

A Prospective, Multicenter, Single Blind, Randomized,
Controlled Trial Comparing the Lutonix Drug Coated
Balloon vs. Standard Balloon Angioplasty for Treatment
of Below-the-Knee (BTK) Arteries
(Lutonix BTK Trial)

Investigational Plan

Version 12.0

Protocol #CL0005-01

Sponsor:

BARD | LUTONIX 

9409 Science Center Drive

New Hope, MN 55428 USA

A subsidiary company of C.R. Bard

Investigational Device: Lutonix[®] Drug Coated Balloon

NCT Number: 01870401 (NCT number added post-approval per CT.gov requirement)

This study will be conducted in compliance with the protocol and all other applicable regulatory requirements including the archiving of essential documents.

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PROTOCOL SIGNATURE PAGE
The Lutonix BTK Trial Investigational Plan

**A Prospective, Multicenter, Single Blind, Randomized, Controlled Trial Comparing the
Lutonix Drug Coated Balloon vs. Standard Balloon Angioplasty for Treatment of Below-
the-Knee (BTK) arteries**

I have read this protocol and agree to adhere to the requirements. I will provide copies of this protocol and all pertinent information to the study personnel under my supervision and my hospital Institutional Review Board/Ethics Committee. I will discuss this material with them and ensure they are fully informed regarding the investigational device and the conduct of the study according to ICH Good Clinical Practice (GCP), ISO 14155, Declaration of Helsinki, 21CFR 50, 56 and 812, and any local regulations.

Clinical Site Name _____

Site Principal Investigator
(Print Name)

Site Principal Investigator
(Signature)

Date

The Lutonix BTK Trial Protocol Summary

Title	A Prospective, Multicenter, Single Blind, Randomized, Controlled Trial Comparing the Lutonix Drug Coated Balloon vs. Standard Balloon Angioplasty for Treatment of Below-the-Knee (BTK) arteries
Test Device	Lutonix® 0.014” OTW Drug Coated PTA Dilatation Catheter (Lutonix DCB Catheter)
Control Device	Non-coated standard percutaneous transluminal angioplasty balloon catheter (standard uncoated PTA catheter)
Study Design	Prospective, Multicenter, Single Blind, Randomized, Safety and Efficacy
Overview	<p>The study will enroll patients presenting with below-the-knee disease (Rutherford Category 3, 4 or 5) and an angiographically significant ($\geq 70\%$) native artery lesion appropriate for angioplasty that is below the tibial plateau and above the tibiotalar joint. After successful protocol-defined pre-dilatation, subjects that continue to meet lesion and outflow angiographic criteria are randomized 2:1 to treatment with either the Lutonix DCB (test) or standard uncoated PTA catheter (control). All target lesion(s) in up to two target vessels are treated with the as-randomized test DCB or control PTA. After the protocol-defined pre-dilatation with a standard uncoated PTA catheter step is completed and if randomized to control, treatment with an additional standard uncoated PTA catheter (control device) is at the discretion of the investigator as long as 0-30% residual stenosis is achieved. Subjects with no target vessels that meet post-predilatation entry criteria are excluded (and treated per standard practice) and followed for safety for 30 days.</p> <p>Primary endpoint assessment is performed at 30 days for safety and at 6 months for efficacy. Doppler is required for all subjects. Clinical follow-up continues through 3 years.</p>
Purpose	To assess the safety and efficacy of the Lutonix DCB for treatment of stenosis or occlusion of native below-the-knee arteries.
Objective	To demonstrate the superior efficacy and non-inferior safety of the Lutonix DCB by direct comparison to standard PTA catheter for treatment of stenosis or occlusion of below-the-knee arteries.
Randomization	Subjects will be randomized 2:1 to Lutonix DCB or standard PTA catheter.
Enrollment	Enrollment will occur at up to 75 global centers. Up to 1000 subjects may be enrolled to obtain up to the maximum of 840 treated vessels for the primary analysis. The study includes interim analyses that occur when 400, 500, 600, and 700 vessels are treated. A Bayesian decision making process will be utilized to determine the final sample size

	<p>for the study based on the predicted probability of study success in the primary effectiveness assessment.</p> <p>At least 50% of randomized enrollment will occur in the US.</p>
Randomized Subject Follow-Up Schedule	<i>Clinical:</i> 1, 6, 12, 24, 36 Months
Primary Endpoints	<p><u>Safety:</u> Freedom from BTK MALE+POD at 30-Days</p> <p>Freedom at 30-Days from the composite of all-cause death, above-ankle amputation or <i>major</i> reintervention (new bypass graft, jump/interposition graft revision, or thrombectomy/thrombolysis) of the index limb involving a below-the-knee artery.</p> <p><u>Efficacy:</u> Composite of Limb Salvage and Primary Patency at 6 Months</p> <p>Defined as freedom from the composite of above ankle amputation, target lesion occlusion, and clinically-driven target lesion reintervention.</p>
Secondary Endpoints	<ul style="list-style-type: none"> • Device (able to deliver, inflate and retrieve), Technical (device success and < 30% residual stenosis) and Procedural Success (restoration of at least 1 infrapopliteal artery with residual stenosis < 30% and inline outflow to the foot) • Comparison of the BTK MALE+POD rate in the test arm to a performance goal at 30 Days • Change in quality of life at 6, 12, 24, and 36 months from baseline, as measured by EQ-5D survey • Late lumen loss at 12 months (cohort with angiography) <p>The following endpoints will be assessed at 30 days and at 6, 12, 24, and 36 months:</p> <ul style="list-style-type: none"> • Wound healing (healed or not; if not, improving, stagnant, worsening) • New or recurrent lesion (target limb) • Change in Rutherford Class (target limb) • Composite of freedom from the following in the index limb: <ul style="list-style-type: none"> Above-ankle amputation, unhealed wound, ischemic rest pain, target vessel occlusion, and clinically-driven TVR • Primary Patency (freedom from occlusion without clinically-driven TLR) • Primary Patency with exclusion of early mechanical recoil (freedom from occlusion without clinically-driven TLR events > 30 days) • Secondary Patency (not occluded, irrespective of TLR)

	<ul style="list-style-type: none"> • Composite of freedom from clinically-driven TLR and from 50% DS by angiography/DUS • Hemodynamic outcome (change in toe & ankle pressures) • Change in Walking Impairment Questionnaire (improvement from baseline) <p>The following endpoints will be assessed at 30 days and at 6, 12, 24, and 36 months:</p> <ul style="list-style-type: none"> • Clinically-driven TLR (all randomized subjects and in AFS cohort) • Total TLR (all randomized subjects and in AFS cohort) • Clinically-driven TVR (all randomized subjects and in AFS cohort) • Total TVR (all randomized subjects and in AFS cohort) • Limb salvage in surviving subjects (target limb) • Unplanned below ankle amputation (including digit) of the target limb • Overall burden of BTK index-limb reinterventions (total number of index limb BTK interventions incurred, all randomized subjects and AFS cohort) • Composite of POD, index limb-related death, below-the-knee reinterventions or major amputation of the index-limb • SVS CLI Endpoint Definitions ((3) Conte 2009 JVS 50:1462-73) <ul style="list-style-type: none"> ▪ MALE: Major adverse Limb Event: Above ankle amputation of the index limb or major reintervention (new bypass graft, jump/interposition graft revision, or thrombectomy/thrombolysis) ▪ MALE+POD: Perioperative death (30 days), or any MALE ▪ MACE: Major Adverse Cardiovascular Event: MI, stroke or death (any cause) ▪ Amputation (Major): Above ankle amputation of the index limb ▪ AFS: Amputation free survival (freedom from above ankle amputation of the index limb or death (any cause)) ▪ RAO: Any reintervention or above ankle amputation of the index limb. ▪ RAS: Any reintervention, above ankle amputation of the index limb, or stenosis ▪ DEATH: Death (any cause)
<p>Inclusion Criteria</p>	<p><u>Clinical Criteria</u></p> <ol style="list-style-type: none"> 1. Male or non-pregnant, non-breastfeeding female ≥ 18 years of age; 2. Rutherford Clinical Category 3, 4, or 5; NOTE: Patients categorized as a Rutherford Clinical Category 3 must have failed medical management per physician discretion. 3. Life expectancy ≥ 1 year;

4. Patient is willing to provide informed consent, is geographically stable, and is willing to comply with the protocol-required follow up visits, testing schedule and recommended medication regimen;
5. No other prior surgical or vascular interventions within 2 weeks before and/or planned 30 days after the protocol treatment;
NOTE: The following are allowed within 2 weeks prior or within 30 days after the procedure:
- Planned transmetatarsal or lower minor amputations
 - Index limb inflow-lesion treatment
 - Contralateral iliac treatment
 - Wound debridement
- NOTE:** Except for allowed iliac treatment (noted above), contralateral limb lesion(s) cannot be treated during the index procedure or within 2 weeks before and/or planned 30 days after in order to avoid confounding complications;

Angiographic Criteria

6. Significant stenosis ($\geq 70\%$) or occlusion of one or two native artery(s) below the tibial plateau and above the tibiotalar joint appropriate for angioplasty per operator visual assessment
NOTE: One or two flow pathways are allowed as artery(s); i.e., peroneal or posterior tibial arteries may involve tibioperoneal trunk lesions and tibial arteries may involve popliteal lesions;
7. Cumulative length of target lesion(s) ≤ 320 mm;
NOTE: Maximum allowed cumulative length of all DCBs ≤ 360 mm;
8. Target lesion(s) not previously stented and at least 20 mm from any previous stent;
9. A patent inflow artery from the aorta to the target lesion free from significant ($\geq 50\%$) stenosis as confirmed by angiography
NOTE: concurrent or staged treatment of iliac/SFA/above-knee popliteal artery is allowed if successfully performed (with residual diameter stenosis $\leq 30\%$ and reconstitution at least 30 mm proximal to tibial plateau) without major vascular complication;
NOTE: If atherectomy is performed on the superficial femoral (SFA) or popliteal lesion(s), use of a distal embolic filter is required.
NOTE: Treatment of the femoropopliteal with a DCB is not allowed during the index procedure.
10. Target vessel(s) diameter between 2 and 4 mm and able to be treated with available device size matrix;

	<p>11. Successful antegrade pre-dilatation of the target lesion with standard PTA catheter appropriate size for the reference vessel diameter; NOTE: Successful pre-dilatation defined by residual stenosis $\leq 50\%$ and operator determination that procedural success may be achievable by angioplasty alone NOTE: Multiple lesions allowed, but ALL target lesions MUST be successfully pre-dilated prior to randomization NOTE: If the popliteal artery is pre-dilated, it MUST meet angiographic inclusion criteria NOTE: Retrograde access for initial wire crossing allowed, but pre-dilatation and treatment must be performed over antegrade wire</p> <p>12. Target vessel(s) reconstitute(s) at or above the ankle with inline flow to at least one patent ($<50\%$ residual stenosis) inframalleolar outflow vessel (planned treatment below-the-ankle is not allowed) NOTE: Outflow must be assessed AFTER pre-dilatation NOTE: Two arteries allowed, but each target vessel MUST demonstrate inline inframalleolar outflow prior to randomization.</p>
<p>Exclusion Criteria</p>	<p>Patients will be excluded if ANY of the following conditions apply:</p> <ol style="list-style-type: none"> 1. Any severe medical comorbidities (untreated CAD/CHF, severe COPD, metastatic malignancy, etc.) that would preclude compliance with the study protocol or currently receiving immune-suppressive, chemotherapeutic, or radiation therapy; 2. Patient is currently participating in an investigational drug or device study or previously randomized or a roll-in subject in this study NOTE: Enrollment in another drug or device study during the follow-up period is not allowed; 3. History of stroke within 3 months; 4. History of MI, thrombolysis or angina within 30 days of enrollment; 5. Gangrene extending proximal to the digit-metatarsal skin crease (index limb); NOTE: Gangrene must be confined to the toe or toes 6. Ischemic ulceration that extends more than 4 cm proximal to digit-metatarsal skin crease (index limb); NOTE: If ulcers are confined to toe, involvement of tendon or bone is acceptable. Ulcers proximal to digit-metatarsal skin crease must be superficial (not involving tendon or bone). 7. Neurotropic ulcer or heel pressure ulcer or ulcer potentially involving calcaneus (index limb); 8. Evidence of osteomyelitis in a bone not intended for resection (index limb);

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Angiographic Core Lab	[REDACTED] [REDACTED] [REDACTED]
DUS Core Lab	[REDACTED] [REDACTED] [REDACTED]
EU Authorized Rep:	[REDACTED] [REDACTED] [REDACTED]
Japan Sponsor Authorized Rep:	[REDACTED] [REDACTED] [REDACTED]

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1 INTRODUCTION

The purpose of this investigation is to assess the safety and efficacy of the Lutonix™ Drug Coated Balloon (DCB) for treatment of a stenosis or occlusion of below-the-knee (BTK) arteries.

1.1 CLINICAL BACKGROUND

Peripheral arterial disease (PAD) is estimated to be present in 3% of people in the age range of 40-59 years and in 20% of people over 70 years¹ of age. Most common clinical presentation comprises intermittent claudication but about one third of patients will progress to critical limb ischemia characterized by rest pain and/or tissue loss, which is the most severe limb manifestation of PAD. Intermittent claudication significantly affects quality of life and is associated with severe functional impairment.² While revascularization should be attempted without delay in all patients presenting with critical limb ischemia, whenever technically possible, the management of intermittent claudication varies depending on the severity of walking impairment and the associated impact of functional disability on individual lifestyle with limb revascularization procedures being pursued when exercise and/or drug therapy fail to improve symptoms.³

Revascularization for intermittent claudication is an appropriate therapy for selected patients with disabling symptoms, after a careful risk-benefit analysis and based on comorbid conditions, degree of functional impairment, and anatomical factors.⁴ Successful revascularization of lower extremity peripheral arterial disease in patients affected by intermittent claudication in addition to improving functional status, reduces the occurrence of future major cardiovascular events (PTA compared to patients manage with conservative therapy 6.4% vs. 16.3%; p=0.003).⁵ The same result has been found in the diabetic patient affected with intermittent cludication there was improve walking performance, and an associated reduction in the incidence of future major

¹ Zeller, T. Current state of endovascular treatmet of femoro-popliteal artery disease. *Vas Med* 12 (2007): 223-234.

² McDermmott MM, Greenland P, Liu K, Guralnik JM, Criqui MH, Dolan NC, et al. Leg symptoms in peripheral arterial disease: associated clinical characteristics and functional impairment. *JAMA* 2001;286:1599-606.

³ Tendera M, Aboyans V, Bartelink ML, Baumgartner I, Clement D, Collet JP, Cremonesi A, De Carlo M, Erbel R, Fowkes FG, et al: ESC Guidelines on the diagnosis and treatment of peripheral artery diseases: Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries: the Task Force on the Diagnosis and Treatment of Peripheral Artery Diseases of the European Society of Cardiology (ESC). *European heart journal* 2011, 32:2851-2906.

⁴ Society for Vascular Surgery Lower Extremity Guidelines Writing Group, Conte MS, Pomposelli FB, Clair DG, Geraghty PJ, McKinsey JF, Mills JL, Moneta GL, Murad MH, Powell RJ, Reed AB, Schanzer A, Sidawy AN; Society for Vascular Surgery. Society for Vascular Surgery practice guidelines for atherosclerotic occlusive disease of the lower extremities: management of asymptomatic disease and claudication. *J Vasc Surg*. 2015 Mar;61(3 Suppl):2S-41S. Erratum in: *J Vasc Surg*. 2015 May;61(5):1382

⁵ Giugliano G1, Di Serafino L, Perrino C, Schiano V, Laurenzano E, Cassese S, De Laurentis M, Schiattarella GG, Brevetti L, Sannino A, Gargiulo G, Franzone A, Indolfi C, Piscione F, Trimarco B, Esposito G. Effects of successful percutaneous lower extremity revascularization on cardiovascular outcome in patients with peripheral arterial disease. *Int J Cardiol*. 2013 Sep 10;167(6):2566-71.

cardiovascular events with PTA over managed conservative therapy.⁶ A recent study evaluating infrapopliteal angioplasty was performed with a paclitaxel-eluting balloon in patients with tibial artery disease in 104 patients. Of the limbs treated 82.6% were critical limb ischemia (Rutherford category 4-6) and 17.4% severe claudication (Rutherford category 3) resulting in significantly lower early restenosis rate of long-segment infrapopliteal disease after treatment with DEBs compared with historical data using uncoated balloons.⁷

While various endovascular treatment modalities have been developed for femoropopliteal lesions, standard percutaneous transluminal angioplasty (PTA) is still most commonly used for below-the-knee (BTK) interventions. The majority of patients undergoing BTK interventions suffer from critical limb ischemia (CLI) with high cardiovascular risk and often significant medical co-morbidities. CLI is typically defined as limb pain that occurs at rest (Rutherford Category 4, 5)⁸, or impending limb loss that is caused by severely compromised blood flow to the affected extremity. The principal threat to these patients is failure of the treatment to restore and maintain adequate blood flow to relieve ulceration, gangrene, or rest pain, leading to the need for a major amputation.

CLI populations are difficult to study due to their very high intermediate-term morbidity and mortality⁹. Most subjects die for reasons that cannot be affected by differences in outcomes of treatment modalities used during a single interventional revascularization procedure. As a consequence less invasive endovascular revascularization has become the preferred first line treatment strategy in many centers due to lower peri-procedural morbidity and mortality as compared to surgical bypass.

Two recent meta-analyses^{10,11} studying BTK-PTA reported 1-year primary patency rates of 46.5% to 58.1%, limb salvage rates of 86.0% to 88.9% and overall 1-year survival rates of 85.7% to 87.0%. Another meta-analysis focused on 'un-reconstructable' CLI reported a 1-year

⁶ Giugliano G1, Perrino C, Schiano V, Brevetti L, Sannino A, Schiattarella GG, Gargiulo G, Serino F, Ferrone M, Scudiero F, Carbone A, Bruno A, Amato B, Trimarco B, Esposito G. Endovascular treatment of lower extremity arteries is associated with an improved outcome in diabetic patients affected by intermittent claudication. *BMC Surg.* 2012;12 Suppl 1:S19.

⁷ Schmidt A, Piorkowski M, Werner M, Ulrich M, Bausback Y, Bräunlich S, Ick H, Schuster J, Botsios S, Kruse HJ, Varcoe RL, Scheinert D. First experience with drug-eluting balloons in infrapopliteal arteries: restenosis rate and clinical outcome. *J Am Coll Cardiol.* 2011 Sep 6;58(11):1105-9.

⁸ Rutherford RB, Baker JD, Ernst C, Johnston KW, Porter JM, Ahn S, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. *J Vasc Surg* 1997;26:517-38.

⁹ Hirsch, AT, Haskal, ZJ, Hertzner, NR, Bakal, CW, Creager, MA, Halperin, JL, Hiratzka, LF, Murphy, WR, Olin, JW, Puschett, JB, Rosenfield, KA, Sacks, D, Stanley, JC, Taylor, LM Jr, White, CJ, White, J, White, RA, Antman, EM, Smith, SC Jr, Adams, CD, Anderson, JL, Faxon, DP, Fust. ACC/AHA 2005 guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): executive summary a collaborative report from the American Association for Vascular Surgery/Society for Vas. *J Am Coll Cardiol* (2006), 47:1239-1312.

¹⁰ Romiti M, Albers M, Brochado-Neto FC, Durazzo AE, Pereira CA and De Luccia N. Meta-analysis of infrapopliteal angioplasty for chronic critical limb ischemia. *J Vasc Surg.* 2008;47:975-981.

¹¹ Conte MS, Geraghty PJ, Bradbury AW, Hevelone ND, Lipsitz SR, Moneta GL, Nehler MR, Powell RJ and Sidawy AN. Suggested objective performance goals and clinical trial design for evaluating catheter-based treatment of critical limb ischemia. *J Vasc Surg.* 2009;50:1462-73

amputation-free survival rate of only 55.1%¹². Two more recent studies, ACHILLES¹³ and DESTINY¹⁴, demonstrated improved patency from use of limus-derived DES in short isolated lesions. However, these results are of questionable applicability to the broader CLI population where long lesions in multiple diseased vessels are common.

