	√	
Baseline Labs (eGFR)	√							

Assessment	Screening / Baseline	Enrollment and Procedure	Discharge[4]	30 Days (±7 days)	6 Months (180±30 days)	12 Months (365±30 days)	24 Months (730±30 days)	TLR
Pregnancy Test	√							
Ankle-Brachial Index/Toe-Brachial Index (ABI/TBI)	√[2]			√	√	√	√	
Rutherford Category (RC)	√			√	√	√	√	
VascuQoL-6 Questionnaire	√			√	√	√	√	
Wound Healing Assessment (including photographs)	√[6]			√	√	√	√	
Medications (anticoagulants & antiplatelets)	√	√	√	√	√	√	√	
Angiogram		√						√[5]
IVUS (sub-study		√[3]						
Duplex Ultrasound (DUS)					√[7]	√[7]		

Assessment	Screening / Baseline	Enrollment and Procedure	Discharge[4]	30 Days (±7 days)	6 Months (180±30 days)	12 Months (365±30 days)	24 Months (730±30 days)	TLR
Adverse Events		√	√	√	√	√	√	√

TLR = target lesion revascularization; DUS = duplex ultrasound; ABI = ankle-brachial index; TBI = toe-brachial index; QoL = quality of life
1. Consent to be obtained within 30 days prior to procedure.
2. Within 60 days prior to procedure.
3. For the IVUS Sub-study, IVUS imaging is required at baseline, immediately post-IVL, and end of procedure.
4. Within 12-24 hours post procedure or prior to hospital discharge, whichever occurs first.
5. Angiographic images acquired as standard of care prior to the TLR should be submitted to the core lab.
6. Within 45 days of procedure.
7. In the event of a non-diagnostic DUS, a 90-day extension is allowed on the upper limit of the window for the 6- and 12-month visits.

7.5 Medications

Anticoagulation/antiplatelet medications should be administered according to the 2017 European Society of Cardiology (ESC) and European Society of Vascular Surgery (ESVS) PAD guidelines [19] and the 2016 American College of Cardiology (ACC) and American Heart Association (AHA) PAD guidelines [5].

Additional recommendations for anticoagulation and antiplatelet medications include:

- Unfractionated heparin dosing should be undertaken according to hospital standard of care.
- Prasugrel or ticagrelor may be used as an alternative to clopidogrel for existing management of acute coronary syndrome (ACS).
- Follow antiplatelet and anticoagulation guidelines for the management of patients with atrial fibrillation.

7.6 Screening/Baseline Procedures

Baseline assessments must be completed within 30 days of the procedure. The following are exceptions: wound assessment which can be completed within 45 days of procedure, ankle-brachial index (ABI) / toe-brachial index (TBI), which can be completed within 60 days of the procedure, and a pregnancy test which must be done within 7 days of the procedure. Informed consent must be obtained prior to any study-specific evaluations needed to assess eligibility which are not considered standard of care. Subjects on warfarin or direct thrombin inhibitors should be followed per institutional standard of care by the physician.

Baseline assessments include:

- Medical history
- Physical examination

  - Vital signs
  - Height and weight
  - Baseline Labs (eGFR)
- ABI or TBI (at rest; use same test for subject throughout study)
- Rutherford Category
- VascuQoL-6 Questionnaire
- Wound Healing Assessment (including photographs)
- Review of medications (anticoagulants and antiplatelets)
- Urine pregnancy test if female of child-bearing age

Note: If treatment of two target lesions is planned across both limbs, the RC category and ABI/TBI for each limb must be assessed. If ABI/TBI cannot be assessed due to non-compressible vessels, this should be documented. If TBI is used, subject should have TBI at each follow-up visit.

eGFR should be calculated using the CKD-EPI formula in absence of a standardized lab test provided by the site.

Wound healing assessments of the target limb(s) must be performed at baseline and all follow-up visits. Photographs must be taken of the wound(s) to document the progression of wound healing throughout the study and kept in the subject's study binder. Photographs will be retained at the site in the study subject's medical record but will not be provided to the Study Sponsor via upload. If photographs are not obtained, a protocol deviation will be issued. At the follow-up visits, the wounds will be recorded in the EDC as healed (completely epithelialized), not healed, recurrent, new, or amputated. If the wound is not healed, it will be further classified as improving, stagnant, or worsening. A wound can only be considered recurrent if it was healed at a prior study visit and subsequently re-appears at the same location.

7.7 Index Procedure

The IVL treatment algorithm is described in the steps below and illustrated in Figure 2. Each investigative site will be using one generator and one connector cable for enrollment in accordance with the IFU. Multiple IVL catheters can be used per subject enrollment.

7.7.1 Procedural Imaging Requirements

An angiographic cine will be obtained for each lesion treated including pre-procedure, post-IVL and end of procedure. (If any non-target lesions are treated, an additional cine will be obtained prior to IVL treatment of any target lesion(s) to ensure no serious angiographic complications have occurred and that the subject still meets criteria to be enrolled.) All angiographic images must be submitted to the core lab for analysis. If intravascular imaging (i.e., IVUS) is performed, images from the three timepoints (baseline, immediately post-IVL, and end of procedure) should be submitted to the IVUS core lab for analysis.

For subjects enrolled in the IVUS Sub-study, angiographic and IVUS images are required at three (3) timepoints: baseline, immediately post-IVL, and end of procedure. The core lab will provide separate angio and IVUS protocols to participating study centers.

7.7.2 Assessment of Calcification

Up to two (2) target lesions may be treated per subject. Calcification of the target lesion(s) may be assessed by angiography or IVUS. To meet eligibility requirements, angiography requires fluoroscopic evidence of calcification on parallel sides of the vessel and extending > 50% the length of the lesion. If assessed by IVUS, there must be ≥270 degrees of calcium over the course of at least 10mm. Note: if calcification does not meet imaging criteria, a lesion may be eligible if found to be non-dilatable, suggestive of calcification.

7.7.3 Treatment of Non-Target Lesions

Non-target lesions must be treated successfully prior to treatment of the target lesion(s). After the maximum number (2) of target lesions has been reached, any additional lesions should be assigned as non-target lesions. Non-target lesions may be treated with any commercially available device; treating a non-target lesion with a device that is not approved or considered investigational will result in a protocol deviation.

Note: In the case where non-target lesions and target lesion are present in both limbs, non-target lesions should be treated successfully first per limb.

Clinically significant inflow lesions in the ipsilateral iliac, femoral, or popliteal arteries must be treated with ≤30% residual stenosis and no serious angiographic complications (e.g., embolism). Significant *non-target* infra-popliteal lesions must be treated with ≤50% residual stenosis with no serious angiographic complications (e.g., embolism). If there are serious angiographic complications following treatment of non-target lesions, the subject should not be enrolled.

