

# **A Prospective, Multicenter, Single-Arm Trial of the Lutonix<sup>®</sup> Drug Coated Balloon for Treatment of Femoropopliteal In-Stent Restenosis**

## **Investigational Plan**

CL0018-01

Version 4.0

**Sponsor:**



9409 Science Center Drive  
New Hope, MN 55428 USA

**Study Device:** LUTONIX<sup>®</sup> Drug Coated Balloon

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**  
Lutonix DCB: SFA-ISR Investigational Plan

**A Prospective, Multicenter, Single-Arm Trial of the Lutonix<sup>®</sup> Drug Coated Balloon for  
Treatment of Femoropopliteal In-Stent Restenosis**

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), Declaration of Helsinki, 21CFR 50, 56 and 812, and any local regulations.

Clinical Site Name \_\_\_\_\_

\_\_\_\_\_  
Site Principal Investigator  
(Print Name)

\_\_\_\_\_  
Site Principal Investigator  
(Signature)


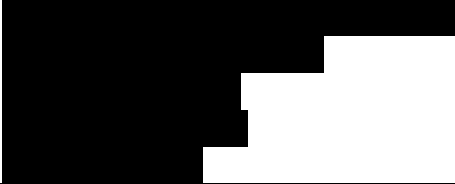


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Date

### The Lutonix SFA ISR Study Summary

<b>Title</b>	A Prospective, Multicenter, Single-Arm Trial of the Lutonix <sup>®</sup> Drug Coated Balloon for Treatment of Femoropopliteal In-Stent Restenosis
<b>Treatment Device</b>	LUTONIX <sup>®</sup> Drug Coated Balloon
<b>Study Design</b>	Prospective, Multicenter, Single-Arm Trial
<b>Overview</b>	<p>The study will enroll patients presenting with claudication or ischemic rest pain (Rutherford Category 2-4) and occlusion or <math>\geq 50\%</math> stenosis of a previously deployed bare, or drug-eluting nitinol stent(s) placed <math>\geq 6</math> months prior to the study index procedure, in the femoropopliteal artery that is appropriate for angioplasty. After successful protocol-defined pre-dilatation, subjects will receive treatment with the LUTONIX<sup>®</sup> Drug Coated Balloon (DCB).</p> <p>The primary safety and efficacy endpoint assessments are performed at 12 months. Clinical follow-up continues through 2 years and telephone follow-up through 3 years.</p>
<b>Purpose</b>	To assess the safety and efficacy of the LUTONIX <sup>®</sup> Drug Coated Balloon for treatment of femoropopliteal artery (SFA) in-stent restenosis (ISR).
<b>Objective</b>	To demonstrate efficacy and safety of the LUTONIX <sup>®</sup> Drug Coated Balloon for treatment of SFA ISR by comparison to an objective performance goal (OPG).
<b>Enrollment</b>	127 Subjects at up to 30 US clinical sites (inclusive of all subjects currently enrolled)
<b>Subject Follow-Up Schedule</b>	<p><i>Clinical:</i> 6, 12, and 24 Months</p> <p><i>Duplex Ultrasound (DUS):</i> 0-6 weeks, 6, 12, and 24 months</p> <p><i>Telephone:</i> 30 days and 3 years (36 months)</p>
<b>Primary Endpoints</b>	<p><i>Efficacy:</i> Primary Patency at 12 months</p> <p><i>Safety:</i> Freedom from all-cause perioperative (<math>\leq 30</math> day) death and freedom at 1 year from index limb amputation (above and below the ankle) index limb re-intervention, and index-limb-related death.</p>
<b>Secondary Endpoints</b>	<p><i>Efficacy</i></p> <ul style="list-style-type: none"> <li>• Device, Technical and Procedural success</li> </ul> <p>The following endpoints will be reported at 6, 12 and 24 Months:</p> <ul style="list-style-type: none"> <li>• Primary and Secondary Patency</li> <li>• Target Lesion Revascularization (TLR) <ul style="list-style-type: none"> <li>○ Clinically-driven</li> <li>○ All TLR</li> </ul> </li> </ul>
<b>Secondary</b>	

