HEROES-DCB

Lutonix or In.Pact for tHE tReatment Of fEmoralpopliteal Stenosis - DCB

Study Protocol Number C5000163

Version 4.0

Coordinating Center

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Study Protocol Acceptance

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I agree to the terms and conditions relating to this study as defined in this protocol and any other protocol-related documents. I will provide copies of this Study Protocol and all pertinent information to study personnel.

Name: _____

Affiliation: _____

Signature: _____ Date: _____

Signed copies of this signature page are stored in the Coordinating Center's study file and in the respective center's investigator site file.

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1. PROTOCOL SYNOPSIS

HEROES - DCB Study Synopsis

Study Author / Coordinating Center	Jaafer Golzar, MD / Advocate Christ Medical Center, Oak Lawn, IL.
Protocol Title	**HEROES – DCB** Lutonix or In.Pact for tHE tReatment Of fEmoralpopliteal Stenosis - DCB
Diagnosis and Main Criterion for Inclusion	Subjects with moderate to severe claudication or ischemic rest pain as defined by Rutherford 2-4 class symptoms, commonly referred for peripheral angiography.
Primary Study Objective	To compare patency and Target Lesion Revascularization rates (TLR), clinical outcomes, and healthcare costs, and healthcare utilizations between the Drug Coated Balloons (DCB's) Lutonix 035 Drug Coated Balloon PTA Catheter and IN.Pact Admiral Paclitaxel-Coated PTA Balloon Catheter.
Primary Endpoint	Successful primary patency at 12 months post procedure, determined by a Duplex Ultrasound PSVR <=2.4 @ 12 months post treatment. (without Target Lesion Revascularization or bypass)
Secondary Endpoints	To examine, describe, compare & contrast within and between DCB groups: • Target lesion revascularization rate • Adverse Event rates • 12 month Total Hospital Costs
Primary Hypothesis	In patients with significant peripheral arterial disease with clinical indications for treatment with angioplasty, there will be a difference in primary (12 month) patency, secondary outcomes, and costs between the 2 treatment groups.
Study Design	A Prospective Randomized1:1 Trial of 2 Drug Coated Balloons.
Duration of Study Participation	Subjects will complete participation after completing the 12 month visit.
End-of-Study Definition	Data collection will be complete when the last subject enrolled finishes their 12month/final follow up visit.
Number of Subjects	250 subjects will be enrolled, with 125 in each group
Number of Sites	Up to 13 potential sites
Study Follow-up	Study visits will occur at baseline, index procedure, pre-discharge, 1 month, 6 months, and 12 months. (*unscheduled visits will be reported if related).

2. SIGNIFICANCE / BACKGROUND

Peripheral artery disease (PAD) is a condition associated with significant morbidity, mortality, and economic costs[1,2]. Several different modalities exist for percutaneous revascularization of the femoropopliteal arteries trying to optimize safety, durability, and cost effectiveness. Percutaneous transluminal angioplasty (PTA) is effective in restoring blood flow however is associated with restenosis[3]. Bare metal nitinol stents and the Zilver PTX drug eluting stent have improved restenosis rates[4,5], however stent fracture and in-stent restenosis (ISR) with these revascularization options provides further complexity for subsequent revascularization[6,7]. Drug coated balloons (DCBs) provide a method of improving restenosis rates without leaving a stent scaffold avoiding stent fracture and ISR.

Several early randomized control trials such as THUNDER, FemPac, PACIFIER, and LEVANT 1 comparing PTA versus DCB showed improved late lumen loss (LLL) and target vessel revascularization (TLR) with DCBs[8,9,10,11]. This was followed by LEVANT 2 and IN.PACT SFA, the two largest randomized control trials comparing PTA with DCB. The Lutonix paclitaxel coated balloon was the DCB studied in LEVANT 2, while the IN.PACT Admiral paclitaxel coated balloon was the DCB studied in IN.PACT SFA. The primary efficacy endpoint for both trials was primary patency at 12 months, defined as freedom from restenosis or clinically driven TLR[12,13]. In both studies primary patency at 12 months was significantly higher in the DCB arm. The Lutonix DCB had primary patency at 12 months of 65.2% versus 52.6% in the PTA arm[12]. The IN.PACT Admiral DCB had a primary patency at 12 months of 82.2% versus 52.4% in the PTA arm; at 24 months, primary patency had decreased to 78.9% versus 50.9% in the PTA arm[13,14]. The primary safety endpoint in LEVANT 2 was a composite of freedom from perioperative death within 30 days and a freedom from amputation, re-intervention, and limb-related death at 12 months[12]. In contrast, the primary safety endpoint in IN.PACT SFA was 30 day device and procedure-related death and amputation, thrombosis, and all cause death at 12 months[13].

Since there are no head to head trials comparing the Lutonix DCB versus the IN.PACT Admiral DCB, the aim of this trial is to do just that. The primary efficacy endpoint is primary patency as defined by freedom from restenosis and TLR at 12 months. The safety endpoint is a composite of freedom from perioperative death within 30 days and freedom from amputation, re-intervention, and limb related death at 12 months. In addition, we aim to analyze the difference in cumulative health care costs at 12 months between the two DCBs.