7.7.4 Tandem Lesion(s)

Tandem lesions (lesions < 3 cm apart) are allowed if the total treated area covers the entire diseased segment. Total treated area is defined as the area treated by any PTA device (pre-dilatation, IVL, post-dilatation, or DCB). Each tandem lesion/diseased segment is considered one target lesion. As tandem lesions are considered one single target lesion, angiographic eligibility must be met as a single lesion.

7.7.5 Definition of Enrollment

The definition of enrollment is when the subject signs informed consent, meets all general & angiographic eligibility criteria, and the IVL catheter has been inserted over a 0.014" guidewire (which had been previously passed across the target lesion).

7.7.6 Pre-IVL Dilatation (if required)

If the operator is unable to pass the IVL balloon across the lesion, a standard PTA balloon up to 2.5mm should be used for pre-dilatation prior to treatment with the IVL Balloon (not applicable for enrollment of non-dilatable lesions).

7.7.7 IVL Device Crossing Failures

If the investigator is not able to advance the IVL Catheter across the target lesion after exhausting pre-dilatation efforts **AND** no pulses were delivered, this will be defined as a Device Crossing Failure. Any further treatment will be done per standard of care without the use of IVL. In the case of a Device Crossing Failure, the subject is considered enrolled; but as treatment with IVL did not occur, will be exited from the study following hospital discharge.

However, if the investigator *cannot fully cross the target lesion with the IVL catheter and pulses were delivered, this is not considered a device crossing failure.* Under those circumstances, a subject is considered enrolled and follow up is required through 24 months (see Protocol Section 7.4, Schedule of Events and Evaluations.)

Note:

- Device crossing failures and devices that did not fully cross still should be documented as a device deficiency/malfunction.
- Use of IVL (i.e., for the purpose of enrollment of lesion/subject) is not permitted if non-conventional PTA treatments -- including atherectomy, laser or cutting/scoring balloons -- were previously used to treat the target lesion.

7.7.8 IVL Treatment

A full description of the IVL procedure is detailed in the Instructions for Use (IFU) including appropriate balloon sizing. Note that there are specific IFUs and labelling provided for the United States (US) and for Outside of the US (OUS).

Select an IVL balloon catheter size that is 1.1:1 based on balloon compliance chart and reference vessel diameter; the largest diameter balloon should be used if 1.1:1 sizing is not available.

Once the IVL balloon is placed in the target lesion area, the balloon must be inflated to 4 atm to deliver one cycle of IVL pulses. Table 2 lists the pulsing sequence for each IVL catheter. For the M^5 and M^{5+} catheters, one cycle = 30 pulses; for the S4 catheter, one cycle = 20 pulses. Insertion of any size IVL Catheter into the IVL Generator will automatically program the IVL Generator with the appropriate treatment sequence. Note that the generator is programmed to force a minimum pause time of 10 seconds following every cycle.

Following delivery of the first IVL cycle, the balloon must be inflated to 6 atm (nominal pressure; refer to IFU) and record lesion response on fluoroscopy. Deflate the balloon and wait 10 seconds to re-establish blood flow. Repeat the steps above to complete a second cycle of pulses to complete a single treatment. Additional treatment cycles can be performed if deemed necessary.

Additional pulses can be performed in a single location to obtain residual stenosis <50%. Multiple treatment locations should be done for long lesions with IVL balloon overlap of 1 cm. For optimal results, treat the entire lesion length with IVL; do not use "spot" IVL.

Caution: Care must be taken not to exceed 160 pulses in the same segment.

Table 2. IVL System Sequence Chart

	M[5]	M[5+]	S[4]
Treatment Frequency	1 Pulse per Second	2 Pulses per Second	1 Pulse per Second
Maximum Number of Continuous Pulses (1 cycle)	30 Pulses	30 Pulses	20 Pulses
Minimum Pause Time (between cycles)	10 Seconds	10 Seconds	10 Seconds
Maximum Total Pulses Per Catheter	300 (10 Cycles)	300 (10 Cycles)	160 (8 Cycles)

7.7.9 Post-Dilatation

Post-dilatation with a semi or non-compliant PTA balloon catheter must be completed when post-IVL results in one of the following:

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

Post-dilatation may also be performed per physician discretion. The physician should use a 1:1 balloon catheter to artery ratio and may post-dilate for several minutes. Follow the angiographic core lab guidelines to complete angiography showing all target lesions with reproducible landmarks for follow-up evaluation and assessment.

7.7.10 Assessment for Acute PTA Failure

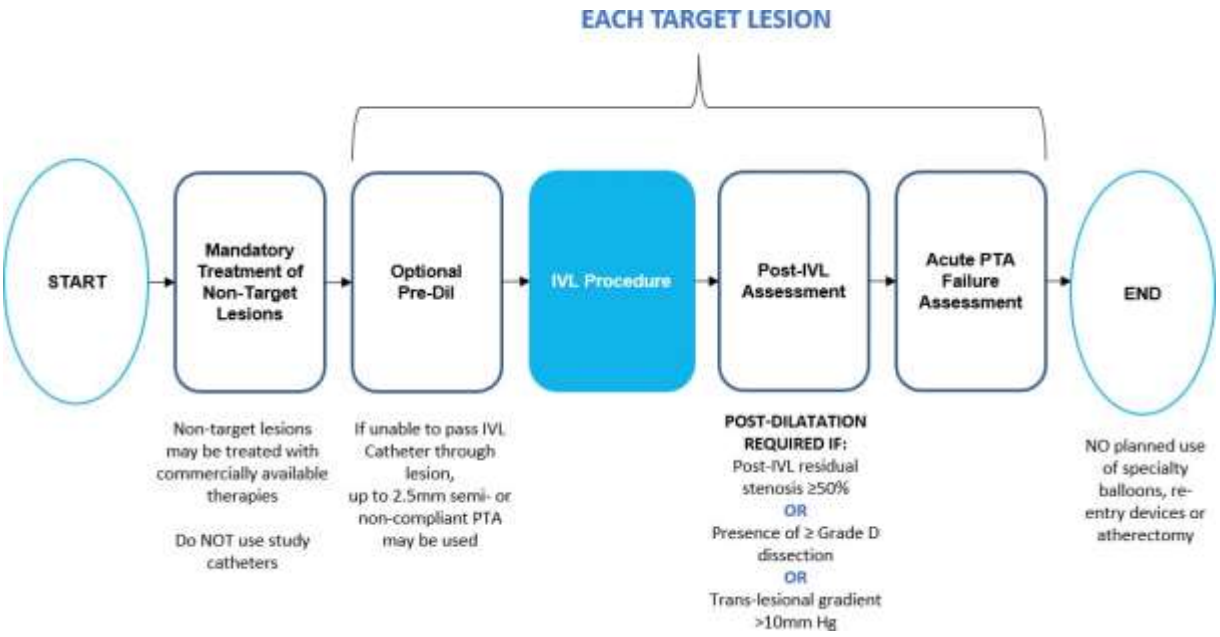
Treatment with a stent or Tack implant is allowed for the following:

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

7.7.11 IVUS Assessment (optional Sub-study)

For subjects enrolled in the IVUS Sub-study, angiographic and IVUS images must be assessed at baseline, immediately post-IVL, and end of procedure. The core lab will provide a separate IVUS protocol to participating study centers.