<b>Endpoints (Continued)</b>	<ul style="list-style-type: none"> <li>• Sustained Clinical Benefit (improvement in Rutherford Class compared to baseline AND freedom from target vessel revascularization)</li> <li>• Change of Rutherford classification from baseline</li> <li>• Change of resting Ankle Brachial Index (ABI) from baseline</li> <li>• Change in Walking Impairment Questionnaire from baseline</li> <li>• Change in quality of life from baseline, as measured by EQ-5D</li> </ul> <p><i>Safety</i></p> <ul style="list-style-type: none"> <li>• Major vascular complications (<math>\leq 30</math> day)</li> </ul> <p>The following endpoints will be reported at 1, 6, 12, 24, and 36 Months:</p> <ul style="list-style-type: none"> <li>• Composite Safety (criteria of the primary safety endpoint)</li> <li>• Death</li> <li>• Amputation (major and minor separately)</li> <li>• Target Vessel Revascularization (TVR)</li> <li>• Target Limb Reintervention</li> </ul>
<b>Inclusion Criteria</b>	<p><i>Clinical Criteria</i></p> <ol style="list-style-type: none"> <li>1. Male or non-pregnant female <math>\geq 18</math> years of age;</li> <li>2. Rutherford Clinical Category 2-4;</li> <li>3. Patient is willing to provide informed consent, is geographically stable and willing to comply with the required follow up visits, testing schedule and medication regimen;</li> </ol> <p><i>Angiographic Criteria</i></p> <ol style="list-style-type: none"> <li>4. Significant (<math>\geq 50\%</math>) restenosis of a previous bare or drug-eluting nitinol stent(s) in the femoropopliteal artery. Drug-eluting stents must have been placed <math>\geq 6</math> months prior to study index procedure.  <i>NOTE:</i> Discrete or composite lesions allowed within a continuous single or overlapped stented segment.  <i>NOTE:</i> Edge restenosis allowed <math>\leq 3</math> cm beyond stent margin (confirmed after pre-dilatation).</li> <li>5. The intended target lesion measures between 4 and 22 cm and can be treated with single or multiple balloons of cumulative balloon length <math>\leq 26</math>cm  <i>NOTE:</i> This balloon length requirement (<math>\leq 26</math> cm) applies to the total length of all devices intended for use, not the length of the treated segment (which is less, since 5mm balloon overlap is required for treatment)</li> <li>6. Target vessel diameter between <math>\geq 4</math> and <math>\leq 6</math> mm and able to be treated with available device size matrix;</li> <li>7. A patent inflow artery free from significant lesion (<math>\geq 50\%</math> stenosis) as</li> </ol>

	<p>confirmed by angiography (treatment of target lesion acceptable after successful treatment of iliac inflow artery lesions); <i>NOTE:</i> Successful inflow treatment is defined as attainment of residual diameter stenosis <math>\leq 30\%</math> without death or major vascular complication.</p> <p>8. Successful crossing with a guidewire and pre-dilatation of the target lesion; <i>NOTE:</i> Successful pre-dilatation is defined as attainment of residual diameter stenosis <math>&lt; 50\%</math>.</p> <p>9. At least one patent native outflow artery to the ankle, free from significant (<math>\geq 50\%</math>) stenosis as confirmed by angiography that has not previously been (nor planned to be) revascularized;</p> <p>10. No other prior vascular or surgical interventions within 2 weeks before and/or planned 30 days after the protocol treatment, except for contralateral iliac treatment.</p>
<b>Exclusion Criteria</b>	<ol style="list-style-type: none"> <li>1. Pregnant or planning on becoming pregnant or men intending to father children;</li> <li>2. Life expectancy of <math>&lt; 1</math> year;</li> <li>3. Patient is currently participating in an investigational drug or other device study which could, in the opinion of the investigator, affect the results of this study, or previously enrolled in this study; <i>NOTE:</i> Enrollment in another drug or device clinical trial during the follow up period is not allowed.</li> <li>4. History of stroke within 3 months;</li> <li>5. History of MI, thrombolysis or angina within 2 weeks of enrollment;</li> <li>6. Prior vascular surgery of the index limb, with the exception of remote common femoral patch angioplasty separated by at least 2 cm from the target lesion;</li> <li>7. SFA disease in the opposite leg that requires treatment at the time of index procedure (note inclusion #10- no planned procedure for 30 days post index procedure);</li> <li>8. Target lesion involves either a previously placed covered stent or drug-eluting stent. Treatment of drug-eluting stents is only allowed if stent was placed <math>\geq 6</math> months prior to study index procedure;</li> <li>9. Grade 4 or 5 stent fracture (mal-aligned components or trans-axial spiral configuration) in the restenotic stent(s);</li> <li>10. Inability to take study medications or allergy to contrast that cannot be adequately managed with pre- and post-procedure medication;</li> <li>11. Significant distal aortic vessel or common femoral artery disease. Successful treatment of iliac disease allowed prior to target lesion</li> </ol>