3. STUDY OVERVIEW

3.1 Design

Multicenter, prospective, randomized (1:1) parallel trial of patients treated in accordance with the cleared indications for the Lutonix and In.Pact Admiral Drug Coated Balloons. Data for

each patient will be collected in accordance with the standard of care at each participating hospital through one- year follow-up. 250 Patients with atherosclerotic disease of the superficial femoral artery and popliteal arteries at up to 13 centers will be enrolled.

3.2 Study Objectives/Endpoints

- Compare patency and TLR rates between the two DCB arms.
- Compare adverse event rate between the two DCB arms
- Examine cumulative healthcare costs and healthcare utilization

3.2.1 Hypothesis

We hypothesize in patients presenting with significant peripheral arterial disease with clinical indications for angioplasty treatment that there will be a difference in primary patency between two drug-coated balloon study arms.

3.2.2 Primary Outcome

12 month Patency in Superficial Femoral/Popliteal arteries.

3.2.3 Primary Endpoint

Primary patency will be determined to be a success when:

1. Peak systolic velocity rate (PSVR) ≤ 2.4 on duplex ultrasound (DUS) at 12 month follow-up visit (as read by blinded central study reading)
2. No target lesion revascularization (TLR) or target lesion bypass at 12 months.

3.2.4 Secondary Endpoint

To examine, describe and compare/contrast within and between DCB groups.

1. Target lesion revascularization rate
2. Safety event rate
3. Healthcare utilization costs

3.3 Study Population

Subjects enrolled in this study will be treated in accordance with the cleared indications outlined in the Instructions for Use for the Lutonix and/or the In.Pact Admiral Drug Coated Balloons. Once the subject has signed the ICF and has met all clinical inclusion criteria and no exclusion criteria, the subject will be considered eligible to be enrolled in the trial. If the subject is found to fail to meet angiographic inclusion criteria or meets angiographic exclusion criteria during index procedure, the subject will be considered a screen failure and will not be enrolled and randomized to the trial, and the subject will not be followed post-procedure.

If the subject meets angiographic eligibility criteria following successful pre-dilatation, the subject will be considered eligible to be randomized and enrolled.

3.3.1 Selection of Study Subjects:

Subjects will be obtained from participating centers and consist of those who present to investigators with atherosclerotic disease of the superficial femoral artery and popliteal arteries. Subjects will exhibit moderate to severe claudication or ischemic rest pain as defined by Rutherford class 2 – 4 symptoms.

Prior to randomization/enrollment, a subject must meet all of the clinical and angiographic inclusion criteria and none of the clinical and angiographic exclusion criteria. The Target Lesion(s) must conform to all angiographic inclusion criteria to be eligible for treatment. Subjects will be randomized during the procedure 1:1 with site stratification to control for differences in geographic patient populations and recruitment numbers.

Clinical and angiographic inclusion and exclusion criteria are below.

3.3.2 Inclusion Criteria

1. Patient is willing and able to provide informed consent, willing and agrees to comply with regular follow up visits, testing, medication regimen compliance any another treatments deemed necessary for treatment of vascular disease.

2. Male or non-pregnant female

3. Age 18 years of age or older

4. Moderate to severe claudication or ischemic rest pain defined by Rutherford class 2 - 4 symptoms

5. <u>Angiographic criteria</u>

    a. $\geq$ 70% stenosis (via visual angiographic estimate in the superficial femoral artery and/or popliteal arteries as appropriate)

    b. 4-7mm vessel diameter

    c. $\leq$ 180 mm total length for all lesion(s) planned to be treated.

    d. Target Lesion(s) are at least 10 mm below the bifurcation of the common femoral artery and at least 10 mm above the tibioperoneal trunk

e. Lesions treated within the target vessel are either de novo lesion(s) or not previously stented restenotic segments of the superficial femoral artery and/or popliteal artery that are greater than 90 days from prior angioplasty procedure

f. If the target vessel has been previously stented the treated lesion(s) must be at least 30 mm from the previously placed stent

g. Lesion(s) must be able to be treated with either drug coated balloon device based on the sizes specifications of both devices according to each device's IFU.

h. Successful, uncomplicated crossing must be possible within the treated lesion(s) either with or without a crossing device

i. Inflow artery must be free from significant occlusive disease (patency > 50%) as confirmed by visual estimation by angiography. Otherwise the inflow artery must be treated before treatment of target lesion(s).

j. At least 1 patent vessel outflow (patency > 50%) from the target vessel treated must be present by angiography

k. $\geq$ 1 tibial run-off vessel at baseline

3.3.3 Exclusion Criteria

1. Unable to meet clinical criteria to have peripheral angioplasty and follow-up treatment (lab values and pregnancy test)

2. Contraindicated to either DCB

3. $\leq$18 years of age at time of consent and/or index procedure

4. Pregnant or breastfeeding

5. In-stent restenosis within the target lesion(s)

6. Target lesion(s) previously treated with drug-coated balloon < 12 months prior to randomization/enrollment

7. Perforated vessel as evidenced by extravasation of contrast media prior to randomization/enrollment

8. Presence of other hemodynamically significant outflow lesion(s) in the target limb requiring intervention $\leq$ 30 days after randomization/enrollment