Figure 2. BTK IVL Treatment Algorithm



7.8 Follow-Up

7.8.1 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:

- Adverse event assessment
- Review of medications (anticoagulants and antiplatelets)

7.8.2 30-Day Follow-Up

The following evaluations will be performed at **30 days** (+/-7 days) post procedure:

- Physical examination
  - Vital signs
  - Target review of symptoms
- ABI or TBI (at rest; keep consistent with screening)
- Rutherford Category
- VascuQoL-6 Questionnaire
- Wound Healing Assessment (including photographs)
- Review of medications (anticoagulants and antiplatelets)
- Adverse event assessment

Note: If treatment of two target lesions is planned across both limbs, the Rutherford Category and ABI/TBI for each limb must be assessed. If ABI/TBI cannot be assessed due to non-compressible vessels, this should be documented.

7.8.3 6-Month Follow-Up

The following evaluations will be performed at **6 months** (180 +/-30 days) post procedure:

- Physical examination
  - Vital signs
  - Target review of symptoms
- ABI or TBI (at rest; keep consistent with screening)
- Rutherford Category
- VascuQoL-6 Questionnaire
- Wound Healing Assessment (including photographs)
- Review of medications (anticoagulants and antiplatelets)
- Adverse event assessment
- Duplex ultrasound (DUS)

Note:

- *If treatment of two target lesions is planned across both limbs, the Rutherford Category and ABI/TBI for each limb must be assessed. If ABI/TBI cannot be assessed due to non-compressible vessels, this should be documented.*
- *In the event of a non-diagnostic DUS, a 90-day extension is allowed on the upper limit of the window for the 6- and 12-month visits*

7.8.4 12-Month Follow-Up

The following evaluations will be performed at **12 months** (365 +/-30 days) post procedure:

- Physical examination
  - Vital signs
  - Target review of symptoms
- ABI or TBI (at rest; keep consistent with screening)
- Rutherford Category
- VascuQol-6 Questionnaire
- Wound Healing Assessment (including photographs)
- Review of medications (anticoagulants and antiplatelets)
- Adverse event assessment
- Duplex ultrasound (DUS)

Note:

- *If treatment of two target lesions is planned across both limbs, the Rutherford Category and ABI/TBI for each limb must be assessed. If ABI/TBI cannot be assessed due to non-compressible vessels, this should be documented.*
- *In the event of a non-diagnostic DUS, a 90-day extension is allowed on the upper limit of the window for the 6- and 12-month visits*

7.8.5 24-Month Follow-Up

The following evaluations will be performed at **24 months** (730 +/-30 days) post procedure:

- Physical examination
  - Vital signs
  - Target review of symptoms
- ABI or TBI (at rest; keep consistent with screening)
- Rutherford Category
- VascuQoL-6 Questionnaire
- Wound Healing Assessment (including photographs)
- Review of medications (anticoagulants and antiplatelets)
- Adverse event assessment

Note: If treatment of two target lesions is planned across both limbs, the Rutherford Category and ABI/TBI for each limb must be assessed. If ABI/TBI cannot be assessed due to non-compressible vessels, this should be documented.

7.8.6 Prior to Target Limb Revascularization

If a target limb procedure is performed during the follow-up period, angiographic images acquired as standard of care should be submitted to the core lab for purposes of adjudication.

7.9 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.

Potential reasons for withdrawal from the study are, but not limited to:

- Subject lost to follow-up
- Pregnancy
- Subject meets exclusion criteria not previously recognized or newly developed

  Safety concerns regarding the device

7.9.1 When and How to Withdraw Subjects

Subjects may be withdrawn at the medical discretion of the physician, or they may voluntarily withdraw their consent at any time without impact to their medical treatment.

Prior to enrollment, the investigative site should provide contact information and detailed instructions to subjects on how to withdraw from the study. When a subject is withdrawn, all data obtained prior to the time of withdrawal may be submitted to the Study Sponsor and be included in the study database, unless otherwise requested by the subject in writing.

In the event a subject is lost to follow-up or cannot be contacted for post-treatment assessments, at least three attempts (two phone calls and a certified letter) will be made to locate the study subject, and these efforts will be documented. If the subject cannot be located, the subject's lost to follow-up status will be documented in the EDC and they will be exited from the clinical study.

Should the subject expire, an adverse event form and a study exit/withdrawal form must be completed. Physician assessment is required to determine if the cause of death was possibly, probably, or definitely related to the IVL System. If available, copies of the death certificate and/or an autopsy report should be included in the research records. The Investigator may need to provide written notification to the IRB/EC upon the death of the study subject, dependent on the IRB/EC policies.

8.0 BENEFITS AND RISKS

8.1 Anticipated Clinical Benefits

There may be no additional benefit from participation since subjects can receive IVL treatment per standard of care. The clinical study will provide safety and effectiveness data associated with Peripheral IVL System treatment of calcified BTK arteries. These clinical results may inform physicians in determining the optimal treatment strategy for this patient population.

8.2 Anticipated Adverse Device Effects

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 (IFU) for the Peripheral IVL System. There are specific IFUs and labelling provided for the US and for OUS.

It is important to ensure that the IFU referred to represents the generation of the device used in the study procedure. Unanticipated risks can occur.

Possible adverse effects are consistent with standard angioplasty. Risks identified as unique to the device and its use are outlined in the IFUs for the M^5, M^{5+}, and S^4 IVL catheters. They include:

- Allergic/immunologic reaction to the catheter material(s) or coating [Incidence is Uncommon or Infrequent (≥0.1% to <1%)]
- Device malfunction or failure [Incidence is Rare (≥0.01% to <0.1%)]
- Excess heat at target site due to malfunction of IVL Generator*

  *Note: Because of testing and clinical evidence, this risk is being removed from later revisions of the IFU.