A novel therapy that is commercially available in some countries and under investigation in others is the drug coated balloon (DCB), an otherwise standard PTA catheter with a drug coating on the balloon surface. During angioplasty, DCBs are designed to deliver an anti-proliferative drug directly to tissues of the treated vessel wall, thus inhibiting neointimal hyperplasia and restenosis without the need for a permanent foreign body implant. The investigational device of the present study, the Lutonix DCB, is one example.

DCBs have the potential to provide a more durable treatment and also to improve clinical outcomes. Early data regarding treatment of BTK lesions with drug-coated balloons (DCB) have been positive. BTK treatment with a paclitaxel coated balloon catheter was reported from a single-center study investigating 104 patients (82.6 % of whom had CLI). One-year target lesion revascularization was 17.3% and limb salvage rates were 95.6 %. Clinical improvement and complete wound healing was 91.2 and 74.2 % respectively.¹⁵ Additionally, results from the single center DEBATE BTK trial showed superiority of DCB over PTA in tibial arteries.¹⁶ Binary restenosis was 27% in the DCB and 74% in the PTA group ($P < 0.001$). Finally, target lesion revascularization (TLR) was lower in patients treated with DCB compared to those treated with PTA (18% versus 43%). However, results from the a randomized trial which studied the Ampherion DCB (manufactured by Medtronic Inc, MN) for BTK treatment (IN.PACT DEEP) has raised concerns pertaining to the safety and efficacy of DCBs in infrapopliteal vessels due to a trend towards an increased major amputation and death rate in CLI patients through 12 months (DCB=8.8% vs. PTA= 3.6%, $p=0.08$).^{17,18}

¹² Benoit, E, O'Donnell, TF Jr, Kitsios, GD, Iafrazi, MD. Improved amputation-free survival in unreconstructable critical limb ischemia and its implications for clinical trial design and quality measurement. *J Vasc Surg* (2012), 55:781-789.

¹³ Schmidt, A. ACHILLES-STUDY (DES for BTK). *Seoul, Korea : Angioplasty Summit TCTAP 2012*, 2012.

¹⁴ Bosiers, M, Scheinert, D, Peeters, P, Torsello, G, Zeller, T, Deloos, K, Schmidt, A, Tessarek, J, Vinck, E, Schwartz, LB. Randomized comparison of everolimus-eluting versus bare-metal stents in patients with critical limb ischemia and infrapopliteal arterial occlusive disease. *J Vasc Surg* (2012), 55:390-398.

¹⁵ Schmidt A, Piorkowski M, Werner M, Ulrich M, Bausback Y, Braunlich S, Ick H, Schuster J, Botsios S, Kruse HJ, Varcoe RL and Scheinert D. First experience with drug-eluting balloons in infrapopliteal arteries: restenosis rate and clinical outcome. *Journal of the American College of Cardiology*. 2011;58:1105-9.

¹⁶ Liistro F, Porto I, Angioli P, Grotti S, Ricci L, Ducci K, Falsini G, Ventoruzzo G, Turini F, Bellandi G and Bolognese L. Drug-eluting balloon in peripheral intervention for below the knee angioplasty evaluation (DEBATE-BTK): a randomized trial in diabetic patients with critical limb ischemia. *Circulation*. 2013;128:615-21.

¹⁷ Zeller T, Baumgartner I, Scheinert D, Brodmann M, Bosiers M, Micari A, Peeters P, Vermassen F, Landini M, Snead DB, Kent KC and Rocha-Singh KJ. Drug-eluting balloon versus standard balloon angioplasty for infrapopliteal arterial revascularization in critical limb ischemia: 12-month results from the IN.PACT DEEP randomized trial. *Journal of the American College of Cardiology*. 2014;64:1568-76.

¹⁸ Laird JR and Armstrong EJ. Drug-Coated Balloons for Infrapopliteal Disease Digging Deep to Understand the Impact of a Negative Trial*. *Journal of the American College of Cardiology*. 2014;64:1577-1579.

Consecutive Leipzig registries^{19,20} demonstrate a similar benefit for single-arm, open-label DCB over historic PTA, with 3-month angiographic occlusion rate of 9.5% for DCB (n = 104) compared to 37.6% for control PTA (n = 50). In the DCB registry, the 1-year TLR rate was 17% and limb salvage was 96%¹⁰, which is significantly better than the outcomes reported for currently-available treatment modalities in the meta-analyses discussed above. DCB also performed better than control PTA in the subset with below-the-knee lesions treated in the “Drug-Eluting Balloon Evaluation for Lower Limb Multilevel Treatment” (DEBELLUM) study²¹. These initial results for DCB are consistent and very promising, and larger randomized trials are warranted to establish the safety and efficacy of DCB used to treat below-the-knee lesions.

1.1.1 THE LEVANT I FIRST-IN-MAN TRIAL SUMMARY

Lutonix recently completed the LEVANT I clinical trial²² in which the Lutonix DCB Catheter was compared to a standard PTA catheter (with and without stenting) for treatment of stenotic femoropopliteal arteries. The primary endpoint was angiographic late lumen loss at 6 months, as determined by an independent angiographic core lab analysis. One hundred-one randomized subjects were enrolled at 9 European centers. After a defined pre-dilatation, subjects were stratified to the balloon strata or stent strata and then randomized to treatment with the Lutonix DCB (n=49) or a standard PTA catheter (n=52, control group).

The Lutonix DCB exhibited significantly less late lumen loss (0.46 ± 1.13 mm) compared to that observed for conventional angioplasty (1.09 ± 1.07 mm) at 6 months ($p=0.016$). There were no unanticipated adverse device effects in the DCB arm, and overall adverse event rates were similar to conventional uncoated balloon angioplasty through 24 months. Taken together, the primary objective of the trial was met, and the angiographic and clinical results of the LEVANT I trial demonstrated the feasibility, safety, and efficacy of use of the Lutonix DCB for treatment of femoropopliteal lesions.

1.1.2 THE LEVANT 2 PIVOTAL IDE TRIAL

The pivotal Levant 2 IDE trial (NCT01412541) was designed in collaboration with physicians and FDA to demonstrate safety and efficacy of the Lutonix Catheter for treatment of femoropopliteal lesions in a larger population and to obtain US FDA approval. Levant 2 is a prospective, multicenter, single blind, 2:1 randomized, controlled trial comparing outcomes after

¹⁹ Schmidt, A, Ulrich, M, Winkler, B, Klaeffling, C, Bausback, Y, Bräunlich, S, Botsios, S, Kruse, HJ, Varcoe, RL, Kum, S, Scheinert, D. Angiographic patency and clinical outcome after balloon-angioplasty for extensive infrapopliteal arterial disease. *Catheter Cardiovasc Interv* (2010), 76:1047-1054.

²⁰ Schmidt, A, Piorowski, M, Werner, M, Ulrich, M, Bausback, Y, Bräunlich, S, Ick, H, Schuster, J, Botsios, S, Kruse, HJ, Varcoe, RL, Scheinert, D. First experience with drug-eluting balloons in infrapopliteal arteries: restenosis rate and clinical outcome. *J Am Coll Cardiol* (2011), 58:1105-1109.

²¹ Fanelli F, Cannavale A, Boatta E, Corona M, Lucatelli P, Wlderker A, Cirelli C, Salvatori FM. Lower limb multilevel treatment with drug-eluting balloons: 6-month results from the DEBELLUM randomized trial. *J Endovasc Ther* (2012), 19:571-580.

²² ClinicalTrials.gov Identifier: NCT00930813

treatment of symptomatic femoropopliteal artery lesions with Lutonix Catheter vs. uncoated PTA.

The trial pre-specified two primary endpoints that must both be met for trial success. The primary effectiveness endpoint is primary patency of the target lesion at 1 year. Primary patency is defined as the absence of target lesion restenosis and freedom from target lesion revascularization (TLR). The primary safety endpoint is freedom from all-cause perioperative (≤ 30 day) death and freedom at 1 year from the following: index limb amputation (above or below the ankle), index limb reintervention, and index-limb-related death. The tested hypothesis was that DCB would demonstrate superior effectiveness and non-inferior safety compared to PTA.

The trial enrolled patients with symptomatic claudication or ischemic rest pain (Rutherford category 2-4) and an angiographically significant atherosclerotic lesion ($>70\%$ diameter stenosis, ≤ 15 cm length) in the superficial femoral and/or popliteal arteries of diameter 4 to 6 mm with a patent outflow artery to the foot.

Enrollment began in July 2011, and randomization of 476 patients ($n = 316$ DCB vs. $N = 160$ PTA) at 55 centers was completed in July 2012. One year follow-up and primary endpoint analysis has been completed, and clinical follow-up is ongoing through 5 years.

Baseline demographics, comorbidities, and lesion characteristics were well matched between groups; 43% of patients were diabetic, 35% were current smokers, and 8% had critical limb ischemia (CLI). The mean lesion length was 62.8 mm and the treated length was 108 mm.

Levant 2 met both pre-specified primary endpoints. Primary patency for Lutonix Catheter (65.2%) was superior to control PTA (52.6%, $p = 0.015$) at 12 months, demonstrating superior efficacy. The primary safety endpoint success rate for Lutonix DCB (83.9%) was non-inferior to control PTA (79.0%, $p = 0.005$). Freedom from TLR was 87.7% for DCB compared to 83.2% for control PTA.

Several secondary endpoints were also analysed but not hypothesis tested. Procedural success ($< 30\%$ residual stenosis without SAE) was similar for Lutonix Catheter and control PTA (88.9% vs. 86.8%), demonstrating effectiveness at acute restoration of patency. The Rutherford scores, walking impairment (WIQ) scores, ABI, six minute walk test, and quality of life questionnaires each showed improvements from before treatment through 12 months in both treatment groups. At 12 months, 88.2% of Lutonix DCB patients and 82.4% of control PTA patients had improved Rutherford Class compared to baseline. Mean improvement in the WIQ total score was $23.9 \pm 27.6\%$ for Lutonix DCB compared to $19.2 \pm 26.5\%$ for control PTA, and improvement in WIQ walking distance was $31.5 \pm 37.0\%$ vs. $22.2 \pm 35.4\%$, respectively. Improvements in ABI, six minute walk test, EQ-5D, and SF-36v2 through 12 months were similar for both groups.

Secondary safety endpoints were generally similar for Lutonix Catheter and control PTA. These included, respectively, all-cause death (2.4% vs. 2.8%), amputation (0.3% vs. 0.0%), amputation-free survival (97.6% vs. 97.2%), thrombosis (0.4% vs. 0.7%), target vessel

revascularization (TVR, 13.3% vs. 18.2%), cardiovascular hospitalization (9.1% vs. 7.1%), and major vascular complications (6.3% vs. 4.9%; defined as hematoma >5 cm, false aneurysm, AV fistula, retroperitoneal bleed, peripheral ischemia/nerve injury, transfusion). Adverse events were similar for both treatment groups and consistent with historic data for the enrolled population with symptomatic PAD.

Levant 2 successfully demonstrated superior efficacy and non-inferior safety of Lutonix Catheter compared to control PTA.

1.2 DEVICE AND STUDY RATIONALE

The Lutonix BTK DCB Catheter is intended for use as a percutaneous transluminal angioplasty (PTA) catheter for dilatation of obstructive de novo or non-stented restenotic lesions in native popliteal, tibial, and peroneal arteries ≥ 2.0 and ≤ 4.0 mm in diameter. The drug coating on the Lutonix DCB contains paclitaxel and excipients (polysorbate and sorbitol) with a history of human safety for intravenous use. Each component has been safely used in other products. PTA catheters have been in commercial use for over 25 years, and the Lutonix DCB Catheter meets international standards (e.g. ISO 10555) developed over time to validate the mechanical safety of dilation catheters. The anti-proliferative drug paclitaxel is a well understood active pharmaceutical ingredient (API) with an extensive history of human use in oncology²³ and drug-eluting stents (DES)²⁴. The maximum total dose of 3.8 mg on the largest peripheral Lutonix DCB Catheter is less than 2% of the dose of approximately 300 mg infused during a single course of cancer therapy. In addition, GLP animal Safety and 4x dose Safety Margin studies have been performed to confirm the safety of the Lutonix DCB Catheter.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 PRIMARY OBJECTIVE

The primary objective of the Lutonix BTK study is to demonstrate the superior efficacy and non-inferior safety of the Lutonix DCB Catheter by direct comparison to standard PTA catheter for treatment of stenosis or occlusion of below-the-knee arteries.

Enrollment will occur at up to 75 global centers. Up to 1000 subjects may be enrolled to obtain up to the maximum of 840 treated vessels for the primary analysis.

Clinical follow-up is scheduled at 30 days, 6, 12, 24 and 36 months.

²³ Pacific Yew: Draft Environmental Impact Statement. Appendices. U.S. Departments of Agriculture, Interior, and Health and Human Services. January 1993.

²⁴ Lasala J, et.al. An Overview of the TAXUS® Express®, Paclitaxel-Eluting Stent Clinical Trial Program. *J Interv Cardiol* (2006), 19:431-442.

2.2 PRIMARY ENDPOINTS

2.2.1 SAFETY

The primary safety endpoint is freedom from BTK MALE (major adverse limb event) + POD (peri-operative death) at 30 Days. This is strictly defined as the composite at 30 days of all-cause death, above-ankle amputation or major reintervention (new bypass graft, jump/interposition graft revision, or thrombectomy/thrombolysis) of the index limb involving a below-the-knee artery.

Percutaneous vascular reintervention involving a BTK artery is considered less major (than death, amputation, bypass, or thrombolysis) and is not counted as a failure of the primary safety endpoint. Since percutaneous reintervention is captured as a failure of the primary efficacy endpoint, this serves to decrease endpoint concordance that would otherwise arise from having the most common serious adverse event in both co-primary endpoints. In addition, not counting percutaneous reintervention as a failure made it possible to determine an expected failure rate, which was necessary for study powering. Unlike at 12-months, from historical studies it is nearly impossible to tease out an expected 30-day rate of percutaneous reintervention with a mandatory 30-day clinical visit. In contrast, there is very good data for MALE and POD. Two recent meta-analyses^{10,11} report 30 day data for elements of the composite safety endpoint.

Major but not minor amputations are considered safety failures. In the enrolled population with significant risk of limb loss, many minor toe amputations will have already been planned at the time of the index procedure and will not constitute major adverse safety events. Pre-defined clinical events, including index limb-relatedness of death, will be adjudicated by the blinded CEC.

Major reinterventions below-the-knee are considered a safety failure but reintervention above-the-knee is not. Since about half of enrolled subjects are expected to also require inflow treatment, and this will be allowed prior to randomization, above-the-knee re-interventions reflect safety of a pre-randomization procedure and could only confound safety assessment of the device used for treatment below-the-knee.

2.2.2 EFFICACY

The primary efficacy endpoint is the composite of Limb Salvage and primary patency at 6 months. The primary efficacy endpoint is defined as freedom from the composite of above ankle amputation, target lesion occlusion, and clinically-driven target lesion reintervention.

Clinically-driven is defined by stagnant or worsening wound healing, new or recurrent wound, or worsening of Rutherford Class in index limb.

Freedom from occlusion must be established by angiography and/or Doppler. Angiography is the gold standard for target lesion assessment, and patency will be determined by angiography if performed. Patency will be assessed by Doppler if angiography is not performed.

Although binary restenosis based on angiographic 50% diameter stenosis (%DS) became popular in the context of coronary stenting, clinical relevance with respect to its use in infrapopliteal artery assessments is uncertain, particularly if ischemic wounds and rest pain have healed and there is in-line flow. A more clinically meaningful measure of target vessel patency in this population may be the original surgeon's definition of patency, i.e. "open" or "closed" vessel. This definition of patency allows a less stringent requirement for angiography. Therefore, the primary efficacy endpoint measure for this study is freedom-from-occlusion and not freedom-from-binary restenosis (arbitrarily 50%DS), which is instead captured as a secondary endpoint.

Doppler is required at all clinical visits. Even in calcified tibial arteries, the presence of antegrade flow through the target vessel can usually be established by Doppler.

2.3 SECONDARY ENDPOINTS

- Device (able to deliver, inflate and retrieve), Technical (device success and < 30% residual stenosis) and Procedural Success (restoration of at least 1 infrapopliteal artery with residual stenosis < 30% and inline outflow to the foot)
- Comparison of the BTK MALE+POD rate in the test arm to a performance goal at 30 Days
- Change in quality of life at 6, 12, 24, and 36 months from baseline, as measured by EQ-5D survey
- Late lumen loss at 12 months (cohort with angiography)
 - The following endpoints will be assessed at 30 days and at 6, 12, 24, and 36 months:
 - Wound healing (healed or not; if not, improving, stagnant, worsening)
 - New or recurrent lesion (target limb)
 - Change in Rutherford Class (target limb)
 - Composite of freedom from the following in the index limb:
Above-ankle amputation, unhealed wound, ischemic rest pain, target vessel occlusion, and clinically-driven TVR
 - Primary Patency (freedom from occlusion without clinically-driven TLR)
 - Primary Patency with exclusion of early mechanical recoil (freedom from occlusion without clinically-driven TLR events > 30 days)
 - Secondary Patency (not occluded, irrespective of TLR)
 - Composite of freedom from clinically-driven TLR and from 50% DS by angiography/DUS
 - Hemodynamic outcome (change in toe & ankle pressures of target limb)
 - Change in Walking Impairment Questionnaire (improvement from baseline)

The following endpoints will be assessed at 30 days and at 6, 12, 24, and 36 months:

- Clinically-driven TLR (all randomized subjects and in AFS cohort)
- Total TLR (all randomized subjects and in AFS cohort)
- Clinically-driven TVR (all randomized subjects and in AFS cohort)

- Total TVR (all randomized subjects and in AFS cohort)
- Limb salvage in surviving subjects (target limb)
- Unplanned minor below ankle amputation (including digit) of target limb
- Overall burden of BTK index-limb reinterventions (total number of index limb BTK interventions incurred, all randomized subjects and AFS cohort)
- Composite of POD, index limb-related death, below-the-knee reinterventions or major amputation of the index-limb
- SVS CLI Endpoint Definitions ((3) Conte 2009 JVS 50:1462-73)
 - MALE: Major adverse Limb Event: Above ankle amputation of the index limb or major reintervention (new bypass graft, jump/interposition graft revision, or thrombectomy/thrombolysis)
 - MALE+POD: Perioperative death (30 days), or any MALE
 - MACE: Major Adverse Cardiovascular Event: MI, stroke or death (any cause)
 - Amputation (Major): Above ankle amputation of the index limb
 - AFS: Amputation free survival (freedom from above ankle amputation of the index limb or death (any cause))
 - RAO: Any reintervention or above ankle amputation of the index limb.
 - RAS: Any reintervention, above ankle amputation of the index limb, or stenosis
 - DEATH: Death (any cause)

3 DEVICE DESCRIPTION

The Lutonix DCB Catheter consists of an OTW catheter with a DCB fixed at the distal tip. The uncoated portion of the device consists of a dual lumen shaft with a high pressure dilatation balloon mounted on the distal tip. Two radiopaque marker bands delineate the working length of the balloon and are located under the proximal and distal ends of the balloon to facilitate fluoroscopic visualization of the DCB during delivery and placement. The balloon surface between the marker bands is coated with a specialized immediate release non-polymer based coating formulation that includes the anti-proliferative drug – paclitaxel - at a surface concentration of $2\mu\text{g}/\text{mm}^2$ and two well-known carriers polysorbate and sorbitol.

The coaxial catheter includes a low profile, semi-compliant balloon formed to a low profile tapered tip to facilitate advancement of the catheter to and through the stenotic region of the vessel. The proximal portion of the catheter includes a female luer lock hub connected to the inflation lumen used to inflate and deflate the balloon, and a female luer lock hub connected to the guidewire lumen. The guidewire lumen ends at the tip of the catheter and permits the use of guidewires for advancement of the catheter through the stenotic lesion.

