June 2, 2025
Medical Device Evaluation Division
Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

Report on the Deliberation Results

Classification	Instrument & Apparatus 7, Organ Function Replacement Device
Term Name	Bioabsorbable drug-eluting stent for lower extremity artery
Brand Name	Esprit BTK Everolimus Eluting Resorbable Scaffold System
Applicant	Abbott Medical Japan LLC
Date of Application	March 28, 2024 (Application for marketing approval)

Results of Deliberation

In its meeting held on June 2, 2025, the Committee on Medical Devices and *In-vitro* Diagnostics reached the following conclusion, and decided that this conclusion should be presented to the Pharmaceutical Affairs Council.

The product should be approved with designation as a medical device subject to a use-results survey. The product is not classified as a biological product or a specified biological product.

The use-results survey period should be 7 years. The product should be approved with the following conditions.

Approval Conditions

1. The product must be used for patients eligible for the treatment, who should be selected by physicians and medical team members with adequate knowledge and experience in the treatment of chronic limb-threatening ischaemia. Before using the product, the physicians and medical team members must have acquired sufficient skills to operate the product and various knowledge, including procedure-associated complications, and medical institutions must have a system prepared for the treatment. To fulfill these requirements, the applicant is required to take necessary measures, such as disseminating the guidelines for proper use prepared in cooperation with relevant academic societies and offering seminars.
2. The applicant is required to conduct a post-marketing surveillance involving all patients treated with the product until data from a specified number of patients have been accumulated, to submit reports on the results of longitudinal analyses of long-term outcomes to the Pharmaceuticals and Medical Devices Agency, and to take appropriate measures as necessary.

3. The applicant is required to submit reports on the results of analyses of long-term outcome data from participants in the clinical studies included in the present application to the Pharmaceuticals and Medical Devices Agency, and to take appropriate measures as necessary.

Review Report

May 15, 2025
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following medical device submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Classification	Instrument & Apparatus 7, Organ Function Replacement Device
Term Name	Bioabsorbable drug-eluting stent for lower extremity artery
Brand Name	Esprit BTK Everolimus Eluting Resorbable Scaffold System
Applicant	Abbott Medical Japan LLC
Date of Application	March 28, 2024
Reviewing Office	Office of Medical Devices II

Review Results

May 15, 2025

Classification	Instrument & Apparatus 7, Organ Function Replacement Device
Term Name	Bioabsorbable drug-eluting stent for lower extremity artery
Brand Name	Esprit BTK Everolimus Eluting Resorbable Scaffold System
Applicant	Abbott Medical Japan LLC
Date of Application	March 28, 2024

Results of Review

Esprit BTK Everolimus Eluting Resorbable Scaffold System (hereinafter referred to as Esprit BTK System) is a balloon-expandable resorbable scaffold system indicated for use to treat infrapopliteal lesions with a reference vessel diameter of ≥2.5 and ≤4.0 mm in patients with chronic limb-threatening ischaemia (CLTI), excluding patients on chronic dialysis. The Esprit BTK System consists of a scaffold and delivery system (rapid exchange balloon catheter). The scaffold is crimped to the balloon at the tip of the delivery system. The scaffold of the Esprit BTK System is made from bioresorbable poly-L-lactic acid so that the scaffold degrades and resorbs after physically maintaining the vessel lumen patency for a period necessary for revascularization. The scaffold is coated with a cytostatic drug (everolimus) and a bioresorbable polymer poly-DL-lactic acid to inhibit neointimal growth after implantation.

The applicant submitted the non-clinical data supporting the physicochemical properties, biological safety, stability and durability, and performance of the Esprit BTK System. No particular problems were identified in the non-clinical data.

To support the clinical evaluation of the Esprit BTK System, the applicant submitted the results of a foreign clinical study (the LIFE-BTK study) that was a randomized controlled study using the standard procedure “percutaneous transluminal angioplasty (PTA)” as a control and a pharmacokinetic study (the LIFE-BTK PK study). The LIFE-BTK study enrolled patients with CLTI of Rutherford-Becker category 4 (ischaemic rest pain) or 5 (minor tissue loss) with de novo or restenotic (treated with prior PTA) infrapopliteal lesions.

The primary efficacy endpoint was a composite rate of limb salvage (freedom from above ankle amputation in index limb) and primary patency (freedom from 100% total occlusion of target vessel, binary restenosis, and clinically-driven target lesion revascularization) at 1 year. The composite rates were 74.5% (111 of 149 subjects) in the Esprit BTK arm and 43.7% (31 of 71 subjects) in the PTA arm. The difference between the treatment arms was 30.8%. The lower limit of its one-sided 97.5% confidence interval was 17.0%, showing that the Esprit BTK arm demonstrated a significant superiority to the PTA arm ($P < 0.0001$). Of the elements comprising the primary efficacy endpoint, the rate of

freedom from binary restenosis was 76.5% (114 of 149 subjects) in the Esprit BTK arm and 50.7% (36 of 71 subjects) in the PTA arm. The difference was significant, demonstrating the efficacy of the Esprit BTK System.

The primary safety endpoint was “freedom from peri-operative death (within 30 days after the index procedure) and major adverse limb events (major amputation and major re-intervention in the index limb within 6 months after the index procedure).” The outcome was 96.9% (155 of 160 subjects) in the Esprit BTK arm and 100.0% (85 of 85 subjects) in the PTA arm. The difference between the treatment arms was −3.1%. The lower limit of its one-sided 97.5% confidence interval was −7.1%, which met the predefined non-inferiority margin of −10%, showing the non-inferiority of the Esprit BTK System to PTA.

Patients eligible for the Esprit BTK System in Japan are expected to have more calcified lesions than patients in Europe or the US. The results from subjects “with calcified lesions” as determined by the study sites or core laboratory (post-hoc) revealed no tendency toward inferiority of the Esprit BTK System to PTA with regard to the primary efficacy endpoint. Therefore, it was concluded that the superiority of the Esprit BTK System to PTA demonstrated in the LIFE-BTK study was not compromised even in the treatment of calcified lesions and that calcified lesions could be included in the indication for the Esprit BTK System. The long-term efficacy outcomes of the Esprit BTK System are acceptable as the superiority of the Esprit BTK System to PTA was maintained at 2 years post-procedure. A tendency toward lower event-free rates was observed in the Esprit BTK arm through 1 and 2 years post-procedure. However, causal assessment of each event showed no relationship between the events and the Esprit BTK System or index procedure and the long-term safety results are also considered acceptable.

Currently, no effective treatment, other than PTA with a balloon catheter, is available for the treatment of CLTI resulting from infrapopliteal arterial occlusion or stenosis, for which the Esprit BTK System is indicated, and the disease often results in repeated restenosis after the procedure and may eventually lead to serious outcomes such as leg amputation. In light of these facts, the Esprit BTK System, which was shown to be superior to PTA with a balloon catheter with regard to freedom from restenosis, etc., has high clinical usefulness and the introduction of the Esprit BTK System into Japan as a new therapeutic option for CLTI is of significance.

The Esprit BTK System will be the first drug eluting resorbable scaffold system to be introduced in Japan for the treatment of infrapopliteal lesions in patients with CLTI. To ensure the effective and safe introduction of the Esprit BTK System into Japan, physicians and medical team members with thorough knowledge of the treatment of CLTI, as well as adequate knowledge and experience in endovascular interventions and post-procedural management of infrapopliteal arteries should appropriately select patients for whom the Esprit BTK System can ensure clinical benefits by maintaining the patency of the infrapopliteal artery and reducing the need for re-intervention. Users must also acquire knowledge and skills required for the Esprit BTK System and procedures through training, etc. Since timely intervention, including surgery, may be required in the case of complications, and foot care including wound

management is essential in the treatment of CLTI, the Esprit BTK therapy must be performed in medical institutions equipped with a well-established system capable of addressing these requirements.

A use-results survey should confirm that patients eligible for the therapy are appropriately selected in post-marketing setting in compliance with the proper use and evaluate the efficacy and safety of the Esprit BTK System in Japanese patients, in whom the proportion of patients with calcified lesions is expected to be higher than that in patients overseas. Additional measures for risk reduction and proper use should be taken as necessary on the basis of the results of this survey. Only limited knowledge about long-term outcomes of the Esprit BTK System, including overseas data, is available. Periodic reports on the submitted clinical study should be submitted to evaluate long-term outcomes.

As a result of its review, PMDA has concluded that the Esprit BTK System may be approved for the intended use shown below with the following approval conditions, and that the results should be presented to the Committee on Medical Devices and *In-vitro* Diagnostics for further deliberation.

Intended Use

Esprit BTK Everolimus Eluting Resorbable Scaffold System is indicated for improving luminal diameter in infrapopliteal lesions in patients with chronic limb-threatening ischaemia (excluding patients on chronic dialysis) with a reference vessel diameter of ≥2.5 and ≤4.0 mm. The maximum total scaffolding length should be 170 mm when multiple Esprit BTK scaffolds are used.

Approval Conditions

1. The product must be used for patients eligible for the treatment, who should be selected by physicians and medical team members with adequate knowledge and experience in the treatment of chronic limb-threatening ischaemia. Before using the product, the physicians and medical team members must have acquired sufficient skills to operate the product and various knowledge, including procedure-associated complications, and medical institutions must have a system prepared for the treatment. To fulfill these requirements, the applicant is required to take necessary measures, such as disseminating the guidelines for proper use prepared in cooperation with relevant academic societies and offering seminars.
2. The applicant is required to conduct a post-marketing surveillance involving all patients treated with the product until data from a specified number of patients have been accumulated, to submit reports on the results of longitudinal analyses of long-term outcomes to the Pharmaceuticals and Medical Devices Agency, and to take appropriate measures as necessary.
3. The applicant is required to submit reports on the results of analyses of long-term outcome data from participants in the submitted clinical studies included in the present application to the Pharmaceuticals and Medical Devices Agency, and to take appropriate measures as necessary.

Review Report

May 15, 2025

1. Product for Review

Classification	Instrument & Apparatus 7, Organ Function Replacement Device
Term Name	Bioabsorbable drug-eluting stent for lower extremity artery
Brand Name	Esprit BTK Everolimus Eluting Resorbable Scaffold System
Applicant	Abbott Medical Japan LLC
Date of Application	March 28, 2024
Proposed Intended Use	Esprit BTK Everolimus Eluting Resorbable Scaffold System is indicated for use to treat infrapopliteal lesions with a reference vessel diameter of ≥2.5 and ≤4.0 mm in patients with chronic limb-threatening ischaemia, excluding patients on chronic dialysis.

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List of Abbreviations

ABI	Ankle-Brachial Index
AT	As-Treated
AUC	Area Under Curve
BMI	Body Mass Index
CD-TLR	Clinically-Driven Target Lesion Revascularization
CEC	Clinical Events Committee
CLTI	Chronic Limb-Threatening Ischemia
DAPT	Dual Antiplatelet Therapy
DCB	Drug Coated Balloon
DSA	Digital Subtraction Angiography
DUS	Duplex Ultrasound
eGFR	estimated Filtration Rate
FEA	Finite Element Analysis
ITT	Intent-To-Treat
IVUS	Intravascular Ultrasound
MALE	Major Adverse Limb Events
MRI	Magnetic Resonance Imaging
NCT	National Clinical Trials
OCT	Optical Coherence Tomography
OFDI	Optical Frequency Domain Imaging
PDLLA	Poly-DL-Lactic Acid
PLLA	Poly-L-Lactic Acid
PSV	Peak Systolic Velocity
PSVR	Peak Systolic Velocity Ratio
PTA	Percutaneous Transluminal Angioplasty
QOL	Quality of Life
QVA	Quantitative Vessel Angiography
RBP	Rated Burst Pressure
TBI	Toe Brachial pressure Index
WIfI	Wound, Ischemia, and foot Infection

I. Product Overview

Esprit BTK Everolimus Eluting Resorbable Scaffold System (hereinafter referred to as Esprit BTK System) is a balloon-expandable resorbable scaffold system indicated for use to treat infrapopliteal lesions with a reference vessel diameter of ≥2.5 and ≤4.0 mm in patients with chronic limb-threatening ischaemia (CLTI), excluding patients on chronic dialysis. The Esprit BTK System consists of a scaffold and delivery system (rapid exchange balloon catheter). The scaffold is crimped to the balloon at the tip of the delivery system (Figure 1). The scaffold of the Esprit BTK System is made from bioresorbable poly-L-lactic acid (PLLA) so that the scaffold degrades and resorbs after physically maintaining the vessel lumen patency for a period necessary for revascularization. The scaffold is coated with a cytostatic drug (everolimus) and a bioresorbable polymer poly-DL-lactic acid (PDLLA) to inhibit neointimal growth after implantation. The Esprit BTK scaffold is developed based on the design of the company's previously approved device intended for use in coronary artery lesions, "Absorb GT1 Bioresorbable Vascular Scaffold System" (Approval No. 22800BZX00406000, hereinafter referred to as the Absorb), and is composed of the same raw materials and drug coating as Absorb. The Esprit BTK scaffold has more size variation than the Absorb, [redacted]. Table 1 presents the size variation of the Esprit BTK scaffold.

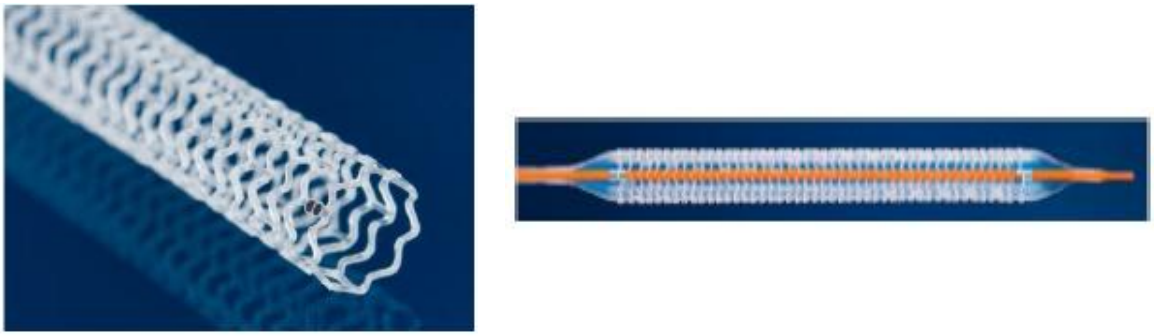


Figure 1. Exterior photograph
(Left, scaffold; right, the scaffold crimped to the delivery system)

Table 1. Size variation

Nominal diameter (mm)	Nominal length (mm)							
	9*[1]	12	15	18	23	28	33	38
2.5	○	○	●	○	○	○	●	●
2.75	●	●	●	●	●	●	●	●
3.0	○	○	●	○	○	○	●	●
3.50	●	○	●	○	○	○	●	●
3.75	●	●	●	●	●	●	●	●

○, Approved sizes of the Absorb
●, Newly added sizes in the Esprit BTK System
*[1] 8 mm for the Absorb

II. Summary of the Data Submitted and Outline of the Review Conducted by the Pharmaceuticals and Medical Devices Agency

The data submitted by the applicant with the present application and the applicant's responses to the inquiries from the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined below.

The expert advisors present during the Expert Discussion on the Esprit BTK System declared that they did not fall under the Item 5 of the Rules for Convening Expert Discussions, etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1. History of Development, Use in Foreign Countries, and Other Information

1.A Summary of the data submitted

1.A.(1) History of development

CLTI resulting from infrapopliteal arterial occlusion or stenosis, among peripheral occlusive arterial diseases, is treated in a stepwise manner, starting from its early stage, i.e., arteriosclerotic lower limb occlusive arterial disease. The treatment progresses from kinesitherapy and other lifestyle modifications to pharmacotherapy and finally revascularization. Revascularization includes surgical procedures (bypass surgery) and endovascular interventions. CLTI is a collective term for lower limb conditions requiring therapeutic intervention, characterized by a risk of limb amputation associated with lower limb ischaemia, tissue loss, neuropathy, and infection. The Olive Registry, which collected the clinical outcomes of endovascular interventions for CLTI in Japan, reveals that culprit blood vessels were the femoropopliteal artery alone in 17% of the cases, both femoropopliteal and infrapopliteal arteries in 41%, and infrapopliteal artery alone in 42%, indicating that infrapopliteal lesions were involved in 83% of CLTI cases.[1] Endovascular interventions for the femoropopliteal artery in Japan include the use of balloon catheters, drug coated balloons, bare metal stents, and drug eluting stents. In Japan, however, only balloon catheters are available for endovascular interventions in the infrapopliteal arteries.

Percutaneous transluminal angioplasty (PTA) using a balloon catheter for infrapopliteal arteries provides high success rates in the acute phase of CLTI, but is associated with a decreased patency rate over time, with a restenosis rate of as high as approximately 70% at 3 months post-procedure, resulting in leg amputation and poor prognosis.[2] A meta-analysis summarizing the outcomes of PTA for infrapopliteal arteries in patients with CLTI showed a mortality of approximately 15% and a leg amputation rate of approximately 15% at 1 year after PTA.[3] Accordingly, the Japanese guidelines recommend that endovascular intervention for infrapopliteal arteries be considered (Class IIa) in patients in whom surgical bypass with an autologous vein is difficult and have a life expectancy of ≤2 years.[4]

Efficacy reports from some clinical studies conducted using drug eluting coronary stents to reduce a risk of restenosis have been published.[5,6,7] However, because stents remain permanently in the blood vessel, they may inhibit vasomotion and limit vascular remodeling, potentially resulting in long-term adverse effects. Stents themselves may not only cause in-stent restenosis and late phase stent thrombosis but also make revascularization difficult and produce artifacts in diagnostic imaging. For these reasons, the use of a drug eluting resorbable scaffold is expected to provide short- and long-term benefits in the treatment of CLTI.

The Esprit BTK System was developed to treat CLTI resulting from infrapopliteal arterial occlusion or stenosis, among peripheral occlusive arterial diseases. Absorb, a drug eluting resorbable scaffold, has been approved in Japan for the treatment of coronary artery disease. The Esprit BTK System is the next generation product of the Absorb, and is composed of the same raw materials for the scaffold and drug as Absorb, with the same drug coating method. The delivery system of the Esprit BTK adopts part of

the design of the Absorb and the drug eluting coronary stent "XIENCE Alpine Drug Eluting Stent" (Approval No. 22600BZX00529000).

Figure 2 presents a comparison of changes over time in radial strength between the Esprit BTK System and the Absorb. [redacted]. Figure 3 presents the *in vitro* degradation profile of [redacted]. The hydrolysis of the polymer does not differ between the placement sites (coronary artery and infrapopliteal artery) and between *in vivo* and *in vitro*.

Figure 2. Comparison of radial strength between [redacted] and the Absorb ([redacted] months)

Figure 3. Changes over time in number average molecular weight (Mn), radial strength, and weight of [redacted] ([redacted] mm)

1.A.(2) Use in foreign countries

The Esprit BTK System was approved in the US in April 2024. Table 2 presents the intended use and sales performance of the Esprit BTK System. [redacted].

Table 2. Intended use and sales performance overseas (as of March 2025)

Country	Intended use	Date of authorization	Sales performance
US	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 and ≤4.00 mm.	April 26, 2024	[redacted]

1.A.(3) Malfunctions and adverse events reported overseas

Table 3 and Table 4 present the numbers of malfunctions and adverse events, respectively, of the Esprit BTK System reported in the US between April 2024 and February 2025.

Table 3. Malfunctions reported in the US

Malfunction	Number of events	Incidence[1]
Advancement difficulty	[redacted]	0.1891%
Removal difficulty		0.1756%
Catheter deformity due to compressive stress		0.0945%
Inability to advance		0.0540%
Deployment failure		0.0270%
Breakage		0.0270%
Damage caused by an adjunct device		0.0270%
Material separation		0.0270%
Partition, disconnection, or breakage of a component		0.0270%
Distortion or twist of a component		0.0270%
Elongation		0.0270%
Device displacement or dislodgement		0.0135%
Device operation failure		0.0135%
Flushing difficulty		0.0135%
Insertion difficulty		0.0135%
Leakage		0.0135%
Deformity of a component		0.0135%
Rupture of a component		0.0135%
Excessive hardness or stiffness of a component		0.0135%
Migration		0.0135%

[1] Calculated using the number of units sold ([redacted]) as the denominator

Table 4. Adverse events reported in the US

Adverse event	Number of events	Incidence[1]
Unplanned medical intervention	[redacted]	0.1080%
Hospitalisation or prolongation of existing hospitalisation		0.0405%
Occlusion		0.0405%
Pain		0.0270%
Thrombosis		0.0135%
Vascular dissection		0.0135%

[1] Calculated using the number of units sold ([redacted]) as the denominator

1.B Outline of the review conducted by PMDA

Unplanned medical interventions reported as adverse events were [redacted] events of additional interventions (PTA and atherectomy) for management of malfunctions during the index procedure or the following day, and [redacted] events of additional interventions for management of occlusion (additional placement of the

Esprit BTK System, PTA, laser, and thrombolytic catheter). The common malfunctions and other events are discussed in Section 6 below, together with their incidence.

