BIBLIOS STUDY: SYNOPSIS

Title	BIBLIOS-study: Belgian-Italian prospective, single-arm, multicentre study to evaluate the efficacy and safety of BTK treatment with the Luminor-14 Paclitaxel coated Percutaneous Transluminal Angioplasty Balloon catheter of iVascular of 150 subjects with Critical Limb Ischemia
Objective	The objective of this clinical investigation is to access the safety and efficacy of the Luminor-14 DCB for the treatment of infrapopliteal lesions in 150 subjects with critical limb ischemia
Methodology	Prospective, single-arm, multicentre, physician initiated clinical study
Enrolment	150 subjects
Primary Endpoint	1. Efficacy endpoint – Freedom from MALE at 6 months Freedom from major adverse limb events (MALE) at 6 months defined as absence of above-ankle target limb amputation or major re-intervention to the target lesion(s) (i.e. new bypass graft, jump/interposition graft revision or thrombectomy/thrombolysis). 2. Safety endpoint – Freedom from MALE or POD at 30 days Freedom from major adverse limb events (MALE) at 30 days defined as absence of above-the-ankle target limb amputation or major re-intervention to the target lesion(s) (i.e. new bypass graft, jump/interposition graft revision or thrombectomy/thrombolysis) Peri-operative death (POD) at 30 days, device or procedure related or any other cause.
Secondary Endpoint	1. Target Vessel Functional Flow Assessment at 6 and 12 months Target vessel functional flow assessment at 6 and 12 months defined as the presence of blood flow using duplex ultrasound. If angiography is available within the 12-month follow-up visit window, it should be used instead of the duplex ultrasound. Evidence of no blood flow within the treated segment indicates loss of patency. 2. Freedom from CD-TLR at 6 and 12 months Freedom from clinical driven target lesion revascularization (CD-TLR) at 6 and 12 months defined as absence of any reintervention due to clinical deterioration, defined as a worsening of the patient's quality of life, reflected by the EQ5D-questionnaire, worsening of the Rutherford category with minimal 1 class or worsening of wound status 3. Amputation free survival at 6 and 12 months Amputation free survival defined as alive with freedom from any above-the-ankle target limb amputation 4. Limb salvage at 6 and 12 months Limb salvage is defined as freedom from any above-the-ankle target limb amputation at 6 and 12 months

5. Procedural success
   Procedural success is defined as restoration of at least 1 below-the-knee (BTK) artery with <30% residual stenosis in the final angiogram and outflow into the foot

6. Wound healing status
   Wound healing status is based on three parameters: the wound's diameter, the wound's depth and the % granulation tissue.

7. Wound healing time
   Wound healing time is defined as the number of days needed for the wound to heal completely after the index procedure

Inclusion criteria

1. Males or non-pregnant females ≥ 18 years of age at the time of consent. Females of childbearing potential have a negative pregnancy test <7 days before the procedure and are willing to use a reliable method of birth control for the duration of study participation. Female participants will be exempted from this requirement in case they are sterile, infertile or have been post-menopausal for at least 12 months
2. Subject has been informed of and understands the nature of the study and provides signed informed consent to participate in the study. If the subject possesses the ability to understand and provide informed consent but due to physical inability, the subject cannot sign the informed consent form. An impartial witness may sign on behalf of the subject.
3. Willing to comply with all required follow-up visits
4. Rutherford Classification 5
5. Significant degree of stenosis >70% or chronic total occlusion (CTO)
6. Infrapopliteal lesion: P3 to the ankle-joint level (not below-the-ankle (BTA)); full length lesions or tandem lesions are allowed
7. WIfI tissue loss grade 1-2 at baseline
8. WIfI foot infection grade of 0-2 at baseline
9. WIfI ischemia grade 2-3 at baseline
10. Estimated life expectancy ≥ 1 year
11. Multiple lesions can be treated if they are located in separate vessels per standard of care but only one (1) BTK vessel can be considered as the target lesion/vessel and need to be treated according the CIP guidelines
12. Target vessel should give direct or indirect run-off to the foot (clearly documented in a foot/BTA angiogram)
13. Patients with in-flow lesions can be included if the lesions are treated successfully (residual stenosis ≤30%) with the same drug coated balloon (DCB) platform, bail-out stenting with a bare-metal stent (BMS)
14. Successful pre-dilatation of the target lesion (≤30% residual stenosis)