A balloon Compliance Chart is included on each device product label.

The Lutonix DCB Catheter is compatible with 0.014” (0.36mm) guidewires and is available in 150cm lengths. Each product has a peelable balloon protector that has been positioned over the

balloon for protection prior to use. To prevent crushing of the Lutonix DCB Catheter wire lumen, a disposable stainless steel stylet resides in the lumen.

The Lutonix DCB Catheter operates on the principle of hydraulic pressurization applied through an inflatable balloon attached to the distal end. Upon inflation, the balloon expands to a specified diameter as defined per the Compliance Chart on the product label.

The catheter is made of common materials typical of standard PTA catheters. The investigator should verify device size availability before each procedure. Always follow the current Instructions for Use (IFU) for procedural information, preparation and use of the Lutonix DCB Catheter.

All devices are provided sterile and are for single-use only. Devices are clearly labeled for investigational use only.

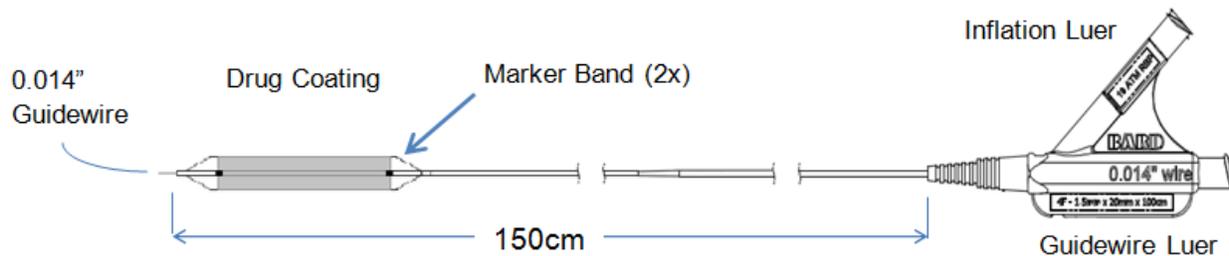


FIGURE 1: LUTONIX 0.014" OTW DRUG COATED PTA DILATATION CATHETER

3.1 INTENDED USE / INDICATIONS FOR USE

The Lutonix DCB Catheter is intended for percutaneous transluminal angioplasty of obstructive *de novo* or non-stented restenotic lesions in the native popliteal, tibial, and peroneal arteries ≥ 2.0 and ≤ 4.0 mm in diameter.

3.2 ACTIVE PHARMACEUTICAL INGREDIENT (API): PACLITAXEL

Paclitaxel, discovered in 1967 and commercially developed by Bristol-Myers Squibb, is a well known mitotic inhibitor indicated for use in the treatment of patients with lung, ovarian, breast, head and neck cancers and advanced forms of Kaposi's sarcoma. Paclitaxel is also approved for the prevention of restenosis. Various dosages are used depending on target treatment and range from multiple 300 mg IV infusions for oncology therapy to a single maximal nominal dose of 282 μ g for devices that treat restenosis, such as coronary stents. Please refer to

Figure 2 and the Investigator's Brochure for a more detailed review of paclitaxel.

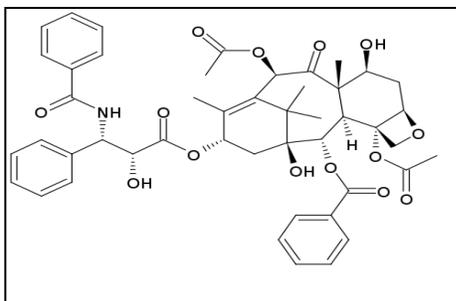


FIGURE 2 : CHEMICAL STRUCTURE OF PACLITAXEL

3.3 EXCIPIENT (DRUG CARRIER)

The balloon coating includes small amounts of well-known excipients (polysorbate and sorbitol) that are approved by the Food and Drug Administration (FDA) as inactive ingredients in drug products for intravenous (IV) drug delivery.

3.4 DEVICE INSTRUCTIONS

A comprehensive set of Instructions for Use (IFU), including warnings and precautions, has been created. Please refer to the most current IFU for complete details on preparation and procedural use of the device. A sample IFU can be found in Appendix E.

3.5 SUPPLY & SUPPORT OF INVESTIGATIONAL DEVICE

An investigational device supply of the Lutonix DCB Catheter will be made available to all activated study sites. The investigational device matrix that is currently available for this study is referenced in the current IFU. Always confirm current site inventory supply prior to enrolling subjects into the study.

Prior to start of study enrollment, Lutonix or their designee will perform device training for study site personnel and support staff. Each study site will receive a supply of the Lutonix DCB Catheters upon completion of the protocol requirements for study initiation. Additional training and support will be provided as needed on an ongoing basis. Any unused devices must be returned to the sponsor at the time site enrollment stops or upon sponsor request. After use, this product may be a potential biohazard. Handle and dispose of in accordance with acceptable medical practices and applicable local, state and federal laws and regulations. For quality control purposes, devices may be requested to be returned to the sponsor before or after use, in which case the site should return devices by requesting a Return Material Authorization (RMA) number from the Sponsor.

4 RISK-BENEFIT ANALYSIS

4.1 POTENTIAL RISKS

The potential risks and benefits of participation in this study are clearly identified in the subject Informed Consent Form (ICF) and are to be explained to the subject and/or their legal representative prior to participating in the study. The Lutonix DCB Catheter and standard

uncoated percutaneous angioplasty catheters are intended to be the only devices used for treatment of the target lesion.

Due to the high similarity of the Lutonix DCB Catheter to other marketed balloon catheters, procedural use is not expected to significantly change or increase risks during the initial procedure. However, it shares the risks of conventional balloon angioplasty treatment of patients with vascular disease in the lower extremities. There may also be risks associated with the drug coating on the Lutonix DCB Catheter that are unknown at this time. Please refer to the Investigator's Brochure for more details on the development of the Lutonix DCB Catheter.

4.1.1 RISKS FOR PERIPHERAL CATHETERIZATION PROCEDURE

Potential adverse events which may be associated with a peripheral balloon dilatation catheterization procedure include, but are not limited to, the following:

- abnormal heart rhythms
- abrupt vessel closure
- allergic reaction
- aneurysm or rupture of the artery
- AV fistula
- bleeding
- death
- dissection
- embolization
- femoral nerve compression with associated neuropathy
- groin area bruising and discomfort
- hematoma
- hypotension/hypertension
- inflammation
- kidney failure
- low blood pressure
- pain or tenderness
- perforation
- pseudoaneurysm
- respiratory failure
- sepsis/infection
- shock
- stroke
- total occlusion or thrombosis
- vessel dissection, perforation, rupture, or spasm that may require re-intervention or surgery
- additional angiographic intervention, surgical intervention, or amputation

There may be other potential adverse events that are unforeseen at this time.

Even if the balloon catheter procedure is deemed successful, it is associated with a meaningful risk of vessel narrowing within 12 months (depending on risk factors). Additional therapy may be required within 12 months such as reintervention using angioplasty or surgery.

Patients undergoing an interventional procedure are often treated with courses of thienopyridines such as clopidogrel or prasugrel, which may cause thrombocytopenic purpura and/or bleeding complications. In rare cases, these drugs may cause a significant reduction in white blood cell count, which may in turn result in serious infections. Aspirin is also a common drug used before and after such procedures. Aspirin is known to contribute occasionally to causing gastrointestinal ulcers (bleeding or non-bleeding). Aspirin may also affect platelet function to the extent of causing bleeding complications (which may be minor, major, or life threatening). If such conditions occur, the patient may require surgery, blood transfusion, or platelet transfusion.

Any of the above could cause prolonged illness, permanent impairment of daily function or, in rare cases, death. Possible treatments could include, but are not limited to emergency PTA and vascular surgery. It is expected that the fluoroscopy time of the interventional procedure will be similar to the time required for conventional percutaneous lower extremity interventional procedures and not pose additional risks to the subject or lab personnel.

4.1.2 ASSOCIATED RISKS FROM THE DRUG COATING

The balloon coating includes the API paclitaxel and small amounts of well-known excipients (polysorbate and sorbitol) that are approved by the Food and Drug Administration (FDA) as inactive ingredients in drug products for intravenous (IV) drug delivery. Additional adverse events that may be unique to the paclitaxel drug coating include:

- allergic/immunologic reaction
- alopecia
- anemia
- blood product transfusion
- gastrointestinal symptoms
- hematologic dyscrasia (including leukopenia, neutropenia, thrombocytopenia)
- hepatic enzyme changes
- histologic changes in vessel wall, including inflammation, cellular damage or necrosis
- myalgia/arthralgia
- peripheral neuropathy

There may be other risks associated with the drug coating that are unknown at this time.

There are no adequate and well-controlled studies published in pregnant women or men intending to father children who have received paclitaxel. Studies performed in rats and rabbits receiving IV paclitaxel during organogenesis revealed evidence of maternal toxicity, embryotoxicity, and fetotoxicity at dosages of 1 and 3 mg/kg, respectively (approximately 3 and

16 times the dose provided by the largest femoropopliteal Lutonix DCB Catheter coated with 3.8 mg of paclitaxel adjusted for body surface area). The drug resulted in increased resorptions and increased fetal deaths. No teratogenicity was observed in gravid rats receiving daily IV paclitaxel doses of 1 mg/kg (a daily dose of approximately 3 times the dose of the largest Lutonix DCB Catheter, adjusted for body surface area). Enrollment of women who are of childbearing potential or in men intending to father children should therefore take reproductive risk into careful consideration.

4.2 RISK MANAGEMENT PROCEDURES

Eligibility criteria have been selected that exclude patients who are at a higher risk for experiencing an anticipated adverse event in order to reduce the risks to subjects who participate in this study. In addition, subjects enrolled in this study should be receiving a defined anti-platelet regimen. In addition, follow-up duplex ultrasound will be performed to assess the target vessel patency. All adverse events are monitored and events will be adjudicated by the Clinical Events Committee per Section 12.3.

Extensive reliability engineering testing has been performed on the Lutonix DCB Catheter to help mitigate any risks to the subjects due to product failure. Additionally, animal studies using the Lutonix DCB Catheter have been conducted to ensure that the device performs as intended without introducing more risks during the interventional procedure.

Investigational device training will be conducted at each initiated study center and appropriate training records will be maintained.

4.3 POTENTIAL BENEFITS

There are no guaranteed benefits from participation in this study; however, it is possible that treatment with the Lutonix DCB Catheter may reduce the potential for restenosis of the lesion(s), thereby reducing the need for repeat hospitalization and/or procedure(s).

Additionally, information gained from the conduct of this study may be of benefit to others with the same medical condition. As with all investigational medical devices, the long-term results of using the Lutonix DCB Catheter are not known at the present time. Alternatives to the use of the Lutonix DCB Catheter include standard or cutting balloon angioplasty, vascular stenting, atherectomy, cryoplasty, or vascular radiation and surgery (vessel bypass with native or synthetic vessel). Lutonix believes that the risk for significant injury or death due to the Lutonix DCB Catheter is extremely low, and the potential benefits of decreased restenosis and decreased need for reintervention is likely, but these potential risks and benefits have yet to be quantified.

4.4 EARLY TERMINATION

Lutonix, Inc. (Sponsor) and the Data Monitoring Committee (DMC) will monitor the progression of the study. If warranted, the study may be suspended or discontinued early if there is an observation of serious adverse reactions presenting an unreasonable risk to the study population.

The Sponsor may terminate Investigator and site participation in the study for issues including but not limited to the following issues:

- Evidence of an Investigator's failure to maintain adequate clinical standards
- Evidence of an Investigator or staff's failure to comply with the protocol
- Inaccuracy or late submission of data forms and core lab images
- Inability to meet enrollment targets (1 subject/month)
- Conditions of approval imposed by the reviewing IRB/EC and/or regulatory agencies
- Evidence of safety concerns or protocol non-compliance
- Change of staff at site that adversely impacts trial conduct

Any evident pattern of non-compliance with respect to these standards will be cause for the site to be put on probation. If corrective actions are not subsequently undertaken, the clinical site will be asked to withdraw from the study and their site may be replaced.

Notification of suspension or termination will occur no later than five (5) working days after the Sponsor makes the determination. In the event of study suspension or termination, the Sponsor will send a report outlining the circumstances to the Institutional Review Board (IRB)/Ethics Committee (EC), and all Investigators and Regulatory Authorities as required by regulation. A suspended or terminated study may not be re-initiated without approval of the reviewing IRB/EC and Regulatory Authorities, as required by regulation.

The Investigator must notify the IRB/EC in writing as soon as possible but no later than within 10 days if the premature termination is related to safety or compliance issues.

5 CLINICAL STUDY DESIGN

The study will enroll patients presenting with below-the-knee disease (Rutherford Category 3, 4, or 5) and an angiographically significant ($\geq 70\%$) native artery lesion appropriate for angioplasty that is below the knee and above the ankle. After successful protocol-defined pre-dilatation, subjects that continue to meet lesion and outflow angiographic criteria are stratified by Rutherford Category and randomized 2:1 to treatment with either the Lutonix DCB (test) or standard uncoated PTA catheter (control). All target lesion(s) in up to two target vessels are treated with the as-randomized (by subject) test DCB or control PTA devices. After the protocol-defined pre-dilatation with a standard uncoated PTA catheter step is completed and if randomized to control, treatment with an additional standard uncoated PTA catheter (control device) is at the discretion of the investigator as long as 0-30% residual stenosis is achieved. Subjects with no target vessels that meet post-pre-dilatation entry criteria are excluded (and treated per standard practice) and followed for safety for 30 days.

All subjects will have ultrasound and clinical follow-up through 36 months. There is no pre-set limit to site enrollment, however site enrollment will be tracked and managed to ensure approximately 50% of the overall randomized enrollment occurs at US sites.

Primary efficacy endpoint assessment is performed at 6 months. Clinical follow-up continues through 36 months. The study treatment algorithm flow-chart is shown below in Figure 3. Bail-

out stenting is allowed only if necessary to avoid surgical bypass or amputation. Proper surgical procedure may be performed whenever appropriate, in the investigator’s judgment.

If a ‘proximal vessel only’ arm of the trial is required per the adaptive study design (see Section 15 of this protocol for additional details), then an additional inclusion criterion which defines this patient population, will be implemented and followed. There are no changes to the procedural steps listed in this section above, that is successful pre-dilatation, randomization 2:1 ratio, 36 month follow-up with primary endpoint at 6 months, will still be followed. The schedule of events listed in Table 3 of this protocol will still also be followed for this study arm.

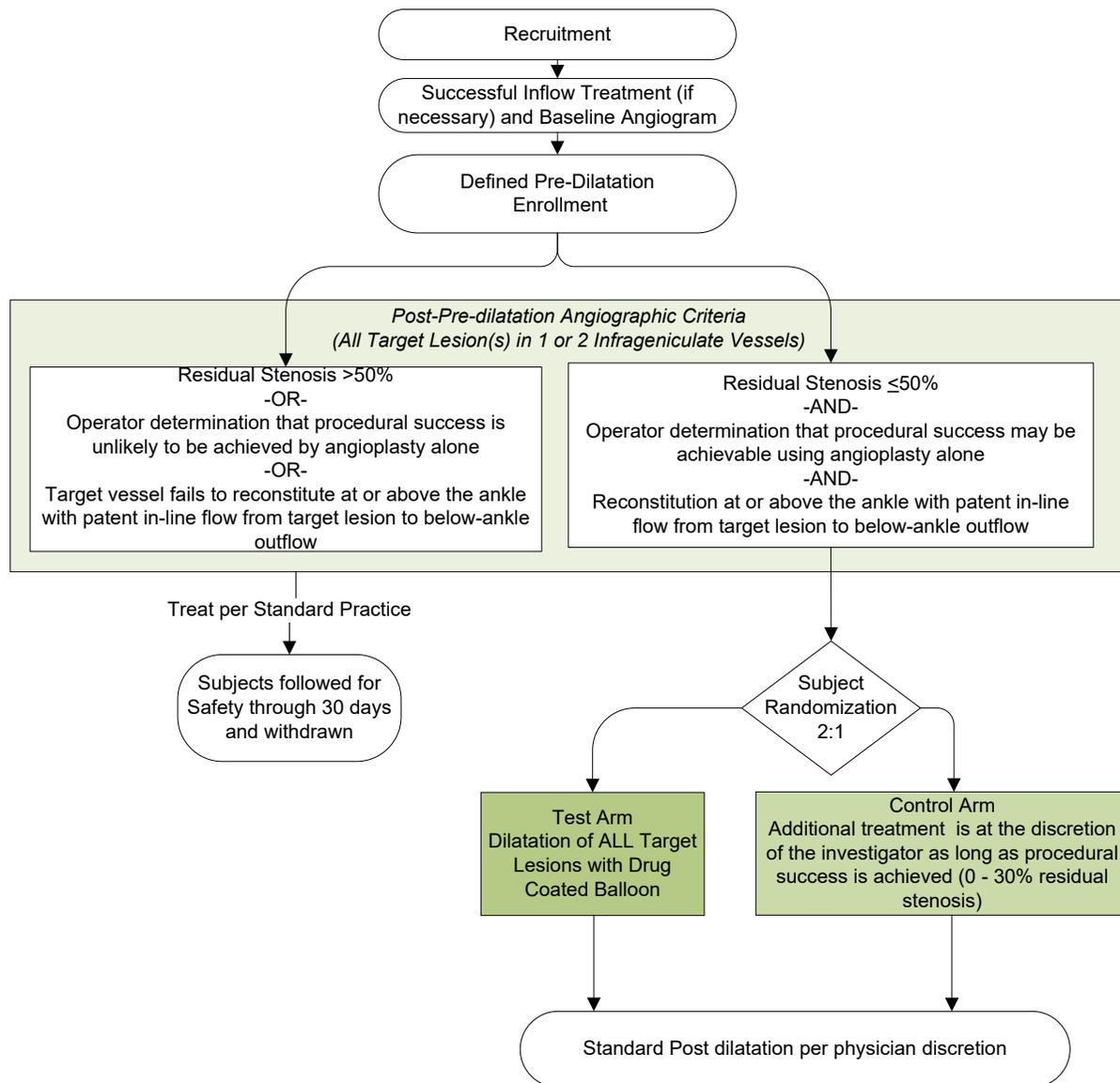


FIGURE 3: STUDY FLOWCHART

5.1 SCREENING PROCEDURES

All Rutherford 3, 4, and 5 patients presenting for a percutaneous revascularization of an artery(s) below the tibial plateau and above the tibiotalar joint should be screened for study eligibility. Patients categorized as a Rutherford Clinical Category 3 must have failed medical management per physician discretion. Once the patient's eligibility has been determined, the Investigator will discuss the study and ask the patient to participate. Prior to enrollment, the patient must sign the Informed Consent Form (ICF) approved for use by the IRB/EC or other appropriate committee. A copy of the signed and dated ICF will be provided to the subject. Subjects will be assured that they may withdraw from the study at any time and for any reason. The background and purpose of the study, participation requirements, as well as the potential benefits and risks of the procedure(s) must be explained to the subject.

The status of all patients screened, whether enrolled, withdrawn, etc., should be captured on the study Screening Log for tracking and reporting purposes.

If not already performed as standard practice, the following clinical assessments and tests must be performed after obtaining informed consent and prior to the index procedure (within 30 days unless otherwise noted) to verify and complete eligibility:

- Physical examination (including blood pressure, heart rate, and temperature)
- Relevant medical history
- Rutherford Classification (index limb)
- Pregnancy Test (blood or urine; if female of child bearing potential)
- Resting TBI (if possible) and ABI (within 90 days)
- Walking Impairment Questionnaire
- EQ-5D Questionnaire
- Wound Assessment (including collection of images)

Information already in the patient's medical record that has been collected as part of standard hospital practice (including, for example, medical history, physical examination, Rutherford Classification, ankle and toe pressures) may be used as baseline data even if collected before the Informed Consent Form was signed.

