SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Stent, infrapopliteal, absorbable

Device Trade Name: Esprit™ BTK Everolimus Eluting Resorbable Scaffold System

Device Procode: NXW

Applicant's Name and Address: Abbott Medical
3200 Lakeside Drive
Santa Clara, CA 95054

Date of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P230036

Date of FDA Notice of Approval: April 26, 2024

Breakthrough Device: Granted breakthrough device status on July 17, 2017, for improving luminal diameter in infrapopliteal lesions in patients with critical limb ischemia (CLI).

II. INDICATIONS FOR USE

The Esprit™ BTK Everolimus Eluting Resorbable Scaffold System is indicated for improving luminal diameter in infrapopliteal lesions in patients with Chronic Limb Threatening Ischemia (CLTI) and total scaffolding length up to 170 mm with a reference vessel diameter of ≥ 2.5 mm and ≤ 4.00 mm.

III. CONTRAINDICATIONS

The Esprit™ BTK Everolimus Eluting Resorbable Scaffold System is contraindicated for use in:

- Patients who cannot tolerate, including allergy or hypersensitivity to, procedural anticoagulation or the post-procedural antiplatelet regimen.
- Patients with hypersensitivity or contraindication to everolimus or structurally related compounds, or known hypersensitivity to scaffold components (poly(L-lactide), poly(D, L-lactide), platinum).

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Esprit™ BTK Everolimus Eluting Resorbable Scaffold System labeling.

V. DEVICE DESCRIPTION

The Esprit™ BTK Everolimus Eluting Resorbable Scaffold System (Esprit BTK System) is composed of a balloon expandable scaffold and a delivery system. The Esprit BTK Scaffold is a resorbable polymeric scaffold with a drug and resorbable polymeric coating. The Esprit BTK Scaffold is temporary and will resorb over time. A schematic of the system is provided in **Figure 1**. The Esprit BTK System is available in the size matrix noted in **Table 1**.

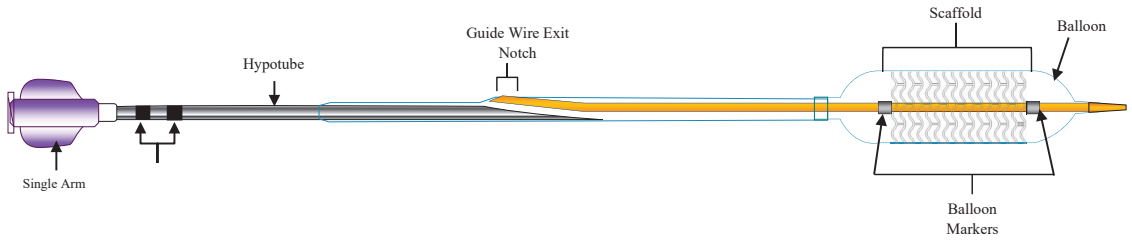


Figure 1: Schematic of the Esprit BTK System (not to scale)

Table 1. Esprit BTK System Size Matrix

Labeled Diameter (mm)	Lengths (mm)							
	9	12	15	18	23	28	33	38
2.5	X	X	X	X	X	X	X	X
2.75	X	X	X	X	X	X	X	X
3	X	X	X	X	X	X	X	X
3.5	X	X	X	X	X	X	X	X
3.75	X	X	X	X	X	X	X	X

Esprit BTK Scaffold

The Esprit BTK Scaffold consists of a resorbable scaffold backbone comprised of 100% poly (L-lactide) (PLLA) and a coating comprised of the active pharmaceutical ingredient everolimus and resorbable poly (D, L-lactide) (PDLLA). Four platinum markers, two each at the proximal and distal ends of the scaffold, are included for radiopacity.

Esprit BTK delivery system

The rapid-exchange (RX) balloon expandable delivery system is a 5F (0.070”/1.8mm) catheter with a semi-compliant balloon with two radiopaque markers located on the catheter shaft to indicate scaffold positioning. The catheter is designed to have a working length of 145 cm, a single access port to the inflation lumen, and compatibility with guidewires ≤ 0.014".

Drug Component - Everolimus

The Esprit BTK Scaffold is coated with a drug / polymer matrix that consists of 50 wt% of the active pharmaceutical ingredient, everolimus, and 50 wt% PDLLA. Everolimus has been evaluated through a number of different clinical studies and is known to have a wide therapeutic window. The drug (everolimus) dose density for Esprit BTK Scaffold is 100 $\mu g/cm^2$.

Everolimus (Chemical name: 40-O-(2-hydroxyethyl)-rapamycin) (**Figure 2**) is a semisynthetic macrolide immunosuppressant obtained through chemical modification of rapamycin. Rapamycin (INN: Sirolimus) is a secondary macrolide metabolite that is produced by certain actinomycete strains.

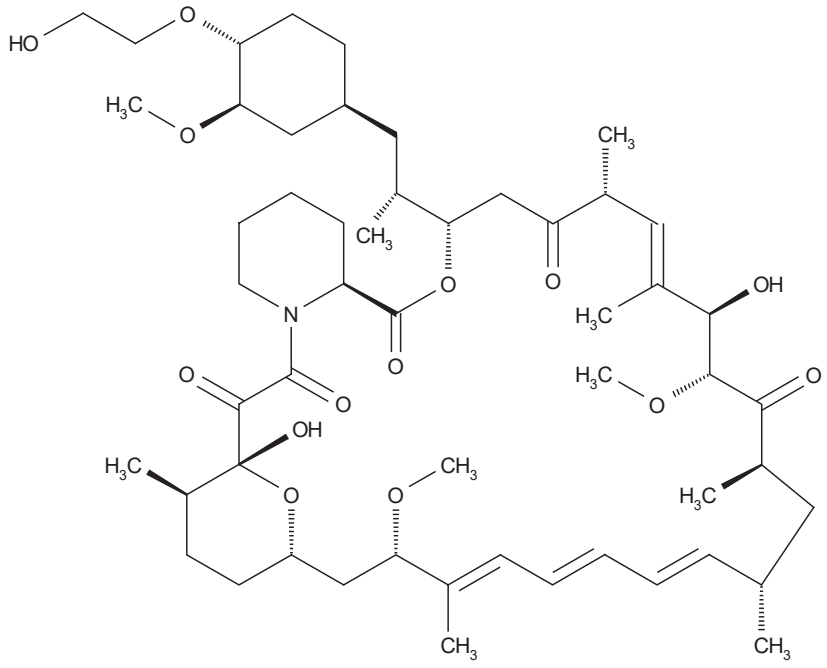


Figure 2: Chemical Structure of Everolimus

At the cellular level, everolimus inhibits growth factor-stimulated cell proliferation. At the molecular level, everolimus forms a complex with the cytoplasmic protein FKBP-12 (FK 506 Binding Protein). This complex binds to and interferes with FRAP (FKBP- 12 Rapamycin Associated Protein), also known as mTOR (mammalian Target of Rapamycin), leading to inhibition of cell metabolism, growth, and proliferation by arresting the cell cycle at the late G1 stage.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the correction of chronic limb threatening ischemia, including medications to help relieve symptoms and improve blood flow to the legs and lifestyle changes such as increasing physical activity, smoking cessation, diet modification and weight loss programs. Percutaneous interventions (balloon angioplasty, atherectomy) and bypass surgery can also be used to restore patency to below the knee

arteries and improve blood flow. A combination of any of the above methods may be used for optimal treatment. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The Esprit™ BTK Everolimus Eluting Resorbable Scaffold System has not been marketed in the United States or any foreign country.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of potential adverse effects associated with the use of the device. These adverse effects include, but are not limited to:

- Allergic reaction or hypersensitivity to: contrast agent, anesthesia, scaffold materials (poly [L-lactide] [PLLA], poly [D, L-lactide] [PDLLA], platinum, or everolimus), and drug reactions to anticoagulation, or antiplatelet drugs
- Vascular access complications which may require transfusion or vessel repair, including:
    - Catheter site reactions
    - Bleeding (ecchymosis, oozing, hematoma, hemorrhage, retroperitoneal hemorrhage)
    - Arteriovenous fistula, pseudoaneurysm, aneurysm, dissection, perforation / rupture, and laceration
    - Embolism (air, tissue, plaque, thrombotic material, or device)
    - Peripheral ischemia
- Target artery complications which may require additional intervention, including:
    - Total occlusion or abrupt closure
    - Arteriovenous fistula, pseudoaneurysm, aneurysm, dissection, perforation / rupture
    - Embolism (air, tissue, plaque, thrombotic material, or device)
    - Artery or scaffold thrombosis
    - Stenosis or restenosis
    - Vasospasm
    - Tissue prolapse / plaque shift
- Bleeding (non-access site)
- Additional surgery such as peripheral artery bypass graft surgery or amputation
- Peripheral nerve injury, neuropathy
- Compartment syndrome
- Tissue necrosis, gangrene, ulcer and acute limb ischemia
- Reperfusion injury
- New or worsening pain
- Intervention due to
    - Damaged scaffolds
    - Partial scaffold deployment

    - Scaffold migration/Unintentional placement of scaffold
- Other general surgical risks, including:
    - Cardiac arrhythmias (including conduction disorders, atrial and ventricular arrhythmias, and blocks)
    - Stroke / cerebrovascular accident (CVA) and transient ischemic attack (TIA)
    - Venous thromboembolism (including pulmonary embolism)
    - Nausea and vomiting
    - Hypotension / hypertension
    - Infection – local and systemic (including post-procedural)
    - Fever
    - Blood cell disorders including heparin induced thrombocytopenia (HIT) and other coagulopathy
    - Death
- System organ failures:
    - Cardiac Failure
    - Cardio-respiratory arrest (including pulmonary edema)
    - Respiratory failure
    - Renal failure
    - Shock

Adverse events associated with daily oral administration of everolimus in doses varying from 1.5 mg to 10 mg daily can be found in the labels for the drug. The risks described below include the anticipated adverse events relevant for the cardiac population referenced in the contraindications, warnings, and precaution sections of the everolimus labels and / or observed at incidences ≥ 10% in clinical trials with oral everolimus for different indications. Refer to the drug labels for more detailed information and less frequent adverse events.

- Abdominal pain
- Anemia
- Angioedema (increased risk with concomitant angiotensin converting enzyme [ACE] inhibitor use)
- Arterial thrombotic events
- Bleeding and coagulopathy (including hemolytic uremic syndrome [HUS], thrombotic thrombocytopenic purpura [TTP], and thrombotic microangiopathy; increased risk with concomitant cyclosporine use)
- Constipation
- Cough
- Diabetes mellitus
- Diarrhea
- Dyspnea
- Embryo-fetal toxicity
- Erythema
- Erythroderma
- Headache

- Hepatic artery thrombosis (HAT)
- Hepatic disorders (including hepatitis and jaundice)
- Hypersensitivity to everolimus active substance, to other rapamycin derivates
- Hypertension
- Infections (bacterial, viral, fungal, or protozoan infections, including infections with opportunistic pathogens). Polyoma virus-associated nephropathy (PVAN), JC virus-associated progressive multiple leukoencephalopathy (PML), fatal infections and sepsis have been reported in patients treated with oral everolimus.
- Kidney arterial and venous thrombosis
- Laboratory test alterations (elevations of serum creatinine, proteinuria, hypokalemia, hyperkalemia; hyperglycemia, dyslipidemia including hypercholesterolemia and hypertriglyceridemia; abnormal liver function tests; decreases in hemoglobin, lymphocytes, neutrophils, and platelets)
- Lymphoma and skin cancer
- Male infertility
- Menstrual irregularities
- Nausea
- Nephrotoxicity (in combination with cyclosporine)
- Non-infectious pneumonitis (including interstitial lung disease)
- Oral ulcerations
- Pain
- Pancreatitis
- Pericardial effusion
- Peripheral edema
- Pleural effusion
- Pneumonia
- Pyrexia
- Rash
- Renal failure
- Upper respiratory tract infection
- Urinary tract infection
- Venous thromboembolism
- Vomiting
- Wound healing complications (including wound infections and lymphocele)

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

IX. SUMMARY OF NONCLINICAL STUDIES

A. Biocompatibility Studies

The Esprit BTK System (the scaffold and the delivery system) has gone through a thorough biocompatibility evaluation per the ISO 10993-1 (2018): *Biological Evaluation of Medical Devices – Part 1: Evaluation and Testing within a Risk Management Process* and the FDA Guidance (2023): *Use of International Standard ISO 10993-1, "Biological*

Evaluation of Medical Devices Part 1: Evaluation and Testing with a Risk Management Process." All testing was performed in compliance with the ISO 10993 series wherever applicable and in accordance with FDA Title 21, CFR Part 58: *Good Laboratory Practice for Non-Clinical Laboratory Studies*.

The Esprit BTK Scaffold is classified as a long-term implant contacting circulating blood for >30 days. The Esprit BTK Scaffolds (uncoated and drug-coated) were tested separately from the Esprit BTK delivery system. The Esprit BTK delivery system is classified as an externally communicating device contacting circulating blood for ≤ 24 hours.

All testing performed met the pre-specified acceptance criteria. The test results of Esprit BTK Scaffold and Esprit BTK delivery system are summarized in **Table 2.**

Table 2. Biocompatibility Tests of the Esprit™ BTK Scaffold and Delivery System

Endpoint	Test	Scaffold	Delivery System	Results
Cytotoxicity (ISO 10993-5)	MEM Elution Assay using L-929 Fibroblasts Cells	X	X	Pass Non-cytotoxic
Sensitization (ISO 10993-10)	Guinea Pig Maximization Test	X	X	Pass Non-sensitizer
Irritation (ISO 10993-23)	Intracutaneous Reactivity Test	X	X	Pass Non-irritant
Material-mediated Pyrogenicity (ISO 10993-11)	Material Mediated Rabbit Pyrogenicity Test	X	X	Non-pyrogenic
Acute Systemic Toxicity (ISO 10993-11)	Acute Systemic Injection Test	X	X	Pass Non-toxic
Hemocompatibility (ISO 10993-4)	Hemolysis (Direct and Indirect) Test	X	X	Pass Non-hemolytic
	Complement Activation (SC5b-9) Test	X	X	Pass Non-compliment activator
	In vivo Thrombogenicity Test	X	X	Pass Non-thrombogenic
	Partial Thromboplastin Time (PTT) Test		X	Comparable to comparator
	Platelet and Leukocyte Count Assay (P&L)		X	Pass Non-thrombogenic
Genotoxicity (ISO 10993-3)	Bacterial Reverse Mutation Assay (Ames Test)	X		Pass Non-mutagenic
	In Vitro Chromosomal Aberration	X		Pass Non-mutagenic
	Clastogencity in Mammalian Cells (Forward Mutation)	X		Pass Non-Clastogenic
	Mammalian Erythrocyte Micronucleus Test	X		Pass Non-mutagenic

Scaffold implantation and delivery system thrombogenicity were evaluated as part of the *in vivo* safety and pharmacokinetics (PK) animal studies which concluded no adverse local tissue reactions following implantation of Esprit BTK Scaffold nor thrombogenicity risks of the Esprit BTK System. The Esprit BTK Scaffold leveraged XIENCE V™ Drug Eluting Stent System (PMA approved under P070015) carcinogenicity and reproductive toxicity studies for the clinical drug doses used for the disease indication. Extensive material assessment (theoretical compositional profiling based on the chemical characterization data from Absorb GT1™ Scaffold) and toxicological risk assessment in addition to genotoxicity testing were performed on the Esprit BTK Scaffold to assess subchronic/chronic systemic toxicity, genotoxicity, and carcinogenicity of the scaffold. The assessment concluded no risks of these biological endpoints.