	<p>treatment;</p> <p>12. Known inadequate distal outflow (&gt;50 % stenosis of distal popliteal and/or all three tibial vessels), or planned future treatment of vascular disease distal to the target lesion;</p> <p>13. Sudden symptom onset, acute vessel occlusion, or acute or sub-acute thrombus in target vessel;</p> <p>14. Intended use of adjunctive treatment modalities (i.e. laser, atherectomy, cryoplasty, scoring/cutting balloon, stents, etc.).</p>
<b>Principal Investigator</b>	
<b>Sponsor/ Contact:</b>	<p>Lutonix, Inc. 9409 Science Center Drive New Hope, MN 55428 USA 763-445-2352</p>
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## Table of Contents

<b>1</b>	<b>INTRODUCTION.....</b>	<b>9</b>
1.1	CLINICAL BACKGROUND .....	9
1.2	DEVICE AND STUDY RATIONALE.....	11
<b>2</b>	<b>STUDY OBJECTIVES AND ENDPOINTS .....</b>	<b>12</b>
2.1	PRIMARY OBJECTIVE.....	12
2.2	PRIMARY ENDPOINTS.....	12
2.3	SECONDARY ENDPOINTS.....	12
<b>3</b>	<b>DEVICE DESCRIPTION.....</b>	<b>13</b>
3.1	INTENDED USE FOR TRIAL .....	13
3.2	ACTIVE PHARMACEUTICAL INGREDIENT (API): PACLITAXEL.....	13
3.3	EXCIPIENT (Drug Carrier) .....	14
3.4	STUDY DEVICES AND INSTRUCTIONS .....	14
<b>4</b>	<b>RISK-BENEFIT ANALYSIS .....</b>	<b>14</b>
4.1	POTENTIAL RISKS.....	14
4.2	RISK MANAGEMENT PROCEDURES .....	15
4.3	POTENTIAL BENEFITS.....	16
4.4	EARLY TERMINATION .....	16
<b>5</b>	<b>CLINICAL STUDY DESIGN .....</b>	<b>17</b>
5.1	SCREENING PROCEDURES.....	17
5.2	PATIENT SELECTION FOR ENROLLMENT .....	17
5.3	SUBJECT INCLUSION AND EXCLUSION CRITERIA .....	18
<b>6</b>	<b>STUDY/TREATMENT PROCEDURES.....</b>	<b>19</b>
6.1	ENROLLMENT .....	19
6.2	LUTONIX® DRUG COATED BALLOON INSTRUCTIONS FOR USE (IFU).....	20
6.3	BASELINE ANGIOGRAM.....	20
6.4	IN-FLOW LESION TREATMENT.....	20
6.5	PRE-DILATATION .....	21
6.6	TREATMENT WITH LUTONIX® DRUG COATED BALLOON .....	21
6.7	POST TREATMENT AND PROVISIONAL (BAILOUT) STENTING .....	21
6.8	UNSCHEDULED ANGIOGRAPHY/REVASCLARIZATION .....	23
<b>7</b>	<b>TREATMENT OF SUBJECT.....</b>	<b>23</b>
7.1	BLINDING PLAN .....	23
7.2	MEDICATIONS.....	23
7.3	STANDARD TESTS, PROCEDURES, AND FOLLOW-UP .....	23
<b>8</b>	<b>ADVERSE EVENTS.....</b>	<b>25</b>
8.1	ADVERSE EVENT REPORTING .....	26