5.2 PATIENT SELECTION FOR ENROLLMENT

Subjects must meet all the clinical eligibility criteria, agree to participate and comply with study protocol requirements and follow-up schedule and provide informed consent.

All subjects are expected to remain available (geographically stable) for the duration of the study follow-up period. If any subject moves away, every effort must be made to maintain the follow-up schedule including having an appropriate physician follow the subject. The Investigator is responsible for ensuring that each follow-up visit occurs at the specified time and that all applicable data is reviewed and entered into the electronic case report form system (eCRF) in a timely fashion.

5.3 SUBJECT INCLUSION AND EXCLUSION CRITERIA

5.3.1 INCLUSION CRITERIA

Subjects must meet all inclusion criteria, 1 - 12 as specified below, to be enrolled in the study.

Clinical Criteria

1. Male or non-pregnant, non-breastfeeding female ≥ 18 years of age;
2. Rutherford Clinical Category 3, 4 or 5
NOTE: Patients categorized as a Rutherford Clinical Category 3 must have failed medical management per physician discretion;
3. Life expectancy ≥ 1 year;
4. Patient is willing to provide informed consent, is geographically stable, and is willing to comply with the protocol-required follow up visits, testing schedule and medication regimen
5. No other prior surgical or vascular interventions within 2 weeks before and/or planned 30 days after the protocol treatment;
NOTE: The following are allowed within 2 weeks prior or within 30 days after the procedure:
 - Planned transmetatarsal or lower minor amputations
 - Index limb inflow-lesion treatment
 - Contralateral iliac treatment
 - Wound debridement**NOTE:** Except for allowed iliac treatment (noted above), contralateral limb lesion(s) cannot be treated during the index procedure or within 2 weeks before and/or planned 30 days after in order to avoid confounding complications;

Angiographic Criteria

6. Significant stenosis ($\geq 70\%$) or occlusion of one or two native artery(s) below the tibial plateau and above the tibiotalar joint appropriate for angioplasty per operator visual assessment
NOTE: One or two flow pathways are allowed as artery(s); i.e., peroneal or posterior tibial arteries may involve tibioperoneal trunk lesions and tibial arteries may involve popliteal lesions;
7. Cumulative length of target lesion(s) ≤ 320 mm;
NOTE: Maximum allowed cumulative length of all DCBs ≤ 360 mm;
8. Target lesion(s) not previously stented and at least 20 mm from any previous stent;
9. A patent inflow artery from the aorta to the target lesion free from significant ($\geq 50\%$) stenosis as confirmed by angiography;
NOTE: concurrent or staged treatment of iliac/SFA/above-knee popliteal artery is allowed if successfully performed (with residual diameter stenosis $\leq 30\%$ and reconstitution at least 30 mm proximal to tibial plateau) without major vascular complication;
NOTE: If atherectomy is performed on the superficial femoral (SFA) or popliteal lesion(s), use of a distal embolic filter is required.
NOTE: Treatment of the femoropopliteal with a DCB is not allowed during the index procedure.

10. Target vessel(s) diameter between 2 and 4 mm and able to be treated with available device size matrix;
11. Successful antegrade pre-dilatation of the target lesion with standard PTA catheter appropriate size for the reference vessel diameter;
NOTE: Successful pre-dilatation defined by residual stenosis $\leq 50\%$ and operator determination that procedural success may be achievable by angioplasty alone
NOTE: Multiple lesions allowed, but ALL target lesions MUST be successfully pre-dilated prior to randomization;
NOTE: If the popliteal artery is pre-dilated, it MUST meet angiographic inclusion criteria;
NOTE: Retrograde access for initial wire crossing allowed, but pre-dilatation and treatment must be performed over antegrade wire.
12. Target vessel(s) reconstitute(s) at or above the ankle with inline flow to at least one patent (<50%) inframalleolar outflow vessel (planned treatment below-the-ankle is not allowed);
NOTE: Outflow must be assessed AFTER pre-dilatation
NOTE: Two arteries allowed, but each target vessel MUST demonstrate inline inframalleolar outflow prior to randomization.

Additional Inclusion Criteria (only applicable if continued enrollment of “proximal vessel only” arm is required per adaptive study design; see Section 15 of this protocol for details):

13. Target lesion is located entirely within the proximal two-thirds of the leg between the tibial plateau and tibiotalar joint.

5.3.2 EXCLUSION CRITERIA

Patients will be excluded if ANY of the following conditions apply:

1. Any severe medical comorbidities (untreated CAD/CHF, severe COPD, metastatic malignancy, etc.) that would preclude compliance with the study protocol or currently receiving immune-suppressive, chemotherapeutic, or radiation therapy;
2. Patient is currently participating in an investigational drug or device study or previously randomized or a roll-in subject in this study
NOTE: Enrollment in another drug or device study during the follow-up period is not allowed;
3. History of stroke within 3 months;
4. History of MI, thrombolysis or angina within 30 days of enrollment;
5. Gangrene extending proximal to the digit-metatarsal skin crease (target limb);
NOTE: Gangrene must be confined to the toe or toes
6. Ischemic ulceration that extends more than 4 cm proximal to digit-metatarsal skin crease(target limb);
NOTE: If ulcers are confined to toe, involvement of tendon or bone is acceptable. Ulcers proximal to digit-metatarsal skin crease must be superficial (not involving tendon or bone).

7. Neurotropic ulcer or heel pressure ulcer or ulcer potentially involving calcaneus(target limb);
8. Evidence of osteomyelitis in a bone not intended for resection(target limb);
9. Signs and symptoms of systemic infection (temperature of $\geq 38.0^{\circ}$ Celsius and/ or WBC of $\geq 12,000$ cells/ μL) at the time of assessment;
NOTE: If infection is adequately treated and controlled (temperature $< 38.0^{\circ}$ C and WBC $< 12,000$ cells/ μL) patient may be enrolled;
10. Planned major amputation (of either leg);
11. Prior major amputation if amputation occurred less than one year prior to enrollment and if patient is not independently ambulating;
12. $\text{GFR} \leq 30$ ml/min per 1.73m^2 ;
13. Allergy to contrast or known allergy to contrast, taxols or polysorbates that cannot be adequately managed with pre- and post-procedure medication;
14. Hemodynamically significant aortic or CFA occlusive disease (concurrent aortic and common femoral artery treatment NOT allowed);
15. Intended use of adjunctive primary treatment modalities (e.g., atherectomy, laser, cutting balloons, radiation therapy, stents) in below-the-knee vessels;
16. Acute limb ischemia (symptom onset within 2 weeks);
17. In-stent restenosis of target lesion;
18. Presence of thrombus in the target vessel.

6 STUDY/TREATMENT PROCEDURES

6.1 ENROLLMENT

Informed consent must be obtained prior to study-specific testing (that would not have been performed per standard-of-care of non-study subjects). A subject is considered enrolled in the study after both of the following steps have occurred:

- Baseline angiographic confirmation that the target lesion(s) meets all appropriate inclusion/exclusion criteria.
- Defined pre-dilatation balloon inflation has begun.

All subjects enrolled and randomized in the trial will be followed for the entire duration of the study and included in the primary and secondary analyses. Subjects that do not meet post-pre-dilatation criteria are enrolled, but not randomized, and treated per standard practice and followed for safety for 30 days via telephone or clinical visit. Subjects with target lesion(s) that, after baseline angiography, do not meet all inclusion/exclusion criteria and are not pre-dilated per protocol are considered screen failures and will not be enrolled or randomized in the study.

Subjects who undergo a major amputation of the target limb (includes amputation of the treated vessel / lesion) will continue being followed for the study. The following are not required for these patients:

- DUS

- TBI/ABI assessment
- Rutherford Classification
- Walking impairment questionnaire (WIQ)

6.2 LUTONIX DCB CATHETER INSTRUCTIONS FOR USE (IFU)

Always follow the current IFU for procedural information, preparation and use of the Lutonix DCB Catheter. Any devices found to be defective or that do not perform as expected should be returned immediately to the Sponsor for evaluation and a Device Malfunction Form must be completed. A balloon compliance chart is included on each device product label.

In order to achieve the best procedural outcomes, the following steps should be completed:

- The Lutonix DCB catheter should be advanced to the target site as fast as possible (~ 30 seconds).
- The DCB should be immediately inflated when reaching the target site to appropriate pressure to ensure full wall apposition (balloon to artery ratio of $\geq 1:1$).
- Maintain the DCB inflation for a minimum of 2 minutes (120 seconds). The balloon may remain inflated as long as is required by the standard of care to achieve a good angioplasty outcome.
- For optimal results, the final percent stenosis should be 0-20%.

If more than one Lutonix DCB Catheter will be needed to treat the entire pre-dilated segment(s)/lesion(s), the combination of lengths available should be carefully considered beforehand to ensure complete coverage of the target lesions (maximum allowed cumulative length of all DCBs ≤ 360 mm) and, at the same time, reduce unnecessary vessel dilatation. The IFU also contains detailed information on lesion coverage.

6.3 BASELINE ANGIOGRAM

DSA- or Cine- angiograms should be obtained per core lab guideline. Standard off-line QVA acquisition procedures will be followed for analysis at the independent imaging core laboratory. All angiography procedures (both index and non-scheduled) must be recorded in such a way that they are suited for off-line QVA. For purposes of ensuring protocol compliance, all angiograms must be submitted to the core laboratory as soon after the case as possible.

6.4 IN-FLOW LESION TREATMENT

Absence of inflow disease ($\geq 50\%$ stenosis) as confirmed by angiography is required for enrollment in the study. Concurrent or staged treatment of iliac, SFA, and above-knee popliteal artery lesion is allowed if successfully performed (residual diameter stenosis $\leq 30\%$) without major vascular complication. If atherectomy is performed on the superficial femoral or popliteal lesion(s), use of distal embolic filter is required. Treatment of SFA/popliteal inflow lesions must terminate 30 mm above the tibial plateau (i.e., there must be a segment of healthy artery between

any treated inflow lesions and potential target vessel lesions below the knee). Treatment of aortic and common femoral lesions is not allowed.

6.5 PRE-DILATATION AND TARGET VESSEL ENTRY CRITERIA

NOTE: All angioplasty balloons used for vessel pre-dilation or treatment of control arm subjects must be uncoated, standard PTA balloons. Balloons that incorporate a contoured surface, external wire support, cutting/scoring component, or other similar modifications may NOT be used for pre-dilation or control arm treatment.

Always refer to the current IFU for complete pre-dilatation requirements. The pre-dilatation balloon should be a standard PTA balloon appropriate size for the reference vessel diameter. Always limit the longitudinal length of the pre-dilatation balloon to avoid creating a region of vessel injury that is outside the boundaries of the area to be treated by the Lutonix DCB (i.e., to avoid geographic miss). In order to reduce dissections and potential exclusion of target vessels after pre-dilatation, careful and controlled pre-dilatation(s) inflations should be performed and recorded (on film).

When possible, it is strongly encouraged to attempt treatment of the vessel perfusing the ischemic tissue (the site of ulceration or gangrene) based on the angiosome concept. This may not always be possible, and treatment of other vessels is allowed to maximally perfuse the at-risk ischemic limb at the operator's discretion. Ensure that all target lesion diameters can be treated with the Lutonix DCB device sizes available; e.g., do not include a popliteal lesion with RVD diameter greater than largest available Lutonix DCB device size of 4.0mm.

Per protocol, target lesions must be located in one or two native artery(s) below the tibial plateau (proximal boundary) and above the tibiotalar joint (distal boundary) (Figure 4).

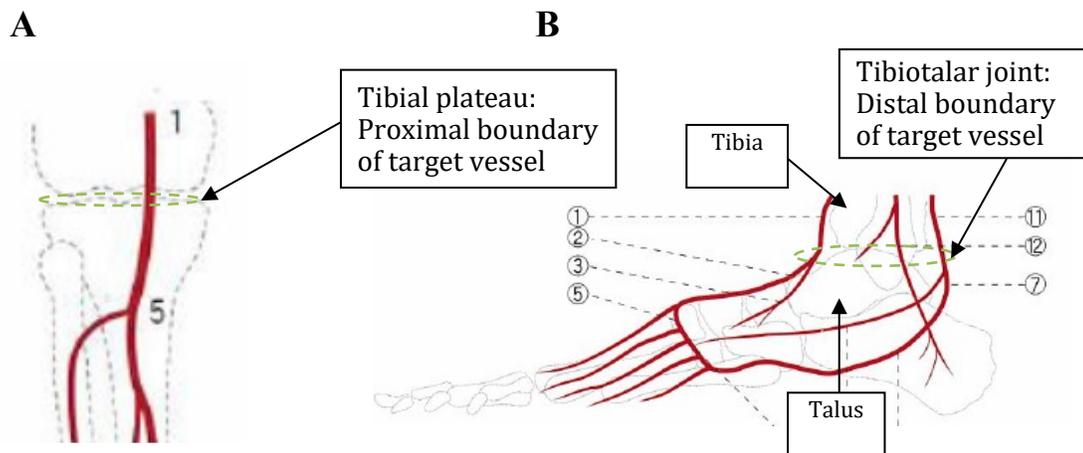


FIGURE 4: PROXIMAL (A) AND DISTAL (B) TARGET VESSEL BOUNDARIES

Retrograde access for initial wire crossing or use of crossing devices is allowed, but predilatation and treatment must be performed over an antegrade wire. Manual pressure hemostasis should be conducted on the retrograde access site (not balloon inflation). One or two flow pathways are allowed as target vessel(s); i.e., peroneal or posterior tibial arteries may involve tibioperoneal trunk lesions and tibial arteries may involve popliteal lesions, as illustrated below in Figure 5. Peroneal or posterior tibial artery lesions (diffuse or focal) that extend into the tibioperoneal trunk can be counted as one target artery (Figure 5A). Similarly, lesions (diffuse or focal) in the anterior tibial artery that extend into the popliteal artery can be counted as one target artery (Figure 5B).

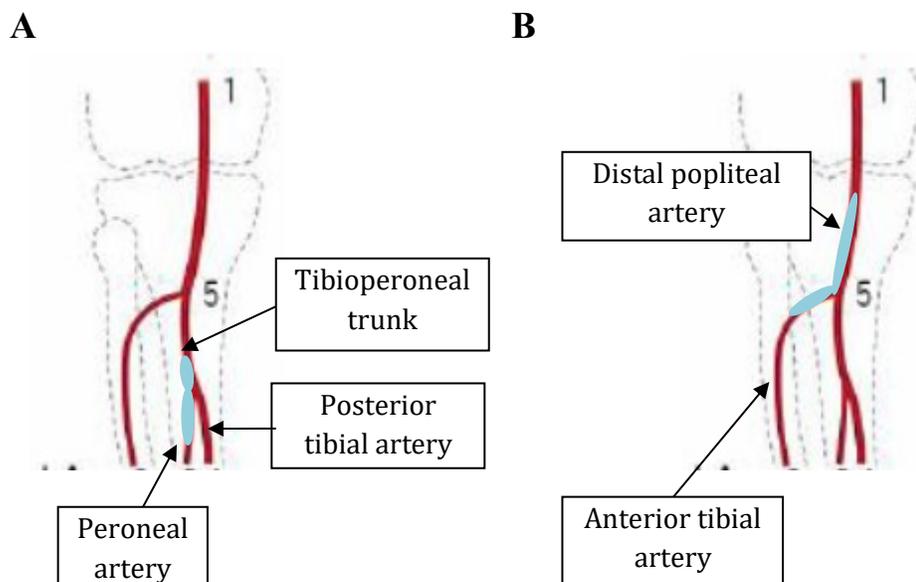


FIGURE 5 : ONE OR TWO FLOW PATHWAYS ARE ALLOWED AS TARGET VESSELS

Only applicable if continued enrollment of “proximal vessel only” arm is required per adaptive study design; see Section 15 of this protocol for details.

In this case, only the target lesions completely within the proximal 2/3rd segment (see Figure 6) will continue to be enrolled in this study.

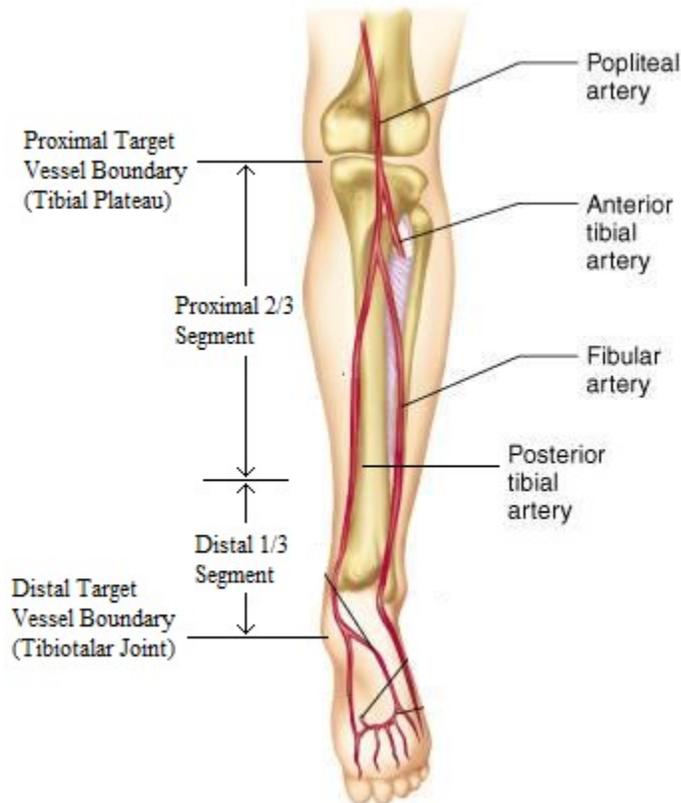


FIGURE 6. PROXIMAL VESSEL SEGMENT (APPLICABLE FOR ENROLLMENT OF PROXIMAL VESSELS ONLY)

Antegrade pre-dilatation of target lesion(s) is performed with a standard PTA catheter appropriate size for the reference vessel diameter. Successful pre-dilatation is defined as residual stenosis $\leq 50\%$ and operator determination that procedural success may be achievable by angioplasty alone. Multiple lesions, up to 320 mm in cumulative length, may be pre-dilated, but ALL target lesions MUST be successfully pre-dilated and assessed prior to randomization. Outflow must be assessed AFTER pre-dilatation. Each target vessel(s) (flow path) must reconstitute(s) at or above the ankle with inline flow to at least one patent ($<50\%$) inframalleolar outflow vessel. Note that planned treatment below-the-ankle is not allowed, and lateral and tarsal branches of the peroneal artery can be considered to represent acceptable patent outflow post-pre-dilatation. In addition, note that a subject with a pre-dilated popliteal artery that fails to meet angiographic inclusion criteria CANNOT be randomized, since the popliteal artery is upstream of all flow from the 3 crural run-off vessels to the foot.

Multiple lesions in two target vessels are allowed, but each target vessel flow path **MUST** demonstrate inline inframalleolar outflow prior to randomization. If pre-dilatation of one vessel is attempted but fails to meet criteria, it is not a target vessel and is instead treated per institutional standard practice. Another vessel may be attempted. If pre-dilatation of two vessels is attempted, and only one meets lesion and outflow criteria, then there is only one target vessel for that subject. The other vessel is treated per institutional standard of care and is not a target vessel. If, after pre-dilatation, no target lesions meet angiographic lesion and outflow criteria, the subject will not be randomized but will be instead treated per institutional standard practice. Non-randomized subjects excluded after pre-dilatation will be followed for 30 days for safety and then withdrawn from the study.

See Table 1 for an overview of target vessel and outflow assessment and outcome.