2. Design and Development

2.(1) Performance and safety specifications

2.(1).A Summary of the data submitted

The proposed performance and safety specifications for the Esprit BTK System are scaffold percent recoil, uniformity of expansion, percent change in scaffold length from pre- to post-deployment, scaffold radial strength (radial force), scaffold expansion diameter limit, scaffold fatigue strength (accelerated fatigue), drug identification, total drug content, drug content uniformity, drug release, the amounts of residual solvents, impurities and degradation products, scaffold coating integrity, scaffold's number-average molecular weight, magnetic resonance imaging (MRI) compatibility, scaffold movement, retraction into guiding catheter/sheath, recommended inflation pressures, catheter preparation, balloon deflation time, rated burst pressure (RBP), tensile strength, inner member collapse, balloon fatigue, particulate matter, hydrophilic coating, radiopacity, maximum guidewire diameter, biological safety, sterility assurance, and bacterial endotoxins.

2.(1).B Outline of the review conducted by PMDA

PMDA asked the applicant to provide the justification for not including the following items, which are included in the specifications for the Absorb but not for the Esprit BTK System:

1) Radial strength (radial force) of the scaffold at [redacted] months
2) Shaft pressure resistance of the balloon catheter

The applicant's explanation:

1) In the design development of the Esprit BTK System, [redacted] Da, [redacted] wt% [redacted] months [redacted]. On the basis of these findings, this test was considered not required.
2) Since the catheter shaft pressure resistance was [redacted], this test was considered not required.

PMDA's view:

Radial strength (radial force) of the scaffold at [redacted] months shown in 1) is an important parameter for characterizing the degradation properties of the Esprit BTK System. Therefore, PMDA instructed the applicant to include this item in the specifications. The applicant agreed. In addition, PMDA reviewed the appropriateness of the proposed items, test methods, and acceptance criteria for performance and safety specifications, and concluded that there was no particular problem.

2.(2) Physicochemical properties

2.(2).A Summary of the data submitted

To support the physicochemical properties of the Esprit BTK System, the applicant submitted the data on *in vitro* degradation behavior and flexibility of the scaffold. The data were from characterization tests. The tests demonstrated that the Esprit BTK scaffold had a similar *in vitro* degradation behavior to that of the Absorb scaffold and flexibility required for the placement of the scaffold in curved segments as anticipated in clinical settings.

2.(2).B Outline of the review conducted by PMDA

PMDA reviewed the data on the physicochemical properties of the Esprit BTK System and concluded that there was no particular problem.

2.(3) Biological safety

2.(3).A Summary of the data submitted

The raw materials of the scaffold, drug, and drug coating of the Esprit BTK System are already used in the Absorb. No new biological safety study was conducted because the biological safety of the Esprit BTK System can be assured.

To support the biological safety of the delivery system, the applicant submitted the results for cytotoxicity, sensitization, irritation, intracutaneous reactivity, pyrogenicity, acute systemic toxicity, and hemocompatibility. The studies showed no noteworthy findings.

2.(3).B Outline of the review conducted by PMDA

PMDA reviewed the data on the biological safety of the Esprit BTK System and concluded that there was no particular problem.

2.(4) Stability and durability

2.(4).A Summary of the data submitted

The Esprit BTK scaffold is designed based on the Absorb scaffold, and all raw materials used have previously been used in the Absorb, with the same sterilization method. Therefore, the 12-month stability can also be assured for the Esprit BTK scaffold, and studies using the Esprit BTK System were not conducted.

The applicant omitted the submission of stability study data to determine the shelf life of the Esprit BTK delivery system and submitted a self-declaration that the shelf life of the Esprit BTK delivery system was determined based on the results of necessary stability evaluation, in accordance with the “Handling of Stability Studies Related to the Determination of the Shelf Life in the Application for Marketing Approvals (Certifications) of Medical Devices (in Japanese)” (PFSB/ELD/OMDE Notification No. 1227-5, dated December 27, 2012).

To assess the durability of the Esprit BTK scaffold, the applicant submitted the results of stress analysis (finite element analysis [FEA]) and fatigue stress analysis (FEA) in the acute phase, which showed that the scaffold endured physiological loads. The applicant also submitted the results of a structural integrity

evaluation (overlapping placement) and particulate characterization (overlapping placement), both of which were conducted under accelerated fatigue conditions, as well as compression load testing. None of the tests demonstrated any particular problem.

2.(4).B Outline of the review conducted by PMDA

PMDA reviewed the data on the stability and durability of the Esprit BTK System. PMDA concluded that the Esprit BTK System had a similar stability and durability profile to that of the Absorb and that there was no particular problem.

2.(5) Tests supporting performance

The applicant submitted the data from design verification and animal studies to support the performance of the Esprit BTK System.

2.(5).1) Design verification

2.(5).1).A Summary of the data submitted

The applicant submitted the results of the following design verification tests: Uniformity of expansion, percent change in scaffold length from pre- to post-deployment, scaffold percent recoil, scaffold radial strength, scaffold expansion diameter limit, scaffold coating integrity, MRI compatibility, catheter preparation, scaffold movement, recommended inflation pressures, balloon deflation time, RBP, tensile strength, inner member collapse, balloon fatigue, retraction into guiding catheter/sheath, particulate matter, hydrophilic coating, radiopacity, delivery performance, kink resistance, balloon inflation time, and torque. The Esprit BTK System met its specifications.

2.(5).1).B Outline of the review conducted by PMDA

PMDA reviewed the data from the design verification studies, among the tests supporting the performance of the Esprit BTK System, and concluded that there was no particular problem.

2.(5).2) Animal studies

2.(5).2).A Summary of the data submitted

The applicant submitted the results from local and systemic safety (28, 90, and 180 days), and PK studies in animals.

In the local and systemic safety study, 1 or 2 Esprit BTK scaffolds or 1 comparator was implanted in each of the 3 porcine coronary arteries. The animals were subjected to clinical observation and pathology, quantitative coronary angiography, optical coherence tomography (OCT), macroscopic tissue observation, and histopathology at each predefined time point. The comparator used was a drug eluting coronary stent “XIENCE Alpine Drug Eluting Stent” at 28 days, and the Absorb at 90 and 180 days.

The results of clinical observation and pathology, imaging examinations, macroscopic tissue observation, and histopathology met all of their acceptance criteria at 28 and 90 days. One animal had chronic active eosinophilic inflammation in multiple organs including the coronary arteries at 180 days. This inflammatory reaction was most likely attributable to potential asymptomatic diseases (unexplained underlying systemic condition due to lymphadenitis causing eosinophilic vasculitis and a lung tumor),

rather than a direct effect of the implantation of the Esprit BTK System. The overall safety in the study could be assured after excluding this animal. The safety study demonstrated that the Esprit BTK System had a safety profile comparable to that of XIENCE Alpine Drug Eluting Stent at 28 days, and to that of the Absorb at 90 and 180 days.

The PK study was conducted to assess drug release rate, drug concentration in the implanted blood vessel and in blood, drug concentrations in vital organs (myocardium, left lung, liver, spleen, and kidneys), and delivery system thrombogenicity at 3 hours, and 1, 3, 7, 14, 28, 60, and 90 days after the implantation of 2 or 3 Esprit BTK scaffolds in each of the 3 porcine coronary arteries.

The study demonstrated the bioequivalence of the Esprit BTK System to the Absorb with regard to the drug release profile. There was no sign of thrombosis due to the delivery system.

2.(5).2).B Outline of the review conducted by PMDA

PMDA reviewed the data from the animal studies, among the tests supporting the performance of the Esprit BTK System, and concluded that there was no particular problem.

3. Conformity to the Requirements Specified in Paragraph 3 of Article 41 of Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices

3.A Summary of the data submitted

The applicant submitted a declaration of conformity declaring that the Esprit BTK System meets the standards for medical devices as stipulated by the Minister of Health, Labour and Welfare in accordance with Paragraph 3 of Article 41 of Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (hereinafter referred to as "the Essential Principles") (MHLW Public Notice No. 122, 2005).

3.B Outline of the review conducted by PMDA

PMDA reviewed the conformity of the Esprit BTK System to the Essential Principles as follows.

(1) PMDA's view on the conformity of the Esprit BTK System to Article 1, which stipulates preconditions, etc. for designing medical devices (particularly requirements for users, such as the expected level of technical knowledge and experience, and the expected level of education and training for users):

As described later in Section "6.B Outline of the review conducted by PMDA," critical elements to maintain the risk-benefit balance of the Esprit BTK System include the selection of eligible patients, users, and medical institutions; user training; and compliance with the guidelines for proper use. To this end, an approval condition will be attached to ensure that necessary measures are taken.

(2) PMDA's view on the conformity of the Esprit BTK System to Article 2, which stipulates requirements for risk management throughout the product life cycle of medical devices:

As described later in Sections "6.B Outline of the review conducted by PMDA" and "7.B Outline of the review conducted by PMDA," the efficacy and safety of the Esprit BTK System should be

evaluated in clinical practice in Japan because neither clinical efficacy nor safety data of the Esprit BTK System in Japan are available. PMDA instructed the applicant to conduct a use-results survey.

(3) PMDA's view on the conformity of the Esprit BTK System to Article 3, which stipulates requirements for the performance and functions of medical devices, and to Article 6, which stipulates the efficacy of medical devices:
As described earlier in Section "2.(5).1).B Outline of the review conducted by PMDA," the performance of the Esprit BTK System was evaluated. As described later in Section "6.B Outline of the review conducted by PMDA," the results of the clinical studies submitted demonstrated the satisfactory results of the Esprit BTK System, showing that selection of eligible patients can ensure the effective and safe use of the Esprit BTK System. The Esprit BTK System conforms to Articles 3 and 6.

(4) PMDA's view on the conformity of the Esprit BTK System to Article 4, which stipulates the shelf-life or durability of medical devices:
As described earlier in Section "2.(4).B Outline of the review conducted by PMDA," the stability and durability of the Esprit BTK System has been confirmed. The Esprit BTK System conforms to Article 4.

(5) PMDA's view on the conformity to Article 7, which stipulates the chemical properties, biological safety, etc. of medical devices:
As described earlier in Sections "2.(2).B Outline of the review conducted by PMDA" and "2.(3).B Outline of the review conducted by PMDA," the justification of the biological safety, etc. of the Esprit BTK System has been confirmed. The Esprit BTK System conforms to Article 7.

(6) PMDA's view on the conformity to Article 8, which stipulates anti-microorganism contamination measures for medical devices:
As described later in Section "5.B Outline of the review conducted by PMDA," the justification for the anti-microorganism contamination measures for the Esprit BTK System was confirmed. The Esprit BTK System conforms to Article 8.

(7) PMDA's view on the conformity of the Esprit BTK System to Article 17, which stipulates requirements for publicizing information including precautionary advice or the communication of information to users via instructions for use, etc. (the Information on Precautions, etc.):
As described later in Section "6.B Outline of the review conducted by PMDA," users must fully understand the risks of the Esprit BTK System, select patients eligible for the Esprit BTK therapy, and use the Esprit BTK System properly in order to maintain its risk-benefit balance. To this end, information should be provided to healthcare professionals through the Information on Precautions, etc., the guidelines for proper use, training, and other measures. Accordingly, PMDA instructed the applicant to provide cautionary advice in the Information on Precautions, etc. to remind of the use of the Esprit BTK System strictly in accordance with the guidelines for proper use that specify the requirements for eligible patients, users, medical institutions, training, etc.

PMDA concluded that there were no particular problems with the conformity of the Esprit BTK System to the Essential Principles.

4. Risk Management

4.A Summary of the data submitted

The applicant submitted a summary of risk management, the risk management system, and its progress in accordance with ISO 14971:2019 "Medical devices – Application of risk management to medical devices."

4.B Outline of the review conducted by PMDA

PMDA comprehensively reviewed the document on risk management taking into account the discussion presented earlier in Section "3.B Outline of the review conducted by PMDA" and concluded that there was no particular problem.

5. Manufacturing Process

5.A Summary of the data submitted

The applicant submitted data on the sterilization method for the Esprit BTK System, including sterilization conditions to ensure the sterility assurance level and bacterial endotoxins.

5.B Outline of the review conducted by PMDA

PMDA reviewed the data on the manufacturing process and concluded that there was no particular problem.

6. Clinical Data or Alternative Data Accepted by the Minister of Health, Labour and Welfare

6.A Summary of the data submitted

To support the clinical evaluation of the Esprit BTK System, the applicant submitted the results of a foreign clinical study (the LIFE-BTK study), which was a randomized controlled study using the standard procedure, PTA, as a control, and of a pharmacokinetic study of everolimus after implantation of the Esprit BTK System (the LIFE-BTK PK study).

6.A.(1) LIFE-BTK study (National Clinical Trial [NCT] No. NCT04227899, study period [redacted])

6.A.(1).1) Study design

The LIFE-BTK study was a prospective, multi-center, randomized, controlled clinical study in patients with CLTI of Rutherford-Becker category 4 (ischaemic rest pain) or 5 (minor tissue loss) with de novo or restenotic (treated with prior PTA) infrapopliteal lesions at 50 study sites in the US, Taiwan, and Australia to evaluate the efficacy and safety of the Esprit BTK System in comparison with PTA.

Table 5 presents an outline of the LIFE-BTK study.

Table 5. Outline of the LIFE-BTK study

Study design	Prospective, randomized (either the Esprit BTK System or PTA at a ratio of 2:1), single-blind, multi-center study
Objective	To evaluate the efficacy and safety of the Esprit BTK System in comparison with standard procedure PTA in patients with CLTI resulting from infrapopliteal lesions
Sample size	261 subjects (173 in the Esprit BTK arm, 88 in the PTA arm)
Primary efficacy endpoint	Composite of limb salvage and primary patency at 1 year • Limb salvage is defined as freedom from major amputation (above-ankle amputation) in the index limb. • Primary patency is defined as freedom from 100% total occlusion of target vessel, binary restenosis of target vessel, and clinically-driven target lesion revascularization (CD-TLR).
Primary safety endpoint	Freedom from peri-operative death and major adverse limb events (MALE) • Peri-operative death is defined as death within 30 days after the index procedure. • MALE is defined as major amputation and major re-intervention on the index limb through 6 months.
Key inclusion criteria	General inclusion criteria 1. Patient has symptomatic CLTI of Rutherford-Becker category 4 (ischaemic rest pain) or 5 (minor tissue loss). 2. Patient has up to 2 de novo or restenotic (treated with prior PTA) infrapopliteal lesions. Anatomic inclusion criteria 1. Patient has lesion(s) meeting the condition[1] in an infrapopliteal artery. Up to 2 lesions may be treated; in such cases, the lesions must be located in different vessels in the same limb. Restenotic (from prior PTA) lesions are allowed to be treated as target lesions. 2. Target lesion(s) must have ≥70% stenosis, per physician's visual assessment at the time of the procedure. If needed, quantitative imaging (online QVA, IVUS, or OCT) can be used to aid accurate sizing of the vessels. 3. Significant lesion (≥50% stenosis) in the inflow arter(ies) must be treated successfully (as per investigator's assessment of the angiography) prior to the treatment of the target lesion. Treatment of the inflow artery can be done within the same trial procedure. 4. Non-target lesion(s) (if applicable) must be located in separate infrapopliteal vessel(s) from the target lesion, and suitable to be treated per standard of care.
Key exclusion criteria	General exclusion criteria 1. Patient is currently on dialysis. 2. Patient has extensive tissue loss that is salvageable only with complex foot reconstruction or non-traditional transmetatarsal amputations.[2] Anatomic exclusion criteria 1. Lesions with severe calcification, in which there is a high likelihood that successful pre-dilatation cannot be achieved 2. Restenotic 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. Target or non-target vessel contains visible thrombus as indicated in the angiographic images. 5. Patient has angiographic evidence of thromboembolism or atheroembolism in the ipsilateral extremity. (Pre- and post-angiographic imaging must confirm the absence of emboli in the distal anatomy.) 6. Unsuccessfully treated inflow-limiting arterial stenosis or inflow-limiting arterial lesions left untreated 7. No angiographic evidence of a patent pedal artery 8. Physician's visual assessment of the target lesion suggests that the lesion cannot be pre-dilated according to the vessel diameter.

[1] 1) Target lesions must be located in the proximal 2/3 of native infrapopliteal vessels, with vessel diameter of ≥2.5 and ≤4.00 mm by physician's visual assessment. 2) Total scaffold length to completely cover/treat a target lesion must not exceed 170 mm (total everolimus drug dose of ≤1,790 μg). 3) The total scaffold length among 2 target lesions must be ≤170 mm. 4) The target vessel cannot have any other angiographic significant lesions (≥50% stenosis). 5) Tandem lesions are allowed if they are <30 mm apart and the total scaffold length (from the most proximal end to the most distal end) used to cover the entire diseased segment is ≤170 mm. Each tandem lesion is considered 1 lesion.

[2] 1) Osteomyelitis that extends proximal to the metatarsal heads. Osteomyelitis limited to the phalanges or metatarsal heads is acceptable for enrollment. 2) Gangrene involving the plantar skin of the forefoot, midfoot, or heel. 3) Deep ulcer or large shallow ulcer (>3 cm) involving the plantar skin of the forefoot, midfoot, or heel. 4) Full thickness heel ulcer with/without calcaneal bone involvement. 5) Any wound with calcaneal bone involvement. 6) Wounds that are deemed to be neuropathic or non-ischaemic in nature. 7) Wounds that would require flap coverage or complex wound management for large soft tissue defect. 8) Full thickness wounds on the dorsum of the foot with exposed tendon or bone

The intent-to-treat (ITT) population (an analysis set including all randomized subjects, regardless of the treatments they actually received) of the LIFE-BTK study consisted of 261 subjects. Of the 173 subjects

randomized to the Esprit BTK arm, 153 completed 1-year follow-up (1 year ± 28 days), while of the 88 subjects randomized to the PTA arm, 78 completed 1-year follow-up (Figure 4). The as-treated (AT) population (an analysis set including all subjects classified according to the treatment they actually received) consisted of 170 subjects in the Esprit BTK arm and 90 subjects in the PTA arm. Among the 173 subjects randomized to the Esprit BTK arm, 1 subject withdrew consent prior to the index procedure and 2 subjects received PTA. The 2 subjects did not drop out of the study and completed 1-year follow-up.