B. *In Vitro* Engineering Testing

In vitro engineering testing, in accordance with "Guidance for and FDA Staff- Non-Clinical Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems", April 2010; ISO 25539-2:2012 *Cardiovascular Implants – Endovascular devices – Part 2: Vascular Stents*; ISO 10555-1: 2013/Amd 1:2017 *Intravascular Catheters – Sterile and Single-use Catheters – Part 1: General Requirements – Amendment*; ISO 10555-4:2013 *Intravascular Catheters – Sterile and Single-use Catheters – Part 4: Balloon Dilatation Catheters*, was conducted on the Esprit BTK System. The testing is summarized in **Table 3**.

Table 3. Esprit™ BTK System *In Vitro* Engineering Testing

Test	Test Description	Acceptance Criteria	Results
Scaffold Dimensional and Functional Testing			
Dimensional Verification	Measure the scaffold dimensions for: • Nominal Scaffold Inner Diameter (ID) • Scaffold Ring Strut Width and Scaffold Tube Wall Thickness • Maximum Crossing Profile Diameter • Maximum Balloon Outside the Stent	Scaffold dimensions shall meet specified/labeled dimensions.	Pass
Length Change (Nominal and Post-Dilated)	Percentage change in length of the scaffold between the un-deployed mounted (crimped) condition and the expanded conditions (nominal and post-dilated diameters at three rotational orientations) after balloon deflation.	The change in scaffold length from un-deployed length to expanded length after balloon deflation shall be ≤ 10%.	Pass

Test	Test Description	Acceptance Criteria	Results
Recoil (Nominal and Post-Dilated)	Percentage by which the outer diameter of a balloon-expandable scaffold decreases from its expanded diameter while on the inflated delivery balloon to its relaxed diameter after deflating the balloon at three rotational orientations.	The percentage of recoil shall be ≤ 10%.	Pass
Radial Strength (Nominal and Post-Dilated)	Determines the radial force or pressure required to permanently deform a deployed scaffold at nominal and post-dilated deployment diameters.	The radial force or pressure required to permanently deform the deployed scaffold shall be ≥ 350 mmHg.	Pass
Uniformity of Expansion	Determine the difference between the largest and smallest diameter measurement on a single scaffold deployed unconstrained to its labeled diameter after deflation of the balloon at three rotational orientations.	The difference between the largest and smallest diameter measurement on a single scaffold deployed unconstrained to its labeled diameter after deflation of the balloon must meet pre-specified values: 2.5 mm: ≤ 0.3 mm 2.75 mm: ≤ 0.3 mm 3.0 mm: ≤ 0.4 mm 3.5 mm: ≤ 0.5 mm 3.75 mm: ≤ 0.5 mm	Pass
Ring Tension	Determine the limit of expansion before strut fracture.	The limit of expansion before strut fracture shall be at least 0.5 mm greater than the labeled diameter.	Pass
Scaffold Dislodgement (Distal and Proximal)	Determine the force required to dislodge a balloon-expandable scaffold from its original, crimped position on a delivery system in either the distal or proximal direction.	The force required to dislodge the scaffold from its crimped position on the delivery system shall be greater than pre-specified values, depending on scaffold diameter and length.	Pass
Scaffold Markers (Nominal and Post-Dilated)	Verify the presence of the scaffold markers after subjecting the scaffold to an environment similar to that seen in ordinary use, including post-dilatation.	There shall be no marker loss upon deployment.	Pass
Scaffold Placement and Visual Inspection	Verify there is no catheter damage and appropriate scaffold placement between the balloon markers in the crimped state.	The catheter must be free from kinks and damage. Scaffold must be appropriately placed between the balloon markers.	Pass

Test	Test Description	Acceptance Criteria	Results
Guiding Catheter Pullback	Test the ability of an un-deployed scaffold system to be withdrawn into a guiding catheter.	The system will sustain 1 cycle of pullback through a 6F / 0.070"/ 1.8 mm inner diameter guiding catheter without scaffold movement.	Pass
Radiopacity	Evaluate the ability to visualize the scaffold using fluoroscopy during scaffold delivery, deployment, and after implantation.	The scaffold shall be able to be visualized using angiographic imaging during scaffold delivery, deployment and after implantation to assure proper scaffold placement.	Pass
Scaffold Integrity	Evaluate scaffolds for damage which could contribute to clinical complications after deployment to the post-dilated diameter.	The scaffold must meet the following to demonstrate scaffold integrity: • Scaffold Markers requirement • Coating Integrity requirement • Ring Tension requirement • Structural Radial Fatigue requirement	Pass
Stress/Strain Analysis/Fatigue Analysis (Finite Element Analysis)	Evaluate the durability and integrity of the scaffold using Finite Element Analysis (FEA). The FEA analysis simulated pulsatile and crush loading conditions relevant to the BTK anatomy.	The FEA analysis must demonstrate that the scaffold maintains acceptable fatigue safety using the Goodman fatigue analysis with a safety factor > 1.	Pass
Accelerated Durability Testing (Structural Radial, Embolic Radial and Crush Fatigue)	Characterize the structural and embolic durability of scaffolds with up to 1-year pulsatile and crush fatigue cycling.	Structural Durability: Scaffold must maintain structural integrity at 3 months. Embolic Radial Fatigue: Tested for characterization of particulates.	Pass/Acceptable Outcomes
Scaffold Percent Surface Area	Percentage which indicates the amount of contact between the scaffold and the scaffolded vessel wall at a labeled scaffold diameter and length.	Scaffold Percent Surface Area is calculated for characterization.	Acceptable Outcomes

Test	Test Description	Acceptance Criteria	Results
Magnetic Resonance Imaging (MRI) Safety and Compatibility	Provide confirmation that the scaffold poses no known hazards resulting from exposure to MR environment in magnetic fields up to static field 7.0 Tesla.	The scaffold must meet the requirements of FDA Guidance documents, *Testing and Labeling Medical Devices for Safety in the Magnetic Resonance (MR) Environment* (dated December 11, 2014), ASTM F2182-11a, ASTM F2052-14, Magnetically Induced Torque Test using Qualitative Torque, ASTM F2119-07 (reapproved 2013). The conditions under which the device can be safely scanned are reflected in the Instructions for Use (IFU).	Acceptable Outcomes
Scaffold Mechanical Properties	Characterize the mechanical properties (i.e., tensile strength in axial and circumferential directions) of PLLA expanded tubing.	The scaffold mechanical properties are evaluated for characterization.	Acceptable Outcomes
Dogboning	Visually determine if the balloon shoulders are growing larger than the scaffold outer diameter at the Rated Burst Pressure of the scaffold delivery system.	The unconstrained balloon diameter is evaluated relative to the scaffold outer diameter for characterization.	Acceptable Outcomes
Scaffold Flare	Determine the change in distance between the OD of the scaffold and the OD of the balloon as manufactured and after tracking through a tortuous path, at the distal and proximal ends.	The change in distance between the OD of the scaffold and the OD of the balloon is evaluated for characterization.	Acceptable Outcomes
Radial Stiffness (Nominal and Post-Dilated)	Determine the radial stiffness at nominal and post-dilated deployment diameters.	Radial Stiffness is evaluated for characterization.	Acceptable Outcomes
Vessel Straightening and Wall Conformity	Vessel Straightening: Measure the amount of vessel straightening that occurs when a stent or scaffold is deployed in a curved vessel. Wall Conformity: Visual assessment of scaffold apposition.	Vessel straightening, determined by quantitative comparison of native vessel vs post-deployment radius of curvature, is evaluated for characterization. Assessment of wall conformity/apposition is evaluated for characterization.	Acceptable Outcomes

Test	Test Description	Acceptance Criteria	Results
Kink Resistance	Characterize the change in lumen diameter as the scaffold is bent.	Determine the smallest radius of curvature that the scaffold can withstand without kinking or diameter reduction of > 50% for characterization.	Acceptable Outcomes
Crush Resistance	Characterize the ability of the scaffold to recover its deployment diameter when subjected to worst-case parallel plate crush deformation.	The ability of the scaffold to recover its deployment diameter from worst-case parallel plate crush deformation is evaluated for characterization.	Acceptable Outcomes
Delivery System Dimensional and Functional Testing			
Dimensional Specification	Measure the catheter dimensions of the delivery system • Balloon Shoulder to Marker (Distal and Proximal) • Tip Length • Tip Entry Outer Diameter • Outer Member Outer Diameter • Hypotube Outer Diameter • Notch Outer Diameter • Proximal Shaft Marker Locations (Femoral and Brachial) • Total Catheter Length • Distal Catheter Length • Guidewire Lumen Dimensions	Catheter dimensions shall meet specified/labeled dimensions.	Pass
Catheter Preparation	Determine the number of double negative aspiration procedures necessary to displace air from the balloon with contrast medium.	The number of double negative aspiration procedures necessary to displace air from the balloon with contrast medium shall be no greater than 3.	Pass
Balloon Deflation Time	Measure the deflation time of the scaffold delivery system.	Deflation time shall be ≤ 30 seconds.	Pass
Balloon Rated Burst Pressure	Determine the pressure at which the balloon ruptures.	The pressure at which the balloon ruptures shall be ≥ 235 psi (16 atm / 1621 kPa).	Pass
Maximum Compliance Label Pressure	Determine the pressure at which the balloon ruptures.	Maximum compliance label pressure shall be ≥ 264 psi (18 atm / 1824 kPa).	Pass

Test	Test Description	Acceptance Criteria	Results
Tensile Strength	Determine the tensile strength of: • Catheter Seal Tensile (Proximal Seal) • Catheter Seal Tensile (Guidewire Notch and Outer member to Hypotube only) • Proximal Adaption Tensile • Tip Tensile	≥ 2.2 N (0.5 lbf) – 15.5 N (3.5 lbf), depending on system diameter and bond.	Pass
Inner Member Lumen Collapse	Determine if Inner Member (IM) collapse is reversible (guide wire movement possible) at negative pressure after inflation to specified pressures.	When the inflation pressure is ≤ 300 psi 20 ATM / 2068 kPa), the IM must recover after inflation.	Pass
Balloon Fatigue Resistance	Determine if a balloon can withstand repeat inflations to rated burst pressure.	The system shall withstand 10 repeated inflations at the rated burst pressure.	Pass
Corrosion Resistance	Determine whether the hypotube of the proximal shaft subassembly is corrosion resistant.	Corrosion shall not be present at 10x magnification.	Pass
Delivery system Characterization Testing			
Catheter Torque	Determine the number of rotations required to break the joints and/or materials or to lose functional integrity.	The number of rotations required to break the joints and/or materials or to lose functional integrity shall be > 1.	Pass
Kink/Flex	Determine the minimum radius of curvature at which the catheter kinks.	The minimum radius of curvature at which the catheter kinks shall be below a pre-specified value.	Pass
Balloon Inflation Time	Measure the inflation time of the scaffold delivery system.	Inflation time is evaluated for characterization.	Pass
Compliance	Provide the scaffold inner diameter (ID) data which equates to the balloon outer diameter over the full range of recommended inflation pressures.	Characterize for development of the balloon compliance curve.	Pass
Esprit BTK System Design Validation Testing			
Delivery, Deployment and Retraction (DDR)	Demonstrate that the Esprit BTK System is able to permit safe, consistent and accurate access to an intended location, deployment of the scaffold, and withdrawal of the delivery system.	The scaffold delivery system shall demonstrate the ability to permit safe, consistent and accurate access to the intended location, accurate deployment of the stent and withdrawal of the delivery system.	Pass

Test	Test Description	Acceptance Criteria	Results
Aseptic Presentation	Demonstrate that the Esprit BTK System is able to be unpackaged and presented aseptically according to the instructions for use.	There is no visible damage / breach in sterile barrier system integrity. The user is able to identify where to begin opening the package. The sterile contents can be aseptically presented.	Pass
Catheter Radiopacity	Demonstrate that the Esprit BTK delivery system catheter is visible during access, placement, deployment, and withdrawal using fluoroscopy.	The radio-detectability of the delivery catheter is clinically acceptable. The user is able to visualize the delivery system balloon markers during the advancement, placement, deployment, post-deployment and retraction into the guiding sheath / introducer sheath.	Pass
Safe Disposal	Demonstrate that the Esprit BTK System can be disposed of safely according to the instructions for use.	User can dispose of the evaluation device in a safe manner in accordance with the IFU.	Pass
Coating Testing			
Coating Integrity	Determine the percent compromised surface area of the scaffold coating after expanding the scaffold to the largest post-dilated diameter within the design.	The percent compromised surface area of the scaffold coating shall not be greater than pre-specified value.	Pass
Tracking Particulate	Count and size particulates generated by tracking one test unit through a tortuosity and then deploying in a 15 mm radius bend.	Particulates with length ≥ 10 µm shall be less than or equal to 6000. Particulates with length ≥ 25 µm shall be less than or equal to ≤ 600.	Pass
Dry Adhesion	Determine the adhesion of the hydrophilic coating on a scaffold delivery system shaft.	The hydrophilic coating remains largely intact on the scaffold delivery system shaft.	Pass
Coefficient of Friction	Determine the kinetic coefficient of friction of hydrophilically-coated shafts on scaffold delivery systems.	The Coefficient of Friction shall be below pre-specified values.	Pass
Coating Thickness	Measure the coating thickness along the length of the drug coated scaffold.	The coating thickness along the length of the scaffold is evaluated for characterization.	Acceptable Outcomes
Longitudinal Content Uniformity	Evaluate the intra-scaffold drug content uniformity along the length of the scaffold.	The content uniformity along the length of the scaffold is evaluated for characterization.	Acceptable Outcomes

Test	Test Description	Acceptance Criteria	Results
Circumferential Content Uniformity	Evaluate the intra-scaffold drug content uniformity around the circumference of the scaffold.	The content uniformity along the circumference of the scaffold is evaluated for characterization.	Acceptable Outcomes
Coating Morphology	Analyze the coating surface and coating microstructure at multiple locations on each scaffold.	The coating surface and coating microstructure are evaluated for characterization.	Acceptable Outcomes
Coating Adhesion After Balloon Rupture	Characterize the coating integrity of the scaffold at the nominal balloon expansion and after over expansion until the balloon ruptures.	Coating adhesion after balloon rupture is evaluated for characterization.	Acceptable Outcomes
Hydrophilic Coating Integrity Visual Inspection	Perform a visual assessment of the catheter coating integrity on the surface of the catheters before and after simulated use.	A visual assessment of the catheter coating integrity is performed for characterization.	Acceptable Outcomes

C. Chemistry, Manufacturing & Controls (CMC) Testing

Where applicable, International Conference on Harmonization (ICH) Guidelines were followed for the testing routinely performed on the Esprit BTK System as part of the finished product release. This testing is summarized in **Table 4.**

Table 4. Esprit BTK System Analytical Release Testing

Test	Test Description
Appearance	A visual inspection is conducted to verify that the Esprit BTK System meets appearance specifications for finished product release.
Identity	Tests are conducted to verify the identity of the drug substance, everolimus, on the Esprit BTK System using two different methods, Ultraviolet/Visible Spectroscopy and High Performance Liquid Chromatography.
Total Content	Assay is conducted to quantitatively verify that the total amount of the drug substance, everolimus, on the Esprit BTK System meets specifications for finished product release.
Content Uniformity	Multiple scaffolds are tested to verify that the uniformity of the drug content between individual Esprit BTK Scaffold is within specifications established for finished product release.
Degradation Products /Impurities	The amount and type of everolimus degradation products / impurities are quantitatively verified to meet specifications established for finished product release
Tracking Particulate	The test collects particles generated acutely from the delivery, deployment, and withdrawal of either a single scaffold or two scaffolds deployed in an overlapped configuration.