9. Presence of aneurysm in the target vessel

10. Major amputation in the target limb

11. Subjects who have undergone prior surgery of the SFA/PPA in the target limb to treat atherosclerotic disease.

12. Acute ischemia and/or acute thrombosis of the SFA-Popliteal segment

13. Use of atherectomy, laser or other debulking devices in the target limb SFA/PPA during the index procedure

14. Known hypersensitivity or contraindication to contrast dye that, in the opinion of the local investigator, cannot be adequately pre-medicated

15. Known hypersensitivity/allergy to the drug or balloon system or protocol related therapies.

16. Immunosuppressant therapy

17. Concomitant renal failure (including serum creatinine >2.0 mg/dL) or dialysis

18. Occurrence of myocardial infarction (MI) or cerebrovascular accident (CVA) $\leq$ 6 months prior to randomization/enrollment

19. Platelet count < 80,000 mm^3 or > 600,000 mm^3, or history of a bleeding diathesis, or in whom antiplatelet, anticoagulant, or thrombolytic therapy is contraindicated

20. Unstable angina pectoris at the time of randomization/enrollment

21. Septicemia at the time of randomization/enrollment

22. Moderate to severely calcified lesions

4. PROCEDURES

All study procedures are to be conducted in accordance with the cleared indications outlined in the Instructions for Use for Lutonix 035 Drug coated Balloon PTA Catheter and IN.PACT Admiral Paclitaxel-Coated PTA Balloon Catheter.

4.1 Randomization

The intervention in this study is randomization to 1 of 2 marketed DCBs (Lutonix 035 Drug coated Balloon PTA Catheter and IN.PACT Admiral Paclitaxel-Coated PTA Balloon Catheter). This will be a 1:1 site stratified randomization to one of the DCB groups.

Randomization will take place during the clinical procedure after successful crossing and pre-dilatation of the target lesion(s) in the superficial femoral/popliteal arteries. Randomization

envelopes will be generated for each site in numbered groups of 20. Following successful pre-dilatation of the Target Lesion(s), envelopes will opened in sequence and study arm will be assigned to subjects.

4.2 Blinding

HEROES – DCB is a single blind trial. Subjects will be blinded to the assigned treatment arm. All subjects will remain blinded until completion of all 12-month follow-up visits (primary endpoint).

The Investigator performing the procedure will not be blinded to the assigned treatment arm or resulting treatment. Study center personnel will be trained not to disclose the treatment assignment to the subject to minimize the potential unblinding of the subject. Site personnel conducting clinical follow-up assessments will be blinded to a subject's treatment assignment whenever possible, except when clinical follow-up visits are performed by the implanting Investigator.

Central Angiography and Duplex Ultrasound (DUS) facility readers/interpreters will be blinded to a subject's treatment assignment during the trial. Those involved in data analysis for the study will remain blinded.

4.3 Recommended Concomitant Medications

Local investigators will prescribe concomitant anticoagulant and antiplatelet medication consistent with current local clinical practice. Information regarding antiplatelet or anticoagulant medications will be collected on case report forms including dose changes, interruptions, and cessation. Additional concomitant medications may be ordered by the investigator or treating physician according to standard of care.

Minimum recommendations include:

- Anticoagulation therapy administered during the procedure should be consistent with current local clinical practice.
- Dual antiplatelet therapy should be administered consistent with current local clinical practice pre-procedure or within 2 hours after the end of the procedure; and for a minimum of sixty days post procedure.
- Antiplatelet therapy should continue consistent with current local practice.

Exception: If a subject has known comorbidities and in local investigator's clinical opinion the combination of dual anti-platelet therapy and anticoagulation could create a significant bleeding risk, or if the subject requires other anticoagulants such as warfarin and similar drugs, this subject may be exempt from antiplatelet requirements per standard of care.

4.4 Schedule of Assessments

	Pre-Procedure/ Baseline (≤ 30 days)	Index Procedure	Pre-Discharge	1 month (+/- 15 days)	6 month (+/- 30 days)	12 month (+/- 30 days)	Unscheduled Visit
Obtain informed consent (before any study procedures)	X						
Inclusion/Exclusion (confirm eligibility)	X						
Medication Assessment (antiplatelet therapy)	X			X	X	X	X
Demographics, Medical History, Height, & Weight	X			X	X	X	X
Obtain lab results (Ser Creatinine, CBC w/platelets, Pregnancy Test[1] –serum or urine)	X[1]						
Rutherford Categorization	X			X	X	X	X
Confirm Angiographic Criteria are met		X					
Copy Angiogram, De-Identify & submit to Coordinating Center		X					X
Collect UB=04's & submit to Coordinating Center		X[2]		X[2]	X[2]	X[2]	X[2]
Ankle Brachial Index (ABI) measurements	X[4] If available			X	X	X	X
Duplex Ultrasound (de-identified copy to core lab)	X[4] If available			X If available	X	X	X
Serious Adverse Event/Adverse Event evaluation		X	X	X	X	X	X
Repeat Revascularization[3] (Including TLR & TVR)			X[3]	X[3]	X[3]	X[3]	X[3]

X[1] For all women of childbearing potential, per site standard.