8.3 Risks Associated with Participation in the Clinical Investigation

All assessments (with the exception of questionnaires) are considered to be standard of care, but may be conducted more frequently to comply with the follow-up visit schedule. Non-invasive testing includes physical exams, ABI/TBI, Rutherford Category assessments, wound healing assessments, and duplex ultrasounds. All of this testing poses minimal risk to the subject. The VascuQol questionnaire may not be standard of care at all centers; however, the assessment is non-invasive, introduces no additional risk, and is not considered to be an additional burden to the subject. For procedure-related risks, please refer to the current IFUs.

A risk management plan was established to outline the study-specific approach that will be implemented to focus on specific risks and area(s) of greatest need, which are considered to have the most potential to impact subject safety and data quality.

8.4 Possible Interactions with Concomitant Medical Treatments

There are no known possible interactions within this study.

8.5 Steps that will be taken to Control or Mitigate the Risks

Only those subjects meeting each inclusion and no exclusion criteria will be enrolled into this clinical study. Investigators will be qualified by education, training, and experience to assume responsibility for the proper conduct of the clinical investigation. Risks of observed or theoretical adverse events will be mitigated through the Instructions for Use, physician training, subject selection in the study protocol, and close monitoring of protocol adherence.

All efforts will be made to minimize risks specifically by:

- Site selection
- Ensuring compliance to the protocol and IFU
- Data Review
- Study monitoring
- Statistical Evaluation
- Vendor Management
- Safety processes – protocol adverse event reporting requirements, CEC oversight, and safety reporting to regulatory authorities including Vigilance reporting
- Review of all device malfunctions and complaints by Shockwave Medical Quality. Risk acceptability thresholds and trend identification methods have been established, and actions will be taken if those are met.

8.6 Rationale for Benefit-Risk Ratio

The Shockwave Peripheral IVL System is market approved for the United States (US) and the European Union (EU) markets and will be used as per standard of care (SOC) at the investigational sites. The safety profile of the Shockwave Peripheral IVL System is well understood and the system is already used as part of standard of care at many sites. Previous clinical investigations have shown that the Shockwave Peripheral IVL System is safe and effective.

Risks and benefits of the Shockwave Peripheral IVL System are evaluated throughout the lifetime of the device as part of the risk management process in accordance with ISO 14971 which includes risk analysis, risk-to-benefit assessment, and risk control. Risk management activities, documentation, and records are held and/or referenced in the Risk Management File. The benefit-risk analysis provides objective evidence that all risks have been reduced as low as possible and no individual risks are unacceptable. Results indicated that the benefits of using the Shockwave Peripheral IVL System outweigh any residual risks.

9.0 DATA ANALYSIS PLAN

9.1 General Statistical Methods

Descriptive statistics will be provided in this clinical study. Analyses will be conducted at pre-specified time points including 30 days, 6, 12 and 24 months.

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

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

Exploratory analyses and clarifications to the protocol specified analysis plan will be documented in the SAP. Statistical analyses will be performed using SAS System® Version 9.4 or higher.

9.2 Primary Endpoints

Exact 95% confidence intervals will be generated for primary endpoints and estimates of proportions.

9.2.1 Primary Safety Endpoint

The primary safety endpoint is Major Adverse Limb Events (MALE) or Post-Operative Death (POD) at 30 days defined as a composite of:

- all-cause death
- above-ankle amputation of the index limb
- major reintervention (new bypass graft, jump/interposition graft revision, or thrombectomy/thrombolysis) of the index limb involving a BTK artery

9.2.2 Primary Effectiveness Endpoint

The primary effectiveness endpoint is Procedure Success defined as ≤50% residual stenosis for all treated target lesions without serious angiographic complications (flow-limiting dissection, perforation, distal embolization, or acute vessel closure) as assessed by the angiographic core lab at the final timepoint.

9.3 Sample Size Determination

The sample size was calculated based on the precision of the exact 2-sided 95% confidence interval (CI) of the primary effectiveness endpoint, using the LIBERTY 360 study results as a reference. The LIBERTY 360 study of endovascular interventions for PAD is one of the largest, real-world, core laboratory–adjudicated studies to include patients with varying degrees of PAD severity. Procedural Success for the RC 4-5 cohort of this large contemporary data set was 75.8% [71.9, 79.3] [20].

The calculation of the Disrupt PAD BTK II sample size was based on a procedural success estimate of 75.8%. Combined with a desired precision of +/- 5.8% and an alpha of 0.05 (95% CI), a sample size of 225 was selected to provide a probability width ("power") of 0.827. Assuming a lost-to-follow-up rate of 10%, up to 250 subjects will be enrolled.

9.4 Populations for Analysis

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

9.5 Handling of Dropouts or Missing Data

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

9.6 Sub-Group Analyses

Analyses to examine the consistency of results across different subgroups will be performed for the primary safety and effectiveness endpoints for the following subgroups, and results will be reported using descriptive statistics:

- Age (>75 vs ≤75 years)
- Gender
- Diabetes (medically treated vs no diabetes or not medically treated)
- Renal insufficiency (eGFR: <30, 30-59, ≥60)
- Lesion length (<100 mm, 100-150mm, >150mm)
- Chronic Total Occlusion (CTO)
- Calcification (moderate vs severe)
- IVUS Sub-study at baseline, immediately post-IVL, and end of procedure
- Wounds at baseline
- Claudicant (RC 3) vs. CLI (RC 4 & 5)

No formal hypothesis testing for subgroup analyses will be performed. However, to examine the consistency of results across different subgroups, the primary safety and effectiveness endpoints will be compared between subgroups using a logistic regression model including an intercept term and fixed effect for the subgroup, with corresponding 95% confidence interval and p-value presented.

10.0 SAFETY EVENTS

Standard definitions and reporting requirements for reportable adverse events for the study are provided below. All adverse events will be coded using MedDRA.

Note: For any of the Adverse Event Definitions listed below, diagnosis should be reported versus individual symptoms leading to diagnosis.

10.1 Adverse Event Definitions

10.1.1 Adverse Event (AE)

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 medical device and whether anticipated or unanticipated.

Note: Abnormal laboratory findings will be reviewed by the site Principal investigator (PI) and/or site Sub-investigator (Sub-I) who use their medical judgement to determine if these abnormal clinical signs are clinically significant (CS) or non-clinically significant (NCS). If the PI or Sub-I deem the abnormal laboratory finding to be clinically significant, it should be treated as an adverse event and documented as such. If found to be non-clinically significant, the PI/Sub-I should document this by writing "NCS" on source document and initial and date.