Test	Test Description
Bacterial Endotoxin USP <85>	The amount of bacterial endotoxins is verified to be within specification limits established for finished product release.
Drug Release	The drug release profile of the drug substance, everolimus, is verified to meet specifications established for finished product release.
Number Average Molecular Weight	The number average molecular weight (M_n) is verified to be within specification limits established for finished product release.
Sterility	The Esprit BTK product is released by verifying that the dose complied with validated sterilization parameters and satisfies the requirement for labeling the finished goods as sterile.
Residual Solvent	The amount of residual solvent (acetone) is verified to meet specification limits established for finished product release.
BHT Content	The BHT content on the Esprit BTK System is quantitatively verified to meet specification limit established for finished product release.

D. Stability/Shelf Life

Stability studies were conducted to establish a shelf life / expiration date for the Esprit BTK System. The stability test attributes, including Appearance, Total Content, Impurities and Degradation Products, Drug Release, Number Average Molecular Weight, Whole Packaging Integrity, Particulate Matter, and Bacterial Endotoxin, were performed at each of the preselected stability time points. BHT Content is tested for characterization only. Analytical test attributes, including Content Uniformity, Identity and Residual Solvent, are performed for initial lot release. Functional testing, including Scaffold Dislodgement, Scaffold Ring Tension, and Radial Strength, was performed at the initial time point. Testing to establish container closure integrity was conducted to ensure that sterility was maintained during the shelf life of the product. The data generated to-date support a shelf life of 12 months for the Esprit BTK System.

E. Sterilization

The Esprit BTK System is sterilized by means of electron-beam (e-beam) radiation, in-house at the Abbott Vascular, Temecula manufacturing facility, to meet a Sterility Assurance Level (SAL) of 10^{-6} in accordance with ISO 11137-1:2006/Amd1:2013 /Amd2:2018, *Sterilization of health care products – Radiation – Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices*. Pursuant to the validation requirements, the Esprit BTK System has been successfully qualified for one time e-beam sterilization. In addition, the amount of bacterial endotoxins was verified to be within the specification limits.

F. Packaging

The Esprit BTK System is packaged in a configuration that ensures sterility and provides protection during handling, storage, and delivery of the final product throughout the labeled shelf life. The packaging validation is composed of the following three components:

- Packaging process validation, which includes a visual inspection of all seals, whole package integrity, seal integrity, and seal strength testing at the nominal, upper and lower parameters of the sealing process.
- Packaging system performance testing, which includes a visual inspection of all seals, whole package integrity, seal integrity, and seal strength testing at the upper and lower limits of the package sealing process parameters following package sterilization, extreme conditioning, and transportation simulation conditioning.
- Packaging system stability testing, which tests the package material for degradation over time, including potential sterilization effects, throughout the product shelf-life.

G. *In Vivo* Animal Studies

A series of GLP *in vivo* studies were conducted in the porcine coronary artery model in order (a) to evaluate the *in vivo* pharmacokinetic profile, and (b) to demonstrate the *in vivo* safety. Studies were conducted using the Absorb GT1™ Bioresorbable Vascular Scaffold (BVS) (PMA approved under P150023) or Esprit BTK Scaffold, as described below. The Esprit BTK Scaffold and the Absorb GT1™ BVS are composed of identical polymer materials (PLLA, PDLLA) and share identical chemical and manufacturing controls which regulate scaffold degradation. Based on the similarities in materials and design between the Esprit BTK System and the Absorb GT1 BVS System, the assessments conducted for the Absorb GT1 BVS were leveraged to support the Esprit BTK Scaffold.

This *in vivo* testing was conducted in accordance with one or more of the following general regulations and guidance documents and the consensus documents:

- Good Laboratory Practices Regulations (21 CFR § 58)
- Guidance for Industry and FDA Staff: General Considerations for Animal Studies for Cardiovascular Devices CDRH. 2010
- Guidance for Industry and FDA Staff: Non-Clinical Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems, 2010
- Schwartz, R. S., et al. "Drug-Eluting Stents in Preclinical Studies: Updated Consensus Recommendations for Preclinical Evaluation." Circ Cardiovasc Intervent **1**(2): 143-153, 2008.
- Schwartz, R. S., et al. "Drug-eluting stents in preclinical studies: recommended evaluation from a consensus group." Circulation **106**(14): 1867-1873, 2002.

- Schwartz, R. S., et al. "Preclinical evaluation of drug-eluting stents for peripheral applications: recommendations from an expert consensus group." Circulation **110**(16): 2498-2505, 2004.

A summary of the preclinical *in vivo* studies conducted is provided below and in **Table 5**.

1. *In Vivo* Pharmacokinetics

A 90-day PK study was conducted to characterize the *in vivo* pharmacokinetics of the Esprit BTK Scaffold, including the drug release profile and drug concentrations in arterial tissues, distal vital organs and systemic circulation. The Esprit BTK Scaffold maintains drug concentrations in implanted arterial tissues up to 90 days. As the drug release profiles between the Esprit BTK Scaffold and the Absorb GT1™ BVS are bioequivalent, the results of the 300-day PK study conducted for Absorb GT1 BVS are leveraged for the Esprit BTK Scaffold to characterize the drug elution profile at longer time points (≥ 120 days) when > 95% to 100% of drug is released.

2. *In Vivo* Degradation

Three *in vivo* degradation studies were conducted for the Absorb GT1 BVS in order to determine the *in vivo* degradation profile. These studies are inclusive of time points from 28 days to 42 months, with results demonstrating complete scaffold resorption by approximately 36 months.

3. *In Vivo* Safety

Three *in vivo* safety studies were conducted in the porcine coronary artery model to demonstrate *in vivo* safety of the Esprit BTK Scaffold relative to XIENCE Alpine™ Stent System (P110019 / S070) (28 days) and Absorb GT1 BVS (90, 180 days). In these studies, the Esprit BTK Scaffold demonstrated comparable safety relative to the respective control at each time point. Several additional studies evaluating the Absorb GT1 BVS are being leveraged to support the safety of the Esprit BTK Scaffold. These safety studies include time points from 12 to 48 months and overlap safety studies (28, 90 days).

Table 5. GLP *In Vivo* Pharmacokinetics, Degradation, and Safety Studies

Study Number (Designation)	Animal Model	Number	Follow-up Duration	Endpoints
Pharmacokinetics	Farm swine	Test: 6 – 7 Esprit BTK Scaffolds per time point Control: N/A	3 hours, 1, 3, 7, 14, 28, 60, and 90 days	Characterization of *in vivo* pharmacokinetics: drug release, blood and tissue drug concentrations
Pharmacokinetics	Farm swine	Test: 6 – 7 Absorb scaffolds per time point Control: N/A	3 hours, 1, 3, 7, 14, 28, 60, 90, 120, 180, and 300 days	Characterization of *in vivo* pharmacokinetics: drug release, blood and tissue drug concentrations

Study Number (Designation)	Animal Model	Number	Follow-up Duration	Endpoints
Polymer Degradation	Farm swine	Test: 12 Absorb scaffolds Control: N/A	28 days	Characterization of *in vivo* degradation profile with respect to Mn, mass loss, and PDI
Polymer Degradation	Farm swine	Test: 12 (90 days), 14 (180 days) Absorb scaffolds per time point Control: N/A	90, 180 days	Characterization of *in vivo* degradation profile with respect to Mn, mass loss, and PDI
Polymer Degradation	Yucatan mini-swine	Test: 8 -12 Absorb scaffolds per time point Control: N/A	12, 18, 24, 30, 36, and 42 months	Characterization of *in vivo* degradation profile with respect to Mn, mass loss, and PDI
Safety	Farm swine	Test: 10 Esprit BTK Scaffolds Control: 7 XIENCE Alpine stents (P110019/S070)	28 days	· Systemic (morbidity, mortality) · Quantitative coronary angiography · Optical coherence tomography · Histomorphology · Endothelialization by SEM (Histomorphometry)
Safety	Farm swine	Test: 10 Esprit BTK Scaffolds Control: 8 Absorb scaffolds	90 days	· Systemic (morbidity, mortality) · Quantitative coronary angiography · Optical coherence tomography · Histomorphology · Endothelialization by SEM Histomorphometry
Safety	Farm swine	Test: 10 Esprit BTK Scaffolds Control: 8 Absorb scaffolds	180 days	· Systemic (morbidity, mortality) · Quantitative coronary angiography · Optical coherence tomography · Histomorphology · Endothelialization by SEM (Histomorphometry)
Safety	Yucatan mini-swine	Test: 12 – 21 Absorb scaffolds	12, 18, 24, 30, 36, 42, and 48 months	· Systemic (morbidity, mortality) · Quantitative coronary angiography · Histomorphology

Study Number (Designation)	Animal Model	Number	Follow-up Duration	Endpoints
		Control: 7 – 13 XIENCE V stents (P070015)		· Endothelialization by SEM (Histomorphometry, OCT, IVUS)
Overlapping safety	Farm swine	Test: 12 pairs Absorb scaffolds Control: 8 pairs XIENCE V stents	28 days	· Systemic (morbidity, mortality) · Quantitative coronary angiography · Histomorphology · Endothelialization by SEM (Histomorphometry, OCT)
Overlapping safety	Farm swine	Test: 12 pairs Absorb scaffolds Control: 9 pairs XIENCE V stents	90 days	· Systemic (morbidity, mortality) · Quantitative coronary angiography · Histomorphology · Endothelialization by SEM (Histomorphometry, OCT)

Mn: number average molecular weight; PDI: Polydispersity Index
SEM: Scanning Electron Microscopy; OCT: Optical Coherence Tomography; IVUS: Intravascular Ultrasound

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study (LIFE-BTK) to establish a reasonable assurance of safety and effectiveness of the revascularization procedure with the Esprit BTK System for the treatment of narrowed infrapopliteal lesions in subjects with chronic limb-threatening ischemia (CLTI) in the US, Singapore, Hong Kong, Taiwan, Australia, and New Zealand under IDE G190111. The LIFE-BTK study consists of a prospective, multi-center, single-blinded, randomized controlled trial (LIFE-BTK RCT) and a non-randomized pharmacokinetics sub-study (LIFE-BTK PK). Data from these clinical studies are the basis for the PMA approval decision. The database for this PMA reflects data collected through 1-year follow-up for the RCT and 60-day follow-up for the PK sub-study. Summaries of the LIFE-BTK RCT and the LIFE-BTK PK sub-study are presented below.

A. Study Design

Subjects were treated between August 18, 2020, and September 14, 2022. The database for this PMA reflected data collected through August 18, 2023, and included 261 subjects. There were 50 investigational sites globally, with at least 50% of subjects enrolled from the United States.

The LIFE-BTK RCT study is a prospective, multi-center, single-blinded, randomized controlled trial. Subjects were randomized in a 2:1 ratio between Esprit BTK therapy and the control therapy, which was PTA (Percutaneous Transluminal Angioplasty). PTA is the current standard of care for treatment of below-the-knee artery disease in the US.

The primary safety endpoint was freedom from Major Adverse Limb Event (MALE) at 6 months and Peri-Operative Death (POD) at 30 days. The primary effectiveness endpoint was a composite of limb salvage and primary patency at 1 year. The patients will be followed through 5 years.

Core laboratories were used for angiography, duplex ultrasound (DUS), Intravascular Ultrasound (IVUS), Optical Coherence Tomography (OCT), and wound assessment. Adverse events were adjudicated by a Clinical Events Committee (CEC) and a Data and Safety Monitoring Board (DSMB) reviewed cumulative data from the clinical investigation at regular intervals.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the LIFE-BTK RCT was limited to subjects who met the following key general inclusion criteria.

General Inclusion Criteria

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

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.
   b. The total scaffold length among all target lesions must not exceed 170 mm.
   c. The target vessel cannot have any other angiographic significant lesions ≥50%).
   d. 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.
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.

Subjects were not permitted to enroll in the LIFE-BTK RCT if they met any of the key following exclusion criteria.

General Exclusion Criteria

1. Pregnant or nursing subjects and those who plan pregnancy during the clinical investigation follow-up period.
2. 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.
3. 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 fluoropolymers that cannot be adequately pre-medicated. Subject has a known contrast sensitivity that cannot be adequately pre-medicated.
4. 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.
5. Subject has life expectancy ≤ 1 year.

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

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

8. Subject is currently on dialysis.

9. 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.

10. 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.

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

12. 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.

13. 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.

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

15. 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.

16. 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.

17. 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.

    a. Subject with extensive tissue loss salvageable only with complex foot reconstruction or non-traditional transmetatarsal amputations [1] This

includes subjects with 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.

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

19. 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 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).

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.

2. Follow-up Schedule

All subjects were scheduled to return for follow-up examinations at 30 days, 3 months, 6 months, and 1 year, and will be continued annually to complete 5 years of follow-up. Additional follow-ups, for subjects presenting with wounds at the time of the index procedure, occurred at 14 days and 42 days.

Preoperatively, laboratory, functional status (RB category), and wound (if applicable) assessments, as well as ABI/TBI (Ankle Brachial Index/Toe Brachial Index) measurement, were conducted to determine subject eligibility. Anatomical eligibility was confirmed at the time of the index procedure, prior to randomization.

Postoperatively, the objective parameters measured during the study included the following key assessments: ABI/TBI measurement, functional status RB assessment, index wound assessment, and DUS. Adverse events and complications are recorded at all visits except the 14-day and 42-day visits.

The key time points are shown in **Table 6** below and are included in the tables summarizing safety and effectiveness.

Table 6. Study Event Schedule Procedure and Assessments

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
Vascular Angiogram, IVUS[1]	✓		✓													✓
Duplex Ultrasound[2]							✓			✓	✓	✓	✓			✓
ABI/TBI measurement[3]	✓	✓				✓			✓	✓	✓	✓	✓	✓	✓	✓
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[4]	✓			✓	✓	✓		✓	✓	✓	✓					✓
New wound assessment[5]						✓			✓	✓	✓	✓	✓	✓	✓	✓

[1] 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.

[2] 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.

[3] 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).

[4]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.

[5] 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.

3. Clinical Endpoints

With regards to safety, the primary safety endpoint was freedom from Major Adverse Limb Event (MALE) at 6 months + Peri-Operative Death (POD) at 30 days. MALE includes above-ankle amputation in index limb and major re-intervention on index limb at 6 months, and POD includes perioperative mortality at 30 days. Major re-intervention includes the creation of a new bypass graft, bypass graft revision, the use of thrombectomy, or thrombolysis related to the target lesion. The hypothesis test is designed to show non-inferiority of Esprit BTK arm to PTA arm with a 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 (-10%).

With regards to effectiveness, the primary effectiveness endpoint was a composite of limb salvage and primary patency at 1 year. It included 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). Binary restenosis was defined as the presence of a hemodynamically significant restenosis > 50% by angiography, or Peak Systolic Velocity Ratio (PSVR) ≥ 2.0 by duplex ultrasound. In the presence of abnormal reference Peak Systolic Velocity (PSV), the duplex ultrasound core laboratory used additional secondary criteria (correlating factors)[1] to identify target lesion stenoses >50% in severity. 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. 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.

The hypothesis test is designed to show superiority of Esprit BTK arm to PTA arm with a 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 effectiveness endpoint rates for the Esprit BTK arm and PTA arm, respectively.

[1] The additional secondary criteria (correlating factors) are as follows:

- 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;
- Review of the B-mode images for plaque burden.

The primary safety endpoint and primary effectiveness endpoint were evaluated when all subjects had completed their 1-year visit. The primary safety endpoint was tested for non-inferiority of Esprit BTK arm to PTA arm. The primary effectiveness endpoint was tested for the superiority of Esprit BTK arm as compared to PTA arm.

Both primary analyses must pass for the trial to be successful.

The primary effectiveness endpoint was modified during the trial to add binary restenosis and change the timepoint from 6 to 12 months. To account for the change in definition, LIFE-BTK RCT also included the original composite primary effectiveness endpoint as one of the two powered secondary endpoints analyzed at 1 year:

- Binary restenosis of the target lesion
- A composite endpoint of freedom from above ankle amputation of the index limb, total occlusion of the target vessel and CD-TLR.