X[2] Collect & De-identify UB04's for all hospitalizations including the Index Procedure and send to the Coordinating Center.

X[3] Collect & De-identify films and procedure reports, send to the Coordinating Center.

X[4] Baseline Duplex Ultrasound and /or Ankle Brachial Index may be performed within 90 days Pre-Procedure

4.5 Screening Pre-Procedure (within 30 days prior to procedure)

1. Site will identify potential subjects based on inclusion/exclusion criteria
2. Coordinator and/or investigator will provide and complete informed consent process with participant.
3. Concomitant medications, medical history, height and weight reviewed.
4. Rutherford Category score assessed and documented.
5. Serum creatinine and platelet count obtained.
6. Pregnancy test obtained on women of child-bearing potential.
7. Ankle-brachial index collected. (may be performed within 90 days pre-procedure)
8. Data collection per schedule of assessments

4.6 Index Procedure (day 0)

1. Verify recommended antiplatelet therapy received prior to index procedure.
2. To standardize location of lesion(s), a radiopaque ruler is required and will be positioned beginning at the bifurcation of the profunda to the popliteal.
3. Start time of index procedure is at guide catheter insertion into sheath for target limb SFA/PPA procedure.
4. Any inflow lesions will be treated prior to target lesion(s) treatment.
5. Prior to randomization, the investigator will determine that participant is a candidate for either DCB
6. Investigators will monitor and manage procedural complications, cardiovascular risks, and comorbidities for all subjects according to standard of care.
7. Diagnostic angiography will be performed as needed using standard techniques to confirm visual angiographic eligibility of the target lesion(s).
8. The vessel will be successfully pre-dilated without flow-limiting dissection. Should a dissection occur, subject will not be randomized or enrolled. Subject will be treated according to local clinical practice.
9. Randomization will be performed.
10. Subjects who are randomized but are unable to have the assigned DCB successfully inserted will be considered “intent to treat”. In this event, subjects will be followed for one month after the index procedure.
11. Administer loading doses of antiplatelet therapy as indicated.
12. Data collection per schedule of assessments

4.7 Post Procedure/Pre-Discharge

1. Verify concomitant medications were given and will be prescribed.
2. Determine and document any adverse events.
3. Data collection per schedule of assessments

4.8 One Month Follow-Up (+/- fifteen days)

1. Diagnostic ultrasound is not required, but any pertinent DUS recording will be sent to central DUS laboratory for reading.
2. Ankle-brachial index
3. Rutherford classification by investigator
4. Adverse events documented
5. Target lesion(s) or target vessel revascularization documented
6. Recommended concomitant medication use documented

4.9 Six Month Follow-Up (+/- 30 days)

1. Diagnostic ultrasound performed and sent to central DUS laboratory for reading.
2. Ankle-brachial index
3. Rutherford classification by investigator
4. Adverse events documented
5. Target lesion(s) or target vessel revascularization documented
6. Recommended concomitant medication use documented
7. Data collection per schedule of assessments

4.10 Twelve Month Folllow-Up (+/- 30 days)

1. Diagnostic ultrasound performed and sent to central DUS laboratory for reading.
2. Ankle-brachial index
3. Rutherford classification by investigator
4. Adverse events documented
5. Target lesion(s) or target vessel revascularization documented
6. Recommended concomitant medication use documented
7. Data collection per schedule of assessments

4.11 Unscheduled Visits (as clinically available)

1. Rutherford classification by investigator
2. Ankle-brachial index
3. Adverse events documented
4. Target lesion(s) or target vessel revascularization documented
5. Recommended concomitant medication use documented
6. Data collection per schedule of assessments

4.12 Healthcare Utilization

Healthcare utilization from UB-04 and billing codes at treating hospital during 12 months of follow-up will be collected

4.13 Withdrawal of Participation

All subjects have the right to withdraw from participation at any point during the study. Whenever possible, the site staff should obtain written documentation from the subject that wishes to withdraw his/her consent for future follow-up visits and contact.

In addition, Principal Investigators also have the ability to withdraw subject participation in the study. Reasons for physician-directed subject withdrawal include, but are not limited to: the subject is not adhering to the Study Protocol requirements, the subject has enrolled in another study that conflicts with this Study Protocol outcomes, or if it is in the best interest for the safety or welfare of the subject to withdraw.

A description of the reason for a subject's withdrawal will be documented in the subject's research record. Reasons for termination include: subject withdrawal, physician-directed subject withdrawal, and lost-to-follow-up.

4.14 Lost to Follow-Up

Every attempt should be made to have all subjects complete the follow-up visits according to the visit schedule. A subject will not be considered lost-to-follow-up unless efforts to obtain compliance are unsuccessful

For lost to follow-up or missed visits, a minimum of three attempts (i.e. two phone calls and a certified letter) should be made to contact the subject or the subject's next of kin. These attempts should be documented in the subject's research record. A subject will be considered lost to follow-up after diligent attempts have failed to establish contact and the 12 month visit window has passed.