<b>9</b>	<b>SUBJECT WITHDRAWAL CRITERIA .....</b>	<b>26</b>
<b>10</b>	<b>DATA COLLECTION AND MONITORING .....</b>	<b>26</b>
10.1	DATA COLLECTION .....	26
10.2	MONITORING .....	26
10.3	SOURCE DOCUMENTATION .....	27
10.4	RECORD RETENTION.....	27
<b>11</b>	<b>DEVICE ACCOUNTABILITY .....</b>	<b>27</b>
11.1	DEVICE SUPPLY.....	28
<b>12</b>	<b>STUDY MANAGEMENT .....</b>	<b>28</b>
12.1	DATA SAFETY MONITORING BOARD .....	28
12.2	CLINICAL EVENTS COMMITTEE .....	28
<b>13</b>	<b>REGULATORY RESPONSIBILITIES.....</b>	<b>28</b>
13.1	ETHICS APPROVAL .....	28
13.2	INFORMED CONSENT .....	29
13.3	SELECTION OF CLINICAL SITES AND INVESTIGATORS .....	29
13.4	INVESTIGATOR’S RESPONSIBILITIES .....	29
13.5	LUTONIX RESPONSIBILITIES .....	29
<b>14</b>	<b>PUBLICATIONS .....</b>	<b>30</b>
<b>15</b>	<b>STATISTICAL ANALYSIS PLAN.....</b>	<b>30</b>
15.1	OVERVIEW OF STUDY DESIGN .....	30
15.2	ANALYSIS POPULATIONS .....	30
15.3	HANDLING MISSING DATA.....	31
15.4	ASSESSMENT OF POOLABILITY OF SITES AND SECONDARY ANALYSIS .....	31
15.5	PRIMARY ENDPOINTS.....	32
15.6	SECONDARY ENDPOINTS.....	36
	<b>APPENDIX A: DEFINITIONS .....</b>	<b>38</b>
	<b>APPENDIX B: SAMPLE WALKING IMPAIRMENT QUESTIONNAIRE .....</b>	<b>47</b>
	<b>APPENDIX C: SAMPLE EQ5D QUESTIONNAIRE.....</b>	<b>49</b>
	<b>APPENDIX D: SAMPLE INFORMED CONSENT FORM .....</b>	<b>51</b>
	<b>Table 1: Bailout Criteria .....</b>	<b>22</b>
	<b>Table 2: Follow Up Schedule and Testing Requirements for Subjects .....</b>	<b>23</b>
	<b>Table 3: Primary Patency for Standard of Care Treatment for SFR ISR .....</b>	<b>32</b>
	<b>Table 4: Primary Patency for Drug Coated Balloon Treatment for SFR ISR.....</b>	<b>33</b>
	<b>Figure 1: LUTONIX® Drug Coated Balloon .....</b>	<b>13</b>



# 1 INTRODUCTION

The purpose of this investigation is to assess the safety and efficacy of the LUTONIX® Drug Coated Balloon for treatment of femoropopliteal artery (SFA) in-stent restenosis (ISR).

## 1.1 CLINICAL BACKGROUND

In-stent restenosis remains a common problem, occurring in 20-40% of patients within the first year following femoropopliteal artery stent placement. Various treatment modalities have been utilized for treatment of SFA ISR; including cutting balloons, additional stenting and rotational or directional atherectomy, and laser. Although some treatments have demonstrated initial technical success, many add complexity to the interventional procedure, and all have documented suboptimal patency rates at 12 months following treatment.<sup>1,2,3,4</sup>

The principle mechanism in the development of primary atherosclerotic plaque in the SFA is thought to be quite different from that of restenotic disease. While white blood cells contribute considerably to primary plaque, restenotic lesions are cellular, comprised mostly of smooth muscle cells (SMC).<sup>5</sup> This may be why current standard of care treatment modalities for in stent restenosis are not proving to be effective over time. The active pharmaceutical ingredient (API) of paclitaxel on the LUTONIX® Drug Coated Balloon is known to inhibit smooth muscle cell proliferation and migration;<sup>6</sup> thereby it is considered to be a viable option for treating ISR in the SFA.