Additionally, index wound measurements and assessment for healing and infection over time were performed by a wound core laboratory. Assessment of new wounds (i.e., wound that was not present at baseline) for etiology was also performed by the core laboratory at the time of first identification. New wound progression was then assessed by the site.

B. Accountability of PMA Cohort (RCT Group)

In LIFE-BTK, a total of 261 subjects (Esprit BTK: 173; PTA:88) were randomized at 50 investigational sites, between August 18, 2020, and September 14, 2022. A total of 179 target lesions were treated in the Esprit BTK arm, and 92 lesions in the PTA arm. Early termination at 1 year, due to lost-to-follow-up, consent withdrawal or death, occurred in 11.6% (20/173) of the subjects in the Esprit BTK arm and 11.4% (10/88) in the PTA arm. The final 1-year follow-up visit for the RCT group occurred on August 17, 2023. The details on subject disposition for intent-to-treat (ITT) population and as-treated (AT) population are presented in **Figure 3** and **Figure 4** respectively.

At 6 months, there were 244 subjects active in the trial. For the evaluation of the primary safety endpoint, if a subject had a safety endpoint event prior to termination, this subject is included in the analysis, or if the terminated subject had no status prior to the lower limit of the 6-month follow-up window, the subject was excluded. At the time of database snapshot, of the 261 subjects enrolled in LIFE-BTK RCT, data on 245 subjects were available for evaluation of the primary safety endpoint at 6 months[2].

At 1 year, there were 231 subjects active in the trial. If a subject had an effectiveness endpoint event prior to termination, this subject is included in the analysis. For the evaluation of the effectiveness endpoint, if a subject did not have imaging information (either DUS or angiography) to confirm vessel patency status at 1-year, the subject was

excluded from the analysis unless they had an effectiveness endpoint event earlier. At the time of database snapshot, based on the above rules, data on 220 subjects were available for the evaluation of the primary effectiveness endpoint at 1 year.

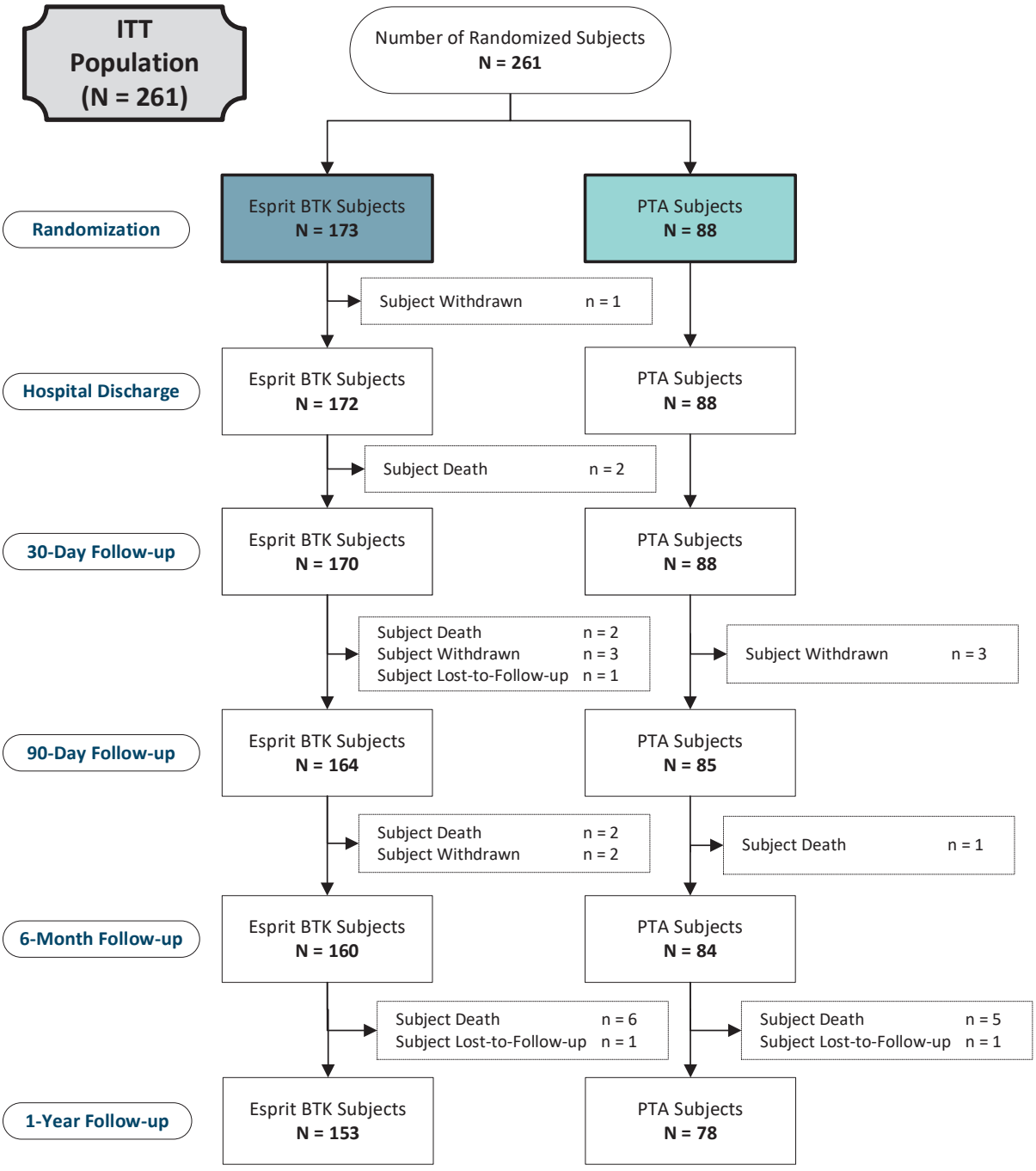


Figure 3: Subject disposition flow chart – Intent-to-Treat Population

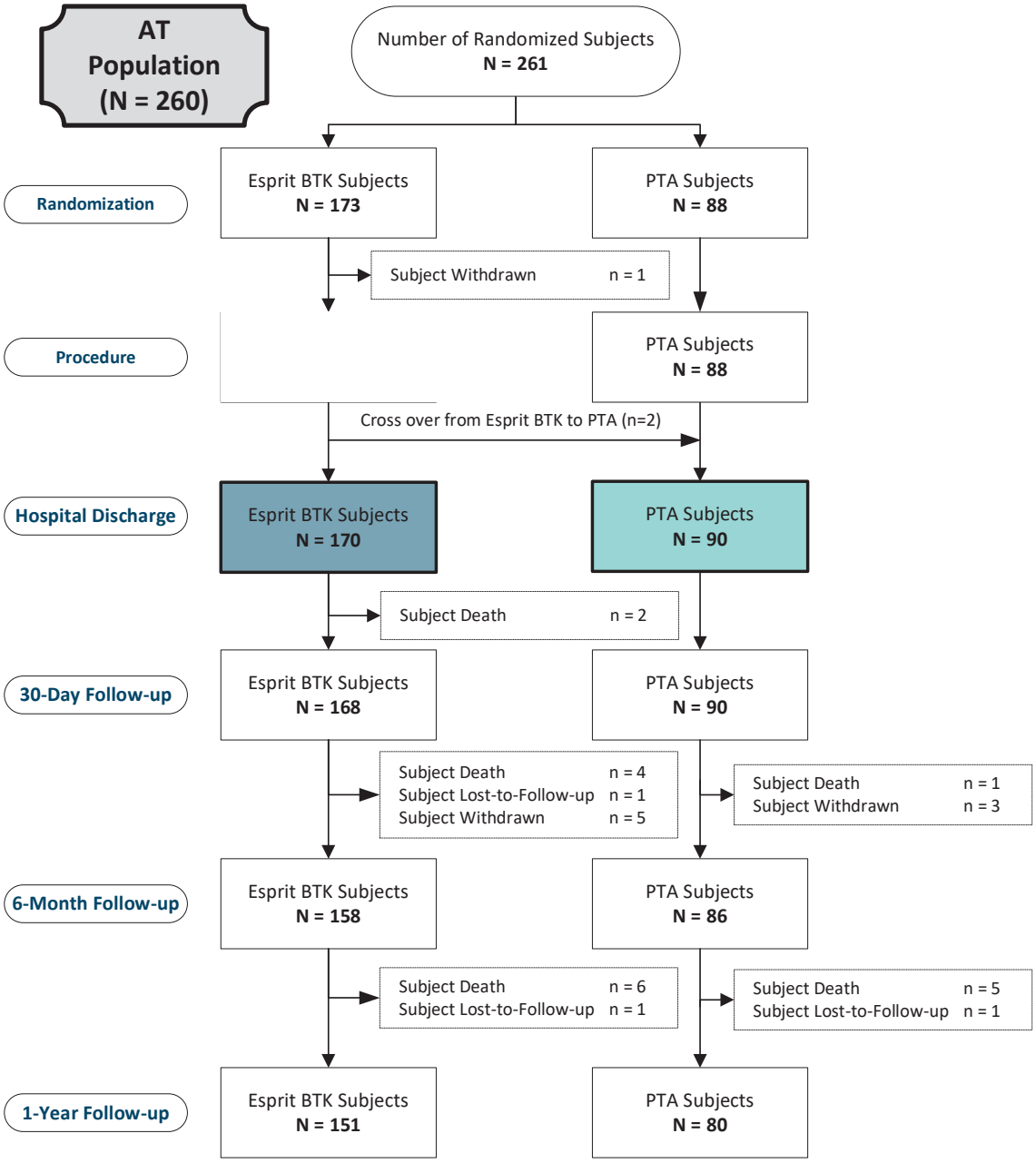


Figure 4: Subject disposition flow chart – As-Treated Population

Note: In the Esprit BTK arm, there were 2 subjects who expired within 30 days post-procedure. These 2 subjects are not counted at the 6-month follow-up on this chart, but they are included in the primary safety endpoint analysis in **Table 9**. Therefore, the total number of evaluable subjects of the Esprit BTK arm for the primary safety endpoint at 6 months was 160 (and not 158 as shown on this flowchart).

In the PTA arm, one subject was withdrawn (as lost-to-follow-up) at day 281 post-procedure. However, the last contact information of the subject in the study was 90 days post-index procedure which was prior to the beginning of the 6-month follow-up windows (180 days - 28 days = 152 days). Therefore, the subject was not included in the primary safety endpoint analysis since there was no information on the status of the subject. This subject is included in the total of 86 active PTA subjects at 6-month follow-up as shown in the flowchart. However, this subject did not have any known endpoint event prior to withdrawal and therefore was excluded from the analysis in **Table 9**.

C. Study Population Demographics and Baseline Parameters

The key baseline demographics and risk factors for the LIFE-BTK RCT population are presented in **Table 7**. The demographics of the study population are typical for a CLTI study, and 80.1% of the subjects were enrolled in the US and 19.9% outside of US. All baseline characteristics were well balanced with no statistical differences between the study arms.

The mean ages were 73.3 ± 9.9 and 71.1 ± 10.4 years in the Esprit BTK and PTA arms, respectively. Over one-third of subjects in both arms were female. Out of the total registered population, 59% were identified as white and 41% as non-white, with 16.5% of the total population identified as Hispanic ethnicity. Mean body mass index values were 27.85 ± 5.47 and 28.94 ± 5.77 kg/m^2 in the Esprit BTK and PTA arms, respectively. Rutherford Becker (RB) Category in both arms was about evenly split between RB 4 and RB 5 and, hence, half of the population in both arms had wound(s) on the index limb at baseline.

Risk factors had a high prevalence in both arms, including diabetes (~70%), hypertension (90-95%), and hyperlipidemia (~80%). About half of the subjects in both arms were tobacco users, one-third of the population had previous percutaneous or surgical coronary revascularization, and about 60% in both arms had multi-vessel peripheral vascular disease. There were no significant differences between the Esprit BTK and PTA arms in baseline characteristics.

Table 7. Baseline Demographics and Medical History (Intent-to-Treat Population)

	Esprit BTK (N=173)	**PTA (N=88)**
DEMOGRAPHICS		
Age (Year)		
Mean ± SD (n)	73.3 ± 9.9 (173)	71.1 ± 10.4 (88)
Range (min, max)	(47, 94)	(49, 92)
Gender		
Male	67.6% (117/173)	69.3% (61/88)
Female	32.4% (56/173)	30.7% (27/88)

	Esprit BTK (N=173)	PTA (N=88)
Race		
White	56.6% (98/173)	63.6% (56/88)
American Indian or Alaska Native	0.0% (0/173)	1.1% (1/88)
Asian	20.8% (36/173)	12.5% (11/88)
- Chinese	77.8% (28/36)	100.0% (11/11)
- South Asian	16.7% (6/36)	0.0% (0/11)
- Other	5.6% (2/36)	0.0% (0/11)
Black or African American	12.1% (21/173)	12.5% (11/88)
Native Hawaiian or Other Pacific Islander	0.6% (1/173)	2.3% (2/88)
Declined or unable to disclose	10.4% (18/173)	8.0% (7/88)
Ethnicity		
Hispanic	17.9% (31/173)	13.6% (12/88)
Non-Hispanic	76.3% (132/173)	79.5% (70/88)
Declined or unable to disclose	5.8% (10/173)	6.8% (6/88)
BMI		
Mean ± SD (n)	27.85 ± 5.47 (173)	28.94 ± 5.77 (88)
Range (min, max)	(18.0, 49.6)	(18.6, 45.9)
RISK FACTORS		
Tobacco Use	52.6% (91/173)	53.4% (47/88)
Hypertension	94.2% (163/173)	90.9% (80/88)
Hyperlipidemia	80.9% (140/173)	81.8% (72/88)
Diabetes Mellitus	71.1% (123/173)	69.3% (61/88)
MEDICAL HISTORY and PRESENTATION		
History of Peripheral Artery Disease	82.7% (143/173)	77.3% (68/88)
Multi-vessel Peripheral Vascular Disease	62.5% (105/168)	61.2% (52/85)
Previous Amputation to Target Limb	9.2% (16/173)	8.0% (7/88)
Cardiac History		
- Prior Myocardial Infarction	16.9% (27/160)	14.8% (13/88)
- Previous Percutaneous or Surgical Coronary Revascularization	34.7% (59/170)	35.6% (31/87)
- Congestive Heart Failure	19.4% (33/170)	19.3% (17/88)
Neurologic and Renal History		
- Cerebrovascular Disease	13.2% (22/167)	17.4% (15/86)
- Prior Cerebrovascular Accident (CVA) or Stroke	11.7% (20/171)	17.0% (15/88)
- Transient ischemic attack	3.5% (6/170)	2.3% (2/87)
- Renal Disease	15.8% (27/171)	16.3% (14/86)
Rutherford Becker Category		
- RB4	52.0% (90/173)	51.1% (45/88)
- RB5	48.0% (83/173)	48.9% (43/88)
ABI of Target Limb, Mean ± SD (n)	0.87 ± 0.32 (150)	0.91 ± 0.33 (77)
TBI of Target Limb, Mean ± SD (n)	0.51 ± 0.31 (50)	0.46 ± 0.24 (29)
Wound on Target Limb at Baseline	49.1% (85/173)	51.1% (45/88)

N: Total number of subjects. n: Number of subjects with available data for variable of interest
Data presented as %(n/N) or Mean ± standard deviation
BMI: Body Mass Index; ABI: Ankle Brachial Index; TBI: Toe Brachial Index

Baseline target lesion characteristics, procedural and post-procedural information are presented in **Table 8**. There were a total of 179 target lesions in 173 subjects in the Esprit BTK arm, and 92 target lesions in 88 subjects in the PTA arm. The largest number of

target lesion segments were located in the anterior tibial artery (AT), with 34.3% (59/172) and 27.0% (24/89) in the Esprit BTK arm and PTA arm, respectively. The mean lesion length (~44mm) and mean reference vessel diameter (~2.9mm) were similar between the arms. The mean pre-procedure percentage of diameter stenosis (%DS) was 72.6 ± 18.9 % in the Esprit BTK arm and 73.7 ± 21.0 % in the PTA arm. At post-procedure, the mean in-device and in-segment %DS were numerically lower in the Esprit BTK arm compared to the PTA arm. The Esprit BTK arm also achieved a higher percentage of final diameter (%DS) < 30% at the rate of 95.9% (163/170), compared to the PTA arm which had a rate of 72.6% (61/84).