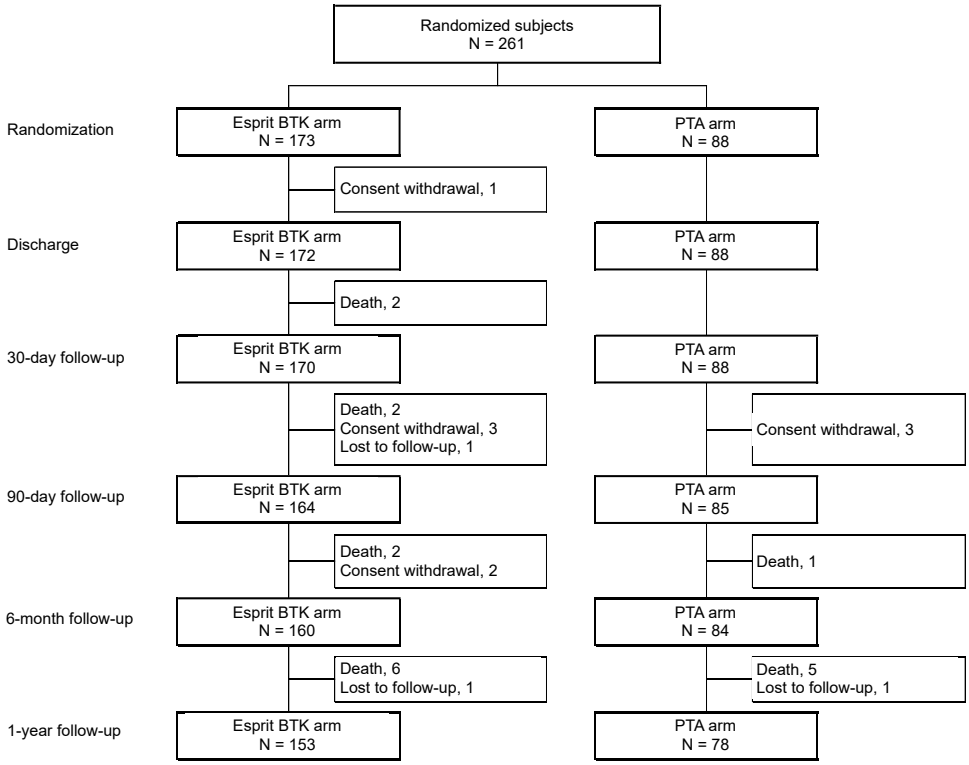


Figure 4. Number of subjects at each follow-up in the ITT population

The primary efficacy endpoint was "limb salvage (freedom from above ankle amputation in index limb) and primary patency (freedom from 100% total occlusion of target vessel, binary restenosis,[a] and clinically-driven target lesion revascularization [CD-TLR][b]) at 1 year." The clinical outcome was estimated to be 75% in the Esprit BTK arm and 55% in the PTA arm with reference to literature reports on drug eluting stents or resorbable scaffolds for infrapopliteal arteries.[3,5,8,9] Assuming a one-sided significance level of 0.0249 and power of 84%, the sample size of 222 was needed. The primary safety endpoint was "freedom from peri-operative death (within 30 days after the index procedure) and major adverse limb events (MALE) (major amputation and major re-intervention[c] on the index limb within 6

[a] Binary restenosis was defined as the presence of a hemodynamically significant restenosis > 50% by angiography, or peak systolic velocity ratio (PSVR) ≥ 2.4 by duplex ultrasound (DUS). In the presence of abnormal reference peak systolic velocity (PSV), the core lab uses the following additional secondary criteria (correlating factors) to identify target lesion stenoses >50% in severity:

- Focal increase in the absolute PSV at the area of visible plaque;
- Spectral broadening of the waveform at the area of stenosis;
- Post-stenotic turbulence (PST) and/or change in the waveform shape and/or drop in velocity distal to the stenosis;
- Review of the B-mode images for plaque burden.

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

[b] Revascularization for recurrent lower limb symptoms with angiographic evidence of >70% stenosis, as adjudicated by the Clinical Events Committee (CEC)

[c] New bypass surgery, bypass revision by jump graft/graft interposition, thrombectomy, thrombolysis, or intervention

months after the index procedure)." With reference to the primary safety outcome of 95.7% in a clinical study in the femoral arteries,[10] the event-free rate of 95% was predicted for both arms. Assuming a non-inferiority margin of -10%, one-sided significance level of 0.025, and power of 90%, a sample size of 235 was needed. Allowing for a dropout rate of 15%, the planned sample size of 260 was determined for the LIFE-BTK study.

The protocol specified the ITT population as the primary analysis set for all analyses.

6.A.(1).2) Patient characteristics

Table 6 presents the patient characteristics of the LIFE-BTK study. Table 7 presents risk factors. Table 8 presents baseline target lesion characteristics as adjudicated by the core laboratory. There were a total of 271 target lesions in 261 enrolled subjects in the study population.

Table 6. Patient characteristics (ITT)

	Overall (N = 261)	Esprit BTK (N = 173)	PTA (N = 88)	Difference [95% CI][1]
Age at consent [min, max]	72.6 ± 10.1 [47, 94]	73.3 ± 9.9 [47, 94]	71.1 ± 10.4 [49, 92]	2.2 [-0.4, 4.9]
Female	31.8% (83/261)	32.4% (56/173)	30.7% (27/88)	1.7% [-10.48%, 13.01%]
BMI (kg/m^2)	28.21 ± 5.58	27.85 ± 5.47	28.94 ± 5.77	-1.09 [-2.55, 0.38]
Rutherford-Becker category (baseline)				
Category 4	51.7% (135/261)	52.0% (90/173)	51.1% (45/88)	0.9% [-11.70%, 13.50%]
Category 5	48.3% (126/261)	48.0% (83/173)	48.9% (43/88)	-0.9% [-13.50%, 11.70%]
Baseline wound	49.8% (130/261)	49.1% (85/173)	51.1% (45/88)	-2.0% [-14.56%, 10.65%]

[1.] By normal approximation for continuous variables and Newcombe score method for binary variables
Note: Subjects with unknown, not applicable, or missing data were not included in the denominator.

Table 7. Risk factors (ITT)

	Overall (N = 261)	Esprit BTK (N = 173)	PTA (N = 88)	Difference [95% CI][1]
Smoking	52.9% (138/261)	52.6% (91/173)	53.4% (47/88)	-0.8% [-13.31%, 11.86%]
Hypertension	93.1% (243/261)	94.2% (163/173)	90.9% (80/88)	3.3% [-3.01%, 11.57%]
Lipid abnormality	81.2% (212/261)	80.9% (140/173)	81.8% (72/88)	-0.9% [-10.21%, 9.77%]
Family history of coronary artery disease	34.0% (66/194)	34.4% (44/128)	33.3% (22/66)	1.0% [-13.21%, 14.35%]
Family history of peripheral artery disease	14.4% (26/181)	14.3% (17/119)	14.5% (9/62)	-0.2% [-12.23%, 9.75%]
Family history of cerebrovascular accident	15.7% (30/191)	14.7% (19/129)	17.7% (11/62)	-3.0% [-15.41%, 7.36%]
Diabetes mellitus	70.5% (184/261)	71.1% (123/173)	69.3% (61/88)	1.8% [-9.45%, 13.80%]
HbA1c >7.0%	43.5% (80/184)	43.9% (54/123)	42.6% (26/61)	1.3% [-13.80%, 15.86%]
History of myocardial infarction	16.1% (40/248)	16.9% (27/160)	14.8% (13/88)	2.1% [-8.09%, 10.95%]
Multi-vessel peripheral vascular disease	62.1% (157/253)	62.5% (105/168)	61.2% (52/85)	1.3% [-10.92%, 14.03%]
Congestive heart failure	19.4% (50/258)	19.4% (33/170)	19.3% (17/88)	0.1% [-10.72%, 9.63%]
Prior percutaneous coronary artery intervention/ coronary artery surgery	35.0% (90/257)	34.7% (59/170)	35.6% (31/87)	-0.9% [-13.39%, 10.94%]
Cerebrovascular disease	14.6% (37/253)	13.2% (22/167)	17.4% (15/86)	-4.3% [-14.57%, 4.61%]
Prior cerebrovascular accident (CVA) or stroke	13.5% (35/259)	11.7% (20/171)	17.0% (15/88)	-5.3% [-15.37%, 3.23%]
Transient ischaemic attack	3.1% (8/257)	3.5% (6/170)	2.3% (2/87)	1.2% [-4.78%, 5.52%]
Chronic obstructive pulmonary disease	13.5% (35/260)	14.0% (24/172)	12.5% (11/88)	1.5% [-8.13%, 9.49%]
Renal disease	16.0% (41/257)	15.8% (27/171)	16.3% (14/86)	-0.5% [-10.83%, 8.37%]
eGFR <30 mL/min/1.73 m^2	7.3% (3/41)	0.0% (0/27)	21.4% (3/14)	-21.4% [-47.59%, -2.80%]
Cancer	11.2% (29/259)	12.3% (21/171)	9.1% (8/88)	3.2% [-5.66%, 10.45%]
Hepatic disease	3.1% (8/256)	1.8% (3/170)	5.8% (5/86)	-4.0% [-11.23%, 0.62%]
Deep vein thrombosis	4.6% (12/261)	4.0% (7/173)	5.7% (5/88)	-1.6% [-8.88%, 3.56%]
Hypotension	12.9% (33/255)	15.4% (26/169)	8.1% (7/86)	7.3% [-1.78%, 14.70%]
Previous amputation to target limb	8.8% (23/261)	9.2% (16/173)	8.0% (7/88)	1.3% [-7.03%, 7.92%]
Previous amputation to non-target limb	6.5% (17/261)	8.1% (14/173)	3.4% (3/88)	4.7% [-2.25%, 10.19%]
Angina pectoris	6.6% (17/257)	5.9% (10/170)	8.0% (7/87)	-2.2% [-10.25%, 4.00%]

[1.] By Newcombe score method

Note: Subjects with unknown, not applicable, or missing data were not included in the denominator.

Table 8. Baseline target lesion characteristics (adjudicated by the core laboratory, ITT)

	Overall (N = 261, L = 271)	Esprit BTK (N = 173, L = 179)	PTA (N = 88, L = 92)	Difference [95% CI][1]
Target vessel				
Anterior tibial artery	31.8% (83/261)	34.3% (59/172)	27.0% (24/89)	7.3% [-4.72%, 18.30%]
Posterior tibial artery (PT)	16.1% (42/261)	15.1% (26/172)	18.0% (16/89)	-2.9% [-13.18%, 6.13%]
Peroneal artery	18.8% (49/261)	16.3% (28/172)	23.6% (21/89)	-7.3% [-18.21%, 2.53%]
Tibioperoneal trunk (TPT)	15.7% (41/261)	15.1% (26/172)	16.9% (15/89)	-1.7% [-11.94%, 7.09%]
TPT – PT	8.8% (23/261)	8.7% (15/172)	9.0% (8/89)	-0.3% [-8.72%, 6.50%]
TPT – peroneal artery	8.8% (23/261)	10.5% (18/172)	5.6% (5/89)	4.9% [-2.97%, 11.18%]
Lesion length (mm) [min, max]	44.11 ± 30.87 [3.82, 148.40]	43.78 ± 31.84 (172) [3.82, 148.40]	44.75 ± 29.07 (89) [5.33, 125.10]	-0.97 [-8.71, 6.76]
% Diameter stenosis (DS) pre-intervention (DS, %) [min, max]	73.0 ± 19.6 (261) [18, 100]	72.6 ± 18.9 (172) [23, 100]	73.7 ± 21.0 (89) [18, 100]	-1.1 [-6.3, 4.1]
% DS <70%	34.1% (89/261)	36.0% (62/172)	30.3% (27/89)	5.7% [-6.55%, 17.04%]
Total occlusion	16.9% (44/261)	15.1% (26/172)	20.2% (18/89)	-5.1% [-15.65%, 4.21%]
Tandem lesions	28.4% (74/261)	32.0% (55/172)	21.3% (19/89)	10.6% [-0.97%, 20.90%]
No or mild calcification	99.6% (260/261)	99.4% (171/172)	100.0% (89/89)	-0.6% [-3.22%, 3.58%]
Moderate calcification	0.4% (1/261)	0.6% (1/172)	0.0% (0/89)	0.6% [-3.58%, 3.22%]
Study site-assessed calcification[2]				
None or mild	69.4% (188/271)	69.3% (124/179)	69.6% (64/92)	-0.3% [-11.34%, 11.55%]
Moderate	27.7% (75/271)	27.4% (49/179)	28.3% (26/92)	-0.9% [-12.49%, 9.85%]
Severe	3.0% (8/271)	3.4% (6/179)	2.2% (2/92)	1.2% [-4.53%, 5.26%]

[1] By normal approximation for continuous variables and Newcombe score method for binary variables
[2] Study site-assessed calcification is cited from the literature[11]
Note: N = Number of subjects, L = Number of lesions.

6.A.(1).3) Index procedure

Table 9 presents the information on the Esprit BTK System used in the index procedure. Core laboratory assessment of post-procedural angiography of the target vessels showed that residual stenosis <30% was achieved in 95.9% (163 of 170) of subjects in the Esprit BTK arm, which was higher than that in the PTA arm (72.6%, 61 of 84 subjects). No angiographic complications (thrombosis, residual dissection, contrast extravasation, in-segment thrombosis, and perforation) were observed in either arm.

Table 9. Information on scaffolds used (ITT)

	Esprit BTK (N = 173, L = 179, S = 342)
Scaffold diameter	
2.5 mm	18.3% (62/339)
3.0 mm	45.7% (155/339)
3.5 mm	27.7% (94/339)
3.75 mm	8.3% (28/339)
Scaffold length	
18 mm	18.3% (62/339)
28 mm	24.5% (83/339)
38 mm	57.2% (194/339)

Note: N = Number of subjects, L = Number of lesions, S = Number of scaffolds.

6.A.(1).4) Study results

6.A.(1).4).(a) Efficacy endpoints

i) Primary efficacy endpoint

Of the 173 subjects enrolled in the Esprit BTK arm, 149 subjects were included in the primary efficacy endpoint analysis, excluding 16 subjects who dropped out of the study because of missing primary efficacy evaluation before the 1 year follow-up and 8 subjects who did not undergo the required occlusion or stenosis assessment. Of the 88 subjects enrolled in the PTA arm, 71 subjects were included in the primary efficacy endpoint analysis, excluding 8 subjects who dropped out of the study because of

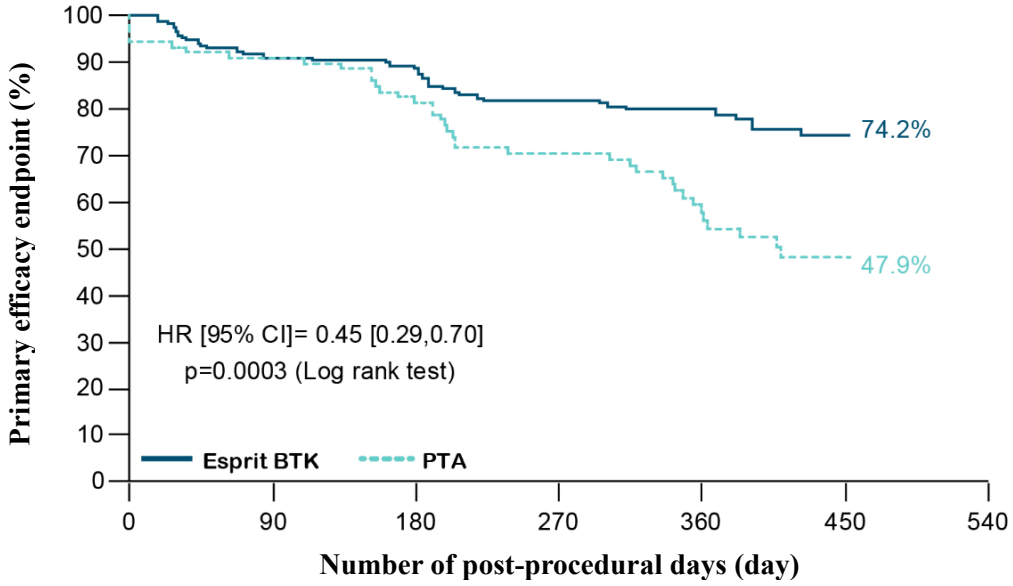
missing primary efficacy evaluation before the 1 year follow-up and 9 subjects who did not undergo the required occlusion or stenosis assessment.

The results of the primary efficacy endpoint in the ITT population were 74.5% (111 of 149 subjects) in the Esprit BTK arm and 43.7% (31 of 71 subjects) in the PTA arm. The difference between the treatment arms was 30.8%, and the lower limit of the one-sided 97.5% confidence interval for the difference was 17.0%, showing that the Esprit BTK arm demonstrated a significantly superior outcome to that of the PTA arm ($P < 0.0001$), indicating the superiority (Table 10). Figure 5 presents the Kaplan-Meier curves of the primary efficacy endpoint, showing the superiority of the Esprit BTK System to PTA ($P = 0.0003$). Of the elements comprising the primary efficacy endpoint, the rate of freedom from restenosis was 76.5% (114 of 149 subjects) in the Esprit BTK arm and 50.7% (36 of 71 subjects) in the PTA arm. The difference was significant (Table 11).

Table 10. Primary efficacy endpoint (ITT)

	Esprit BTK (N = 173)	**PTA (N = 88)**	**Difference (lower limit of one-sided 97.51% CI)[2]**	***P*-value[3]**
Primary efficacy endpoint (limb salvage and primary patency at 1 year) [95% CI][1]	74.5% (111/149) [66.7%, 81.3%]	43.7% (31/71) [31.9%, 56.0%]	30.8% (17.0%)	<0.0001

[1] Clopper-Pearson exact confidence interval
[2] By Newcombe score method
[3] From One-sided chi-squared test, to be compared at significance level of 0.0249.
Note: Major amputation and CD-TLR were adjudicated by the Clinical Events Committee (CEC). Total occlusion and restenosis were adjudicated by the core laboratory.



Time after index procedure (days)						
	0 days	30 days	90 days	180 days	365 days	453 days
Esprit BTK						
Number at risk	173	163	152	142	95	42
Number of events	0	6	15	19	33	38
Event-free rate	100.0%	96.5%	91.1%	88.6%	79.8%	74.2%
Incidence of events	0.0%	3.5%	8.9%	11.4%	20.2%	25.8%
% SEM	0.0%	1.4%	2.2%	2.5%	3.2%	3.8%
PTA						
Number at risk	88	82	78	67	33	15
Number of events	5	6	8	16	36	39
Event-free rate	94.3%	93.2%	90.9%	81.2%	54.5%	47.9%
Incidence of events	5.7%	6.8%	9.1%	18.8%	45.5%	52.1%
% SEM	2.5%	2.7%	3.1%	4.2%	5.8%	6.2%

Test between groups	Test method	Chi-Square	Degree of freedom	*P*-value
	Log-Rank	13.104	1	0.0003

Note: Events include only each subject's first occurrence of the composite endpoint.

Figure 5. Kaplan-Meier curves of the primary efficacy endpoint (ITT)

Table 11. Primary efficacy endpoint and components (ITT)

	Overall (N = 261)	**Esprit BTK (N = 173)**	**PTA (N = 88)**	**Difference [95% CI][1]**
Limb salvage (freedom from major amputation)	98.2% (216/220)	97.3% (145/149)	100.0% (71/71)	-2.68% [-6.70%, 2.70%]
Freedom from 100% total occlusion	86.4% (190/220)	87.9% (131/149)	83.1% (59/71)	4.82% [-4.50%, 16.04%]
Freedom from binary restenosis	68.2% (150/220)	76.5% (114/149)	50.7% (36/71)	25.81% [12.30%, 38.70%]
Freedom from CD-TLR	90.0% (198/220)	92.6% (138/149)	84.5% (60/71)	8.11% [-0.40%, 18.76%]

[1.] By Newcombe score method

Note: Major amputation and CD-TLR were adjudicated by the CEC. 100% total occlusion and binary restenosis were adjudicated by the core laboratory.

ii) Major amputation

Four subjects in the Esprit BTK arm underwent major amputation (above-ankle amputation) within 1 year after the procedure (Table 12). The 4 subjects were classified as Rutherford-Becker category 5 at baseline and were hospitalized because of the exacerbation of wounds in the index limb, which led to major amputation. No major amputations were considered to be related to the device or procedure.

Table 12. List of subjects with major amputation

	Outcome	Date of amputation	Target lesion patency	Esprit BTK therapy	Causal analysis	Related to procedure[1]
1	Below-the-knee amputation of left foot	53	Yes	Left anterior tibial artery 3.0 × 38 mm, 4; 3.0 × 18 mm, 1	There was an absence of the pedal arch and digital arteries, with the foot being mainly perfused through collateral vessels, leading to insufficient blood flow.	Unrelated
2	Below-the-knee amputation of left foot	148	Yes	Left peroneal artery 2.5 × 38 mm, 1	Severe progression of diabetic foot infection resulted in poor wound healing.	Unrelated
3	Below-the-knee amputation of left foot	194	Yes	Left anterior tibial artery 3.0 × 38 mm, 2; 3.5 × 28 mm, 1	Severe chronic osteomyelitis impaired wound healing.	Unrelated
4	Below-the-knee amputation of left foot	281	Unknown	Left anterior tibial artery 3.5 × 38 mm, 1	Severe diabetic foot infection and deterioration of cardiovascular condition	Unrelated

[1] CEC-adjudicated. Since the CEC was blinded to the randomization results in the LIFE-BTK study, a causal relationship to the device was not adjudicated.

iii) Wound healing

In the LIFE-BTK study, the independent core laboratory assessed wounds. Subjects were examined for not only wounds existing at the time of the index procedure but also new wounds occurring during the follow-up period.