**TABLE 1: POST-PRE-DILATATION ANGIOGRAPHIC TARGET LESION AND OUTFLOW CRITERIA
 (ALL TARGET LESIONS IN 1 OR 2 INFRAGENICULATE VESSELS)**

Angiographic Criteria	Vessel Outcome	Subject Treatment
Residual Stenosis > 50% -OR- Operator determination that procedural success is unlikely to be achieved by angioplasty alone -OR- Target vessel fails to reconstitute at or above the ankle with patent in-line flow from target lesion to below-ankle outflow	Not a target vessel. Vessel is treated per standard of care.	If this criteria applies to ALL potential target vessels, then subject is not randomized, but followed for safety through 30 days, i.e. "Standard Practice"
Residual Stenosis ≤50% -AND- Operator determination that procedural success may be achievable using angioplasty alone -AND- Reconstitution at or above the ankle with patent in-line flow from target lesion to below-ankle outflow	It is a target vessel and will be treated with the as-randomized device after subject randomization	Subject is randomized 2:1 to treatment with Lutonix DCB vs. Control PTA (if two target vessels meet this criteria, both are target vessels and treated as-randomized with Lutonix DCB or control PTA)

NOTE: If the popliteal artery has been pre-dilated but failed to meet angiographic entry criteria, the subject cannot be randomized but is instead to be treated per investigator’s standard practice.

NOTE: Whenever possible, it is preferable to complete all intended interventional procedures on non-target vessels prior to randomization. This is to ensure a balanced distribution between arms, and to allow for proper attribution of any complications prior to randomization.

Below are 3 possible treatment Scenarios for randomization:

Scenario 1: One potential target vessel identified, pre-dilated and meets post-pre-dilatation criteria for randomization. The subject has a single target vessel and is randomized to either the Lutonix DCB or Control PTA; the target vessel is treated with the as-randomized device, as in Figure 3.

Scenario 2: Two potential target vessels are identified and pre-dilated, but only one vessel meets the post-pre-dilatation criteria for randomization. The subject has a single target vessel and is randomized to either the Lutonix DCB or Control PTA, as in Figure 3. The target vessel meeting criteria is treated with the as-randomized DCB or control PTA. The pre-dilated vessel that did not meet post-pre-dilatation criteria is NOT a target vessel and is treated per Investigator's standard practice and is NOT treated with the investigational device. Non-target vessels are excluded from all endpoint analyses.

Scenario 3: Two potential target vessels are identified and pre-dilated, and both vessels meet the post-pre-dilatation criteria for randomization. The subject has TWO target vessels and is randomized to either the Lutonix DCB or Control PTA, as in Figure 3. Both vessels MUST be treated with the as-randomized device (the same treatment, either Lutonix DCB or Control PTA, as randomized for that subject). Both target vessels are included in endpoint analyses. If two target vessel flow pathways are successfully identified, attempting treatment of a third is not allowed.

6.6 RANDOMIZATION

If after pre-dilatation(s), subjects are determined to meet the criteria for randomization, they will be stratified by Rutherford Class and randomized using a pre-specified site randomization system. Subjects will be randomized in a 2:1 fashion in each strata to Test (Lutonix DCB Catheter) or Control (standard PTA catheter), and all target lesions in up to two target vessels (meeting entry criteria) are treated with the as-randomized device.

Any pre-dilated vessel that did not meet angiographic lesion and outflow criteria is NOT a target vessel and is NOT treated with the investigational device. Any vessel failing to meet criteria after pre-dilatation is instead treated per Investigator's standard practice.

6.6.1 TREATMENT WITH STANDARD PTA CATHETER (CONTROL)

For subjects randomized to the control arm, treatment with an additional standard uncoated PTA catheter (control device) is at the discretion of the investigator. Control PTA treatment should maintain balloon inflation for minimum of 2 minutes.

NOTE: All angioplasty balloons used for vessel pre-dilation or treatment of control arm subjects must be uncoated, standard PTA balloons. Balloons that incorporate a contoured surface,

external wire support, cutting/scoring component, or other similar modifications may NOT be used for pre-dilation or control arm treatment.

Multiple lesions may be treated independently in the one or two pre-specified target vessels with control PTA. The total length of treated lesions (in target vessels) should not exceed 320 mm (for consistency with the treatment length limitation in the test arm).

Pre-dilated vessels that did not meet post-pre-dilatation criteria are not target vessels and are treated with PTA or per institutional standard practice and are excluded from endpoint analyses.

6.6.2 TREATMENT WITH LUTONIX DCB (TEST)

Please refer to the current Lutonix DCB IFU for detailed information on device use.

The Lutonix DCB should extend at least 5 mm proximally and distally of the pre-dilated segment or the lesion (whichever is longer) in order to avoid geographic miss. Care should be taken not to extend the entire injury segment unnecessarily.

Multiple lesions may be treated independently in the one or two pre-specified target vessels with test devices. Multiple DCBs may be used; each balloon may be used only once for adequate drug delivery to the vessel wall. DCBs may be overlapped as necessary to ensure coverage of a pre-dilated injury segment or lesion without geographic miss. The total length of the all DCBs used during the procedure is limited to 360 mm.

6.7 POST-TREATMENT AND PROVISIONAL (BAILOUT) STENTING PROCEDURES

The current trial design is intended to minimize the need for bailout stenting, and it is expected that stents will be used in < 5% of procedures. Bailout stenting should only be performed if it is deemed that a stent is required in order to avoid surgical bypass or amputation after attempting prolonged balloon inflations and/or nitroglycerin.

If bailout stenting is necessary, a bare metal (not drug eluting) stent must be used, since no data is available on potential drug interactions and the allowed treatments must be similar in both arms (the only difference being the as-randomized presence or absence of the drug coating). The physician should use the shortest stent possible to treat only the clinically necessary segment and not the entire target lesion. Antiplatelet therapy should be prescribed per the stent manufacturer's IFU.

Data obtained from bailout stenting procedures will be analyzed as per the Statistical Analysis Plan.

6.8 UNSCHEDULED ANGIOGRAPHY/REVASCLARIZATION

A DUS should be performed prior to any subsequent angiography of the index limb below the knee vessels, and the images should be submitted to the DUS Core Lab. Hemodynamic and clinical status should also be evaluated prior to angiography, including Rutherford classification, wound status (including collection of images, if applicable) and ABI and/or toe pressures.

All subsequent angiograms for the below the knee vessels (index limb only) should be forwarded to the Angiographic Core Lab for review and analysis. Attempts should be made to record the same views and angles as from the index procedure. Treatment of any new non-target lesions is left to the discretion of the Investigator. However, use of drug-device combination products (e.g. DES or DCB) is not recommended within 90 days of the index procedure.

7 TREATMENT OF SUBJECT

Lutonix (or its designee) reserves the right to attend index or follow-up procedures in order to ensure protocol compliance, proper device handling and adequate image capture.

7.1 BLINDING PLAN

In order to minimize the introduction of bias into the study, a pre-specified blinding plan has been developed. The subject will remain blinded to the treatment until after completion of the 6 month clinical visit. Members of the Clinical Events Committee (CEC) will be blinded to the subject's treatment assignment.

At scheduled follow-up visits or interim visits for evaluation of recurrent symptoms, the WIQ and EQ-5D should be completed by the Subject prior to the Investigator evaluation so as to provide the Investigator with patient input prior to the examination. Blinding procedures will be reviewed at the time of each site initiation by a Sponsor representative. Blinding procedures and instructions are as follows:

Time point	Blinding Procedure
Informed Consent/ Pre-Procedure	During review of the study and the informed consent process with the patient, blinding procedures, timelines and rationale should be discussed with the subject and any care takers.
Randomization	Communication to the Investigator performing the procedure as to the randomized treatment should be done in such a way as to prevent the subject from overhearing which group they have been allocated to. Hand signals, written codes, scripts or headphones can all be employed to ensure the subject remains blinded. Each site must develop a system that best works with lab work flow.
Post-Procedure	It is important that recovery and hospital/clinic staff is educated to the protocol blinding requirements and that the subject and care taker are not inadvertently unblinded during the recovery period. In addition, the medical record should clearly identify the subject as a study participant and the type of treatment should be kept confidential.
Follow-up	The WIQ and EQ-5D should be completed by the Subject prior to evaluation by the investigator. The clinical status of the subject (for assessment of clinical and primary safety endpoints) should be established prior to performing the required DUS and angiography (for assessment of the primary efficacy endpoint).
Unblinding	A subject may not become unblinded prior to the completion of the 6 month follow up unless it should become medically necessary as determined by the investigator.

7.2 MEDICATIONS

Table 2 displays the suggested anticoagulation medication regimen for this study and is consistent with standard hospital practice for angioplasty procedures. All anti-platelet, anti-coagulant, and cardiovascular related medications administered will be recorded in the subject's medical record and the appropriate eCRF. Anti-platelet therapy labeling and use vary by country; and approved treatments for the Investigational Sites' geography should be followed. It is preferred that all subjects be treated with clopidogrel and aspirin for one month, followed by aspirin thereafter throughout the duration study. Prolonged dual antiplatelet therapy may be indicated for non-study reasons and is allowed at the investigators discretion. For subjects on chronic Coumadin, it is not required for both aspirin and a P₂Y₁₂ inhibitor be continued for at least 1 month; per protocol and per standard of care, only a single agent (in addition to Coumadin) is sufficient once INR is therapeutic. In subjects ≥ 75 years of age and/or < 60 kg, prasugrel is generally not recommended because of the increased risk of fatal and intracranial bleeding and uncertain benefit, except in high-risk situations (diabetes or history of prior MI) where its effect appears to be greater and its use may be considered. Always refer to the current package insert.

TABLE 2 : SUGGESTED MEDICATION SCHEDULE

Drug	Pre-Procedure	Procedure	Post-Procedure *
Aspirin	75-325 mg/day	NA	75-100 mg/day indefinitely
Clopidogrel OR	75 mg or 300 mg loading dose	NA	75 mg daily for at least 1 month
Ticagrelor OR	180 mg loading dose	NA	90 mg BID
Prasugrel	10 mg/day or loading dose of 60 mg	NA	for at least 1 month (discontinue with active bleeding) >60 kg - 10 mg/day <60 kg - 5 mg/day**
Anticoagulation	Per Hospital Standard Practice		

*For cases of provisional (bailout) stenting, refer to the Stent IFU for dosing instructions

**The effectiveness and safety of this dose has not been prospectively studied

7.2.1 PRE-PROCEDURE

If the subject is known to be receiving a stent for a non-target lesion (i.e. inflow lesion), it is suggested that 3 days before the intervention clopidogrel (75 mg per day) or prasugrel (10 mg per day) be prescribed. The initial loading dose of clopidogrel or prasugrel should attempt to be started prior to the index procedure, but should occur no later than 2 hours after the completion of the index procedure.

7.2.2 INTRA-PROCEDURE

All subjects must receive adequate anticoagulation according to hospital standard practice. It is recommended that subjects that are already taking daily chronic aspirin therapy should receive a dose of 75-325 mg aspirin within 24 hours prior to the index procedure and those subjects not already taking daily chronic aspirin therapy should be given at least 300 mg aspirin at least 2 hours and preferably 24 hours before the procedure is performed.

7.2.3 POST-PROCEDURE

Approved vascular closure devices are allowed. Dual anti-platelet medication should be prescribed for at least 1 month, unless a stent is placed, in which case anti-platelet therapy should be prescribed per the stent manufacturer's IFU, or the subject is on chronic Coumadin, in which case one agent should be discontinued after the INR is therapeutic. Updated guidelines will be implemented via note-to-file if changes in the recommended doses occur.

7.3 STANDARD TESTS, PROCEDURES, AND FOLLOW-UP

Table 3 displays the required schedule for randomized subject treatment and evaluation. This schedule is consistent with standard clinical care pre- and post-interventional procedures. The times for each test are broad enough to fit into most hospital routine testing procedures.

Subjects enrolled, but not randomized, and treated per standard practice will be followed for safety through 30 days. The 30 day follow-up visit can be performed as a telephone or clinical visit. Duplex ultrasound imaging is not a protocol requirement for this group. Details of each testing requirement can be found in the sections below.

TABLE 3: FOLLOW-UP SCHEDULE AND TESTING REQUIREMENTS FOR RANDOMIZED SUBJECTS

Event	Screening ³ (pre-consent)	Pre- Procedure	Procedure	Post- Procedure	30 days	6 Month	12 Month	24 Month	36 Month
					±2 weeks	±1 month	±1 month	±2 month	±2 month
Visit Window	30 days	30 days							
Inclusion/Exclusion Criteria	√	√	√						
Informed Consent		√							
Medical History	√								
Physical Exam		√		√	√	√	√	√	√
ABI-TBI ¹		√			√	√	√	√	√
Rutherford Classification		√			√	√	√	√	√
Pregnancy Test (blood or urine) ²		√							
WIQ and EQ-5D Questionnaires		√			√ ⁵	√	√	√	√
Angiogram			√						
Adverse Event Monitoring			√	√	√	√	√	√	√
Duplex Ultrasound (after clinical assessment)					√	√	√	√	√
Wound Healing Assessment ⁴		√			√	√	√	√	√

¹TBI in cohort where data is available. Resting ABI is required within 90 days of Index Procedure

²Pre-procedure and females of childbearing potential only

³Screening (pre-consent, to determine which patients to consent) must be based only on information available from the patient's medical record or collected as part of standard hospital practice; any additional protocol-required assessments must be performed after signing Informed Consent Form.

⁴Wound imaging (including collection of images, if applicable)

⁵Only the WIQ is required at the 30 day time point

At 6, 12, 24 and 36 month follow-up visits and interim visits, the clinical status of the subject (for assessment of clinical endpoints) should be established prior to performing the required DUS, and DUS should be performed prior to angiography.

7.3.1 TESTING

7.3.1.1 PREGNANCY TEST

A pregnancy test (blood or urine) must be done on females of child bearing potential pre-procedure.

7.3.1.2 ANKLE AND TOE SYSTOLIC PRESSURE AND BRACHIAL INDICES (ABI-TBI)

Resting ABI/TBI measurements will be recorded on the appropriate study eCRF. Resting ABI and TBI should be performed per local hospital standard, and consistently among subjects over the lifespan of the study. Non-compressible vessel status will be recorded. PVR/Doppler waveforms or TcPO₂ data may optionally be obtained. Data will be recorded on the appropriate study eCRF. If TBI cannot be conducted, it will not be considered a deviation.

7.3.1.3 RUTHERFORD SCALE

Rutherford classification can be measured with or without treadmill, but must be performed consistently among subjects over the lifespan of the study. Rutherford classification should be of the Index limb at baseline and follow-up procedures.

7.3.1.4 WALKING IMPAIRMENT QUESTIONNAIRE

The WIQ form will be completed at pre-procedure and at 30 days, 6, 12, 24 and 36 months.

See Appendix C for the questionnaire form.

7.3.1.5 QUALITY OF LIFE QUESTIONNAIRE

The EQ-5D surveys will be completed at pre-procedure and at 6, 12, 24 and 36 months.

See Appendix D for the questionnaire form.

7.3.1.6 DUPLEX ULTRASOUND GUIDELINES

The initial baseline DUS must be performed after the index procedure at the 30 day visit and again at 6, 12, 24 and 36 months. Since DUS is critical to assessing study endpoints, the quality of this test is extremely important, and DUS should be performed prior to angiography (if necessary). The Core Labs will be closely monitoring the quality of all incoming images for compliance. Sites should ensure that only DUS operators who are trained on the DUS guidelines are performing these tests. Refer to the Duplex Ultrasound Guidelines Manual of Operations for the most current version of the documentation requirements. See Appendix H for detailed core lab guidelines.

7.3.1.7 ANGIOGRAPHY GUIDELINES

Initial baseline angiograms should be performed at the time of procedure. All angiograms should be submitted to the core laboratory as soon after the case as possible. Refer to the Angiography Guidelines Manual of Operations for the most current version of the documentation requirements. See Appendix G for detailed core lab guidelines.

7.3.1.8 WOUND HEALING ASSESSMENT

Wound healing assessments must be performed at the pre-procedure, 30 day, 6, 12, 24 and 36 month clinical visits of the target limb. Photographs of the wound must be taken to document wound healing progression at each clinical visit.

Wound healing assessments will be recorded on the appropriate eCRF as healed (completely epithelialized), not healed, or amputated. In addition, if the wound is not healed, wound progression will be recorded on the eCRF as improving, stagnant, or worsening and a photograph of any wounds must be taken and placed in the subject's study chart for reference at each visit.

Note: Sites must have a wound care process/program in place for patients participating in the study. Follow-up wound care for patients can be conducted at the site's affiliated wound care center or equivalent wound care facility.

7.3.2 FOLLOW-UP PROCEDURES

All randomized subjects will return for follow-up at 30 days, 6, 12, 24 and 36 months post-procedure. See Table 3 for required testing at each follow-up visit time point. Refer to Section 7.1 Blinding Plan for specifics on maintaining the blind during the follow-up visits.

Subjects will be instructed to report adverse events to their study physician between evaluation visits.

Anti-platelet, anti-coagulant, and cardiovascular medications will be recorded on the eCRF. Anti-platelet therapy compliance including dose, periods of interruption (and reason for interruption), and invasive procedures deterred due to the need to take anti-platelet therapy will also be recorded on the eCRF.

8 ADVERSE EVENTS

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. The following will be adjudicated by the CEC: all stroke events, all Major Adverse Cardiovascular Events (MACE) which includes stroke, Myocardial Infarctions, and death (all cause), all target limb related events, and all device- and / or procedure-related AEs. See Appendix A for detailed AE definitions.

8.1 ADVERSE EVENT REPORTING

All adverse events occurring since the start of the study procedure must be recorded in the eCRF. All adverse events occurring in this study will be classified in accordance with the adverse event signs or symptoms. Any Serious Adverse Event must be reported in the EDC within 5 working days of knowledge. All adverse events must be reported to the IRB/EC per local requirements.

9 SUBJECT WITHDRAWAL CRITERIA

Subjects can withdraw from the study at any time for any reason; the reason for withdrawal will be documented. All data available at the time of withdrawal (if any) will be used for analysis. There will be no further follow-up (per this study protocol) on the subject who has withdrawn. Subjects who withdraw from the study will not be replaced, however loss-to-follow-up has been considered for sample size statistics.

If a visit is missed, the site is required to document a minimum of three (3) attempts to contact the subject within the follow-up window. If the subject only misses one protocol required visit, the site should repeat the three (3) attempts to contact the subject followed by a certified letter. When a subject misses two (2) consecutive follow-up visits with failure of all contact attempts, the subject may then be considered lost to follow up and exited from the study.

10 DATA COLLECTION AND MONITORING

10.1 DATA COLLECTION

The Investigator (or designated hospital staff) will assure primary data collection based on source-documented hospital chart reviews. These documents will be completed in an expedited fashion.

10.1.1 ELECTRONIC CASE REPORT FORMS (eCRF)

All required clinical data for this trial will be collected in web-based standardized eCRFs. Clinical trial data will be collected in accordance with the Guidance for Industry: Collection of Race and Ethnicity Data in Clinical Trials. Subject personal information should be blinded. Site numbers, subject numbers and initials (when allowed by local regulatory bodies) will be used to track subject information throughout the study.

10.1.2 ANGIOGRAMS AND DUPLEX ULTRASOUNDS

All core lab raw data will be sent to the independent Core Lab listed in the study summary. This information will be documented on a study form and the data entered onto an eCRF.

10.2 MONITORING

A formal written Monitoring Plan will be developed in accordance to FDA guidelines 53 CFR 4723 and the study protocol for this study. Appropriately trained and qualified monitoring personnel will monitor the progress of this study. Prior to protocol submission to the site, a formal Site Qualification Visit will be conducted by a Lutonix clinical employee or designee at sites who have not previously been involved in Lutonix-sponsored trials. Visits are conducted to confirm the appropriate staff, experience, resources, equipment, and patient population exist for this protocol.

Each site will have an initiation visit performed by a Study Monitor and a member of the Lutonix clinical staff. This visit will ensure that the investigator understands his/her responsibility for

conducting this study at his/her center. This includes, but is not limited to, device accountability, protocol compliance, informed consent process, enrolling appropriate subjects, and IRB/EC submissions, approvals, and continuing reviews.