Table 8. Baseline, Procedure and Post-Procedure Target Lesion Characteristics (Intent-to-Treat Population)

	Esprit BTK (N=173) (L=179)	**PTA (N=88) (L=92)**
Baseline Angiographic Core Laboratory Reported Lesion Characteristics		
Artery Segment		
- Anterior Tibial	34.3% (59/172)	27.0% (24/89)
- Posterior Tibial	15.1% (26/172)	18.0% (16/89)
- Peroneal	16.3% (28/172)	23.6% (21/89)
- Tibioperoneal Trunk	15.1% (26/172)	16.9% (15/89)
- Tibioperoneal Trunk – Posterior Tibial	8.7% (15/172)	9.0% (8/89)
- Tibioperoneal Trunk – Peroneal	10.5% (18/172)	5.6% (5/89)
Lesion Length (mm)		
Mean ± SD (l)	43.78 ± 31.84 (172)	44.75 ± 29.07 (89)
Range (min, max)	(3.82, 148.40)	(5.33, 125.10)
Reference Vessel Diameter Pre-intervention		
Mean ± SD (l)	2.94 ± 0.77 (147)	2.82 ± 0.74 (80)
Range (min, max)	(1.37, 5.23)	(1.35, 4.79)
Calcification		
None	99.4% (171/172)	100.0% (89/89)
Moderate	0.6% (1/172)	0.0% (0/89)
Thrombus		
Absent	100.0% (172/172)	100.0% (89/89)
Ulceration	0.0% (0/172)	0.0% (0/89)
Aneurysm	0.0% (0/172)	0.0% (0/89)
TASC II Type		
A	48.3% (83/172)	52.8% (47/89)
B	35.5% (61/172)	25.8% (23/89)
C	16.3% (28/172)	21.3% (19/89)
D	0.0% (0/172)	0.0% (0/89)
% Diameter Stenosis (DS) Pre-intervention		
Mean ± SD (l)	72.6 ± 18.9 (172)	73.7 ± 21.0 (89)
Range (min, max)	(23, 100)	(18, 100)
Total Occlusion at Treatment Site	15.1% (26/172)	20.2% (18/89)
Angiographic Core Laboratory Reported Post-Procedure Measurements		
Residual %DS after Pre-dilatation/PTA		
Mean ± SD (l)	30.0 ± 12.6 (84)	25.0 ± 8.7 (3)
Range (min, max)	(3, 61)	(15, 31)
Post-procedure In-Device %DS		
Mean ± SD (l)	13.1 ± 8.2 (170)	21.8 ± 11.4 (84)
Range (min, max)	(-9, 35)	(-7, 48)

	Esprit BTK (N=173) (L=179)	PTA (N=88) (L=92)
Post-procedure In-Segment %DS		
Mean ± SD (l)	17.0 ± 9.3 (170)	22.8 ± 11.2 (84)
Range (min, max)	(-6, 60)	(-5, 48)
Final Diameter Stenosis < 30%	95.9% (163/170)	72.6% (61/84)
Residual Dissection Post-Intervention	0.0% (0/170)	0.0% (0/84)
Procedural Characteristics (Site-Reported)		
Pre-dilation Performed	100.0% (179/179)	100.0% (92/92)
Scaffold Post-dilated Without Complications	99.4% (176/177)	NA
Metal Stent Bailout	0.0% (0/173)	5.7% (5/88)

N: number of subjects. L: Total number of target lesions. : Number of target lesions with available data for variable of interest
Data presented as %(l/L) or Mean ± standard deviation.

The procedural endpoints for technical and device success are described in **Table 9**. Technical Success is 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. Measurements of % diameter stenosis for technical success were per angiographic core laboratory. Device success is 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.

Table 9. Procedural Endpoints

	Esprit BTK (N = 173) (L = 179) (D = 356)	PTA (N = 88) (L = 92)	Difference [95% CI][1]
Technical Success	95.9% (163/170)	72.6% (61/84)	23.26% [13.91%, 33.84%]
Device Success	95.2% (339/356)	N/A	N/A

[1] By Newcombe score method. The confidence interval was calculated without any multiplicity adjustment.

N: Total number of subjects. L: Number of target lesions. D: Number of devices. NA: Not applicable.

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the as-treated population (AT) of 260 subjects. Data on a total of 245 subjects were available for the evaluation of the primary safety endpoint at 6 months post-procedure. The key safety outcomes for this study are presented below in **Table 10**, and in **Figure 5**. Adverse effects are reported in **Table 11** and **Table 12**.

As shown in **Table 10,** the primary safety endpoint was met (p-value = 0.0019). The individual components of the primary safety endpoint are presented in **Table 10**, in a non-hierarchical fashion. A total of 5 events in 5 subjects occurred in the Esprit BTK

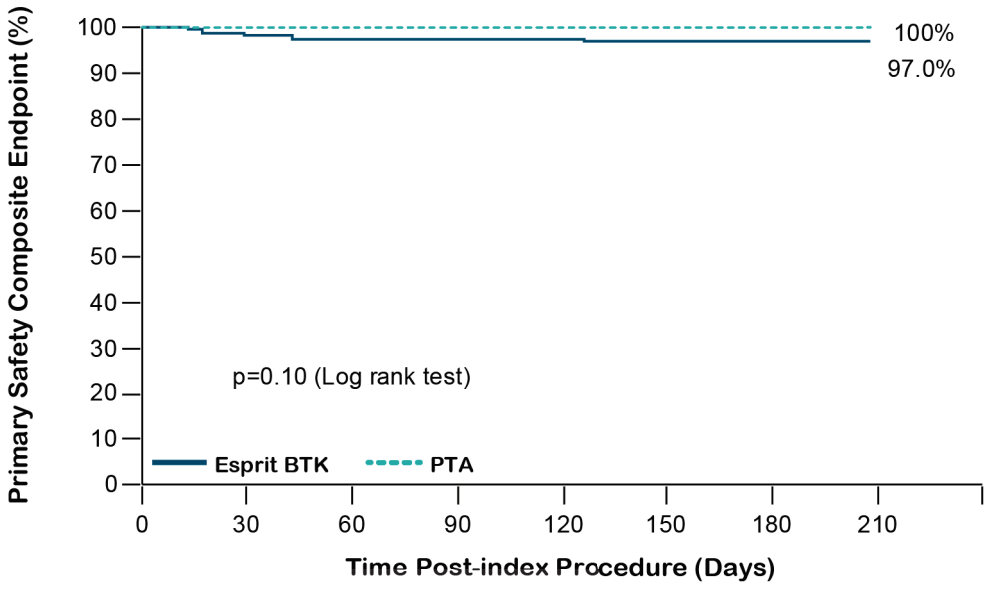
arm, and none in the PTA arm. These events were two peri-operative deaths, two above ankle amputations and one major re-intervention on the index limb. All 5 events were assessed by the investigator as not related to the study procedure and not related to the study device.

Table 10. Primary Safety Endpoint

Primary Safety Endpoint As-Treated (AT) (N=260)	**Esprit BTK (N=170)**	**PTA (N=90)**	**Difference (One Sided Lower 97.5% CL)[1]**	**P-value[2]**
Freedom from MALE[3] at 6 months and POD at 30 days	96.9% (155/160)	100.0% (85/85)	-3.13% (-7.11%)	0.0019
Components	**Esprit BTK**	**PTA**	**Difference [95% CI][1]**	-
Freedom from Major Adverse Limb Events at 6 months	98.1% (157/160)	100.0% (85/85)	-1.88% [-5.37%, 2.62%]	-
Freedom from Above Ankle Amputation in Index Limb	98.8% (158/160)	100.0% (85/85)	-1.25% [-4.44%, 3.17%]	-
Freedom from Major Re-intervention on Index Limb	99.4% (159/160)	100.0% (85/85)	-0.63% [-3.45%, 3.73%]	-
Freedom from Peri-Operative (POD) Death at 30 days	98.8% (158/160)	100.0% (85/85)	-1.25%	-

[1]By Newcombe score method.
[2]Farrington-Manning non-inferiority (NI) test, with NI margin of δ set at -10%, to be compared at one-sided significance level of 0.025.
[3]For the MALE component, the adverse event start date is used as the treatment date.
N: Total number of subjects.
The confidence intervals were calculated without multiplicity adjustment.

The Kaplan-Meier curve showing the composite rates of MALE at 6-month + POD at 30-day in the as-treated population is presented in **Figure 5**.



Time After Index Procedure (days)						
	0	**30**	**60**	**90**	**180**	**208**
Esprit BTK:						
# At Risk	170	166	162	162	153	152
% Survived	100.0%	98.2%	97.6%	97.6%	97.0%	97.0%
PTA:						
# At Risk	90	90	89	87	84	84
% Survived	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%

Test Between Groups	**Test**	**Chi-Square**	**DF**	**p-value**
	Log-Rank	2.684	1	0.10

Note: Data are presented as the event-free rates (binary) through 6 months (208 days post index procedure) for the Major Adverse Limb Event by CEC adjudication, and through 30 days post Index procedure for the Peri-operative Death by CEC adjudication.
Note: Events include only each subject's first occurrence of the composite endpoint.
Note that the p-value presented here was not adjusted for multiplicity.

Figure 5: Kaplan-Meier Survival Curve: Primary Safety Endpoint (Freedom from MALE + POD) by Treatment through 6 Months (As-Treated Population)

There were two PODs in the Esprit BTK arm. The site investigators assessed the two subject deaths as not related to the study procedure and not related to the study device. In addition, the CEC also adjudicated both events as not related to index procedure and not related to COVID-19. One subject passed away on Day 13 due to cardiovascular death and another subject passed away on Day 17 due to non-cardiovascular death.

Adverse effects that occurred in the PMA clinical study:

The lists of site-reported serious adverse events (SAEs) and non-serious adverse events (non-SAEs) for all randomized subjects through 1 year are presented in **Table 11** and **Table 12**, respectively. The incidence rate and number of adverse events were tabulated by MedDRA system organ class (SOC).

The percentages of subjects with SAEs, as reported by the investigators, were similar in both arms (51.4% in the Esprit BTK arm and 51.1% in the PTA arm). Non-serious AEs were reported in 60.7% of subjects in the Esprit BTK arm and 68.2% of subjects in the PTA arm.

Within the SAEs, the most reported events per SOC were 1) injury, poisoning, and procedural complications; and 2) infections and infestations, in both arms. And within the non-SAEs, the most reported events per SOC were 1) injury, poisoning, ;and procedural complications; 2) musculoskeletal and connective tissue disorders; and 3) vascular disorders.

Device and procedural relationship were determined by the trial investigators, and included the following categories: not related, unlikely related, possibly related, probably related and definitely/causally related. Information on procedure and device relationship with the AE, for the categories of possibly related, probably related, and definitely/causally related, is provided in **Table 13**. The 10 events assessed as probably related to the procedure in the Esprit BTK arm are peripheral edema (2), hemorrhage (2), hematoma, arterial rupture, vascular stent insertion, arterial thrombosis, arterial occlusive disease (2). The 16 events assessed as possibly related to the procedure in the Esprit BTK arm are peripheral artery dissection, wound complication (3), arterial occlusive disease, pain in extremity (3), incision site abscess, vascular access complications, arterial stenosis (2), peripheral edema, small intestine obstruction, skin wound (2). The 16 events assessed as definitely/causally related to the procedure in the Esprit BTK arm are vascular access complications (3), hematoma (3), wound complication, renal failure, arterial stenosis, arterial occlusive disease, arterial rupture (2), artery dissection (2), rash, vasospasm. The 5 events assessed as probably related to the device in the Esprit BTK arm are vascular stent insertion, arterial thrombosis, peripheral ischemia, arterial occlusive disease (2). The 10 events assessed as possibly related to the device in the Esprit BTK arm are wound complication (2), arterial occlusive disease (2), pain in extremity (4), skin wound (2).

Table 11. Summary of Site-Reported Serious Adverse Events through 1 Year (Intent to-Treat; N=261)

System Organ Class Preferred Term	Total		Esprit BTK		PTA	
	Number of Events	Number of Subjects (N=261)	Number of Events	Number of Subjects (N=173)	Number of Events	Number of Subjects (N=88)
Any SAE	**349**	**51.3% (134/261)**	**252**	**51.4% (89/173)**	**97**	**51.1% (45/88)**
Blood and Lymphatic System Disorders	7	2.3% (6/261)	3	1.7% (3/173)	4	3.4% (3/88)
Cardiac Disorders	36	7.3% (19/261)	30	8.1% (14/173)	6	5.7% (5/88)
Gastrointestinal Disorders	8	2.7% (7/261)	8	4.0% (7/173)	0	0.0% (0/88)
General Disorders and Administration Site Conditions	16	5.0% (13/261)	12	5.2% (9/173)	4	4.5% (4/88)
Hepatobiliary Disorders	2	0.4% (1/261)	2	0.6% (1/173)	0	0.0% (0/88)
Infections and Infestations	47	12.6% (33/261)	32	13.9% (24/173)	15	10.2% (9/88)
Injury, Poisoning, and Procedural Complications	74	21.1% (55/261)	55	22.5% (39/173)	19	18.2% (16/88)
Investigations	4	1.5% (4/261)	1	0.6% (1/173)	3	3.4% (3/88)
Metabolism and Nutrition Disorders	5	1.9% (5/261)	4	2.3% (4/173)	1	1.1% (1/88)
Musculoskeletal and Connective Tissue Disorders	21	6.5% (17/261)	15	6.9% (12/173)	6	5.7% (5/88)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts And Polyps)	3	1.1% (3/261)	0	0.0% (0/173)	3	3.4% (3/88)
Nervous System Disorders	17	5.4% (14/261)	11	5.8% (10/173)	6	4.5% (4/88)
Psychiatric Disorders	2	0.8% (2/261)	0	0.0% (0/173)	2	2.3% (2/88)
Renal and Urinary Disorders	18	5.7% (15/261)	12	5.8% (10/173)	6	5.7% (5/88)
Respiratory, Thoracic and Mediastinal Disorders	21	6.9% (18/261)	17	8.1% (14/173)	4	4.5% (4/88)
Skin and Subcutaneous Tissue Disorders	9	3.1% (8/261)	8	4.0% (7/173)	1	1.1% (1/88)
Surgical and Medical Procedures	22	8.0% (21/261)	16	8.7% (15/173)	6	6.8% (6/88)
Vascular Disorders	37	10.7% (28/261)	26	11.6% (20/173)	11	9.1% (8/88)

Note: Include adverse events only on or post index procedures.
Note: The numerator counts only each subject's first occurrence of each event.
Note: N is the total number of subjects.