Exclusion Criteria

1. Previous bypass graft in the target limb
2. Acute limb ischemia, defined as symptom onset during less than 14 days prior to the index procedure
3. Prior or planned above-the-ankle amputation to the target limb (this does not apply to ray amputation of ≤2 digits, simple digital amputations or ulcer debridement)
4. Previous DCB treatment in target vessel 6 months prior to index procedure
5. WIfI tissue loss grade 0 or 3 at baseline
6. WIfI foot infection grade 3 at baseline
7. WIfI ischemia grade 0-1 at baseline

8. Any systemic infection or immunocompromised state. Patients with an ascending infection/deep foot infection or abscess/white blood count (WBC)≥12.000/or febrile state or CRP>5mg/L
9. Endovascular or surgical procedure (not including diagnostic procedures, planned simple digital amputation or wound debridement) to the target limb within 30 days after the index procedure
10. Existing stent implant in the target vessel
11. Use of alternative therapies: atherectomy, cutting/scoring balloons, laser, …
12. Known coagulopathy, hypercoagulable state, bleeding diathesis, other blood disorder, or a platelet count less than 80.000/µL or greater than 500.000/µL
13. Any subject in which antiplatelet, anticoagulant or thrombolytic therapy is contraindicated
14. Myocardial infarction, coronary thrombolysis or angina less than 30 days prior to the index procedure
15. History of stroke or transient ischemic attack (TIA) less than 90 days prior to the index procedure
16. Known hypersensitivity or contraindication to nickel-titanium alloy (Nitinol)
17. Has other comorbidities that, in the opinion of the investigator, would preclude them from receiving this treatment and/or participating in study-required follow-up
18. Patients on haemodialysis
19. Known hypersensitivity or allergy to contrast agents that cannot be medically managed
20. Known hypersensitivity or allergy to heparin, aspirin, paclitaxel, clopidogrel or other antiplatelet/anticoagulant therapies
21. Inadequate inflow lesion treatment (>30% residual stenosis)
22. Inadequate result of pre-dilatation (>30% residual stenosis)
23. Inadequate run-off to the foot
24. Bilateral BTK enrolment in this study

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Study conduct The study will be conducted in accordance with the Declaration of Helsinki and ISO 14155:2011 and comply with requirements regarding Ethics Committees and any other applicable regulations.

Study investigations

Time		Tests and Procedures
Pre-Procedure (up to 24 hours before procedure, unless otherwise noted)	1. 2. 3. 4. 5. 6. 7.	Screening inclusion/exclusion criteria Consenting patient Physical exam (ABI, Rutherford) WIfI assessment Medical History Medication Registration EQ5D-questionnaire
Procedure	1. 2. 3. 4.	Angiographic inclusion/exclusion criteria Study inclusion Intervention details Adverse Event recording/reporting
Pre-Discharge	1. 2. 3. 4. 5. 6.	Medication Registration Physical Examination (ABI, Rutherford) WIfI assessment Wound healing status EQ5D-questionnaire Adverse Event recording/reporting
Weekly follow-up by a dedicated wound care specialist until the wound is healed (does not need to be in the hospital)	1. 2.	Wound healing status Picture with ruler
1-month Follow-up (± 14 days)	1. 2. 3. 4. 5. 6. 7.	Medication Registration Physical Examination (ABI, Rutherford) WIfI assessment Wound healing status EQ5D-questionnaire Target vessel functional flow assessment on color flow doppler ultrasound Adverse Event recording/reporting
6-month Follow-up (± 30 days)	1. 2. 3. 4. 5. 6. 7.	Medication Registration Physical Examination (ABI, Rutherford) WIfI assessment Wound healing status EQ5D-questionnaire Target vessel functional flow assessment on color flow doppler ultrasound Adverse Event recording/reporting
12-month Follow-up (± 30 days)	1. 2. 3. 4. 5. 6. 7.	Medication Registration Physical Examination (ABI, Rutherford) WIfI assessment Wound healing status EQ5D-questionnaire Target vessel functional flow assessment on color flow doppler ultrasound Adverse Event recording/reporting

Descriptive data summaries will be used to present and summarize the collected data. For categorical variables (e.g. Gender) frequency distributions and cross tabulations will be given. For numeric variables (e.g. Patient age) minimum, maximum, mean, median and standard deviation will be calculated. For all variables a 95% confidence interval for the relevant parameters of the underlying distribution will be calculated. For all time-dependent events life-tables will be calculated using the Kaplan Meier estimate method, for a period starting on the date of the procedure up to and including the 12-month follow-up visit. Stratification to pre-procedural risk factors, Rutherford-, WIfI-classifications and lesion criteria will be performed and the log rank test will be used to compare between the different outcomes, associated p-values < 0.05 are defined as significant.