Abbott	Clinical Investigation Plan Cover Page

NCT05208905
LIFE-BTK PK Sub-Study
LIFE-BTK (pivotaL Investigation of saFety and Efficacy of BRS treatment-Below The Knee)
Study Document No: [redacted]
[redacted]
Date: 22-SEP-2022

Sponsor Abbott

[redacted]

[redacted]

Clinical Investigation Plan

CIP Number: [redacted]
Study Number: [redacted]
LIFE-BTK (pivotaL Investigation of saFety and Efficacy of BRS treatment-Below The Knee) Randomized Controlled Trial

Version Number	[redacted]
Date	[redacted]
Study Co-Principal Investigators	[redacted]
Planned Number of Sites and Region(s)	Approximately 65 clinical sites in the US, Asia, Australia and New Zealand (maximum 55 sites in the US: 50 sites for the LIFE-BTK RCT plus 5 sites for the Pharmacokinetics sub-study).
Clinical Investigation Type	Prospective, randomized (2:1, Esprit™ BTK:PTA), single-blind, multi-center clinical investigation
Abbott Medical Expert	[redacted]
Sponsor/Trial Monitor/Data Monitoring	Abbott Cardiovascular Systems, Inc., [redacted]
Registration/Randomization Service	Oracle Clinical
Electronic Data Capture Software	Oracle Clinical
Core Laboratories	[redacted]
Clinical Events Committee Administration	[redacted]
Data Monitoring Committee Administration	[redacted]
CIP Author	[redacted]

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SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

I have read and agree to adhere to the clinical investigation plan and all regulatory requirements applicable in conducting this clinical investigation.

Site Principal Investigator:

Printed name:
Signature:
Date:

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STUDY PRINCIPAL INVESTIGATOR
SIGNATURE PAGE

I have read and agree to adhere to the clinical investigation plan and all regulatory requirements applicable in conducting this clinical investigation.

Study Principal Investigator:

Printed name:
Signature:
Date:

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COMPLIANCE STATEMENT:

This clinical investigation will be conducted in accordance with this Clinical Investigation Plan, the Declaration of Helsinki, applicable Good Clinical Practices and regulations (e.g., US 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 812, 45 CFR Part 46 and OUS ISO14155:2020) and the appropriate local legislation(s). The most stringent requirements, guidelines or regulations must always be followed. The conduct of the clinical investigation will be approved by the appropriate Institutional Review Board (IRB)/Ethics Committee (EC) of the respective investigational site and by the applicable regulatory authorities (e.g., FDA, TGA, HSA, TFDA, PMDA, etc.).

If the local regulation requires additional process and/or documents, local site must follow the requirements.

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1.0 INTRODUCTION

The LIFE-BTK Randomized Controlled Trial (RCT) is designed to perform a pre-market evaluation of the Esprit™ BTK Everolimus Eluting Bioresorbable Scaffold System for the planned treatment of narrowed infrapopliteal lesions. This is a prospective, single blinded randomized clinical trial (2:1) evaluating planned treatment of BTK lesions with Esprit BTK versus planned treatment with PTA (Percutaneous Transluminal Angioplasty), in patients with arterial narrowing in infrapopliteal lesions causing CLI (Critical Limb Ischemia), who satisfy the key inclusion and exclusion criteria for the trial.

The Esprit BTK system is a bioresorbable polymeric scaffold with the everolimus drug and a bioresorbable polymeric coating mounted on a balloon dilatation catheter. This device, manufactured by Abbott Vascular, is intended to be used for improving luminal diameter in infrapopliteal lesions in patients with CLI.

CLI is a debilitating disease affecting 5-10% of patients with peripheral artery disease (PAD)[1] [2]. CLI is characterized by impaired blood flow to lower limb and associated with pedal pain. If left untreated, CLI can lead to major amputations. Patients experiencing major amputations face a severely decreased quality of life. PTA is currently the only approved dilatation device for use in BTK arteries in the United States. In Europe, both PTA and drug-eluting stents (DES) are approved therapies. Although reasonable rates of acute success are achieved with PTA, residual stenosis post-procedure and progressive reduction in patency in the months after intervention have been observed, resulting in a persistent reduction of perfusion to the distal extremity with increased morbidity and mortality. Therefore, PTA only provides a short term and sub-optimal solution for patients suffering from CLI due to infrapopliteal lesions, which highlights an unmet need for this patient population. Likewise, although DES have improved upon PTA in terms of patient outcomes, detrimental long-term effects such as having a permanent implant with risks of restenosis and stent thrombosis still exist. The Esprit BTK system is an innovative technology that offers the potential to address this unmet medical need for patients with BTK lesions and suffering from CLI. Like a metallic drug-eluting stent (DES), Esprit BTK provides support to the vessel to prevent acute recoil post-procedure and elutes everolimus to prevent arterial re-narrowing. Unlike metallic drug-eluting stents, Esprit BTK resorbs over time, leaving the artery free of permanent implant. Therefore, Esprit BTK has the potential to combine the benefits of PTA (no implant left behind) and DES (vessel support, and prevention of arterial re-narrowing).

The objective of the LIFE-BTK RCT is to evaluate the safety and efficacy of the Esprit BTK, compared to PTA, in the planned treatment of diseased infrapopliteal lesions in patients with critical limb ischemia with up to two *de novo* or restenotic (prior PTA) lesions in separate vessels.

This clinical investigation will be conducted under an investigational device exemption (IDE) and in accordance with this CIP. All investigators involved in the conduct of the clinical investigation will be qualified by education, training, and experience to perform their tasks and this training will be documented appropriately.

1.1. Background and Rationale

1.1.1. Background

Literature on clinical performance of PTA, DES (drug-eluting stent) and Absorb BVS for BTK lesions treatment is summarized below, and in **Appendix IV**.

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PTA is an approved revascularization treatment for arterial narrowing in CLI patients and is the initial therapy of choice for CLI patients who are candidates for either surgery or endovascular therapy. Although PTA has a high rate of immediate success, clinical studies have consistently documented a progressive reduction in patency in the months after intervention. Meta-analysis results indicate that even after treatment with PTA, 1-year death and amputation rates are approximately 15% [3]. Drug coated balloons (DCB) have only seen a modest improvement in treatment efficacy when compared to PTA. In a recent ongoing trial [4] (LUTONIX) that compares DCB and PTA (N=442), early results only demonstrated a modest 10% improved efficacy at 6 months for DCB (73.7%) compared to PTA (63.5%), p=0.0273.

Drug eluting stents (DES) offer advantages that are not provided by balloon angioplasty. The stent provides a structurally stable scaffold for the vessel and reduces the rate of acute vessel closure, and the presence of drug coating such as everolimus is crucial for reducing restenosis. The benefit of using stents is shown by Scheinert et al. who compared safety and efficacy of treating PAD patients using SES (sirolimus-eluting stent) or PTA (N=200) [5]. Patient survival (89.9% for SES vs. 88.1% for PTA), freedom from CD-TLR (90% for SES vs. 83.5% for PTA) and limb salvage rates (86.2% for SES vs. 80% for PTA) at 1 year were found to be high for both devices. Lower angiographic restenosis rates (22.4% for SES vs.41.9% for PTA, p=0.019) and greater vessel patency (75.0% for SES vs. 57.1% for PTA, p=0.025) were observed in patients treated with SES, showing superior treatment efficacy in SES compared to PTA.

In a separate study (N=140), where Bosiers observed higher 1-year primary patency rate for everolimus-eluting stent (XIENCE) (85%) than for BMS (54%), p=0.0001 [6]. Similar to observations by Scheinert, patient survival rate is high for both devices (84% for BMS and 82% for XIENCE). However, freedom from TLR is higher for XIENCE (91.3%) compared to BMS (66.4%), p=0.001. When treatment with XIENCE was extended to longer lesions (30-100 mm) in DESTINY2 trial, high primary patency rate (75.4%), freedom from TLR (84.9%), limb salvage (94.4%) and survival rates (90%) at 1 year were also observed, illustrating the successful use of a drug-coated metal stent for treating CLI with longer lesions [7].

The decreased efficacy of BMS is further illustrated by Rastan et al. (N=161), where primary patency rates (80.6% for SES vs. 55.6% for BMS, p=0.004) and improvement in Rutherford classification (83.9% for SES vs. 61.9% for BMS, p=0.004) at 1 year are higher in SES compared to BMS [8].

The above-mentioned studies have demonstrated that the use of DES for treatment of CLI have improved patency rates. However, these metallic implants impose detrimental long-term effects on the vessel wall, as they inhibit vasomotion, autoregulation and adaptive modeling by leaving behind a permanent implant. They may cause in-stent restenosis and late stent thrombosis, impede future revascularization, and create artifact on cross-sectional imaging. For these reasons, the use of a drug-eluting scaffold such as Esprit BTK offers both short-term and long-term benefits for the treatment of CLI. The scaffold provides support to the vessels and resorbs over time and presents a superior solution for the treatment of CLI.

The clinical performance of Absorb BVS, the predecessor of Esprit BTK, in treatment of patients with chronic lower limb ischemia (Rutherford category 3-6) was demonstrated in the single-arm study by Varcoe et al. (N=48) [9]. The study reported patency rates of 92.2% at 12 months, 90.3% at 24 months and 81.1% at 36 months. This was also met by freedom from CD-TLR of 97.2%, at both 12 and 24 months and 87.3% at 36 months. There were no reports of death within 30 days in the 48 patients, no reports of amputation or target limb bypass surgery through 2 years, and a single patient report of thrombosis. The thrombosis event that occurred on day 2 was thought to be related to the patient having been taken off warfarin prior to the index procedure and no antiplatelet therapy having been commenced following the procedure.

A separate study by Xue [10] and Kum [11] evaluated 1-year outcomes in the use of Absorb GT1 BVS treatment in CLI patient population (89.3% Rutherford Becker Category 5-6), where high 1-year rates of primary patency (87.1%) and freedom from TLR (96.7%) were reported. Similar results were seen in a study by Shah et al. (N=31) [12]. At 1 year, no stent thrombosis, and high primary patency (96.7%), limb salvage (100%) and improved Rutherford classification were observed in 96.8% of patients treated with Absorb.

Given the encouraging results from Absorb studies, where no procedure related mortality or major morbidity was observed within 30 days, and the 1-year patency rates and freedom from TLR rates were high, Esprit BTK is a promising new technology that offers the potential to tackle an unmet medical need for treatment of lower limb lesions. Esprit BTK provides a unique approach to treat BTK disease by scaffolding the treated vessel, preventing acute recoil, eluting everolimus thus reducing risk of re-narrowing, and resorbing into tissue over time. It offers superior acute outcomes, lower restenosis and re-intervention rates similar to XIENCE, and also addresses the inherent limitations of metallic DES by resorbing into tissue over time, eliminating the need for a permanent implant.

1.1.2. Rationale for Conducting this Clinical Investigation

The rationale for conducting the proposed clinical investigation is based on the growing concern of PAD in infrapopliteal lesions and the limited treatment options for those patients burdened with the disease. Currently, the approved therapies (PTA in the United States, PTA/stenting in Europe) to treat narrowed infrapopliteal arteries are sub-optimal and/or unsustainable resulting in continuous reintervention and disease progression. As detailed in the literature review, recent clinical studies evaluating the Absorb BVS, predecessor of the Esprit BTK, showed the potential clinical benefits derived from the use of a bioresorbable scaffold for treatment of infrapopliteal lesions.

Esprit BTK has the potential to provide superior outcomes to PTA, by providing: 1) vessel scaffolding thus preventing acute recoil; 2) elution of everolimus, thus preventing arterial re-narrowing and reducing the risk of revascularization; 3) preservation of additional treatment option for treated vessel thanks to scaffold resorption over time.

Given the unmet needs for effective CLI treatment and the potential benefit offered by a bioresorbable scaffold, it is appropriate to evaluate Esprit BTK System in this randomized controlled trial.

2.0 CLINICAL INVESTIGATION OVERVIEW

2.1. Clinical Investigation (LIFE-BTK RCT) Objective

The objective of this clinical investigation is to evaluate the safety and efficacy of the Esprit BTK, compared to PTA, in the planned treatment of diseased infrapopliteal lesions in patients with critical limb ischemia with up to two *de novo* lesions in separate vessels.

2.1.1. Pharmacokinetics Sub-Study Objective

The objective of the pharmacokinetics (PK) sub-study is to determine the pharmacokinetics of everolimus delivered by the Esprit BTK scaffold in a separate and non-randomized cohort of subjects receiving the Esprit BTK for the planned treatment of narrowed infrapopliteal lesions.

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The LIFE-BTK PK sub-study subjects will not be included in the primary analysis population of the LIFE-BTK RCT and will not contribute to the determination of the LIFE-BTK RCT primary endpoints.

A total of 7 subjects will be registered in the PK sub-study, in the United States (US) and outside of US, with a maximum of 5 sites in the US.

For more details on the PK sub-study, refer to **Appendix X**. This appendix only applies to sites that will be participating in the PK sub-study. For sites only participating in the PK sub-study (and not participating in the LIFE-BTK RCT), only some sections of the RCT protocol apply; applicable sections are listed in the PK sub-study synopsis in **Appendix X**.

2.2. Device(s) To Be Used in the Clinical Investigation

2.2.1. Name of the Device Under Investigation

The investigational device to be used in the clinical investigation is the Esprit BTK Everolimus Eluting Bioresorbable Scaffold System, which is Abbott's Next Generation Bioresorbable Vascular Scaffold System. The investigational device will be referred to "Esprit BTK" throughout this clinical investigation plan. The Esprit BTK is not approved by FDA and not commercially available in the United States, or outside the United States. This clinical investigation is being conducted under an investigational device exemption (IDE).

A diagram of the Esprit BTK, with its delivery catheter, is provided below.

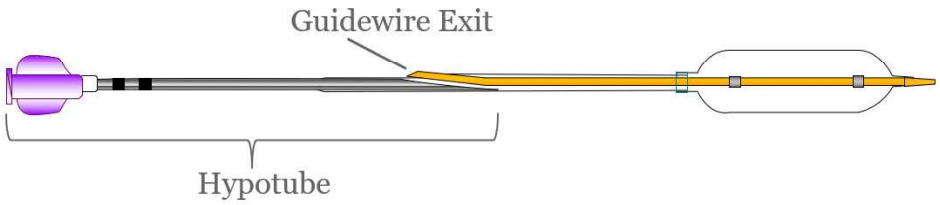

Figure 2.2.1-1: Diagram of Esprit BTK System (product diagram not to scale)

The Esprit BTK is manufactured by Abbott Vascular, Santa Clara. The part numbers for each scaffold size are provided in **Appendix XIII**. Every unit is also assigned a lot number for traceability.

For further details on the device, refer to the Instructions for Use (IFU).

2.2.2. Intended Indication for Use

The Esprit BTK is a temporary scaffold that will fully resorb over time and is indicated for improving luminal diameter in infrapopliteal lesions in patients with critical limb ischemia (CLI). In all cases, the treated lesion length should be less than the total scaffolding length with a reference vessel diameter of ≥ 2.5 mm and ≤ 4.00 mm.

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2.2.3. Description of the Device Under Investigation

A description of the device under investigation is provided in this section. For further details, refer to the IFU.

Esprit BTK was developed using the same principles, design and materials as its predecessor device, Absorb GT1 BVS.

The Esprit BTK Everolimus Eluting Bioresorbable Scaffold System is a bioresorbable polymeric scaffold with a drug and bioresorbable polymeric coating mounted on a balloon dilatation catheter, the specific components of which are:

- A bioresorbable scaffold backbone comprised of 100% poly(L-lactide) (PLLA), identical to that of the Absorb GT1 BVS ([redacted]).
- A coating comprised of the active pharmaceutical ingredient everolimus and bioresorbable poly(D,L-lactide) (PDLLA), identical to that of the Absorb GT1 BVS.
- Identical to Absorb GT1 BVS, four platinum markers of the same mass, two each embedded at the proximal and distal ends of the scaffold for radiopacity.
- A delivery system that incorporates design features from the Absorb GT1 Bioresorbable Vascular Scaffold (BVS) System1 and XIENCE Alpine® Everolimus Eluting Coronary Stent System.2

Compared to Absorb GT1 BVS system, Esprit BTK System has reduced strut thickness and an expanded size matrix, with a total of 40 product sizes indicated below in **Table 2.2.3-1** by the letter "X". The original 14 sizes in the Absorb GT1 BVS System size matrix are highlighted in gray. Four scaffold designs encompass these product diameters. The 2.5/2.75 mm scaffold design includes a total of 16 sizes, while the 3.0 mm, 3.5 mm, and 3.75 mm scaffold designs includes a total of 8 sizes each. The balloon diameter, balloon length, and balloon marker separation are scaled across the size matrix to accommodate the diameter and length of the scaffold. The Esprit BTK System will be available in a Rapid Exchange (RX) configuration.

Table 2.2.3-1: Esprit BTK Size Matrix

Scaffold Design	Scaffold Diameter (mm)	Product Length (mm)							
		9*	12	15	18	23	28	33	38
2.5/2.75	2.5	X	X	X	X	X	X	X	X
	2.75	X	X	X	X	X	X	X	X
3.0	3.0	X	X	X	X	X	X	X	X
3.5	3.5	X	X	X	X	X	X	X	X
3.75	3.75	X	X	X	X	X	X	X	X

* Absorb GT1 BVS has an 8 mm scaffold instead of 9 mm

[1] Absorb GT1 BVS System was filed under [redacted] and was approved on July 5, 2016.
[2] XIENCE Alpine® Everolimus Eluting Coronary Stent System (XIENCE Alpine Stent System; [redacted] approved September 3, 2014).

[redacted]

2.2.3.1. Scaffold design

The Esprit BTK System, like the Absorb GT1 BVS System, is based upon the same design principles as metallic balloon expandable stent systems (MULTI-LINK family of coronary stent systems). The Esprit BTK backbone is fabricated from PLLA and is comprised of a series of circumferentially oriented sinusoidal rings connected by linear links (**Figure 2.2.3-1**). Two permanent platinum markers are embedded at each end ring to enable fluoroscopic visualization.

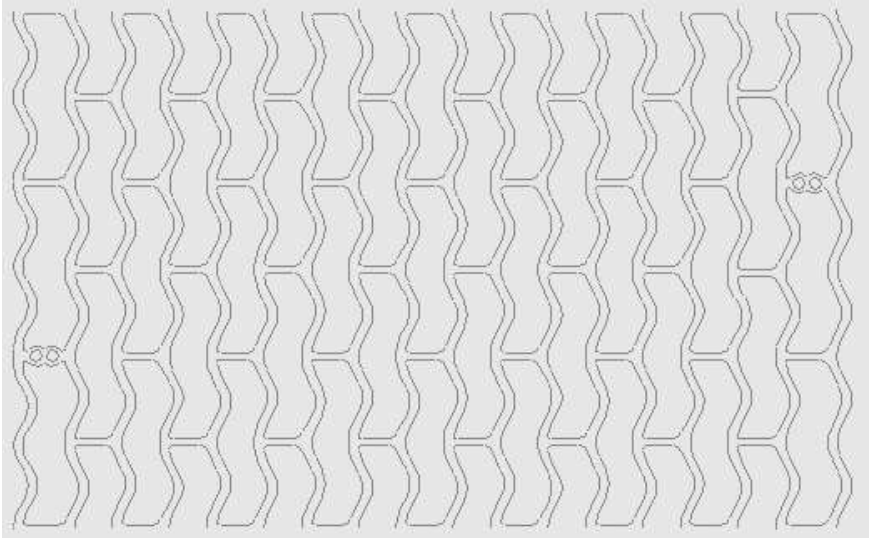

Figure 2.2.3-1: Representative Esprit BTK Pattern Design for the 2.5/2.75 mm Sizes

2.2.3.2. Scaffold polymer

The backbone of the scaffold is manufactured from 100% PLLA, identical to that used in the Absorb GT1 BVS. The scaffold is coated with the identical drug/polymer matrix as Absorb GT1 BVS. The PDLLA polymer contains and controls the release of the antiproliferative drug everolimus.

2.2.3.3. Drug/polymer coating

The Esprit BTK bioresorbable polymer drug coating is a single drug/polymer matrix layer comprised of the amorphous random copolymer PDLLA, which contains and controls the release of the drug everolimus. Everolimus is an antiproliferative drug (Zortress®, Afinitor®, Novartis Pharmaceuticals Corp.) that is blended with PDLLA in a 1:1 (w:w) proportion and is applied to the entire surface (i.e., sidewalls, luminal, and abluminal) of the scaffold. The drug compounding and spray processes are identical to those of the Absorb GT1 BVS.

Everolimus has been evaluated through a number of different clinical studies and is known to have a wide therapeutic window. The drug dose densities for XIENCE V, Absorb GT1 BVS, and Esprit BTK are all identical at 100 µg/cm^2, and the total content specifications remain the same (90-110% of label claim). However, since the surface areas for the three devices are different, the total drug content will vary accordingly. **Table 2.2.3-2** presents the Esprit BTK surface area and total nominal everolimus content for each length within the size matrix, along with a comparison to Absorb GT1 BVS. For a given scaffold diameter and length, the Esprit BTK drug content is bracketed between XIENCE V on the lower end and Absorb GT1 BVS on the upper end.

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In a preclinical study, systemic and local exposure to 1341 µg of everolimus was demonstrated to be safe (three 3.0x12 mm XIENCE V stents coated at a maximum drug dose density of 800 µg/cm^2, 447 µg per stent). The total drug content for the longest Esprit BTK lengths of the largest diameters (3.5/3.75 x 33 and 38 mm) falls below this maximum dose; the safety limit is more than 3.5 times the total everolimus content of the largest size.

Table 2.2.3-2: Comparison of Esprit BTK and Absorb GT1 BVS Size Matrices and Nominal Everolimus Content

Scaffold Diameter, Nominal (mm)	Scaffold Length (mm)	Drug Dose Density (µg/cm^2)	Esprit BTK Nominal Everolimus Content (µg)	Absorb GT1 BVS Nominal Everolimus Content (µg)
2.5, 2.75[1]	8	100	N/A	76
	9		69	N/A
	12		93	114
	15		116	N/A
	18		139	181
	23		178	228
	28		217	276
	33		256	N/A
	38		295	N/A
3.0	8	100	N/A	76
	9		75	N/A
	12		98	114
	15		121	N/A
	18		144	181
	23		189	228
	28		227	276
	33		273	N/A
	38		311	N/A
3.5	9	100	94	N/A
	12		119	135
	15		153	N/A
	18		188	197
	23		239	246
	28		290	308
	33		341	N/A
	38		391	N/A
3.75[1]	9	100	89	N/A
	12		125	N/A
	15		161	N/A
	18		188	N/A
	23		242	N/A
	28		296	N/A
	33		350	N/A
	38		404	N/A

[1] 2.75, 3.75 mm not available for Absorb GT1 BVS

2.2.3.4. Delivery system

[redacted]

The Esprit BTK delivery system incorporates elements of both the Absorb GT1 BVS System and the XIENCE Alpine Stent System. The Esprit BTK delivery system utilizes a similar inner member and tip design as XIENCE Alpine and is otherwise identical to the Absorb GT1 BVS System.

2.2.3.5. Packaging and Sterilization

The Esprit BTK System utilizes the same packaging components as the Absorb GT1 BVS System. The peelable foil pouch containing the final product is then electron beam (e-beam) sterilized, using the same process and dose as the Absorb GT1 BVS System.

2.2.4. Control Device(s)

Subjects randomized to the PTA arm will be treated with standard PTA balloon(s), currently approved for use below the knee and commercially available in the clinical site's geography. Appropriate balloon diameter, balloon length and catheter length will be determined by the investigator. PTA balloons and catheters will be used per standard of care and following the IFU of the product.

PTA was chosen as the comparator because it is currently the standard of care for treatment of BTK lesions in patients with CLI.

2.2.5. Device Handling

Information on device handling, usage and storage are included in the IFU.

Sponsor requires all investigational products to be stored according to the investigational product labeling and Instructions for Use in a secure area to prevent unauthorized access or use.

3.0 CLINICAL INVESTIGATION DESIGN

This clinical investigation is designed to evaluate the safety and efficacy of the everolimus eluting Esprit BTK System for the planned treatment of narrowed infrapopliteal lesions.

This is a prospective, single-blinded, randomized controlled clinical investigation randomizing approximately 225 subjects between Esprit BTK therapy and PTA therapy. Subjects will be randomized in a 2:1 ratio (Esprit BTK:PTA). Subject registration is capped at 45 (20% of total sample size) per site.

[redacted]

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The clinical investigation will be conducted at approximately 65 clinical sites in the US, Asia, Australia, and New Zealand.

One pre-specified interim analysis for sample size re-estimation is planned for this study. Per the planned interim analysis, if this analysis indicates a need for sample size increase, the sample size can be adjusted up to a total of 315 subjects.

The primary safety endpoint at 6 months and primary efficacy endpoint at 1 year will be evaluated when all subjects have completed their 1-year visit. The primary safety endpoint will be tested for non-inferiority of Esprit BTK to PTA. The primary efficacy endpoint will be tested for superiority of Esprit BTK as compared to PTA.

These primary endpoints will also be analyzed at 1 month, 3, 6 months, and 1, 2, 3, 4 and 5 years. All secondary endpoints will be analyzed at the same time points as the primary endpoints.

Core laboratories will be used for angiography, duplex ultrasound, IVUS, OCT and wound assessment. Adverse events will be adjudicated by a Clinical Events Committee (CEC), as described in the CEC charter. A Data Monitoring Committee (DMC), also known as Data and Safety Monitoring Board (DSMB), will review cumulative data from the clinical investigation at regular intervals, as described in the DSMB charter.

The clinical investigation has been designed to involve as little pain, discomfort, fear, and any other foreseeable risk as possible for subjects. Refer to the Risks Analysis section of this clinical investigation plan for details.

For the CIP version [redacted] revision, the primary efficacy endpoint is updated and the sample size is adjusted to approximately 260 subjects.

3.1. Clinical Investigation Procedures and Follow-up Schedule

Subjects who satisfy eligibility criteria become registered in the clinical investigation. Subjects have follow-up visits at 14 days, 30 days, 42 days, 3 months, 6 months, 1 year and annually through 5 years.

A detailed description of procedures/assessments performed at each follow-up visit can be found in **Section 6.7**.

The subject screening and registration flow chart, and follow-up requirements, for this clinical investigation are described below in **Figure 3.1-1**

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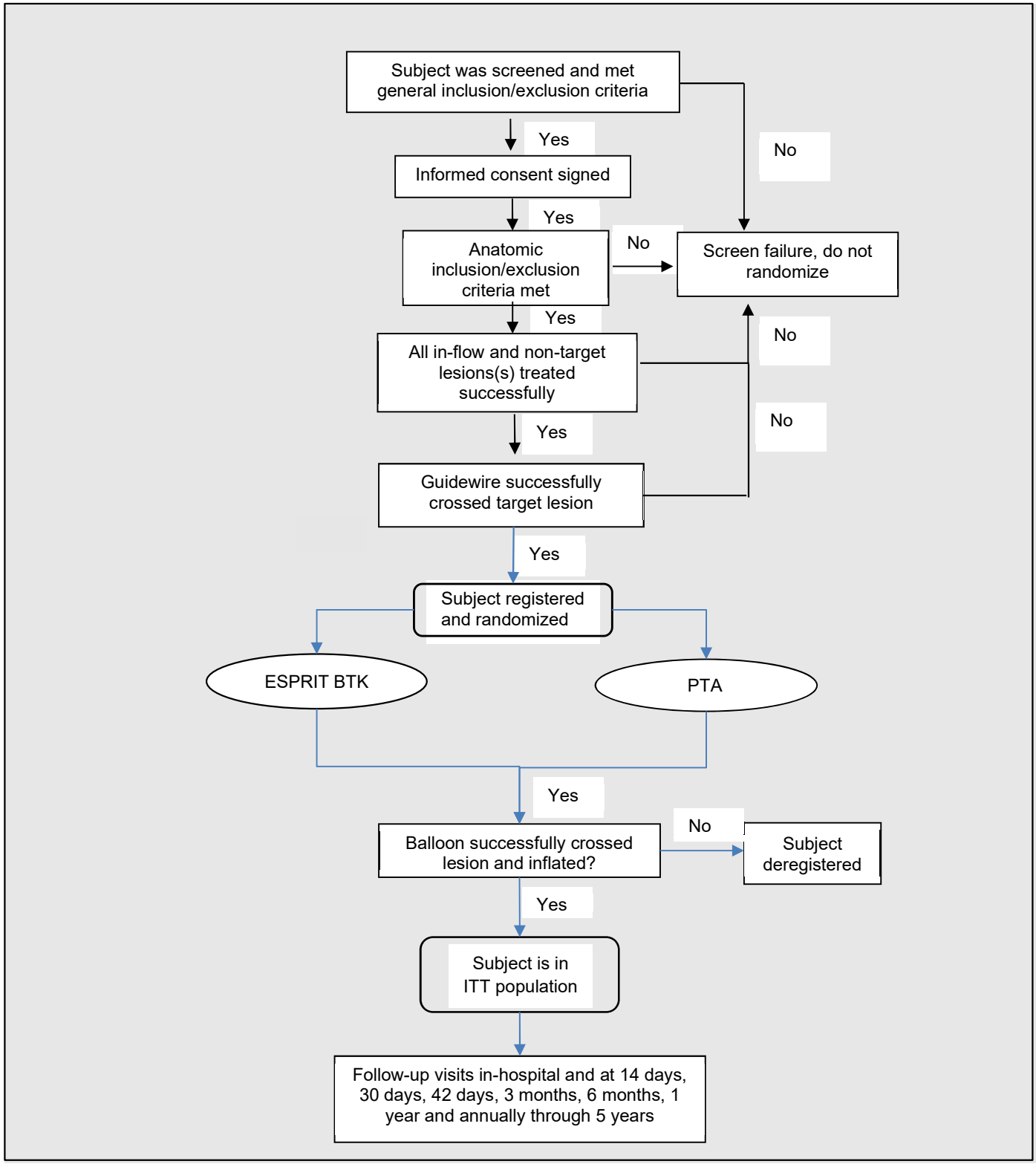

Figure 3.1-1: Clinical Investigation Flow Chart

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3.2. Measures Taken to Avoid and Minimize Bias

In the LIFE-BTK RCT, several measures will be taken to avoid and minimize bias, such as randomization and blinding. Additionally, as mentioned above, core laboratories, DMC and CEC will be used in this clinical investigation.