Table 92. Summary of Site-Reported Non-Serious Adverse Events through 1 Year (Intent-to-Treat; N=261)

System Organ Class Preferred Term	Total		Esprit BTK		PTA	
	Number of Events	Number of Subjects (N=261)	Number of Events	Number of Subjects (N=173)	Number of Events	Number of Subjects (N=88)
Any NSAE	**382**	**63.2% (165/261)**	**255**	**60.7% (105/173)**	**127**	**68.2% (60/88)**
Blood and Lymphatic System Disorders	3	1.1% (3/261)	2	1.2% (2/173)	1	1.1% (1/88)
Cardiac Disorders	16	4.6% (12/261)	11	4.6% (8/173)	5	4.5% (4/88)
Ear and Labyrinth Disorders	3	1.1% (3/261)	3	1.7% (3/173)	0	0.0% (0/88)
Endocrine Disorders	1	0.4% (1/261)	1	0.6% (1/173)	0	0.0% (0/88)
Eye Disorders	2	0.8% (2/261)	1	0.6% (1/173)	1	1.1% (1/88)
Gastrointestinal Disorders	14	5.0% (13/261)	9	4.6% (8/173)	5	5.7% (5/88)
General Disorders and Administration Site Conditions	23	7.7% (20/261)	14	7.5% (13/173)	9	8.0% (7/88)
Hepatobiliary Disorders	3	0.8% (2/261)	2	0.6% (1/173)	1	1.1% (1/88)
Immune System Disorders	1	0.4% (1/261)	0	0.0% (0/173)	1	1.1% (1/88)
Infections and Infestations	28	9.2% (24/261)	21	9.8% (17/173)	7	8.0% (7/88)
Injury, Poisoning, and Procedural Complications	79	21.8% (57/261)	51	21.4% (37/173)	28	22.7% (20/88)
Investigations	6	2.3% (6/261)	4	2.3% (4/173)	2	2.3% (2/88)
Metabolism and Nutrition Disorders	8	2.7% (7/261)	8	4.0% (7/173)	0	0.0% (0/88)
Musculoskeletal and Connective Tissue Disorders	69	21.1% (55/261)	41	20.2% (35/173)	28	22.7% (20/88)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts And Polyps)	8	2.7% (7/261)	7	3.5% (6/173)	1	1.1% (1/88)
Nervous System Disorders	17	6.1% (16/261)	13	6.9% (12/173)	4	4.5% (4/88)
Psychiatric Disorders	2	0.8% (2/261)	1	0.6% (1/173)	1	1.1% (1/88)
Renal and Urinary Disorders	9	3.4% (9/261)	8	4.6% (8/173)	1	1.1% (1/88)
Reproductive System and Breast Disorders	1	0.4% (1/261)	1	0.6% (1/173)	0	0.0% (0/88)
Respiratory, Thoracic and Mediastinal Disorders	10	3.8% (10/261)	6	3.5% (6/173)	4	4.5% (4/88)
Skin and Subcutaneous Tissue Disorders	13	5.0% (13/261)	8	4.6% (8/173)	5	5.7% (5/88)
Surgical and Medical Procedures	9	3.4% (9/261)	3	1.7% (3/173)	6	6.8% (6/88)
Vascular Disorders	57	16.9% (44/261)	40	16.8% (29/173)	17	17.0% (15/88)

Note: Include adverse events only on or post-index procedures.
Note: The numerator counts only each subject's first occurrence of each event.
Note: N is the total number of subjects.

Table 103. Summary of Procedure and Device Relationship to Adverse Events, per Site Investigator Assessment

	Esprit BTK		PTA	
	Procedure Relatedness	**Device relatedness**	**Procedure Relatedness**	**Device relatedness**
Definite/causal	3.16% (16/507)	0.00% (0/507)	3.57% (8/224)	0.00% (0/224)
Probable	1.97% (10/507)	0.99% (5/507)	2.23% (5/224)	0.00% (0/224)
Possible	3.16% (16/507)	1.97% (10/507)	8.48% (19/224)	0.89% (2/224)

2. Effectiveness Results

The analysis of effectiveness was based on the intent-to-treat population of 261. Data on a total of 220 subjects were available for the evaluation of the primary effectiveness endpoint at 1-year post-procedure. The key effectiveness outcomes are presented in **Table 14**, **Table 16**, and **Figure 6**.

As shown in 4, the primary effectiveness endpoint was met. The composite rates of primary patency and limb salvage were 74.5% (111/149) in the Esprit BTK arm and 43.7% (31/71) in the PTA arm with a difference between the two treatment arms of 30.8%, favoring the Esprit BTK arm. The Esprit BTK arm was superior to PTA arm with a superiority p-value of <0.0001 for observed rates at 1 year. The components of the primary effectiveness endpoint are presented in **Table 16** in a non-hierarchical fashion. Except for above ankle amputation, the observed "freedom from" rates are numerically higher in the Esprit BTK arm, as compared to the PTA arm.

There were four above ankle amputations in the Esprit BTK arm, two within the first 6 months and two between 6 months and 1 year. For the amputations that occurred after 6 months, one was assessed by the investigator as not related to the procedure and not related to the study device, and one was assessed as unlikely related to the procedure and the study device. All four subjects with amputation had diabetes and presented with index wounds. Three subjects had patent scaffolds at the time of amputation. The fourth subject had a site-reported duplex ultrasound suggesting scaffold occlusion which at follow-up was found to be patent on angiography.

Table 14. Primary Effectiveness Endpoint

Intent-to-Treat (N=261)	Esprit BTK (N=173)	PTA (N=88)	Difference (One Sided Lower 97.51% CL)[1]	P-value[2]
Limb Salvage and Primary Patency at 1 year	74.5% (111/149)	43.7% (31/71)	30.83% (17.01%)]	<0.0001

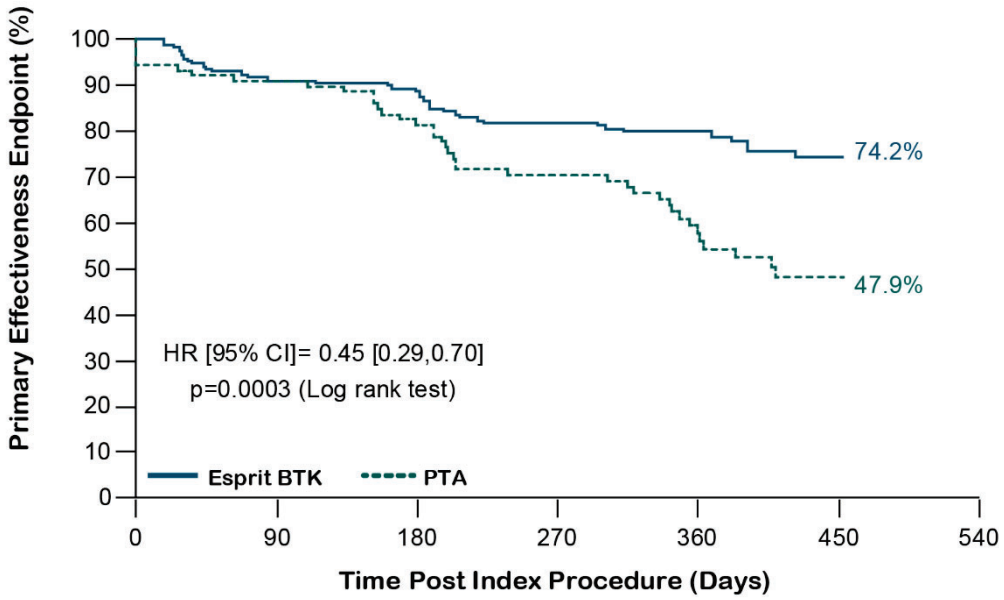
Limb salvage and primary patency is defined as freedom from: above ankle amputation in index limb, 100% total occlusion of target vessel, binary restenosis of the target lesion and clinically-driven target lesion revascularization (CD-TLR). For the amputation and CD-TLR components, the adverse event start date is used as the treatment date.
[1]By Newcombe score method.
[2]From One-sided Chi-square test, to be compared at one-sided significance level of 0.0249. The final alpha level of 0.0249 was adjusted down from the nominal 0.025 due to a pre-specified interim look by an independent statistician for sample size re-estimation.

The Kaplan-Meier (KM) curve showing the composite rates of limb salvage and primary patency through 1 year (primary effectiveness endpoint) in the intent-to-treat population is presented below. Two of the primary effectiveness endpoint components (100% total occlusion of target vessel and binary restenosis of target lesion) were dependent on imaging, mainly duplex ultrasound (DUS). DUS exams that were non-diagnostic (i.e., not analyzable by the core laboratory) were asked to be repeated. **Table 15** summarizes the number of final diagnostic and non-diagnostic DUS exams at 1-year follow-up. The 1-year window was extended to 453 days to allow for these repeat DUS exams to occur and ensure a totality of DUS data collection. Therefore, the KM curve below extends to 453 days.

Table 15. Number of Subjects with Diagnostic and non-Diagnostic Duplex Ultrasound

	1-Year Follow-up
Subjects Complete Follow-up Visit	218
Subjects Complete a DUS	96.8% (211/218)
Diagnostic	205
Non-Diagnostic	6
Subjects who had repeated DUS*	8.5% (18/211)
Subjects Missed DUS	3.2% (7/218)

Note: When a subject has both or multiple Diagnostic and Non-Diagnostic DUS at a visit, only count the 'final' Diagnostic.
*The repeated DUS exam subjects were subjects who had their first DUS exam as non-diagnostic and repeated the exam. The final result of the exam can either be diagnostic or non-diagnostic.



Time After Index Procedure (days)						
	0	**30**	**90**	**180**	**365**	**453**
Esprit BTK:						
# At Risk	173	163	152	142	95	42
% Survived	100.0%	96.5%	91.1%	88.6%	79.8%	74.2%
PTA:						
# At Risk	88	82	78	67	33	15
% Survived	94.3%	93.2%	90.9%	81.2%	54.5%	47.9%

Test Between Groups	**Test**	**Chi-Square**	**DF**	**p-value**
	Log-Rank	13.104	1	0.0003

Note: Data are presented as the event-free rates through the 1-year post Index procedure.
Note: Events include only each subject's first occurrence of the composite endpoint.
Note that the p-value and the 95% CI were calculated without multiplicity adjustment.

Figure 6: Kaplan-Meier Survival Curve: Primary Effectiveness Endpoint by Treatment through 1 Year (ITT Population)

Table 16. Primary Effectiveness Endpoint and Components (Intent-to-Treat Population)

	Esprit BTK (N=173)	PTA (N=88)	Difference [95% CI][1]
Primary Effectiveness Endpoint Limb Salvage and Primary Patency at 1 year	74.5% (111/149)	43.7% (31/71)	30.83% [17.02%, 43.45%]
Freedom from Above Ankle Amputation in Index Limb	97.3% (145/149)	100.0% (71/71)	-2.68% [-6.70%, 2.70%]
Freedom from 100% Total Occlusion of Target Vessel	87.9% (131/149)	83.1% (59/71)	4.82% [-4.50%, 16.04%]
Freedom from Binary Restenosis of the Target Lesion	76.5% (114/149)	50.7% (36/71)	25.81% [12.30%, 38.70%]
Freedom from CD-TLR	92.6% (138/149)	84.5% (60/71)	8.11% [-0.40%, 18.76%]

[1]By Newcombe score method.
The confidence intervals were calculated without multiplicity adjustment.
For the amputation and CD-TLR components, the adverse event start date is used as the treatment date.

The LIFE-BTK trial had two powered secondary endpoints, which are presented below in **Table 17**. Both powered secondary endpoints were met.

For the first powered secondary endpoint, binary restenosis of the target lesion at 1 year, the rates were 23.5% (35/149) for the Esprit BTK arm and 49.3% (35/71) for the PTA arm with a difference of -25.8%. The Esprit BTK arm demonstrated superiority to PTA arm with a p-value of <0.0001 for observed rates at 1 year.

For 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 at 1 year, the rates were 83.2% (124/149) for the Esprit BTK arm and 69.0% (49/71) for the PTA arm with a difference of 14.2%. The Esprit BTK arm demonstrated superiority to PTA arm with a p-value of 0.0081 for the observed rates at 1 year.

Table 17. Powered Secondary Endpoint – Binary Restenosis of the Target Lesion and Limb Salvage and Primary Patency (without Binary Restenosis Component) (Intent-to-Treat)

	Esprit BTK (N=173)	PTA (N=88)	Difference (One Sided 97.5% CL)[1]	P-value[2]
Binary Restenosis of the Target Lesion at 1 year	23.5% (35/149)	49.3% (35/71)	-25.81% (-12.30%)	<0.0001
Limb Salvage and Primary Patency at 1 year	83.2% (124/149)	69.0% (49/71)	14.21% (2.48%)	0.0081

Limb salvage and primary patency is defined as freedom from: above ankle amputation in index limb, 100% total occlusion of target vessel, and clinically-driven target lesion revascularization (CD-TLR). For the amputation and CD-TLR components, the adverse event start date is used as the treatment date.
[1]By Newcombe score method.
[2]From One-sided Chi-square test, to be compared at one-sided significance level of 0.025.
Data presented as % (n/N)

LIFE-BTK RCT collected comprehensive and quantitative wound data from a CLTI population. Wound care was not mandated or standardized in the trial. In LIFE-BTK RCT, wounds present on the target limb were assessed by a wound core laboratory, using wound images taken by the investigator with a dedicated camera system provided by the core laboratory. Wounds were assessed at baseline to determine etiology and assessed for healing through 1 year. Wound images were required through 90-day follow-up. If the wound was not healed at 90 days, there was an additional assessment at 6- and 12-month follow-ups. Of the 184 wounds in 130 subjects (115 wounds in 85 subjects in the Esprit BTK arm and 69 wounds in 45 subjects in the PTA arm), 73.4% (71.3% in the Esprit BTK arm and 76.8% in the PTA arm) were assessed by the core laboratory as "arterial insufficiency only" wounds. The remaining wounds were assessed as "mixed etiology" wounds and included diabetic, venous stasis, traumatic, Charcot's joint and pressure related pressure-related wounds.

The mean number of wounds per subject was 1.4 ± 0.8 in the Esprit BTK arm and 1.5 ± 0.9 in the PTA arm.

At 1 year follow-up, the cumulative percentage of wounds healed was similar in both arms with 76.1% (54/71) of wounds healed in the Esprit BTK arm and 80% (40/50) in the PTA arm (Difference: -3.94%; 95% CI [-18.08%, 11.58%]), as shown in **Figure 7**. The cumulative percentage of subjects with healed index wound(s) was 44.6% (37/83) of wounds healed in the Esprit BTK arm and 55.6% (25/45) in the PTA arm (Difference: -10.98%; 95% CI [-27.91%, 6.94%]), as shown in **Figure 8**. Note that, for subjects presenting with more than one wound at index, all wounds had to be healed for a subject to be considered as having "wound healed". It is important to note that the trial was not powered to detect differences in wound healing between the two arms.

Occurrence of new wounds, defined as a wound below the knee in the index limb that was not identified at the time of the index procedure or wound that recurred in the same location following the healing of the index wound, was a descriptive endpoint in LIFE-BTK RCT. The occurrence of new wounds was similar with 18.5% in the Esprit BTK arm and 14.8% in the PTA arm.