At 1 year post-procedure, the cumulative percentage of wounds healed was 76.1% (54 of 71 of wounds) in the Esprit BTK arm and 80% (40 of 50 of wounds) in the PTA arm (Figure 6). The cumulative percentage of subjects with healed index wound(s) was 44.6% (37 of 83 of subjects) in the Esprit BTK arm and 55.6% (25 of 45 of subjects) in the PTA arm (Figure 7). The mean wound area decreased over time in both arms (Figure 8). In the Esprit BTK arm, infection was observed at 2 wounds at baseline, 1 wound at 14 days post-procedure, and 1 wound at 90 days post-procedure. The PTA arm had no infected wounds. The Esprit BTK arm had 57 new wounds in 32 subjects, while the PTA arm had 18 new wounds in 13 subjects (Table 13).

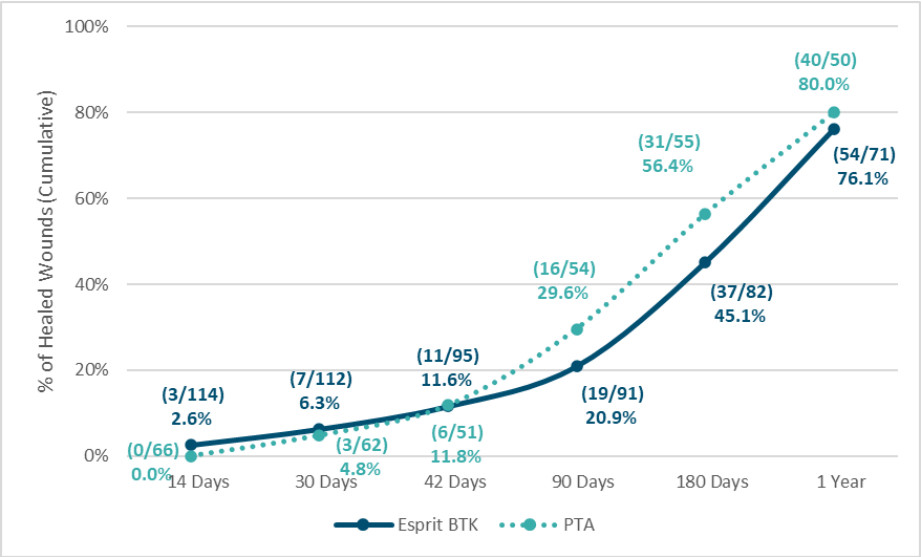


Figure 6. Healing of wounds existing at the index procedure (wound-level) (ITT)

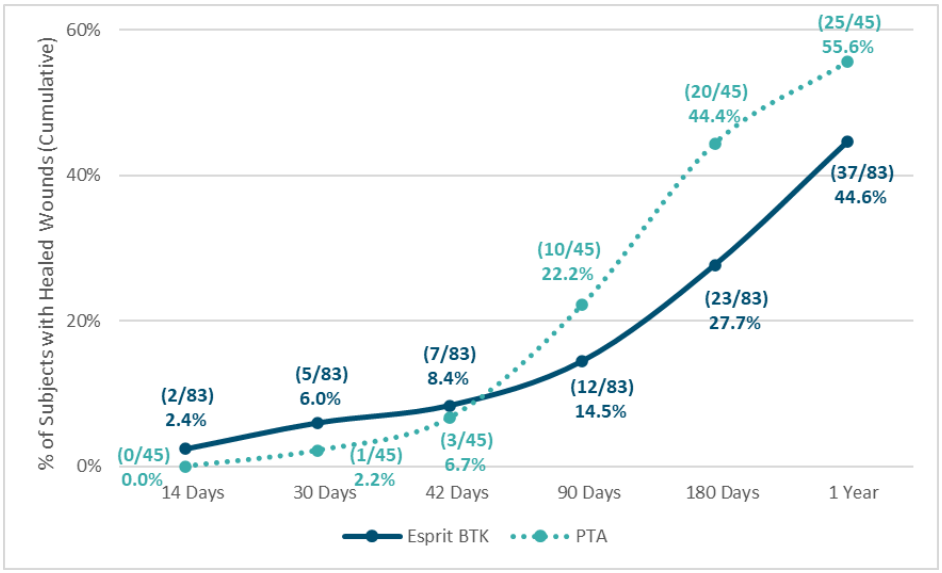


Figure 7. Healing of wounds existing at the index procedure (subject-level) (ITT)

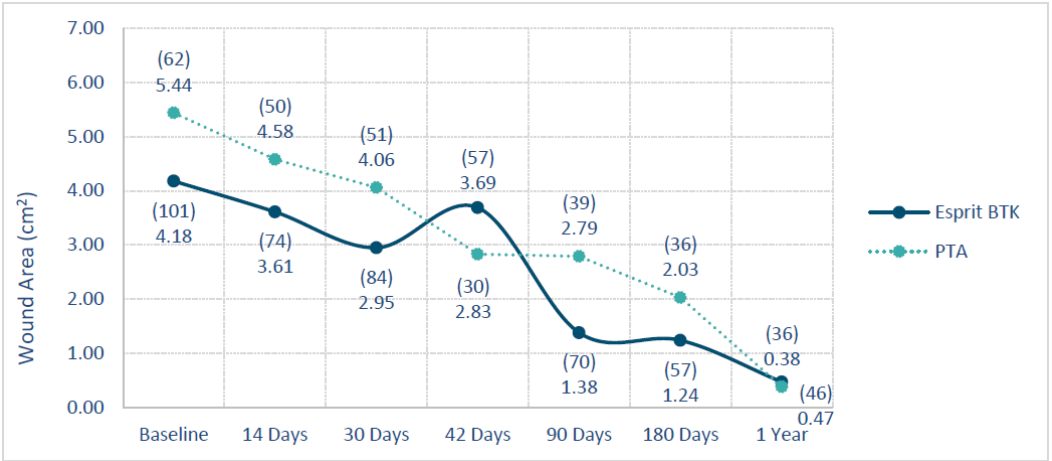


Figure 8. Mean area of wounds existing at the index procedure (subject-level) (ITT)

Table 13. New wound characteristics (ITT)

	Overall (N = 45, W = 75)	Esprit BTK (N = 32, W = 57)	PTA (N = 13, W = 18)	Difference [95% CI][1]
New wound	75	57	18	
New wound per subject	1.7 ± 1.0	1.8 ± 1.0	1.4 ± 1.1	0.4 [-0.3, 1.1]
Lower limb				
Left lower limb	41.3% (31/75)	45.6% (26/57)	27.8% (5/18)	17.84% [-8.30%, 37.76%]
Right lower limb	58.7% (44/75)	54.4% (31/57)	72.2% (13/18)	-17.84% [-37.76%, 8.30%]
Wound location				
Toe	44.0% (33/75)	42.1% (24/57)	50.0% (9/18)	-7.89% [-32.01%, 16.73%]
Calf	2.7% (2/75)	3.5% (2/57)	0.0% (0/18)	3.51% [-14.26%, 11.92%]
Foot	18.7% (14/75)	15.8% (9/57)	27.8% (5/18)	-11.99% [-36.20%, 7.18%]
Heel	2.7% (2/75)	3.5% (2/57)	0.0% (0/18)	3.51% [-14.26%, 11.92%]
Shin	24.0% (18/75)	26.3% (15/57)	16.7% (3/18)	9.65% [-14.89%, 26.31%]
Sole	8.0% (6/75)	8.8% (5/57)	5.6% (1/18)	3.22% [-17.59%, 14.37%]
Wound type				
Arterial insufficiency only	68.0% (51/75)	66.7% (38/57)	72.2% (13/18)	-5.56% [-25.58%, 19.96%]
Mixed etiology in addition to arterial insufficiency	32.0% (24/75)	33.3% (19/57)	27.8% (5/18)	5.56% [-19.96%, 25.58%]
- Venous stasis	16.0% (12/75)	15.8% (9/57)	16.7% (3/18)	-0.88% [-24.57%, 14.97%]
- Diabetic	4.0% (3/75)	3.5% (2/57)	5.6% (1/18)	-2.05% [-22.41%, 7.53%]
- Traumatic	5.3% (4/75)	7.0% (4/57)	0.0% (0/18)	7.02% [-11.08%, 16.70%]
- Surgical wounds	1.3% (1/75)	1.8% (1/57)	0.0% (0/18)	1.75% [-15.89%, 9.29%]
- Unable to assess	5.3% (4/75)	5.3% (3/57)	5.6% (1/18)	-0.29% [-20.79%, 9.90%]
Necrotic tissue present	12.2% (9/74)	14.3% (8/56)	5.6% (1/18)	8.73% [-12.61%, 21.06%]
Wound infection suspected	0.0% (0/74)	0.0% (0/56)	0.0% (0/18)	0.00% [-17.59%, 6.42%]

[1.] By normal approximation for continuous variables and Newcombe score method for binary variables

Note: N represents the unique subjects who have any new wound core lab data. W represents the total new wounds from the new wound core lab data.

Note: Sites were asked to only take picture for new wound appearing on the index (target) limb. No pictures were taken and sent to core lab for new wound on non-index limb.

Note: Data in Foot under the Wound location do not include data in Toe.

iv) Rutherford-Becker category and hemodynamics

Figure 9 presents change in Rutherford-Becker category at each follow-up visit. Improvement in category was observed at 30 days post-procedure. At 1 year post-procedure, the proportion of subjects with category 0 to 3 was 81.4% in the Esprit BTK arm and 72.5% in the PTA arm. A comparison between baseline and 1 year post-procedure showed improvement in category in 85.0% in the Esprit BTK arm and 76.8% in the PTA arm. There was no difference between the 2 arms at any time point.

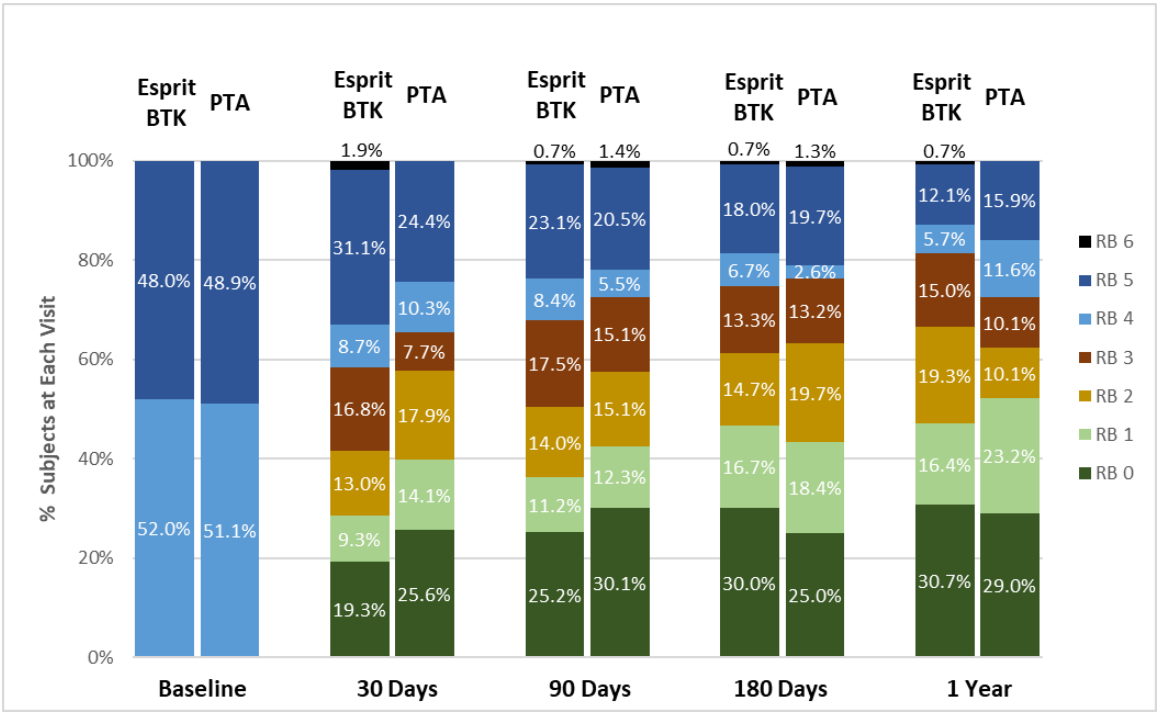


Figure 9. Change in Rutherford-Becker category at each follow-up visit (ITT)

Table 14 presents a change in the mean ankle-brachial index (ABI) of the index limb. The mean ABI was 0.87 ± 0.32 in the Esprit BTK arm and 0.91 ± 0.33 in the PTA arm at baseline, 1.06 ± 0.26 in the Esprit BTK arm and 1.05 ± 0.28 in the PTA arm at 30 days post-procedure, and 1.06 ± 0.30 in the Esprit BTK arm and 1.02 ± 0.28 in the PTA arm at 1 year post-procedure, showing a persistent improvement in both arms. Abnormal ABI values (>1.4) were observed at each follow-up visit (28 subjects in the Esprit BTK arm, 13 subjects in the PTA arm). Many of these subjects had multiple abnormal values, suggesting the possible existence of underlying conditions in the subjects contributing to these abnormalities. There was no clear relationship between the abnormalities and calcification.

Table 15 presents a change in the mean toe-brachial pressure Index (TBI) of the index limb. The mean TBI was 0.51 ± 0.31 in the Esprit BTK arm and 0.46 ± 0.24 in the PTA arm at baseline, 0.65 ± 0.32 in the Esprit BTK arm and 0.64 ± 0.21 in the PTA arm at 30 days post-procedure, and 0.67 ± 0.23 in the Esprit BTK arm and 0.61 ± 0.22 in the PTA arm at 1 year post-procedure, showing a persistent improvement.

Table 14. Change in mean ABI of the index limb (ITT)

	Overall (N = 261)	Esprit BTK (N = 173)	PTA (N = 88)	Difference [95% CI][1]
Baseline [min, max]	0.88 ± 0.32 (227) [0.02, 1.88]	0.87 ± 0.32 (150) [0.02, 1.88]	0.91 ± 0.33 (77) [0.16, 1.80]	-0.05 [-0.14, 0.04]
30 days [min, max]	1.06 ± 0.27 (216) [0.32, 2.47]	1.06 ± 0.26 (143) [0.32, 2.07]	1.05 ± 0.28 (73) [0.56, 2.47]	0.01 [-0.07, 0.09]
90 days [min, max]	1.05 ± 0.26 (193) [0.30, 2.11]	1.06 ± 0.27 (132) [0.30, 2.11]	1.05 ± 0.24 (61) [0.69, 1.82]	0.01 [-0.07, 0.09]
180 days [min, max]	1.02 ± 0.30 (213) [0.04, 2.48]	1.01 ± 0.29 (141) [0.04, 1.84]	1.03 ± 0.31 (72) [0.50, 2.48]	-0.02 [-0.11, 0.06]
1 year [min, max]	1.04 ± 0.30 (198) [0.27, 1.97]	1.06 ± 0.30 (129) [0.27, 1.97]	1.02 ± 0.28 (69) [0.49, 1.92]	0.03 [-0.05, 0.12]

[1.] By normal approximation
Note: ABI values of '0' are excluded in the analysis.
Note: The figures in parentheses represent the numbers of subjects included in the analysis.

Table 15. Change in TBI of the index limb (ITT)

	Overall (N = 261)	Esprit BTK (N = 173)	PTA (N = 88)	Difference [95% CI][1]
Baseline [min, max]	0.49 ± 0.29 (79) [0.01, 1.43]	0.51 ± 0.31 (50) [0.01, 1.43]	0.46 ± 0.24 (29) [0.01, 1.03]	0.06 [-0.07, 0.18]
30 days [min, max]	0.65 ± 0.27 (90) [0.15, 1.41]	0.65 ± 0.32 (49) [0.15, 1.41]	0.64 ± 0.21 (41) [0.32, 1.25]	0.01 [-0.11, 0.12]
90 days [min, max]	0.66 ± 0.26 (88) [0.15, 1.37]	0.64 ± 0.26 (49) [0.15, 1.29]	0.69 ± 0.25 (39) [0.29, 1.37]	-0.06 [-0.17, 0.05]
180 days [min, max]	0.58 ± 0.26 (92) [0.05, 1.49]	0.61 ± 0.29 (51) [0.05, 1.45]	0.56 ± 0.23 (41) [0.16, 1.49]	0.05 [-0.06, 0.15]
1 year [min, max]	0.65 ± 0.23 (86) [0.15, 1.20]	0.67 ± 0.23 (50) [0.24, 1.20]	0.61 ± 0.22 (36) [0.15, 1.16]	0.06 [-0.04, 0.16]

[1.] By normal approximation
Note: TBI values of' '0' are excluded in the analysis.
Note: The figures in parentheses represent the numbers of subjects included in the analysis.

6.A.(1).4).(b) Safety endpoints

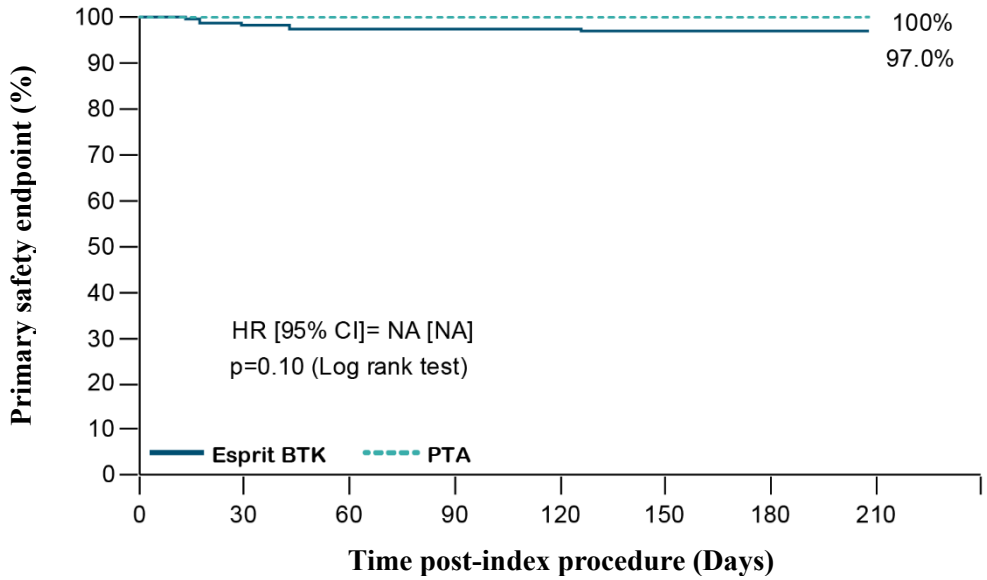
i) Primary safety endpoint

The primary safety endpoint in the AT population were 96.9% (155 of 160 subjects) in the Esprit BTK arm and 100.0% (85 of 85 subjects) in the PTA arm. The difference between the treatment arms was −3.1%, and the lower limit of the one-sided 97.5% confidence interval for the difference was −7.1%, which met the predefined non-inferiority margin of −10%, showing the non-inferiority of the Esprit BTK System to PTA (Table 16). Figure 10 presents the Kaplan-Meier curves of the primary safety endpoint. Table 17 presents the results of each component of the primary safety endpoint. The Esprit BTK arm had major amputation in 2 subjects, major re-intervention on the index limb in 1 subject, and peri-operative death (30 days post-procedure) in 2 subjects (1 and 2 in Table 12, and Table 18).

Table 16. Primary safety endpoint results (AT)

	Esprit BTK (N = 170)	PTA (N = 90)	Difference (lower limit of one-sided 97.5% CI)[2]	*P*-value for non-inferiority[3]
Primary safety endpoint (freedom from peri-operative death and MALE) [95% CI][1]	96.9% (155/160) [92.9%, 99.0%]	100.0% (85/85) [95.8%, 100.0%]	-3.1% (-7.1%)	0.0019

[1.] Clopper-Pearson exact confidence interval
[2.] By Newcombe score method
[3.] Farrington-Manning non-inferiority (NI) test, with NI margin of δ set at -10%, to be compared at a one-sided significance level of 0.025.



Time after index procedure (days)						
	0 days	30 days	90 days	180 days	365 days	453 days
Esprit BTK						
Number at risk	170	166	162	162	153	152
Number of events	0	3	4	4	5	5
Event-free rate	100.0%	98.2%	97.6%	97.6%	97.0%	97.0%
Incidence of events	0.0%	1.8%	2.4%	2.4%	3.0%	3.0%
% SEM	0.0%	1.0%	1.2%	1.2%	1.3%	1.3%
PTA						
Number at risk	90	90	89	87	84	84
Number of events	0	0	0	0	0	0
Event-free rate	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
Incidence of events	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
% SEM	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%

Test between groups	Test method	Chi-Square	Degree of freedom	*P*-value
	Log-Rank	2.684	1	0.10

Note: CEC-adjudicated
Note: Events include only each subject's first occurrence of the composite endpoint.