3.2.1. Randomization

Subjects will be randomized 2:1 in the primary analysis (test device: Esprit BTK vs. control device/treatment strategy: PTA). Randomization will be performed after all eligibility criteria have been met, all in-flow and non-target lesion(s) have been treated successfully, and the guidewire successfully crossed the target lesion. For laboratory assessments where multiple values for that test are present, it will be up to the physician's discretion to determine which value will be used to assess subject eligibility, as long as one of the laboratory values is within the eligibility range. In cases where two target lesions are being treated, there needs to be strong assurance that both target lesions can be successfully crossed by the guidewire.

Once randomization is completed and a treatment is assigned, crossover to the other treatment group is not permitted. Regardless of the actual device the subject received, the subject will be included in the ITT population per the original randomization assignment. An Esprit BTK may never be used in a subject randomized to PTA. However, if the subject is randomized to Esprit BTK and the scaffold cannot be delivered, any device approved for BTK in that geography may be used as per label indication. If a complication occurs in a patient randomized to Esprit BTK, such as dissection, another BVS should be used (first choice), or any other approved device in the geography, as necessary in the best interests of the subject.

Randomization assignments will be given through the Oracle EDC system.

The subject is considered to be successfully registered in this study and considered in the ITT population at the point of randomization.

3.2.2. Blinding

This is a single-blinded clinical investigation. [redacted]

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[redacted]

3.3. Early Termination of the Clinical Investigation

No formal statistical rule for early termination of the trial is defined.

While no formal statistical rule for early termination of the clinical investigation for insufficient effectiveness of the device under investigation is defined, the Sponsor reserves the right to discontinue the clinical investigation at any stage or reduce the follow-up period with suitable written notice to the investigator. Possible reason(s) may include, but are not limited to:

- Unanticipated adverse device effect (e.g., UADE) occurs and it presents an unreasonable risk to the participating subjects
- An oversight committee (e.g., Steering/Executive Committee, Data Monitoring Committee) makes a recommendation to stop or terminate the clinical investigation (such as higher frequency of anticipated adverse device effects)
- Further product development is cancelled.

3.3.1. Subject Follow-up for of Early Termination or Suspension of Study

If the Sponsor suspends or prematurely terminates the clinical investigation at an individual site in the interest of safety, the Sponsor will inform all other Principal Investigators.

If suspension or premature termination occurs, the Sponsor will remain responsible for providing resources to fulfill the obligations from the CIP and existing agreements for following the subjects enrolled in the clinical investigation. Details for such subjects follow up will be provided. The Principal Investigator or authorized designee will promptly inform the enrolled subjects at his/her site, if appropriate.

The investigator will be return all clinical investigation materials (including devices) to the Sponsor, unless instructed otherwise and provide a written statement to the IRB/EC (if applicable). All applicable clinical investigation documents shall be subject to the same retention policy as detailed in **Section 11.5** of the CIP.

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A Principal Investigator, IRB/EC or regulatory authority may suspend or prematurely terminate participation in the clinical investigation at the investigational site(s) for which they are responsible. The investigators will follow the requirements specified in the Clinical Trial Agreement.

If a suspended investigation is to be resumed, a prior approval should be obtained from the EC/IRB and a notification should be sent to the regulatory bodies, and if subjects were informed of suspension, they shall be informed of the resumption of the clinical investigation.

4.0 ENDPOINTS

4.1. Primary Endpoints and Rationale

The LIFE-BTK RCT has two primary endpoints: a primary efficacy endpoint and a primary safety endpoint.

The primary efficacy endpoint is a composite of limb salvage and primary patency at 1 year. It includes freedom from: above ankle amputation in index limb, 100% total occlusion of target vessel, binary restenosis of target lesion, and clinically-driven target lesion revascularization (CD-TLR). This efficacy endpoint was chosen because it allows to assess whether Esprit BTK is efficacious at maintaining patency (CD-TLR and binary restenosis), and at preventing catastrophic limb events such as total vessel occlusion or major amputation. Other than showing how the vessel maintains patency, binary restenosis at the target lesion can support evaluating disease progression over time.

The primary safety endpoint is freedom from MALE+POD (Major Adverse Limb Event + Peri-Operative Death). MALE includes above ankle amputation in index limb, major re-intervention on index limb at 6 months and POD includes perioperative (30-day) mortality. This safety endpoint was chosen because it is a commonly used endpoint to assess the safety of devices used in lower limb treatment, including treatment of lesions below the knee. Additionally, this endpoint assesses whether the device is associated with acute and sub-acute harm such as death and limb loss.

4.2. Powered Secondary Endpoints

LIFE-BTK RCT has two powered secondary endpoints. The first powered secondary endpoint is binary restenosis of the target lesion at 1 year. This endpoint was added to better evaluate the device performance as binary restenosis can be used as a marker for disease progression over time.

The second powered secondary endpoint is a composite endpoint that includes freedom from: above ankle amputation in index limb, 100% total occlusion of target vessel and clinically-driven target lesion revascularization (CD-TLR) at 1 year. This endpoint was chosen because it is important to assess whether Esprit BTK is efficacious at maintaining patency and preventing catastrophic limb events beyond 1 year.

4.3. Descriptive Secondary Endpoints

The following secondary endpoints will be evaluated during the course of the clinical trial:

Procedural:

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- Acute procedure success
- Device success - for Esprit arm only
- Technical success
- Clinical success
- Angiographic acute gain (in-segment)
- Angiographic acute gain (in-device) - for Esprit arm only

Clinical endpoints evaluated at 1 month, 3 months, 6 months, 1 year and annually through 5 years are:

- Composite of limb salvage and primary patency (primary efficacy endpoint)
- Freedom from MALE+POD (primary safety endpoint)
- Freedom from: above ankle amputation in index limb, 100% total occlusion of target vessel and clinically-driven target lesion revascularization (CD-TLR)
- Freedom from major amputation and clinically-driven target lesion revascularization (CD-TLR)
- Freedom from above ankle amputation
- Freedom from restenosis
- Binary restenosis of the target lesion (first powered secondary endpoint)
- Amputation-free survival §
- All-cause death
- Arterial thrombosis
- Major re-intervention on index limb
- Primary assisted patency
- Secondary patency
- Clinically-driven target lesion revascularization (CD-TLR)
- Clinically-driven target vessel revascularization (CD-TVR)
- Clinically-driven target vessel revascularization distal to the target lesion
- Clinically-driven target vessel revascularization proximal to the target lesion

- Index wound assessment for healing (14 days, 30 days, 42 days, 90 days, 180 days and 1 year)*
- Index wound assessment for infection (14 days, 30 days, 42 days, 90 days, 180 days and 1 year)*
- Rutherford Becker clinical category, and change from baseline for the treated limb
- Occurrence of new wound †
- Acute limb ischemia
- Peripheral embolization

Note: Patency by duplex ultrasound will be assessed 30 ± 14 days post-procedure, and at 6 months, 1, 2, and 3 years.

§ Amputation-free survival includes freedom from above ankle amputation and death.
* Index wound assessment for healing and infection will be assessed by the core laboratory through 90 days (14 days, 30 days, 42 days and 90 days). For index wounds that are not healed by 90 days, the index wound will be assessed by the core laboratory at 180 days. If the index wound is not healed by 180 days, index wound assessment by the core laboratory will be carried out at 1 year. Index wounds that have healed by 90 days will not be assessed by the core laboratory at 180 days and 1 year.
† New wound is defined as wound below the knee in the index limb that was not identified at the time of the index procedure or wound that has recurred in the same location following the healing of the index wound. The new wound will be assessed firstly by the wound assessment core laboratory for etiology. Subsequently, the new wound will be evaluated by the site per protocol until the wound is healed through the 5-year follow-up. After the etiology assessment, the wound will no longer be evaluated by the core laboratory. If a new wound is first observed at 5-year follow-up, a picture will be taken for etiology assessment by the core laboratory. As this will be the final patient visit for the trial, no additional pictures of the new wound will be required following the initial picture submitted to the core laboratory.

4.4. Informational Endpoints

Patient Reported Outcomes:

The following Patient Reported Outcomes will be analyzed as informational endpoints at baseline, 30 days, 3 months, 6 months and 1 year:

- Overall health status using the EQ-5D-5L (EuroQoL-5D-5L) questionnaire
- Walking capacity using WIQ (Walking Impairment Questionnaire)
- Disease-specific health status using PAQ (The Peripheral Arterial Questionnaire)

Cost-Effectiveness:

Cost per quality adjusted life year (QALY) and cost per clinical event avoided will be evaluated using standardized methods [13].

5.0 SUBJECT SELECTION AND WITHDRAWAL

5.1. Subject Population

This clinical investigation will enroll subjects from all genders with arterial narrowing in infrapopliteal lesions causing critical limb ischemia. Subjects must meet all eligibility criteria and provide written informed consent prior to conducting any investigation-specific procedures not considered standard of care.

5.2. Subject Screening and Informed Consent

5.2.1. Subject Screening

Subjects admitted for a lower limb revascularization procedure must be screened for clinical investigation eligibility by a member of the clinical investigation team (physician and/or research coordinator) previously trained to the clinical investigation protocol and if applicable will be entered into a site-specific screening log.

In case the subject does not meet all inclusion criteria or meets any of the exclusion criteria, the subject is considered a screening failure. It is extremely important that the Principal Investigator or the delegated clinical investigation personnel record the screening failure in the hospital records and on a screening log.

Subjects meeting the general inclusion criteria and none of the exclusion criteria will be fully informed about the clinical investigation and asked to sign an informed consent. Pre-procedure (or baseline) imaging will be used for the final assessment of subject eligibility (details are described in Section 5.3). Subjects who do not satisfy the anatomic inclusion and exclusion criteria are considered screen failures and will not be registered and proceed further in the trial. All screened subjects will be entered into the screening log. Also, the reason for screen failure as well as supporting data will be entered into the log. Subjects satisfying the anatomic inclusion/exclusion criteria, and in whom the following two conditions are met, will be randomized:

- All in-flow and non-target lesion(s) successfully treated
- Guidewire successfully crossed the target lesion

Subjects will be registered into the clinical investigation at the point of randomization.

Subject data will be collected following enrollment into the clinical investigation.

5.2.2. Informed Consent

The Investigator or his/her authorized designee (if applicable) will conduct the Informed Consent process, as required by applicable regulations and the center's IRB/EC. This process will include a verbal discussion with the patient on all aspects of the clinical investigation that are relevant to the patient's decision to participate, such as details of clinical investigation procedures, anticipated benefits,

and potential risks of clinical investigation participation. Sites must inform patients about their right to withdraw from the clinical investigation at any time and for any reason without sanction, penalty or loss of benefits to which the patient is otherwise entitled. Withdrawal from the clinical investigation will not jeopardize their future medical care or relationship with the investigator.

During the discussion, the Principal Investigator or his/her authorized designee will avoid any improper influence on the patient and will respect patient's legal rights. Financial incentives will not be given to the patients. Patients may be compensated for time and travel directly related to the participation in the clinical investigation. The site shall provide the patient with the Informed Consent form written in a language that is understandable to the patient and that has been approved by the center's IRB/EC. The patient shall have adequate time to review, ask questions, and consider participation. The Principal Investigator or his/her authorized designee will make efforts to ensure that the patient understands the information provided. If the patient agrees to participate, they must sign and date the Informed Consent form, along with the person obtaining the consent prior to any clinical investigation-specific procedures. The site will file the signed original in the patient's hospital or research chart, and provide a copy to the patient.

Sites should report any failure to obtain informed consent from a patient to the Sponsor within 5 working days and to the reviewing center's IRB/EC according to the IRB's/ EC's reporting requirements.

If, during the clinical investigation, new information becomes available that can significantly affect a subject's future health and medical care, the Principal Investigator or his/her authorized designee (if applicable) will provide this information to the subject. If relevant, sites will ask the subject to confirm their continuing informed consent in writing.

5.2.2.1. Special Circumstances for Informed Consent

This clinical investigation excludes individuals unable to make the decision to participate in a clinical investigation on their own or 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.
This clinical investigation excludes individuals under the age of 18 or age of legal consent from the clinical investigation population.

Sites may enroll individuals unable to read or write in this clinical investigation. Sites will obtain informed consent through a supervised oral process. An independent witness will be present throughout the Informed Consent process. A member of the site's clinical investigation team previously trained to the CIP will read the written Informed Consent form and any other information aloud and explain to the prospective subject or his/her legally acceptable representative and will sign and personally date the Informed Consent form. The witness will also sign and personally date the Informed Consent form attesting that the information was accurately explained, and that informed consent was freely given. In addition, no incentives or financial inducements will be provided to these patients or their legally authorized representatives for their participation in the clinical investigation.

The clinical investigation excludes pregnant or breastfeeding women.

In addition, sites must obtain an authorization for use and disclosure of the subject's protected health information, in accordance with the Health Insurance Portability and Accountability Act (HIPAA), from the subject or their legally acceptable representative.

All other aspects of the Informed Consent process will follow **Section 5.2.2**.

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For live cases at congresses, the patients need to sign a specific Live Case ICF, approved by the IRB/EC and by the Sponsor, as well as by the respective regulatory or competent authorities (e.g., FDA), as applicable. The investigator must request Sponsor approval prior to performing a Live Case.

5.3. Eligibility Criteria

5.3.1. General Eligibility Criteria

Assessment for general eligibility criteria is based on medical records of the site and interview with a candidate subject. If any of the clinical and laboratory tests are not included in site standard tests, they must be done but after written informed consent is obtained. Subjects must meet ALL of the inclusion criteria to be considered for the clinical investigation. If ANY of the exclusion criteria are met, the subject is excluded from the clinical investigation and cannot be registered.

5.3.2. Inclusion Criteria

5.3.2.1. General Inclusion Criteria

1. Subject must provide written informed consent prior to any clinical investigation related procedure.
2. Subject has symptomatic Critical Limb Ischemia (CLI), Rutherford Becker Clinical Category 4 or 5.
3. Subject requires primary treatment of up to two de novo or restenotic (treated with prior PTA) infrapopliteal lesions
4. Subject must be at least 18 years of age.
5. Female subject of childbearing potential should not be pregnant and must be on birth control.

   Note: Female subjects of child-bearing potential must have a negative pregnancy test done within 7 days prior to the index procedure per site standard test.

5.3.2.2. Anatomic Inclusion Criteria

1. Up to two native infrapopliteal lesions, each lesion located in separate infrapopliteal vessel in the same limb. Restenotic (from prior PTA) lesions are allowed.

   a. Lesion must be located in the proximal 2/3 of native infrapopliteal vessels, with vessel diameter of ≥ 2.5 mm and ≤ 4.00 mm by investigator visual assessment.
   Note: see vessel sizing under “treatment strategy” section.

   b. Total scaffold length to completely cover/treat a target lesion must not exceed 170 mm (total everolimus drug dose of 1790 µg).

   c. The total scaffold length among all target lesions must not exceed 170 mm.

   d. The target vessel cannot have any other angiographic significant lesions (≥50%).

   e. Tandem lesions are allowed if they are < 3 cm apart and the total scaffold length used to cover the entire diseased segment is ≤ 170 mm. Each tandem lesion is considered one lesion.

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2. Target lesion(s) must have ≥ 70% stenosis, per visual assessment at the time of the procedure. If needed, quantitative imaging (angiography, IVUS, and/or OCT) can be used to aid accurate sizing of the vessels.

3. The distal margin of the target lesion must be located ≥ 10 cm proximal to the proximal margin of the ankle mortise. The vessel segment distal to the target lesion must be patent all the way to the ankle, with no significant lesion (≥ 50% stenosis).

4. Significant lesion (≥ 50% stenosis) in the inflow artery(ies) must be treated successfully (as per physician's assessment of the angiography) through standard of care prior to the treatment of the target lesion. Treatment can be done within the same trial procedure

5. Non-target lesion(s) (if applicable) must be located in separate infrapopliteal vessel(s) from the target lesion, and suitable to be treated per institution standard of care.

6. Guidewire must cross the target lesion successfully. Crossing in an antegrade fashion is preferred, but retrograde crossing may be used. However, the treatment must be delivered antegrade.

5.3.3. Exclusion Criteria

5.3.3.1. General Exclusion Criteria

1. Subject is currently participating in another clinical investigation that has not yet completed its primary endpoint.

2. Pregnant or nursing subjects and those who plan pregnancy during the clinical investigation follow-up period.

3. Presence of other anatomic or comorbid conditions, or other medical, social, or psychological conditions that, in the investigator's opinion, could limit the subject's ability to participate in the clinical investigation or to comply with follow-up requirements.

4. Incapacitated individuals, defined as persons who are mentally ill, mentally handicapped, or individuals without legal authority, are excluded from the study population.

5. Subject has had any amputation to the ipsilateral extremity other than the toe or forefoot, or subject has had major amputation to the contralateral extremity < 1 year prior to index procedure and is not independently ambulating.

6. Subject has known hypersensitivity or contraindication to device material and its degradants (everolimus, poly (L-lactide), poly (DL-lactide), lactide, lactic acid) and cobalt, chromium, nickel, platinum, tungsten, acrylic and fluoro polymers that cannot be adequately pre-medicated. Subject has a known contrast sensitivity that cannot be adequately pre-medicated.

7. Subject has known allergic reaction, hypersensitivity or contraindication to aspirin; or to ADP antagonists such clopidogrel, prasugrel or ticagrelor; or to anticoagulants such as heparin or bivalirudin, and therefore cannot be adequately treated with study medications. Subject with planned surgery or procedure necessitating discontinuation of antiplatelet medications, within 12 months after index procedure. Planned amputation that will necessitate discontinuation of antiplatelet medications is allowed.

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8. Subject has life expectancy ≤ 1 year.

9. Subject has had a stroke within the previous 3 months with residual Rankin score of ≥ 2.

10. Subject has renal insufficiency as defined as an estimated GFR < 30 ml/min per 1.73m^2.

11. Subject is currently on dialysis.

12. Subject has platelet count < 100,000 cells/mm^3 or > 700,000 cells/mm^3, a WBC < 3,000 cells/mm^3, or hemoglobin < 9.0 g/dl.

13. Subject has known serious immunosuppressive disease (e.g., human immunodeficiency virus), or has severe autoimmune disease, that requires chronic immunosuppressive therapy (e.g., systemic lupus erythematosus, etc.), or subject is receiving immunosuppression therapy for other conditions. Subjects treated for HIV (Human Immunodeficiency Virus) and who have undetectable viral load, such that their immune system is not considered compromised, are eligible.

14. Subject has Body Mass Index (BMI) <18.

15. Subject is receiving or scheduled to receive anticancer therapy for malignancy within 6 months prior to index procedure or within 1 year after the procedure. Patients taking medications classified as chemotherapy but who have been in remission for at least 6 months are eligible.

16. Subject has coagulation disorder that increases the risk of arterial thrombosis. Subjects with deep vein thrombosis and disorders that increase the risk of deep vein thrombosis can be included in the study.

17. Subject who requires thrombolysis as a primary treatment modality or requires other treatment for acute limb ischemia of the target limb.

18. Subject has previously had, or requires surgical revascularization involving any vessel of the ipsilateral extremity. Prior femoropopliteal or aortobifemoral bypass is allowed. Any bypass to the tibial arteries is not allowed.

19. Subject has signs or symptoms of advanced limb infection or septicemia (fever > 38.5, WBC > 15,000 cells/microliter, hypotension) at the time of assessment. Osteomyelitis of the phalanges or metatarsal heads (as described in exclusion criteria #21a) or cellulitis of the foot amenable to treatment with IV antibiotics at the time of revascularization is acceptable.

20. Subject is bedridden or unable to walk (with assistance is acceptable). Subjects in wheelchair who are able to mobilize on their own can be enrolled.

21. Subject with extensive tissue loss salvageable only with complex foot reconstruction or non-traditional transmetatarsal amputations [14]. This includes subjects with:

    a Osteomyelitis that extends proximal to the metatarsal heads. Osteomyelitis limited to the phalanges or metatarsal heads is acceptable for enrollment.

    b Gangrene involving the plantar skin of the forefoot, midfoot, or heel

c Deep ulcer or large shallow ulcer (> 3 cm) involving the plantar skin of the forefoot, midfoot, or heel

d Full thickness heel ulcer with/without calcaneal involvement

e Any wound with calcaneal bone involvement

f Wounds that are deemed to be neuropathic or non-ischemic in nature

g Wounds that would require flap coverage or complex wound management for large soft tissue defect

h Full thickness wounds on the dorsum of the foot with exposed tendon or bone.

22. Subject is unable or unwilling to provide written consent prior to enrollment

23. Subject has active symptoms and/or a positive test result of COVID-19 or other rapidly spreading novel infectious agent within the prior 2 months.

5.3.3.2. Anatomic Exclusion Criteria

1. Lesions with severe calcification, in which there is a high likelihood that successful pre-dilatation cannot be achieved.

2. Lesion that has prior metallic stent implant.

3. Significant (≥ 50% stenosis) lesion in a distal outflow artery that would be perfused by the target vessel and that requires treatment at the time of the index procedure.

4. Subject has had or will require treatment in any vessel with an everolimus drug-coated or drug-eluting device < 30 days pre-study procedure, or during the index procedure, such that the cumulative (Esprit BTK plus everolimus-eluting device) everolimus drug dose exceeds 1790 µg.

5. Target or (if applicable) non-target vessel contains visible thrombus as indicated in the angiographic images.

6. Subject has angiographic evidence of thromboembolism or atheroembolism in the ipsilateral extremity. (Pre- and post-angiographic imaging must confirm the absence of emboli in the distal anatomy.)

7. Unsuccessfully treated proximal inflow limiting arterial stenosis or inflow-limiting arterial lesions left untreated.

8. No angiographic evidence of a patent pedal artery.

9. Target or (if applicable) non-target lesion location requiring bifurcation treatment method that requires scaffolding of both branches (provisional treatment, without intention of scaffolding both branches is acceptable).

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10. Aneurysm in the iliac, common femoral, superficial femoral, popliteal or target artery of the ipsilateral extremity.

11. Visual assessment of the target lesion suggests that the investigator is unable to pre-dilate the lesion according to the vessel diameter.

12. Target lesion has a high probability that atherectomy will be required at the time of index procedure for treatment of the target vessel.

5.4. Subject Enrollment

A patient is considered enrolled in the clinical investigation from the moment the patient provides written informed consent.

Subjects who satisfy all inclusion and exclusion criteria (general and anatomic) after pre-procedure screening, and in whom the guidewire has successfully crossed the target lesion, will be registered and proceed further to randomization.

If subjects are registered into the clinical investigation and are later found to have met exclusion criteria or not all inclusion criteria, these subjects will continue follow-up in the clinical investigation and will be included in the intent-to-treat analysis population. These subjects will not be deregistered from the clinical investigation. These subjects are considered CIP deviations.

5.4.1. Enrollment of Medicare Beneficiaries

This section is only applicable to sites enrolling subjects in the United States.

This clinical investigation will enroll Medicare beneficiaries and therefore conforms to all standards of Medicare coverage requirements. The Risks and Benefits section describes how all enrolled subjects, including Medicare beneficiaries, may be affected by the device under investigation.

A portion of the subjects enrolled in the clinical investigation display characteristics consistent with the Medicare population based on age. The clinical investigation results will be analyzed by age (< 65 years and ≥ 65 years) and compared to ensure that the outcomes are similar between the Medicare and non-Medicare populations.

5.4.2. Historically Under-Represented Demographic Subgroups

The Sponsor intends to implement FDA's guidance on sex-specific data in medical device clinical investigations to ensure adequate representation of women and other traditionally under-represented demographic subgroups in this clinical investigation. As noted in the guidance, some barriers to participation of women and ethnic minorities in clinical investigations have traditionally been:

- Lack of understanding about main obstacles to participation of such subgroups in clinical research
    - Inclusion/exclusion criteria potentially not needed to define the clinical investigation population may unintentionally exclude specific subgroups

- Under diagnosis of disease etiologies and pathophysiology leading to under referral of demographic subgroups
- Avoidance of specific subgroups by investigators and Sponsors due to the perception that it takes more time and resources to recruit them
- Fear of fetal consequences (for female participants)
- Family responsibilities limiting women's ability to commit time for follow-up requirements

The Sponsor will take the following steps to ensure adequate representation of women and racial or ethnic minorities in this clinical investigation:

- The Sponsor will provide training to investigational site personnel to ensure adequate representation of these demographic subgroups
- The Sponsor will regularly review enrollment data to investigate whether there is under-representation of these demographic subgroups
- The Sponsor will regularly review withdrawal rates for under-represented subgroups and compare these rates with that in the overall clinical investigation population
- As appropriate and necessary, the Sponsor will retrain sites on the importance of recruiting and retaining subjects in the clinical investigation
- The Sponsor will approach sites without bias or consideration for specific demographic subgroups
- The Sponsor will have informed consent materials in alternative languages and will work with sites and IRBs/ECs on recruitment materials

5.5. Subject Deregistration

If balloon is unable to cross the lesion or to inflate at nominal size, the subject will be deregistered. The subject will be followed for 30 days and will not be included in the intent-to-treat analysis population.

5.6. Subject Withdrawal

Each registered subject shall remain in the clinical investigation until completion of the required follow-up period; however, a subject's participation in any clinical investigation is voluntary and the subject has the right to withdraw at any time without penalty or loss of benefit. Conceivable reasons for discontinuation may include, but not be limited to, the following:

- Subject death
- Subject voluntary withdrawal
- Withdrawal by the investigator as clinically-indicated

- Subject lost-to follow-up as described below
- Subject's follow-up is terminated according to **Section 3.3** Early termination of the Clinical Investigation

The Sponsor must be notified of the reason(s) for subject discontinuation. The site will provide this information to the Sponsor. Investigators must also report this to their respective IRB/EC as defined by their institution's procedure(s).

No additional follow–up will be required or data recorded from subjects once withdrawn from the clinical investigation, except for the status (deceased/alive).

However, if a subject withdraws from the investigation due to problems related to the safety or performance of the device under investigation, the investigator shall ask for the subject's permission to follow his/her status/condition outside of the clinical investigation.

In case of subject withdrawal of consent, the site should make attempts to schedule the subject for a final clinical investigation visit. At this final follow-up visit, the subject will undergo the following assessments:

- Review of adverse events
- Review of protocol and concomitant medications
- Administration of patient reported outcomes

Lost-to-Follow-up

If the subject misses two consecutive scheduled follow-up time points and the attempts at contacting the subject detailed below are unsuccessful, then the subject is considered lost-to-follow-up. Site personnel shall make all reasonable efforts to locate and communicate with the subject (and document these efforts in the source documents), including the following, at each contact time point:

- A minimum of two telephone calls on different days over the specified follow-up windows to contact the subject should be recorded in the source documentation, including date, time and initials of site personnel trying to make contact.
- If these attempts are unsuccessful, a letter (certified if applicable) should be sent to the subject.
- If a subject misses one or more non-consecutive follow-up contact time points, it will be considered a missed visit. The subject may then return for subsequent visits. If the subject misses two consecutive time points and the above-mentioned attempts at communicating with the subject are unsuccessful, the subject will be considered lost-to-follow-up.

Note: Telephone contact with General Practitioner, non-clinical investigation cardiologist or relative without the presence of the subject or indirect documentation obtained via discharge letters will not be considered as subject contact.

Missed visits

If a subject misses one or more non-consecutive follow-up contact time points, the visit will be considered a missed visit and subject is not lost-to-follow-up.

If subject responds via written communication (including email correspondence), providing the protocol required data, these data will be collected in the case report form and the visit will not be considered a missed visit.

5.7. Number of Subjects

Approximately 225 subjects were originally planned to be registered in the clinical investigation. [redacted]

5.8. Total Expected Duration of the Clinical Investigation

[redacted]. The expected duration of each subject's participation is 5 years, including the scheduled visits and data collection for this clinical investigation that will occur in-hospital and at 14 days, 30 days, 42 days, 3 and 6 months, and at 1, 2, 3, 4 and 5 years. Subjects will be exited from the trial at the conclusion of their 5-year (60 months) follow-up visit. Therefore, the total duration of the clinical investigation is expected to be [redacted]

6.0 TREATMENT AND EVALUATION OF ENDPOINTS

6.1. Baseline Assessments

Subject preparation will occur in accordance with standard hospital policy for the care of interventional endovascular subjects. The baseline assessments described below must be obtained within 30 days prior to study procedure, unless indicated otherwise. They will be documented in the subject medical record and on the eCRF as appropriate.

The schedule of events for this trial is located in **Section 6.7.7**.

6.1.1. Subject Demographics and Medical History

Subject history will include but not be limited to the following demographics, risk factors and comorbidities: age, height, weight, body mass index (BMI), gender, hypertension, hyperlipidemia, diabetes mellitus, smoking, ischemic heart disease (history of myocardial infarction, angina pectoris, previous percutaneous or surgical coronary revascularization), history of peripheral vascular disease (previous percutaneous or surgical revascularization), congestive heart failure, renal insufficiency, liver disease, cerebrovascular disease (known carotid artery disease, history of minor or major stroke or transient ischemic attack), and chronic obstructive pulmonary disease (COPD).

6.1.2. Medication History

A medication history should be documented which includes chronic concomitant medications and protocol required medications. This history should include:

[redacted]

- Anticoagulants (warfarin, unfractionated or low molecular weight heparins, etc.);
- Antithrombotic agents (acetylic salicylic acid, thienopyridines, glycoprotein IIb/IIIa inhibitors, direct thrombin inhibitors, etc.);
- Statins or other lipid lowering agents; beta-blockers; angiotensin converting enzyme inhibitors; angiotensin-II receptor antagonists;
- Insulin and oral hypoglycemic agents;
- Medications for the treatment of intermittent claudication (IC) (e.g., Cilostazol, pentoxifylline, etc.).

6.1.3. Clinical assessments

The systolic blood pressure in the dorsalis pedis or posterior tibial arteries will be obtained for the target limb. Any index wounds (present at baseline) in the distal ipsilateral extremity shall be assessed. New wound is defined as wound below the knee in the index limb that was not identified at the time of the index procedure or wound that has recurred in the same location following the healing of the index wound. The new wound will be assessed firstly by the wound assessment core laboratory for etiology. Subsequently, the new wound will be evaluated by the site per protocol until the wound is healed through the 5-year follow-up. If a new wound is first observed at 5-year follow-up, a picture will be taken for etiology assessment by the core laboratory. As this will be the final patient visit for the trial, no additional pictures of the new wound will be required following the initial picture submitted to the core laboratory.

6.1.4. Hemodynamic Evaluation

Ankle brachial index (ABI) measurement will be obtained for the target limb. In cases in which the ABI is above 1.4 or cannot be reliably measured, toe pressure measurement and determination of the toe brachial index (TBI) should be used.

The visit at baseline will be used to determine if a reliable ABI measurement is possible for the subject. If a reliable ABI measurement is not possible at baseline and TBI measurement was taken, the TBI measurements should be performed on the subject throughout the follow-up period.

6.1.5. Functional Status

Functional status using the Rutherford Becker Clinical Categories [15] will be determined for the target limb.