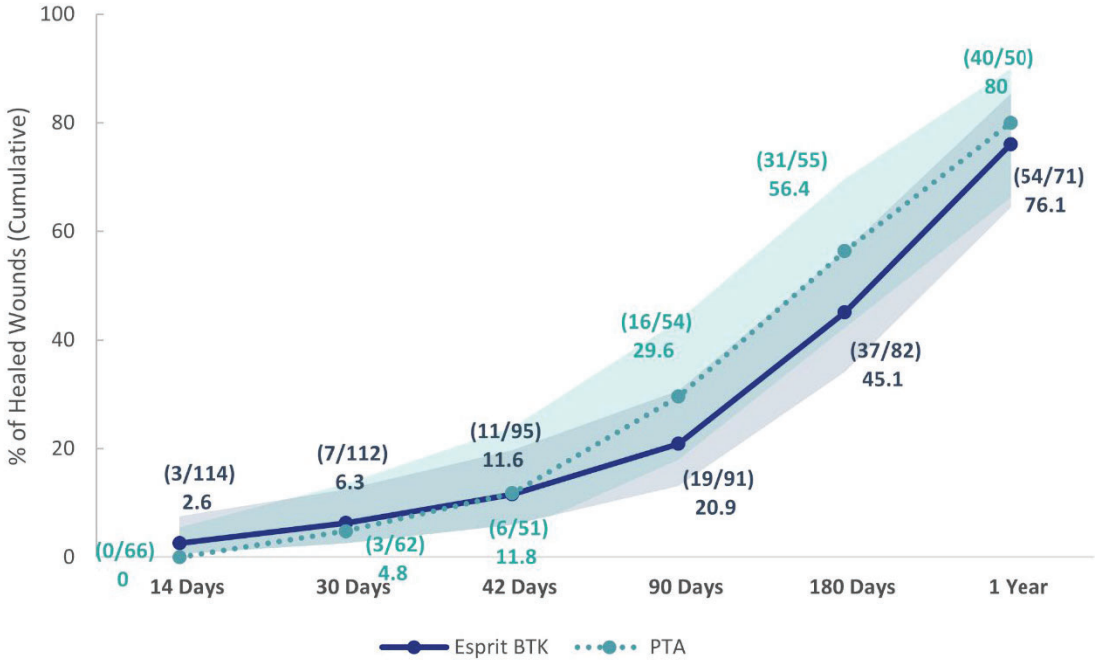


Figure 7: Cumulative Index Wound Healing at Each Timepoint – Wound-Level

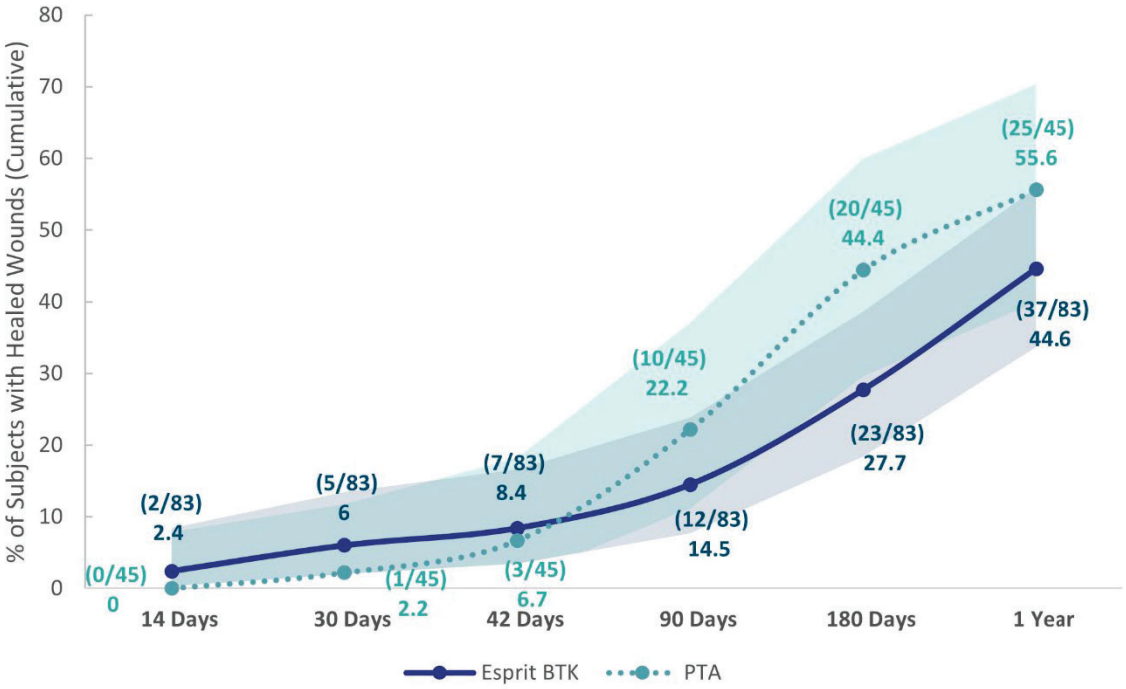


Figure 8: Cumulative Index Wound Healing at Each Timepoint – Subject-Level

3. Subgroup Analyses

The following preoperative characteristics were evaluated for potential association with outcomes: gender, race/ethnicity, age, and region of enrollment. These subgroup analyses are presented in **Table 18** to **Table 21**.

Gender Analysis

The gender analysis is presented in **Table18**. Female subjects represented 31.8% (83/261) of the randomized population. Compared to the overall population, females had similar event rates for the primary safety and primary effectiveness endpoints. The five events in the Esprit BTK arm for the primary safety endpoint all occurred in the male population, which represents 68.2% of the population enrolled in LIFE-BTK RCT. For the primary effectiveness endpoint, event rates in males and females were similar to the overall population. The observed difference in primary effectiveness endpoint rates between Esprit BTK and PTA arms, in both males and females, was consistent with the difference of about 30% in the overall population. The assessment of gender effect for the primary safety and effectiveness endpoints showed no significant treatment interaction.

Table 118. Primary Safety and Effectiveness Endpoints by Gender

	Esprit BTK	PTA	Interaction p-value
Primary Safety Endpoint: Freedom from MALE[1] at 6-month and POD at 30 days.			
Male (N=167) Female (N=78)	95.4% (103/108) 100.0% (52/52)	100.0% (59/59) 100.0% (26/26)	0.9696
Primary Effectiveness Endpoint – Limb Salvage and Primary Patency at 1 year[2]			
Male (N=148) Female (N=72)	73.5% (72/98) 76.5% (39/51)	44.0% (22/50) 42.9% (9/21)	0.7546

Primary Safety Endpoint: As-Treated Population (N=260) – Total evaluable population for primary safety endpoint: n=245.
Primary Effectiveness Endpoint: Intent-to-Treat Population (N=261) – Total evaluable population for primary effectiveness endpoint: n=220.
Note: The treatment by subgroup interaction for the primary endpoints is evaluated using logistic regression, and the interaction p-value is provided. Interaction effect between treatment and gender on the primary endpoints is tested against an alpha level of 0.15.
[1]For the MALE component, the adverse event start date is used as the treatment date.
[2]For the amputation and CD-TLR components, the adverse event start date is used as the treatment date.

Race and Ethnicity Analysis

The race and ethnicity analyses are presented in **Table19**. The subject population enrolled in LIFE-BTK RCT was composed of 59% white and 12.3% Black or African American. Other races included 18% Asian, 1.1% native Hawaiian or Other Pacific Islander, 0.4% American Indian or Alaska Native, and 4.3% of subjects identified as "Other" for their race. A total of 9.6% of subjects declined or were unable to disclose their race. Note that some subjects may have multiple races. Safety and effectiveness outcomes by race subgroups are presented in **Table19**.

In **Table 19**, for the safety endpoint, all five events occurred in the white population, which represents the majority of the population enrolled in LIFE-BTK RCT. For the endpoint of limb salvage and primary patency at 1 year, the lowest rate was observed in the White population, in the Esprit BTK arm, but still maintaining a 19.6% difference between Esprit BTK and PTA arms. In the other two race subgroups, event rates were similar to the overall population. The biggest difference between Esprit BTK and PTA arms (49.5%) was observed in the "Other" race subgroup, which was mainly composed of Asian subjects (94% in the primary safety endpoint analysis and 96% in the primary effectiveness analysis). Despite this observed difference, the assessment of race effect for the primary safety and effectiveness endpoints showed no significant treatment interaction by race.

The race outcomes must be interpreted with caution, as the sample size in some subgroups is very small and information is too limited to comment on any potential associations. The trend for safety and effectiveness outcomes in the Hispanic or Latino population is aligned with outcomes observed in the overall LIFE-BTK RCT population.

Table 19. Primary Safety and Effectiveness Endpoints by Race (All Races) and Ethnicity

Primary Safety Endpoint – Freedom from MALE[1] at 6 months and POD at 30 days			
	Esprit BTK (N = 170)	**PTA (N = 90)**	**Interaction p-value**
Race			
White (N = 141)	94.4% (84/89)	100.0% (52/52)	0.9992
Black or African American (N = 30)	100.0% (19/19)	100.0% (11/11)	
Other (N = 50)	100.0% (35/35)	100.0% (15/15)	
Race (All Races)			
White (N=141)	94.4% (84/89)	100.0% (52/52)	
Black or African American (N=30)	100.0% (19/19)	100.0% (11/11)	
American Indian or Alaska Native (N=1)	NA	100.0% (1/1)	
Asian (N=47)	100.0% (35/35)	100.0% (12/12)	NS
Native Hawaiian or Other Pacific Islander (N=3)	100.0% (1/1)	100.0% (2/2)	
Ethnicity			
Hispanic or Latino (N=39)	89.3% (25/28)	100.0% (11/11)	NS
Not Hispanic or Latino (N=193)	98.4% (122/124)	100.0% (69/69)	
Primary Effectiveness Endpoint – Limb Salvage and Primary Patency at 1 year[2]			
	Esprit BTK (N = 173)	**PTA (N = 88)**	**Interaction p-value**
Race			
White (N = 123)	69.6% (55/79)	50.0% (22/44)	0.2041
Black or African American (N = 28)	77.8% (14/18)	40.0% (4/10)	
Other (N = 47)	82.9% (29/35)	33.3% (4/12)	
Race (All Races)			
White (N=123)	69.6% (55/79)	50.0% (22/44)	
Black or African American (N=28)	77.8% (14/18)	40.0% (4/10)	
American Indian or Alaska Native (N=1)	NA	0.0% (0/1)	NS
Asian (N=45)	82.9% (29/35)	40.0% (4/10)	
Native Hawaiian or Other Pacific Islander (N=2)	100.0% (1/1)	0.0% (0/1)	
Ethnicity			
Hispanic or Latino (N=37)	74.1% (20/27)	40.0% (4/10)	
Not Hispanic or Latino (N=171)	74.6% (85/114)	43.9% (25/57)	NS

Primary Safety Endpoint: As-Treated Population (N=260) – Total evaluable population for primary safety endpoint: n=245.
Primary Effectiveness Endpoint: Intent-to-Treat Population (N=261) – Total evaluable population for primary effectiveness endpoint: n=220.
Note: The treatment by subgroup interaction for the primary endpoints is evaluated using logistic regression, and the interaction p-value is provided. Interaction effect between treatment and race on the primary endpoints is tested against an alpha level of 0.15.
NA: Not Available; NS: Not pre-specified.
[1]For the MALE component, the adverse event start date is used as the treatment date.
[2]For the amputation and CD-TLR components, the adverse event start date is used as the treatment date.

Age analysis

Of the 261 subjects randomized in the LIFE-BTK RCT, 76.2% (199/261) were ≥ 65 years old and 23.8% (62/261) were < 65 years old. Safety and effectiveness outcomes by age subgroups are presented in **Table 20**.

The safety endpoint rates in both age groups were consistent with the overall population.

As for the effectiveness endpoint, observed rates for limb salvage and primary patency in the ≥ 65-year-old group were consistent with the overall population, with an observed difference of 33.1% between Esprit BTK and PTA arms. In the < 65-year-old group the observed difference between Esprit BTK and PTA arms was slightly lower (25.5%) but still favoring the Esprit BTK arm. Despite these observed differences between age groups, the assessment of age effect for the primary safety and effectiveness endpoints showed no significant treatment interaction by age.

Table 12. Primary Safety and Effectiveness Endpoints by Age

Primary Safety Endpoint – Freedom from MALE[1] at 6-month and POD at 30 days			
	Esprit BTK (N = 170)	**PTA (N = 90)**	**Interaction p-value**
Age Age < 65 years (N = 58) Age ≥ 65 years N = 187	 94.3% (33/35) 97.6% (122/125)	 100.0% (23/23) 100.0% (62/62)	0.9983
Primary Effectiveness Endpoint – Limb Salvage and Primary Patency at 1 year[2]			
	Esprit BTK (N = 173)	**PTA (N = 88)**	**Interaction p-value**
Age Age < 65 years (N = 51) Age ≥ 65 years N = 169	 78.1% (25/32) 73.5% (86/117)	 52.6% (10/19) 40.4% (21/52)	0.7364

Primary Safety Endpoint: As-Treated Population (N=260) – Total evaluable population for primary safety endpoint: n=245.
Primary Effectiveness Endpoint: Intent-to-Treat Population (N=261) – Total evaluable population for primary effectiveness endpoint: n=220.
Note: The treatment by subgroup interaction for the primary endpoints is evaluated using logistic regression, and the interaction p-value is provided. Interaction effect between treatment and age on the primary endpoints is tested against an alpha level of 0.15.
[1]For the MALE component, the adverse event start date is used as the treatment date.
[2]For the amputation and CD-TLR components, the adverse event start date is used as the treatment date.

Region Analysis

Of the 261 subjects in LIFE-BTK RCT, 209 (80.1%) subjects were enrolled in the United States (US) and 52 (19.9%) were enrolled outside the US (OUS). Safety and effectiveness outcomes by region are presented in **Table 21**.

For the safety endpoint, all five events occurred in the subjects enrolled in the US, which represents the largest population in LIFE-BTK RCT. For the endpoint of limb salvage and primary patency, the highest rate was observed in the OUS population treated with Esprit BTK System. In the US population the observed difference in primary effectiveness endpoint rate between Esprit BTK and PTA arms was 26.1%, whereas it was 52.7% in the OUS population. The assessment of region effect showed a significant treatment interaction (p-interaction = 0.1488 against a significance level of 0.15) by region for the primary effectiveness endpoint, and no significant treatment interaction by region for the primary safety endpoint. This result should be interpreted with caution due to the relatively small sample size for the PTA in the OUS group (n=11), where one event would contribute to approximately 10% to the endpoint rate.

Table 21. Primary Safety and Effectiveness Endpoints by Region

Primary Safety Endpoint – Freedom from MALE[1] at 6-month and POD at 30 days			
	Esprit BTK (N = 170)	**PTA (N = 90)**	**Interaction p-value**
Region US (N=194) OUS (N=51)	 95.9% (118/123) 100.0% (37/37)	 100.0% (71/71) 100.0% (14/14)	 0.9756
Primary Effectiveness Endpoint – Limb Salvage and Primary Patency at 1 year[2]			
	Esprit BTK (N = 173)	**PTA (N = 88)**	**Interaction p-value**
Region US (N=174) OUS (N=46)	 72.8% (83/114) 80.0% (28/35)	 46.7% (28/60) 27.3% (3/11)	 0.1488

Primary Safety Endpoint: As-Treated Population (N=260) – Total evaluable population for primary safety endpoint: n=245.
Primary Effectiveness Endpoint: Intent-to-Treat Population (N=261) – Total evaluable population for primary effectiveness endpoint: n=220.
Note: The treatment by subgroup interaction for the primary endpoints is evaluated using logistic regression, and the interaction p-value is provided. Interaction effect between treatment and region on the primary endpoints is tested against an alpha level of 0.15.
[1]For the MALE component, the adverse event start date is used as the treatment date.
[2]For the amputation and CD-TLR components, the adverse event start date is used as the treatment date.

4. Pharmacokinetics (PK) – LIFE-BTK PK Sub-Study

The objective of the LIFE-BTK 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 System for the planned treatment of narrowed infrapopliteal lesions. The LIFE-BTK PK sub-study subjects are not included in the primary analysis population and have not contributed to the determination of the LIFE-BTK RCT primary endpoints.

The LIFE-BTK PK sub-study is a prospective, single-arm, open-label, non-blinded, non-randomized sub-study that planned to enroll approximately 7 subjects treated with Esprit BTK Scaffold at selected clinical trial sites. Subjects were stipulated to be distributed as follows:

- 4 subjects treated with Esprit BTK System in below the knee artery(ies) in whom drug-coated balloons (DCB) were not used.
- 3 subjects treated with Esprit BTK System in below the knee artery(ies) in whom DCB were used for treatment of inflow disease.