Figure 10. Kaplan-Meier curves of the primary safety endpoint (AT)

Table 17. Results of each component of the primary safety endpoint (AT)

Components	Overall (N = 260)	Esprit BTK (N = 170)	PTA (N = 90)	Difference [95% CI][1]
Freedom from MALE	98.8% (242/245)	98.1% (157/160)	100.0% (85/85)	-1.9% [-5.4%, 2.6%]
Freedom from major amputation	99.2% (243/245)	98.8% (158/160)	100.0% (85/85)	-1.2% [-4.4%, 3.2%]
Freedom from major re-intervention on the index limb	99.6% (244/245)	99.4% (159/160)	100.0% (85/85)	-0.6% [-3.5%, 3.7%]
Freedom from peri-operative death	99.2% (243/245)	98.8% (158/160)	100.0% (85/85)	-1.2% [-4.4%, 3.2%]

[1.] By Newcombe score method
Note: CEC-adjudicated

Table 18. List of subjects with major re-intervention on the index limb and peri-operative (30 days post-procedure) deaths

	Event	Day	Outline	Outcome	Related to device[1]	Related to procedure[2]
1	Major re-intervention on the index limb	52	Laser atherectomy of the right superficial femoral artery and popliteal artery, and thrombosis suction in the peroneal artery	Resolved	Related	Related
2	Peri-operative death	13	Death from concurrent severe cardiovascular disease	Death	Unrelated	Unrelated
3	Peri-operative death	17	Death from necrotizing perirectal infection	Death	Unrelated	Unrelated

[1.] Study site-assessed, [2.] CEC-adjudicated

ii) Death

Table 19 presents Clinical Events Committee (CEC)-adjudication of the deaths. Deaths in 18 subjects (12 in the Esprit BTK arm, 6 in the PTA arm) had been reported by the 1-year follow-up. Of these, 11 deaths were adjudicated as cardiovascular deaths and 7 as non-cardiovascular deaths. None of the cardiovascular deaths was adjudicated as related to the index procedure or COVID-19. Among the non-cardiovascular deaths, 1 death in the Esprit BTK arm was adjudicated as related to the index procedure, and 1 death in the PTA arm was adjudicated as related to COVID-19.

Table 19. List of deaths through 1 year

	Treatment arm	Days to death	CEC-adjudication	Cause of death	Related to procedure[1]	Related to Covid-19[1]
1	Esprit BTK	13	Cardiovascular death	Unknown	Unrelated	Unrelated
2	Esprit BTK	17	Non-cardiovascular death	Unknown	Unrelated	Unrelated
3	Esprit BTK	34	Cardiovascular death	Unknown	Unrelated	Unrelated
4	Esprit BTK	43	Non-cardiovascular death	Unknown	Related	Unrelated
5	Esprit BTK	127	Cardiovascular death	Unknown	Unrelated	Unrelated
6	PTA	132	Cardiovascular death	Unknown	Unrelated	Unrelated
7	Esprit BTK	141	Cardiovascular death	Unknown	Unrelated	Unrelated
8	Esprit BTK	209	Cardiovascular death	Myocardial ischaemia	Unrelated	Unrelated
9	PTA	213	Cardiovascular death	Terminal-phase pulmonary fibrosis and cardiomyopathy	Unrelated	Unrelated
10	Esprit BTK	227	Cardiovascular death	Unknown	Unrelated	Unrelated
11	Esprit BTK	252	Cardiovascular death	Heart disease	Unrelated	Unrelated
12	PTA	290	Non-cardiovascular death	Septic shock	Unrelated	Unrelated
13	Esprit BTK	295	Non-cardiovascular death	Unknown	Unrelated	Unrelated
14	Esprit BTK	299	Cardiovascular death	Hypoxic or anoxic brain damage and brain oedema after cardiac arrest	Unrelated	Unrelated
15	PTA	337	Non-cardiovascular death	Unknown	Unrelated	Related
16	PTA	354	Non-cardiovascular death	Sepsis	Unrelated	Unrelated
17	Esprit BTK	358	Cardiovascular death	Unknown	Unrelated	Unrelated
18	PTA	378	Non-cardiovascular death	Unknown	Unrelated	Unrelated

[1] CEC-adjudicated

iii) Loss of patency (total occlusion, restenosis, or CD-TLR)

In the LIFE-BTK study, 26 events of total occlusions were reported as adverse events in 23 subjects (15 events in 13 subjects in the Esprit BTK arm, 11 events in 10 subjects in the PTA arm). Among these, in 2 subjects, the sites assessed the occlusions as related to the device and attributed them to thrombosis, and in other 2 subjects, thrombectomy was performed and the occlusions were assessed as unrelated to the device (all in the Esprit BTK arm). Of these 4 subjects, details were unknown in 1 subject due to withdrawal from the clinical study. The remaining 3 subjects received thrombectomy. Thrombosis was observed from the inflow vessel to the target lesions. A causal relationship between the thrombosis and

the Esprit BTK System remains unknown (Table 20). Apart from these 4 subjects, neointimal hyperplasia was considered the primary cause of loss of patency.

Table 20. List of subjects with thrombosis-related total occlusion through 1 year

	Treatment arm	Days to event	Description	Related to device[1]	Related to procedure[2]
1	Esprit BTK	28	Infrapopliteal vascular occlusion. Further information is not available because of consent withdrawal.	Related	Related
2	Esprit BTK	29	Occlusion extending from the inflow vessel. The inflow vessel (femoropopliteal vessel) was treated with laser atherectomy and drug eluting stents. The target vessel and non-target infrapopliteal vessel were treated by PTA and mechanical thrombectomy.	Related	Unrelated
3	Esprit BTK	188	Occlusion of the inflow vessel and the target lesion. The inflow vessel (femoropopliteal vessel) was treated with mechanical thrombectomy and drug-coated balloons. The target vessel was treated with PTA.	Unrelated	Unrelated
4	Esprit BTK	295	Occlusion extending from the inflow vessel. The inflow vessel (femoropopliteal vessel) was treated with drug-coated balloons and PTA. The target vessel was treated with PTA and mechanical thrombectomy.	Unrelated	Unrelated

[1.] Study site-assessed, [2.] CEC-adjudicated

A total of 34 restenosis events were reported in 31 subjects (15 events in 13 subjects in the Esprit BTK arm and 19 events in 18 subjects in the PTA arm). A total of 27 CD-TLR events were reported in 25 subjects (10 events in 10 subjects in the Esprit BTK arm and 17 events in 15 subjects in the PTA arm).

iv) Device- or procedure-related adverse events

The Esprit BTK arm had 13 device-related adverse events (Table 21). Events related to the primary disease, including wounds, infection, and lower limb ischaemia, were expected to occur in the clinical study, and none of these events resulted in a serious condition. Therefore, these adverse events were considered clinically acceptable. Since PTA is the standard procedure, a relationship between the adverse events and the device in the PTA arm was not assessed. A total of 42 procedure-related adverse events were reported in the Esprit BTK arm and 32 in the PTA arm, with no substantial difference in incidence between the two arms (Table 22).

Table 21. Study site-reported device-related adverse events through 1 year

System organ class (SOC) Preferred term (PT)	Esprit BTK	
	Number of events	Number of subjects (N = 173)
All device-related adverse events	13	6.4% (11/173)
Injury, poisoning and procedural complications	4	1.7% (3/173)
Skin wound	2	0.6% (1/173)
Wound complication	2	1.2% (2/173)
Musculoskeletal and connective tissue disorders	2	1.7% (3/173)
Pain in extremity	2	1.7% (3/173)
Surgical and medical procedures	1	0.6% (1/173)
Vascular stent insertion	1	0.6% (1/173)
Vascular disorders	6	3.5% (6/173)
Arterial occlusive disease	3	1.7% (3/173)
Arterial thrombosis limb	1	0.6% (1/173)
Peripheral embolism	1	0.6% (1/173)
Peripheral ischaemia	1	0.6% (1/173)

Table 22. Study site-reported procedure-related adverse events through 1 year

	Overall		Esprit BTK		PTA	
System organ class (SOC) Preferred term (PT)	**No. of events**	**No. of subjects (N = 261)**	**No. of events**	**No. of subjects (N = 173)**	**No. of events**	**No. of subjects (N = 88)**
All procedure-related adverse events	74	22.6% (59/261)	42	20.2% (35/173)	32	27.3% (24/88)
Cardiac disorders	1	0.4% (1/261)	0	0.0% (0/173)	1	1.1% (1/88)
Cardiac failure congestive	1	0.4% (1/261)	0	0.0% (0/173)	1	1.1% (1/88)
Gastrointestinal disorders	1	0.4% (1/261)	1	0.6% (1/173)	0	0.0% (0/88)
Small intestinal obstruction	1	0.4% (1/261)	1	0.6% (1/173)	0	0.0% (0/88)
General disorders and administration site conditions	3	1.1% (3/261)	3	1.7% (3/173)	0	0.0% (0/88)
Oedema peripheral	3	1.1% (3/261)	3	1.7% (3/173)	0	0.0% (0/88)
Infections and infestations	1	0.4% (1/261)	1	0.6% (1/173)	0	0.0% (0/88)
Incision site abscess	1	0.4% (1/261)	1	0.6% (1/173)	0	0.0% (0/88)
Injury, poisoning and procedural complications	27	8.8% (23/261)	16	6.9% (12/173)	11	12.5% (11/88)
Arterial restenosis	10	3.8% (10/261)	3	1.7% (3/173)	7	8.0% (7/88)
Incision site haematoma	1	0.4% (1/261)	1	0.6% (1/173)	0	0.0% (0/88)
Incision site haemorrhage	1	0.4% (1/261)	1	0.6% (1/173)	0	0.0% (0/88)
Open wound	1	0.4% (1/261)	0	0.0% (0/173)	1	1.1% (1/88)
Post procedural haematoma	1	0.4% (1/261)	1	0.6% (1/173)	0	0.0% (0/88)
Skin wound	3	0.8% (2/261)	2	0.6% (1/173)	1	1.1% (1/88)
Vascular access complication	4	1.5% (4/261)	4	2.3% (4/173)	0	0.0% (0/88)
Wound complication	6	1.9% (5/261)	4	1.7% (3/173)	2	2.3% (2/88)
Investigations	1	0.4% (1/261)	0	0.0% (0/173)	1	1.1% (1/88)
Anticoagulation drug level below therapeutic	1	0.4% (1/261)	0	0.0% (0/173)	1	1.1% (1/88)
Musculoskeletal and connective tissue disorders	9	3.1% (8/261)	3	1.2% (2/173)	6	6.8% (6/88)
Compartment syndrome	1	0.4% (1/261)	0	0.0% (0/173)	1	1.1% (1/88)
Pain in extremity	8	2.7% (7/261)	3	1.2% (2/173)	5	5.7% (5/88)
Nervous system disorders	1	0.4% (1/261)	0	0.0% (0/173)	1	1.1% (1/88)
Hypoaesthesia	1	0.4% (1/261)	0	0.0% (0/173)	1	1.1% (1/88)
Renal and urinary disorders	2	0.8% (2/261)	1	0.6% (1/173)	1	1.1% (1/88)
Renal failure	2	0.8% (2/261)	1	0.6% (1/173)	1	1.1% (1/88)
Skin and subcutaneous tissue disorders	1	0.4% (1/261)	1	0.6% (1/173)	0	0.0% (0/88)
Rash	1	0.4% (1/261)	1	0.6% (1/173)	0	0.0% (0/88)
Surgical and medical procedures	3	1.1% (3/261)	1	0.6% (1/173)	2	2.3% (2/88)
Peripheral revascularisation	2	0.8% (2/261)	0	0.0% (0/173)	2	2.3% (2/88)
Vascular stent insertion	1	0.4% (1/261)	1	0.6% (1/173)	0	0.0% (0/88)
Vascular disorders	24	8.8% (23/261)	15	8.7% (15/173)	9	9.1% (8/88)
Arterial occlusive disease	3	1.1% (3/261)	3	1.7% (3/173)	0	0.0% (0/88)
Arterial rupture	3	1.1% (3/261)	3	1.7% (3/173)	0	0.0% (0/88)
Arterial thrombosis limb	1	0.4% (1/261)	1	0.6% (1/173)	0	0.0% (0/88)
Artery dissection	1	0.4% (1/261)	1	0.6% (1/173)	0	0.0% (0/88)
Haematoma	2	0.8% (2/261)	2	1.2% (2/173)	0	0.0% (0/88)
Haemorrhage	2	0.8% (2/261)	1	0.6% (1/173)	1	1.1% (1/88)
Iliac artery stenosis	1	0.4% (1/261)	0	0.0% (0/173)	1	1.1% (1/88)
Intermittent claudication	1	0.4% (1/261)	0	0.0% (0/173)	1	1.1% (1/88)
Peripheral arterial occlusive disease	1	0.4% (1/261)	1	0.6% (1/173)	0	0.0% (0/88)
Peripheral artery dissection	8	2.7% (7/261)	2	1.2% (2/173)	6	5.7% (5/88)
Angiospasm	1	0.4% (1/261)	1	0.6% (1/173)	0	0.0% (0/88)

v) Device failures and malfunctions

A total of 113 events of device failures or malfunctions were reported through 1-year follow-up. Of these, 99 were events in which the temperature monitor attached to the back of the outer box of the Esprit BTK System displayed a status other than "Use." Due to its characteristics, the Esprit BTK System is required to be stored at ≤25°C, and these events occurred prior to its use in subjects. The remaining 14 events (e.g., difficulty in insertion, catheter advancement, and removal) were reported during the procedure, which led to no adverse events.

6.A.(2) LIFE-BTK PK study (NCT No. NCT05208905, study period [redacted])

The LIFE-BTK PK study was conducted at 5 study sites in the US, Taiwan, and Australia to evaluate the pharmacokinetics of everolimus after implantation of the Esprit BTK System.

Table 23 presents an outline of the LIFE-BTK PK study.

Table 23. Outline of the LIFE-BTK PK study

Objective	To evaluate the pharmacokinetics of everolimus released from the scaffold when the Esprit BTK System is used in patients with CLTI due to infrapopliteal lesions
Sample size	9 subjects
Investigational device	Esprit BTK System
Observation period	Baseline, peri-procedure (immediately after first scaffold implantation and subsequently every 15 minutes), 0 minutes (immediately after last scaffold implantation), 10, and 30 minutes, 1, 2, 4, 6, 12, and 24 hours (1 day), and 2, 3, 4, 5, 7, 14, 30, and 60 days
Follow-up period	Up to 5 years post-procedure

Nine subjects received multiple Esprit BTK scaffolds. To evaluate the pharmacokinetics at higher doses, the maximum dose of everolimus was set at [redacted] μg. The number of scaffolds implanted per subject was [redacted] ± [redacted] ([redacted]-[redacted]) and the total length of scaffolds implanted per subject was [redacted] ± [redacted] mm ([redacted]-[redacted] mm). Since it is anticipated in clinical practice that drug-coated balloons may be used to treat inflow vessels or non-target lesions during the same procedure as implantation of the Esprit BTK System, this study enrolled 4 subjects who received paclitaxel-coated balloons to treat the inflow vessels or non-target lesions and 5 subjects who did not receive paclitaxel-coated balloons.

Blood was withdrawn at baseline, peri-procedure (immediately after first scaffold implantation and subsequently every 15 minutes), 0 (immediately after last scaffold implantation), 10, and 30 minutes, and 1, 2, 4, 6, 12, and 24 hours, and 2, 3, 4, 5, 7, 14, 30, and 60 days.

The maximum blood concentration (C_{max}) was 9.6 to 50.5 ng/mL (mean, 21.3 ng/mL). The time to the maximum blood concentration (t_{max}) was 0.25 to 0.817 hours (mean, 0.328 hours). The AUC_{0-24} was 97 to 337 h.ng/mL (mean, 192.3 h.ng/mL) with AUC_t of 243 to 1,100 h.ng/mL (mean, 568.2 h.ng/mL) and $AUC_{0-\infty}$ of 262 to 1,151 h.ng/mL (mean, 612.3 h.ng/mL). The blood half-life ($t_{1/2}$) was 65.6 to 211.2 hours (mean, 109.2 hours). A stratified analysis based on the use of paclitaxel-coated balloons to treat the inflow vessels or non-target lesions showed no differences in the pharmacokinetic parameters between the arms (Table 24).

Table 24. Pharmacokinetics of everolimus in whole blood in subjects treated with the Esprit BTK System

	Dose of everolimus (μg)	**C_{max} (ng/mL)**	**t_{max} (h)**	**AUC_{0-24} (h.ng/mL)**	**AUC_t (h.ng/mL)**	**$AUC_{0-\infty}$ (h.ng/mL)**	**$t_{1/2}$ (h)**
All subjects (N = 9)	1,820.9 (243.6)	21.3 (12.7)	0.328 (0.28)	192.3 (79.2)	586.2 (285.3)	612.3 (291.6)	109.2 (45.3)
DCB (N = 4)	1,757.8 (303.4)	24.9 (17.5)	0.204 (0.167)	196.3 (104.7)	604.0 (357.1)	636.0 (367.3)	106.1 (70.4)
Non-DCB (N = 5)	1,871.4 (206.1)	18.4 (8.4)	0.427 (0.329)	189.2 (65.5)	572.0 (258.1)	593.4 (260.5)	111.7 (18.9)

DCB = Drug-coated balloon, C_{max} = Maximum blood concentration, t_{max} = Time to maximum blood concentration, AUC_{0-24} = Area under the blood everolimus concentration curve (AUC) from time 0 to 24 hours after scaffold implantation, AUC_t = AUC from time 0 to the last measurable everolimus concentration time point t, $AUC_{0-\infty}$ = AUC from time 0 to time extrapolated to infinity, $t_{1/2}$ = Elimination half-life
Note: The figures in parentheses are standard deviations.

The results of this PK study were compared with those of a PK study conducted in the US using Absorb BVS, a product that differs from Absorb only in the delivery system. The data of Absorb BVS was submitted for the clinical evaluation of Absorb. The comparison showed the equivalence of the pharmacokinetic parameters adjusted for the dose of everolimus between the 2 studies.

In clinical use of everolimus in organ transplantation and oncology, the duration of administration is relatively long, typically ranging from several weeks to several months. A report describes that the C_{max} stabilized at 114 ± 36 ng/mL at maximum after oral administration of everolimus to patients with renal transplant, with a satisfactory safety and tolerability profile.[12] The C_{max} in the LIFE-BTK PK study was lower than this level and acutely decreased, suggesting the limited systemic exposure to everolimus during the Esprit BTK therapy.

The adverse events reported in the LIFE-BTK PK study were related to concurrent diseases or the progression of the primary disease. No subject experienced unknown adverse events. The systemic exposure to everolimus in the pharmacokinetic study was limited and transient, and within the ranges in the previous PK studies of Absorb and "XIENCE Alpine Drug Eluting Stent," suggesting the satisfactory safety and tolerability profile of the Esprit BTK System.

6.B Outline of the review conducted by PMDA

6.B.(1) Extrapolability of the LIFE-BTK study to Japanese population

The applicant's explanation:

The Esprit BTK System is a scaffold that locally releases a cytostatic drug to prevent restenosis of treated lesions. Given that the drug is delivered directly to the target site, ethnic differences in its preventive effect on restenosis are considered unlikely. Randomized clinical studies in Europe, the US, Japan, and China demonstrated similar therapeutic efficacy results of Absorb in coronary lesions. The 2016 AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease[13] in the US and the Guideline for Management of Peripheral Arterial Occlusive Diseases (2022 revised version)[4] in Japan are used as the guidelines for CLTI treatment. Both guidelines classify revascularization as Class I recommendation. In both countries, PTA was the only device approved for endovascular intervention of infrapopliteal lesions at the time of the LIFE-BTK study. Therefore, no substantial differences in the medical environment between the 2 countries were considered.