Note: This definition includes events related to the investigational medical device or the comparator.

Note: This definition includes events related to the procedures involved.

Note: For users or other persons, this definition is restricted to events related to the use of investigational medical devices or comparators.

10.1.2 Serious Adverse Event (SAE)

Adverse event that led to any of the following

a) death,

b) serious deterioration in the health of the subject, users, or other persons as defined by one or more of the following:

1) a life-threatening illness or injury, or

2) a permanent impairment of a body structure or a body function including chronic diseases, or

3) in-patient or prolonged hospitalization, or

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

c) fetal distress, fetal death, a congenital abnormality, or birth defect including physical or mental impairment.

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

10.1.3 Adverse Device Effect (ADE)

Adverse event related to the use of an investigational device.

Note: 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.

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

Note: This includes "comparator" if the comparator is a medical device.

10.1.4 Serious Adverse Device Effect (SADE)

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

10.1.5 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 risk assessment.

Note: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk assessment.

10.2 Adverse Event Device and Procedure Relatedness

Based on clinical judgment, the Investigator must provide a determination of device and procedure relationship for adverse events 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".

- 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.

10.3 Device Deficiencies

10.3.1 Definitions

Device Deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety, or performance.

Note: Device deficiencies include malfunctions, use errors, failure to fully cross lesion and inadequacy in the information supplied by the manufacturer including labelling.

Note: This definition includes device deficiencies related to the investigational medical device or the comparator.

Device Malfunction is a failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or Clinical Investigation Plan (CIP), or Investigator Brochure (IB).

Note: An IB is deemed not required as the IFUs and product labelling together with available commercial product information is deemed sufficient information for the use of the device within its approved indication.

10.3.2 Reporting

All device deficiencies and malfunctions will be documented on the eCRF and reported to the Study Sponsor within 48 hours after the designated study site personnel first learns of the event, and reported to the IRB/EC (if required) within the IRB/EC required timeframe. Device deficiencies and malfunctions will trigger an EDC notification to be sent directly to the Study Sponsor. All deficient/malfunctioned devices should be securely stored and prepared for return to Shockwave Medical.

In the event that EDC is unavailable, a paper Device Malfunction CRF must be submitted by the site to swmbtk2@shockwavemedical.com.

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, or performance of a device after it is released for distribution), a Complaint Form will be completed by a Shockwave representative and entered into the company's complaint system, as per Shockwave Medical's internal procedure. The Shockwave Medical Quality representative is responsible for assessing the need for and submitting any Vigilance reports, and/or Medical Device Reporting (MDR) reports to the relevant regulatory agencies in line with country specific regulations and guidance documents, if required.

10.4 Serious and Non-serious Adverse Event Reporting Requirements

10.4.1 AE Reporting Requirements

All AE information will be collected from enrollment through 24 months follow-up. Reporting will be carried out in accordance with national regulations. Site personnel will enter all AEs into an AE eCRF in EDC. AEs should be reported in the subject's medical records as applicable and on the Adverse Event Case Report Form (AE CRF). Data reported should include date of onset, treatment, resolution, and an assessment of both seriousness and relationship to the study device and procedure. AEs 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).

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

10.4.2 SAE Reporting Requirements

Any AE meeting any of the criteria for an SAE occurring at any time during the study (enrollment through 24 months) must be reported to the Study Sponsor within 48 hours after the designated study site personnel first learns of the event. The SAE must also be reported to the IRB/EC per the institution's policy for reporting SAEs. SAEs should be reported in the subject's medical records as applicable and on the Adverse Event Case Report Form (AE CRF). Data reported should include date of onset, treatment, resolution, and an assessment of both seriousness and relationship to the study device and procedure. 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).

It is the responsibility of the Investigator to inform their IRB/EC of SAEs as required by their IRB/EC policies. The Investigator should forward a copy of this report to the Study Sponsor and file in the site regulatory binder.

SAEs will trigger an EDC notification to be sent directly to the Study Sponsor.

In the event that EDC is unavailable, a paper AE CRF must be submitted by the site to swmbtk2@shockwavemedical.com.

After data entry completion, a notification of SAE and/or device/procedure-related AE will be triggered and sent to the Study Sponsor, and any device and/or procedure related AE notifications will be sent directly to Shockwave Medical Quality for review.

10.4.3 Non-serious ADE Reporting Requirements

All ADE information will be collected from enrollment through 24 months. ADEs will be recorded in the subject's medical records as applicable and on the Adverse Event Case Report Form (AE CRF). Each ADE must be evaluated to determine if the event meets the definition of SADEs. Data reported should include date of onset, treatment, resolution, and an assessment of both seriousness and relationship to the study device and procedure. 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). All ADEs must be reported to the Study Sponsor as soon as possible after the designated study site personnel first learns of the event.

10.4.4 SADE Reporting Requirements

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

10.4.5 USADE Reporting Requirements

Investigators are required to submit a report of a USADE to the Study Sponsor as soon as possible, but not later than 48 hours after the designated study site personnel first learns of the event and to the ECs within the required timeframe. Investigators are required to report a UADE to the reviewing IRB/EC and the Study Sponsor as soon as possible, but in no event later than 10 working days after the Investigator first learns of the effect.

10.4.6 AE and Device Deficiency Reporting Time Frames

Table 3 summarizes the time sensitive reporting requirements for serious and non-serious adverse events and device deficiencies. The Study Sponsor or designee is the contact person for these reporting requirements.

Table 3. Investigator Responsibilities for Reporting Adverse Events

Type of Event	Process
Device deficiencies (including malfunctions)	Report to the Study Sponsor within 48 hours after the designated study site personnel first learns of the event and to the IRB/EC (if required) within the IRB/EC required timeframe.
Serious adverse events (SAE, SADE)	Report to the Study Sponsor within 48 hours after the designated study site personnel first learns of the event and to the IRB/EC within the IRB/EC required timeframe.
Unanticipated serious adverse device effect (USADE)	Report to the Study Sponsor as soon as possible, but no later than 48 hours, after the designated study site personnel first learns of the event and to the IRB/EC within the IRB/EC required timeframe.
Non-serious adverse events (AE, ADE)	Report to the Study Sponsor as soon as possible after the designated study site personnel first learns of the event, and to the IRB/EC (if required) within the IRB/EC required timeframe.

11.0 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.