5. INVESTIGATOR RESPONSIBILITIES

5.1 Institutional Review Board Approval / Ethics Committee Approval

Prior to enrolling patients into the study, the investigator will ensure that proper Institutional Review Board (IRB) / Ethics Committee (EC) approval is obtained, in accordance with applicable local state and federal laws and regulations. The IRB/EC shall approve study documents, including the final protocol, amendments to the protocol, and the informed consent.

5.2 Informed Consent

The investigator is responsible for ensuring that a signed informed consent is obtained according to national, state, and local Institutional Review Board (IRB) / Ethics Committee (EC) requirements prior to inclusion of patients in the study.

5.3 Adherence to Protocol/Amendments and Applicable Law

The investigator is responsible for ensuring that the study is conducted according to this protocol and in accordance with any conditions imposed by the reviewing Institutional Review Board (IRB) or Ethics Committee (EC), and all other applicable regulations. The investigator shall approve and adhere to this protocol and any amendments that arise during the course of the study.

It is the investigator's responsibility to ensure that the staff assisting with the study have the appropriate qualifications, are fully instructed on the study procedures.

5.4 Case Report Form Completion

The investigator and study staff shall complete the case report forms (CRFs) associated with this study. Patient numbers shall be used to identify individual patients in this study. The CRFs should be a complete and accurate record of patient data collected during the study. It is the investigator's responsibility to ensure the quality of the data collected and recorded.

5.5 Reports

The investigator will be responsible for the following reports:

5.5.1 Protocol Deviation

Any deviations from the protocol identified during Coordinating Center review or through other means should be clearly documented. These include but are not limited to:

- Subject does not meet inclusion/exclusion criteria
- Failure to sign informed consent
- Improperly signed or incomplete informed consent
- Delayed reporting of serious, device related, or unexpected adverse events

5.5.2 Adverse Event Reporting

In this study we will only be collecting Adverse Events (AEs) related to the procedure or device, unanticipated adverse device effects (UADE), and all Serious Adverse Events (SAEs) from the time of enrollment/randomization through study exit. If an AE occurs that is not related to the procedure or device, it is not reportable under this Protocol.

All AEs reported during the study will be documented using the AE reporting form included in the study CRFs. AE reports will be reported to the Study Coordinating Center with the next follow up visit and will include:

- a description of the event,
- the date of onset,

- the timing of the event (during or after procedure)
- the primary relationship
- the classification of the event as serious or non-serious as defined in
- the treatment administered,
- the outcome of treatment, and
- the resolution date.

Each reported AE will be assessed by the Investigator for its primary relationship to the device, procedure, disease, or may be unknown. Only one primary relationship will be assigned to each AE. AE Reports will be submitted to the sites IRB following institutional guidelines, and to governmental regulatory agencies following agency guidelines as indicated.

5.5.3 SAE Reporting

All participating study sites should report SAEs to the Study Coordinating Center with the next follow up visit and in accordance with applicable national regulations. It is the responsibility of each Investigator to report all serious AEs to the reviewing IRB according to national regulations and IRB requirements.

An event need not be reported as a SAE if it represents only a relapse or an expected change or progression of a comorbid condition that was prior to enrollment. This type of event is considered an AE, and may not be reportable.

5.5.4 UADE Reporting

If a complication occurs that the Investigator believes may be a potential UADE, the site should immediately contact the Device Manufacturer to determine reporting requirements.
The Investigator shall submit to the reviewing IRB a report of any UADE occurring during an investigation as soon as possible,

5.6 Withdrawal of Approval

The investigator shall report to the Coordinating Center immediately if, for any reason, the approval to conduct the study is withdrawn by the IRB/EC. The report will include a complete description of the reason(s) for which approval was withdrawn. The investigator shall submit all reports in a timely manner.

5.7 Records Retention

The investigator shall maintain the records associated with this study for a period of at least two years after the date on which the investigation is completed. These records include the following:

- Correspondence with the Coordinating Center or designee, the IRB/EC, and other investigators.
- Patient records, including informed consent forms, copies of all completed CRFs, and supporting documents.
- Current study protocol.
- Reports of any serious adverse event or adverse device effects.
- A copy of all approvals related to the protocol.
- The approved, blank, informed consent form.
- Certification that the investigational plan has been approved by the IRB/EC.
- Signed investigator agreements.

6. COORDINATING CENTER RESPONSIBILITIES

6.1 Training

During study initiation, the Coordinating Center will provide training for the investigator and study staff on the protocol as well as the CRFs.

6.2 Investigator List

The Coordinating Center shall keep a list of the names, addresses, and professional positions of the investigators for the study.

6.3 Adverse Event Reporting

The Coordinating Center shall evaluate adverse event reports received from the study sites and shall report them to the regulatory bodies and other investigational sites as appropriate.

6.4 Data Monitoring

Coordinating Center will utilize centralized monitoring during the trial. Standardized CRFs will be used for queries and query resolution.

6.4.1 Site Initiation Visit

This will be conducted remotely or in certain cases on site as feasible to train the study staff on study requirements, and other relevant training.