Subjects enrolled in the LIFE-BTK PK sub-study were stipulated to be treated with multiple scaffolds such that the total length of scaffold received by the subject was between 170 and 256 mm. The target everolimus drug dose range, based on a total scaffold length of 170 to 256 mm, was 1319 to 2714 µg.

Arterial or venous blood was scheduled to be drawn at the following timepoints:

1. Baseline (prior to implantation of the first Esprit BTK Scaffold)

2. Immediately after the first scaffold was implanted, and one blood sample every 15 minutes after the first scaffold has been implanted until the last scaffold has been implanted
3. Immediately after the last Esprit BTK Scaffold implantation at 0 minute , and a sample each at 10 and 30 minutes, 1 hour (h), 2 h, 4 h, 6 h, 12 h, 24 h (1 day), 48 h (2 days), 72 h (3 days), 96 h (4 days), 120 h (5 days), 168 h (7 days), 336 h (14 days), 720 h (30 days), and 1440 h (60 days)

In addition to having their blood drawn, all PK subjects are scheduled to be clinically followed through 5 years, with visits at 30 days, 60 days, 90 days, 180 days, 1, 2, 3, 4 and 5 years.

Wound assessment was per site standard of care. Duplex ultrasound imaging for the PK study subjects was scheduled to be conducted at 30 days, 180 days and 1 year.

Blood samples for PK analyses were temporarily stored at -30ºC or lower at investigational sites and were shipped to the central core laboratory. The concentration of everolimus in human whole blood samples was determined by a fully validated Liquid Chromatography-Mass Spectrometry/Mass Spectrometry (LC-MS/MS) assay. The lower limit of quantification (LLOQ) of everolimus in the blood samples was 0.1 ng/mL.

Pharmacokinetic analysis of the everolimus blood concentration-time data was conducted by the pharmacokinetics core laboratory using non-compartmental methods. The PK parameters that were calculated are listed below in **Table 22**. Individual whole blood concentration-time data were listed by treatment and nominal sampling time. PK parameters were tabulated and descriptively summarized.

Table 22. PK Parameters

λ_z or K_{el} (1/h)	Terminal rate constant, determined by the log-linear regression of the terminal phase.
$T_{1/2}$ (h)	Terminal half-life, calculated as $t_{1/2} = 0.693/\lambda_z$.
C_{max} (ng/mL)	Maximal blood everolimus concentration.
T_{max} (h)	Time corresponding to C_{max}.
$AUC_{0\text{-}24}$ (ng.h/mL)	Area under the blood concentration time curve from administration to the concentration at 24 hours measured by trapezoidal rule (linear trapezoidal/linear interpolation).
AUC_t (ng.h/mL)	Area under the blood concentration time curve from administration to last observed concentration at time t measured by trapezoidal rule (linear trapezoidal/linear interpolation).
$AUC_{0\text{-}\infty}$ or AUC_{inf} (ng.h/mL)	Area under the blood everolimus concentration vs. time curve from time zero and extrapolated to infinity, calculated as $AUC_{inf} = AUC_t + (C_{last}/\lambda_z)$, where C_{last} is the last quantifiable concentration.

$\%AUC_{extra}$	Percentage of $AUC_{0-\infty}$ obtained by extrapolation, calculated as: $\%AUC_{extra} = 100*(AUC_{inf} - AUC_t)/AUC_{inf}$.
CL (L/h)	Apparent blood clearance, calculated as $Dose/AUC_{inf}$.

Accountability of Subjects

Subject registration in the LIFE-BTK PK sub-study began on February 10, 2022. The PK sub-study completed enrollment on February 22, 2023, with a total of 9 subjects at 5 clinical sites (3 US sites and 2 OUS sites). The last subject 60-day follow-up visit was on April 18, 2023, and all subjects enrolled in the PK sub-study have completed their stipulated 60-day follow-up.

Study Population Demographics and Baseline Parameters

The LIFE-BTK PK sub-study registered subjects with a mean age of 67.8 ± 8.8 years (range 54-82). The sub-study had 77.8% (7/9) of male and 22.2% (2/9) of female subjects, with 66.7% (6/9) of white subjects and 33.3% (3/9) of Asian subjects. There was a high prevalence of co-morbidities, with hypertension observed in 88.9% (8/9) of subjects, hyperlipidemia in 77.8% (7/9) of subjects, and diabetes mellitus in 77.8% (7/9) of subjects.

Results

The pharmacokinetics of everolimus eluted from the Esprit BTK Scaffold was evaluated in 9 subjects. The everolimus dose administered to subjects registered in the LIFE-BTK PK sub-study ranged from 1397 to 2074 μg, with a mean of 1821 μg. The whole blood concentration-time curve of everolimus and clinical PK parameters of everolimus are presented in **Figure 9** and **Table 23** respectively.

Following Esprit BTK Scaffold deployment, everolimus blood concentrations increased transiently, leading to individual t_{max} values with median of 0.25 h, mean of 0.328 h, and maximum of 0.817 h. Everolimus concentrations declined thereafter in a biexponential fashion, with a terminal half-life ranging from 65.6 to 211.2 h and mean of 109.2 h for all subjects with no obvious dose-related trend.

The systemic exposure of everolimus is indicated by the C_{max} and the area under the concentration-time curve (AUC). Individual C_{max} ranged from 9.6 ng/ml to 50.5 ng/ml, with mean of 21.3 ng/ml. Individual AUC_t ranged from 243 to 1100 h.ng/ml, with a mean of 586.2 h.ng/ml.

The results of the LIFE-BTK PK sub-study were compared with a previous clinical study using Absorb BVS (ABSORB III PK sub-study), predecessor to Absorb GT1™ BVS, that was previously reported. Plasma dose-normalized concentration-time profiles in the LIFE-BTK PK sub-study were comparable to ABSORB III PK study. On the other hand, the last time point up to which whole blood concentrations of everolimus could be quantified ranged from 96 to 168 h post-implantation for ABSORB III vs 168 to 720 h in the LIFE-BTK PK sub-study. This is expected since

the doses administered in the LIFE-BTK PK sub-study (1397 to 2074 µg) were higher compared to the ABSORB III PK study (181 to 443 µg). Collectively, these data suggest that the release profile of everolimus from both scaffolds (Absorb GT1 BVS and Esprit BTK Scaffold) is comparable and dose proportional.

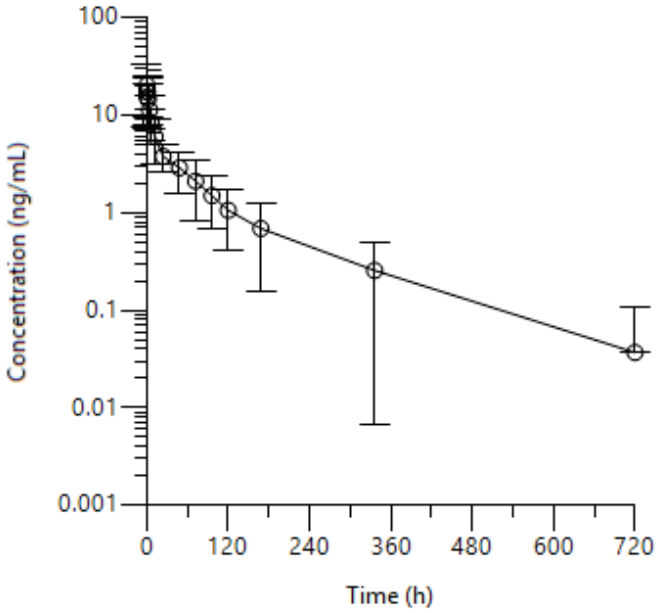


Figure 9: Average Whole Blood Concentration-Time Curves of Everolimus after Implantation of Esprit BTK

Table 23. Pharmacokinetics Results of Everolimus After Implantation of Esprit BTK

Variable	LIFE-BTK PK Sub-Study
Number of subjects in the LIFE-BTK PK sub-study	9
Number of scaffolds used per subject – range	5 – 8
Dose range received per subject (µg	1397 – 2074
C_{max} range (ng/ml)	9.6 – 50.5
AUC_t range (ng·h/ml)	243 – 1100
$t_{1/2}$ range (h)	65.6 – 211.2
Median t_{max} (h)	0.25

In conclusion, the rapid disappearance of everolimus from the circulation after implantation of Esprit BTK Scaffold limits the extent of systemic exposure and is therefore considered safe.

5. Pediatric Extrapolation

In this premarket application, existing clinical data were not leveraged to support approval of a pediatric patient population.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 146 investigators of which none were full-time or part-time employees of the sponsor and 4 had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0
- Significant payment of other sorts: 4
- Proprietary interest in the product tested held by the investigator: 0
- Significant equity interest held by investigator in sponsor of covered study: 0

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

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

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

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The nonclinical and preclinical testing conducted on the Esprit BTK Scaffold and delivery system demonstrated that the performance characteristics of the device met the product specifications. The test results obtained from sterilization testing demonstrated that the product can be adequately sterilized and is acceptable for clinical use. The shelf-life testing has established acceptable performance for a labeled shelf life of 12 months.

The prospective, multi-center, single-blinded, randomized controlled trial (LIFE-BTK RCT) was designed to evaluate the safety and effectiveness of the Esprit BTK System, compared to percutaneous transluminal angioplasty (PTA), in the planned treatment of diseased infrapopliteal lesions in patients with CLTI with up to two *de novo* or restenotic (prior PTA) lesions in separate vessels. The primary effectiveness endpoint was a composite of limb salvage and primary patency at 1 year including freedom from above-ankle amputation in the index limb, 100% total occlusion of the target vessel, binary restenosis of the target lesion and clinically driven target lesion revascularization (CD-TLR). The Esprit BTK arm demonstrated superiority to the PTA arm with rates of 74.5% (111/149) versus 43.7%

(31/71), respectively, with the observed difference of 30.8% favoring Esprit BTK (17.0% lower one-sided 97.51% CL; p-value < 0.0001). Non-hierarchical components of the effectiveness endpoint at 1 year suggest that the difference in binary restenosis drove the endpoint (25.8% difference favoring Esprit BTK). The primary endpoint results were also supported by several prespecified sensitivity analyses along with two powered secondary endpoints analyses of binary restenosis of the target lesion at 1 year (23.5% (35/149) for Esprit BTK versus 49.3% (35/71) for PTA; p <0.0001) and a composite endpoint that includes freedom from: above ankle amputation in the index limb, 100% total occlusion of the target vessel, and CD-TLR at 1 year (83.2% (124/149) for Esprit BTK versus 69.0% (49/71); p=0.0081). Subgroup analyses for gender, age, race, and country did not reveal clinically substantive differences. Patients generally experienced improvements in Rutherford category and wound healing.

B. Safety Conclusions

The risks of the device are based on biocompatibility and animal studies as well as data collected in the clinical studies conducted to support PMA approval as described above. The biocompatibility and *in vivo* animal testing demonstrated that the acute and chronic *in vivo* performance characteristics of the Esprit BTK System provide reasonable assurance of safety and acceptability for the intended use. The risks of the device are based on nonclinical laboratory and/or animal studies as well as data collected in a clinical study conducted to support PMA approval as described above.

The primary safety endpoint of freedom from Major Adverse Limb Event + Peri-Operative Death (MALE+POD) was 96.9% for Esprit BTK and 100% for PTA. The primary safety endpoint assessment showed non-inferiority of the Esprit BTK arm compared to the PTA arm, with a p-value of 0.0019. There were no 30-day MAE (MALE/POD) in the PTA arm, and there were five 30-day MAE (MALE/POD) in five subjects in the Esprit BTK arm: two above ankle amputations in index limb; one major re-intervention on index limb; and two deaths within 30 days. Assessment of all adverse events, serious adverse events, and key events specifically relevant to the current device/procedure does not indicate any concerning trends in the treatment arm compared to the control arm. No unanticipated adverse device effects were observed, and no deaths were attributable to the device or procedure throughout the observed period.

C. Benefit-Risk Determination

The probable benefits of the device are based on data collected in the randomized blinded clinical study and nonclinical studies conducted to support PMA approval as described above. The probable benefits of using the device to treat diseased infrapopliteal lesions in subjects with CLTI are improved patient quality of life by reducing the symptoms of arterial disease, improved blood flow to the lower limbs, facilitating wound healing and reducing major amputations. The probable risks of the device are based on data collected in the clinical studies and reflect expected rates associated with percutaneous procedures.

1. Patient Perspective

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

In conclusion, given the available information above, the data demonstrate a reasonable assurance of device safety and effectiveness and that the probable benefits outweigh the probable risks for the Esprit BTK System for improving luminal diameter in infrapopliteal lesions in patients with chronic limb-threatening ischemia (CLTI) and total scaffolding length up to 170 mm with a reference vessel diameter of ≥ 2.5 mm and ≤ 4.00 mm.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of the Esprit BTK System when used in accordance with the indications for use. The results from preclinical and clinical studies indicate that the Esprit BTK System meets safety and performance specifications. The conclusions based on the results from the LIFE-BTK RCT support the conclusion that the Esprit BTK System is safe and effective in the treatment of diseased infrapopliteal lesions in patients with CLTI when used in accordance with device labeling and the instructions for use (IFU).

XIII. CDRH DECISION

CDRH issued an approval order on [date of approval order]. The final non-clinical condition of approval cited in the approval order is described below.

1. Long-term drug stability studies will be completed on three total finished product batches representing the commercial process each year, evaluating one lot of the largest-longest device size, one lot of an intermediate size, and one lot of the shortest-smallest device size manufactured during that time period. All batches for these studies will be stored at Long Term Conditions of 25°C ± 2°C/60% RH ± 5%, per ICH Q1A(R2). Testing for all studies will occur at 0, 6, and 12 months.

The final clinical conditions of approval cited in the approval order are described below.

2. *LIFE-BTK RCT Continued Follow-Up Study:* This study is a prospective, randomized (2:1, Esprit BTK:PTA), single-blinded, multi-center follow-up of the pivotal LIFE-BTK RCT trial (G190111) that treated 261 subjects at 50 investigational sites. The study will evaluate the long-term safety and effectiveness of the Esprit™ BTK System. All 231 remaining subjects, active at the end of the 1-year evaluation will continue to be followed at 2, 3, 4 and 5 years.

   Follow-up at the timepoints will include the following assessments: medication review, adverse events review, Ankle-Brachial Index (ABI)/Toe-Brachial Index (TBI) measurements, functional status (Rutherford Becker), new wound assessment, and duplex ultrasound (1-year, 2-year and 3-year follow-ups only).

3. *Esprit BTK Post-Approval Study (Esprit BTK PAS) – New Enrollment Study:* This study is a prospective, single-arm, multi-center post-approval observational study designed to assess continued safety and effectiveness of Esprit™ BTK System under commercial use in subjects with diseased infrapopliteal lesions. The study will enroll 200 patients at up to 50 sites in the United States (U.S.). Additional sites may be added outside of the U.S. (OUS) with a minimum of 50% of patients in the U.S.

   Patients will be followed at discharge, 30 days, 6 months, 1 year, 2 years and 3 years.

   The primary safety endpoint is Major Adverse Limb Events (MALE) at 6 months + Peri-Operative Death (POD) through 30 days. The primary effectiveness endpoint is Freedom from clinically driven target lesion revascularization (CD-TLR) at 1 year.

   Key secondary endpoints to be evaluated are all-cause mortality, amputation (minor, major), amputation-free survival, Ankle-Brachial Index (ABI)/Toe-Brachial Index (TBI), Rutherford Becker category, and wound healing.

   Follow-up assessment will also include medication review and adverse events. The study endpoint analyses will be summarized with descriptive statistics.

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

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.

XV. REFERENCES

1. Mills, J.L., Sr., et al., The Society for Vascular Surgery Lower Extremity Threatened Limb Classification System: risk stratification based on wound, ischemia, and foot infection (WIfI). J Vasc Surg, 2014. 59(1): p. 220-34 e1-2.