11.1 IRB/EC Approval

The Investigator must obtain approval to conduct the clinical study prior to screening any potential subjects and comply with annual continuing approval requirements where applicable. The role of the IRB/EC is to ensure that the rights of the study subjects are protected and to ensure that the research meets high ethical and scientific standards. All correspondence with the IRB/EC should be maintained in the site's study files.

11.2 Informed Consent

The Investigator is responsible for ensuring that all applicable local, national, Declaration of Helsinki, EU MDR 2017/745, and ISO 14155:2020 requirements in the clinical 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 designated representative of a vulnerable subject, is obtained prior to the initiation of any study-related procedures. As per ISO 14155:2020, vulnerable subjects are defined as individuals who are unable to fully understand all aspects of the investigation that are relevant to the decision to participate, or who could be manipulated or unduly influenced as a result of a compromised position, expectation of benefits, or fear of retaliatory response.

Inclusion of vulnerable subjects in this clinical study is considered ethical given that this is a post-market clinical investigation without additional invasive or burdensome procedures.

The Investigator must comply with the requirements specified in protocol **Section 7.3**.

11.3 Protocol Compliance and Delegation of Authority

The Investigator shall conduct the clinical study in compliance with this study protocol and ensure that the clinical study is appropriately staffed with qualified study personnel throughout the duration of the clinical study. In addition, the facilities where the clinical study is being conducted must be maintained to allow for proper study conduct. Changes to either study staff or facilities must be documented. The Investigator must maintain a Delegation of Authority Form of appropriately qualified persons to whom the Investigator has delegated significant study related duties.

11.4 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 vulnerable subjects are identified and protected,
- 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,
- 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, and
- Continue to treat subjects at his/her discretion according to local standard of care following study exit, temporary halt, or early termination of the clinical study.

11.5 Safety Reporting

The Investigator must comply with the safety reporting requirements specified in protocol **Section 10.0.**

11.6 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 Study Sponsor. Study Sponsor and Investigator will agree to all amendments made to the protocol or the Informed Consent form before submitting to the local IRB/EC for approval. If protocol changes affect the scientific soundness of the clinical investigation, or affect the health, welfare, safety and rights of subjects, Investigator and/or Study Sponsor will submit all amendments to the local IRB/EC to obtain written approval before implementing changes.

11.7 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 clinical study is completed or terminated. The Study Sponsor must 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 him/her.

12.0 STUDY SPONSOR RESPONSIBILITIES

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

12.1 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 Principal Investigator, Sub-Investigator(s), and Research Coordinator(s). Initial protocol and device training will be conducted by Shockwave Medical or its designees and will be ongoing as required. The Principal Investigator will delegate roles and responsibilities to the Sub-Investigator(s) and Research Coordinators(s) as documented on the Delegation of Authority Log.

A 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. A copy of the signed training record must be submitted to Shockwave Medical or its designee, and the original signed training record(s) should be filed in the site's study Regulatory Binder.

12.2 Monitoring

12.2.1 Monitoring Methods

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

All monitoring activities shall be documented in a written report. 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 IRB/EC, 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.

12.2.2 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 duration of the clinical study as required per the

monitoring plan, and upon completion of the clinical study. 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. Restrictions to on-site monitoring visits may require that alternative monitoring strategies be implemented including the use of remote monitoring or risk-based approaches.

12.3 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. The investigators shall not deviate from the study protocol. The Investigator must document and notify Shockwave Medical of any deviation from the study protocol as soon as possible. The use of waivers from the protocol is not permitted.

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

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 Study Sponsor and the IRB/EC. Such deviations shall be documented in writing and reported to the Study Sponsor and the IRB/EC as soon as possible, and no later than 5 working days.

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

12.4 Device Accountability

The Study Sponsor will only provide investigational devices to the site once evidence of required IRB/EC approval has been provided to the Study Sponsor or designee.

Lot numbers are applied to all finished investigational devices and associated components. It is the responsibility of each investigational site to maintain records of the lot numbers of the IVL Systems and components received, used, returned, or disposed of by the site via accountability logs.

All unused and/or expired study devices will be collected and returned to Shockwave Medical as per instruction by the Study Sponsor. In case of a device deficiency or malfunction, study staff must contact the Study Sponsor for a Return Material Authorization (RMA) Number and a return kit, and will be required to return the device(s) in question to Shockwave Medical as soon as possible. The site should observe their site-specific instructions pertaining to handling of biohazardous materials.

12.5 Study/Site Suspension or Early Termination

The Study 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, IRB/EC, 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 IRB/EC or regulatory authorities, the Study Sponsor shall suspend the clinical study while the risk is assessed. The Study 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 such as insufficient Investigator involvement in the clinical study, inappropriate delegation of authority, or non-compliance to GCP

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 Study Sponsor shall keep each other informed of any communication received from the IRB/EC or any regulatory authority.

If, for any reason, Shockwave Medical suspends or prematurely terminates the clinical study at an individual site, the Study Sponsor shall inform the IRB/EC. If the suspension or premature termination was in the interest of safety, the Study 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. It is the Investigator's responsibility to follow subjects according to local standard of care in such instances.

Routine closeout activities shall be conducted to ensure that the Principal Investigator's records are complete, all documents needed for the Study 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 Clinical Study after Temporary Suspension:

When the Study Sponsor completes an analysis of the reason(s) for the suspension, implements the necessary corrective actions, and decides to lift the temporary suspension, the Study Sponsor shall inform the Principal Investigators and the IRB/EC, and provide them with the relevant data supporting this decision. Concurrence shall be obtained from the IRB/EC 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.

12.6 Study Completion

The clinical study is considered completed after all subjects have undergone all of their protocol required follow-up visits, data entry for all eCRFs has been completed, all queries have been resolved, all action items have been closed, and all site payments have been made. All unused study

materials and study devices will be collected and returned to Shockwave Medical as per instruction by the Study Sponsor. A final clinical study report will be completed no later than 12 months after clinical study completion, even if the clinical study was terminated prematurely.

12.7 Audits / Inspections

Shockwave Medical, regulatory agencies, and ECs may conduct audits or inspections at the study sites during the course of or after completion of the clinical study. Access to all study records, including source documents, for inspection and duplication may be requested.

12.8 Publication Policies

The Study Sponsor and the study investigators are committed to timely and complete dissemination of the clinical study results. Publications based on the results of the clinical study will follow the process outlined in the Investigator Agreement. At the conclusion of the clinical study, a multi-center manuscript will be prepared for publication in a reputable peer-reviewed scientific journal. The principal results will also be presented at a scientific congress.

The publication of the results from any single site experience within the clinical 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 clinical study is registered with www.clinicaltrials.gov and anzctr.org.au.