PMDA's view:

The guidelines state that, in Japan, approximately 70% to 80% of patients with CLTI have diabetes mellitus and 50% are on dialysis, both of which are higher proportions than those in Europe and the US, and that vascular lesions in patients with diabetes mellitus or on dialysis are often multi-segmental or calcified and tend to involve severe disease extending from the infrapopliteal arteries to the pedal arteries.[4]

The subjects enrolled in the LIFE-BTK study were not on dialysis. The disease characteristics (Table 6) and risk factors (Table 7) did not substantially differ between the subjects in the LIFE-BTK study and Japanese patients with CLTI.[1] Wound, Ischaemia, and foot Infection (WIfI) classification system, a comprehensive limb severity classification system recommended in the guidelines,[4] was not used in the LIFE-BTK study. However, tissue loss, ischaemia, and foot infection, which are elements comprising this classification system, were assessed, confirming that the LIFE-BTK study included subjects with similar clinical symptoms to those of Japanese patients with CLTI. Taken together with the applicant's explanation, the impact of differences in ethnicity and the medical environment on the results of the LIFE-BTK study was acceptable.

For the lesion characteristics, subjects without calcification accounted for 99.6% (260 of 261 subjects) and subjects with moderate calcification accounted for 0.4% (1 of 261 subjects). Almost all enrolled subjects had no or mildly calcified lesions (as adjudicated by the core laboratory). The mean target lesion length was approximately 4 cm in the LIFE-BTK study, whereas it has been reported to be approximately 20 cm in Japanese patients with CLTI who were not on dialysis,[14] indicating that lesion length in the LIFE-BTK study was shorter compared with real-world characteristics of CLTI in Japan. Although the severity of calcification and the length of lesions in the LIFE-BTK study cannot necessarily be regarded as reflecting the real-world clinical setting in Japan, the results of the LIFE-BTK study can be extrapolated to the Japanese population within the scope of the patient population studied. Taking into consideration the comments from the Expert Discussion, eligible patients in whom the efficacy and safety of the Esprit BTK System can be ensured must be selected in the post-marketing setting.[d]

6.B.(2) Justification for the design of the LIFE-BTK study

6.B.(2).(a) Revision of the primary efficacy endpoint during the study

The applicant's explanation:

Originally, the primary efficacy endpoint was defined as "limb salvage and primary patency (freedom from major amputation in the index limb, 100% total occlusion of the target vessel, and CD-TLR) at 6 months," and the definition of primary patency did not include freedom from binary restenosis of the target lesion. However, a blinded analysis of the primary endpoint in the first approximately 100 subjects enrolled showed that the event-free rate was higher than expected. Accordingly, binary restenosis of the target lesion (assessed by peak systolic velocity ratio [PSVR] using duplex ultrasound [DUS]) was added to the definition of primary patency, and the timepoint of the primary endpoint assessment was changed from 6 months to 1 year. The primary endpoint was revised to "limb salvage and primary patency (freedom from major amputation in the index limb, 100% total occlusion of the target vessel, binary restenosis of the target lesion, and CD-TLR) at 1 year" (the underlines denote changes). In association with these changes to the definition and timepoint of the primary endpoint, the true values in both arms were changed from 85% to 75% in the Esprit BTK arm and from 65% to 55% in the PTA arm, and the planned sample size was increased from 225 to 260 in order to avoid a type II error. The justification for changing the definition and timepoint of the assessment is shown below:

- PSVR as measured by DUS is generally used to assess restenosis in the treatment of femoral arterial lesions. This parameter indicates the need for future revascularization and therefore is of certain clinical significance. In the treatment of infrapopliteal lesions, PSVR-based assessment of restenosis is not common in clinical practice because measurement of long lesions in small vessels is difficult. However, it is not uncommon to use this parameter in clinical studies.[15]
- The timepoint of the primary endpoint assessment was changed from 6 months to 1 year because, in addition to the expectation of an increased number of events, findings from the previous clinical studies of endovascular intervention devices for the treatment of the infrapopliteal artery[16,17] suggested that the durability of the therapeutic efficacy might not be adequately demonstrated at 6 months post-procedure.

[d] Corrected after the deliberation by the Committee on Medical Devices and *In-vitro* Diagnostics (Note: The text herein has been corrected in accordance with the errata sheet of the Japanese review report.)

PMDA concluded that the applicant's explanations were acceptable because the changes to the primary efficacy endpoint (addition of the endpoint parameter and sample size, as well as the extension of the evaluation period) made in the course of the LIFE-BTK study were intended to enable a more accurate evaluation of the efficacy of the Esprit BTK System, although there are technical limitations to PSVR measurement in infrapopliteal lesions.

6.B.(2).(b) Justification for the endpoints

For the following reasons, PMDA concluded that the efficacy and safety endpoints in the LIFE-BTK study were acceptable for evaluation of the effect of revascularization in the treatment of CLTI: The primary efficacy endpoint components included the performance (primary patency) and therapeutic goal (limb salvage) of the Esprit BTK System; the primary safety endpoint components included peri-operative death and MALE; and the other endpoint components included acute success, evaluation of hemodynamic parameters, and wound healing (core laboratory adjudication of tissue loss healing and foot infection). The endpoints of the LIFE-BTK study, excluding WIfI classification, are consistent with those recommended in the "Endpoints for clinical evaluation of medical devices to treat chronic limb-threatening ischaemia (draft) (in Japanese),"[18] which is planned to be released. The WIfI classification system was not used in the LIFE-BTK study, which was acceptable because as described in Section "6.B.(1) Extrapolability of the LIFE-BTK study to Japanese population," the LIFE-BTK study assessed individual elements comprising the WIfI classification system.

6.B.(3) Efficacy and safety of the Esprit BTK System

6.B.(3).1) Efficacy

6.B.(3).1).(a) Efficacy outcomes of the Esprit BTK System in the LIFE-BTK study

PMDA's view:

Although only freedom from restenosis showed a significant difference between the treatment arms among the components of the primary efficacy endpoint in the LIFE-BTK study, the Esprit BTK arm tended to have more favorable point estimates than the PTA arm for freedom from total occlusion and CD-TLR, suggesting the superiority of the Esprit BTK System to PTA with regard to vascular patency in infrapopliteal lesions. However, major amputation occurred only in the Esprit BTK arm within 1 year post-procedure. Furthermore, PMDA asked the applicant to explain the reasons for the lower percentage of subject-level wound healing at 1 year and the higher incidence of new wounds in the Esprit BTK arm than in the PTA arm.

The applicant's explanation:

A detailed review of the amputation cases revealed that all of the 4 subjects with major amputation had wounds at the time of the index procedure. The major amputation cases were not related or probably not related to the device or procedure in the opinion of the study sites. CEC-adjudication also ruled out a relationship between the amputation and the procedure in all of these subjects. Of the 4 subjects, 3 subjects maintained the patency of the vascular segments treated with the Esprit BTK System, suggesting its efficacy (outcome unknown in the remaining 1 subject). All of them had severe diabetic vascular disorder, with existing ischaemic wounds remaining unhealed, and 1 of the subjects had an infection associated with severe osteomyelitis.

The clinical study enrolled patients with Rutherford-Becker category 4 or 5, and excluded patients with Rutherford-Becker category 6, which represents more serious disease with high risks of leg amputation. The incidence of major amputation (4 subjects, 2.4%) in the Esprit BTK arm was within the range (1.6%-8.8%) reported in previous clinical studies of infrapopliteal arterial interventions.[5,8,19,20] Although major amputation occurred only in the Esprit BTK arm, the LIFE-BTK study was not powered enough to analyze uncommon events such as major amputation and this can be interpreted as resulting from variability.

The LIFE-BTK study was not designed to assess wound healing and new wounds. The process of wound healing is complicated and it is difficult to identify the underlying causes of the findings. The LIFE-BTK PK study showed low blood concentrations of everolimus. In addition, animal studies demonstrated a limited distribution of everolimus to other organs. Those findings suggest that everolimus is unlikely to contribute to delayed wound healing.

PMDA's view:
The applicant explained that all of the major amputation cases were likely associated with the underlying diseases (blood flow in the foot arteries and diabetes mellitus) or the severity of wounds, and were not or probably not related to the Esprit BTK System. The applicant's explanation was acceptable. Although the proportion of subjects without wound healing or with new wounds at 1 year tended to be higher in the Esprit BTK arm, the underlying causes remain unclear, and based on the data available to date, these findings cannot be attributed to implantation of the Esprit BTK System. Since CLTI is characterized by the involvement of multiple vascular territories and multiple lesions, identification of culprit lesions is essential. It is ideal to select patients having a clear relationship between treated vessels and wounds in interventional studies particularly in infrapopliteal vascular lesions.[18] In the LIFE-BTK study, while the target lesions were to be treated with the Esprit BTK or PTA, treatment of non-target infrapopliteal lesions through standard of care was also allowed. As a result, approximately 30% of the study population underwent the treatment of non-target infrapopliteal lesions. PMDA asked the applicant to explain the possible influence of the treatment of non-target infrapopliteal lesions on the results of the LIFE-BTK study.

The applicant's explanation:
A sub-analysis of data from subjects who underwent the index procedure to treat only target lesions in the Esprit BTK study (114 subjects in the Esprit BTK arm, 55 subjects in the PTA arm) showed similar patient characteristics, risk factors, and lesion description to those in the overall study population. For the primary efficacy endpoint, the Esprit BTK arm showed more favorable results than the PTA arm, consistent with the overall study population. The results showed the superiority of the Esprit BTK System to PTA with regard to freedom from restenosis and CD-TLR among the elements comprising the primary efficacy endpoint (Table 25). Wound healing was observed in 72.7% of subjects in the Esprit BTK arm and 78.3% in the PTA arm at 1 year post-procedure, with no difference between the arms (Table 26). The mean ABI and TBI in the index limb improved in both arms at 30 days post-procedure, and the effect was sustained through 1 year post-procedure, with no difference between the arms (Tables 27 and 28).

Table 25. Primary efficacy endpoint (subjects with only target lesions treated)

Event	Overall (N = 169)	Esprit BTK (N = 114)	PTA (N = 55)	Difference [95% CI]
Primary efficacy endpoint (limb salvage and primary patency)	67.8% (97/143) [59.51%, 75.39%]	78.8% (78/99) [69.42%, 86.36%]	43.2% (19/44) [28.35%, 58.97%]	35.61% [18.43%, 50.77%]
Limb salvage (freedom from major amputation)	100.0% (143/143) [97.45%, 100.00%]	100.0% (99/99) [96.34%, 100.00%]	100.0% (44/44) [91.96%, 100.00%]	0.00% [-3.74%, 8.03%]
Freedom from total occlusion	87.4% (125/143) [80.84%, 92.37%]	90.9% (90/99) [83.44%, 95.76%]	79.5% (35/44) [64.70%, 90.20%]	11.36% [-0.45%, 26.03%]
Freedom from binary restenosis	70.6% (101/143) [62.44%, 77.94%]	78.8% (78/99) [69.42%, 86.36%]	52.3% (23/44) [36.69%, 67.54%]	26.52% [9.87%, 42.43%]
Freedom from CD-TLR	93.0% (133/143) [87.52%, 96.60%]	97.0% (96/99) [91.40%, 99.37%]	84.1% (37/44) [69.93%, 93.36%]	12.88% [3.18%, 26.48%]

Note: Clopper-Pearson exact confidence interval for the 95% confidence intervals of the percentages and Newcombe's score method for the 95% confidence intervals of the differences between the treatment arms

Table 26. Wound healing (subjects with only target lesions treated)

	Esprit BTK (N = 47, W = 68)		PTA (N = 24, W = 39)		Difference [95% CI][1]
Timing of assessment	Wound healing rate (wound-level)	Wound healing rate (subject-level)	Wound healing rate (wound-level)	Wound healing rate (subject-level)	Wound healing rate (subject-level)
Baseline	0.0% (0/68)	0.0% (0/45)	0.0% (0/39)	0.0% (0/24)	0.00% [-13.80%, 7.87%]
14 days	2.9% (2/69)	2.2% (1/45)	0.0% (0/39)	0.0% (0/24)	2.22% [-11.70%, 11.57%]
30 days	7.5% (5/67)	6.7% (3/45)	5.7% (2/35)	4.2% (1/24)	2.50% [-14.16%, 14.20%]
42 days	13.8% (8/58)	8.9% (4/45)	14.8% (4/27)	12.5% (3/24)	-3.61% [-22.88%, 10.77%]
90 days	19.6% (11/56)	11.1% (5/45)	29.6% (8/27)	20.8% (5/24)	-9.72% [-30.34%, 7.24%]
180 days	44.0% (22/50)	22.2% (10/45)	53.6% (15/28)	41.7% (10/24)	-19.44% [-41.21%, 2.76%]
1 year	72.7% (32/44)	40.0% (18/45)	78.3% (18/23)	45.8% (11/24)	-5.83% [-28.92%, 17.27%]

[1.] By Newcombe score method

Table 27. Changes in mean ABI in the index limb (subjects with only target lesions treated)

	Overall (N = 169)	Esprit BTK (N = 114)	PTA (N = 55)	Difference [95% CI][1]
Baseline [min, max]	0.89 ± 0.33 (152) [0.02, 1.88]	0.88 ± 0.34 (103) [0.02, 1.88]	0.91 ± 0.29 (49) [0.40, 1.64]	-0.02 [-0.13, 0.08]
30 days [min, max]	1.06 ± 0.25 (142) [0.33, 2.47]	1.07 ± 0.23 (96) [0.33, 1.80]	1.05 ± 0.29 (46) [0.58, 2.47]	0.02 [-0.07, 0.12]
90 days [min, max]	1.04 ± 0.22 (126) [0.30, 1.80]	1.05 ± 0.23 (89) [0.30, 1.80]	1.02 ± 0.21 (37) [0.69, 1.77]	0.02 [-0.06, 0.10]
180 days [min, max]	1.03 ± 0.29 [0.31, 2.48]	1.04 ± 0.28 (99) [0.31, 1.84]	1.02 ± 0.31 (45) [0.62, 2.48]	0.03 [-0.08, 0.13]
1 year [min, max]	1.05 ± 0.31 (132) [0.27, 1.96]	1.06 ± 0.31 (88) [0.27, 1.96]	1.01 ± 0.29 (44) [0.49, 1.92]	0.05 [-0.06, 0.16]

[1.] By normal approximation
Note: ABI values of '0' are excluded in the analysis.
Note: The figures in parentheses represent the numbers of subjects included in the analysis.

Table 28. Changes in mean TBI in the index limb (subjects with only target lesions treated)

	Overall (N = 169)	Esprit BTK (N = 114)	PTA (N = 55)	Difference [95% CI][1]
Baseline [min, max]	0.54 ± 0.33 (42) [0.01, 1.43]	0.57 ± 0.35 (27) [0.02, 1.43]	0.49 ± 0.29 (15) [0.01, 1.03]	0.08 [-0.12, 0.29]
30 days [min, max]	0.69 ± 0.27 (51) [0.15, 1.41]	0.71 ± 0.31 (28) [0.15, 1.41]	0.66 ± 0.22 (23) [0.33, 1.25]	0.04 [-0.10, 0.19]
90 days [min, max]	0.68 ± 0.29 (55) [0.15, 1.37]	0.65 ± 0.29 (32) [0.15, 1.29]	0.72 ± 0.29 (23) [0.29, 1.37]	-0.07 [-0.23, 0.09]
180 days [min, max]	0.58 ± 0.26 (58) [0.11, 1.49]	0.60 ± 0.27 (32) [0.11, 1.10]	0.56 ± 0.26 (26) [0.16, 1.49]	0.04 [-0.10, 0.18]
1 year [min, max]	0.65 ± 0.23 (56) [0.15, 1.20]	0.69 ± 0.25 (33) [0.24, 1.20]	0.59 ± 0.21 (23) [0.15, 1.00]	0.10 [-0.02, 0.22]

[1] By normal approximation
Note: TBI values of '0' are excluded in the analysis.
Note: The figures in parentheses represent the numbers of subjects included in the analysis.

PMDA's view on the efficacy of the Esprit BTK System demonstrated in the Esprit BTK study:
The primary efficacy endpoint was achieved, and comparable results to those in the overall population were also observed in the subgroup of subjects treated for target lesions only, suggesting that the clinical performance of the Esprit BTK System was demonstrated. Although major amputation occurred only in the Esprit BTK arm in the overall study population, no such events were observed in the subgroup treated for target lesions only, suggesting a clinical significance of the Esprit BTK System in maintaining patency of the target lesions to a certain degree. The Esprit BTK study failed to show the superiority of the Esprit BTK System to PTA with regard to freedom from major amputation or improvement in clinical symptoms (wound healing and hemodynamics). However, CLTI is a complicated disease in which many factors, including systemic risks, lower limb severity, and anatomical complication of vascular lesions, are involved. The applicant explained that the Esprit BTK study was not designed to show the superiority of the Esprit BTK System with regard to these clinical outcomes. PMDA concluded that the applicant's explanation was acceptable.

The Olive Registry[1] has reported that approximately 80% of Japanese patients with CLTI have infrapopliteal lesions and that PTA, which is widely performed in Japan as an endovascular intervention for such lesions, provides only very limited long-term vascular patency.[2] Not only restenosis but also CD-TLR were significantly reduced particularly in the subgroup of subjects treated with the Esprit BTK System for target lesions only (Table 25). These results suggest that scaffold implantation physically maintained the patency of the infrapopliteal arteries, which most likely reduced the need for future reintervention and therefore is of clinical significance. PMDA concluded that the efficacy of the Esprit BTK System was demonstrated in the patient population of the Esprit BTK study.

6.B.(3).1).(b) Efficacy of the Esprit BTK System in calcified lesions

As described in Section "6.(B).(1) Extrapolability of the LIFE-BTK study to Japanese population," it is important to clarify the severity of calcification in lesions evaluated in the LIFE-BTK study in order to discuss the eligibility of lesions for the Esprit BTK System in Japan based on the results of the foreign clinical study.

The LIFE-BTK study excluded "lesions with severe calcification, in which there was a high likelihood that successful pre-dilatation could not be achieved." Review of lesion characteristics in the enrolled subjects showed a discrepancy in the assessment of calcification severity between the core laboratory

and study sites (Table 8). According to the core laboratory, almost all subjects were classified as having no or mild calcification, with only 1 subject classified as having moderate calcification in the Esprit BTK arm, whereas study site assessments classified 27.7% as moderate and 3.0% as severe. PMDA asked the applicant to provide the definitions of calcification used by the core laboratory and the study sites, and representative imaging data for each severity grade as objective information, as well as to explain the severity of calcification in the enrolled subjects together with their therapeutic outcomes.

The applicant's explanation:
The primary objective of the core laboratory adjudication in the LIFE-BTK study was not to assess calcification but to quantify lesion size, which requires digital subtraction angiography (DSA) images. To assess calcification in the peripheral arteries based only on angiographic data, non-contrast and contrast images taken at different angles are required. However, the protocol did not require all images to be provided to the core laboratory. For this reason, the core laboratory mainly reviewed DSA images. On the other hand, the study sites comprehensively assessed calcification based not only on DSA data, but also on standard angiographic data, and other information. Therefore, calcification assessments by the study sites are more reliable than those by the core laboratory.

In the LIFE-BTK study, the use of intravascular ultrasound (IVUS) or OCT was permitted. Post-hoc quantification of calcification (calcification angle determination) performed by the core laboratory using IVUS or OCT revealed calcification in 31 of 62 lesions (50%) in total; 22 of 37 lesions based on IVUS data and 9 of 25 lesions based on OCT data. The lesions assessed by IVUS or OCT accounted for 23% of a total of 271 lesions. Although they do not necessarily represent all lesions, this finding does not support the claim that no calcified lesions were treated in the LIFE-BTK study.

The primary efficacy endpoint (a composite of limb salvage and primary patency through 1 year post-procedure) in subjects with calcified lesions was compared with that in subjects without calcified lesions in the LIFE-BTK study (Table 29). The analysis sets used for the comparisons are as shown below. IVUS or OCT was performed at the investigator's discretion. OCT data were from almost a single study site.

- Subjects with calcification assessment by the study sites (149 subjects in the Esprit BTK arm, 71 subjects in the PTA arm)
- Subjects with post-hoc intravascular image analysis (IVUS or OCT) by the core laboratory (33 subjects in the Esprit BTK arm, 18 subjects in the PTA arm)
  - Of these, subjects in whom IVUS image analysis was performed (18 subjects in the Esprit BTK arm, 10 subjects in the PTA arm)
  - Of these, subjects in whom OCT image analysis was performed (15 subjects in the Esprit BTK arm, 8 subjects in the PTA arm)

In subjects with calcification assessment by the study sites, the primary efficacy endpoint rate in the Esprit BTK arm was 70.0% (28 of 40 subjects) in subjects with moderately or severely calcified lesions and 76.1% (83 of 109 subjects) in subjects without calcified lesions, being slightly lower in the calcified group. Similar results were observed in the PTA arm.