6.4.2 Interim Monitoring

Conducted as needed to ensure the study site is operating in compliance with this protocol, and completing the CRFs. Clinical monitoring will include review and resolution of missing or inconsistent data and source document checks to ensure the accuracy of the reported data. CRFs for all enrolled patients will be submitted to the Coordinating Center for review as

described in the manual of operations. The Coordinating Center will evaluate the CRFs submitted and identifying repeated data problems specifying recommendations for resolution of noted deficiencies. To facilitate this monitoring, certain source documents may be requested. These may include, but are not limited to, patient informed consent, history and physical, operative report, imaging reports, and discharge summary.

6.4.3 Study Close-Out Phone Call

This is conducted at the termination of the study to resolve any outstanding data queries and reconcile trial documents.

6.5 Data Management

Data entry will be performed at the investigational sites utilizing standardized CRFs as provided through the Study Coordinating Center. Investigators are responsible for completion and timely submission of the data to the Coordinating Center. Questions or problems with submitted data will be addressed with the principal investigator or designee via direct contact. Investigators, clinical coordinators, data managers, and Coordinating Center personnel will have access to project information and study data. Incoming data to the Coordinating Center are to be reviewed for quality and consistency and will be entered into the Advocate HealthCare Redcap Database by designated Coordinating Center personnel.

All hard copy forms and data files will be secured to ensure confidentiality. Investigators are required to maintain source documents required by the protocol, including laboratory results, patient report forms, supporting medical records, and Informed Consent Forms.

7. CONTACT INFORMATION

The address of Coordinating Center is:

Advocate Christ Medical Center
Clinical Research Department
4440 West 95th Street – Suite 154 NOB
Oak Lawn, Il 60453
Tel. (708) 684-4631
Fax (708) 684-4451

8. ETHICAL REQUIREMENTS

8.1 IRB/EC Approval

The investigator is responsible for ensuring that the study is conducted according to any conditions imposed by the reviewing Institutional Review Board (IRB) or Ethics Committee (EC), and all other applicable regulations. It is the responsibility of the investigator to obtain approval of the study protocol from the IRB/EC and to keep the IRB/EC informed of any

unexpected serious adverse events, serious adverse device effects, and amendments to the protocol, as applicable. All correspondence with the IRB/EC should be filed by the investigator and copies sent to the Coordinating Center or its designee.

8.2 Patient Information and Consent

It is the responsibility of the investigator to give each patient full and adequate verbal and written information regarding the objective and procedure of the study and the possible risks involved and to obtain signed informed consent from all patients prior to inclusion in the study. The original, signed consent is filed with the patient study records, and a copy is provided to the patient or legally authorized representative.

8.3 Patient Data Protection

The patients will be identified in the CRFs with a unique patient identifier. Only the investigator will have access to individual patient data, as will the Coordinating Center or its designee for monitoring purposes only. Furthermore, the subjects should be informed about the possibility of inspection of relevant parts of the hospital records, including angiograms and other imaging scans, by the Coordinating Center or other health authorities, including the FDA.

9. STATISTICAL PROCEDURES

9.1 Sample Size Justification

The primary outcome in this study is percentage of patients who achieved primary patency at 12 month follow-up. Previous research has shown that primary patency was achieved in 65% of the Lutonix group 12 and 82% in the IN.Pact group 13. Given this difference of 17% for between-group patency, 102 subjects per group (total n = 204) are needed to achieve a power of 80% given $\alpha = 0.05$. We are seeking to enroll 125 subjects per group (total n = 250) to account for attrition as the follow-up period is 12 months.

9.2 General Statistical Methods

Descriptive statistics will be presented as means and standard deviations for continuous data and as counts and percentages for dichotomous and categorical data. The primary endpoint of 12 month patency will be compared between treatment groups using Pearson's chi-square analysis.

The secondary endpoints of adverse events and healthcare utilization will be analyzed using the independent t test, Mann Whitney U or Pearson's chi-square as appropriate.

Tabulations of adverse events will be presented with descriptive statistics at immediate post procedure and follow-up visits. Adverse event incidence rates will be summarized by category

and seriousness of the adverse event. Events will also be reported by relationship to the device.

Intent to treat population (ITT), which includes all those who were enrolled and randomized, is pre-specified as the primary analysis population. An analysis based on the per-protocol population, which excludes patients with pre-specified major protocol deviations, will be performed to further support results from the primary analysis. All ITT patients will be analyzed within the arm they were randomized to.

10 PUBLICATION OF INFORMATION

The results of this study may be offered for publication and/or presentation. The investigators and the Coordinating Center shall collaborate in the writing of the study to ensure accuracy. The investigator agrees to use this data only in connection with this study and will not use it for other purposes without written permission from the Coordinating Center.

11 DEFINITIONS

Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence in a subject. This definition does not imply that there is a relationship between the adverse event and the device under investigation.

Adverse Device Effect
An adverse device effect is any untoward and unintended response to a medical device. This definition includes any event resulting from insufficiencies or inadequacies in the instructions for use for preparation or deployment of the device. It also includes any event that is a result of a user error.

Anticipated Adverse Event
Any undesirable health related experience occurring to a subject whether or not considered related to the investigational product(s) or drug regimen prescribed as part of the protocol, predefined in the protocol and/or Instructions For Use (IFU) that is identified or worsens during a clinical study.

Clinical Adverse Events
Clinical AEs are defined as any untoward medical occurrence in a subject, once randomized in the study, whether device-related or not. All AEs will be documented in the subject's permanent medical record, recorded on the appropriate CRF, and reported in accordance with applicable local IRB and national regulations.