Sites will be monitored according to the approved Monitoring Plan.

10.3 PROTOCOL DEVIATIONS

The investigator will not deviate from the protocol without the prior written approval of the Sponsor except in medical emergencies or in unforeseen, isolated instances where minor changes are made that will not increase the patient's risk or affect the validity of the trial. Continued deviations from the protocol could result in study termination.

10.4 SOURCE DOCUMENTATION

Medical IRB/ECs, the study Sponsor (Lutonix), the Sponsors designees (Clinical Research Organizations) and regulatory authorities may have access to the medical records related to this study. Original or certified copies of all relevant clinical findings, observations, and other activities throughout the clinical investigation must be recorded and maintained in the medical file of each enrolled subject.

The Investigator will permit study-related monitoring, audits, IRB/EC review and authority inspections by allowing direct access to the source data.

10.5 RECORD RETENTION

Lutonix and Investigator will maintain the following accurate, complete, and current records relating to the conduct of the investigation according to national requirements. The data for some of these records may be available in computerized form from the CRO, but the final responsibility for maintaining study records remains with the Investigator. These include:

- All correspondence with another Investigator, an IRB/EC, a Core Laboratory, Lutonix, their designees, or regulatory agency, including required reports;
- Records of receipt, use, or disposition of the investigational device, including receipt dates, serial and/or lot numbers, names of all persons who received or used the device, why and how many devices were returned to or otherwise disposed of. Device reconciliation logs should be kept current and available to Lutonix and their designees upon request;
- Records of each subject's case history, source documents, evidence of informed consent, all relevant observations of adverse study device effects, the condition of each subject upon entering and during the course of the investigation, relevant medical history, the results of all diagnostic testing, and the date of each study treatment;
- Screening log and study personnel visit log;
- Any other records that the regulations require to be maintained.

10.6 STUDY PROCESSING

10.6.1 COMMUNICATION

During the course of the study, regular teleconference calls between Lutonix, the Study Monitor(s) and each clinical site (if necessary) may be conducted to resolve any problems concerning the protocol and data collection. Every effort will be made to ensure compliance with the protocol.

10.6.2 TRAINING

The training of appropriate clinical site personnel and support staff will be the responsibility of Lutonix or their designee. To ensure proper device usage, uniform data collection and protocol compliance, Lutonix or their designee will present a formal documented training session(s) to study site personnel which will include, but may not be limited to, the following:

- Techniques for the identification of eligible subjects
- Investigational Plan
- Device Training
- Core lab Instructions (angiographic and Doppler), as applicable
- Instructions on study and adverse event data collection
- Schedules for follow-up with the study site coordinators
- Regulatory requirements

Detailed feedback regarding completion of forms will be provided by Lutonix or designee, through regular site monitoring.

11 DEVICE ACCOUNTABILITY

All investigational Lutonix DCB Catheter must be stored in a locked storage facility to which only the Investigator and/or designated study staff will have access. The Investigator is responsible for device accountability at the trial site. The Investigator may assign the responsibility for the device accountability to an appropriate study staff member, but remains the final responsible person. The Investigator must ensure that the device is used only in accordance with the protocol and current IFU. The Investigator must maintain records that document device delivery to the trial site, the inventory at the site and administration to each subject. These records must include dates, quantities, batch/serial numbers, expiration dates, and the unique code numbers assigned to the trial subjects. The Investigator must maintain records that adequately document which device the subject received according to the protocol and the assigned randomization. In the case where a device has failed, the Investigator must make every possible effort to return the device to Lutonix; Contact Lutonix for a return manufacturer authorization number (RMA #).

11.1 SUPPLY AND SUPPORT OF INVESTIGATIONAL DEVICE

An investigational device supply will be made available to all study sites. The device matrix will include various diameter and lengths to accommodate the anatomy of the target population. Prior to the start of study enrollment, Lutonix or their designee will perform formal device training of study site personnel and support staff. Each study site will receive a supply of the Lutonix DCB Catheters upon completion of the protocol requirements for study initiation. Additional training and support will be provided on an ongoing basis.

For re-supply of Lutonix DCB Catheters, the site is to contact Lutonix or its designee.

12 STUDY MANAGEMENT

12.1 ADVISORY COMMITTEE

The Advisory Committee (AC) will meet as needed by conference or teleconference to monitor enrollment, clinical site progress, and protocol compliance. The specific tasks of the AC are to:

- Act upon recommendations of the Data Monitoring Committee
- Resolve problems in cooperation with the Clinical Trial Manager
- Sole discretion for stopping or otherwise modifying the study based on clinical data collected
- Provide publication policy

The Advisory Committee may be comprised of representatives from Lutonix, the Principal Investigators, core lab directors and selected physicians representing Interventional Cardiology and Vascular Surgery specialties.

12.2 DATA MONITORING COMMITTEE

The Data Monitoring Committee (DMC) is responsible for the oversight and safety monitoring of the study. The DMC advises the Sponsor regarding the continuing safety of the trial subjects and those yet to be recruited to the trial, as well as the continuing validity and scientific merit of the trial. The DMC members are leading experts in peripheral vascular disease, cardiovascular medicine and biostatistics who are not participating in the trial and have no affiliation with Lutonix.

During the enrollment phase of the trial, the DMC will review accumulating safety data to monitor for incidence of serious vascular events that would warrant modification or termination of the trial.

The DMC will meet at regular intervals to review the safety data. DMC responsibilities, membership, meeting frequencies, and procedures will be outlined in the DMC charter.

12.3 CLINICAL EVENTS COMMITTEE

The Clinical Events Committee (CEC) will consist of a minimum of three clinicians with expertise in vascular intervention and who are not participants in the study or members of the

SC. The members of the CEC will be blinded to the subject's treatment. The CEC is charged with the development of specific criteria used for the categorization of clinical events and clinical endpoints in the study which are based on the protocol.

At the onset of the trial, the CEC will establish explicit rules outlining the minimum amount of data required in order to classify a clinical event. All members of the CEC will be blinded to the primary results of the trial. The CEC will review and adjudicate the following events: all stroke events, all Major Adverse Cardiovascular Events (MACE) which includes strokes, Myocardial Infarctions, and death (all cause), all target limb related events, , and all device- and / or procedure-related AEs. Reportable AEs do NOT include dissection (Grade A or B) which do not require intervention, because dissection is an expected outcome of the angioplasty procedure and will be reported by the angiography core lab based on the Grade A-F (National Heart, Lung, and Blood Institute Dissection Classification System).

13 REGULATORY RESPONSIBILITIES

13.1 IRB/EC APPROVAL

Investigators must submit the study protocol to their IRB/EC and obtain written approval before being allowed to conduct and participate in the study. Annual re-approval must also be obtained. The Investigator is also responsible for fulfilling any conditions of approval imposed by the IRB/EC, such as regular safety reporting, study timing, etc. The Investigator will provide Lutonix or designee with copies of such approvals and reports.

Any amendments to the protocol, as well as possible associated information and consent form changes, will be submitted to the IRB/EC and written approval obtained prior to implementation.

13.2 REGULATORY APPROVAL

In the USA an IDE application must be submitted to the FDA. IDE approval must be received prior to the inclusion of the first US subject.

In the EU, the study must be submitted to the Competent Authorities in each country in which the study is being conducted, according to the national requirements. Approval or a confirmation that the study may start from the applicable authority must be received prior to the inclusion of the first EU subject. In Japan, PMDA must review and approve the Clinical Trial Notification (CTN) prior to device shipment and enrollment of the first subject.

13.3 INFORMED CONSENT

Part of the IRB/EC approval must include approval of an Informed Consent Form (ICF) that is specific to the study and approved by the FDA and any other relevant regulatory bodies. The Investigator must administer this approved ICF to each prospective study subject, and obtain the subject's signature on the ICF prior to enrollment in the study. The ICF may be modified to suit the requirements of the individual site. The Investigator will provide Lutonix or designee with a

copy of the approved ICF for his/her site. Lutonix or designee must pre-approve each ICF prior to initial submission to the IRB/EC; major changes must be approved by the FDA.

The study must be explained in a language that is understandable to the subject and he/she must be allowed sufficient time to decide whether to participate. All subjects will be assured that they have the right to withdraw from the study at any time during the course of the protocol and this decision will not influence his/her relationship with the Investigator (treating physician) and/or study staff.

13.4 SELECTION OF CLINICAL SITES AND INVESTIGATORS

Lutonix will select Investigators who are qualified and experienced to participate in the investigation of the study devices. Sites will be selected based upon a review of a recent site assessment and the qualifications of the (primary) Investigator(s) at the site. Investigators must submit a current curriculum vitae (CV) as part of the qualification process.

All Investigators must be approved by the Sponsor prior to participation in the study.

Any site that becomes deactivated by the Sponsor or by the individual site itself prior to first site enrollment will be replaced.

Due to the potential for an imbalance in the randomization ratio from low enrolling sites, any site not able to enroll a subject within 2 months (60 days) of formal initiation may be replaced. The Sponsor will proactively be tracking site-based enrollment throughout the study and may implement enrollment restrictions to assist in balanced enrollment across sites.

13.5 INVESTIGATOR'S RESPONSIBILITIES

Each Investigator is responsible for ensuring the investigation is conducted according to all signed agreements, the Investigational Plan and applicable laws and regulations. The site Principal Investigator will select qualified co-investigators at each site and will maintain responsibility for oversight of all procedures and data collection. All co-Investigators must be trained on all aspects of the protocol prior to enrolling and performing procedures. All interventionalists performing procedures must be trained as co-investigators in the study.

The Investigator may not begin enrollment or receive the initial shipment of the investigational devices until Lutonix or designee receives and approves (when necessary) the following minimum documents:

- Complete Signed Investigator Agreement
- Financial Disclosure Forms for all participating Investigators
- IRB/EC Roster
- IRB/EC Protocol and Informed Consent Approvals
- Investigators' and Co-Investigators' current curricula vitae (CV)
- Laboratory Normal Values and Lab Certification
- Site Signature and Responsibility Form

13.5.1 STUDY COORDINATOR

To ensure proper execution of the Investigational Plan, each Investigator must identify a Study Coordinator for the site. Working with and under the authority of the Investigator, the Study Coordinator helps ensure that all study requirements are fulfilled, and is the contact person at the site for all aspects of study administration. The Investigator has the ultimate responsibility of all study requirements.

13.5.2 REPORTS

Table 4 below displays a list of the reports that are the Investigator's responsibility to generate. The table also shows to whom the report is to be sent, and with what frequency or time constraints. While some of these reports will be developed by or with the assistance of Lutonix or their designee, the final responsibility rests with the Investigator.

TABLE 4: REPORTS REQUIRED FROM CLINICAL INVESTIGATORS

Report Type	Prepared For:	Time Constraints of Notification
Subject death during investigation	Lutonix/CRO/IRB/EC	To Lutonix/CRO: in eCRF within 24 hours of knowledge. To IRB/EC: Written documentation of the event within 10 working days
SAE	Lutonix/CRO/IRB/EC	Within 5 working days of knowledge and to IRB/EC per local reporting requirements
UADE	Lutonix/CRO/IRB/EC	Within 24 hours
Report of subject enrollment	CRO	By eCRF within 24 hours
Subject withdrawal	Lutonix/CRO	By eCRF within 5 working days
Withdrawal of IRB/EC approval	Lutonix/CRO	Immediately by telephone followed by a copy of the notification within 5 working days
Continuing IRB/EC re-approval	IRB/EC	Prior to continuing review date.
Progress report	Lutonix/CRO/IRB/EC	Submitted at regular intervals or annually
Failure to obtain ICF	Lutonix/CRO	Within 5 working days
Final summary report	Lutonix/CRO	Within 3 months

13.6 LUTONIX RESPONSIBILITIES

An Investigator Meeting and site initiation visit will occur with each study site in order to orient the Investigator and staff to information such as: the investigational device, the Investigational Plan, applicable regulations and requirements, and expectations of the study, including the numbers and time frame for subject enrollment, subject selection, informed consent, required clinical data, and record keeping.

Lutonix or designee (CRO) will maintain the following records:

- All correspondence which pertains to the investigation
- Signed Investigator Agreements/Compensation Agreements, and Curriculum Vitae
- Adverse effects and complaints
- All Case Report Forms (signed by the Investigator)

- Investigational Plan
- Qualification Visit Form
- Monitoring Reports

14 PUBLICATIONS

The trial will be registered in the ClinicalTrials.gov website upon approval by a human subject review board of the appropriate national health authorities in order to meet the criteria of the International Committee of Medical Journal Editors. All publications will follow the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (www.icmje.org, October 2008).

After the conclusion and final analysis of the trial results, a formal abstract presentation may be made at a major cardiovascular conference and the study results, approved by the Principal Investigator and the Steering Committee, will be submitted to a reputable scientific journal.

Following the publication of the main manuscript, secondary analyses proposals will be considered for publication from either the Steering Committee members or individual Investigators. No submissions may be made without the written approval from Lutonix.

15 STATISTICAL ANALYSIS PLAN

The Lutonix BTK Trial is a global, multi-center, randomized, controlled clinical trial comparing the Lutonix DCB Catheter to standard PTA for the treatment of stenosis or occlusion of below-the-knee arteries. The primary effectiveness will consider analyses of all vessels and proximal vessels only. Up to 1000 subjects may be enrolled to obtain up to the maximum of 840 treated vessels at up to 75 global centers. The study sample size will be determined using a Bayesian decision making method that evaluates the predicted probability of a significant primary effectiveness result at the full planned sample size to assess futility and at the existing enrollment to assess if the current sample size provides sufficient power. Assessment for predicted probability for futility and success will be performed when the 400th, 500th, 600th, and 700th vessels are treated. If the study enrollment is not ended at the 700 vessel evaluation, the study will continue to enroll until 840 vessels are treated. Subject randomization will be allocated 2:1 Lutonix DCB (test arm) to standard PTA catheter (control arm) after successful pre-dilatation and all vessels within a subject will receive the same therapy. US and non-US enrollment will be contemporaneously monitored throughout the study to ensure at least 50% of randomized subjects occur at US sites.

Subjects are considered enrolled in the study after being consented and the defined pre-dilatation balloon inflation has begun. Based on angiographic results after pre-dilatation, some subjects will not meet criteria for randomization, and these nonrandomized patients are followed only for safety and do not contribute to the required sample size of 840 treated vessels. However, since

the patient underwent a protocol defined pre-dilatation, they are considered to be enrolled even though they are not randomized.

Successful pre-dilatation is defined as operator determination that procedural success may be achievable using angioplasty alone, $\leq 50\%$ residual stenosis of the target lesion, and reconstitution of the target vessel above the ankle with patent in-line flow from the target lesion to below-ankle outflow. Subjects with a target vessel meeting these criteria are randomized. Subjects who do not meet post-pre-dilatation lesion success criteria are not randomized and are instead treated per hospital standard practice, followed for safety for 30 days, and then withdrawn. Subjects who are enrolled and randomized will be followed clinically for 6 months to assess the primary efficacy endpoint with further follow-up extending out to 3 years.

The primary analysis is based on a repeated-measures logistic model of vessel success that includes treatment and a subject random effect using available data from all randomized subjects on an intent-to-treat basis. Safety endpoints are assessed per subject and efficacy endpoints per target vessel. For the study to be considered successful, superiority of Lutonix DCB Catheter must be demonstrated for the primary efficacy endpoint, non-inferiority of the Lutonix DCB Catheter must be demonstrated for the primary safety endpoint, and Lutonix DCB Catheter must meet the performance goal of the powered secondary safety endpoint. Secondary time-to-event analyses will also be conducted.

As the study includes interim assessments of the sample size, the primary effectiveness analysis includes an adjustment to the significance level used in the final analysis in order to maintain the overall Type I error level of the study. Section 15.3.2 provides details of the primary effectiveness analysis. Appendix J provides complete details on the operating characteristics of the adaptive study design.

15.1 ASSESSMENT OF COMPARABILITY OF TREATMENT GROUPS AND POOLABILITY OF SITES AND SECONDARY ANALYSES

To demonstrate the comparability of the Control to Test subjects, the samples will be compared using t-tests or nonparametric Wilcoxon rank sum tests for means and X^2 -tests for proportions: age, gender, smoking, obesity, dyslipidemia, hypercholesterolemia, hypertension, diabetes mellitus, vessels treated, total target lesion length and maximum percent stenosis of the target lesion (via core lab analysis), previous target lesion intervention, target limb hemodynamics, and Rutherford grade.

All primary endpoints will also be presented by site, and the sites will be tested for differences in the endpoints. Sites with 3 or fewer randomized subjects will be combined for this purpose.

An analysis will be performed to examine the potential for interaction of site and treatment group. A mixed effects logistic regression model will be fit that includes a fixed effect for treatment group, and random effects for individual, site, and the interaction of treatment group

and site. If the p-value for the interaction term variance component is <0.15 , it will be considered evidence of a statistically significant interaction effect, and additional analyses will be performed to explore the differences between sites to assess their potential causes and whether or not they are clinically meaningful. The random effect for individuals will accommodate the potential for correlation between observations for subjects with two treated pathways.

All primary endpoints will also be presented by geography (US versus OUS). An analysis will be performed to examine the potential for interaction of geography and treatment group. A logistic regression model will be fit that includes fixed effects for treatment group, geography, and the interaction of treatment group and geography. If the p-value for the interaction term is <0.15 , it will be considered evidence of a statistically significant interaction effect, and additional analyses will be performed to explore the differences between geographies to assess their potential causes and whether or not they are clinically meaningful. The model will also include a random effect for individual to accommodate the potential for correlation between observations for subjects with two treated pathways.

In addition, a descriptive analysis that examines the impact of important covariates on study results will be performed. Baseline covariates include age, gender, smoking, obesity, dyslipidemia, hypertension, diabetes mellitus, vessels treated, total target lesion length, and maximum percent stenosis of the target lesion (via core lab analysis), previous target lesion intervention, target limb hemodynamics, and Rutherford grade. A binary assessment of target limb hemodynamics will also include an evaluation of whether the subject had an ankle pressure ≤ 70 mm Hg, toe pressure ≤ 50 mm Hg, TCP02 ≤ 50 , or non-pulsatile metatarsal/toe PVR are document. These covariates at a minimum will be included along with treatment group in a logistic regression model in order to understand their potential impact on study results and to account for chance imbalances between the randomized groups.

To assess the consistency of results under different analyses, secondary as-treated (AT) and per-protocol (PP) analyses may be performed for the primary and secondary endpoints. The AT dataset will include only those subjects treated with either an investigational or control device, and the comparison will be based on the actual device used, not randomized assignment. The PP dataset will include all randomized subjects that are characterized by appropriate exposure to treatment (procedurally correct as pre-specified), and the absence of major protocol violations including violations of entry criteria. An additional supportive analysis of patients with and without bailout stenting will also be performed based on descriptive statistics, and data will further be presented for PP analysis of subjects with and without bailout stenting. It is expected that 5% or less of randomized subjects will receive a bail-out stent.

15.2 HANDLING OF MISSING DATA

Endpoints may be missing because subjects have died, have un-interpretable imaging data or have withdrawn from the study prior to the time the endpoint is measured. The *reason* for the censoring of all subjects with missing endpoints will be reported. A tipping-point analysis will be

performed for each primary endpoint, in addition to the standard analysis, in which assumptions about missing data are varied from worst-case to best-case to examine at what point the missing data would alter the results of the analysis. In addition, a multiple imputation analysis will be performed using available results and baseline variables identified for the assessment of poolability in Section 15.1. This set of analyses will constitute sensitivity analyses of the effect of missing data on the study results.

Secondary analyses will also be conducted using survival analysis techniques (Kaplan-Meier estimates), wherein unobserved endpoints are a standard part of the analysis; they are known as “censored observations”. As long as the censoring is unrelated to the treatment, this method of handling missing endpoints produces unbiased estimates of the freedom-from-event rates.