On the other hand, post-hoc comparisons of the primary efficacy endpoint by the core laboratory between subjects with calcified lesions as assessed by intravascular image analysis (IVUS or OCT) and subjects without calcified lesions showed similar results between the subgroups; 64.7% (11 of 17 subjects) in the calcified subgroup and 68.8% (11 of 16 subjects) in the non-calcified subgroup. Interpretation of the results in the PTA arm was difficult because intravascular imaging was performed only in 18 subjects.

A comparison of the results in calcified lesions between the Esprit BTK arm and the PTA arm showed no tendency for inferior outcomes in the Esprit BTK arm compared with the PTA arm. The results in non-calcified lesions also tended to be in favor of the Esprit BTK arm rather than the PTA arm.

Table 29. Primary efficacy endpoint results in subjects with and without calcification in the target lesion

		Treatment arm	Overall	With calcified lesions	Without calcified lesions
Assessment by study site		Esprit BTK	74.5% (111/149) [66.7%, 81.3%]	70.0% (28/40) [53.5%, 83.4%]	76.1% (83/109) [67.0%, 78.6%]
		PTA	43.7% (31/71) [31.9%, 56.0%]	36.4% (8/22) [17.2%, 59.3%]	46.9% (23/49) [32.5%, 61.7%]
Image analysis (post-hoc) by the core laboratory	Intravascular imaging (IVUS or OCT)	Esprit BTK	66.7% (22/33) [48.2%, 82.0%]	64.7% (11/17) [38.3%, 85.8%]	68.8% (11/16) [41.3%, 89.0%]
		PTA	38.9% (7/18) [17.3%, 64.3%]	50.0% (3/6) [11.8%, 88.2%]	33.3% (4/12) [9.9%, 65.1%]

PMDA's view on the target patient population for the Esprit BTK based on the calcification assessments: Ideally, the LIFE-BTK study should have been conducted using a protocol that could ensure objective assessment of calcification. However, the protocol of the LIFE-BTK study did not require the core laboratory to assess calcification in target lesions or the severity using objective measures or predefined definition. The applicant explained that the results of calcification assessments by the core laboratory during the LIFE-BTK study might not be appropriate. The applicant's explanation may be acceptable under the circumstances.

The results of the post-hoc IVUS and OCT image analyses by the core laboratory demonstrate that the LIFE-BTK study included some multi-segmental calcified lesions with a calcification angle of >180°. The applicant's explanation that the LIFE-BTK study included a certain number of subjects with calcified lesions was acceptable. The results of the primary efficacy endpoint did not tend to be inferior in the Esprit BTK arm to the PTA arm in the subgroup of subjects "with calcified lesions" as determined by the study site or through the post-hoc review by the core laboratory. Therefore, the superiority of the Esprit BTK System to PTA was not compromised in calcified lesions. On the basis of the results of the LIFE-BTK study and taking into account the comments from the Expert Discussion, calcified lesions could be included in the indication for the Esprit BTK System.

Since the protocol of the LIFE-BTK study did not specify diagnostic imaging modalities or criteria for assessing the severity of calcification, it is difficult to clearly determine the severity of calcification in the target lesions. Therefore, no specific criteria for calcification severity has been included in the Intended Use or Indication section. Since the LIFE-BTK study excluded "severe calcification, in which there was a high likelihood that successful pre-dilatation could not be achieved," pre-dilatation, which

is essential for implantation of the Esprit BTK System, has been specified in the directions for use and assessment of the effect of pre-dilatation and the detailed conditions of lesions has been specified in the guidelines for proper use. In post-marketing surveillance, information on the relationship between calcification severity and clinical outcomes of the Esprit BTK System in each lesion should be collected by requiring, in principle, acquisition of intravascular imaging such as IVUS or optical frequency domain imaging (OFDI), and the guidelines for proper use should be revised as necessary to ensure the efficacy and safety of the Esprit BTK System in Japan.

6.B.(3).2 Safety

PMDA's view:

On the basis of the following findings, the safety of the Esprit BTK System is clinically acceptable.

- The Esprit BTK study demonstrates the non-inferiority of the Esprit BTK System to PTA with regard to the primary safety endpoint.
- Of deaths in 17 subjects reported through 1-year follow-up, only death in 1 subject in the Esprit BTK arm was related to the index procedure. However, the event was associated with exacerbation of lung disease. The death was unlikely to have directly resulted from implantation of the Esprit BTK System.
- A total of 15 events of total occlusions were reported as adverse events in 13 subjects who received the Esprit BTK System, including 9 events originating from the inflow vessel and 6 events involving infrapopliteal lesions alone. A relationship with the Esprit BTK System was ruled out for all of the events. Similar findings were observed for CD-TLR and restenosis events. To date, no loss of patency due to thrombosis has been confirmed to be directly related to implantation of the Esprit BTK System.
- The clinical study of Absorb suggested that [redacted] may be one of the causes of stent thrombosis, and that accurate measurement of the reference vessel diameter, selection of an appropriate stent size, and proper post-dilatation are important.[21] The Esprit BTK System is [redacted] than Absorb, and measures to reduce risks associated with the implantation method used with Absorb have been continuously taken. As a result, although total occlusions due to thrombosis occurred in 4 subjects through 1 year post-procedure in the LIFE-BTK study, none of the events had a clear causal relationship with the Esprit BTK System.
- Since neither unexpected device-related adverse events nor adverse events resulting in a serious outcome occurred, new risks of concern associated with the Esprit BTK System appear to be limited. There was no procedure-related adverse event whose incidence substantially differed between the Esprit BTK arm and the PTA arm. In addition, in the Esprit BTK arm, adverse events were generally infrequent other than vascular disorders or wounds related to primary diseases.
- No adverse events associated with device failures or malfunctions occurred.
- The LIFE-BTK PK study, in which everolimus was administered at a total amount of 1,397 to 2,074 μg (mean, 1,821 μg) per subject, verified the safety of everolimus at higher doses than the total maximum dose of the Esprit BTK System (scaffold length, 170 mm; total everolimus dose 1,790 μg).

6.B.(3).3 Long-term outcomes

The applicant's explanation:

The composite efficacy endpoint rate (limb salvage and primary patency) at 2 years post-procedure in the ITT population was 61.5% (75 of 122 subjects) in the Esprit BTK arm and 32.8% (21 of 64 subjects) in the PTA arm (Table 30), indicating a persistent superiority of the Esprit BTK System to PTA.

In the AT population, the primary safety endpoint rate at 1 year (freedom from peri-operative death and MALE at 1 year) was 94.2% (145 of 154 subjects) in the Esprit BTK arm and 100.0% (82 of 82 subjects) in the PTA arm, and the primary safety endpoint rate at 2 years (freedom from peri-operative death and MALE at 2 years) was 90.4% (123 of 136 subjects) in the Esprit BTK arm and 95.9% (70 of 73 subjects) in the PTA arm, being comparable in both arms (Table 31).

Table 30. Results of efficacy endpoint and each component at 2 years (ITT)

Event	Overall (N = 261)	Esprit BTK (N = 173)	PTA (N = 88)	Difference [95% CI][1]
Efficacy endpoint (2 years) (limb salvage and primary patency)	51.6% (96/186)	61.5% (75/122)	32.8% (21/64)	28.66% [13.59%, 41.76%]
Limb salvage (freedom from major amputation)	94.6% (176/186)	93.4% (114/122)	96.9% (62/64)	-3.43% [-9.70%, 4.79%]
Freedom from 100% total occlusion	79.6% (148/186)	81.1% (99/122)	76.6% (49/64)	4.59% [-7.12%, 17.71%]
Freedom from binary restenosis	57.0% (106/186)	64.8% (79/122)	42.2% (27/64)	22.57% [7.52%, 36.37%]
Freedom from CD-TLR	84.4% (157/186)	88.5% (108/122)	76.6% (49/64)	11.96% [0.89%, 24.50%]

[1.] By Newcombe score method

Table 31. Results of safety endpoint and each component at 1 and 2 years (AT)

Event	Overall (N = 260)	Esprit BTK (N = 170)	PTA (N = 90)	Difference [95% CI][1]
Safety endpoint (1 year)	96.2% (227/236)	94.2% (145/154)	100.0% (82/82)	-5.84% [-10.73%, -0.60%]
Freedom from MALE at 1 year	97.0% (229/236)	95.5% (147/154)	100.0% (82/82)	-4.55% [-9.08%, 0.50%]
Freedom from major amputation	98.3% (232/236)	97.4% (150/154)	100.0% (82/82)	-2.60% [-6.49%, 2.15%]
Freedom from major re-intervention on the index limb[2]	98.7% (233/236)	98.1% (151/154)	100.0% (82/82)	-1.95% [-5.57%, 2.71%]
Freedom from peri-operative (30 days) death	99.2% (234/236)	98.7% (152/154)	100.0% (82/82)	-1.30% [-4.61%, 3.27%]
Safety endpoint (2 years)	92.3% (193/209)	90.4% (123/136)	95.9% (70/73)	-5.45% [-12.13%, 2.81%]
Freedom from MALE at 2 years	93.3% (195/209)	91.9% (125/136)	95.9% (70/73)	-3.98% [-10.39%, 4.11%]
Freedom from major amputation	95.2% (199/209)	94.1% (128/136)	97.3% (71/73)	-3.14% [-8.80%, 4.16%]
Freedom from major re-intervention on the index limb[2]	97.6% (204/209)	97.1% (132/136)	98.6% (72/73)	-1.57% [-6.09%, 4.68%]
Freedom from peri-operative (30 days) death	99.0% (207/209)	98.5% (134/136)	100.0% (73/73)	-1.47% [-5.20%, 3.64%]

[1.] By Newcombe score method
[2.] New bypass surgery, bypass revision by jump graft/graft interposition, thrombectomy, thrombolysis, or intervention

For endothelialization after implantation of the Esprit BTK System, OCT observations in the clinical study of Absorb in coronary arteries have confirmed that the struts were almost completely covered with tissue at 6 months post-procedure. In this clinical study, treatment of moderately calcified lesions was allowed. However, the struts were almost completely covered with tissue even in these calcified lesions at 6 months post-procedure,[e] suggesting that any delay in coverage in calcified lesions is unlikely to be

[e] In this study, 18.2% (8 of 44) of subjects had moderate or severe calcification. Nevertheless, the strut coverage rate was 98% at 6 months post-procedure.

clinically significant. The Esprit BTK System, which [redacted], is expected to provide early strut coverage.[22]

A case report has described distal embolism potentially associated with late scaffold fracture of Absorb.[23] However, this case involved additional implantation of a scaffold in the proximal segment to treat dissection that occurred after implantation of a drug-eluting stent, and therefore did not follow the recommended method of use specified by Abbott.

In the OCT assessments conducted in some subjects in the LIFE-BTK study, no data regarding early coverage in the infrapopliteal arteries are available. However, in the LIFE-BTK study, neither scaffold thrombosis nor distal embolism related to the Esprit BTK System was reported.[f]

PMDA's view:
The superiority of the Esprit BTK System to PTA with regard to freedom from restenosis and CD-TLR at 1 year post-procedure was maintained at 2 years post-procedure, and the long-term efficacy outcomes of the Esprit BTK System are acceptable. A tendency toward lower event-free rates was observed in the Esprit BTK arm through 1 and 2 years post-procedure and causal assessment of each event showed no relationship between the events and the Esprit BTK System or index procedure. Therefore, the long-term safety results are considered acceptable.

Since the Esprit BTK scaffold has bioresorbable properties, there are concerns about the influence on the degradation and resorption characteristics of the scaffold when implanted in infrapopliteal lesions with high possibility of calcification, as well as the risks of thrombosis and distal embolism. However, to date, no data suggesting these concerns have been identified based on the results of the LIFE-BTK study, *in vitro* degradation characterization of Absorb (the previous generation product) and the Esprit BTK System, the course of *in vivo* endothelialization observed with Absorb, the influence of calcified lesions on endothelialization, and the incidence of distal embolism. Nevertheless, long-term follow-up data from the foreign clinical study should be reviewed over time after approval to revise the post-marketing safety measures as necessary since data only up to 2 years post-procedure are currently available. As described later in Section 7, the use-results survey may include a higher proportion of calcified lesions than that in the LIFE-BTK study. Therefore, the impact of calcified lesions on long-term outcomes should be evaluated.

6.B.(3).4) Antiplatelet therapy

Since the Esprit BTK System remains implanted for a certain period until it resorbs and may increase the risk of thrombosis, PMDA asked the applicant to explain the recommended duration of antiplatelet therapy.

The applicant's explanation:
The protocol of the LIFE-BTK study was revised during the study with regard to the recommended duration of antiplatelet therapy based on a report suggesting a higher antiplatelet effect and less

[f] Peripheral arterial embolism in 1 patient in the Esprit BTK group in the LIFE-BTK study occurred in a non-index limb.

haemorrhage risk of a P2Y12 inhibitor than aspirin[24] (Table 32). The actual use of antiplatelet agents in the LIFE-BTK study is shown in Table 33.

Table 32. DAPT recommended in the LIFE-BTK study

	Before modification	After modification
Esprit BTK	DAPT, 12 months Aspirin, 12 months to 5 years	DAPT, 12 months Aspirin or P2Y12 inhibitor, 12 months to 5 years
PTA	DAPT, 1 month Aspirin, 1 month to 5 years	DAPT, 1 month Aspirin or P2Y12 inhibitor, 1 month to 5 years
Esprit BTK with continuous anticoagulant therapy	Anticoagulant + single antiplatelet, 5 years	Anticoagulant + single antiplatelet, 5 years
PTA with continuous anticoagulant therapy	Anticoagulant + single antiplatelet, 12 months Continuous aspirin therapy beyond 12 months recommended	Anticoagulant + single antiplatelet, 12 months Continuous antiplatelet therapy beyond 12 months recommended

DAPT = Dual antiplatelet therapy

Table 33. Post-procedural antiplatelet therapy (ITT)

	Overall (N = 261)	Esprit BTK (N = 173)	PTA (N = 88)	Difference [95% CI][3]
Single antiplatelet	17.2% (45/261)	17.9% (31/173)	15.9% (14/88)	2.0% [-8.32%, 10.91%]
Aspirin	6.9% (18/261)	8.7% (15/173)	3.4% (3/88)	5.3% [-1.73%, 10.87%]
Duration of use (day)[1] [min, max]	342.1 ± 124.3 (18) [0, 393]	360.7 ± 99.2 (15) [14, 393]	249.0 ± 216.5 (3) [0, 393]	111.7 [-397.9, 621.4]
On Aspirin at 30 days[2]	88.9% (16/18)	93.3% (14/15)	66.7% (2/3)	26.7% [-9.04%, 72.89%]
On Aspirin at 180 days[2]	94.1% (16/17)	100.0% (14/14)	66.7% (2/3)	33.3% [-1.34%, 79.23%]
On Aspirin at 365 days[2]	87.5% (14/16)	100.0% (13/13)	33.3% (1/3)	66.7% [15.41%, 93.85%]
P2Y12 inhibitor	10.3% (27/261)	9.2% (16/173)	12.5% (11/88)	-3.3% [-12.45%, 4.26%]
Duration of use (day)[1] [min, max]	305.9 ± 150.3 (27) [8, 393]	285.1 ± 165.2 (16) [8, 393]	336.0 ± 127.1 (11) [62, 393]	-50.9 [-167.0, 65.2]
On P2Y12 inhibitor at 30 days[2]	96.3% (26/27)	93.8% (15/16)	100.0% (11/11)	-6.2% [-28.33%, 20.14%]
On P2Y12 inhibitor at 180 days[2]	87.0% (20/23)	84.6% (11/13)	90.0% (9/10)	-5.4% [-33.46%, 26.98%]
On P2Y12 inhibitor at 365 days[2]	87.0% (20/23)	84.6% (11/13)	90.0% (9/10)	-5.4% [-33.46%, 26.98%]
Clopidogrel	10.0% (26/261)	9.2% (16/173)	11.4% (10/88)	-2.1% [-11.12%, 5.18%]
Prasugrel	0.0% (0/261)	0.0% (0/173)	0.0% (0/88)	0.0% [-4.18%, 2.17%]
Ticagrelor	0.4% (1/261)	0.0% (0/173)	1.1% (1/88)	-1.1% [-6.16%, 1.23%]
Ticlopidine	0.0% (0/261)	0.0% (0/173)	0.0% (0/88)	0.0% [-4.18%, 2.17%]
Others	0.0% (0/261)	0.0% (0/173)	0.0% (0/88)	0.0% [-4.18%, 2.17%]
DAPT	82.4% (215/261)	81.5% (141/173)	84.1% (74/88)	-2.6% [-11.53%, 7.78%]
Aspirin and clopidogrel	76.6% (200/261)	76.9% (133/173)	76.1% (67/88)	0.7% [-9.54%, 12.13%]
Aspirin and prasugrel	0.8% (2/261)	1.2% (2/173)	0.0% (0/88)	1.2% [-3.11%, 4.12%]
Aspirin and ticagrelor	4.2% (11/261)	2.9% (5/173)	6.8% (6/88)	-3.9% [-11.38%, 1.27%]
Aspirin and ticlopidine	0.0% (0/261)	0.0% (0/173)	0.0% (0/88)	0.0% [-4.18%, 2.17%]
Aspirin and other	0.8% (2/261)	0.6% (1/173)	1.1% (1/88)	-0.6% [-5.60%, 2.23%]
Duration of use (day)[1] [min, max]	323.1 ± 124.9 (215) [1, 393]	322.0 ± 126.9 (141) [1, 393]	325.1 ± 121.7 (74) [4, 393]	-3.1 [-38.1, 32.0]
On DAPT at 30 days[2]	97.6% (207/212)	98.6% (136/138)	95.9% (71/74)	2.6% [-1.94%, 9.88%]
On DAPT at 180 days[2]	87.6% (177/202)	87.1% (115/132)	88.6% (62/70)	-1.5% [-10.19%, 9.17%]
On DAPT at 365 days[2]	78.6% (154/196)	79.7% (102/128)	76.5% (52/68)	3.2% [-8.31%, 16.06%]
No antiplatelet therapy	0.4% (1/261)	0.6% (1/173)	0.0% (0/88)	0.6% [-3.63%, 3.20%]

[1.] Duration of use was calculated by designating the day of index procedure as Day 0. When subjects were on the therapy at 1-year follow-up, the duration of use was recorded as 393 days.
[2.] To be considered on the medication at a specific time point, a minimum of 1 day of use of the specific medication during the acceptable time window of each follow-up is required.
[3.] By normal approximation for continuous variables and Newcombe score method for binary variables

To patients in Japan, dual antiplatelet therapy (DAPT) for at least 12 months after implantation of the Esprit BTK System will be recommended. In addition, cautionary information about the use of antiplatelets according to the patient's condition based on a risk-benefit balance is planned to be included in the Information on Precautions, etc.

PMDA's view:
The recommendation in the "Information on Precautions, etc." that DAPT should be administered for at least 12 months after surgery, is acceptable. Continued use of DAPT should be evaluated by the treating physician according to the patient's condition. In addition, necessary information should be collected through the post-marketing surveillance in Japan and the long-term follow-up of the LIFE-BTK study, and when any additional risks are identified, the information should be provided to healthcare professionals.

As explained in Sections 6.(B).(3).1) to 6.(B).(3).4), the LIFE-BTK study demonstrated the efficacy and safety of the Esprit BTK System. Although the analyses were post hoc, no tendency for inferior outcomes of the Esprit BTK System compared with PTA was observed in calcified lesions. However, limitations of the LIFE-BTK study design were also identified, including the lack of evaluation of the impact of superior vascular patency over PTA on the clinical outcomes and insufficient objective assessment of the severity of lesion calcification. Therefore, it is important to fully inform physicians about the patient population included in the LIFE-BTK study and the results obtained, and to ensure appropriate patient selection. In addition, the effect of calcification on the efficacy and safety of the Esprit BTK System should be continuously investigated in the post-marketing surveillance and communicated to healthcare professionals to support the selection of patients eligible for the therapy and thereby ensure the efficacy of the Esprit BTK System. Considering that the major malfunctions and adverse events of the Esprit BTK System reported overseas, as described earlier in Section 1.A.(3), are similar to those occurred in the LIFE-BTK study, no particular safety concerns have been identified at present. However, given the bioresorbable nature of the Esprit BTK System and the fact that it remains implanted for a certain period until complete resorption, long-term data of the LIFE-BTK study must be continuously reviewed to take additional risk reduction measures as necessary. PMDA concluded that the Esprit BTK System is useful in Japan, where treatment options remain limited, considering that a favorable risk–benefit balance can be ensured provided that, in addition to these measures, the measures described in "6.B.(5) Post-marketing safety measures" are appropriately implemented.