6.1.6. Patient Report Outcomes

The overall health status (EQ-5D-5L), disease-specific health status (PAQ) and walking performance (WIQ) assessment tools should be completed.

6.1.7. Laboratory Assessments

A pregnancy test must be administered to all female subjects of childbearing potential within 7 days prior to the procedure.

The following laboratory tests must be obtained for all subjects within 30 days prior to the index procedure.

- Hematology

- hemoglobin,
- hematocrit,
- absolute platelet count,
- white blood cell count (differential is highly recommended)

Blood chemistry

- serum creatinine,
- blood urea nitrogen (BUN)

It is also highly recommended to obtain the following laboratory tests within 30 days prior to index procedure:

- fasting blood glucose
- glycosylated hemoglobin (HbA1c)
- serum bilirubin
- serum glutamic-pyruvic transaminase (SGPT/ALT),
- serum glutamic-oxaloacetic transaminase (SGOT/AST)
- lipid profile (total cholesterol, high density lipoprotein, low density lipoprotein, triglycerides)

6.1.8. Angiographic assessment

Anatomic characteristics should be obtained during the baseline or pre-procedure angiogram that includes ipsilateral runoff to the distal foot to allow evaluation of the entire ipsilateral arterial vasculature. Presence of multilevel disease by anatomic level or arterial segment, inflow and outflow, specific location of the lesion, lesion length, stenosis or occlusion, and presence of calcification should be documented in the angiographic image and in the eCRF.

In the case of a vessel occlusion within a stenosed segment, both the length of the stenosed segment and length of the occluded segment should be recorded.

6.2. Randomization

Subject will be randomized after the following is confirmed:

- Investigator has assessed vessel diameter and confirmed it meets the inclusion criterion (RVD between 2.5 mm and 4.00 mm). Refer to the vessel sizing section under “Treatment Strategy” for more details on sizing.

- All other eligibility criteria (general and anatomic) are met
- All in-flow and non-target lesion(s) have been treated successfully
- The guidewire successfully crossed the target lesion. If there are two target lesions, there needs to be strong assurance that both lesions can be crossed successfully. Randomization will occur after successful crossing of the first lesion.

During the randomization phase, the subject is considered randomized after the randomization assignment has been provided through the Oracle Clinical EDC system and a device has been assigned (Esprit BTK or PTA). The subject is considered registered and in the ITT population at the point of randomization. Once randomization is completed and a treatment arm is assigned, crossover to the other arm is not permitted. Regardless of the actual device the subject received, the subject will be included in ITT population per the original randomization assignment.

Registered subjects are counted toward the total sample size in LIFE-BTK RCT.

6.3. Blinding

This is a single-blind clinical investigation. Subjects will be blinded to the treatment arms and the site personnel will be trained not to disclose the treatment arm to the subject. Subject blinding must be maintained until completion of the final follow-up visit for all subjects.

More details on blinding are provided in **Section 3.2.2.**

6.4. Index Procedure

6.4.1. Procedures Involved in the Use of the Device Under Investigation

For appropriate use of the Esprit BTK device, refer to the IFU, the physician's training materials, and the treatment strategy section below.

6.4.2. Pre-procedure Antiplatelet Medications

Subjects selected for treatment with Esprit BTK or PTA must receive a loading dose of ≥ 300 mg of aspirin within 24 hours. Subjects are also required to receive a loading dose of an ADP antagonist within 24 hours prior to the index procedure (preferred), but in all cases no greater than 1 hour after the end of the procedure. ADP antagonist administered must include one of the following: a peri-procedural loading dose at least 300 mg of clopidogrel bisulfate, or 60 mg of prasugrel or 180 mg of ticagrelor.

The aspirin loading dose can be omitted if the subject was on chronic aspirin for ≥ 7 days prior to the index procedure, and the subject received their maintenance dose on the day of the index procedure.

The prasugrel loading dose may be omitted for those subjects on chronic prasugrel therapy (5 or 10 mg daily, or according to prescribing information) for ≥ 7 days prior to the index procedure; however, it is recommended that a loading dose (≥ 30 mg) be re-administered. The ticagrelor loading dose may be omitted for those subjects on chronic ticagrelor therapy (90 mg twice daily, or according to prescribing information). The clopidogrel loading dose may be omitted for those subjects on chronic clopidogrel therapy (minimum of 75 mg daily, or according to prescribing information) for ≥ 7 days prior to the index

procedure; however, it is recommended that a loading dose (≥ 300 mg) be re-administered. A loading dose of prasugrel or ticagrelor may be safely given to patients maintained on chronic clopidogrel therapy, or even in those in whom a clopidogrel loading dose was recently administered. Ticlopidine may be used as a substitute at a dose in accordance with standard hospital practice only if the subject develops hypersensitivity or intolerance to clopidogrel, prasugrel, or ticagrelor.

For subjects on chronic aspirin and chronic ADP antagonist, loading of both antiplatelet can be omitted if the subject received their maintenance dose on the day of index procedure.

For subjects on chronic oral anticoagulants, loading with a single antiplatelet is acceptable, as per physician's decision.

Refer to respective prescribing information for ADP antagonist for further details regarding loading practice.

6.4.3. Anti-Coagulation Medications

Subjects must receive appropriate anticoagulation and other therapy according to standard hospital practice. Either unfractionated heparin or bivalirudin may be used for procedural anticoagulation, as per the discretion of the investigator. Subjects having been treated with low molecular weight heparin (LMWH) prior to the procedure must receive their last dose more than 8 hours prior to the index procedure. LMWH and fondaparinux are not permitted as procedural anticoagulants in this protocol.

Use of glycoprotein IIb/IIIa inhibitors will be at the discretion of the investigator. Any change in medication regime performed per the protocol, and not as routine hospital practice, can only occur after obtaining Informed Consent.

6.4.4. Pre-procedure Measurements and Imaging

ABI measurement for the target limb (as described in the "Baseline Assessments" section), or TBI in cases where ABI cannot be reliably measured, and angiographic assessment will be performed pre-procedure. Angiography will be completed as per the core laboratory manual of operations.

Angiographic assessment of the potential target lesion(s) to be treated must be done to ensure anatomic criteria are met with special attention to the vessel diameter. This clinical investigation allows treatment of lesions in vessel with diameters of ≥ 2.5 mm and ≤ 4.00 mm by investigator visual assessment. Therefore, initial assessment of vessel diameter must be performed using visual estimation. Quantitative method such as IVUS or OCT is strongly recommended if the site is experienced with these techniques. Sites using IVUS or OCT for vessel sizing will be asked to provide their IVUS or OCT images in addition to their angiographic images, to the core laboratory. Analysis will be conducted to assess vessel sizing.

6.4.5. Treatment Strategy

All inclusion criteria (general and anatomic), and none of the exclusion criteria (general and anatomic), must be met for subjects to be registered in the clinical investigation.

The clinical investigation allows for the treatment of up to two lesions in two separate native infrapopliteal lesions in separate arteries located in the proximal 2/3 of the vessel with angiographically visible above the ankle reconstitution; restenotic lesions from prior PTA treatment are allowed.

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Planned minor amputations are allowed at the time of the index procedure or within one month post index procedure per site standard of care. These planned minor amputations will not be considered an adverse event. However, if there are any complications of these amputations, they will be considered adverse events. Any unplanned amputation at the time of the index procedure will be considered an adverse event.

Significant lesion (≥ 50% stenosis) in the inflow artery(ies) must be treated successfully, per standard of care, prior to the treatment of the target lesion (treatment can be done within same procedure).

Non-target lesion treatment can occur only in a non-target vessel and must be treated successfully prior to randomization. All non-target lesions should be treated per standard of care.

Success for treatment of non-target and in-flow arteries is defined as per site standard of care.

For treatment of inflow lesions and non-target lesions using atherectomy, it is highly recommended to use embolic protection device such as Emboshield NAV6 Embolic Protection System, for collection of debris.

Randomization can only occur following successful crossing of the target lesion with the guidewire. Each target vessel and lesion should also be such that the operator believes that it can be treated by Esprit BTK.

Atherectomy, scoring/cutting balloons and shock wave lithotripsy are not allowed for treatment of target lesion, in either arm.

Type of access (contralateral or ipsilateral) and guide catheter sizes used will be per investigator discretion and standard of care at the site.

Staged procedures are allowed in the trial. Angiographic assessments and treatment of inflow and non-target lesions can be done first, in a procedure separate from the index procedure. The treatment of these inflow and non-target lesions must be successful before the index procedure can be performed on the subject. The patient can be brought back for the trial index procedure within 4 weeks of the treatment of the inflow or non-target lesions. During the index procedure, the wire must successfully cross the lesion before the subject is randomized.

For treatment of two target lesions, the following process should be followed. Wire crossing should be performed first on the lesion that can be treated more easily. Once the wire has successfully crossed the first target lesion, the subject can then be randomized. For subjects randomized to Esprit arm, this first lesion will then be treated with Esprit. For subjects randomized to PTA, treatment of the first lesion can proceed after successful wire crossing. Once the first lesion has been treated, wire crossing and treatment of the second target lesion, as per randomization assignment, can occur. If the wire does not successfully cross the second lesion, it will be considered a non-target lesion and will be treated per institution standard of care.

6.4.5.1. Treatment Strategy for Esprit BTK

6.4.5.1.1. Pre-dilatation and Device Sizing

- Pre-dilatation must be performed with an angioplasty balloon. Non-compliant balloons (if available) are strongly recommended for pre-dilatation.

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- If non-compliant balloon is not available, a semi-compliant balloon can be used. To prevent dissection, the balloon compliance chart should be used as a reference; do not inflate the balloon beyond the estimated RVD.

- The pre-dilatation balloon should be sized 1:1 to the visually estimated RVD and should be no more than 0.25 mm smaller than RVD.

- As the goal of pre-dilatation is to achieve a 1:1 (balloon: RVD) ratio, a step-wise approach using increasing balloon sizes can be done to achieve this goal.

- The pre-dilatation balloon length should be such that the balloon goes from healthy-to-healthy tissue, on each side of the target lesion.

- Pre-dilatation of the planned target lesions(s) must be performed and be successful before Esprit BTK device implantation in that lesion. Full balloon expansion with the pre-dilatation balloon must be achieved before device implantation. If there is any question that the target lesion has residual stenosis ≥ 30% or that any significant resistance to expansion from the lesion remains, the lesion should be re-dilated with a non-compliant balloon (sized 1:1 to the RVD) at higher pressure. Every attempt should be made to ensure < 30% residual stenosis is achieved. It is understood that after achieving <30% stenosis and the pre-dilatation balloon is removed, slight acute recoil may occur. If this occurs, Esprit BTK may still be implanted.

- If intravascular imaging is not used, check that pre-dilatation balloon is fully expanded using 2 orthogonal views.

- The final diameter achieved with pre-dilatation balloon will be used to determine the choice of scaffold size for treatment.

- To re-estimate vessel size after pre-dilatation, and determine appropriate Esprit BTK size for implantation, the compliance chart for the final/largest pre-dilatation balloon should be used.

- Successful pre-dilatation is defined as diameter stenosis of < 30%, lesion length still within the requirements of the protocol/CIP and no angiographic complications.

6.4.5.1.2. Re-assessment of Vessel Size and Device Size after Pre-dilatation

- Vessel size must be re-assessed after pre-dilatation, to ensure that RVD size criterion is still met (RVD must be between 2.5 mm and 4.00 mm by visual assessment)

- To exclude enrollment of excessively small vessels, if the operator believes that based on visual angiographic assessments, the distal reference vessel diameter is ≤ 2.75 mm such that the plan is to implant a 2.5 mm scaffold in a target lesion, it is strongly recommended that intravascular imaging (ultrasound or optical coherence tomography) is used and demonstrates that the measured distal RVD for this target lesion is ≥ 2.50 mm (by at least one of these imaging modalities). This measurement must be done prior to randomization. If the distal RVD measures <2.5 mm, that lesion IS NOT ELIGIBLE for randomization. Such a lesion may be treated as a non-target lesion

- Quantitative methods such as IVUS is strongly recommended. OCT can also be used if the site is experienced with these techniques; it needs to be taken into account that IVUS tends to over-estimate lumen RVD compared to visual estimation and OCT.

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- If the reassessed RVD after pre-dilatation exceeds the original assessment but remains within the allowed range, the investigator can select a different size scaffold.

- The scaffold size to implant for the vessel sizes can be referred to in **Table 6.4.5.1.2-1**.

Table 6.4.5.1.2-1: Esprit scaffold sizes for implantation with different vessel sizes

		Vessel Size						
		2.5 mm	2.75 mm	3.0 mm	3.25 mm	3.5 mm	3.75 mm	4.0 mm
Scaffold Size	2.5 mm							
	3.0 mm							
	3.5 mm							
	3.75 mm							

6.4.5.1.3. Lesion treatment

- It is strongly recommended that the length of the Esprit BTK be selected to allow at least 2 mm of normal or nearly normal reference vessel at each edge. The area of vessel that was pre-dilated should be covered with scaffold(s).

- If the Esprit BTK cannot reach or cross the lesion or additional lesion preparation is required, the Esprit BTK must be removed and a new Esprit BTK must be introduced after subsequent pre-dilatation(s) with the same sized or larger non-compliant balloon at higher pressure. Note: the Esprit BTK should not be “dottered” across the lesion if it does not cross easily.

- If the Esprit BTK is unable to reach or cross the target lesion after multiple attempts (maximum of two Esprit BTK; including additional lesion preparation), any device approved for BTK use in that geography may be used as per label indication. If the device used contains a drug it should ideally be olimus based.

- Successful target lesion treatment is defined as final diameter stenosis < 30% with final number of run-off vessels equivalent to or greater than number of run-off vessels at pre-procedure, with no residual dissection NHLBI grade ≥ type C, and no transient or sustained angiographic complications (e.g., distal embolization, perforation, thrombosis)

- For Esprit BTK, the scaffold should be deployed slowly, by pressurizing the delivery system in 2 atm increments each over 5 seconds, until the scaffold is completely expanded. Pressure should be maintained for 30 seconds.

- For Esprit BTK and the delivery balloon, do not exceed the rated burst pressure (RBP) per the IFU for the individual device.

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- When using multiple scaffolds, an abutted (non-overlapping) configuration is preferred. When abutting the devices, the operator must consider that the scaffold extends 0.8 mm beyond the proximal marker and 0.3 mm beyond the distal marker. When scaffold abutting is used, ensure that the gap between the two scaffolds is no more than 1 mm. If overlap is used, it is recommended to aim for ~ 1 mm overlap by lining up the balloon markers (proximal or distal depending on overlap direction) [16].

- For planned use of multiple Esprit BTK, the distal scaffold should be deployed first, followed by deployment of proximal scaffold. Treatment performed in this order alleviates the need to cross the proximal scaffold in placement of the distal scaffold and reduces the chances for dislodging the proximal scaffold.

6.4.5.1.4. Post-dilatation

Post-dilatation of the scaffold must be performed for all Esprit BTK treated lesions. For post-dilatation of the target lesion treated with Esprit BTK, the following guidance is given:

- If a scaffold cannot be re-crossed easily, excessive force with the balloon dilatation catheter or imaging catheter should be avoided. If it is necessary to re-cross the device, options to consider include changing the guide catheter orientation to reduce wire bias; consider use of a different wire or a wiggle wire or a buddy wire; attempt to cross the device with a balloon at 0 atm (rather than negative pressure); or inflate and deflate the balloon to wing it to help centralize the tip.

- A low profile, high pressure, non-compliant or semi-compliant, balloon dilatation catheter that has not been previously inflated must be used.

- Post-dilatation must always be performed with either a non-compliant or semi-compliant balloon, sized 1:1 to the vessel.

- For non-compliant balloons, use > 16 atm of pressure.

- For semi-compliant balloons, select a pressure between the nominal pressure and the rated burst pressure that will size the balloon between 1:1 and no more than 0.5 mm above the nominal scaffold diameter.

- The post-dilatation balloon length must be selected such that the balloon stays within the margins of the scaffold so as to avoid an edge dissection.

- The Esprit BTK must not be expanded beyond the dilatation limit which is 0.5 mm above the nominal diameter. Doing so may result in scaffold damage. Thus, the compliance chart of the non-compliant balloon selected must be carefully reviewed prior to dilatation and an appropriate maximum pressure must be used to ensure that the scaffold is not over-dilated.

- Ensure post-dilatation is done on the entire treated segment.

After treatment of the target lesion(s), the vessel distal to the treated segment must be patent (< 50% stenosis) with in-line blood flow to the forefoot and (if applicable) wound area.

6.4.5.2. Treatment Strategy for PTA arm

Treatment of target lesions with PTA should be per standard of care. It is highly recommended that length of the PTA balloon chosen to treat the target lesion be selected to allow at least 2 mm of normal or nearly normal reference vessel at each edge of the lesion.

6.4.5.3. Bailout or Alternative Procedures

The use of a non-study implantable device or treatment strategy in either the treatment or control arms to achieve acute procedure success (defined in Section 6.4.5.3.1 and Appendix II), will be counted as a target lesion revascularization event at the time of index procedure. Although off-label use of devices is allowed under the practice of medicine and is at the discretion of the treating physician, it is recommended that the treating physician consider use of the non-study implantable device such as XIENCE to avoid potential drug interactions. If another DES is used, it would ideally be olimus based.

The location of the non-study implantable device (proximal or distal to the index-procedure device) must be documented on the appropriate case report form. If the bailout procedure was a result of an adverse event/serious adverse event, the appropriate case report form must be completed for this event. If a non-study stent or Esprit BTK is used for bailout, an appropriate length should be placed; abutting configuration is preferred, ensuring that the gap between the two devices (stent/scaffold) is no more than 1 mm. If overlap is used, it is recommended to aim for ~ 1 mm overlap.

6.4.6. Post-procedure Imaging

At a minimum, the following angiographic views must be recorded post-procedure:

- Anterior posterior shot from the knee to mid-lower leg
- Anterior posterior shot from the mid-lower leg to the ankle joint
- Lateral foot view

For more details on post-procedure imaging, refer to the angiographic core laboratory manual of operations.

6.5. Post-procedure Medications

6.5.1. CIP-required antiplatelet therapy

Subjects implanted with Esprit will be treated with aspirin and one of the P2Y12 inhibitors (clopidogrel, prasugrel, or ticagrelor) for a minimum of 12 months. After the 12 months, subjects implanted with Esprit must receive a daily dose of aspirin monotherapy or one of the P2Y12 medications (clopidogrel, prasugrel, or ticagrelor) through 5 years follow-up during the study (except for subjects on chronic oral anticoagulant; see paragraph below for antiplatelet regimen in these subjects). In subject implanted with Esprit, the monotherapy of either aspirin or P2Y12 inhibitor should continue indefinitely. A P2Y12 assay is recommended if, after 12 months, the subject will be on P2Y12 monotherapy instead of aspirin monotherapy.

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Subjects treated with only PTA will receive treatment with aspirin and one of the P2Y12 inhibitors (clopidogrel, prasugrel, or ticagrelor) for a minimum of one month. After one month, subjects treated with PTA treatment must receive aspirin monotherapy or one of the P2Y12 medications (clopidogrel, prasugrel, or ticagrelor) daily through 5 years of follow-up during the study (except for subjects on chronic oral anticoagulant; see paragraph below for antiplatelet regimen in these subjects). A P2Y12 assay is recommended if, after 1 month, the subject will be on P2Y12 monotherapy instead of aspirin monotherapy.

A daily aspirin dosage between ≥75 to ≤ 100 mg is strongly recommended, but 325 mg daily is also allowed. It is recommended to take a minimum of 75 mg of clopidogrel daily or 5 or 10 mg of prasugrel daily (10 mg preferred in most patients), or 90 mg twice daily of ticagrelor. Ticagrelor can be used per standard of care for countries outside the United States. For prasugrel subjects < 60 kg in weight or ≥75 years of age, a maintenance dose of 5 mg per day is allowable. Patients with prior stroke or TIA should receive clopidogrel or ticagrelor, not prasugrel.

In cases where subjects are implanted with Esprit in one lesion and treated with PTA in the second lesion, the subject will follow the medication regimen in the Esprit arm.

Subjects that were on chronic oral anticoagulants before the procedure may be maintained on oral anticoagulants plus a single antiplatelet agent for a minimum of 12 months following the procedure. After 12 months, the use of aspirin or a monotherapy of one of the P2Y12 medications (clopidogrel, prasugrel or ticagrelor) in subjects that were treated with PTA at index procedure is strongly recommended; however, per physician's discretion, subjects may be maintained on chronic oral anticoagulants alone if there is any bleeding concern. Subjects on chronic oral anticoagulants who were treated with Esprit BTK must receive aspirin or one of the P2Y12 medications (clopidogrel, prasugrel or ticagrelor) daily through 5 years follow-up and are recommended to continue aspirin or one of the P2Y12 medications indefinitely after 5 years.

These medications can be halted for medical necessity, if required, however, reporting as protocol deviation is required to document medical justification and the medication regimen must be resumed as soon as possible per physician discretion.

The start of antiplatelet medications, any changes to and termination of will be documented in the eCRF.

6.5.2. Other chronic concomitant medications

It is also highly recommended that subjects be maintained on high intensity statin or other lipid lowering agents and guideline directed anti-hypertensive therapy. The dosage for each drug shall be determined by physician per standard of care and label indication.

6.6. Discharge Plan / Assessments

Discharge is defined as the subject leaving the treating or referral hospital. Discharge will be performed per standard of care.

Subjects that smoke or use tobacco products should be asked to attend at least one tobacco cessation class. Subjects that are diabetic should be counseled on blood sugar control in which the recommended HbA1c target is < 7%.

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6.7. Follow-up Assessments

All subjects registered into the clinical investigation will have follow-up assessments, which include an office/hospital visit at the investigational center, or if necessary, to aid in follow-up compliance, an independent service may be utilized to provide in-home visits for clinical follow-up at the time points listed below. The assessments performed at each time point are listed in **Table 6.7.1-1.**

In addition, for an unscheduled visit that required re-intervention to the index limb, a duplex ultrasound for all vessels (target, non-target, and inflow vessels) of the index limb that were re-intervened on, is required within 30 days-day (±14 days) of post-reintervention.

Table 6.7.1-1: Summary of follow-up time points and assessments

Contact Period	Assessments
14 days (± 3 days)	Index wound assessment[1, *]
30 days (± 7 days)	Medications review, adverse events review, ABI/TBI measurement, functional status (Rutherford Becker), index wound assessment[1], new wound assessment[2], WIQ, PAQ, EQ-5D-5L
30 days (± 14 days)	Duplex Ultrasound[3]
42 days (± 7 days)	Index wound assessment[1, *]
90 days (± 14 days)	Medications review, adverse events review, ABI/TBI measurement, functional status (Rutherford Becker), index wound assessment[1], new wound assessment[2], WIQ, PAQ, EQ-5D-5L
180 days (± 28 days)	Duplex Ultrasound[3], medications review, adverse events review, ABI/TBI measurement, functional status (Rutherford Becker), index wound assessment[1], new wound assessment[2], WIQ, PAQ, EQ-5D-5L
1 year (± 28 days)	Duplex Ultrasound[3], medications review, adverse events review, ABI/TBI measurement, functional status (Rutherford Becker), index wound assessment[1], new wound assessment[2], WIQ, PAQ, EQ-5D-5L
2 years (± 28 days)	Duplex Ultrasound[3], medications review, adverse events review, ABI/TBI measurement, functional status (Rutherford Becker), new wound assessment[2]
3 years (± 28 days)	Duplex Ultrasound[3], medications review, adverse events review, ABI/TBI measurement, functional status (Rutherford Becker), new wound assessment[2]
4 years (± 28 days)	Medications review, adverse events review, ABI/TBI measurement, functional status (Rutherford Becker), new wound assessment[2]
5 years (± 28 days)	Medications review. adverse events review, ABI/TBI measurement, functional status (Rutherford Becker), new wound assessment[2]

[1] Index wound assessment for healing and infection will be assessed by the core laboratory through 90 days (14 days, 30 days, 42 days and 90 days). For index wounds that are not healed by 90 days, the index wound will be assessed by the core laboratory at 180 days. If the index wound is not healed by 180 days, index wound assessment by the core laboratory will be carried out at 1 year. Index wounds that have healed by 90 days will not be assessed by the core laboratory at 180 days and 1 year. A formal office visit is highly recommended at 14-day and 42-day follow-up for evaluation of index wound. The option to take wound pictures remotely at 14 days and 42 days in accordance to the core laboratory wound imaging guidelines is for subjects that are unable to complete an office visit. No wound images will be collected outside of the protocol defined timepoints.

* If a subject does not have an index wound at baseline, they will not need to return to the site at 14 days and 42 days.

[2] New wound is defined as wound below the knee in the index limb that was not identified at the time of the index procedure or wound that has recurred in the same location following the healing of the index wound. The new wound will be assessed firstly by the wound assessment core laboratory for etiology. Subsequently, the new wound will be evaluated by the site per protocol until the wound is healed through the 5-year follow-up. If a new wound is first observed at 5-year follow-up, a picture will be taken for etiology assessment by the core laboratory. As this will be the final patient visit for the trial, no additional pictures of the new wound will be required following the initial picture submitted to the core laboratory.

[3] Duplex ultrasound is required at 30 ± 14 days post-procedure, at 180 days and 1-year, 2-year and 3-year follow-up; if a patient is symptomatic or occlusion is suspected, duplex as well as angiogram should be completed.

6.7.1. Duplex Ultrasound

Lesion patency will be assessed by duplex ultrasound (DUS). Refer to the DUS core laboratory manual for detailed information.

6.7.2. Medication History

The medication history should be updated as needed to include modifications to the chronic concomitant medications and protocol required antiplatelet therapy.

6.7.3. Hemodynamic Evaluation

Ankle brachial index (ABI) measurement will be obtained for the target limb. In cases in which the ABI is above 1.4 or cannot be reliably measured, toe pressure measurement and determination of the toe brachial index (TBI) should be used.

The visit at baseline will be used to determine if a reliable ABI measurement is possible for the subject. If a reliable ABI measurement is not possible at baseline and TBI measurement was taken, then TBI measurements should be performed on the subject throughout the follow up period.

6.7.4. Functional Status

To assess a change in post-study procedure functional status Rutherford Becker Clinical Categories will be determined for the target limb.

These results will be compared to baseline measures.

6.7.5. Wound Assessment

Index wound

Any index wounds (present at baseline) in the distal ipsilateral extremity shall be assessed for healing and infection.

Pictures of index wound are only required for subjects that have a wound at the time of index procedure. This is to allow the healing of this index wound after treatment to be documented. A formal office visit is highly recommended at 14-day and 42-day follow-up for evaluation of index wound. The option to take wound pictures remotely at 14 days and 42 days in accordance to the core laboratory wound imaging guidelines is for subjects that are unable to complete an office visit.

For subjects that do not have any wound at index procedure, the 14-day and 42-day visits will not be required. These missed visits will not be classified as protocol deviation for visit not done or required testing/assessment not done at these 2 follow-ups.

During the first 90 days post-procedure, subjects are required to have wound assessments until the index wound is completely healed, as assessed by the site. At the 30-day visit, sites will assess if index wound is healed and will acquire a picture of the site of the index wound to document healing. If the index wound is healed by the 30-day visit, subjects will not be required to return for wound assessment at 42 days. This missed visit will not be classified as protocol deviation for visit not done or required testing/assessment not done at 42 days. However, all subjects that had a wound at the time of the index procedure are required to have the picture of the site of the index wound taken and assessed by the core laboratory at the 90-day follow-up even if the index wound was healed by 30-day visit. This will confirm that the index wound remains healed.

After the 90-day follow-up, pictures of the index wound are only required for subjects whose index wound was not healed by 90 days post-procedure. These subjects will have index wound pictures taken at 6 months and 1 year, as needed. However, if the index wound is healed by the 6-month visit, no picture will be required at 1-year visit unless the recurrence of the wound has occurred in the same location. No wound images will be collected outside of the protocol defined timepoints.

New wound

During the course of the trial, any new wound which is defined as wound below the knee in the index limb that was not identified at the time of the index procedure or wound that has recurred in the same location following the healing of the index wound, will be assessed firstly by the wound assessment core laboratory for etiology. Subsequently, the new wound will be evaluated by the site per protocol until the wound is healed through the 5-year follow-up. If a new wound is first observed at 5-year follow-up, a picture will be taken for etiology assessment by the core laboratory. As this will be the final patient visit for the trial, no additional pictures of the new wound will be required following the initial picture submitted to the core laboratory.

Planned minor amputation

In the case of a planned minor amputation, two pictures must be taken and sent to the core laboratory. The first picture is the identified area prior to the amputation and the second picture is the surgical site post minor amputation. If the minor amputation re-opens, it needs to be assessed as a new wound and will be sent to core laboratory for adjudication.

6.7.6. Patient Reported Outcome (PRO) Measures

The Coordinator or designee will administer patient-reported outcome questionnaires. It is important the subject understands the meaning of all words and instructions in the questionnaires. The subject should be instructed to ask any questions about the questionnaires if further explanation is needed. Once the questionnaires are completed, the Coordinator or designee will review for completeness to verify that all questions have been answered according to the directions provided.

The following PRO measures will be collected according to the CIP requirements at baseline and at each follow-up time points up to and including at 1 year (30 days, 3 months, 6 months and 1 year).

- EQ-5D-5L
- WIQ
- PAQ

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The EuroQoL 5D (EQ-5D-5L) [17] is a validated self-administered two-part instrument. The first part consists of 5 questions to assess current health state in 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). The second part is a 20 cm visual analog scale that ranges from 0 (worst imaginable health state) to 100 (best imaginable health state used to assess Overall Health Status.

The Walking Impairment Questionnaire (WIQ) [18] is a validated questionnaire used to assess patient-perceived walking performance. The self-administered questionnaire consists of 4 domains (symptom severity, walking distance, walking speed, and stair climbing) across 22 questions and takes approximately 6 minutes to complete.

The Peripheral Arterial Questionnaire (PAQ) [19] is a validated questionnaire used to assess disease-specific health status. The self-administered questionnaire consists of 5 domains (physical limitation, symptoms, quality of life, social function, and treatment satisfaction) across 20 questions and takes approximately 5 minutes to complete.