12.9 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 are responsible for the accuracy and completeness of all study data recorded. The Principal Investigator is responsible for confirming the integrity of the data and for full, transparent public reporting of the results. Aspects with respect to the management and storage of data will also be outlined in the Patient Informed Consent Form for site specific factors.

Shockwave Medical intends to utilize the data obtained from the clinical study for commercial uses including publication and/or presentation of results at congresses, regulatory agency submissions, continued product development activities, and marketing of their vascular products. All data when used in these activities will be in a de-identified format. Data obtained during this clinical study will not be utilized in a database without first gaining the consent of participants.

All required data for this study will be collected via a web-based electronic data capture (EDC) system (ClinTrak®) as supplied by the Clinical Research Organization (CRO) Medpace.

ClinTrak® EDC provides a centralized location for the study team to review real-time case report form (CRF) data. The system allows for the secure and accurate collection and cleaning of the data from each study. This comprehensive tool provides functionality in the areas of study design, data entry, data clean-up, coding of terms, data changes, reporting, real-time web access, audit trail, and export of the clinical data for analysis purposes.

ClinTrak® EDC has been validated in accordance with Medpace Standard Operating Procedures (SOPs) that describe the processes, activities, and deliverables necessary to comply with applicable predicate rules (GxP) and FDA 21 CFR Part 11. The system has been confirmed to be fit for purpose and the features and functionality have been determined to perform reliably and consistently as intended. Appropriate controls of the system are in place and documented evidence is available to support the application of those controls.

Medpace will provide training in the use of ClinTrak® EDC to all necessary site personnel. Each investigator and staff participant will be assigned a unique password and only that individual should access subject records under that password.

12.9.1 Case Report Forms

All required data for this clinical study will be entered in electronic Case Report Forms (eCRFs).

All data collected during the clinical study will be de-identified. For this purpose, a unique study identifier will be assigned to each study subject. All information about the subject, including the study identifier, will be recorded on the eCRF. The database will contain only the study identifier to identify the subject. The code with subject name and study number will be maintained by the Principal Investigator in a secured location. Subject names will not be released to Shockwave Medical at any stage of the clinical study.

12.9.2 Transmission of Data

Required data will be recorded on the appropriate eCRFs at the time of or as soon as possible after the subject visit. The eCRF and any requested supporting source documents (including medical imaging files) must be sent to Shockwave Medical and/or retrieved from the Investigator during monitoring visits. Where possible, data sent to Shockwave Medical will be done so utilizing a password secured web-based system.

12.9.3 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.

12.9.4 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 longer if required by applicable local regulations. The data will be retained in a secure, password protected database and stored in the United States of America.

13.0 STUDY COMMITTEES

13.1 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 certain pre-specified clinical event types described in the CEC charter. In order to enhance objectivity and reduce the potential for bias, the CEC shall be independent of the Study Sponsor as well as the study sites / Investigators.

The CEC is made up of clinicians with pertinent expertise who are not participants in the clinical 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 clinical study. Criteria will be established for selected complications and clinical events.

At the onset of the clinical 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). The methodology for performing these responsibilities shall be developed and outlined in the CEC Charter.

14.0 ETHICAL and REGULATORY CONSIDERATIONS

14.1 Role of Shockwave Medical

As the Study Sponsor of this clinical study, Shockwave Medical has the overall responsibility for conduct of the clinical study, including assurance that the clinical study will be conducted according to ICH Good Clinical Practices (GCP), applicable elements of 21 CFR 812, 820, 50, 54, and 56, Declaration of Helsinki, applicable IRB/EC requirements, as well as EU MDR 2017/745 and ISO 14155:2020 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 specific federal regulations, international standards, and/or guidelines required to be followed are outlined within the protocol. The Study Sponsor will provide insurance coverage to subjects for any clinical investigation related damages according to applicable legal requirements and will maintain a valid subject liability insurance for the duration of the clinical study.

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

Shockwave Medical as the Study Sponsor will ensure financing of the clinical investigation in line with the contracts between the Study Sponsor or its designee and study sites.

14.2 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.

15.0 DEFINITIONS and ABBREVIATIONS

15.1 Study Definitions

Abrupt or Acute Closure: Angiographic documentation of significantly reduced flow due to mechanical dissection, thrombus, or severe vessel spasm in the treatment area.

Acute Limb Ischemia: A sudden decrease in limb perfusion that causes a potential threat to limb viability (manifested by ischemic rest pain, ischemic ulcers, and/or gangrene) in patients who present within two weeks of the acute event.

Adverse Device Effect (ADE): Adverse event related to the use of an investigational medical device.

Note: 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.

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

Note: This includes "comparator" if the comparator is a medical device.

Adverse Event (AE): 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 medical device and whether anticipated or unanticipated.

Note: This definition includes events related to the investigational medical device or the comparator.

Note: This definition includes events related to the procedures involved.

Note: For users or other persons, this definition is restricted to events related to the use of investigational medical devices or comparators.

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

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 post-procedure that was not previously planned as part of the overall treatment strategy.

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

Below the Knee (Lesion Location): From center of knee joint space to ankle joint.

Calcification Classification (PARC): Calcification will be assessed by the angiographic core lab according to the Peripheral Academic Research Consortium (PARC) definition [21].

PARC Degree of Lesion Calcification

Focal	Degree of lesion calcification
Mild	<180° and greater than one-half of the total lesion length
Moderate	≥180° (both sides of vessel at same location) and less than one-half of the total lesion length
Severe	>180° (both sides of the vessel at the same location) and greater than one-half of the total lesion length

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.

Critical Limb Ischemia: Clinical manifestation of peripheral arterial disease characterized by Rutherford Category of 4-6. (For the purposes of this clinical study, only subjects with Rutherford Category of 3, 4, and 5 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).

Device Deficiency: Inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety or performance.

Note: Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling.

Note: This definition includes device deficiencies related to the investigational medical device or the comparator.

Device Malfunction: A failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or Clinical Investigation Plan (CIP), or Investigator Brochure (IB).

Note: An IB is deemed not required as the IFUs and product labelling together with available commercial product information is deemed sufficient information for the use of the device within its approved indication.

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 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.

Embolization, Distal: Any distal emboli confirmed by imaging considered to be related to the target lesion(s).

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.

Intravascular Lithotripsy (IVL): Shockwave Medical's proprietary balloon angioplasty catheter including lithotripsy technology that creates pulsatile mechanical energy for disrupting calcified vascular plaque.

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.

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

Non-Target Lesion: A lesion not intended to be treated per BTK II protocol eligibility but treated per institutional standard of care in the same enrollment procedure.