Non-Serious Adverse Events
Generally uncomplicated, resolving without intervention, extension of ongoing medical therapy, or consequence to the subject.

A SAE is an adverse event that

1. led to death,

2. led to serious deterioration in the health of the subject that either resulted in:
    a. life-threatening illness or injury, or
    b. permanent impairment of a body structure or a body function, or
    c. in-patient hospitalization or prolonged hospitalization, or
    d. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.

3. led to fetal distress, fetal death or a congenital abnormality or birth defect.

Serious Adverse Device Effect (SADE)

A SADE is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune.

Unanticipated Adverse Device Event (UADE)

An unanticipated adverse device effect (UADE) is defined in 21 CFR 812.3(s) as any serious adverse effect on health or safety, or any life threatening problem or death caused by or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational devices IFU's or Informed Consent Form, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Relationship to the Device

An AE is considered to be device-related when it is reasonable to believe that the event may have been caused by or is related to the device. Following definitions will be used to assess the relationship of the adverse event to the use of study device. Any grading for relatedness other than 'unrelated' will be considered device related.

- Definite: The temporal sequence is relevant and the event abates upon device application completion/removal, or reappearance of the event on repeat device application.

- Probable: The temporal sequence is relevant or the AE abates upon device application completion/removal or the AE cannot be reasonably explained by the subject's condition or comorbidities. The AE is related or most likely associated with the device.

- Possible: The temporal sequence between the device and the AE is such that the relationship is not unlikely or there is no contradicting evidence that can reasonably explain the study subject's condition. There is a possibility of a relationship between the AE and the device.

- Unrelated: The AE is not associated with the device. There is no relation between the AE and the device

Adverse Event Severity
For the purposes of this trial, the investigator will use the following definitions to rate the severity of each adverse event.

- Mild: Awareness of a sign or symptom that does not interfere with the patient's usual activity or is transient, resolves without treatment and with no sequelae.

- Moderate: interferes with routine activity and/or requires symptomatic therapy.

- Severe: Severe discomfort and significant impact on the subject's ability to perform routine activities despite symptomatic therapy.

Similar grading will be used for assessing the relationship and severity of the event to the procedure.

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

Amputation of the Index Limb
Amputation includes all amputations including both Major Amputations (above the ankle) and Minor Amputations (including amputations below the ankle).

Ankle-brachial Index (ABI)
The ratio between the systolic pressure measured at the ankle and the systolic pressure measured in the arm.

Ankle-Brachial Index (ABI) Classifications at rest

1. Ankle-brachial ratio > 1.3: Non-compressible vessels
2. Ankle-brachial ratio ≥ 0.95: Normal
3. Ankle-brachial ratio < 0.95: Peripheral Vascular Disease\
4. Ankle-brachial ratio < 0.6: Intermittent Claudication
5. Ankle-brachial ratio < 0.4: Chronic limb ischemia

Balloon Treatment Area
The entire length over which balloon(s) was inflated against the vessel wall during index procedure.

Bleeding Complication
Includes, hematoma, bleeding at percutaneous catheterization site, and/or retroperitoneal bleeding. Bleeding that requires surgery qualifies as an SAE.

Calcification Classification
Readily apparent densities seen within the artery wall and site of lesion as an x-ray-absorbing mass.

- none/mild (no or minimal radio-opacities noted prior to contrast injection)
- moderate (multiple radio-opacities noted prior to contrast injection)
- severe (diffuse radio-opacities noted on both sides of the arterial wall prior to contrast injection)

Clinical Deterioration
Downgrade in Rutherford classification of 1 or more categories as compared to pre-procedure.

Death
Cardiac death: any death due to immediate cardiac cause (e.g. MI, low-output failure, fatal arrhythmia). Unwitnessed death and death of unknown cause will be classified as cardiac death. This includes all procedure related deaths including those related to concomitant treatment.
Non-cardiovascular death: any death not covered by the above definitions, including death due to infection, sepsis, pulmonary causes, accident, suicide, or trauma.

Device Success
Exact deployment of the device according to the instruction for use as documented with suitable imaging modalities and in case of digital subtraction angiography, in at least two different imaging projections. If a device is inserted into the subject but not used due to user error (e.g. inappropriate balloon length or transit time too long), this device will not be included in the Device Success assessment. There will be an additional subset analysis to include any devices in this category.

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

Diameter Stenosis
The maximal narrowing of the target lesion relative to the reference vessel diameter.

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

0. None
A. Intraluminal radiolucent defect.
B. Extraluminal “cap” (without staining).
C. Extraluminal “cap” with persistence of contrast dye (staining)
D. Spiral defects.
E. Persistent filling defects*.
F. Filling defect with total occlusion*.
* Type E & F dissections may represent thrombus.

Distal Embolization
Migration of a filling defect, or thrombus, to distally occlude the target vessel or one of its branches.

Intent-To-Treat
The principle of including outcomes of all subjects in the analysis who are randomized into the study, regardless of the treatment actually received.

In-Lesion Measurement
The measurements either within the study treated segment or within 5 mm proximal or distal to the edges.