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6.7.7. Schedule of Events

PROCEDURE/TEST	Baseline (within 30 days prior to index procedure)	Pre-Procedure (within 24 hours)	Procedure	Post-Procedure	14 days (± 3 d) office visit/ remote index wound image*	30 days (± 7 d) office visit*	30 days (± 14 d) office visit*	42 days (± 7 d) office visit/ remote index wound image*	90 days (± 14 d) office visit*	180 days (± 28 d) office visit*	1 yr (± 28 d) office visit*	2yrs (± 28 d) office visit*	3 yrs (± 28 d) office visit*	4 yrs (± 28 d) office visit*	5 yrs (± 28 d) office visit*	Unscheduled visits
Subject Medical/Clinical History (Age, Sex, Risk Factors)	✓															
Subject Informed Consent (Must be obtained prior to any study related testing or procedures)[1]	✓															
General Inclusion/Exclusion Criteria	✓															
Anatomic Inclusion/Exclusion Criteria[2]	✓	✓	✓													
Pregnancy Test (if applicable)[3]	✓															
Hematology and blood chemistry[4]	✓															
Vascular Angiogram, IVUS[5]	✓		✓													✓
Duplex Ultrasound[6]							✓			✓	✓	✓	✓			✓
ABI/TBI measurement[7]	✓	✓				✓			✓	✓	✓	✓	✓	✓	✓	✓
Study device information			✓													
Per Protocol Medications		✓	✓	✓		✓			✓	✓	✓	✓	✓	✓	✓	✓
Concomitant Medications	✓		✓	✓		✓			✓	✓	✓	✓	✓	✓	✓	✓
Adverse Events			✓	✓		✓			✓	✓	✓	✓	✓	✓	✓	✓
Patient Reported Outcome Instruments (WIQ, PAQ, EQ-5D-5L)	✓					✓			✓	✓	✓					
Rutherford Becker category assessment	✓					✓			✓	✓	✓	✓	✓	✓	✓	✓
Index wound assessment[8]	✓			✓	✓	✓		✓	✓	✓	✓					✓
New wound assessment[9]						✓			✓	✓	✓	✓	✓	✓	✓	✓

[1] Informed consent can be obtained any time prior to study related procedure.
[2] Anatomic inclusion/exclusion criteria can be verified at baseline during a diagnostic catheterization and/or pre-procedure; some of the criteria need to be verified during the procedure.

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[3] Pregnancy test (if applicable) must be conducted within 7 days prior to the procedure.
[4] For complete list of tests, refer to section 6.1.7 (Laboratory Assessments). Baseline laboratory assessments must be obtained for all subjects within 30 days prior to index procedure, and these results must be entered in the electronic case report form. However, if it is not possible to undertake the laboratory assessments 30 days prior to the index procedure, laboratory results longer than 30 days prior to index procedure are acceptable, and these results can be used per physician's discretion to confirm patient's eligibility.
[5] Angiogram to confirm eligibility criteria can be done within 30 days prior to index procedure or during the procedure, as long as it is carried out prior to randomization of the patient. IVUS should only be captured if it is the standard-of-care of the site PI to use IVUS in his/her patients in this population.
[6] Duplex ultrasound is required at 30 days ± 14 days post-procedure, at 180 days, and at 1, 2 and 3 years; if a patient is symptomatic or occlusion is suspected, duplex as well as angiogram should be completed. Additionally, a duplex ultrasound must be completed within 30 days (±14 days) post-reintervention to the index limb.
[7] While ABI/TBI measurement is listed at both "baseline" and "pre-procedure" time points, this measurement only needs to occur once before the procedure (either at baseline or at pre-procedure time point).

[8]Index wound needs to be assessed before the procedure to confirm patient eligibility (ischemic arterial wound). If the picture of the wound was taken within 7 days prior to index procedure, the picture does not need to be repeated the day of index procedure. If the picture was taken > 7 days prior to index procedure, a second picture must be taken the day of index procedure and can be taken up to 24 hours post-procedure. In cases where picture is taken on the day of index procedure, baseline will be defined as "within 24 hours post-procedure". Index wound assessment for healing and infection will be assessed by the core laboratory through 90 days (14 days, 30 days, 42 days and 90 days). For index wounds that are not healed by 90 days, the index wound will be assessed by the core laboratory at 180 days. If the index wound is not healed by 180 days, index wound assessment by the core laboratory will be carried out at 1 year. Index wounds that have healed by 90 days will not be assessed by the core laboratory at 180 days and 1 year. A formal office visit is highly recommended at 14-day and 42-day follow-up for evaluation of index wound. The option to take wound pictures remotely at 14 days and 42 days in accordance to the core laboratory wound imaging guidelines is for subjects that are unable to complete an office visit. No wound images will be collected outside of the protocol defined timepoints.

[9] New wound is defined as wound below the knee in the index limb that was not identified at the time of the index procedure or wound that has recurred in the same location following the healing of the index wound. The new wound will be assessed firstly by the wound assessment core laboratory for etiology. Subsequently, the new wound will be evaluated by the site per protocol until the wound is healed through the 5-year follow-up. If a new wound is first observed at 5-year follow-up, a picture will be taken for etiology assessment by the core laboratory. As this will be the final patient visit for the trial, no additional pictures of the new wound will be required following the initial picture submitted to the core laboratory. The 14-day and 42-day visits are not required for subjects with new wounds.

* To aid in follow-up compliance, if necessary, an independent service may be utilized to provide in-home visits for clinical follow-up.

6.8. Requirement for Clinical Laboratories

The following core laboratories will be used in this clinical investigation, for independent evaluation of the clinical investigation data:

- Angiographic core laboratory will be used for analysis of angiographies associated with baseline, index procedure and adverse events
- IVUS core laboratory will be used for analysis of intravascular images associated with baseline, index procedure and adverse events
- Duplex ultrasound core laboratory will be used at each follow-up time points, as described in the schedule of events above
- Wound assessment core laboratory will be used for analysis of wounds, as described in section 6.7.5 Wound Assessment.
- OCT core laboratory will be used for analysis of intravascular images captured using OCT (for sites that are experienced).

6.8.1. Health Economic Data Collection

Data on resource utilization will be collected prospectively for the index hospitalization and the full follow-up period using standardized case report forms. Procedural costs will be assessed using a resource-based approach to convert standard measures such as procedural duration and device utilization (e.g., scaffolds, balloons, guidewires, etc.) into costs. Other hospital costs will be assessed using an "event-driven" approach in which specific complications and outcomes are assigned standard costs based on external data. Additional costs will be assigned for follow-up hospitalizations and repeat revascularization procedures, emergency room visits, outpatient diagnostic testing, and cardiovascular medications. In each case, costs will be assessed from the perspective of the U.S. healthcare system.

Cost and quality of life data will be used to perform a cost-effectiveness analysis from the perspective of the U.S. healthcare system.

7.0 ADVERSE EVENTS

To comply with worldwide standards and guidelines on clinical investigation adverse event reporting, the Sponsor has adopted uniform and worldwide applicable standard definitions and reporting timelines to be used and adhered to by the investigators.

7.1. Definition

7.1.1. Adverse Event

An adverse event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons in the context of a clinical investigation, whether or not related to the investigational medical device.

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As part of ISO14155 Section 3.2, the Adverse Event definition has the following notes:

Note 1: This definition includes events related to the investigational medical device or the comparator.

Note 2: This definition includes events related to the procedures involved.

Note 3: For users or other persons, this definition is restricted to events related to medical devices under investigation.

7.1.2. Serious Adverse Event

Serious Adverse Event is an AE that led to any of the following:

a). death,

b). serious deterioration in health of the subject, that resulted in any of the following:

1. life-threatening illness or injury,

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

3. hospitalization or prolongation of patient hospitalization

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

5. chronic disease

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

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

7.1.3. Device Deficiency/Device Malfunction

Device deficiency is defined as any inadequacy in the identity, quality, durability, reliability, usability, safety or performance of an investigational device including malfunction, use errors or inadequacy in the information supplied by the manufacturer including labeling.

Note 1: The definition includes the device deficiencies related to the investigational medical device or comparator.

Note 2: Cyber-security incidents related to the investigational product, shall be reported as device deficiencies

A device malfunction is the failure of an investigational device to perform in accordance with its intended purpose when used in accordance with the instructions for use or CIP, or IB.

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7.2. Device Relationship

Determination of whether there is a reasonable possibility that an investigational product or device under investigation caused or contributed to an AE is to be determined by the Investigator and recorded on the appropriate CRF form. Determination should be based on assessment of temporal relationships, evidence of alternative etiology, medical/biologic plausibility, and patient condition (pre-existing condition).

7.2.1. Unanticipated (Serious Adverse) Device Effect [U(S)ADE]

Unanticipated serious adverse device effect (USADE) refers to any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

7.2.2. Serious Health Threat

Serious Health Threat is a signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in subjects, users or other persons, and that requires prompt remedial action for other subjects, users or other persons

Note: This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.

7.3. Adverse Event and Device Deficiency/Device Malfunction Reporting

7.3.1. Adverse Event (AE) Reporting

General AE Reporting

Safety surveillance and AE reporting, for all randomized subjects, starts when the guiding catheter enters the subject's vasculature. Safety surveillance and reporting will continue until the last follow-up visit has been performed, the subject is deceased, the subject concludes participation in the clinical investigation or the subject withdraws from the clinical investigation. Adverse event data, including deaths and device deficiency data, will be collected throughout the time period defined above and will be reported to the Sponsor on a CRF. Additional information with regards to an adverse event should be updated within the appropriate CRF.

Unchanged, chronic, non-worsening or pre-existing conditions are not AEs and should not be reported.

An offline form will be made available to allow the investigator to report SAEs in the event the entry cannot be made in the EDC. This does not replace the EDC reporting system. All information must still be entered in the EDC system as soon as feasible.

All adverse events will be collected on each subject through the 1-year follow-up visit. After 1-year, only the following will be collected:

- All serious AEs. This includes deaths, arterial thrombosis (including occlusion), any amputation, major limb re-intervention, any revascularization of the target limb.
- All trial device-related events and events for which the relationship to the trial device is unknown
- All unanticipated adverse device effects
- New wound on the index limb

In addition, the following adverse events will be collected:

- Revascularization, including the use of bail-out device during the index procedure
- Stent/scaffold thrombosis
- Occlusion or stenosis of 50% or more of the target vessel

Abnormal laboratory values, in themselves, will not be considered AEs unless:

- The investigator determined that the value is clinically significant.
- The abnormal laboratory value required intervention, or
- The abnormal laboratory value required subject withdrawal from the clinical investigation.

SAE Reporting

The investigator should report all SAEs to the Sponsor as soon as possible but no later than outlined below.

Clinical Site	Reporting timelines
All Sites	SAEs must be reported to the Sponsor no later than 3 calendar days from the day the site personnel became aware of the event or as per the investigative site's local requirements, if the requirement is more stringent than those outlined.

The date the site staff became aware the event met the criteria of an SAE must be recorded in the source document. The Investigator will further report the SAE to the local IRB/EC according to the institution's IRB/EC reporting requirements.

7.3.2. Unanticipated Serious Adverse Device Effect Reporting to Sponsor and IRB

The Sponsor requires the Investigator to report any USADE to the Sponsor within 3 calendar days of the investigator's knowledge of the event, unless local requirements are more stringent, and to the IRB/EC per IRB/EC requirements.

7.3.3. Device Deficiency/Malfunction Reporting

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All device deficiencies/malfunctions for the investigational device should be reported on the appropriate CRF form.

The investigator should report all device deficiencies/malfunctions to the Sponsor as soon as possible but no later than outlined below.

Clinical Sites	Reporting timelines
All Sites	Device deficiencies/malfunctions must be reported to the Sponsor no later than 3 calendar days from the day the site personnel became aware of the event or as per the investigative site's local requirements, if the requirement is more stringent than those outlined.

The device, if not implanted or not remaining in the subject, should be returned to the Sponsor.

Device deficiencies/malfunctions should be reported to the IRB/EC per the investigative site's local requirements.

An offline form will be made available to allow the investigator to report device deficiencies/malfunctions in the event that the entry cannot be made in the EDC system. This does not replace the EDC reporting system. All information must still be entered in the EDC system as soon as feasible.

In case a device deficiency/malfunction occurred before the subject ID and/or randomization number has been assigned, the device deficiency should be reported to the Sponsor via the offline reporting form.

7.3.4. Adverse Event Reporting to Country Regulatory Authorities by the Sponsor

The Sponsor will report SAEs and reportable device deficiencies/malfunctions to the country regulatory authority, per local requirements.

Note: Reportable device deficiencies/malfunctions include device deficiencies/malfunctions that might have led to an SAE if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate. These are handled under the SAE reporting system.

8.0 STATISTICAL CONSIDERATIONS

The following section describes the statistical methods for the clinical investigation. [redacted].

8.1.1. Intent-to-Treat Population (ITT)

[redacted]

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8.1.2. As-Treated Population (AT)

[redacted]

8.1.3. Per-Protocol Population (PP)

[redacted]

- [redacted]

[redacted]

- [redacted]

This is the secondary analysis population for the primary endpoint analysis.

8.2. Statistical Analyses

8.2.1. Primary Endpoint(s) Analyses

The primary efficacy endpoint, a composite of limb salvage and primary patency at 1 year , will be evaluated using the difference in endpoint rates in the ITT population. The hypothesis test is designed to show superiority of Esprit BTK to PTA for the primary efficacy endpoint with one-sided alpha of 0.025. The null (H_0) and alternative (H_1) hypotheses are:

$$H_0: \ P_{BTK} - P_{PTA} \leq 0$$
$$H_1: \ P_{BTK} - P_{PTA} > 0$$

where P_{BTK} and P_{PTA} are the primary efficacy endpoint rates for the Esprit BTK arm and PTA arm respectively.

A sensitivity analysis for the primary efficacy endpoint will be performed for the AT, modified AT and PP populations.

The primary safety endpoint, will be evaluated using the difference in endpoint rates in the AT population. The hypothesis test is designed to show non-inferiority of Esprit BTK to PTA for the primary safety endpoint with one-sided alpha of 0.025. The null (H_0) and alternative (H_1) hypotheses are:

$$H_0: \ q_{BTK} - q_{PTA} \leq \delta$$
$$H_1: \ q_{BTK} - q_{PTA} > \delta$$

where q_{BTK} and q_{PTA} are the primary safety endpoint rates for the Esprit BTK arm and PTA arm, respectively. The non-inferiority margin of δ is set at -0.1.

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A sensitivity analysis for the primary safety endpoint will be performed for the modified AT, ITT and PP populations. In addition, landmark Kaplan-Meier analyses will be performed for the primary safety and efficacy endpoints from 0 to 30 days, 30 days to 6 months, and 30 days to 1 year.

[redacted]

[redacted]

[redacted]

8.2.2. Powered Secondary Endpoints Analysis

The first powered secondary endpoint, binary restenosis of target lesion at 1 year, will be evaluated using the difference in endpoint rates in the ITT population at 1 year. The hypothesis test is designed to show superiority of Esprit BTK to PTA with one-sided alpha of 0.025.

The null (H_0) and alternative (H_1) hypotheses are:

$$H_0: \ R_{BTK} - R_{PTA} \geq 0$$
$$H_1: \ R_{BTK} - R_{PTA} < 0$$

where R_{BTK} and R_{PTA} are the first secondary endpoint rates for the Esprit BTK and PTA arms respectively.

The second powered secondary endpoint, a composite of freedom from: above ankle amputation in index limb, 100% total occlusion of target vessel and CD-TLR. The hypothesis test is designed to show superiority of Esprit BTK to PTA with one-sided alpha of 0.025.

The null (H_0) and alternative (H_1) hypotheses are:

$$H_0: \ S_{BTK} - S_{PTA} \leq 0$$
$$H_1: S_{BTK} - S_{PTA} > 0$$

where S_{BTK} and S_{PTA} are the second secondary endpoint rates for the Esprit BTK and PTA arms respectively.

[redacted]

8.2.3. Descriptive Secondary Endpoints Analyses

Secondary endpoints will be summarized descriptively for the ITT population. For further details refer to the statistical analysis plan (SAP).

8.3. Sample Size Calculation and Assumptions

8.3.1. Sample Size Calculation and Assumptions for Primary Endpoints

[redacted]

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For the primary efficacy endpoint, [redacted] The power calculation is based on the statistical hypotheses and the following assumptions:

$$H_0: \ P_{BTK} - P_{PTA} \leq 0$$
$$H_1: \ P_{BTK} - P_{PTA} > 0$$

- One-sided type I error rate = 0.025
- Randomization ratio is 2:1 (Esprit BTK vs. PTA)
- [redacted]
- Superiority test

[redacted]

For the primary safety endpoint, [redacted] The power calculation is based on the statistical hypotheses and the following assumptions:

$$H_0: \ q_{BTK} - q_{PTA} \leq \delta$$
$$H_1: \ q_{BTK} - q_{PTA} > \delta$$

- One-sided non-inferiority test
- One-sided type I error rate = 0.025
- Randomization ratio is 2:1 (Esprit BTK vs. PTA)
- [redacted]
- Non-inferiority margin (δ) of -10%

[redacted]

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[redacted]

8.3.2. Assumptions for Powered Secondary Endpoints

For the first powered secondary endpoint of target lesion binary restenosis at 1 year, the binary restenosis will be determined as the presence of a hemodynamically significant restenosis ≥ 50% by angiography, or PSVR ≥ 2.0 by duplex ultrasound.

The power calculation is based on the statistical hypotheses and the following assumptions:

$$H_0: \ R_{BTK} - R_{PTA} \geq 0$$
$$H_1: \ R_{BTK} - R_{PTA} < 0$$

- One-sided type I error rate = 0.025
- Randomization ratio is 2:1 (Esprit BTK vs. PTA)
- [redacted]
- Superiority test

[redacted]

For the second powered secondary endpoint of freedom from: above ankle amputation in index limb, 100% total occlusion of target vessel and CD-TLR at 1 [redacted]

The power calculation is based on the statistical hypotheses and the following assumptions:

$$H_0: \ S_{BTK} - S_{PTA} \leq 0$$
$$H_1: \ S_{BTK} - S_{PTA} > 0$$

- One-sided type I error rate = 0.025
- Randomization ratio is 2:1 (Esprit BTK vs. PTA)

[redacted]

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- [redacted]
- Superiority test

[redacted]

[redacted]

[redacted]

8.4. Timing of Analysis

The primary endpoint analysis will be performed when all subjects in ITT population have completed their 1-year follow-up visit and the clinical investigation becomes unblinded.

8.5. Subgroup Analysis

Subgroup analyses will be performed per gender, race, and age. [redacted]

8.6. Multiplicity

[redacted]

8.7. Planned Interim Analysis

[redacted]

8.8. Statistical Criteria for Termination

There are no statistical criteria for termination of this clinical investigation.

8.9. Success Criteria

[redacted]

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8.10. Deviations from Statistical Plan

Any major changes to the statistical plan will be documented in an amendment to the statistical analysis plan. Less significant changes to the planned analyses will be documented in the final report.

9.0 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator/institution will permit direct access to source data/documents for the purpose of performing clinical investigation-related monitoring, audits, IRB/EC review and regulatory inspections.

Subjects providing informed consent are agreeing to allow clinical investigation monitors or regulatory authorities including foreign countries to review, in confidence, any records identifying the subjects in this clinical investigation. This information may be shared with regulatory agencies; however, Sponsor undertakes not to otherwise release the subject's personal and private information.

10.0 QUALITY CONTROL AND QUALITY ASSURANCE

10.1. Selection of Clinical Sites and Investigators

The Sponsor will select investigators qualified by training and experience to participate in the clinical investigation. Sites will be selected based upon review of a recent site assessment, if applicable, and the qualifications of the investigators who will participate in the clinical investigation.

10.2. Site Principal Investigator Responsibilities

The role of the Site Principal Investigator is to implement, oversee the management of the day-to-day conduct of the clinical investigation as well as ensure data integrity and the rights, safety and well-being of the subjects involved in the clinical investigation. The principal investigator shall support monitoring and reporting to IRB/EC and local competent authorities as necessary, throughout the conduct of the clinical investigation.

The principal investigator is responsible for ensuring adequate training and qualification of the investigation site team and for maintaining oversight of their activities. The principal investigator may delegate tasks to members of the investigation site team but retains responsibility for the clinical investigation. This also applies when activities are outsourced to an external organization by the principal investigator in which case he/she shall exercise oversight to ensure the integrity of all tasks performed and any data generated by this external organization.

10.3. Clinical Investigation Finances and Agreements

The clinical investigation will be financed by Abbott. Investigational sites will be compensated by Abbott for participation in the clinical investigation per the conditions of agreement between the Sponsor and the Investigational site.

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10.4. CIP Amendments

Approved CIP amendments will be provided to the Investigators by the Sponsor prior to implementing the amendment. The Principal Investigator is responsible for notifying the IRB/EC or equivalent committee of the CIP amendment (administrative changes) or obtaining IRB's/EC's approval of the CIP amendment (changes in subject care or safety), according to the instructions provided by the Sponsor with the CIP amendment.

Acknowledgement/approval by the IRB/EC of the CIP amendment must be documented in writing prior to implementation of the CIP amendment. Copies of this documentation must also be provided to the Sponsor.

10.5. Training

10.5.1. Site Training

All Investigators and clinical investigation personnel are required to attend Sponsor training sessions, which may be conducted at an Investigator's meeting, a site initiation visit, or other appropriate training sessions. Over-the-phone or self-training may take place as required. Training of Investigators and clinical investigation personnel will include, but is not limited to, the CIP requirements, investigational device usage, electronic case report form completion and clinical investigation personnel responsibilities. All Investigators and clinical investigation personnel that are trained must sign a training log (or an equivalent) upon completion of the training. Prior to signing the training log, Investigators and clinical investigation personnel must not perform any CIP-related activities that are not considered standard of care at the site.

10.5.2. Training Required for the Use of the Device

All physicians will be trained on the use of the device, as per the training plan described in the physician's training materials. Proof of training will be documented and stored in the appropriate archiving system.
Additionally, each physician will have to provide images, from a requested number of their standard of care cases, to the core laboratory for analysis before being allowed to enroll in the trial.

10.6. Monitoring

Sponsor and/or designee will monitor the clinical investigation over its duration according to the CIP-specific monitoring plan which will include the planned extent of source data verification.

Prior to initiating any procedure, the Sponsor monitor (or delegate) will ensure that the following criteria are met:

- The investigator understands and accepts the obligation to conduct the clinical investigation according to the CIP and applicable regulations, and has signed the Investigator Agreement (for US clinical sites) or the Clinical Trial Agreement (for OUS clinical sites).
- The Investigator and his/her staff should have sufficient time and facilities to conduct the clinical investigation and should have access to an adequate number of appropriate subjects to conduct the clinical investigation.

- Source documentation (including original medical records) must be available to substantiate proper informed consent procedures, adherence to CIP procedures, adequate reporting and follow-up of adverse events, accuracy of data collected on case report forms, and device information.

- The Investigator/site will permit access to such records. A monitoring visit sign-in log will be maintained at the site. The Investigator will agree to dedicate an adequate amount of time to the monitoring process. The Investigator and/or research coordinator will be available for monitoring visits. It is expected that the Investigator will provide the monitor with a suitable working environment for review of clinical investigation-related documents.

10.7. Deviations from CIP

The Investigator should not deviate from the CIP for any reason except in cases of medical emergencies when the deviation is necessary to protect the rights, safety and well-being of the subject or eliminate an apparent immediate hazard to the subject. In that event, the Investigator will notify Sponsor immediately by phone or in writing.

No waivers for CIP deviations will be granted by the Sponsor. All deviations must be reported to the Sponsor using the Deviation CRF. The occurrence of CIP deviations will be monitored by the Sponsor for evaluation of investigator compliance to the CIP and regulatory requirements and dealt with according to written procedures. Investigators will inform their IRB/EC or equivalent committee of all CIP deviations in accordance with their specific IRB/EC or equivalent committee reporting policies and procedures.

In the event of repeated non-compliance, as determined by the Sponsor, a Sponsor's monitor or company representative will attempt to secure compliance by one or more of the following (and not limited to):

- Visiting the investigator and/or delegate

- Telephoning the investigator and/or delegate

- Corresponding with the investigator and/or delegate

Repeated non-compliance with the signed agreement, the CIP or any other conditions of the clinical investigation may result in further escalation in accordance with the Sponsor's written procedures, including securing compliance or, at its sole discretion, Sponsor may terminate the investigator's participation in the clinical investigation.

The following categories of protocol deviations will be considered major:

- Informed Consent deviation

- Eligibility deviation (General/Anatomic)

- Serious adverse event reporting deviation

- Treatment/procedure compliance deviation

- Registration/randomization

- Unauthorized personnel performing study related procedures
- Missing data
- Missed visit

Other types of deviations will be considered minor.

10.8. Quality Assurance Audit

A Sponsor representative or designee may request access to all clinical investigation records, including source documentation, for inspection during a Quality Assurance audit.

In the event that an investigator is contacted by a Regulatory Agency in relation to this clinical investigation, the Investigator will notify the Sponsor immediately. The Investigator and Research Coordinator must be available to respond to reasonable requests and audit queries made during the audit process. The Investigator must provide Sponsor with copies of all correspondence that may affect the review of the current clinical investigation (e.g., Form FDA 483, Inspectional Observations, Warning Letters, Inspection Reports, etc.). The Sponsor may provide any needed assistance in responding to regulatory audits.

10.9. Sponsor Auditing

The Sponsor shall prepare an audit plan as well as the operating procedures for the related duties, and conduct audits in accordance with the audit plan and the operating procedures.

- Individual engaged in auditing (hereinafter referred to as "auditor") shall be different than those in charge of medical device development or monitoring.
- The auditor shall prepare an audit report documenting the matters confirmed in the audit to certify and verify that the audit has been conducted, and submit them to the Sponsor.

10.10. Committees

10.10.1. Steering Committee

The Steering Committee is assigned by the Sponsor and consists of investigators. The Sponsor will also be represented on the committee. The Chairman of the core laboratories and other sponsor's personnel may also participate in the Committee meetings if appropriate. Meeting minutes from this committee will be filed with the sponsor.

The Steering Committee is responsible for overseeing the scientific and operational aspects of the clinical investigation. This committee will meet regularly to monitor subject enrollment, general data collection and non-compliance with the CIP at individual centers, to review and act upon recommendations of the Data Monitoring Committee (DMC), also known as Data and Safety Monitoring Board (DSMB), to review operational issues that may arise and warrant a CIP amendment or other corrective action and to determine policy regarding any publications arising from data generated from the performance of the clinical investigation.

10.10.2. Publications Committee

A Publication Committee shall be established to oversee clinical investigations publications, including publication planning and authorship determinations. Publication Committee membership may include members of the Steering Committee, Principal Investigators, a representative of the Sponsor and a statistician. The Publication Committee will determine policy and strategies regarding individual presentations and/or publications arising from clinical investigation generated data. The committee will also review all external requests for accessing clinical investigation-related data and strategies aligning with the Sponsor's presentation and publication team expectations. The committee will also follow the Sponsor's applicable policies and Standard Operating Procedures.

10.10.3. Data Monitoring Committee (DMC)

The Data Monitoring Committee (DMC), also known as Data and Safety Monitoring Board (DSMB), is an independent multidisciplinary group restricted to individuals free of apparent significant conflicts of interest. The source of these conflicts may be financial, scientific, or regulatory in nature. The DMC is typically composed of at least two physicians with experience relevant to the clinical investigation and a biostatistician.

The DMC will serve in an advisory role to the Sponsor to ensure safety by reviewing cumulative data from the clinical investigation at prescribed intervals for the purpose of safeguarding the interests of enrolled subjects and those patients yet to be enrolled, as well as the continuing validity and scientific merit of the clinical investigation. The composition, frequency of the meetings and the statistical monitoring guidelines are described in detail in the DMC charter.

The DMC may consider a recommendation for modifications or termination of the clinical investigation based on any perceived safety concerns regardless of statistical significance. The recommendations of the DMC are not binding, and all final decisions related to clinical investigations modifications rest with the Sponsor.

10.10.4. Clinical Events Committee (CEC)

The Clinical Events Committee (CEC) is an independent adjudication body comprised of qualified physicians who are not participants in the clinical investigation. The CEC will review and adjudicate pre-specified events reported by investigators or identified by Safety personnel for the clinical investigation as defined in the CEC charter and according to definitions provided in this CIP.

11.0 DATA HANDLING AND RECORD KEEPING

Sponsor and/or its affiliates will maintain documentation of the systems and procedures used in data collection for the duration of the clinical investigation.

CRF data collection will be performed through a secure web portal and only authorized personnel will access the Electronic Data Capture (EDC) system using a unique username and password to enter, review or correct data. Passwords and electronic signatures will be strictly confidential.

The data will be subjected to consistency and validation checks within the EDC system and supplemental review by the Sponsor.

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At the conclusion of the clinical investigation, completed CRF images with the date-and-time stamped electronic audit trail indicating the user, the data entered, and any reason for change (if applicable) will be provided to the investigational sites.

For the duration of the clinical investigation, the Investigator will maintain complete and accurate documentation including, but not limited to, medical records, clinical investigation progress records, laboratory reports, CRFs, signed ICFs, device accountability records, correspondence with the IRB/EC and clinical investigation monitor/Sponsor, adverse event reports, and information regarding subject discontinuation or completion of the clinical investigation.

11.1. Protection of Personally Identifiable Information

The Sponsor respects and protects personally identifiable information collected or maintained for this clinical investigation.

The Sponsor implements technical and physical access controls to ensure that Personal Information is accessible only to and processed only on a 'need to know' basis, including periodic review of access rights, and revocation of access when an individual's employment is terminated or the individual transitions to a role that does not require access to Personal Information, and appropriate restrictions on physical access to premises, facilities, equipment, and records containing Personal Information.

The Sponsor requires the investigational sites to enter only pseudonymous Personal Information (key-coded) necessary to conduct the Clinical Investigation, such as the patient's medical condition, treatment, dates of treatment, etc., into Sponsor's data management systems. The Sponsor discloses as part of the clinical investigation informed consent process that some Sponsor representatives still may see Personal Information at the participating sites for technical support of the participating physicians on the device implant or procedures, monitoring and quality control purposes. All parties will observe confidentiality of Personal Information always throughout the clinical investigation. All reports and data publications will preserve the privacy of each subject and confidentiality of his/her information.

The Sponsor data management systems and processes were designed, developed, and tested according to industry standards to appropriately safeguard Confidential Information (including any Personal Information) against unauthorized access and/or interference by third parties, intrusion, theft, destruction, loss or alteration. Clinical Investigation data are encrypted in transit and at rest.

The Sponsor maintains a Privacy Incident procedure that complies in all respects with Applicable Law and industry best practices.

11.2. Data Management Plan

A Data Management Plan (DMP) will describe procedures used for data review, data cleaning, and issuing and resolving data discrepancies. If appropriate, the DMP may be updated throughout the duration of the clinical investigation. All revisions will be tracked and document controlled.