Note: If there are excess lesions after the maximum number of target lesions has been reached, these excess lesions should be assigned as non-target lesions AND treated successfully first.

P3 segment of popliteal artery: From center of knee joint space to origin of anterior tibial artery.

Perforation: Puncture of an arterial wall.

Restenosis: Reoccurrence of narrowing or blockage of target lesion.

Rutherford Category: 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- nonhealing ulcer, focal gangrene with diffuse pedal ischemia.
III	6	Ulceration or gangrene- extending above TM (transmetatarsal) level, functional foot no longer salvageable.

Serious Adverse Device Effect (SADE): Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Serious Adverse Event (SAE): Adverse event that led to any of the following:

- death,
- serious deterioration in the health of the subject, user, or other persons as defined by one or more of the following:
    - a life-threatening illness or injury, or
    - a permanent impairment of a body structure or a body function including chronic diseases, or
    - in-patient or prolonged hospitalization, or
    - medical or surgical intervention to prevent life-threatening illness or injury, or permanent impairment to a body structure or a body function, or
- fetal distress, fetal death, a congenital abnormality, or birth defect including physical or mental impairment.

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

Target Lesion: A lesion eligible per BTK II protocol and intended to be treated with BTK II provided research IVL catheter.

Note: Device crossing failures or device malfunction causing no actual IVL treatment are still considered target lesions.

Target Lesion Revascularization, Clinically-driven (TLR): A target lesion revascularization performed due to target lesion diameter stenosis ≥50% and either evidence of clinical or functional ischemia (e.g., recurrent/progressive life-limiting intermittent claudication, claudication unresponsive to medical therapy, CLI) or recurrence of the clinical syndrome for which the initial procedure was performed. Clinically driven target lesion revascularization occurs in the absence of protocol directed surveillance ultrasound or angiography.

Target Vessel Revascularization, Clinically-driven (TVR), non-TLR: A target vessel revascularization performed due to non-target lesion diameter stenosis ≥50% and either evidence of clinical or functional ischemia (e.g., recurrent/progressive life-limiting intermittent claudication, claudication unresponsive to medical therapy, CLI) or recurrence of the clinical syndrome for which the initial procedure was performed. Clinically driven target vessel revascularization occurs in the absence of protocol directed surveillance ultrasound or angiography.

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

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

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 risk assessment.

Note: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk assessment.

Wound: Foot ulcer or gangrene. After debridement and/or minor amputation, a wound is characterized as a healed wound when it is completely epithelialized.

15.2 List of Abbreviations

ABI	Ankle-Brachial Index
ACC	American College of Cardiology
ACS	Acute Coronary Syndrome
ADE	Adverse Device Effect
AE	Adverse Event
AHA	American Heart Association
BTK	Below-the-Knee
CD-TLR	Clinically-Driven Target Lesion Revascularization
CE	European Conformity
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CI	Confidence Interval

CIP	Clinical Investigation Plan
CKD	Chronic Kidney Disease
CLI	Critical Limb Ischemia
CRF	Case Report Form
CRO	Contract Research Organization
CR-TLF	Clinically Relevant Target Lesion Failure
CTA	Computed Tomography Angiogram
CTO	Chronic Total Occlusion
DCB	Drug-Coated Balloon
DES	Drug-Eluting Stent
DUS	Duplex Ultrasound
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EC	Ethics Committee
ESC	European Society of Cardiology
ESVS	European Society of Vascular Surgery
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IFU	Instruction for Use
IRB	Institutional Review Board
ISO	International Organization for Standardization
ITT	Intent-to-Treat
IVL	Intravascular Lithotripsy
IVUS	Intravascular Ultrasound
MAE	Major Adverse Event
MALE	Major Adverse Limb Event
MDR	Medical Device Reporting (US)
MedDRA	Medical Dictionary for Regulatory Activities
MRA	Magnetic Resonance Angiography
OTW	Over-the-Wire
PAD	Peripheral Artery Disease
PARC	Peripheral Academic Research Consortium

PCB	Printed Circuit Board
POD	Post-Operative Death
PTA	Percutaneous Transluminal Angioplasty
QoL	Quality of Life
RC	Rutherford Category
RMA	Return Material Authorization
RVD	Reference Vessel Diameter
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
TBI	Toe-Brachial Index
TLR	Target Lesion Revascularization
TMA	Transmetatarsal Amputation
TVR	Target Vessel Revascularization
USADE	Unanticipated Serious Adverse Device Effect

16.0 REFERENCES

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17.0 SUBJECT INFORMED CONSENT

The subject informed consent template will be provided as a separate attachment.

18.0 CASE REPORT FORMS

Draft case report forms will be provided as a separate attachment.

19.0 REVISION HISTORY

Revision	Release Date	DCO #	Reason(s) for Revision	Doc Owner
A	07/29/2021	22175	Initial release.	Clinical
B	04/25/2022	23339	• Revisions throughout the document to be in compliance with EU MDR 2017/745 and ISO 14155:2020. • General administrative changes and corrections throughout document. • Changed Primary Performance Endpoint to Primary Effectiveness Endpoint and included time point for evaluation by angiographic core lab throughout document. • Changed from significant to serious angiographic complications for lesion success secondary endpoint. • Clarified primary patency endpoint will be assessed by DUS core lab, and CD-TLR will be adjudicated by CEC. • Clarified CEC will adjudicate Clinically Relevant Target Lesion Failure secondary endpoint. • Added IVUS sub-study information throughout document. • Created, clarified, or changed inclusion and exclusion criteria. • Indicated there are specific IFUs and labelling for each geography. • Added Baseline Labs (eGFR) to list of baseline assessments and indicated how eGFR should be calculated in absence of lab value. • Specified photographs needed for Wound Healing Assessments. • Added incidence of risks for IVL catheters and verbiage regarding risk management plan; updated risk sections. • Removed unlikely from relatedness categories for AE assessments. • Updated device malfunction definition and abbreviation list.	Clinical

Revision	Release Date	DCO #	Reason(s) for Revision	Doc Owner
C	08/22/2023	26506	• Updated language to include primary patency at lesion level. • CR-TLF endpoint was removed and updated to clearer definition of CD-TLR • MAE language added • Amputation language added to clarify major target limb amputations • Added exploratory endpoints. These do not have any impact on patient safety or existing data. • Added language regarding toe amputation • Clarified window for sites to submit wound assessment images extended from 30 days to 45 days. • Added definition of recurrent wound. • Providing tandem lesion definition to ensure clearer guidelines for labeling lesions <3 cm apart. • Added clearer adverse event documentation	Clinical