15.3 PRIMARY ENDPOINTS

Primary Safety Endpoint

The primary safety endpoint is a composite of freedom from BTK MALE + POD at 30 Days. This is defined as freedom from the composite of all-cause death, above-ankle amputation or *major* reintervention (new bypass graft, jump/interposition graft revision, or thrombectomy/thrombolysis) of the index limb involving a below-the-knee artery. These events are called “safety events” in the following text.

Primary Efficacy Endpoint

The primary efficacy endpoint is a composite of limb salvage and primary patency at 6 Months. This is defined as freedom from the composite of above ankle amputation, target lesion occlusion, and clinically-driven target lesion reintervention. These events are called “efficacy events” in the following text.

15.3.1 PRIMARY SAFETY ENDPOINT: BACKGROUND CONSIDERATIONS & OUTCOME EXPECTATIONS

Standard of care is surgical bypass or percutaneous transluminal angioplasty (PTA), and a difference between arms cannot be expected at the early time point of 30 days.

Two recent meta-analyses^{10,11} report 30 day data for elements of the composite safety endpoint (“safety events”). Conte et al. reported 2.8% deaths and 6.1% MALE. It is unknown how much subject overlap there may be in these endpoints (cumulatively 8.9%, if none). Similarly, Romiti et al. reported 6.6% amputations and 1.8% death within 30 days along with $37/1743 = 2.1\%$ thromboses and $17/1743 = 0.98\%$ emboli. It is unknown how much subject overlap there may be in these endpoints (cumulatively 11.5%, if none); also reported were $22/1743 = 1.3\%$ non-amputation surgeries. Both meta-analyses demonstrate a similar failure rate ≤ 9 to 11%. As an estimate accounting for subject overlap, a 9% incidence of safety events is assumed for the purpose of power calculations.

15.3.2 PRIMARY SAFETY ENDPOINT: HYPOTHESES AND SAMPLE SIZE CALCULATION

Objective: To assess whether the proportion of subjects free from any safety event* in the Test group is inferior or not inferior to that of Control group through 30-days post-index procedure.

H₀: The proportion of subjects free from safety events in the Test group through 30-days post-index procedure is clinically inferior to that of the Control group.

H₁: The proportion of subjects free from safety events in the Test group through 30-days post-index procedure is clinically non-inferior to that of the Control group.

$$\mathbf{H_0: \phi_{CONTROL} - \phi_{TEST} \geq \delta \quad \text{vs.} \quad \mathbf{H_1: \phi_{CONTROL} - \phi_{TEST} < \delta^{**}}$$

*All-cause death, above-ankle amputation, or *major* reintervention (new bypass graft, jump/interposition graft revision, or thrombectomy/thrombolysis) of the index limb involving a below-the-knee artery are safety events. ** δ is the margin of noninferiority.

The statistical analysis will be a Farrington & Manning test for non-inferiority of proportions; the test will be a one-sided test at $\alpha=0.025$. The response variable in each subject will be the presence or absence of at least one safety event from the time following the index procedure through 30-days. The primary analysis will be the dataset of all randomized subjects ITT based on either all subjects and subjects with one or more proximal vessel as indicated by the primary effectiveness analysis outcome (refer to Section 15.3.4), and a significant rejection of the null hypothesis with one-sided p-value less than 0.025 indicates success for this endpoint. In addition to the primary analysis, secondary as-treated analyses and per-protocol analyses will also be reported.

The proportions at 30-days post-index procedure, and the confidence intervals of these rates in each group, will also be reported.

Sample Size Estimate: The sample size estimate assumed the following:

- The true 30-days proportion in the Test group is 100% - 9% = 91%. The true 30-days proportion in the Control group is 100% - 9% = 91%.
- A 2:1 randomization ratio.
- Farrington & Manning test for non-inferiority of proportions.
- The Type 1 error, $\alpha = 0.025$ (one-sided).
- The Type 2 error, $\beta = 0.10$ (Power = 1 - $\beta = 90\%$).
- The non-inferiority margin, $\delta = 0.12$.
- Subjects who are censored without having an event will be omitted from the analysis.

According to PASS 2008 (using the Farrington and Manning test for non-inferiority of proportions), the evaluable sample size required for 90% power is 254 (85 Control plus 169 Test).

Based on the minimum study sample size of 400 treated vessels and assuming 1.15 vessels per subject, the study should include approximately 350 subjects. Allowing for 10% drop-out, the study is expected to provide at least 313 evaluable subjects and will provide more than 90% power. Hence the safety endpoint is not a driver of the sample size of the study.

15.3.3 PRIMARY EFFICACY ENDPOINT: BACKGROUND CONSIDERATIONS & OUTCOME EXPECTATIONS

Although the unmet clinical need is significant, there is little data from well-designed, randomized, controlled studies that compare the outcomes of different treatment modalities. The primary efficacy endpoint is a composite of limb salvage and primary patency at 6 months, defined as freedom from the composite of above ankle amputation, target lesion occlusion, and clinically-driven target lesion reintervention.

Standard of care is surgical bypass or PTA. For PTA recent meta-analyses¹⁰ report 6 month limb salvage rates of 88.2% and overall 6 month survival rates of 92.3%. Since Rutherford Class 6 patients are excluded in the present study, a slightly lower amputation rate of 10% is assumed for both arms.

One or two flow pathways are allowed as target vessel(s); i.e., peroneal or posterior tibial arteries may involve tibioperoneal trunk lesions and tibial arteries may involve popliteal lesions. Multiple lesions in up to two target vessels may be treated. All target vessels are identified prior to randomization. Failure of efficacy requires amputation or total occlusion (no flow through the flow pathway), independent of the number of target lesions, and therefore the sample size for testing of the efficacy endpoint is the number of treated vessels. If an upstream treated segment included in two otherwise distinct flow pathways fails (e.g., the treated popliteal artery fails in a subject with both AT and PT as treated target vessels), then at least one target vessel fails. Both target vessels fail if neither of the two distal branches (e.g., the AT or PT) can be demonstrated to be open. However, if one or both distal branches are demonstrated to be open (e.g., the AT or PT are open, filled by collaterals around an occluded popliteal), then only a single target vessel (1 of 2) is considered to have failed for purposes of efficacy endpoint analyses. Doppler-demonstrated antegrade flow through the target vessel is considered a patency and primary efficacy endpoint success (in subjects without an amputation or clinically-driven TLR), even if angiography was refused.

Preliminary randomized and registry data has been reported for another manufacturer's DCB (Medtronic/Invatec's Amphirion In.Pact). In the DEBATE BTK study, n = 92 subjects were randomized to DCB or PTA¹⁶. Multiple infrapopliteal vessels were treated in 28% (26/92) of subjects (118 infrapopliteal lesions in 92 subjects), with concomitant treatment of inflow vessels (SFA in 33% and popliteal in 18%). After 12 months, there were no major amputations in either arm; deaths included 7% (3/44) for DCB vs. 10% (5/49) for control, and the re-occlusion rate was 16% for DCB vs. 52% for control PTA. Consecutive Leipzig registries^{19,20} demonstrate a

similar benefit for single-arm, open-label DCB over historic PTA, with 3 month angiographic occlusion rate of 9.5% for DCB (n = 104) compared to 37.6% for control PTA (n = 50).

A beneficial treatment effect difference of 36% at 1 year was observed in the randomized study, and a difference of 28% at 3 months was observed in consecutive registries.

In the LEVANT 2 randomized study (pivotal study for the Lutonix DCB in SFA), the observed primary patency rate was 81.2% (DCB test) vs. 64.8% (PTA control) at 6 months for beneficial treatment effect difference of 16.4%.

Given that the Lutonix DCB with the same Lutonix drug coating is used in this trial as was used in the LEVANT 2 study, the treatment effect of at least 15% benefit for test DCB is assumed for the difference in total occlusion rate for the purpose of power calculations.

Together with the 10% expected amputation rate, the expected composite primary endpoint success rate 55% for test DCB and 40% for control is assumed for power calculations.

15.3.4 PRIMARY EFFICACY ENDPOINT: HYPOTHESIS AND SAMPLE SIZE

Objective: To assess whether the proportion of target vessels free from any efficacy event* in the Control group is less than or not to that of the Test group through 6-months post-index procedure.

The primary effectiveness analysis will be performed in a staged fashion by evaluating all vessels for significance and, if that does not reach significance, then the analysis will be completed for only proximal vessels. The α levels for the overall and proximal vessels analyses have been adjusted to ensure the overall study preserves a one-sided Type I error rate of less than or equal to 0.025. The study will be considered to have demonstrated effectiveness for all subjects if the all vessels analysis reaches significance and for proximal vessels in the event only the proximal vessel analysis reaches the significance level.

For each analysis, all vessels and proximal vessels, the treatment effect will be estimated via a repeated measures logistic regression model, with random effects to account for correlation within subjects. The logistic regression model takes the form:

$$\log\left(\frac{p_{ij}}{1-p_{ij}}\right) = \alpha + \gamma_i + \beta t_{ij} \quad (1)$$

$$X_{ij} \sim \text{Bern}(p_{ij})$$

where X_{ij} is a Bernoulli random variable for 6-month success (1=success, 0=failure) for patient i and vessel j ($j = 1,2$); p_{ij} is the failure-free (success) rate for patient i and vessel j ; α is the log odds of success (failure-free) for patients in the control group; β is the increment in log odds of success for patients in the treatment group; t_{ij} is an indicator variable equal to 1 if in treatment group and 0 if in control group; and $\gamma_i \sim N(0, \tau)$ is a random intercept for patient i that follows a

normal distribution with mean 0 and variance τ . The parameter τ represents the between-subject variance of response. The model is fitted using restricted maximum likelihood methods (REML); hence the primary analysis is not Bayesian and does not depend on any prior distributions.

The hypothesis test for superiority is the following:

$$\begin{aligned} H_0: \beta &\leq 0 & (2) \\ H_1: \beta &> 0 \end{aligned}$$

The experimental treatment will be determined superior to control if the one-sided p-value of the above hypothesis is less than or equal to 0.0085. This cut-off will be applied to the all vessels analysis and, if that is not significant, the cut-off will be applied to the proximal vessel population. The cut-off of 0.0085 is selected to control the overall Type I error of the adaptive design below 0.025 under the trial's design assumptions as well as planned sensitivities to those assumptions, as detailed in Appendix J.

This analysis will be based on an ITT population with available results. Sensitivity analyses are included in Section 15.2 above.

In addition to the primary analysis, secondary as-treated analyses and per-protocol analyses will also be reported but may not be the basis of labeling claims.

The proportions at 6-months post-index procedure, and the confidence intervals of these rates in each group, will also be reported.

The sample size was selected based on simulation work that demonstrated that a maximum possible sample size of 840 treated vessels and prevalence rates of proximal vessels of 55%, 70%, and 80%. The analysis approach provides power of at least 0.902 at the assumed response rates of 40.0% in the PTA arm and 55% in the DCB arm allowing for 15% drop-out depending upon the rate of proximal vessels. If the PTA and DCB rates are both 40%, then the design achieves a power of no more than 0.0236 and an average sample of no more than 542 vessels allowing for 15% drop-out depending upon the prevalence rate of proximal vessels. Hence, the design preserves the study-wide 0.025 one-sided Type I error rate for the staged effectiveness analyses of all vessels and proximal vessels only. Additional calculations for power and Type I error for various scenarios are provided via simulation in Appendix J.

15.4 INTERIM ANALYSIS

Interim evaluations will be performed at the time 400, 500, 600, and 700 vessels have been treated. A Bayesian decision process will be used to adjust the finalized sample size for the study. At each interim analysis, the study will either continue to enroll subjects or enrollment will be considered complete. If the study is not complete at the 700 vessel interim analysis, the study will enroll the full 840 vessels. The study analysis of results will be performed once all of the enrolled subjects has completed their 6 month assessment. The sole objective of the interim evaluation is to identify the study sample size.

Interim analyses will evaluate for predictive probability (based on current enrollment) and futility (based on full sample size enrollment of 840) for superiority for effectiveness in the 1) all vessels population or 2) subgroup of proximal vessel population (see Figure 6 for definition of proximal vessel). Interim decision rules based on these analyses are the following:

1. If predictive probability for success is shown to be greater than 0.9 for either the all vessels population or the proximal vessel subgroup, the accrual is stopped and full follow-up will be observed and final analysis for success will take place (all vessels analysis, followed by proximal vessels analysis if all vessels analysis does not meet success criteria).
2. If futility (predictive probability < 0.01) is shown for both the all vessels population and the proximal vessel subgroup, then accrual is stopped for futility.
3. If futility is shown for the all vessels population but not for the proximal vessel subgroup, enrollment continues for the proximal vessel population only for any future next interim analysis. This is referred to as the 'proximal vessel only' arm of the trial. All subsequent interims and final analysis will only evaluate hypothesis corresponding to the proximal vessel population only.
4. If none of the above criteria are met, the trial continues enrolling to the next interim analysis or the maximum sample size of 840. If the maximum sample size of 840 vessels is enrolled then the defined primary analysis (all vessels analysis, followed by proximal vessels analysis if all vessels analysis does not meet success criteria) occurs 6 months after the 840th vessel is enrolled.

This approach is detailed in Appendix J.

15.5 ADDITIONAL ANALYSES

To assess the consistency of results under different analyses, secondary as-treated (AT) and per-protocol (PP) analyses will be performed for the primary and secondary endpoints. The AT dataset will include only those subjects treated with either an investigational or control device, and the comparison will be based on the actual device used, not randomized assignment. The PP dataset will include all subjects in the full analysis dataset that are characterized by appropriate exposure to treatment (procedurally correct as pre-specified), availability of measurements, and the absence of major protocol violations including violations of entry criteria. An additional supportive analysis of patients with and without bailout stenting will also be performed based on descriptive statistics, and data will further be presented for PP analysis of subjects with and without bailout stenting. It is expected that 5% or less of randomized subjects will receive a bailout stent.

In addition to the primary proportion based analyses, secondary time-to-event analyses will also be conducted.

15.6 OTHER SECONDARY ENDPOINTS WITH HYPOTHESIS TESTING

The following secondary endpoints will be evaluated with hypothesis tests. To control for multiplicity, no secondary endpoints will be tested unless both primary objectives and the powered secondary performance goal objective are successful. The testing of the following

secondary objectives will be performed in a hierarchical fashion in the order in which they are listed below. This means that as soon as a null hypothesis is *not rejected*, no further hypotheses will be tested. This hierarchical testing scheme ensures that the study-wide Type 1 error rate is 0.05 when all of the secondary endpoints are tested at $\alpha = 0.05$. The secondary analysis will only be tested in all vessels or all proximal vessels depending upon the outcome of the primary effectiveness analysis.

15.6.1 SECONDARY ENDPOINT: PRIMARY PATENCY WITH EXCLUSION OF EARLY MECHANICAL RECOIL AT 6 MONTHS

Objective: To assess whether the Primary Patency rate with exclusion of early mechanical recoil (the proportion of target vessels free from both clinically-driven TLR and total occlusion by DUS events > 30 days) in the Test arm is greater than in the Control arm through 6 months post the index procedure.

H₀: The proportion of target vessels with primary patency with exclusion of early mechanical recoil in the Test group through 6-months post-index procedure is equal to or less than in the Test group.

H₁: The proportion of target vessels with primary patency with exclusion of early mechanical recoil in the Test group through 6-months post-index procedure is greater than in the Control group.

$$H_0: P1_{TEST} \leq P1_{CONTROL} \quad \text{vs.} \quad H_1: P1_{TEST} > P1_{CONTROL}$$

The statistical analysis will be a repeated measures logistic model evaluating the treatment and included subject as a repeated effect with a compound symmetry covariance structure; the test will be a one-sided test at $\alpha=0.05$. The response variable for each target vessel will be the presence or absence of any clinically-driven TLR or total occlusion (or both) events > 30 days through 6 months.

The proportions at 6-months post-index procedure, and the confidence intervals of these rates in each group, will be reported.

15.6.2 SECONDARY ENDPOINT: PRIMARY PATENCY AT 6 MONTHS

Objective: To assess whether the Primary Patency rate (the proportion of target vessels free from both clinically-driven TLR and total occlusion by DUS) in the Test arm is greater than in the Control arm through 6 months post the index procedure.

H₀: The proportion of target vessels with primary patency in the Test group through 6-months post-index procedure is equal to or less than in the Test group.

H₁: The proportion of target vessels with primary patency in the Test group through 6-months post-index procedure is greater than in the Control group.

$$H_0: P2_{TEST} \leq P2_{CONTROL} \quad \text{vs.} \quad H_1: P2_{TEST} > P2_{CONTROL}$$

The statistical analysis will be a repeated measures logistic model evaluating the treatment and included subject as a repeated effect with a compound symmetry covariance structure; the test

will be a one-sided test at $\alpha=0.05$. The response variable for each target vessel will be the presence or absence of any clinically-driven TLR or total occlusion (or both) through 6 months.

The proportions at 6-months post-index procedure, and the confidence intervals of these rates in each group, will be reported.

15.6.3 SECONDARY ENDPOINT: CLINICALLY-DRIVEN TLR AT 6 MONTHS

Objective: To assess whether the proportion of target vessels with a clinically-driven TLR in the Control group is greater than that in the Test group through 6-months post-index procedure.

H₀: The proportion of target vessels with a clinically-driven TLR in the Control group through 6-months post-index procedure is less than or equal to that of the Test group.

H₁: The proportion of target vessels with a TLR in the Control group through 6-months post-index procedure is greater than that of the Test group.

$$H_0: P_{3CONTROL} \leq P_{3TEST} \quad \text{vs.} \quad H_1: P_{3CONTROL} > P_{3TEST}$$

The statistical analysis will be a repeated measures logistic model evaluating the treatment and included subject as a repeated effect with a compound symmetry covariance structure; the test will be a one-sided test at $\alpha=0.05$. The response variable for each target vessel will be the presence or absence of a clinically-driven TLR by 6 months.

The proportions at 6-months post-index procedure, and the confidence intervals of these rates in each group, will be reported.

15.6.4 SECONDARY ENDPOINT: COMPOSITE EVENTS AT 6 MONTHS

Objective: To assess whether the proportion of subjects free from a “composite event” in the index limb is higher in the Test group than in the Control group at 6 months. A “composite event” is defined as an above-ankle amputation, unhealed wound, ischemic rest pain, target vessel occlusion, and clinically-driven TVR.

H₀: The proportion of subjects free from any “composite event” in the Test group at 6-months is equal to or lower than that in the Control group.

H₁: The proportion of subjects free from any “composite event” in the Test group at 6-months is higher than that in the Control group.

$$H_0: P_{4TEST} \leq P_{4CONTROL} \quad \text{vs.} \quad H_1: P_{4TEST} > P_{4CONTROL}$$

The statistical analysis will be a Z-test for binomial proportions; the test will be a one-sided test at $\alpha=0.05$. The response variable for each target vessel will be the presence or absence of a “composite event” at 6 months.

For clarity, any above-ankle amputation, target vessel occlusion, and clinically-driven TVR are counted as a “composite event” whether it occurred prior to or during the 6-month follow-up

window, while unhealed wound and ischemic rest pain are as-assessed at the 6 month clinical follow-up visit. I.e., an unhealed wound at a 1 month clinical follow-up visit that is healed (completely epithelialized) at 6 months is NOT counted as a “composite event” at 6 months. Subjects without 6-month clinical follow-up are censored.

The proportions at 6-months post-index procedure, and the confidence intervals of these rates in each group, will be reported.

15.7 SECONDARY ENDPOINTS WITH DESCRIPTIVE STATISTICS

The following secondary endpoints will have descriptive statistics estimated. For each endpoint, the estimated mean and standard deviation or proportion and sample size will be calculated and reported for the Control group and for the Test group. Any target pathway or vessel based analysis will be completed with repeated measures models adjusted for the potential for repeated observations within a subject. (NOTE: Some of these endpoints are also tested endpoints; these were presented above). In addition to the primary analysis based on all randomized subjects, descriptive statistics will also be estimated for the primary endpoints and for each of the following secondary endpoints based on as-treated (AT) and per-protocol (PP) analyses. In addition, descriptive statistics will also be estimated for the subsets of subjects with and without bailout stenting and for patients in the PP dataset with and without bailout stenting.