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11.3. Source Documentation

Regulations and GCP require the Investigator to maintain information in the subject's original medical records that corroborates data collected on the CRFs. In order to comply with these regulatory requirements/GCP, the following information should be included in the subject record at a minimum and if applicable to the clinical investigation:

- Medical history/physical condition of the subject before involvement in the clinical investigation sufficient to verify CIP entry criteria
- Dated and signed notes on the day of entry into the clinical investigation referencing the Sponsor, CIP number, subject ID number and a statement that informed consent was obtained
- Dated and signed notes from each subject visit (for specific results of procedures and exams)
- Adverse events reported and their resolution, including supporting documents, such as discharge summaries, catheterization laboratory reports, ECGs, and lab results including documentation of site awareness of SAEs and of investigator assessment of device relationship for SAEs.
- CIP-required laboratory reports, reviewed and annotated for clinical significance of out-of-range results.
- Notes regarding CIP-required and prescription medications taken during the clinical investigation (including start and stop dates)
- Subject's condition upon completion of or withdrawal from the clinical investigation
- Any other data required to substantiate data entered into the CRF
- Patient reported outcome measures may be completed using CRF worksheets. These serve as the source documentation.

11.4. Electronic Case Report Form Completion

Primary data collection based on source-documented hospital and/or clinic chart reviews will be performed clearly and accurately by site personnel trained on the CIP and eCRF completion. The investigator will ensure accuracy, completeness, legibility and timeliness of the data reported to the Sponsor on the eCRFs and in all required reports. eCRF data will be collected for all subjects that are registered into the trial.

Only authorized site personnel will be permitted to enter the eCRF data through the EDC system deployed by the Sponsor. An electronic audit trail will be used to track any subsequent changes of the entered data.

11.5. Record Retention

The Sponsor and Investigator/Site will archive and retain all documents pertaining to the clinical investigation as per the applicable regulatory record retention requirements. The Investigator must obtain

permission from Sponsor in writing before destroying or transferring control of any clinical investigation records.

11.6. Investigational Devices Accountability

The Sponsor ships investigational products (Esprit BTK) only to the Principal Investigator (the responsible leader of the investigational site) or his/her legal designee of each site, after sites receive documentation of site activation and shipping authorization is complete.

The Investigator or an authorized designee must maintain adequate records of the receipt and disposition of each investigational device, including part number, batch number, and serial number (if applicable), date used, subject identification, and treating physician.

Storage locations for the devices at investigational sites must be locked with access restricted only to investigators and authorized personnel.

Inventory Accountability Log supplied by the Sponsor will be used. The Inventory Accountability Log must document the disposition of all investigational devices including those that have been returned to Sponsor.

All investigational devices that are associated with a device failure or device deficiency must be returned immediately to the Sponsor.

12.0 ETHICAL CONSIDERATION

12.1. Institutional Review Board/Medical Ethics Committee Review and Approval

Institutional Review Board (IRB)/ Ethics Committee (EC) approval for the CIP and ICF/other written information provided to the patient will be obtained by the Principal Investigator at each investigational site prior to consenting and enrolling patients in this clinical investigation. The approval letter must be received prior to the start of this clinical investigation and a copy must be provided to the Sponsor.

Any amendments to the CIP as well as associated ICF changes will be submitted to the IRB/EC/Competent Authority and written approval obtained prior to implementation, according to each institution's IRB/EC requirements.

No changes will be made to the CIP or ICF or other written information provided to the patient without appropriate approvals, including IRB/EC, the Sponsor, and the regulatory agencies (if applicable).

Until the clinical investigation is completed, the Investigator will advise his/her IRB/EC of the progress of this clinical investigation, per IRB/EC requirements. Written approval must be obtained from the IRB/EC yearly to continue the clinical investigation, or according to each institution's IRB/EC requirements.

No investigative procedures other than those defined in this CIP will be undertaken on the enrolled subjects without the written agreement of the IRB/EC and the Sponsor.

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13.0 CLINICAL INVESTIGATION COMPLETION

The clinical investigation will end when the last visit of the last subject enrolled has been completed.

The clinical investigation will be concluded when:

- All sites are closed AND
- The final report has been provided to investigators or the Sponsor has provided formal documentation of clinical investigation closure.

14.0 PUBLICATION POLICY

The data and results from the clinical investigation are the sole property of the Sponsor. The Sponsor shall have the right to access and use all data and results generated during the clinical investigation. The Investigators will not use this clinical investigation-related data without the written consent of the Sponsor for any purpose other than for clinical investigation completion or for generation of publication materials, as referenced in the Clinical Trial Agreement. Single-center results are not allowed to be published or presented before the multi-center results. Any proposals for publications or presentations by the investigators must be reviewed and approved by the Sponsor in a timely manner to enable Sponsor review in compliance with the Sponsor's publication policy set forth in the Clinical Trial Agreement.

This clinical investigation is registered on ClinicalTrials.gov (NCT04227899). A full report of the pre-specified outcomes, including any negative outcomes, will be made public through the ClinicalTrials.gov website no later than 12-months after clinical trial completion, as required by section 801 of the FDA Amendments Act. If this clinical investigation is terminated early for safety, the Sponsor will make every effort to hasten the release of the pre-specified outcomes through the ClinicalTrials.gov website.

15.0 RISK ANALYSIS

15.1. Anticipated Clinical Benefits

Treatment options for peripheral artery disease are few, with PTA being the only approved dilatation device for use in BTK arteries in the United States. Although acute clinical outcomes with PTA are acceptable, clinical studies have consistently shown that this treatment strategy is not durable, as evidenced by progressive reduction in patency in the months following the intervention. Given the limitations of PTA, amputation and re-interventions are common clinical sequelae. These shortcomings of PTA underscore the need for lumen stabilization to improve its mechanical results and reduce the debilitating and devastating outcomes that can result from unsuccessful PTA treatment.

Esprit BTK offers the potential to address an unmet medical need for treatment of BTK lesions given the poor treatment options available today. As described in **Section 1.1.1**, the Absorb BVS, which is the predecessor of Esprit BTK, has shown lasting clinical benefit in BTK evaluations, with high rates of patency at 1 year, which were maintained at 3 years. The Absorb BTK results from the Varcoe and Xue/Kum studies are consistent with XIENCE BTK treatment, showing that everolimus elution is effective across multiple platforms. There is a realistic expectation of patient benefit with fewer repeat procedures with Esprit BTK given the growing body of clinical evidence with Absorb BVS.

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Given the above unmet needs, Esprit BTK offers the following potential benefits: 1) potential for superior outcomes to PTA by scaffolding the treated segment for prevention of acute recoil; 2) eluting everolimus to prevent arterial re-narrowing 3) preserving long term treatment options for the target vessel since the scaffold resorbs over time

15.2. Foreseeable Adverse Events and Anticipated Adverse Device Effects

Risks associated with the Esprit BTK and the procedure, together with their likely incidence, are described in the IFU and **Appendix V**. There may be risks related to the device under investigation that are unknown at present. Likewise, the exact frequency of the risk may be unknown.

15.3. Residual Risks Associated with the Device Under Investigation, as Identified in the Risk Analysis Report

The residual risks to the patient were identified from literature review or the complaint data review.

Risk analysis of the Esprit BTK device has been performed in accordance with the Risk Management Plan (Ref: [redacted]) and the Failure Mode Effect Analysis (FMEA) (Ref: [redacted]) to systemically identify potential hazards associated with the design and use of this device. Based upon bench testing and prior Abbott sponsored clinical study data, all risks have been identified and mitigated as far as possible through application of appropriate controls and inspections and determined to be within acceptable levels.

Residual risks are likewise disclosed in the IFU in the form of clear instructions of what actions to take or to avoid, to avoid a hazardous situation of harm from occurring (contra-indications, warnings, and precautions). The anticipated AEs disclosed in the IFU (and CIP Appendix V) provide further information to enable the user, and potentially the patient, to make an informed decision that weighs the residual risk against the benefit of using the device.

15.4. Risks Associated with Participation in this Clinical Investigation

The risks related to the procedure have been included in **Appendix V**.

15.5. Possible Interactions with Protocol-Required Concomitant Medications (if applicable)

The most prevalent risks associated with the anticoagulant and antiplatelet medications have been included in **Appendix V**.

15.6. Steps Taken to Control or Mitigate Risks

In-depth recommendations, special precautions and instructions regarding patient selection, device handling, device placement and system removal are included in the IFU.

Risks associated with the use of the Esprit BTK during this clinical study are minimized through device design, investigator selection and training, pre-specified patient eligibility requirements, study monitoring to ensure adherence to the protocol and the use of a DMC.

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These risk management aspects are detailed below:

Device Design: the design of the Esprit BTK includes many features aimed at minimizing potential risks. The major safety features of the device are described below:

- [redacted]

Investigator Selection and Training: It is also stated in the IFU that the devices can only be used by physicians who have received appropriate training on how to use the device. This statement is interpreted to mean that the physician users are expected to be aware of the known and foreseeable safety risks associated with the use of the devices including the surgical and/or non-surgical treatment of these conditions.

- Only physicians who are skilled in the manipulation of catheter-based technology in the vasculature and heart and have a good understanding of the risks associated with these manipulations, will be selected as investigators for this trial. In addition, site investigators will undergo training on the techniques required to optimally place the device in the BTK arteries. The physician users are expected to be aware of the known and foreseeable safety risks associated with the use of the devices including the surgical and/or non-surgical treatment of these conditions.

- Emergency surgical back-up should be available as per the institution's standard procedures.

- The Sponsor will be available to provide technical support to answer questions regarding the function of the Esprit BTK.

- Pre-specified patient eligibility requirements - as stated in **Section 5** of the protocol.

[redacted]

Clinical Investigation Plan

Ensuring strict adherence to the clinical investigation protocol

The clinical investigation will be carefully monitored by the Sponsor monitor (or designee) to ensure adherence to the Clinical Investigational Plan. Adverse events and device deficiencies will be reported to Abbott/designee and will be monitored internally for safety surveillance purposes. A DMC will be used for the study. Stopping rules will be discussed with the DMC and applied for subject safety through enrollment.

15.7. Risk to Benefit Rationale

The foreseeable rates of the anticipated adverse events associated with the procedure and implantation of Esprit BTK are all below 10% (see **Appendix V**). Moreover, as detailed in **Section 15.1**, there is an unmet need for treatment of BTK lesions, with limited options currently available. Recent clinical data on the Absorb BVS, the predecessor of Esprit BTK, have shown the benefit of bioresorbable scaffold for the treatment of stenotic infrapopliteal lesions.
Taking these into consideration, the clinical benefit that may be expected from treatment of BTK lesions with the Esprit BTK outweigh the possible risks that patients may experience when participating in this trial.

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APPENDIX I: ABBREVIATIONS AND ACRONYMS

Acronym/ Abbreviation	Term
%DS	Percent Diameter Stenosis
ABI	Ankle-brachial index
ACR	American College of Radiology
AE	Adverse Event
AFS	Amputation-Free Survival
AHA/ACC	American Heart Association/American College of Cardiology
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
BMI	Body Mass Index
BMS	Bare metal stent
BVS	Bioresorbable Vascular Scaffold
CA	Competent Authority
CEC	Clinical Events Committee
CFA	Common Femoral Artery
CIP	Clinical Investigation Plan
CL	Clearance
CLI	Critical Limb Ischemia
Cm	Centimeter
CRA	Clinical Research Associate
CRF	Case Report Form
DES	Drug Eluting Stent
dL	Deciliter
DMC	Data Monitoring Committee
DSMB	Data and Safety Monitoring Board
DS	Diameter Stenosis
DUS	Duplex Ultrasound
EC	Ethics Committee
ECG	Electrocardiogram
EES	Everolimus-Eluting Stent
EQ-5D-5L	EuroQoL (Quality of Life)-5D-5L
FDA	Food and Drug Administration
F/U	Follow-up
GCP	Good Clinical Practice
GI	Gastrointestinal
HDL	High Density Lipoprotein
ICAVL	International Commission for the Accreditation of Vascular Laboratories
ICH	International Committee on Harmonization
IFU	Instructions for Use
ITT	Intent-to-treat

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LDL	Low-density lipoprotein
MAE	Major Adverse Events
mg	Microgram
MALE	Major Adverse Limb Events
mg	Milligram
MHLW	Ministry of Health, Labor and Welfare (Regulatory Agency)
MLD	Minimum Luminal Diameter
mm	Millimeter
MOP	Manual of Operations
MR	Magnetic Resonance
NHLBI	National Heart, Lung, and Blood Institute
OCT	Optical Coherence Tomography
PAD	Peripheral Arterial Disease
PAQ	Peripheral Arterial Questionnaire
PI	Principal Investigator
PLA	Poly Lactic Acid
POD	Peri-operative (30-day) death
PSV	Peak Systolic Velocity
PSVR	Peak Systolic Velocity Ratio
PTA	Percutaneous Transluminal Angioplasty
RCT	Randomized Clinical Trial
RVD	Reference Vessel Diameter
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SD	Standard Deviation
SES	Sirolimus-eluting stent
SPTA	Standard Percutaneous Transluminal Angioplasty
TASC	Trans-Atlantic Inter-Society Consensus
TBI	Toe Brachial Index
TLR	Target Lesion Revascularization
TVR	Target Vessel Revascularization
US	United States
VO	Volume Obstruction
WBC	White Blood Cell Count
WIQ	Walking Impairment Questionnaire

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APPENDIX II: DEFINITIONS

Acute Gain

Acute gain is defined as the difference between post- and preprocedural minimal lumen diameter (MLD).

Acute Limb Ischemia

A rapid decrease in lower limb blood flow due to acute occlusion of peripheral artery or bypass graft.

Acute Procedure Success

Successful target lesion treatment is defined as final diameter stenosis < 30% with final number of run-off vessels equivalent to or greater than number of run-off vessels at pre-procedure, with no residual dissection NHLBI grade ≥ type C, and no transient or sustained angiographic complications (e.g., distal embolization, perforation, thrombosis). Achieved using balloons plus Esprit BTK in the treatment arm and balloons in the control arm. This is defined on a per lesion basis.

Amputation

The removal of a body extremity by surgery. For this study, the definition of amputation will only apply to amputations of the limb that was treated.

Minor amputation refers to toe amputation(s), ray amputation(s) limited to the metatarsal head and distal half of the metatarsal bone, and trans-metatarsal amputation. Major amputation will be defined as limb loss at or proximal to the transtibial level. Major amputations will be specified as below-the-knee and above-the-knee amputations.

Analysis lesion

Analysis lesion is defined as the target lesion.

Aneurysm

A localized abnormal expansion or protrusion of a blood vessel resulting from a disease or weakening of the vessel's wall (all 3 layers) that exceeds the reference vessel diameter (RVD) of the vessel by 1.5 times.

Ankle Brachial Index (ABI)

The ABI is the ratio of the ankle to arm pressure, and it is calculated by dividing the systolic blood pressure in the ankle of the one leg by the higher of the two systolic blood pressures in the arms.

An ABI of 0.9 – 1.4 is a normal range. A reduced ABI (less than 0.9) is consistent with peripheral artery occlusive disease, with values below 0.8 indicating moderate disease and below 0.5 indicates severe disease. A value greater than 1.4 is considered abnormal suggesting calcification of the walls of the arteries and noncompressible vessels, reflecting severe peripheral vascular disease. Subjects with ABI values greater than 1.4 will be excluded from the analysis.

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Calculation of the Ankle Brachial Index:

(Highest Ankle Systolic Pressure/Highest Brachial Systolic Pressure = ABI)

Arterial Inflow

Good inflow implies that vessels proximal to a target treatment site are free of hemodynamically significant lesions (≥ 50%).

Arterial Outflow

For a lesion in the infrapopliteal artery, outflow refers to combined levels distal to the lesion, including the following arteries: dorsalis pedis, plantar and pedal. Good outflow implies that the distal arteries is free of hemodynamically significant lesions (≥ 50%) and that there is in-line flow into the foot.

Arterial Thrombosis

Arterial thrombosis is defined as a total occlusion documented by duplex ultrasound and/or angiography at the site of the treated lesion with or without symptoms.

- Acute thrombosis: 0 - 24 hours post study procedure
- Subacute thrombosis: > 24 hours - 30 days post study procedure
- Late thrombosis: 31 days – 1 year post-procedure
- Very late thrombosis: > 1 year post-procedure

Thrombosis should be reported as a cumulative value at the different time points and with the different separate time points. Time 0 is defined as the time point after the arterial sheath has been removed and the subject has left the interventional lab.

Bleeding (Hemorrhagic) Complications

These may include hematoma requiring transfusion or surgical repair, and any bleeding event associated with hemoglobin drop > 5 g/dl or requiring transfusion or surgical repair (e.g., retroperitoneal bleed, GI bleed, access site bleed).

Binary Restenosis

Binary restenosis will be presented as the presence of a hemodynamically significant restenosis > 50% by angiography, or PSVR ≥ 2.0 by duplex ultrasound. In the presence of abnormal reference PSV, the core lab uses the following additional secondary criteria (correlating factors) to identify target lesion stenoses >50% in severity:

- Focal increase in the absolute PSV at the area of visible plaque
- Spectral broadening of the waveform at the area of stenosis
- Post-stenotic turbulence (PST) and/or change in the waveform shape and/or drop in velocity distal to the stenosis

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- Review of the B-mode images for plaque burden

If both angiogram and Duplex Ultrasound (DUS) were performed, the angiogram data will take precedence over DUS for the determination of binary restenosis.

Chronic Concomitant Medications

Medication that has been:

- prescribed or over-the-counter (OTC) that has been taken or will continue to be taken regularly for at least a period of 6 months, or
- is required to be taken indefinitely by the subject, or
- prescribed or OTC that has been taken multiple times (each time for at least 6 months)

Death

When possible, death will be classified according to underlying cause. Death within 30 days of the study procedure will be classified as procedure related unless medical history or autopsy findings demonstrate otherwise.

Cardiac death:

Any death due to proximate cardiac cause (e.g., MI, low-output failure, fatal arrhythmia), unwitnessed death, or death of unknown cause.

Vascular death:

Death caused by noncoronary vascular causes, such as cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular diseases.

Non-cardiovascular death:

Any death not covered by the above definitions, such as death caused by infection, malignancy, sepsis, pulmonary causes, accident, suicide, or trauma.

Clinical Success

Defined on a per patient basis, as the attainment of a final residual stenosis of < 30% using the study device(s) and/or any adjunctive device at all intended target lesion(s) without complications within 2 days after the index procedure or at hospital discharge, whichever is sooner.

Device Malfunction

A malfunction is a failure of a device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling of the device. The intended performance of a device refers to the intended use for which the device is labeled.

Device Success

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Defined on a per device basis, as the achievement of successful delivery and deployment of the study device(s) at the intended target lesion and successful withdrawal of the delivery catheter.

Diabetes Mellitus:

Criteria for diagnosis of diabetes mellitus [26]

Symptoms of diabetes plus casual plasma glucose concentration ≥ 200 mg/dl (11.1 mmol/l). Casual is defined as any time of day without regard to time since the last meal.

or

Fasting plasma glucose (FPG) ≥ 126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8hours.

or

The subject takes insulin or oral hypoglycemic medication

Dissection Grades

National Heart, Lung, and Blood Institute (NHLBI) Dissection Classification System:

A. Minor radiolucencies within the lumen during contrast injection with no persistence after dye clearance.
B. Parallel tracts or double lumen separated by a radiolucent area during contrast injection with no persistence after dye clearance.
C. Extraluminal cap with persistence of contrast after dye clearance from the lumen.
D. Spiral luminal filling defects.
E. New persistent filling defects.
F. Non-A-E types that lead to impaired flow or total occlusion.

Note: Type E and F dissections may represent thrombus.

Edge Dissections

Edge dissections for OCT and IVUS will be tabulated as:

- Major (%): ≥60 degrees of the circumference of the vessel at the site of dissection and ≥3 mm in length
- Minor (%): any visible edge dissection <60 degrees of the circumference of the vessel or <3 mm in length

Edge dissections will be further classified as:

- Intimal (limited to the intima layer, i.e., not extending beyond the internal elastic lamina)
- Medial (extending into the media layer)
- Adventitial (extending through the external elastic membrane/lamina)

Embolism

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Formation of a thrombus within the target lesion with migration or atherosclerotic emboli migration to a distal artery

Enrollment

The subject will be considered enrolled into the clinical investigation from the moment the subject provides written informed consent.

Hematoma

A localized collection of blood in a space or tissue.

Hypertension

As defined by the Joint National Committee on Prevention, Detection, and treatment of High Blood Pressure [27] or if the subject is on antihypertensive therapy for the indication of hypertension:

- Normal blood pressure: systolic < 120 mmHg and diastolic <80 mmHg
- Prehypertension: systolic 120-139 mmHg or diastolic 80-89 mmHg
- Stage 1 hypertension: systolic 140-159 mmHg or diastolic 90-99 mmHg
- Stage 2 hypertension: systolic ≥ 160 mmHg or diastolic ≥ 100 mmHg

Hyperlipidemia

Per accepted standards or National Cholesterol Education Program Adult Treatment Panel III or if the subject is taking blood lipid-lowering medication for the indication of hyperlipidemia [28].

Intent-to-Treat (ITT) Population

All subjects in the analysis who are randomized into the clinical trial/investigation, regardless of the treatment actually received.

Major Adverse Event

Major amputation of the ipsilateral extremity, new bypass graft, jump/interposition graft revision, thrombectomy/thrombolysis related to the target lesion, Q-wave myocardial infarction, death.

Major Limb Re-interventions

Includes the creation of a new bypass graft, bypass graft revision, the use of thrombectomy or thrombolysis [29].

MALE+POD

Major adverse limb events (major amputation or major re-interventions including new bypass graft, jump/interposition graft revision, or thrombectomy / thrombolysis related to the target lesion) occurring within 6 months, or peri-procedural (or peri-operative) (30-day) death (MALE+POD).

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Non-Traditional Transmetatarsal Amputation

Non-traditional transmetatarsal amputation does not allow for standard division of the metatarsal bones and rotation of the plantar flap up over the end of the wound. Examples would be an "open" transmetatarsal amputation, or any other partial foot amputation such as a Symes or Choparts.

Occlusion

Angiography: Incomplete vessel opacification distal to the lesion or if the distal vessel fills via collateral circulation.

Duplex ultrasound: Pulsed wave Doppler: no detectable flow from within vessel segment, complete filling of the artery by b-mode image, no flow detected by color Doppler, high resistance waveform proximal to occluded segment and delayed systolic upstroke with decreased velocities distal to occluded segment.

Chronic Occlusion

An occlusion presumed to have been present for at least 1 month prior to the procedure.

Total Occlusion:

Angiography: A complete occlusion with no ante grade filling of contrast to the distal segment
Duplex Ultrasound: A complete occlusion with no detected flow signals in the lumen of an imaged vessel. Distal (collateral) waveforms are monophasic with reduced systolic velocities.

Sub-total Occlusion:

Angiography: A small amount of contrast flows through the stenosis but fails to opacify the artery beyond, and there is collateral filling of the distal segment.
Duplex Ultrasound: Focal increase in the peak systolic velocity, with visible lumen loss by b-mode image and or presence of post stenotic turbulence or decrease in PSV distal to stenosis.

Percent Diameter Stenosis

The value calculated as 100 * (1 - MLD/RVD) using the mean values from two orthogonal views (when possible) by QA.

Persisting Dissection

Dissection at follow-up that was present post-procedure.

Primary Assisted Patency

Defined as patency of the target lesion following endovascular reintervention at the target vessel site in case of symptomatic restenosis [30]

Primary Patency and Limb Salvage

The composite of primary patency and limb salvage is defined as freedom from: above ankle amputation in index limb, 100% total occlusion of target vessel, binary restenosis of target lesion, and clinically-driven target lesion revascularization (CD-TLR). Primary patency ends

at the first occurrence of one of the following: 100% total occlusion of the target vessel, binary restenosis of target lesion, clinically-driven target lesion revascularization, or above ankle amputation due to target lesion restenosis or occlusion.

Popliteal Artery

Defined as the vessel located between Hunter's canal and the trifurcation of the anterior tibial, posterior tibial and peroneal arteries.

Principal Investigator

A physician responsible for conducting the clinical trial at each investigational site, which is responsible for the overall conduct of the trial at their site and compliance with protocol and relevant regulatory requirements.

Reference Vessel Diameter (RVD)

An approximation of the diameter of the vessel at the location of the target lesion. RVD is visually estimated during angiography by the Investigator and it is measured during QA by the Angiographic Core Laboratory.

Registration

The subject will be considered registered into the study upon the completion of all of the following:

- A signed subject informed consent,
- General inclusion criteria for enrollment have been met,
- Anatomic criteria for enrollment have been met,
- Successful treatment of the ipsilateral inflow artery(ies), and non-target lesion(s) without complication, if applicable,
- Target lesion(s) successfully crossed by the guidewire (as evidenced by guidewire placement in the distal arterial lumen) without complication

Restenosis

Re-narrowing of the artery following the alleviation of a previous narrowing. It is defined as the presence of a hemodynamically significant restenosis (≥ 50%), as determined by angiography.

Revascularization

Target Lesion Revascularization (TLR)

Target lesion revascularization (TLR) is defined as any repeat percutaneous intervention of the target lesion or bypass surgery of the target vessel performed for restenosis or other complication of the target lesion.

Clinically-Driven Target Lesion Revascularization (CD-TLR)

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Repeat intervention on the target lesion due to recurrent symptoms AND stenosis > 70% by angiography. Bailout with metallic stent, in either study arm, due to acute closure or to achieve < 30% stenosis during index procedure will be considered a CD-TLR. Recurrent symptoms are such as delayed or worsening wound healing, new or recurrent wound at the treatment site, or worsening Rutherford class.

Clinically-driven target vessel revascularization (CD-TVR)

Repeat intervention on the target vessel due to recurrent symptoms AND stenosis > 70% by angiography. Recurrent symptoms are such as delayed or worsening wound healing, new or recurrent wound at the treatment site, or worsening Rutherford class.

Clinically-driven target vessel revascularization (CD-TVR) distal to the target lesion

CD-TVR that occurred at least 5 mm of tissue distal to the target lesion

Clinically-driven target vessel revascularization (CD-TVR) proximal to the target lesion

CD-TVR that occurred at least 5 mm of tissue proximal to the target lesion

Rutherford/Becker Categories - Chronic Limb Ischemia [15]

Grade	Category	Clinical Description	Objective Criteria
	0	Asymptomatic, no hemodynamically significant occlusive disease	Normal results of treadmill*/stress test
I	1	Mild claudication	Treadmill* exercise complete, post exercise AP is greater than 50 mm Hg but more than 25 mm Hg less than normal
	2	Moderate claudication	Symptoms between those of categories 1 and 3
	3	Severe claudication	Treadmill* exercise cannot be completed post exercise AP is less than 50 mm Hg
II	4	Ischemic rest pain	Resting AP of 40 mm Hg or less, flat or barely pulsatile ankle or metatarsal plethysmographic tracing, toe pressure less than 30 mm Hg
III	5	Minor tissue loss, non-healing ulcer, or focal gangrene with diffuse pedal ischemia	Resting AP of 60 mm Hg or less, flat or barely pulsatile ankle metatarsal plethysmographic tracing flat or barely pulsatile, toe pressure less than 40 mm Hg
	6	Major tissue loss, extending above transmetatarsal level, functional foot no longer salvageable	Same as category 5

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*5 minutes at 2 mph on a 12^0 incline

Worsening Rutherford Becker Clinical Category

A deterioration (an increase) in the Rutherford Becker Clinical Category by more than 2 categories from the earliest post-procedural measurement or to a category 6.

Secondary Patency

Patency of the target lesion after treatment of a (re)occlusion of the index lesion [30].

Study Principal Investigator

A physician-specialist, related to the study, which is responsible for the overall conduct of the trial at all sites.

Successful Pre-Dilatation

Pre-dilatation has been successfully completed without complications if all of the following apply:

- diameter stenosis < 30% (by visual estimation)
- lesion length still within the requirements of the protocol/CIP
- no angiographic complications

Target Lesion

The continuous diseased segment that is intended to be treated by the study device(s) during the index procedure.

Target Extremity

Target extremity includes any arterial segment(s) outside of the target lesion.

Toe Brachial Index (TBI)

Toe brachial index (TBI) is a calculation based on the systolic blood pressures of the arm and the systolic blood pressures of the toes. A TBI is performed when the ABI is abnormally high due to plaque and calcification of the arteries in the leg. The abnormally high ABI is >1.4.

The TransAtlantic Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II) defined a TBI <0.70 as an abnormal finding [31].

Technical Success

Defined on a per lesion basis as the attainment of a final residual stenosis of < 30% at the intended target lesion(s) following use of the study device(s). Standard pre-dilatation catheters and post-dilatation catheters (if applicable) may be used. Bailout at lesion level does not impact technical success if the above criteria are met.

Treated Site

Located within the margins of the scaffold, or PTA balloon.

Treated Segment

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Located within the margins of the scaffold, or PTA balloon, including 5 mm proximal and/or distal to the scaffold.

Vascular Complications

Access Site Occlusion

Access site occlusion is defined as total obstruction of the artery usually by thrombus (but may have other causes) usually at the site of access requiring surgical repair.

Arteriovenous Fistula

AV Fistula is defined as a connection between the access artery and the accompanying vein that is demonstrated by angiography or ultrasound and most often characterized by a continuous bruit. Indicate whether an arteriovenous (AV) Fistula occurred at the site of percutaneous entry during the procedure or after lab visit but before any subsequent lab visits.

Peripheral Embolization

Peripheral embolization refers to the evidence of distal embolization subsequent to the index procedure and peri-procedural period. Signs and symptoms suggest of peripheral embolization may include 1) acute change in vascular exam (sudden onset rest pain, pallor, coolness, or other signs of acute ischemia), 2) petechiae, or 3) sub-ungal hemorrhage.

Pseudoaneurysm

Pseudoaneurysm is defined as the occurrence of a disruption and dilation of the arterial wall without identification of the arterial wall layers demonstrated by angiography or ultrasound. The location of the pseudoaneurysm should be indicated.

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APPENDIX III: SITE CONTACT INFORMATION

A list of trial site coordinators can be obtained upon request from the Clinical Project Manager for the clinical investigation.

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APPENDIX IV: LITERATURE REVIEW

A summary of results from the literature review is provided below.