Lesion Length
Measured as the distance from the proximal shoulder to the distal shoulder of the lesion, in the view that demonstrates the stenosis in its most elongated projection.

Major Bleeding Complications
Bleeding will be considered major if:

- It leads to death;
- It leads to permanent disability;
- It is clinically suspected or proven to be intracranial
- It produces a fall in hemoglobin of at least 5 gm/dl;
- It leads to transfusion of 5 units of blood;
- Peripheral vascular surgery is necessary.
- All other bleeding will be considered as minor.

Major Vascular Complications

- Hemorrhagic vascular complications included the following:
- Hematoma at access site >5 cm
- False aneurysm
- AV fistula
- Retroperitoneal bleed
- Peripheral ischemia/nerve injury
- Vascular surgical repair

Minimum Lumen Diameter (MLD)
The average of two orthogonal views (when possible) of the narrowest point within the area of assessment- in lesion or in segment. MLD is visually estimated during angiography by the Investigator; it is measured during QVA by the Angiographic Core Lab.

Patent Run-off
A vessel starting at the popliteal artery to the foot presenting a hemodynamically insignificant stenosis of <50%, as determined by duplex ultrasound.

Perforation
Perforations are classified as follows:

- Angiographic perforation: perforation detected by the clinical site or Angiographic Core Laboratory at any point during the procedure.
- Clinical perforation: perforation requiring additional treatment (including efforts to seal the perforation), or resulting in significant hemodynamic compromise, abrupt closure, or death.

Primary Patency
Primary Patency of the target lesion is defined as the absence of binary restenosis based on DUS peak systolic velocity ratio 2:2.4.

Repeat Intervention (Percutaneous and /or Surgery)
Either repeat percutaneous transluminal angioplasty (PTA) or artery bypass surgery, performed subsequently to the subject leaving the cath lab after the index procedure.

Reference Vessel Diameter (RVD) of Normal Artery Segment
The interpolated reference vessel diameter is based on a computed estimation of the original diameter of the artery at the level of the obstruction (minimal luminal diameter)

Restenosis
Peak Systolic Velocity Ratio (PSVR) of >2.4, determined by blinded Duplex ultrasound.

Restenotic Lesion
A lesion in a vessel segment that had undergone a prior percutaneous treatment

Rutherford Clinical Classification
A classification system of clinical categories of chronic limb ischemia ranging from 0 to 6.

Grade	Category	Clinical Description
0	0	Asymptomatic
I	1	Mild claudication
I	2	Moderate claudication
I	3	Severe claudication
II	4	Ischemic rest pain
II	5	Minor tissue loss-nonhealing ulcer, focal gangrene with diffuse pedal edema
III	6	Major tissue loss – extending above MT level

Screen Failures
Subjects screened, but not meeting all study entry criteria and hence are not enrolled, are considered screening failures and will be documented as such on the Screening Logs.

Source Data
All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical investigation, necessary for the reconstruction and evaluation of the trial. Source data are contained in the source documents (original records).

Source Document
Original documents, data or records.

> Examples: Hospital records, laboratory notes, device accountability records, photographic negatives, radiographs, records kept at the investigation site, at the laboratories and at the medico-technical departments involved in the clinical investigation.

Target Lesion
Lesion that is to be treated during the index procedure. For study inclusion, the lesion are at least 10 mm below the bifurcation of the common femoral artery and at least 10 mm above the tibioperoneal trunk.

Target Lesion Revascularization
A repeat revascularization procedure (percutaneous or surgical) of the original target lesion site.

Target Vessel
The entire vessel in which the target lesion is located.

Target Vessel Revascularization (TVR)
A repeat revascularization procedure (percutaneous or surgical) of a lesion in the target vessel, exclusive of the target lesion site.

Thrombosis
A total occlusion documented by duplex ultrasound and/or angiography at the treatment site with or without symptoms. The presence of thrombus at the target lesion will be noted as an adverse event in the CRF.

Total Occlusion
100% stenosis within an artery.

12 ABBREVIATIONS

ABI:	Ankle-Brachial Index
AE:	Adverse Event
AHC:	Advocate Health Care
CFR:	Code of Federal Regulations
CMC:	Christ Medical Center
CRF:	Case Report Form
CTO:	Chronic Total Occlusion
DAP:	Dual Antiplatelet Therapy
DCB:	Drug Coated Balloon
DUS:	Duplex Ultrasound
FDA:	Federal Drug Administration
HRP:	Human Research Protection
IFU:	Instructions for Use
IRB:	Institutional Review Board
ISR:	In-stent restenosis
ITT:	Intent to Treat
LLL:	Late Lumen Loss
PAD:	Peripheral Artery Disease
PHI:	Personal Health Information
PSVR:	Peak Systolic Velocity Ratio
PPA:	Posterior Popliteal Artery
PTA:	Percutaneous Transluminal Angioplasty
SAE:	Serious Adverse Event
SFA:	Superficial Femoral Artery
TLR:	Target Lesion Revascularization
TVR:	Target Vessel Revascularization
UADE:	Unanticipated Adverse Device Effect
UB04:	A uniform billing claim form used hospitals and other healthcare facilities

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