- Device (able to deliver, inflate and retrieve), Technical (device success and < 50% residual stenosis) and Procedural Success (restoration of at least 1 infrapopliteal artery with residual stenosis < 50% and inline outflow to the foot)
- Comparison of the BTK MALE+POD rate in the test arm to a performance goal of 15% at 30 Days (e.g. null hypothesis is that event rate is greater than or equal to 15%)
- Change in quality of life at 6, 12, 24, and 36 months from baseline, as measured by EQ-5D survey
- Late lumen loss at 12 months (cohort with angiography)

The following endpoints will be assessed at 30 days and at 6, 12, 24, and 36 months:

- Wound healing (healed or not; if not, improving, stagnant, worsening)
- New or recurrent lesion
- Change in Rutherford Class
- Composite of freedom from the following in the index limb:
 - Above-ankle amputation, unhealed wound, ischemic rest pain, target vessel occlusion, and clinically-driven TVR
- Primary Patency (freedom from occlusion without clinically-driven TLR)
- Primary Patency with exclusion of early mechanical recoil (freedom from occlusion without clinically-driven TLR events > 30 days)
- Secondary Patency (not occluded, irrespective of TLR)
- Composite of freedom from clinically-driven TLR and from 50% DS by angiography/DUS

- Hemodynamic outcome (change in toe & ankle pressures)
- Change in Walking Impairment Questionnaire (improvement from baseline)

The following endpoints will be assessed at 30 days and at 6, 12, 24, and 36 months:

- Clinically-driven TLR (all randomized subjects and in AFS cohort)
- Total TLR (all randomized subjects and in AFS cohort)
- Clinically-driven TVR (all randomized subjects and in AFS cohort)
- Total TVR (all randomized subjects and in AFS cohort)
- Limb salvage in surviving subjects
- Unplanned minor below ankle amputation (including digit)
- Overall burden of BTK index-limb reinterventions (total number of index limb BTK interventions incurred, all randomized subjects and AFS cohort)
- Composite of POD, index limb-related death, below-the-knee reinterventions or major amputation of the index-limb
- SVS CLI Endpoint Definitions ((3) Conte 2009 JVS 50:1462-73)
 - MALE: Major adverse Limb Event: Above ankle amputation of the index limb or major reintervention (new bypass graft, jump/interposition graft revision, or thrombectomy/thrombolysis)
 - MALE+POD: Perioperative death (30days), or any MALE
 - MACE: Major Adverse Cardiovascular Event: MI, stroke or death (any cause)
 - Amputation (Major): Above ankle amputation of the index limb
 - AFS: Amputation free survival (freedom from above ankle amputation of the index limb or death (any cause))
 - RAO: Any reintervention or above ankle amputation of the index limb.
 - RAS: Any reintervention, above ankle amputation of the index limb, or stenosis
 - DEATH: Death (any cause)

16 APPENDIX A: 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.

Serious Adverse Event (SAE)

An SAE is an adverse event with one of the following outcomes:

- Death
- Life-threatening
 - The patient was at substantial risk of dying at the time of the adverse event.
- Hospitalization (initial or prolonged)
 - Admission to the hospital or prolongation of hospitalization was a result of the adverse event.
- Disability or Permanent Damage
 - The adverse event resulted in a significant, persistent or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities and/or quality of life.
- Required Intervention to Prevent Permanent Impairment or Damage
- Medical or surgical intervention was necessary to preclude permanent impairment of a body function, or prevent permanent damage to a body structure, either situation suspected to be due to the use of the Investigational Device

Serious Adverse Device Effect (SADE)

An untoward medical occurrence that happens in a subject, is related to the investigational device, and is serious, but is not unanticipated. Untoward medical occurrences that are not

unanticipated are identified in the Investigator's Brochure, Protocol, and Informed Consent Form (ICF).

Unanticipated Adverse Device Effect (UADE)

An untoward medical occurrence that happens in a subject, is related to the investigational device, and is serious, and is not listed in the Investigator's Brochure, Protocol and ICF.

Adverse Event Severity Stratification

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 subject's usual activity or is transient, resolved without treatment and with no sequelae.
Moderate	Interferes with the subject's usual activity and/or requires symptomatic treatment.
Severe	Symptom(s) causing severe discomfort and significant impact of the subject's usual activity and requires treatment.

Relationship to study device

The Investigator will use the following definitions to assess the relationship of the adverse event to the use of study device:

Not Related	The event is definitely not associated with study device. The adverse event is due to an underlying or concurrent illness or effect of another device or drug.
Unlikely	An adverse event has little or no temporal relationship to the study device and/or a more likely alternative etiology exists.
Possible	The temporal sequence between device use and the event is such that the relationship is not unlikely or subject's condition or concomitant therapy could have caused the AE.
Probable	The temporal sequence is relevant <u>or</u> the event abates upon device application completion/removal or the Event cannot be reasonably explained by the subject's condition.
Highly Probable	The temporal sequence is relevant <u>and</u> the event abates upon device application completion/removal, or reappearance of the event on repeat device application (re-challenge).

Relationship to study procedure

The Investigator will use the following definitions to assess the relationship of the adverse event to the use of study procedure:

Not Related	The event is definitely not associated with procedure. The adverse event is due to an underlying or concurrent illness or effect of another procedure.
Unlikely	An adverse event has little or no temporal relationship to the procedure and/or a more likely alternative etiology exists.
Possible	The temporal sequence between the procedure and the event is such that the relationship is not unlikely or subject's condition or concomitant therapy could have caused the AE.
Probable	The temporal sequence is relevant <u>or</u> the event abates upon procedure completion or the Event cannot be reasonably explained by the subject's condition.
Highly Probable	The temporal sequence is relevant <u>and</u> the event abates upon procedure completion, or reappearance of the event on repeat procedure (re-challenge).

Abrupt or Acute Closure

Angiographic documentation of significantly reduced flow due to mechanical dissection, thrombus, or severe vessel spasm in the treatment area.

Acute Limb Ischemia

Acute limb ischemia is defined as a sudden decrease in limb perfusion that causes a potential threat to limb viability (manifested by ischemic rest pain, ischemic ulcers, and/or gangrene) in patients who present within two weeks of the acute event.

Acute Technical Success

Acute technical success is defined as the achievement of successful delivery and deployment of the study device(s) as intended at the intended target lesion with < 50% residual percent stenosis and a successful withdrawal of the catheter system.

All Cause Perioperative Death (POD)

All-cause Perioperative Death is defined as death within 30 days of the index procedure.

Amputation of the Index Limb

Amputation is categorized as Major (above the ankle) or Minor (transmetatarsal or lower, including digits). Minor amputations are categorized as Planned (intended prior to the index procedure) or Unplanned.

Amputation-Free Survival (AFS)

Freedom from above-ankle amputation of the index limb and death (any cause)

Ankle Brachial Index Assessment

Ankle systolic pressure/brachial systolic pressure, measured by constructing a ratio from the peak systolic pressure measured during the deflation of the ankle cuffs during Doppler detection to the systolic brachial pressure. Non-compliant vessels complicate interpretation and are excluded from secondary endpoint analysis.

As-Treated

The As-Treated analysis is based only on those subjects (and target vessels) treated with either an investigational or control device, and the comparison is based on the actual device used, not randomized assignment.

Binary Restenosis

The presence of a hemodynamically significant restenosis (>50%) as determined by the independent core lab analysis by angiography (if performed) or by duplex ultrasound (based on study correlation of ultrasound core lab peak systolic velocity ratios with angiographic data in the cohort with both).

Clinically Driven Target Lesion Revascularization

Revascularization at the target lesion due to worsening of Rutherford Class of the index limb, stagnant or worsening wound healing, or a new or recurrent wound in the index limb.

Clinically Driven Target Vessel Revascularization

Revascularization at the target vessel due to worsening of Rutherford Class of the index limb, stagnant or worsening wound healing, or a new or recurrent wound in the index limb.

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.

Device Success

Acute device success is defined as, a per device basis, the achievement of successful delivery and deployment of the study device(s) as intended at the intended target lesion, without balloon rupture or inflation/deflation abnormalities and a successful withdrawal of the study system. 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.

Discharge

The time point at which the subject was released from the admitting hospital or transferred to another facility.

Dissections

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

- 0: None
- A. Minor radiolucencies within the lumen during contrast injection with no persistence after dye clearance.
- B. Parallel tracts or double lumen separated by a radiolucent area during contrast injection with no persistence after dye clearance.
- C. Extraluminal cap with persistence of contrast after dye clearance from the lumen.
- D. Spiral luminal filling defects.
- E. New persistent filling defects.
- F. Non-A-E types that lead to impaired flow or total occlusion.

Note: Type E and F dissections may represent thrombus.

Enrollment

Enrollment in the study occurs after both of the following steps have occurred:

- Baseline angiographic confirmation that the target lesion(s) meets all appropriate inclusion/exclusion criteria.
- Defined pre-dilatation balloon inflation has begun.

Intent-To-Treat (ITT)

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

Independently Ambulate

To perform daily activities (walking, dressing, etc.) without assistance.

Index Limb Related Death

Any death adjudicated by the CEC as “likely related” to a complication of the index limb.

Limb Salvage

Freedom from above-ankle amputation of the index limb.

Major Adverse Cardiovascular Event (MACE)

MI, stroke or death (any cause)

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 (see stroke)

- It produces a fall in hemoglobin of at least 3 mmol/l;
- It leads to transfusion of 2 or more units of whole blood of packed cells;
- Peripheral vascular surgery is necessary.
- All other bleeding will be considered as minor.

Major Vascular Complications (during Index procedure)

Hemorrhagic vascular complications included the following:

- Haematoma at access site >5 cm
- False aneurysm
- AV fistula
- Retroperitoneal bleed
- Peripheral ischemia/nerve injury
- Any transfusion required will be reported as a vascular complication unless clinical indication clearly other than catheterization complication
- Vascular surgical repair

Major Adverse Limb Event (MALE)

Above ankle amputation of the index limb or major reintervention (new bypass graft, jump/interposition graft revision, or thrombectomy/thrombolysis)

MALE+POD (any MALE or Perioperative Death)

Above ankle amputation of the index limb or major reintervention (new bypass graft, jump/interposition graft revision, or thrombectomy/thrombolysis) or death (all cause) within 30 days of the index procedure.

Patent Run-off (or Patent Outflow)

Reconstitution of the target vessel at or above the ankle with inline flow to at least one patent (<50% diameter stenosis) inframalleolar outflow vessel that has not previously been revascularized. Patent lateral calcaneal and tarsal branches of the peroneal artery are considered patent outflow, in addition to the dorsalis pedis and posterior tibial arteries and their terminal branches.

Per-Protocol (PP)

The PP analysis is based on all subjects (and target vessels) that are characterized by appropriate exposure to treatment (procedurally correct as pre-specified), availability of measurements, and the absence of major protocol violations including violations of entry criteria.

Primary Patency

Primary Patency of the target lesion is defined as the absence of total occlusion (100% diameter stenosis) of the target lesion without prior target lesion revascularization. Occlusion is

determined by independent core lab analysis of angiographic data (if performed) or by ultrasound (if angiography not performed). [Freedom from Binary Restenosis ($\geq 50\%$ diameter stenosis) without reintervention is reported as an independent secondary endpoint.]

Procedural success

Restoration of at least 1 infrapopliteal artery with residual stenosis $\leq 30\%$ by independent core lab analysis with inline outflow to the foot without major adverse events during the index procedure.

Popliteal Artery

The vessel located between Hunter's canal and the trifurcation.

PSVR

Peak Systolic Velocity Ratio

RAO

Any reintervention or above ankle amputation of the index limb.

RAS

Any reintervention, above ankle amputation of the index limb, or restenosis

Reference Vessel Diameter (RVD)

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

See Binary Restenosis.

Restenotic Lesion

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

Rutherford Categories

Category	Clinical Description
0	Asymptomatic, no hemodynamically significant occlusive disease
1	Mild Claudication
2	Moderate Claudication
3	Severe Claudication
4	Ischemic rest pain
5	Minor tissue loss, non-healing ulcer, or focal gangrene with diffuse pedal ischemia
6	Major tissue loss, extending above transmetatarsal level, functional foot no longer salvageable

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.

Secondary Patency

Secondary Patency of the target lesion is defined as the absence of total occlusion (100% diameter stenosis) based on angiography (if performed) or ultrasound as analyzed by independent core lab, independent of whether or not patency is re-established via an endovascular procedure.

Stroke

Clinical signs/symptoms of focal neurological deficit lasting longer than 24 hours.

Target Lesion

Lesion(s) that are to be treated during the index procedure.

The proximal margin of the target lesion must originate below the tibial plateau and terminate above the tibiotalar joint. Multiple target lesions (up to 320 mm in cumulative length) may be treated in up to two Target Vessels. All Target Lesion(s) must be successfully pre-dilated (successful pre-dilatation defined by residual stenosis $\leq 50\%$ and operator determination that procedural success may be achievable by angioplasty alone) and meet post-pre-dilatation lesion and outflow criteria. All Target Lesion(s) are to be treated with the as-randomized test or control device.

Target Lesion Revascularization

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

Target Vessel Revascularization

A repeat revascularization procedure (percutaneous or surgical) of a lesion in the target vessel.

Target Vessel

The entire vessel in which the target lesion is located. One or two below-the-knee arterial flow pathways to the foot are allowed as Target Vessel(s); i.e., peroneal or posterior tibial arteries may involve tibioperoneal trunk lesions and tibial arteries may involve popliteal lesions. Each target vessel(s) (flow path) must reconstitute(s) at or above the ankle with inline flow to at least one patent (<50%) inframalleolar outflow vessel (planned treatment below-the-ankle is not allowed).

Technical Success

Acute technical success of the balloon procedure is defined as the achievement of successful delivery and deployment of the study device(s) as intended at the intended target lesion and a successful withdrawal of the study system with the achievement of < 30% residual percent stenosis without deployment of a bail-out stent.

Thrombosis

A total occlusion documented by duplex ultrasound and/or angiography at the treatment site with or without symptoms. Thrombosis may be categorized as acute (<1 day), subacute (1-30 days) and late (>30 days). The presence of thrombus at the target lesion must be noted as an adverse event in the eCRF.

Toe Brachial Index Assessment

Toe systolic pressure/brachial systolic pressure, measured by constructing a ratio from the peak systolic pressure measured during the deflation of the toe cuffs during Doppler detection to the systolic brachial pressure. Non-compliant vessels complicate interpretation and are excluded from secondary endpoint analysis.

Transient Ischemic Attack (TIA)

Clinical signs/symptoms of focal neurological deficit lasting up to 24 hours without evidence of infarct on imaging studies.

Treatment Area

The entire treated vessel segment(s) in which angioplasty balloons were inflated (the injury segment) in Target Vessel(s) including the Target Lesion(s).

Walking Impairment Questionnaire (WIQ)

A measure of subject-perceived walking performance for subjects with PAD and/or intermittent claudication. This questionnaire estimates walking distance, walking speed and stair climbing capacity.

Worsening Rutherford Clinical Category

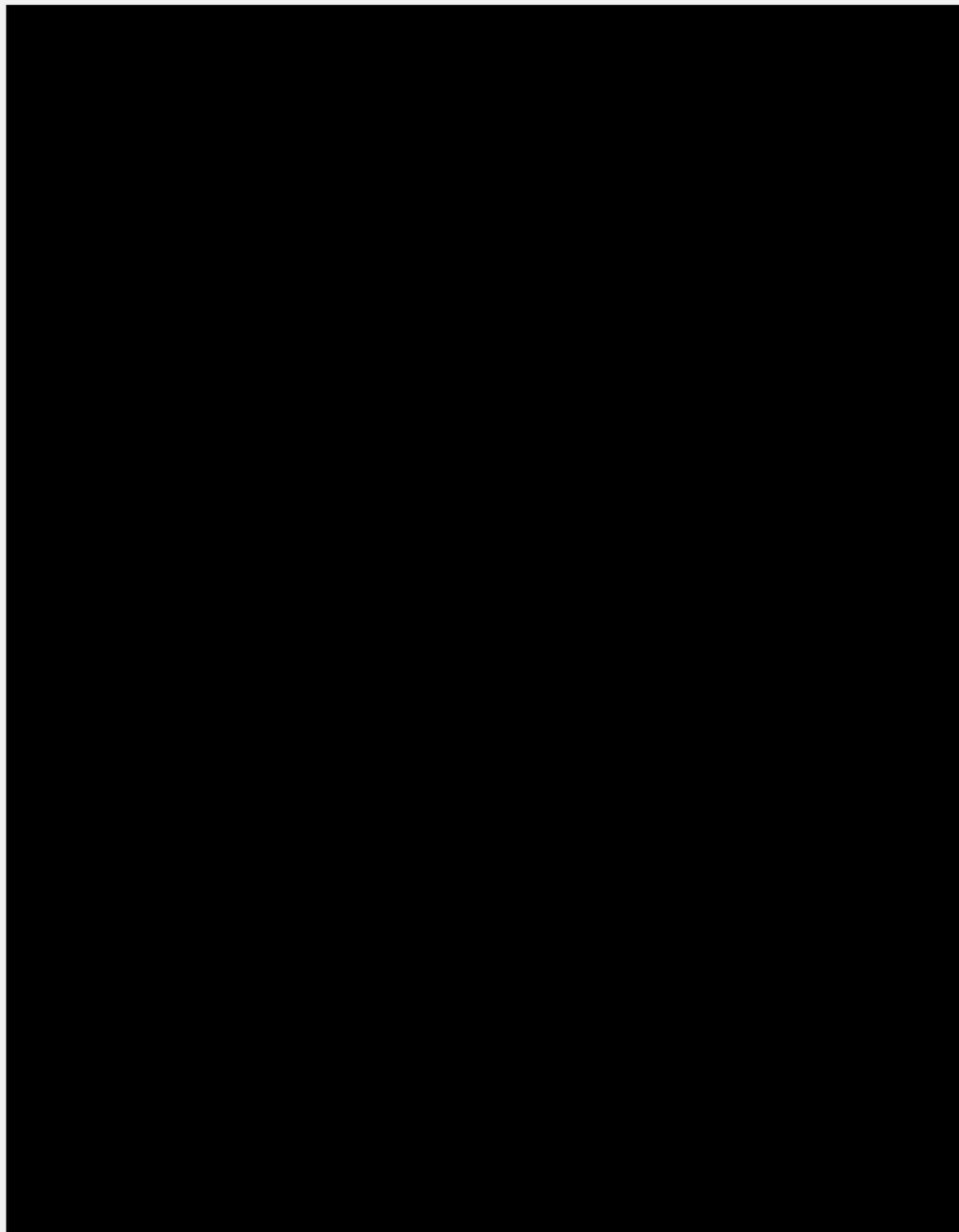
A deterioration (an increase) in the Rutherford Category of the index limb by more than 1 category from the earliest post-procedural measurement.

Wound

Foot ulcer or gangrene. After debridement and/or minor amputation, a wound is characterized as a healed wound when it is completely epithelialized.

17 APPENDIX B: DRAFT CASE REPORT FORM ELEMENTS

18 APPENDIX C: SAMPLE WALKING IMPAIRMENT QUESTIONNAIRE





19 APPENDIX D: SAMPLE EQ5D QUESTIONNAIRE

[REDACTED]

20 APPENDIX E: SAMPLE INSTRUCTIONS FOR USE

21 APPENDIX F: SAMPLE INFORMED CONSENT FORMS

22 APPENDIX G: ANGIOGRAPHIC ACQUISITION GUIDELINES

23 APPENDIX H: DUPLEX ULTRASOUND CORE LAB GUIDELINES

24 APPENDIX I: SPONSOR-QUALIFIED INVESTIGATIONAL SITES

25 APPENDIX J: INTERIM ANALYSIS PLAN (ADAPTIVE DESIGN)