Clinical Investigation	Objective	Treatment arms	Patient population	Endpoints	Results
"A Prospective Randomized Multicenter Comparison of Balloon Angioplasty and Infrapopliteal Stenting With the Sirolimus-Eluting Stent in Patients With Ischemic Peripheral Arterial Disease: 1-Year Results From the ACHILLES Trial" Scheinert et al. 2012 J Am Coll Cardiol 2012;60:2290–5 Randomized multi-center study consisting of 2 arms that compared safety and efficacy of using sirolimus-eluting stent (SES) or percutaneous transluminal balloon angioplasty (PTA) to treat patients with critical limb ischemia (N=200).	To investigate the efficacy and safety of a balloon expandable, sirolimus-eluting stent (SES) in patients with symptomatic infrapopliteal arterial disease.	Patients were randomized to receive SES stent or percutaneous transluminal balloon angioplasty (PTA) for treatment.	Inclusion: Patients with symptomatic peripheral arterial disease (PAD; Rutherford class 3-5) manifested in the infrapopliteal arterial territory. Exclusion: Patients with significant stenoses (>50%) distal to the target lesion that might require revascularization or impede runoff; angiographically evident thrombus or history of thrombolysis within 72 h; untreated lesions (>75% stenosis) in the common or external iliac; common or superficial femoral and popliteal artery; infrapopliteal trifurcation lesions requiring 2- or 3-branch treatment; stent placement across or within 1 cm of the knee joint or in an artery subject to external compression; prior stenting within the target vessel(s) or aneurysm in the SFA or popliteal artery; history of thrombophlebitis, deep venous thrombosis, or impaired renal function (Cr >2.5 mg/dl); life expectancy <12 months;	1°: 12-month in-segment binary restenosis (in and/or 5 mm proximal/distal to treated length) determined by quantitative angiography. 2°: Death, repeat revascularization, index-limb amputation, various angiographic parameters, stent fractures (plain x-ray film assessment) at 12 months, and index-limb wound status at screening, 6 weeks, and 6 and 12 months.	• Primary endpoint at 1 year: 22.4% (SES), 41.9% (PTA), p=0.019 • Survival at 1 year: 89.9% (SES), 88.1% (PTA), p=0.822 • CD-TLR at 1 year: 10.0% (SES), 16.5% (PTA), p=0.257 • TVR at 1 year: 6.4% (SES), 2.4% (PTA), p=0.263 • Vessel patency at 1 year: 75% (SES), 57.1% (PTA), p=0.025 • Index limb amputation at 1 year: 13.8% (SES), 20% (PTA), p=0.307 • Stent fractures at 1 year: 0.9% (SES), 0% (PTA) • Rutherford class improvement at 1 year: 76.06% (SES), 67.11% (PTA) at 1 year (p=0.2315)

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			or known intolerance to antiplatelet medication.		
"Randomized comparison of everolimus-eluting versus bare-metal stents in patients with critical limb ischemia and infrapopliteal arterial occlusive disease." Bosiers et al. J Vasc Surg 2012;55:390-9. Prospective, randomized, controlled multicenter trial to compare treatment of patients with chronic symptomatic peripheral arterial disease using everolimus-eluting stent (Xience V) or bare-metal stent (Multi-Link Vision) (N=140).	DESTINY trial: To test if treatment of infrapopliteal arterial occlusive lesions with an everolimus-eluting stent (Xience V) would provide superior patency to treatment with a bare-metal stent (Multi-Link Vision).	Patients with critical limb ischemia and infrapopliteal arterial occlusive disease were randomized to receive either everolimus-eluting stent (Xience V) or bare-metal stent (Multi-Link Vision) for treatment.	Inclusion: Symptomatic PAD (Rutherford category 4-5) due to a maximum of two focal de novo atherosclerotic target lesions in one or more infrapopliteal vessels. Lesions with ≥50% diameter stenosis with length ≤40 mm and diameters of 2.0 to 3.5 mm. All patients were required to have at least one patent tibial artery that provided in-line circulation to the foot. At least single-vessel outflow to the foot (distal to the target lesion). Exclusion: Not specified	1°: Primary patency (absence of ≥50% in-stent binary restenosis at 12 months). 2°: Clinical success (defined as an improvement of Rutherford classification of one or more classes at the 12- month follow-up), freedom from target lesion revascularization (TLR), limb salvage (defined as freedom from major amputation at or above the ankle), and patient survival.	• Amputation at 12 months: 2 for Vision, 1 for Xience V. • Primary patency: 85% (Xience), 54% (Vision), p=0.0001 • Clinical success at 12 months: 56% (Vision), 60% (Xience), p=0.68 • 12-month patient survival: 84% (Vision), 82% (Xience), p=0.96 • 12-month freedom from TLR: 66.4% (Vision), 91.3% (Xience), p=0.001
"Outcome of a drug-eluting stent in longer below-the-knee lesions in patients with critical limb ischemia." Bosiers et al. J Cardiovasc Surg 2017;58:49-54. Prospective, multi-center, non-randomized, single arm study of patients undergoing treatment of atherosclerotic lesions BTK with the Xience Prime™ Everolimus-Eluting Coronary Stent System (N=60).	DESTINY2 trial: To evaluate the immediate and long-term (up to 12 months) outcome of the Xience Prime™ Everolimus-Eluting Coronary Stent System (Abbott Vascular) in a controlled, prospective, multi-center investigation for long lesions up to 10 cm.	Patients with critical limb ischemia and long infrapopliteal lesions between 30 and 100 mm were treated with Xience Prime™ Everolimus-Eluting Coronary Stent System.	Inclusion: Patients with critical limb ischemia and total lesion length between 3-10 cm with a diameter between 2.0-3.5 mm. An inflow stenosis needed to be treated without complications. Exclusion: Previous surgery, aneurysm or non-atherosclerotic disease and acute thrombosis. Patients with severe comorbidities resulting in a life expectancy of <1 year and patients presenting with sepsis or bacteremia.	1°: Primary patency at 12 months (absence of restenosis (≥50% stenosis) or occlusion) 2°: Technical success, clinical success (improvement of Rutherford classification of one class or more), limb-salvage rate (defined as absence of major amputation), freedom from target lesion revascularization (TLR), secondary patency and survival.	• Primary patency: 75.4% • Technical success: 100% • Freedom from TLR: 84.9% • Freedom from amputation at 12 months: 94.4% • Improvement in Rutherford classification: 85.7% • Survival at 1 year: 89.3%

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"Sirolimus-eluting stents vs. bare-metal stents for treatment of focal lesions in infrapopliteal arteries: a double-blind, multi-centre, randomized clinical trial." Rastan et al. Eur Heart J 2011;32:2274-81. Prospective, randomized, double-blind trial to compare a polymer-free sirolimus-eluting stent with a placebo-coated bare-metal stent in patients with either intermittent claudication or critical limb ischaemia who had a de-novo lesion in an infrapopliteal artery (N=161).	YUKON trial: To compare a polymer-free sirolimus-eluting stent (SES) with a placebo-coated bare-metal stent (BMS) in patients with intermittent claudication or critical limb ischaemia who had a de-novo lesion in an infrapopliteal artery.		Inclusion: Patients with peripheral artery disease with Rutherford–Becker class of 3 to 5. Patients with lifestyle-limiting claudication RC 2 can be included after successful intervention of TASC A (single stenosis less than 3 cm of the superficial femoral artery or popliteal artery) femoro-popliteal lesions to improve run-off status. Presence of a single primary target lesion in a native IPA that was 2.5–3.5 mm in diameter and that did not exceed 45 mm in length; diameter stenosis of at least over 70%. Exclusion: Visible thrombus within target lesion, known systemic coagulopathy, Buerger's disease, acute limb ischaemia, and life expectancy less than 1 year, or an intolerance of aspirin, clopidogrel, and heparin.	1°: Primary patency rate after 1 year (freedom from in-stent-restenosis (luminal narrowing of <50%) detected with DU or angiography). 2°: 6-month primary patency rate, secondary patency rate, and changes in Rutherford–Becker classification after 1 year.	• Primary patency at 1 year: 80.6% (SES), 55.6% (BMS), p=0.004 • 6-month primary patency rate: 85.9% (SES), 68.7% (BMS), p=0.02 • Secondary 1-year patency rates: 91.9% (SES), 71.4% (BMS), p=0.005 • Improvement in Rutherford classification at 1 year: 83.9% (SES), 61.9% (BMS), p=0.004 •
LUTONIX® BTK Trial: A Prospective, Multicenter, Single Blind, Randomized, Controlled Trial Comparing the Lutonix Drug Coated Balloon vs. Standard Balloon Angioplasty for Treatment of Below-the-Knee (BTK) Arteries Mustapha, Vascular Interventional Advances (VIVA), November 2018.	To demonstrate the superior efficacy and non-inferior safety of the Lutonix DCB by direct comparison to standard PTA for treatment of stenosis or occlusion of below-the-knee arteries	Patients with CLI were randomized to receive either Lutonix DCB or standard PTA catheter.	Inclusion: Patients with CLI Rutherford 3-5, life expectancy ≥ 1 year, ≥70% stenosis, patent inflow artery, target vessel diameter 2-4 mm. Exclusion: Patients with history of stroke within 3 months, history of MI, thrombolysis or angina within 30 days of enrollment, GFR ≤ 30 ml/min per 1.73m^2, acute limb ischemia, in-stent	1° Safety Freedom from Major Adverse Limb Events (MALE) & All-Cause Perioperative Death (POD) at 30 days (above ankle amputation and major re-intervention). 1° Efficacy Freedom from a composite of above ankle amputation, target vessel occlusion, and clinically-driven target lesion revascularization at 6 months.	• Freedom from primary safety event at 30 days: 99.3% (DCB), 99.4% (PTA), p<0.0001 • Freedom from primary efficacy failure at 6 months: 73.7% (DCB), 63.5% (PTA), p=0.0273

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Prospective, multicenter, single blind, randomized controlled trial comparing Lutonix Drug Coated Balloon and Standard Balloon Angioplasty for Treatment of BTK Arteries (N=442).			restenosis of target lesion.		
"Three-Year Results of the Absorb Everolimus-Eluting Bioresorbable Vascular Scaffold in Infrapopliteal Arteries. " Varcoe et al. J Endovas Ther 2018 Dec;25(6):694-701 Single-arm study that used Absorb to treat patients with critical limb ischemia (N=48).	To examine the efficacy of Absorb in de novo atherosclerotic lesions of the infrapopliteal arteries.	Each target lesion was pre-dilated with a noncompliant angioplasty balloon before implantation.	Inclusion: Patients with chronic lower limb ischemia (Rutherford category 3–6) and with >60% de novo stenosis ⩽5 cm long in distal popliteal or tibial arteries measuring 2.5 to 4.0 mm in diameter. Exclusion: Patients who had a short life expectancy (<12 months), allergy/renal impairment that precluded angiography, or where known to be intolerant to dual antiplatelet therapy.	1°: Binary restenosis based on color-flow Doppler examination and a sensitive peak systolic velocity ratio >2.0. 2°: Clinically driven target lesion revascularization (CD-TLR), major or minor amputation, bypass surgery, cardiovascular and all-cause mortality, as well as any related morbidity.	• 100% technical success (defined as no amputation, death, or target limb bypass surgery within 30 days of the index procedure.) • Freedom from CD-TLR was estimated as 97.2%, 97.2%, and 87.3% at 12, 24, and 36 months. • Primary patency rate was 92.2% at 12 months, 90.3% at 24 months, and 81.1% at 36 months. • At ultrasound follow-up, 6 (8%) of 71 scaffolds had developed a binary restenosis. • All but one binary restenosis was in the 50% to 75% range, and only two resulted in clinical deterioration that required revascularization at 24 and 26 months, respectively, after scaffold implantation. • No late scaffold thrombosis. • For wound status and patient symptoms, 51 (93%) of 55 limbs were clinically improved, 4 (7%) were unchanged, and none was worse. • Of the 39 limbs with ischemic tissue loss (Rutherford category 5 or 6), 36 (92%) had completely healed wounds during the follow-up period.
"Outcomes of Bio-absorbable stent for Below Knee Critical Limb Ischaemia." Xue and Ho, Asian Society for Vascular	To investigate the outcomes, efficacy and safety of bioabsorbable vascular stents (BVS) in patients with	Absorb was implanted in patients. A minimum of 1mm stent overlap was placed if multiple	Inclusion: Patients with critical limb ischemia (Rutherford category 4–6).	1°: Vessel patency, target lesion revascularization (TLR) and limb salvage rates.	• 100% technical success rate (defined as successful delivery and deployment of the stent at the intended target lesion, successful withdrawal of the delivery catheter,

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Surgery (ASVS) Congress, October 2016. Retrospective analysis of cases where patients with critical limb ischemia were treated using Absorb (N=28).	below knee critical limb ischaemia.	BVS stents were used. Post BVS insertion, ultrasound duplex was used to evaluate vessel patency and arterial flow.	Exclusion: Not specified.	2°: Not specified.	and attainment of a final residual stenosis of <30%). • High primary patency rates of 96.7%, 93.5% and 90.3% at 1 month, 6 months and 1 year respectively.
"1 Year Results in Real World Patients with ABSORB BTK." Kum, Leipzig Interventional Course, January 2017. Treatment of patients with critical limb ischemia treated using Absorb (N=28).	To study the safety and clinical efficacy of a novel Bioabsorbable Everolimus Eluting Bioresorbable Vascular Scaffold System (BVS, Abbott Vascular) in subjects with critical limb ischemia (CLI) following percutaneous transluminal angioplasty (PTA) of the tibial arteries.	Infrapopliteal stenting using Absorb.	Inclusion: Symptomatic critical limb ischemia (Rutherford 4, 5, 6) Exclusion: Not specified.	1°: Vessel patency, target lesion revascularization (TLR) and limb salvage rates. 2°: Not specified.	• 100% technical success rate. • Safe: no 30 day MACE or MALE. • Primary patency 93.5%, 90.3% and 87.1% at 1 month, 6 months and 1 year. • Freedom from TLR rate was 96.7%. • Limb salvage at 6 months was 96.7%.
"Clinical Effectiveness of the ABSORB Bioresorbable Scaffold in Patients with Complex Infrapopliteal Disease." Shah et al. LINC 19, January 2019. Single center, retrospective study that used Absorb to treat patients with critical limb ischemia or complex infrapopliteal disease (N=31).	To assess safety and efficacy of Absorb BVS for treatment of patients with complex infrapopliteal disease.	Patients were treated with the ABSORB BVS.	Inclusion: Patients with critical limb ischemia (Rutherford category 3-6) with life expectancy > 12 months Exclusion: Not specified	Clinical endpoints: Stent thrombosis, primary patency (defined as freedom from target vessel occlusion and clinically driven target lesion revascularization evaluated at 12 months), limb salvage (defined as freedom from major amputation above the ankle), and ultrasound designated patency (cutoff velocity of 2m/sec).	• At 12 months: 0% stent thrombosis, 96.7% primary patency, 100% limb salvage. • Improved Rutherford Becker classification for 30/31 (96.8%) patients.

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APPENDIX V: RATES OF FORSEEABLE ADVERSE EVENTS

Potential risks associated with the PTA procedure are similar to those for standard limb salvage, angiography and catheterization techniques, administration of anesthesia, and use of fluoroscopy. Although anticipated risks for PTA are described below, due to the nature of this study, there may also be other risks, which are not known at this time. Likewise, the exact frequency of the risk may be unknown.
The frequencies of the foreseeable events indicated in the table below are based on clinical trials using the DESTINY Trial, where XIENCE V drug-eluting stent (DES) was used to treat focal infrapopliteal peripheral arterial disease (140 patients were randomized 1:1 (XIENCE V DES: MULTI-LINK VISION bare metal stent) at 5 clinical sites in the European Union). Currently no data is available for the same indication using the Esprit BTK. The rationale for basing frequencies on the DESTINY Trial is that the indications for this trial and the DESTINY Trial are identical; moreover, the Esprit BTK also contains the drug Everolimus, albeit in a bioresorbable scaffold. Other adverse events that were not observed in the DESTINY Trial but where reported as commercial complaints for XIENCE stents used for BTK/ infrapopliteal were included in the list and rates provided are based on said complaints.

Additionally, the foreseeable adverse events related to Everolimus included in this CIP, the ICF, and the IFU are associated with daily oral administration of everolimus in doses varying from 1.5 mg to 10 mg daily, and can be found in the Summary of Product Characteristics (SPC) and labels for the drug (1,2,3,4,5). The risks related to Everolimus described in the Adverse Events section include the anticipated adverse events relevant for the peripheral artery disease population referenced in the contraindications, warnings and precaution sections of the everolimus labels and/or SPCs. They are observed at incidences ≥ 10% in clinical trials with oral everolimus for different indications. Please refer to the drug SPCs and labels 1, 2, 3, 4, 5 for more detailed information and less frequent adverse events.

[1-Certican® UK label Mar 2015. 2-Animator® EU authorization SPC Dec 2014. 3-Votubia® EU SPC Sept 2014. 4-Animator® US label Jan 2015. 5-Zortress® US label Sept 2015. Refer to www.MHRA.gov.uk, www.ema.europa.eu, and www.fda.gov for the most recent versions of these SPC/labels.]

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Anticipated adverse event	Frequency observed in the DESTINY I clinical study				
	Very common: ≥10%	Common: ≥ 1.0% to < 10%	Uncommon: ≥ 0.1% to < 1.0%	Rare: ≥ 0.01% to < 0.1%	Very Rare: < 0.01%
Allergic reactions or hypersensitivity to latex, contrast agent, anaesthesia, stent material (everolimus, cobalt, chromium), and drug reactions to anticoagulation, or antiplatelet drugs					X
Vascular access complications which may require transfusion or vessel repair, including:					
Catheter site reactions		X			
Bleeding (including ecchymosis, oozing, hematoma, hemorrhage, retroperitoneal hemorrhage)		X			
Arteriovenous fistula, pseudoaneurysm, aneurysm, dissection, perforation/rupture, vascular occlusion					X
Emboli (air, thrombotic material, device, device component)			X		
Target artery complications which may require additional intervention, including:					
Total occlusion or abrupt closure		X			
Arteriovenous fistula, pseudoaneurysm, aneurysm, dissection, perforation/rupture, vessel spasm		X			
Embolism (air, tissue, plaque, thrombotic material, or device)			X		
Stenosis or restenosis			X		
Vasospasm		X			
Peripheral nerve injury, neuropathy or nerve injury, neurologic complication		X			
Cardiac arrhythmias (including conduction disorders, atrial and Ventricular arrhythmias)					X
Cardiac ischemic conditions (including myocardial ischemia, myocardial infarction (including acute), coronary artery spasm, and unstable or stable angina pectoris):		X			
Amputation		X			
Other Infarction/Ischemia including: Other Infarction/Ischemia including: Bowel ischemia, Tissue/organ infarction or ischemia, Worsening or exacerbation of the pre-existing condition, Blue toe syndrome, Tissue necrosis, Gangrene, Ulcer, And Acute limb ischemia		X			

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New or worsening Pain		X			
Nausea and vomiting		X			
Blood cell disorders including heparin induce thrombocytopenia and other coagulopathy		X			
Hypotension/hypertension		X			
Hyperperfusion syndrome					X
Infection - local and systemic (including post-procedural)			X	X	
Fever			X		
Death					X
Stroke/Cerebrovascular accident (CVA) and Transient Ischemic Attack(TIA)				X	
System organ failures:					
Cardiac failure		X			
Cardio-respiratory arrest (including pulmonary edema)					X
Respiratory failure			X		
Renal failure					X
Shock		X			

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APPENDIX VI: LABELS

Label information for the investigational product, including the IFU and packaging information, are provided under a separate cover.

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APPENDIX VII: CASE REPORT FORMS

Final draft CRFs will be sent under a separate cover.

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APPENDIX VIII: INFORMED CONSENT FORM

A template informed consent form, will be sent under a separate cover.

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APPENDIX IX: MONITORING PLAN

A copy of the Monitoring Plan can be obtained upon request from the Sponsor Clinical Project Manager for the clinical investigation.

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APPENDIX X: LIFE-BTK Pharmacokinetics sub-study

CIP Number: [redacted]
Study Number: [redacted]

LIFE-BTK
PHARMACOKINETICS (PK) SUB-STUDY SYNOPSIS

Version Number	[redacted]
Date	[redacted]
Planned Number of Sites and Region(s)	Subjects will be enrolled in the United States (US) and outside the US with a maximum of 5 sites in the US. Note: these 5 sites are additional sites, and not included in the maximum 50 US sites for the LIFE-BTK RCT study.
Clinical Investigation Type	Prospective, single-arm, open-label, non-blinded clinical investigation
Abbott Vascular Medical Expert	[redacted]
Sponsor / Trial Monitor/Data Monitoring	Abbott Cardiovascular Systems, Inc., [redacted]
Registration/Randomization Service	Oracle Clinical
Electronic Data Capture Software	Oracle Clinical
Blood Sample Analysis Core Laboratory	[redacted]
Clinical Events Committee	[redacted]
Data Monitoring Committee Administration	[redacted]
Sub-study Author	[redacted]

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Study Name	**LIFE-BTK PK Sub-study** CIP Number: [redacted] Study Number: [redacted]
Investigational Device	Esprit™ BTK Everolimus Eluting Bioresorbable Scaffold System Scaffold diameters: 2.5, 2.75, 3.0, 3.5 and 3.75 mm Scaffold lengths: 9, 12, 15, 18, 23, 28, 33 and 38 mm
Objective	To determine the pharmacokinetics of everolimus delivered by the Esprit BTK scaffold in a separate and non-randomized cohort of subjects receiving the Esprit BTK for the planned treatment of narrowed infrapopliteal lesions. The LIFE-BTK PK sub-study subjects will not be included in the primary analysis population and will not contribute to the determination of the LIFE-BTK primary endpoints.
Sub-study Design	A prospective, single-arm, open-label, non-blinded, non-randomized sub-study enrolling approximately 7 subjects treated with Esprit BTK at selected clinical trial sites. Subjects will be distributed as follows: • 4 subjects treated with Esprit BTK in below the knee artery(ies) in whom drug-coated balloons (DCB) were not used • 3 subjects treated with Esprit BTK in below the knee artery(ies) in whom DCB were used for treatment of inflow disease Note: The use of DCB will be at the investigator discretion and recorded in the Case Report Form. Number of registered subjects with and without DCB use, towards enrollment total, will be tracked by the Sponsor.
Subject Number and Drug Doses	Total number of subjects: approximately 7 subjects treated with multiple scaffolds such that the total length of scaffold received by the subject is between 170 and 256 mm. The targeted everolimus drug dose range, based on a total scaffold length of 170 to 256 mm, is 1319 to 2714 µg. The drug content for each size of Esprit BTK is indicated in **Table 1**. Shown in bold are the scaffold sizes available in the LIFE-BTK trial. The same sizes will be available in the PK sub-study.

Table 1: Drug Content in Esprit BTK

Esprit BTK Diameter (mm)	Esprit BTK Length (mm)	Drug Dose (µg)
2.5, 2.75	9	69
2.5, 2.75	12	93
2.5, 2.75	15	116
2.5, 2.75	**18**	**139**
2.5, 2.75	23	178
2.5, 2.75	**28**	**217**
2.5, 2.75	33	256
2.5, 2.75	**38**	**295**
3.0	9	75

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	3.0 | 12 | 98 3.0 | 15 | 121 **3.0 | 18 | 144** 3.0 | 23 | 189 **3.0 | 28 | 227** 3.0 | 33 | 273 **3.0 | 38 | 311** 3.5 | 9 | 94 3.5 | 12 | 119 3.5 | 15 | 153 **3.5 | 18 | 188** 3.5 | 23 | 239 **3.5 | 28 | 290** 3.5 | 33 | 341 **3.5 | 38 | 391** 3.75 | 9 | 89 3.75 | 12 | 125 3.75 | 15 | 161 **3.75 | 18 | 188** 3.75 | 23 | 242 **3.75 | 28 | 296** 3.75 | 33 | 350 **3.75 | 38 | 404** Subjects will be included in the PK analysis only if all intended Esprit BTK scaffolds are implanted.
Blood Sampling Timing for Analysis of Everolimus Pharmacokinetics	Pre-Esprit BTK implantation: Baseline Baseline is defined as prior to implantation of the first Esprit BTK; the blood sample will be drawn on the day of the index procedure either through a heparin lock, venous sheath, or venipuncture. During Esprit BTK implantation: • Collect a blood sample immediately after the first scaffold has been implanted • Collect one blood sample every 15 min after the first scaffold has been implanted until the last scaffold has been implanted Post-Esprit BTK implantation: 0 min (immediately after last scaffold implantation), 10 and 30 minutes, 1 hr, 2 hrs, 4 hrs, 6 hrs, 12 hrs, 24 hrs (1 day), 48 hrs (2 days), 72 hrs (3 days), 96 hrs (4 days), 120 hrs (5 days), 168 hrs (7 days), 336 hrs (14 days), and 720 hrs (30 days), 1440 hrs (60 days) Post-final scaffold implantation blood samples will be drawn at the time intervals stated above; timing of the post-implantation sampling will begin when the last Esprit BTK is deployed, i.e., last Esprit BTK delivery catheter is removed from the body.

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Table 2: Blood Sample Collection Time Windows:

Time Point	Allowed Time Window
Pre-procedure	On the day of index procedure prior to implantation of the first Esprit BTK
During Index procedure	First blood draw Immediately after first Esprit BTK has been implanted, this can be arterial from sheath Additional blood draws every 15 minutes after first Esprit BTK has been implanted until the last Esprit BTK has been implanted, the blood samples can be draw arterial from sheath
Post Procedure	
0 minute	When the last Esprit BTK is deployed, i.e. last Esprit BTK delivery catheter is removed from the body.
10 minutes	± 2 minutes
30 minutes	± 6 minutes
1 hour	± 12 minutes
2 hours	± 24 minutes
4 hours	± 48 minutes
6 hours	± 72 minutes
12 hours	± 144 minutes
24 hours (1 day)	± 4.8 hours
48 hours (2 days)	± 9.6 hours
72 hours (3 days)	± 14.4 hours
96 hours (4 days)	± 19.2 hours
120 hours (5 days)	± 24 hours
168 hours (7 days)	± 33.6 hours
336 hours (14 days)	± 67.2 hours
720 hours (30 days)	± 144 hours
1440 hours (60 days)	± 288 hours

Note: Each post-procedure time point allows an up to +/- 20% time-window (based on time duration from 0 minute to the intended time point) for blood sample collection. For example, time window for 1 hour post procedure is ± (1 hour * 20%) = ±12 minutes.

Clinical Follow-up	30 days, 60 days, 90 days, 180 days, 1, 2, 3, 4 and 5 years Follow-up for PK sub-study subjects will not include administration of the Patient Reported Outcomes (PRO) tools (WIQ, PAQ and EQ-5D-5L) nor wound imaging follow-up. Wound assessment will be per site standard of care. Duplex ultrasound for the PK study subjects will be conducted at 30 days ,180 days and 1 year.
PK Parameters	• t_{max} • C_{max} • AUC_{0-24h}

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	• AUC_{0-t} • $AUC_{0-\infty}$ • λ_z • $t_{1/2term}$ • CL
Safety Monitoring	Refer to *Section 7.0 Adverse Events*
Subject Enrollment and Registration	A subject is considered enrolled in the PK sub-study upon signing the informed consent form. Subjects will not be registered into the sub-study until after a) successful pre-dilatation and b) completion of the index procedure, with total scaffold length implanted between 170 and 256 mm. Blood collection post-Esprit BTK implantation will not be conducted if the subject did not receive the required total scaffold length (170 to 256 mm).
Exclusion from Analysis and Follow-up	Subjects in whom Esprit BTK enters the body but no scaffold were implanted will be excluded from the sub-study analysis. A 30-day safety follow-up will be required for these subjects. Subjects who received at least one Esprit BTK scaffold, but in whom some of the intended scaffolds were not implanted successfully will be excluded from the sub-study analysis and will require 5-year follow-up as per the time points described above in the "Clinical Follow-up" section. These subjects may have their follow-up via phone visit. The following assessments will not be required for these subjects: duplex ultrasound, wound imaging, completion of PRO tools. Subjects who received less than the required total scaffold length (170 to 256mm) will be excluded from the sub-study analysis and will require 5-year follow-up as per the time points described above in the "Clinical Follow-up" section. These subjects may have their follow-up via phone visit. The following assessments will not be required for these subjects: duplex ultrasound, wound imaging, completion of PRO tools. In all the above cases, subjects will be replaced in the PK sub-study.
Inclusion Criteria	**General Inclusion Criteria:** Refer to *Section 5.3.2.1 General Inclusion Criteria* of the LIFE-BTK protocol for complete list. The general inclusion criteria for LIFE-BTK PK sub-study are the same as those for the RCT, except for general inclusion criterion # 3 below. General Inclusion Criterion # 3: Subject requires primary treatment of one or more de novo or restenotic (treated with prior PTA) infrapopliteal lesions. **Anatomic Inclusion Criteria:** 1. One or more native infrapopliteal lesions, including de novo lesions in the same limb. Restenotic (from prior PTA) lesions are allowed.

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	a. Lesion must be located in the proximal 2/3 of native infrapopliteal vessels, with vessel diameter of ≥ 2.5 mm and ≤ 4.00 mm by investigator visual assessment. i. Note: see vessel sizing under "treatment strategy" section within the LIFE-BTK protocol. b. Total scaffold length to completely cover/treat target lesion(s) must be between 170 and 256 mm (maximum total everolimus drug dose of 2714 µg). c. The target vessel can have any other angiographic significant lesions (≥50%) that should be treated per institution standard of care prior to treatment of the target lesion. d. Tandem lesions are allowed and the total scaffold length used to cover the entire diseased segment must be ≤ 256 mm. 2. Target lesion(s) must have ≥ 70% stenosis, per visual assessment at the time of the procedure. If needed, quantitative imaging (angiography, IVUS, and/or OCT) can be used to aid accurate sizing of the vessels. 3. The distal margin of the scaffold must be located ≥ 10 cm proximal to the proximal margin of the ankle mortise. . If the vessel segment distal to the target lesion has a significant lesion (> 50% stenosis), it should be treated per institution standard of care prior to deployment of the scaffold. 4. Significant lesion (≥ 50% stenosis) in the inflow artery(ies) must be treated successfully (as per physician's assessment of the angiography) through standard of care prior to the treatment of the target lesion. Treatment must be done within the same trial procedure. Treatment allowed for inflow artery lesions are PTA, atherectomy, cutting/scoring balloon, Shockwave balloon, bare metal stent, drug-eluting stents or drug-coated balloon. Everolimus-coated or eluting devices are not allowed. 5. It is acceptable for non-target lesion(s) (if applicable) to be located in the same infrapopliteal vessel(s) as the target lesion, and suitable to be treated per institution standard of care. Non-target lesions must be treated successfully prior to target lesions and not requiring re-cross of the scaffold. 6. Crossing of the target lesion in an antegrade fashion is preferred, but retrograde crossing may be used. However, the treatment must be delivered antegrade.
Exclusion Criteria	**General Exclusion Criteria:** Refer to *Section 5.3.3.1 General Exclusion Criteria* of the LIFE-BTK protocol for the complete list. **Anatomic Exclusion Criteria:** 1. Lesions with severe calcification, in which there is a high likelihood that successful pre-dilatation cannot be achieved. 2. Lesion that has prior metallic stent implant. .