6.B.(4) Intended use or indication of the Esprit BTK System

The LIFE-BTK study demonstrated the superiority of the Esprit BTK System to PTA with regard to vascular patency, but did not evaluate its influence on the clinical outcomes, which should be clarified in the Intended Use. Considering that approximately half of patients with CLTI in Japan are on dialysis,[4] ideally, the development of the Esprit BTK System should have included patients on dialysis. However, PMDA does not rule out the applicant's plan to limit the indication of the Esprit BTK System to patients who are not on dialysis.

As described earlier in Section "6.B.(3) Efficacy and safety of the Esprit BTK System," PMDA concluded that although calcified lesions can be included in the indication for the Esprit BTK System as in the LIFE-BTK study, the severity of calcification should be specified in the guidelines for proper use so that it can be carefully assessed based on the results of the post-marketing surveillance and that the indication should be revised based on data collected.

Accordingly, PMDA concluded that the Intended Use or Indication of the Esprit BTK System should be defined as shown below.

Intended use or indication (the underline denotes a major change)
Esprit BTK Everolimus Eluting Resorbable Scaffold System is indicated for <u>improving luminal diameter</u> in infrapopliteal lesions in patients with chronic limb-threatening ischaemia (excluding patients on chronic dialysis) with a reference vessel diameter of ≥2.5 and ≤4.0 mm. The maximum total scaffolding length should be 170 mm when multiple Esprit BTK scaffolds are used.

6.B.(5) Post-marketing safety measures

6.B.(5).1) Guidelines for proper use

The Esprit BTK System will be the first drug eluting resorbable scaffold system to be introduced in Japan for the treatment of infrapopliteal lesions in patients with CLTI. On the basis of the results from the LIFE-BTK study, it is essential to appropriately select patients for whom scaffold implantation can ensure a favorable risk-benefit balance of the Esprit BTK System by maintaining the patency of the infrapopliteal artery and reducing the need for re-intervention. For the effective and safe introduction of the Esprit BTK System into Japan, therefore, PMDA considers that the following conditions should be met:

(a) Physicians and medical team members with thorough knowledge of the treatment of CLTI, as well as adequate knowledge and experience in endovascular interventions and post-procedural management of infrapopliteal arteries must appropriately select patients for whom a favorable risk-benefit balance of the Esprit BTK System can be ensured.
(b) Physicians and medical team members must have procedural knowledge and techniques to ensure the effective and safe use of the Esprit BTK System.
(c) Physicians and medical team members must have knowledge and techniques required for management of complications or adverse events associated with use of the Esprit BTK System, as well as post-procedural care (including foot care, such as wound management), and must be able to respond in a timely manner.
(d) On the basis of post-marketing therapeutic outcomes, the guidelines for proper use should be revised as necessary, or additional safety measures should be promptly implemented as appropriate.

PMDA concluded that requirement (b) is reasonable because treating physicians will learn necessary information through product training provided by the applicant (Table 34). Taking into consideration the comments from the Expert Discussion, PMDA also concluded that requirements (a) to (d) are acceptable because the guidelines for proper use (draft) (Table 35) prepared by the relevant academic societies (the Japanese Association of Cardiovascular Intervention and Therapeutics, the Japanese Society for Vascular Surgery, and the Japanese Society of Interventional Radiology) specify the use of the Esprit BTK System in medical institutions with extensive experience in multidisciplinary treatment of CLTI. These requirements should be included as Approval Condition 1.

Table 34. Outline of the training programs

- Classroom product training by Abbott Medical-certified trainers
  - Summary of product
  - Product handling
  - Directions for use and procedure (including pre-dilatation, vessel sizing, and post-dilatation, which were found important based on the experience in the LIFE-BTK study and the Absorb therapy)
  - Information on Precautions, etc. (e.g., Warnings, Contraindications, Precautions, and Important Precautions)
  - Summary of the LIFE-BTK study
  - Case study
- Each physician must attend the treatment of at least 1 patient after the classroom training.

Table 35. Guidelines for proper use (draft)

Item	Description
Use criteria	Lesions considered appropriate for implantation of the Esprit BTK System, defined as stenosis (≥70% stenosis, per visual assessment) or occlusion in infrapopliteal arteries in patients with CLTI who are not on dialysis. Lesions must meet all of the following criteria: (1) Lesions located within the proximal 2/3 of arteries distal to the distal popliteal segment (P3), with the distal end located at least10 cm away proximal to the ankle joint (proximal end of the talocrural joint fossa) (2) Vessel diameter of ≥2.5 and ≤4.0 mm by visual assessment (3) Lesion length <15 cm (4) No ≥50% stenosis distal to the target lesion with an in-line flow maintained from below the ankle to the wound. When the target lesion is in the peroneal artery, blood vessels below the ankle must be well visualized via peripheral collateral circulation. (5) Severely calcified lesions (1. bilateral calcification of 5 cm or ≥1/3 of the lesion length; 2. the presence of fluoroscopically visible calcified nodules; 3. calcification that makes balloon dilatation difficult) are excluded. (6) Lesions in which pre-dilatation is expected to achieve sufficient lumen expansion to avoid incomplete expansion or inadequate apposition of the Esprit BTK System (7) Non-bifurcated lesions that do not cross major side branches at the time of implantation Note The foreign clinical study did not evaluate the efficacy and safety of the Esprit BTK System in patients, limbs, or lesions shown below: (1) Patients on dialysis (2) Patients with hypersensitivity to poly-L-lactic acid (PLLA) (material of the Esprit BTK System), everolimus (the coated drug), and resorbable poly-DL-lactic acid (PDLLA) (polymer) (3) Limbs with extensive tissue loss (clinically defined as Rutherford category 6) or limbs in which limb salvage is not considered feasible without atypical minor amputation or skin flap transplantation (4) Lesions requiring a total scaffold length of >17 cm (5) Lesions requiring a total everolimus dose of >1790 μg (6) Severely calcified lesions (7) Lesions in bifurcation (strut dilatation or double-stenting in a side branch is not recommended) (8) Blood vessels with different diameters between proximal and distal segments (stent dilatation with ≥0.5 mm oversizing is not recommended) (9) Lesions in which no ≥50% stenosis remains in the inflow (10) Restenotic lesions following implantation of a metallic stent
Qualifications for treating physicians	Treating physicians must meet all of the following requirements: (1) Treating physicians must be physicians certified by the Japanese Association of Cardiovascular Intervention and Therapeutics, specialist physicians of the Japanese Society of IVR, or physicians specialized in endovascular intervention certified by the Japanese Society for Vascular Surgery. (2) Treating physicians must complete the training programs of the Esprit BTK System.
Qualifications for medical institutions	Medical institutions must meet all of the following requirements: (1) Medical institutions must be one of the following: a training facility or training-related facility certified by Japanese Association of Cardiovascular Intervention and Therapeutics; a training facility for IVR specialists; or a training facility certified by the Japanese Board of Cardiovascular Surgery (2) Medical institutions must have an operating room or angiography suite equipped with a DSA system. (3) Medical institutions must be capable of performing emergency operations to manage treatment-associated complications or have established arrangements with institutions capable of providing such care. (4) Medical institutions must have a multidisciplinary system for CLTI medical care, including foot care and assessment of patient's eligibility for the therapy. (5) Medical institutions must have a system that determines whether the Esprit BTK System has been implanted adequately using intravascular imaging (e.g., IVUS and OFDI).

7. Plan for Post-marketing Surveillance, etc. Stipulated in Paragraph 1 of Article 2 of Ministerial Ordinance on Good Post-marketing Study Practice for Medical Devices

7.A Summary of the data submitted

Table 36 presents a summary of the proposed use-results survey plan of the Esprit BTK System aiming to evaluate its safety and efficacy in post-marketing clinical practice.

Table 36. Use-results survey plan (draft)

Survey population	All patients with severe chronic limb-threatening ischaemia (CLTI) with infrapopliteal lesions who are eligible for the treatment with the Esprit BTK System will be enrolled in the survey in a consecutive manner. This use-results survey will enroll only patients who meet the criteria stipulated in the guidelines for proper use issued by the Japanese Association of Cardiovascular Intervention and Therapeutics (CVIT) and other relevant academic societies.
Survey period	7 years from approval date (marketing preparation, 6 months; patient registration, 1 year; follow-up, 5 years post-procedure; analysis and preparation for application, 6 months)
Planned target sample size	150 patients Rationale: This sample size allows clinical evaluation of the composite primary safety endpoint of the clinical study (freedom from peri-operative death and MALE), total occlusion of target vessels, and CD-TLR.
Key survey items	Major amputation and primary patency of target lesions (freedom from total occlusion of target vessels and CD-TLR) Freedom from peri-operative death and MALE
Survey items	1. Baseline information 2. Procedural information 3. In-hospital outcomes 4. Follow-up information At discharge: Date, medications, ABI, TBI, and adverse events At 6 months, and at 1, 2, 3, 4, and 5 years, as well as at irregular intervals Date, medications, ABI, TBI, DUS, WIfI classification, pain, Rutherford-Becker category, and adverse events 5. Malfunctions or dysfunctions of the Esprit BTK System

The applicant's explanation about the justification of the sample size of the planned use-results survey:
As in the LIFE-BTK study, the incidence of major amputation is estimated to be several percent in patients with Rutherford-Becker category 4 or 5, and it is difficult to estimate the incidence of major amputation with sufficient precision. Based on the predicted value of 95% for the primary safety endpoint rate in the LIFE-BTK study, as well as the observed incidences of total occlusion of target vessel (12.1%) and CD-TLR (8.4%), the sample size was determined to enable evaluation with a reasonable level of precision, assuming that each event occurs at a frequency comparable to or higher than that observed in the Esprit BTK arm in the LIFE-BTK study.

After the market launch, the Esprit BTK System will be introduced in a limited number of medical institutions (approximately [redacted] institutions), and all patients treated at these institutions will be enrolled in the use-results survey until the sample size reaches 150. Although the use-results survey will be conducted at selected medical institutions, once the efficacy and safety of the Esprit BTK System have been confirmed in 150 patients, the Esprit BTK System will be distributed to more medical institutions according to the criteria shown below.

[Phase 1]
When the rate of freedom from target lesion restenosis and CD-TLR through 6-month follow-up is ≥81%, the definition of the lesion conditions in the guidelines for proper use and additional risk reduction measures to ensure safety should be discussed with the relevant academic societies to allow the distribution of the Esprit BTK System to more medical institutions. When the rate of freedom from these events is 78% to 81%, the distribution of the Esprit BTK System will not be expanded. Only the medical institutions enrolled in the use-results survey are allowed to continue to use the Esprit BTK System. The survey will proceed to Phase 2.

[Phase 2]
When the event-free rate through 1-year follow-up is ≥70%, the definition of the lesion conditions in the guidelines for proper use and additional risk reduction measures to ensure safety should be discussed with the relevant academic societies to allow the distribution of the Esprit BTK System to more medical institutions.

7.B Outline of the review conducted by PMDA

PMDA's view:

Since the Esprit BTK System has never been used in Japan, a use-results survey should be conducted, and based on the data obtained, post-marketing safety measures should be implemented, including optimization of patient selection in Japan and additional measures to ensure safety. It is also necessary to assess whether the efficacy of the Esprit BTK System can be assured in the Japanese clinical setting.

The proposed sample size for the use-results survey is acceptable since it allows evaluation of the composite events of the primary safety endpoint with a level of precision comparable to that in the LIFE-BTK study, as well as evaluation of the efficacy with regard to total occlusion of target vessel and CD-TLR with a reasonable level of precision based on the incidence in the LIFE-BTK study.

Given that the Esprit BTK scaffold is intended to be implanted in blood vessels for a long period of time, that no data are available on its long-term degradation and resorption behavior in infrapopliteal arteries, and that continued evaluation of the risks of scaffold thrombosis and distal embolism associated with calcified lesions is important, the survey period of 5 years is appropriate.

The proportion of calcified lesions in the post-marketing setting is likely to be higher than that in the LIFE-BTK study, and lesion calcification is one of the major factors of poor clinical outcomes.[4] Therefore, it is reasonable to conduct the use-results survey under a framework that allows objective assessment of the severity of calcification, including requirements for participating institutions to be capable of providing IVUS or OFDI images and for such images to be objectively evaluated by a third party.

Although some calcified lesions were included in the LIFE-BTK study, the severity of calcification was not assessed appropriately. Therefore, PMDA considered it acceptable that the applicant plans to evaluate whether to expand the use of the Esprit BTK System to include medical institutions where imaging assessments using IVUS or OFDI cannot be performed, based on whether the rates of freedom from target lesion restenosis and CD-TLR exceed the predefined performance goals.

PMDA concluded that the draft use-results survey plan proposed by the applicant including the survey items was appropriate and decided to impose this as Approval Condition 2. Given that the long-term results of the foreign Esprit BTK study provide important information for determining the indication of the Esprit BTK therapy and implementing safety measures in Japan, PMDA concluded that periodic reporting of follow-up results should be imposed as Approval Condition 3.

8. Documents Relating to Information on Precautions, etc. Specified in Paragraph 1 of Article 63-2 of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices, in Relation to Notification Pursuant to the Same Paragraph of the Act

8.A Summary of the data submitted

The applicant submitted Information on Precautions, etc. (draft) as an attachment in accordance with the Notification titled "Application for Marketing Approval of Medical Devices" (PFSB Notification No. 1120-5, dated November 20, 2014).

8.B Outline of the review conducted by PMDA

On the basis of the conclusion of the Expert Discussion, as described earlier in Section "6.B. Outline of the review conducted by PMDA," PMDA concluded that there were no particular problems with the proposed Information on Precautions, etc., provided that the applicant advises necessary caution.

III. Results of Compliance Assessment Concerning the New Medical Device Application Data and Conclusion Reached by PMDA

PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The medical device application data were subjected to a document-based inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

IV. Overall Evaluation

In the review of the Esprit BTK System, PMDA's view primarily focused on (1) the efficacy and safety of the Esprit BTK System and (2) post-marketing safety measures. PMDA reached the following conclusions, taking account of deliberations at the Expert Discussion.

(1) Efficacy and safety of the Esprit BTK System

The LIFE-BTK study evaluated the efficacy and safety of the Esprit BTK System in comparison with the standard procedure PTA in patients with CLTI of Rutherford-Becker category 4 or 5 with de novo or restenotic (treated with prior PTA) infrapopliteal lesions. The primary efficacy endpoint of the LIFE-BTK study was a composite rate of limb salvage (freedom from above ankle amputation in index limb) and primary patency (freedom from 100% total occlusion of target vessel, binary restenosis, and CD-TLR) at 1 year. The composite rates were 74.5% (111 of 149 subjects) in the Esprit BTK arm and 43.7% (31 of 71 subjects) in the PTA arm, showing that the Esprit BTK arm demonstrated a significant superiority to the PTA arm ($P < 0.0001$). Of the elements comprising the primary efficacy endpoint, the rate of freedom from binary restenosis was 76.5% (114 of 149 subjects) in the Esprit BTK arm and 50.7% (36 of 71 subjects) in the PTA arm. The difference was significant, demonstrating the efficacy of the Esprit BTK System. The primary safety endpoint was "freedom from peri-operative death (within 30 days after the index procedure) and MALE (major amputation and major re-intervention on the index limb within 6 months after the index procedure)." The outcome was 96.9% (155 of 160 subjects) in the

Esprit BTK arm and 100.0% (85 of 85 subjects) in the PTA arm. The difference between the treatment arms met the predefined non-inferiority margin of -10%, showing the non-inferiority of the Esprit BTK System to PTA.

Patients eligible for the Esprit BTK System in Japan are expected to have more calcified lesions than patients in Europe or the US. The results from subjects "with calcified lesions" as determined by the study sites or core laboratory (post-hoc) revealed no tendency toward inferiority of the Esprit BTK System to PTA with regard to the primary efficacy endpoint. Therefore, PMDA concluded that the superiority of the Esprit BTK System to PTA demonstrated in the LIFE-BTK study was not compromised even in the treatment of calcified lesions and that calcified lesions could be included in the indication for the Esprit BTK System. The long-term efficacy outcomes of the Esprit BTK System are acceptable as the superiority of the Esprit BTK System to PTA was maintained at 2 years post-procedure. As for the safety, a tendency toward lower event-free rates was observed in the Esprit BTK arm through 1 and 2 years post-procedure. However, causal assessment of each event showed no relationship between the events and the Esprit BTK System or index procedure and the long-term safety results were acceptable.

Currently, no effective treatment, other than PTA with a balloon catheter, is available for the treatment of CLTI resulting from infrapopliteal arterial occlusion or stenosis, for which the Esprit BTK System is indicated, and the disease often results in repeated restenosis after the procedure and may eventually lead to serious outcomes such as leg amputation. In light of these facts, the Esprit BTK System, which was shown to be superior to PTA with a balloon catheter with regard to freedom from restenosis, etc., has high clinical usefulness. PMDA concluded that the introduction of the Esprit BTK System into Japan as a new therapeutic option for CLTI is of significance.

(2) Post-marketing safety measures

The Esprit BTK System will be the first drug eluting resorbable scaffold system to be introduced in Japan for the treatment of infrapopliteal lesions in patients with CLTI. To ensure the effective and safe introduction of the Esprit BTK System into Japan, physicians and medical team members with thorough knowledge of the treatment of CLTI, as well as adequate knowledge and experience in endovascular interventions and post-procedural management of infrapopliteal arteries should appropriately select patients for whom a favorable risk-benefit balance of the Esprit BTK System can be ensured. Given that treating physicians are responsible for managing complications or adverse events associated with use of the Esprit BTK System as well as post-procedural care (including foot care, such as wound management), PMDA concluded that treatment with the Esprit BTK System must be performed in medical institutions equipped with a well-established system capable of addressing these requirements. To this end, it is important to comply with the guidelines for proper use to be developed by the relevant academic societies. This requirement should be included as Approval Condition 1.

Since the Esprit BTK System has never been used in Japan, a use-results survey should be conducted to collect information about adverse events and procedure, or patient characteristics after introduction in Japan and based on the data obtained, post-marketing safety measures should be implemented, including optimization of patient selection in Japan and additional measures to ensure safety. The period of the

use-results survey of the Esprit BTK System should be 7 years (preparation, 6 months; patient registration, 1 year; follow-up, 5 years post-procedure; analysis and preparation for application, 6 months). This requirement should be included as Approval Condition 2. Given that the long-term results of the foreign Esprit BTK study provide important information for determining the indication of the Esprit BTK therapy and implementing safety measures in Japan, PMDA concluded that periodic reporting of follow-up results should be imposed as Approval Condition 3.

As a result of the above review, PMDA has concluded that the Esprit BTK System may be approved for the intended use as shown below.

Intended Use

Esprit BTK Everolimus Eluting Resorbable Scaffold System is indicated for improving luminal diameter in infrapopliteal lesions in patients with chronic limb-threatening ischaemia (excluding patients on chronic dialysis) with a reference vessel diameter of ≥2.5 and ≤4.0 mm. The maximum total scaffolding length should be 170 mm when multiple Esprit BTK scaffolds are used.

Approval Conditions

1. The product must be used for patients eligible for the treatment, who should be selected by physicians and medical team members with adequate knowledge and experience in the treatment of chronic limb-threatening ischaemia. Before using the product, the physicians and medical team members must have acquired sufficient skills to operate the product and various knowledge, including procedure-associated complications, and medical institutions must have a system prepared for the treatment. To fulfill these requirements, the applicant is required to take necessary measures, such as disseminating the guidelines for proper use prepared in cooperation with relevant academic societies and offering seminars.
2. The applicant is required to conduct a post-marketing surveillance involving all patients treated with the product until data from a specified number of patients have been accumulated, to submit reports on the results of longitudinal analyses of long-term outcomes to the Pharmaceuticals and Medical Devices Agency, and to take appropriate measures as necessary.
3. The applicant is required to submit reports on the results of analyses of long-term outcome data from participants in the submitted clinical studies included in the present application to the Pharmaceuticals and Medical Devices Agency, and to take appropriate measures as necessary.

The product is not classified as a biological product or a specified biological product. The product is designated as a medical device subject to a use-results survey. The use-results survey period should be 7 years.

PMDA has concluded that the present application should be subjected to deliberation by the Committee on Medical Devices and *In-vitro* Diagnostics.

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