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	3. Coronary or peripheral artery treated with everolimus-eluting device during index procedure, or within 90 days prior to index procedure. 4. Target or (if applicable) non-target vessel contains visible thrombus as indicated in the angiographic images. 5. Subject has angiographic evidence of thromboembolism or atheroembolism in the ipsilateral extremity. (Pre- and post-angiographic imaging must confirm the absence of emboli in the distal anatomy.) 6. Unsuccessfully treated proximal inflow limiting arterial stenosis or inflow-limiting arterial lesions left untreated. 7. No angiographic evidence of a patent pedal artery. 8. Target or (if applicable) non-target lesion location requiring bifurcation treatment method that requires scaffolding of both branches (provisional treatment, without intention of scaffolding both branches is acceptable). 9. Aneurysm in the iliac, common femoral, superficial femoral, popliteal or target artery of the ipsilateral extremity. 10. Visual assessment of the target lesion suggests that the investigator is unable to pre-dilate the lesion according to the vessel diameter. 11. Target lesion has a high probability that atherectomy will be required at the time of index procedure for treatment of the target vessel. Note: staged procedures are not allowed in LIFE-BTK PK sub-study.
Index Procedure and Treatment Strategy	Refer to *Section* 6.*4 Index Procedure* in the LIFE-BTK protocol. In the PK sub-study, all target lesions are to be treated with the Esprit BTK only Subjects in the PK sub-study will not be randomized; any references to randomization should be disregarded
Post-procedure medications	Refer to *Section 6.5 Post-procedure Medications* of the LIFE-BTK protocol for required antiplatelet medications and highly recommended concomitant medications.

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LIFE-BTK PK Sub-study: Schedule of Events

PROCEDURE/ TEST	Baseline	Baseline (within 7 days)	Pre-procedure (within 24 hours)	Procedure#	Post-procedure up to 12 hours								1-14 days post-procedure							30 days	60 days	90 days (± 14 d)	180 days (± 28 d)	1 year (± 28 d)	2, 3, 4, 5 years (± 28 d)	Unscheduled visits
Exact Timing					0 minute*	10 minutes	30 minutes	1 hour	2 hours	4 hours	6 hours	12 hours	24 hours (1 day)	48 hours (2 days)	72 hours (3 days)	96 hours (4 days)	120 hours (5 days)	168 hours (7 days)	336 hours (14 days)	720 hours (30 days)	1440 hours (60 days)					
Blood draw for PK study			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓					
Subject Medical/Clinical History (Age, Sex, Risk Factors)	✓																									
Subject Informed Consent (Must be obtained prior to any study related testing or procedures)	✓																									
General Inclusion/Exclusion Criteria	✓																									
Angiographic Inclusion/Exclusion Criteria	✓		✓																							
Pregnancy Test (if applicable)		✓																								

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Hgb, Platelet Count, Creatinine, HbA1c, eGFR, WBC	✓												
Vascular Angiogram, IVUS or OCT	✓			✓									
Duplex Ultrasound							✓			✓	✓		✓
ABI/TBI measurement	✓^		✓^				✓		✓	✓	✓	✓	✓
Study device information				✓									
Per Protocol Medications			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Concomitant Medications				✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Adverse Events				✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Rutherford Becker category assessment	✓						✓		✓	✓	✓	✓	✓
Wound assessment (site reported only, no images will be taken)	✓				✓	✓	✓		✓	✓	✓	✓	

Note: each post-procedure visit can be a Study Doctor's office visit, a hospital visit, or an in-home visit.
Note: Each post-procedure time point allows an up to +/- 20% time-window (based on time duration from 0 minute to the intended time point) for blood sample collection. For example, time window for 1 hour post procedure is ± (1 hour * 20%) = ±12 minutes.
[#] Collect a blood sample immediately after the first scaffold has been implanted. Collect one blood sample every 15 min after the first scaffold has been implanted until the last scaffold has been implanted
*0 minute is defined as when the last Esprit BTK is deployed, i.e., last Esprit BTK delivery catheter is removed from the body.
[^] Only one ABI/TBI measurement is needed at either baseline or pre-procedure.

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APPENDIX XI: REVISION HISTORY

[redacted]

[redacted]

Amendment Number	Version	Date	Details	Rationale
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

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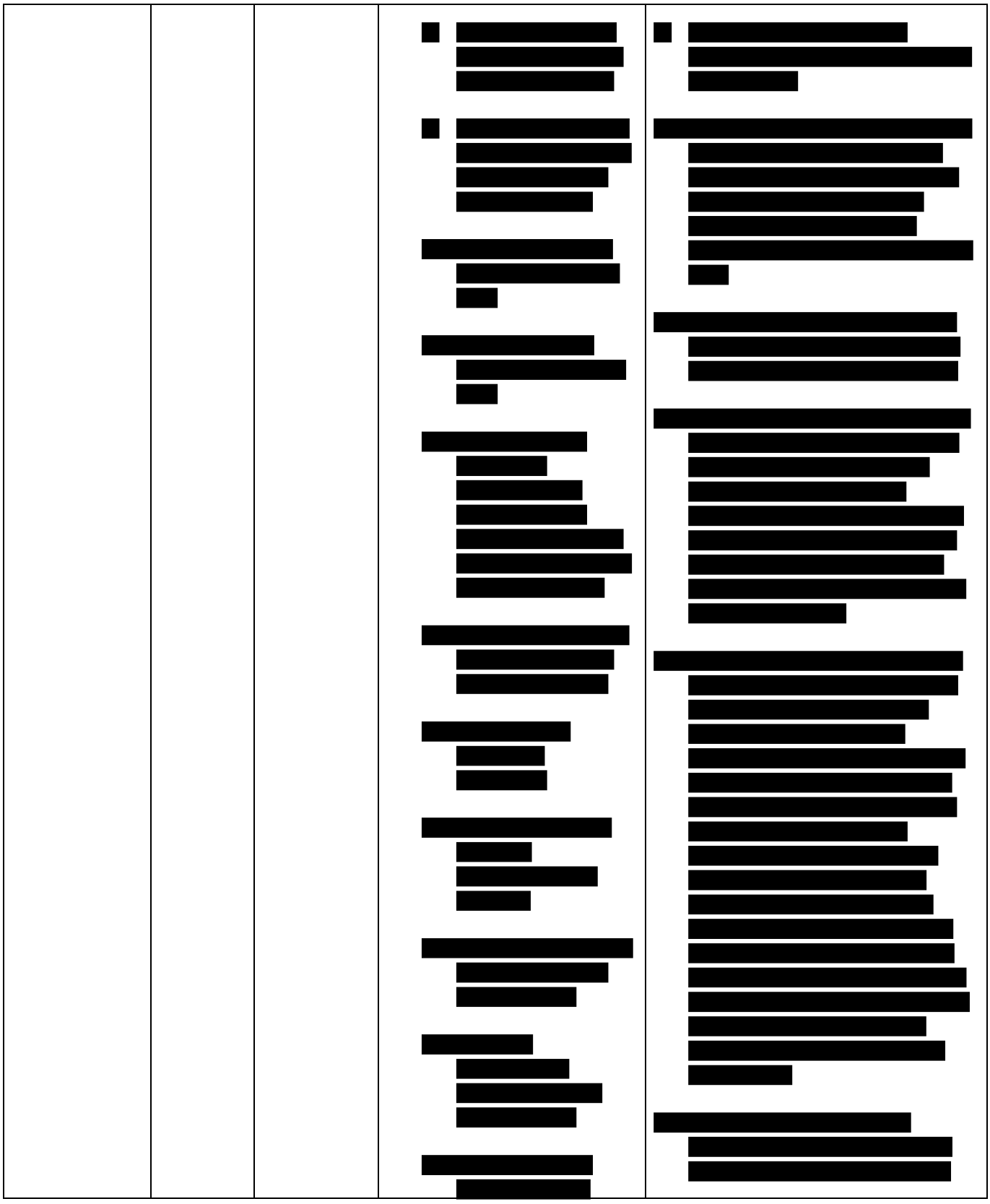

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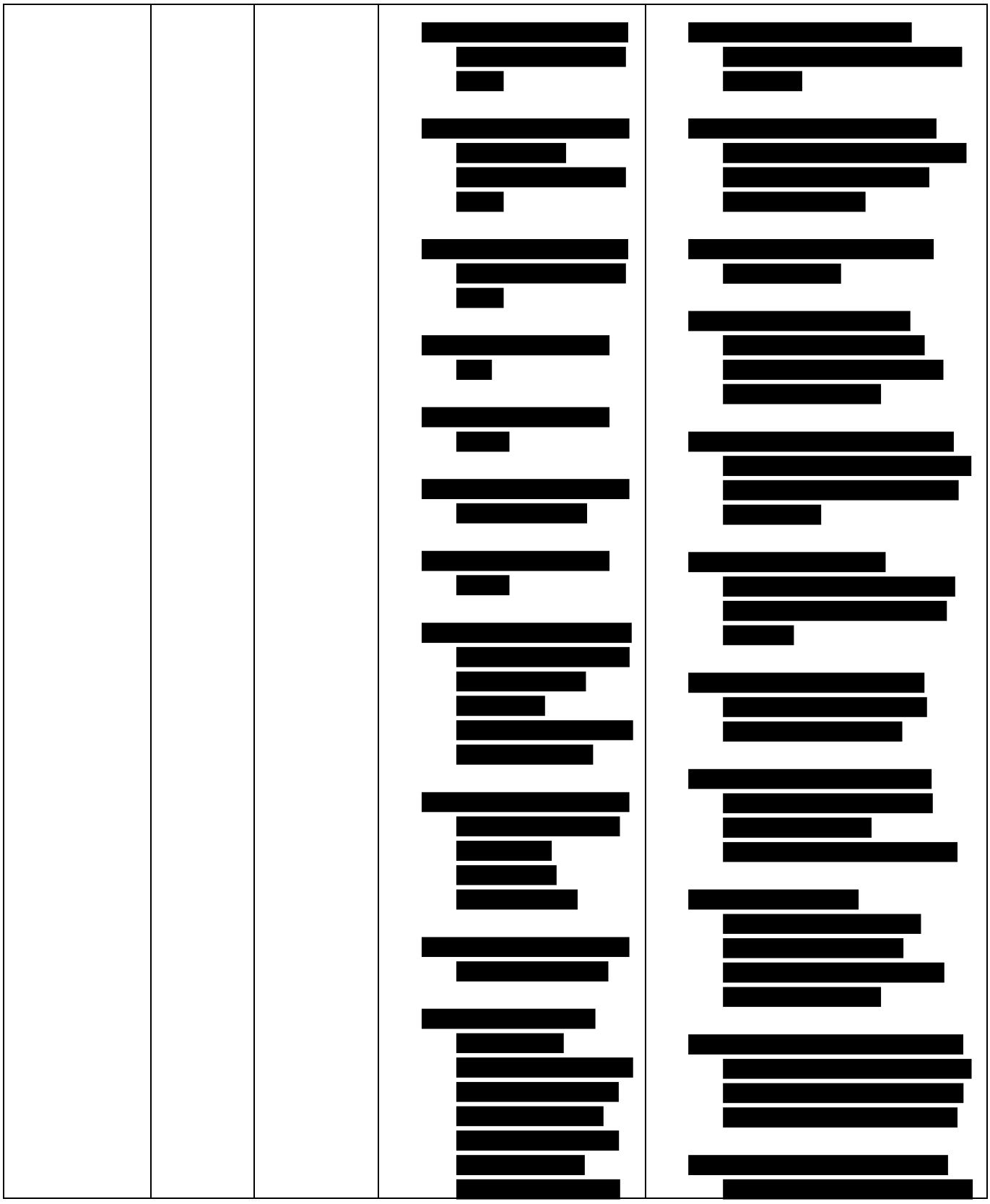

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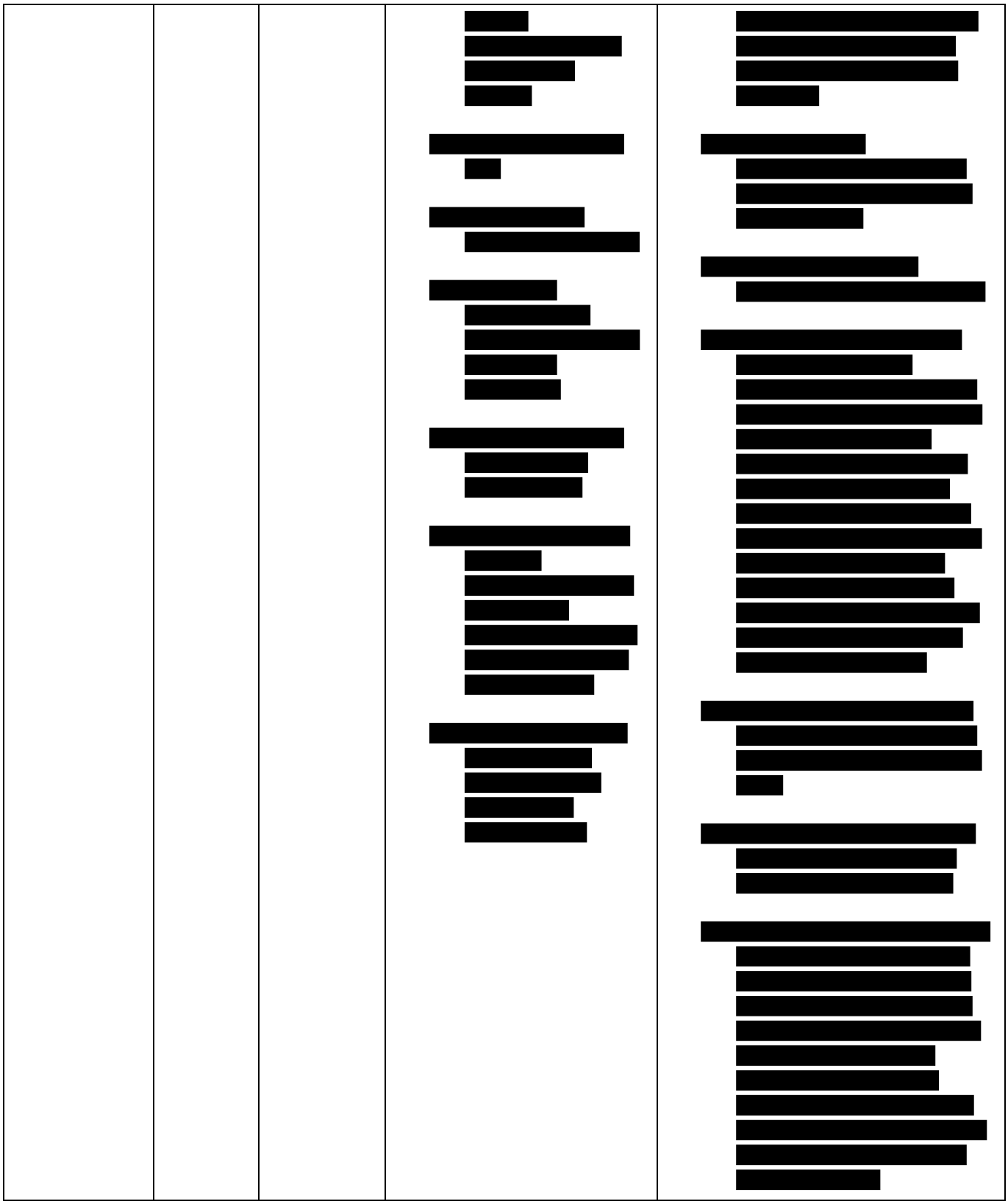

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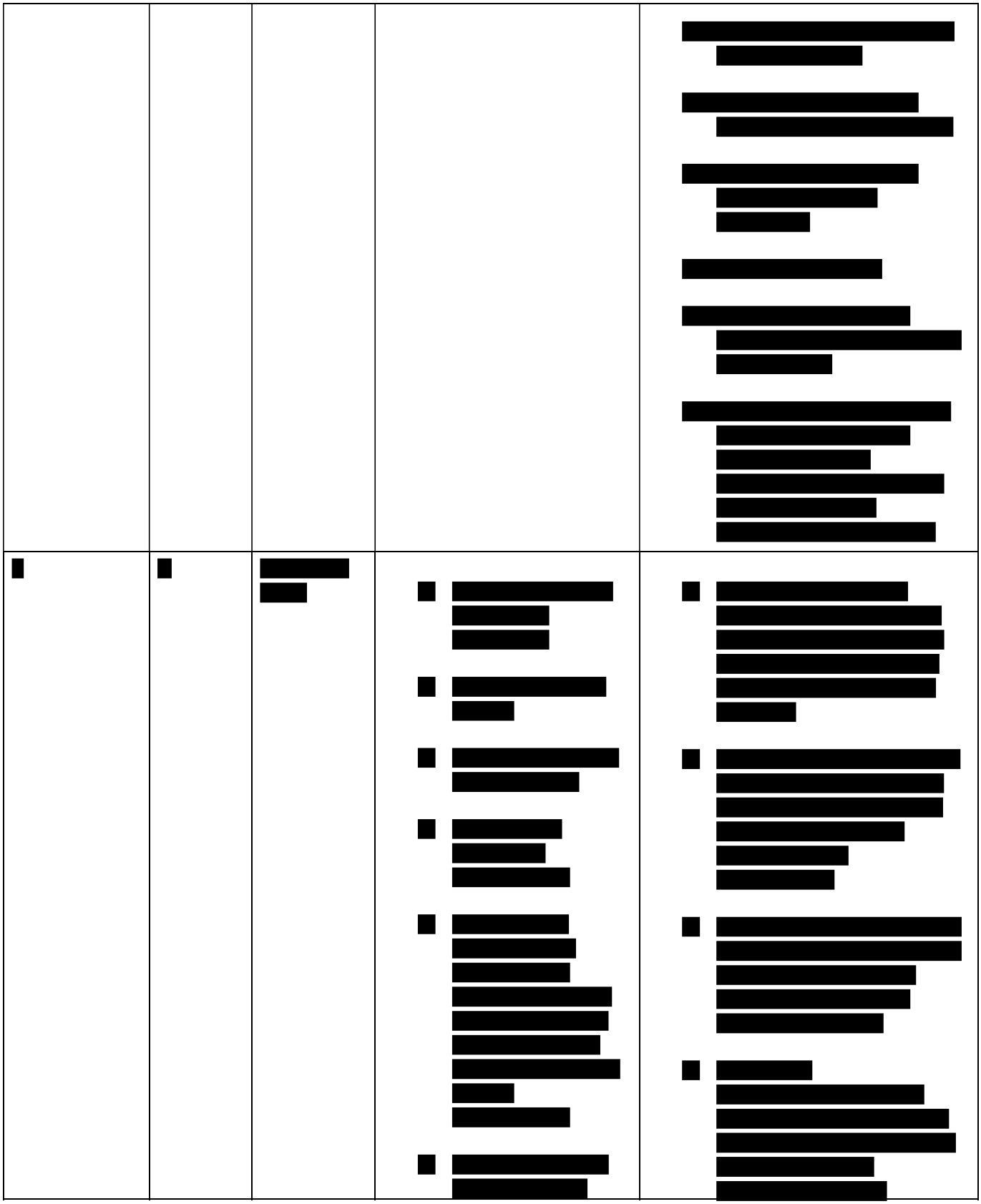

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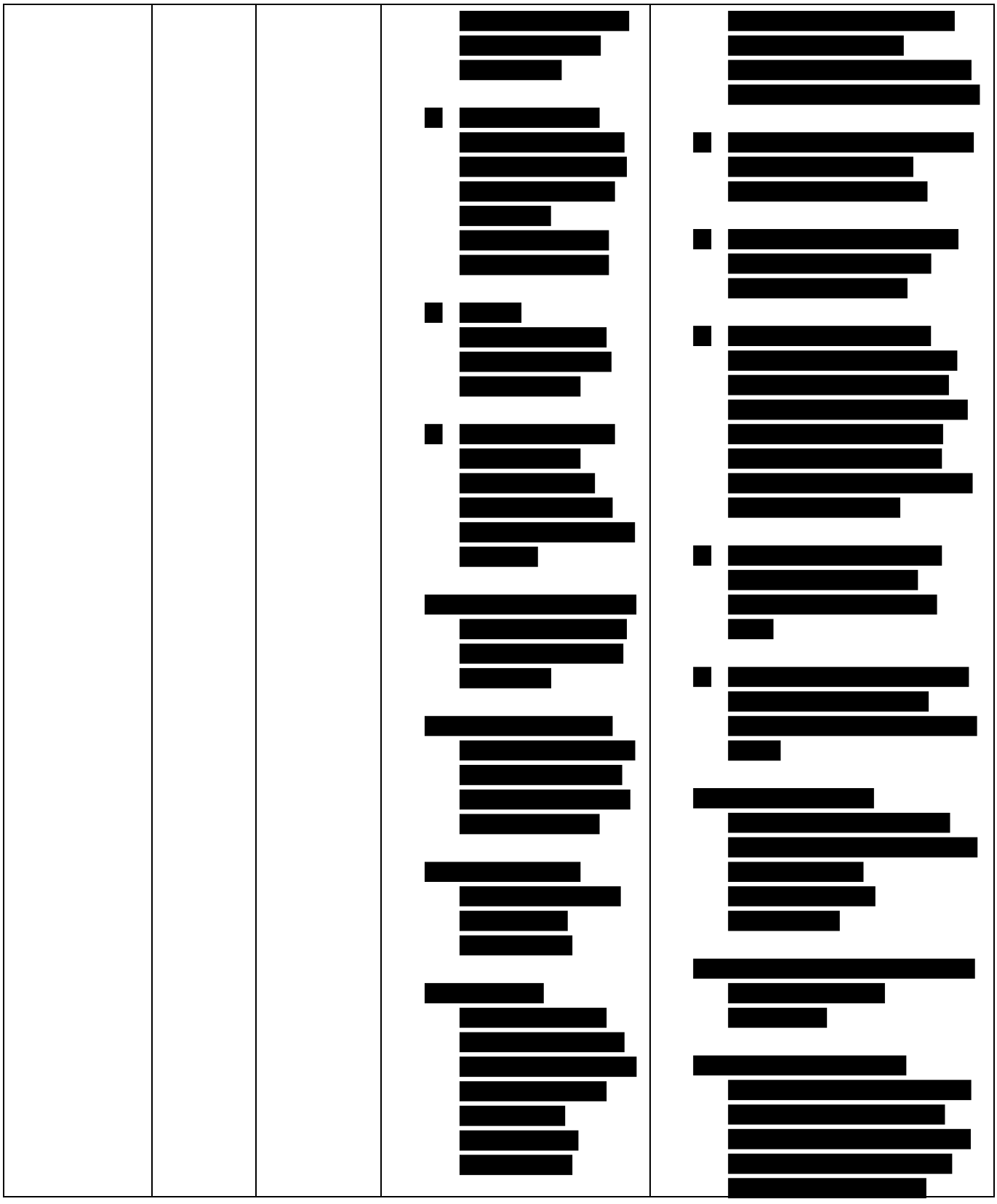

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			[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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			[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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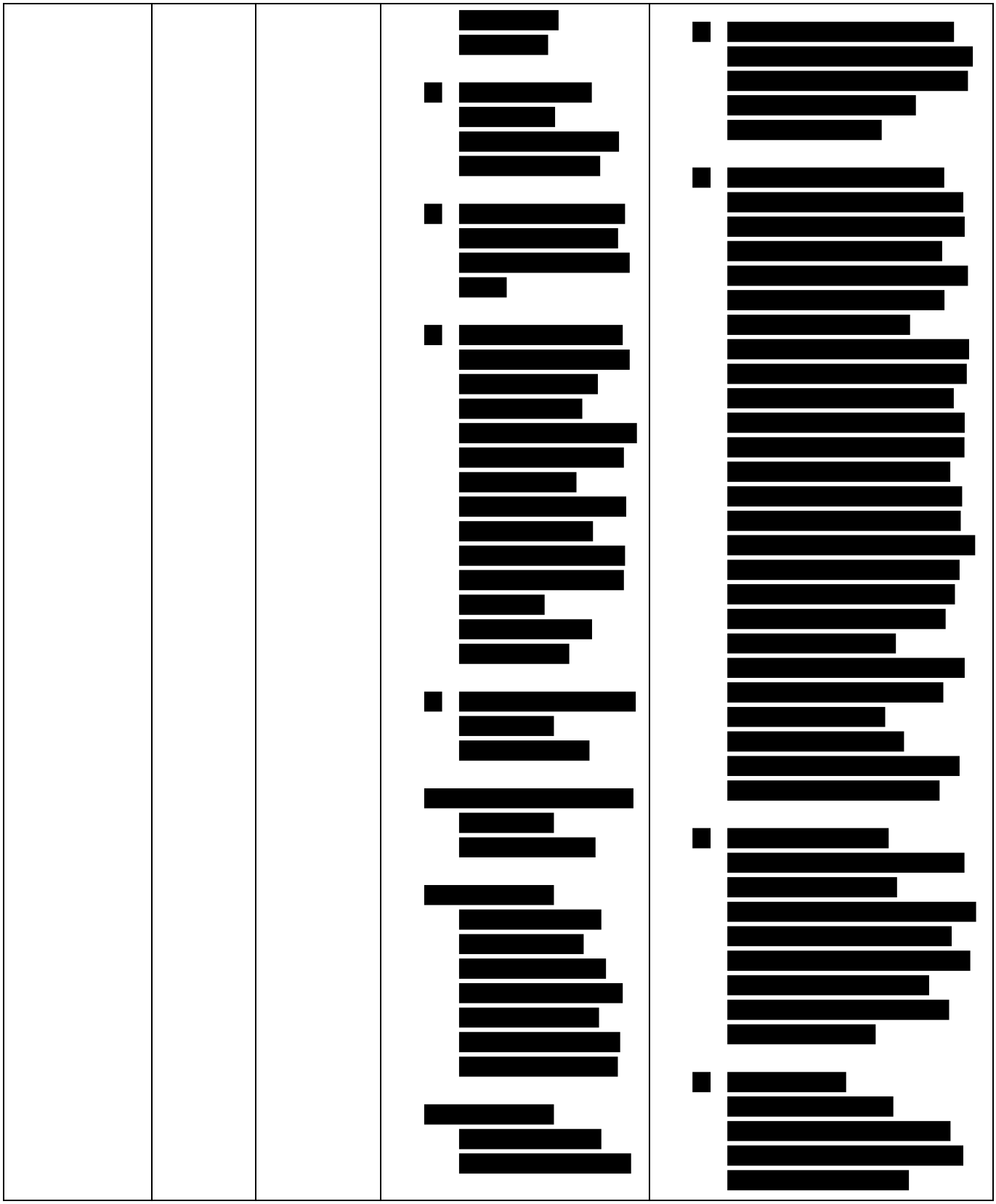

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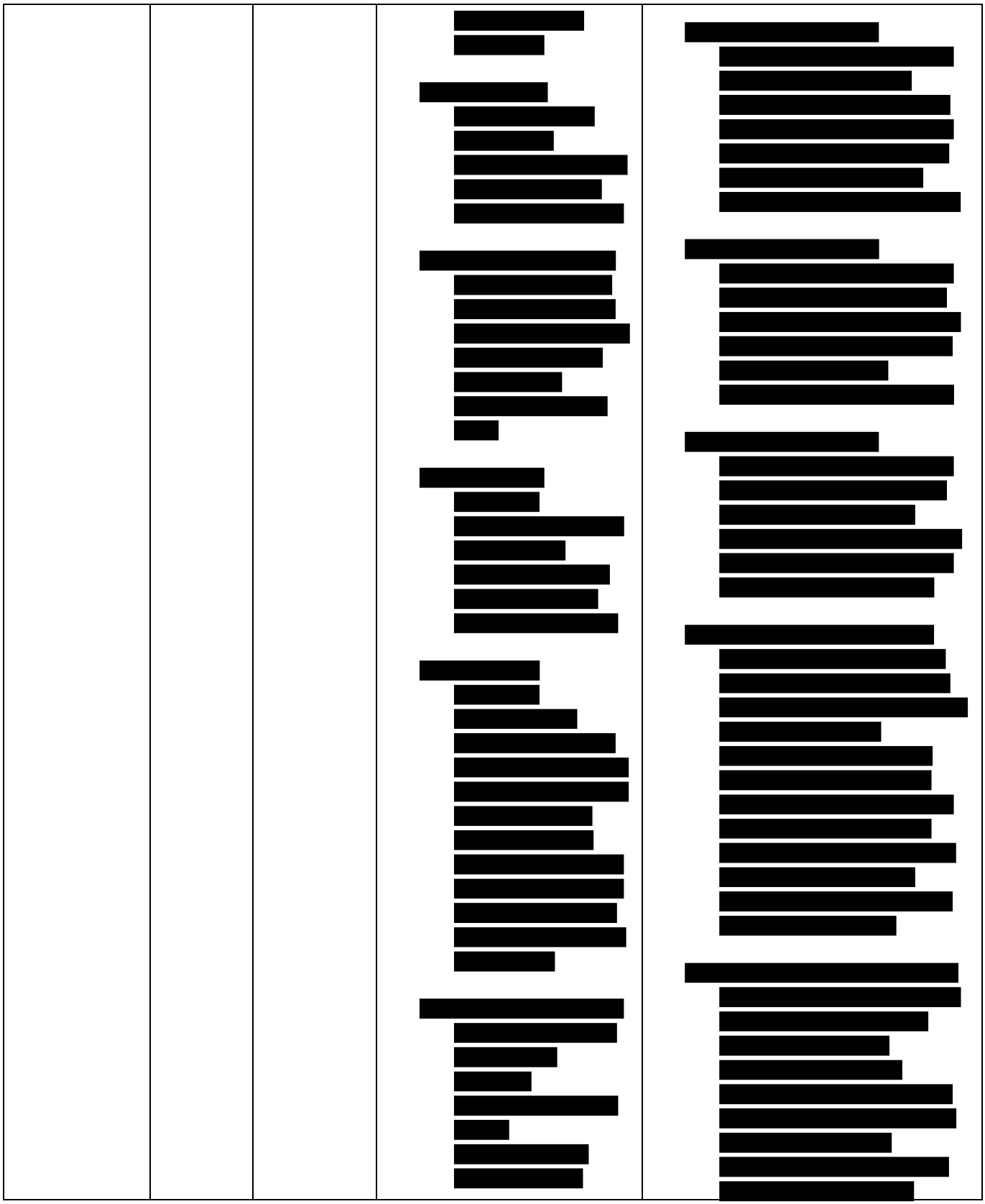

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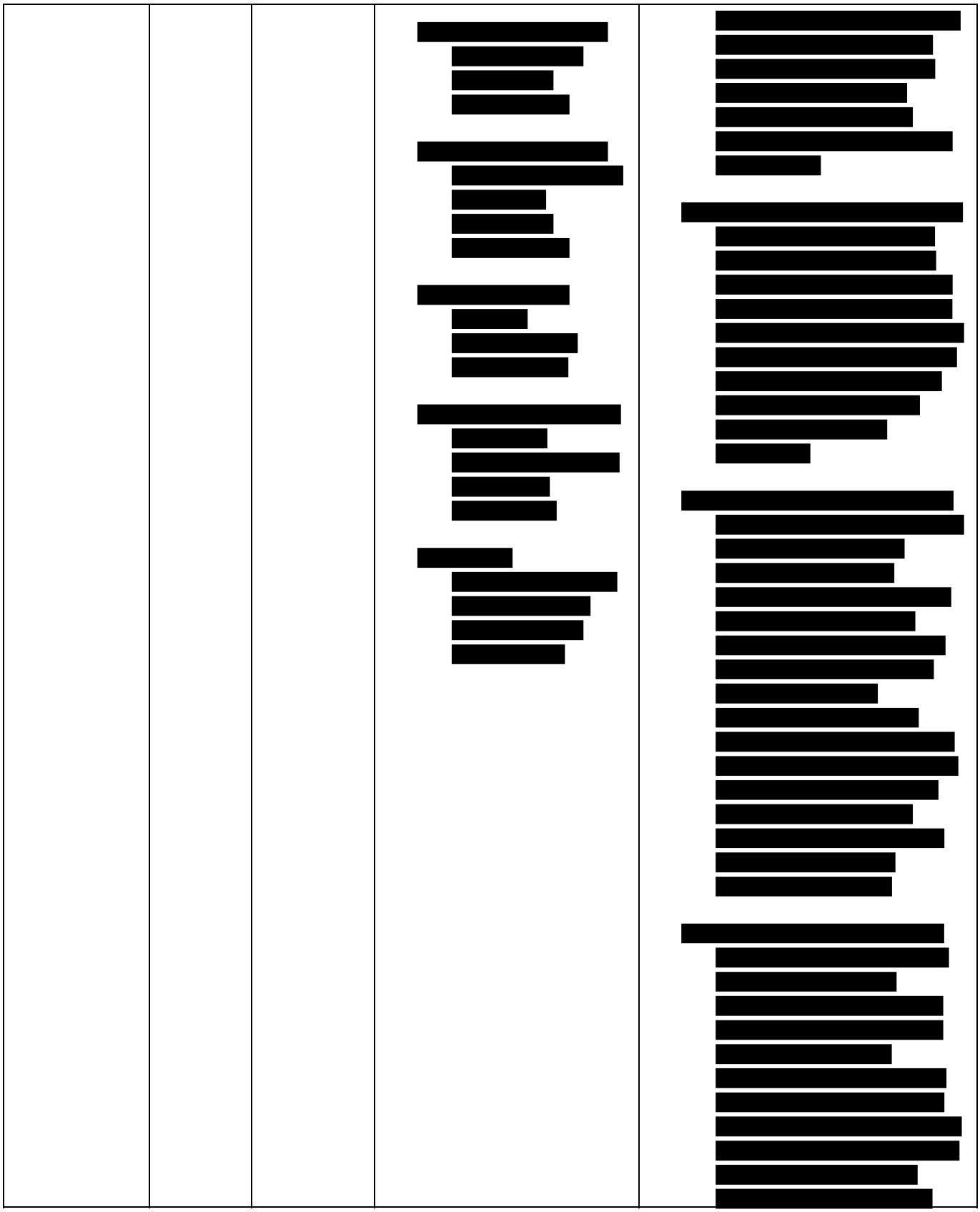

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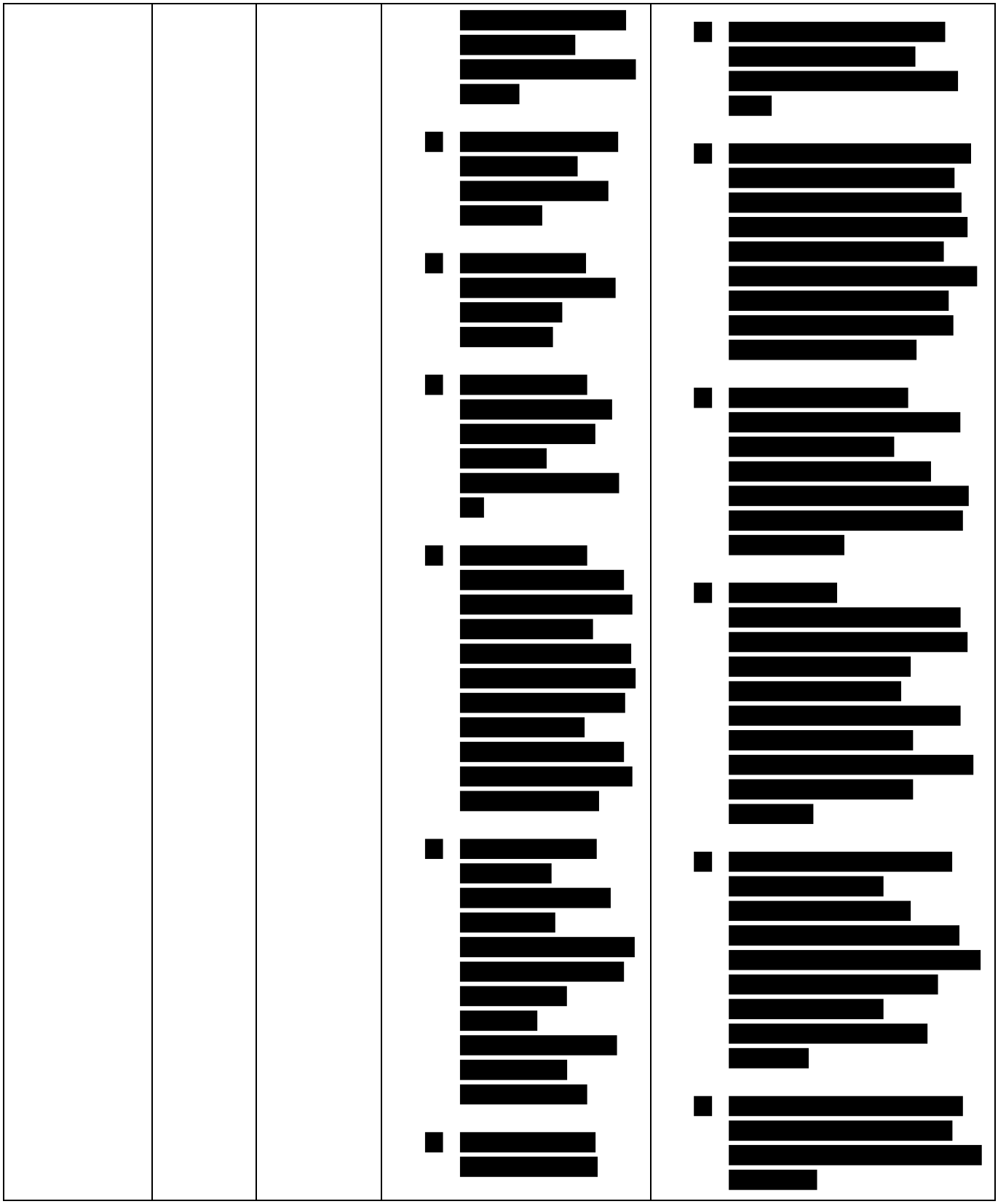

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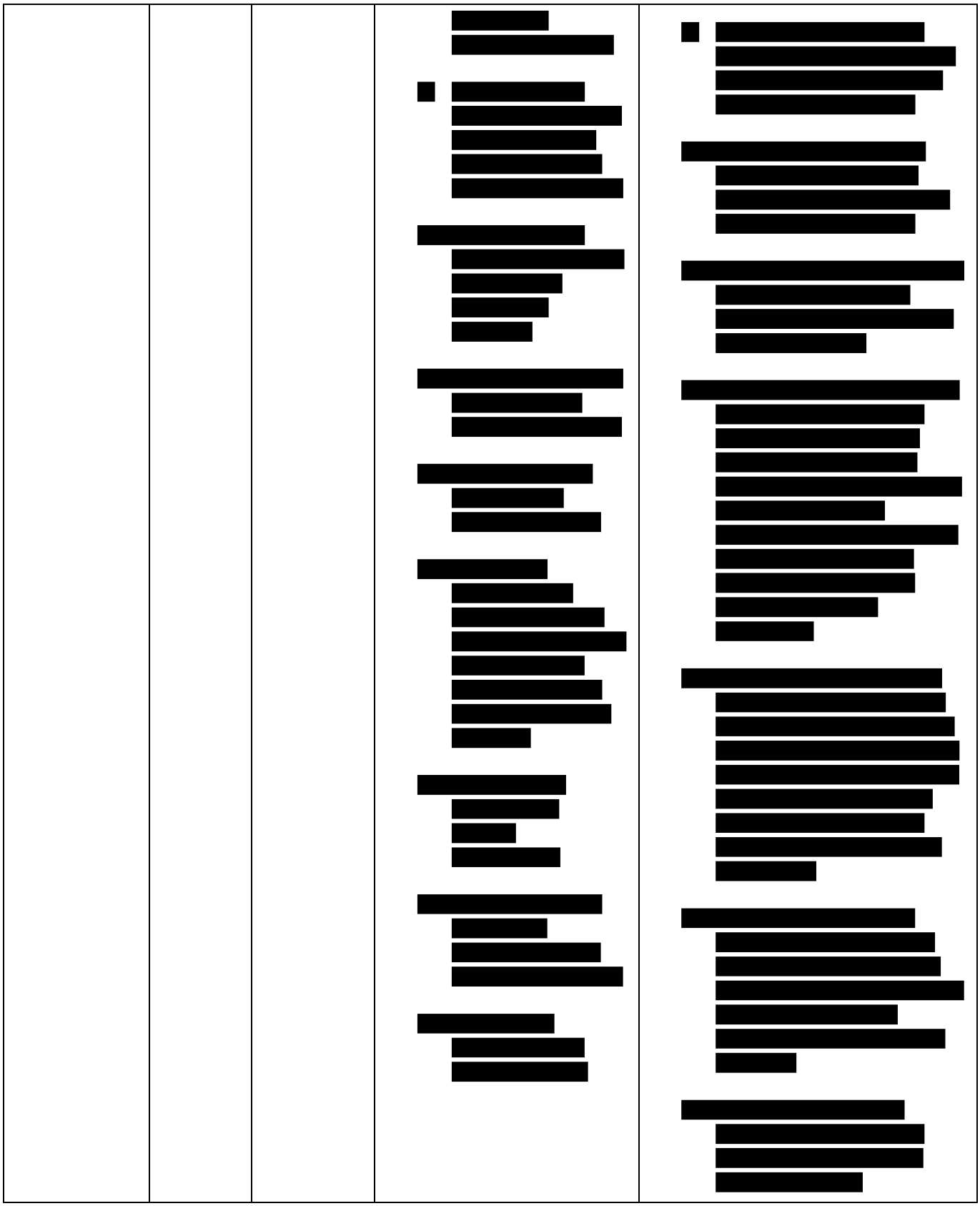

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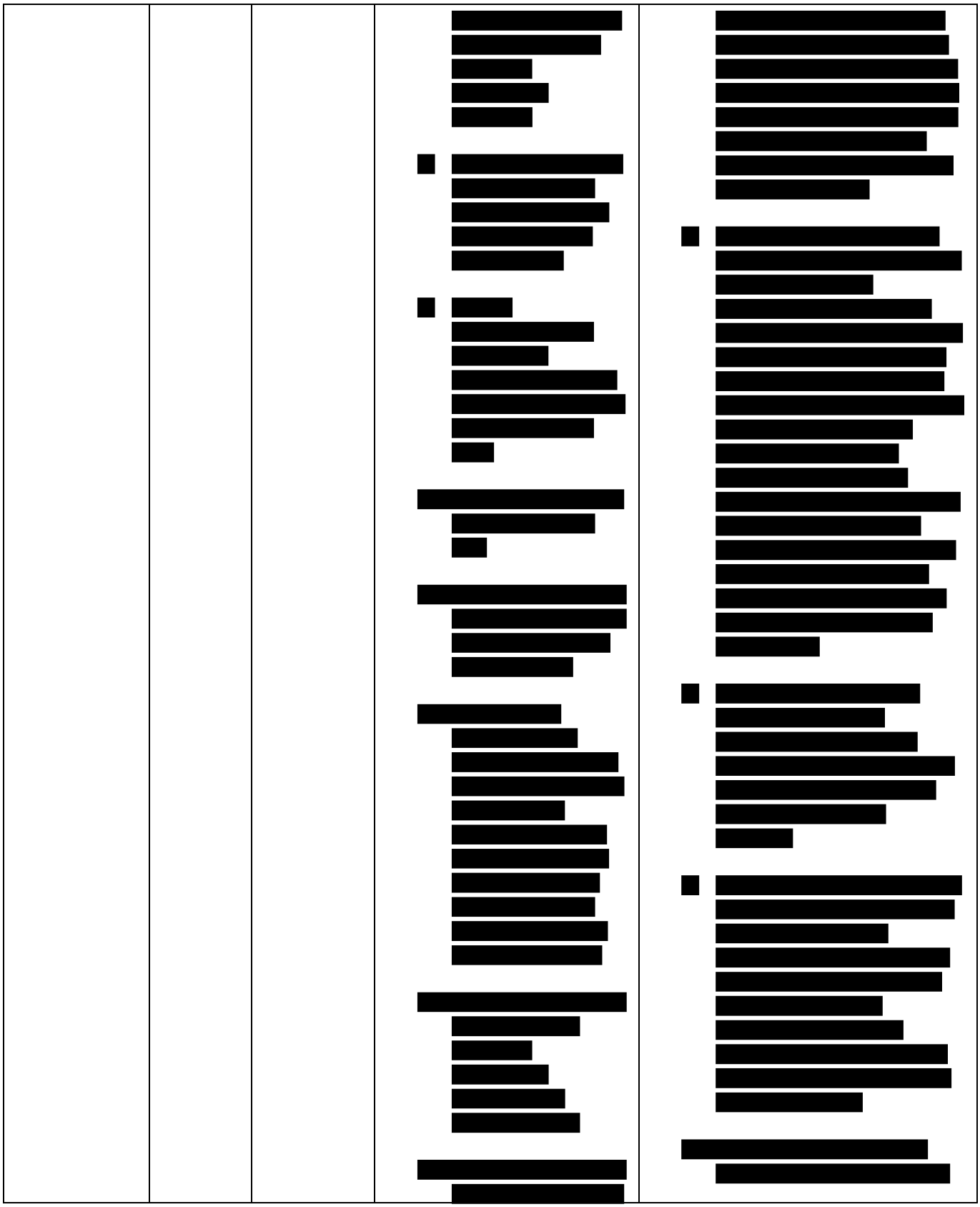

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			[redacted]	[redacted]

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APPENDIX XII: CIP SUMMARY

Trial Name	LIFE-BTK Randomized Controlled Trial
Purpose	Pre-market clinical evaluation of the everolimus eluting Esprit BTK System for the planned treatment of narrowed infrapopliteal lesions.
Study Design	Prospective, randomized clinical trial (2:1) evaluating planned treatment of below-the-knee (BTK) lesions with Esprit BTK versus planned treatment with PTA. Approximately 225 subjects and up to 315 subjects, in approximately 65 clinical sites in the US, Asia, Australia and New Zealand (maximum 55 sites in the US: 50 sites for the LIFE-BTK RCT plus 5 sites for the pharmacokinetics sub-study). Subject registration is capped at 45 (20% of total sample size) per site.
Study Device	Esprit BTK
Study Population	Patients with arterial narrowing in infrapopliteal lesions causing CLI who satisfy the key inclusion and exclusion criteria described below.
Primary Endpoints	**Primary Efficacy Endpoint** • Composite of limb salvage and primary patency at 1 year testing for superiority ○ Includes freedom from above ankle amputation in index limb, 100% total occlusion of target vessel, binary restenosis of target lesion, and clinically-driven target lesion revascularization **Primary Safety Endpoint** • Freedom from MALE+POD testing for non-inferiority Above ankle amputation in index limb; Major re-intervention on index limb at 6 months and perioperative (30 day) mortality
Key Inclusion Criteria	**General Inclusion Criteria** 1. Subject must provide written informed consent prior to any clinical investigation related procedure. 2. Subject has symptomatic Critical Limb Ischemia (CLI), Rutherford Becker Clinical Category 4 or 5. 3. Subject requires primary treatment of up to two de novo or restenotic (prior PTA) infrapopliteal lesions 4. Subject must be at least 18 years of age. 5. Female subject of childbearing potential should not be pregnant and must be on birth control. Note: Female subjects of child-bearing potential must have a negative pregnancy test done within 7 days prior to the index procedure per site standard test.

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	Anatomic Inclusion Criteria 1. Up to two native infrapopliteal lesions, each lesion located in separate infrapopliteal vessel, in the same limb. Restenotic (prior PTA) lesions are allowed. a. Lesion must be located in the proximal 2/3 of native infrapopliteal vessels, with vessel diameter of ≥ 2.5 mm and ≤ 4.00 mm by investigator visual assessment. Note: see vessel sizing under "treatment strategy" section. b. Total scaffold length to completely cover/treat a target lesion must not exceed 170 mm (total everolimus drug dose of 1790 µg). c. The total scaffold length must not exceed 170 mm. d. The target vessel cannot have any other angiographic significant lesions (≥50%). e. Tandem lesions are allowed if they are < 3 cm apart and the total scaffold length used to cover the entire diseased segment is ≤ 170 mm. Each tandem lesion is considered one lesion. 2. Target lesion(s) must have ≥ 70% stenosis, per visual assessment at the time of the procedure. If needed, quantitative imaging (angiography, IVUS, and/or OCT) can be used to aid accurate sizing of the vessels. 3. The distal margin of the target lesion must be located ≥ 10 cm proximal to the proximal margin of the ankle mortise. The vessel segment distal to the target lesion must be patent all the way to the ankle, with no significant lesion (≥ 50% stenosis). 4. Significant lesion (≥ 50% stenosis) in the inflow artery(ies) must be treated successfully (as per physician's assessment of the angiography) through standard of care prior to the treatment of the target lesion. Treatment can be done within same trial procedure. 5. Non-target lesion(s) (if applicable) must be located in separate infrapopliteal vessel(s) from the target lesion, and suitable to be treated per institution standard of care 6. Guidewire must cross the target lesion successfully. Crossing in an antegrade fashion is preferred, but retrograde crossing may be used. However, the treatment must be delivered antegrade.
Key Exclusion Criteria	**General Exclusion Criteria** 1. Subject is currently participating in another clinical investigation that has not yet completed its primary endpoint. 2. Pregnant or nursing subjects and those who plan pregnancy during the clinical investigation follow-up period. 3. Presence of other anatomic or comorbid conditions, or other medical, social, or psychological conditions that, in the

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	investigator's opinion, could limit the subject's ability to participate in the clinical investigation or to comply with follow-up requirements. 4. Incapacitated individuals, defined as persons who are mentally ill, mentally handicapped, or individuals without legal authority, are excluded from the study population. 5. Subject has had any amputation to the ipsilateral extremity other than the toe or forefoot, or subject has had major amputation to the contralateral extremity < 1 year prior to index procedure and is not independently ambulating. 6. Subject has known hypersensitivity or contraindication to device material and its degradants (everolimus, poly (L-lactide), poly (DL-lactide), lactide, lactic acid) and cobalt, chromium, nickel, platinum, tungsten, acrylic and fluoro polymers that cannot be adequately pre-medicated. Subject has a known contrast sensitivity that cannot be adequately pre-medicated. 7. Subject has known allergic reaction, hypersensitivity or contraindication to aspirin; or to ADP antagonists such as clopidogrel, prasugrel or ticagrelor; or to anticoagulants such as heparin or bivalirudin, and therefore cannot be adequately treated with study medications. Subject with planned surgery or procedure necessitating discontinuation of antiplatelet medications, within 12 months after index procedure. Planned amputation that will necessitate discontinuation of antiplatelet medications is allowed. 8. Subject has life expectancy ≤ 1 year. 9. Subject has had a stroke within the previous 3 months with residual Rankin score of ≥ 2. 10. Subject has renal insufficiency as defined as an estimated GFR < 30 ml/min per 1.73m^2. 11. Subject is currently on dialysis. 12. Subject has platelet count < 100,000 cells/mm^3 or > 700,000 cells/mm^3, a WBC < 3,000 cells/mm^3, or hemoglobin < 9.0 g/dl. 13. Subject has known serious immunosuppressive disease (e.g., human immunodeficiency virus), or has severe autoimmune disease, that requires chronic immunosuppressive therapy (e.g., systemic lupus erythematosus, etc.), or subject is receiving immunosuppression therapy for other conditions. Subjects with HIV and who have undetectable viral load, such that their immune system is not considered compromised, are eligible. 14. Subject has Body Mass Index (BMI) <18. 15. Subject is receiving or scheduled to receive anticancer therapy for malignancy within 6 months prior to index procedure or within 1 year after the procedure. Patients taking medications classified

as chemotherapy but who have been in remission for at least 6 months are eligible.

16. Subject has coagulation disorder that increases the risk of arterial thrombosis. Subjects with deep vein thrombosis and disorders that increase the risk of deep vein thrombosis can be included in the study.
17. Subject who requires thrombolysis as a primary treatment modality, or requires other treatment for acute limb ischemia of the target limb
18. Subject has previously had, or requires surgical revascularization involving any vessel of the ipsilateral extremity. Prior femoropopliteal or aortobifemoral bypass is allowed. Any bypass to the tibial arteries is not allowed.
19. Subject has signs or symptoms of advanced limb infection or septicemia (fever > 38.5, WBC > 15,000 cells/microliter, hypotension) at the time of assessment. Osteomyelitis of the phalanges or metatarsal heads (as described in exclusion criteria #21a) or cellulitis of the foot amenable to treatment with IV antibiotics at the time of revascularization is acceptable.
20. Subject is bedridden or unable to walk (with assistance is acceptable). Subjects in wheelchair who are able to mobilize on their own can be enrolled.
21. Subject with extensive tissue loss salvageable only with complex foot reconstruction or non-traditional transmetatarsal amputations. This includes subjects with: Osteomyelitis including and/or proximal to the metatarsal head
    a. Osteomyelitis that extends proximal to the metatarsal heads. Osteomyelitis limited to the phalanges or metatarsal heads is acceptable for enrollment.
    b. Gangrene involving the plantar skin of the forefoot, midfoot, or heel
    c. Deep ulcer or large shallow ulcer (> 3 cm) involving the plantar skin of the forefoot, midfoot, or heel
    d. Full thickness heel ulcer with/without calcaneal involvement
    e. Any wound with calcaneal bone involvement
    f. Wounds that are deemed to be neuropathic or non-ischemic in nature
    g. Wounds that would require flap coverage or complex wound management for large soft tissue defect
    h. Full thickness wounds on the dorsum of the foot with exposed tendon or bone
22. Subject is unable or unwilling to provide written consent prior to enrollment

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	23. Subject has active symptoms and/or a positive test result of COVID-19 or other rapidly spreading novel infectious agent within the prior 2 months. **Anatomic Exclusion Criteria** 1. Lesions with severe calcification, in which there is a high likelihood that successful pre-dilatation cannot be achieved. 2. Lesion that has prior metallic stent implant. 3. Significant (≥ 50% stenosis) lesion in a distal outflow artery that would be perfused by the target vessel and that requires treatment at the time of the index procedure. 4. Subject has had or will require treatment in any vessel with an everolimus drug-coated stent or drug-eluting device < 30 days pre-study procedure, or during the index procedure, such that the cumulative (Esprit BTK plus everolimus-eluting device) everolimus dose exceeds 1790 µg. 5. Target or (if applicable) non-target vessel contains visible thrombus as indicated in the angiographic images. 6. Subject has angiographic evidence of thromboembolism or atheroembolism in the ipsilateral extremity. (Pre- and post-angiographic imaging must confirm the absence of emboli in the distal anatomy.) 7. Unsuccessfully treated proximal inflow limiting arterial stenosis or inflow-limiting arterial lesions left untreated. 8. No angiographic evidence of a patent pedal artery. 9. Target or (if applicable) non-target lesion location requiring bifurcation treatment method that requires scaffolding of both branches (provisional treatment of target lesions, without intention of scaffolding both branches is acceptable). 10. Aneurysm in the iliac, common femoral, superficial femoral, popliteal or target artery of the ipsilateral extremity. 11. Visual assessment of the target lesion suggests that the investigator is unable to pre-dilate the lesion according to the vessel diameter. 12. Target has a high probability that atherectomy will be required at the time of index procedure for treatment of the target vessel.
Primary Analysis Sample Size justification	**Primary Efficacy Endpoint:** Sample size of this study is based on primary efficacy endpoint of 1 year composite of limb salvage and patency based on the following assumptions: • One-sided alpha =0.025 (Superiority) • [redacted] • [redacted] • [redacted]

[redacted]

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	Primary Safety Endpoint Non-inferiority analysis for the primary safety endpoint based on the following assumptions: • One-sided alpha =0.025 • [redacted] • Non-inferiority margin - 10% • [redacted] [redacted]
Quality of Life Endpoints	Quality of Life at baseline, 30 days, 3 and 6 months, and 1 year follow-up. The following questionnaires will be used in this study till 1 year follow-up: • Walking Improvement Questionnaire (WIQ) • Peripheral Arterial Questionnaire (PAQ) in CLI module • Measure of Health Outcome (EQ-5D-5L)

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Follow-up Schedule

The follow-up schedule§ and endpoint assessments are shown below.

Time	Endpoints assessed
14 days (± 3 days)	Index wound assessment[1,*]
30 days (± 7 days)	Medications review, adverse events review, ABI/TBI measurement, functional status (Rutherford Becker), index wound assessment[1], new wound assessment[2], WIQ, PAQ, EQ-5D-5L
30 days (± 14 days)	Duplex Ultrasound[3]
42 days (± 7 days)	Index wound assessment[1,*]
90 days (± 14 days)	Medications review, adverse events review, ABI/TBI measurement, functional status (Rutherford Becker), index wound assessment[1], new wound assessment[2], WIQ, PAQ, EQ-5D-5L
180 days (± 28 days)	Duplex Ultrasound[3], medications review, adverse events review, ABI/TBI measurement, functional status (Rutherford Becker), index wound assessment[1], new wound assessment[2], WIQ, PAQ, EQ-5D-5L
1 year (± 28 days)	Duplex Ultrasound[3], medications review, adverse events review, ABI/TBI measurement, functional status (Rutherford Becker), index wound assessment[1], new wound assessment[2], WIQ, PAQ, EQ-5D-5L
2 years (± 28 days)	Duplex Ultrasound[3], medications review, adverse events review, ABI/TBI measurement, functional status (Rutherford Becker), new wound assessment[2]
3 years (± 28 days)	Duplex Ultrasound[3], medications review, adverse events review, ABI/TBI measurement, functional status (Rutherford Becker), new wound assessment[2]
4 years (± 28 days)	Medications review, adverse events review, ABI/TBI measurement, functional status (Rutherford Becker), new wound assessment[2]
5 years (± 28 days)	Medications review. adverse events review, ABI/TBI measurement, functional status (Rutherford Becker), new wound assessment[2]

[1] Index wound assessment for healing and infection will be assessed by the core laboratory through 90 days (14 days, 30 days, 42 days and 90 days). For index wounds that are not healed by 90 days, the index wound will be

	assessed by the core laboratory at 180 days. If the index wound is not healed by 180 days, index wound assessment by the core laboratory will be carried out at 1 year. Index wounds that have healed by 90 days will not be assessed by the core laboratory at 180 days and 1 year. A formal office visit is highly recommended at 14-day and 42-day follow-up for evaluation of index wound. The option to take wound pictures remotely at 14 days and 42 days in accordance to the core laboratory wound imaging guidelines is for subjects that are unable to complete an office visit. No wound images will be collected outside of the protocol defined timepoints. * If a subject does not have an index wound at baseline, they will not need to return to the site at 14 days and 42 days. [2] New wound is defined as wound below the knee in the index limb that was not identified at the time of the index procedure or wound that has recurred in the same location following the healing of the index wound. The new wound will be assessed firstly by the wound assessment core laboratory for etiology. Subsequently, the new wound will be evaluated by the site per protocol until the wound is healed through the 5-year follow-up. If a new wound is first observed at 5-year follow-up, a picture will be taken for etiology assessment by the core laboratory. As this will be the final patient visit for the trial, no additional pictures of the new wound will be required following the initial picture submitted to the core laboratory. [3] Duplex ultrasound is required at 30 ± 14 days post-procedure, at 180 days and at 1, 2 and 3 years; if a patient is symptomatic or occlusion is suspected, duplex as well as angiogram should be completed.

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APPENDIX XIII: ESPRIT BTK Part Numbers

Scaffold size	Part Number
2.5 x 9 mm	[redacted]
2.5 x 12 mm	[redacted]
2.5 x 15 mm	[redacted]
2.5 x 18 mm	[redacted]
2.5 x 23 mm	[redacted]
2.5 x 28 mm	[redacted]
2.5 x 33 mm	[redacted]
2.5 x 38 mm	[redacted]
2.75 x 9 mm	[redacted]
2.75 x 12 mm	[redacted]
2.75 x 15 mm	[redacted]
2.75 x 18 mm	[redacted]
2.75 x 23 mm	[redacted]
2.75 x 28 mm	[redacted]
2.75 x 33 mm	[redacted]
2.75 x 38 mm	[redacted]
3.0 x 9 mm	[redacted]
3.0 x 12 mm	[redacted]
3.0 x 15 mm	[redacted]
3.0 x 18 mm	[redacted]
3.0 x 23 mm	[redacted]
3.0 x 28 mm	[redacted]
3.0 x 33 mm	[redacted]
3.0 x 38 mm	[redacted]
3.5 x 9 mm	[redacted]
3.5 x 12 mm	[redacted]
3.5 x 15 mm	[redacted]
3.5 x 18 mm	[redacted]
3.5 x 23 mm	[redacted]
3.5 x 28 mm	[redacted]
3.5 x 33 mm	[redacted]
3.5 x 38 mm	[redacted]
3.75 x 9 mm	[redacted]
3.75 x 12 mm	[redacted]
3.75 x 15 mm	[redacted]
3.75 x 18 mm	[redacted]
3.75 x 23 mm	[redacted]
3.75 x 28 mm	[redacted]
3.75 x 33 mm	[redacted]
3.75 x 38 mm	[redacted]

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APPENDIX XIV: REFERENCES

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