Initial trials with drug coated balloons in *de novo* SFA lesions have been proven safe and have demonstrated lower rates of re-intervention compared to standard percutaneous transluminal angioplasty (PTA).<sup>7,8</sup> However, only preliminary data is available with DCBs in ISR. Medtronic's In.Pact DCB has shown promising results in a single center registry trial<sup>9</sup> using a similar DCB coated with the same paclitaxel API as the LUTONIX® Drug Coated Balloon. In summary, despite its frequent occurrence in clinical practice, few studies have been conducted regarding the effectiveness of endovascular interventions for ISR, and a durable treatment for

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<sup>1</sup> Zeller, T et al. Long-term results after directional atherectomy of femoro-popliteal lesions. *J Am Coll Cardiol*. 2006;48(8), 1573-1578. doi: 10.1016/j.jacc.2006.07.031

<sup>2</sup> Dick, P et. al. Conventional balloon angioplasty versus peripheral cutting balloon angioplasty for treatment of femoropopliteal artery in-stent restenosis: initial experience. *Radiology*. 2008; 248(1), 297-302. doi: 10.1148/radiol.2481071159

<sup>3</sup> Laird, JR et.al. Excimer laser with adjunctive balloon angioplasty and heparin-coated self-expanding stent grafts for the treatment of femoropopliteal artery in-stent restenosis: twelve-month results from the SALVAGE study. *Catheter Cardiovasc Interv*. 2012; 80(5), 852-859. doi: 10.1002/ccd.23475

<sup>4</sup> Yeo, K. K., Malik, U., & Laird, J. R. Outcomes following treatment of femoropopliteal in-stent restenosis: a single center experience. *Catheter Cardiovasc Interv*. 2011; 78(4), 604-608. doi: 10.1002/ccd.23022

<sup>5</sup> Edlin R, et al. Characterization of primary and restenotic atherosclerotic plaque from the superficial femoral artery: Potential role of Smad3 in regulation of SMC proliferation. *J Vasc Surg*, 2009; 49(5), 1289-1295, doi: 10.1016/j.jvs.2008.11.096

<sup>6</sup> Axel DI, et al. Paclitaxel inhibits arterial smooth muscle cell proliferation and migration in vitro and in vivo using local drug delivery. *Circulation*. 1997 Jul 15;96(2):636-45.

<sup>7</sup> Tepe G, et al. Local delivery of paclitaxel to inhibit restenosis during angioplasty of the leg. *N Engl J Med*. Feb 2008;14;358(7):689-99.

<sup>8</sup> Scheinert, D. (2010), "LEVANT I: A Prospective Randomized Trial of a Paclitaxel-Eluting Balloon Compared to a Non-Drug-Eluting Balloon With and Without Stenting in Patients with Diseased Femoropopliteal Arteries," *TCT*, Washington DC

<sup>9</sup> Stabile, E et al. Drug-eluting balloon for treatment of superficial femoral artery in-stent restenosis. *J Am Coll Cardiol*, 2012; 60(18), 1739-1742. doi: 10.1016/j.jacc.2012.07.033

ISR remains elusive.<sup>10</sup> The LUTONIX<sup>®</sup> Drug Coated Balloon is being evaluated in this clinical trial to provide a viable alternative to current standard of care.

### ***1.1.1 CLINICAL EXPERIENCE WITH THE LUTONIX<sup>®</sup> DRUG COATED BALLOON***

#### ***1.1.1.1 THE LEVANT I FIRST IN MAN STUDY***

The LEVANT I trial (NCT00930813) compared femoropopliteal treatment with the LUTONIX<sup>®</sup> Drug Coated Balloon to a standard PTA catheter (with and without stenting) in one hundred one subjects. In the ITT population, the primary endpoint of mean late lumen loss at 6 months was significantly lower in the LUTONIX<sup>®</sup> Drug Coated Balloon arm ( $0.46 \pm 1.13$ ) compared to the PTA arm ( $1.09 \pm 1.07$ ), with a p value of 0.016, consistent with efficacy of LUTONIX<sup>®</sup> Drug Coated Balloon for this indication. There were no unanticipated adverse device effects in the drug-coated balloon arm, and overall adverse event rates were similar to conventional uncoated balloon angioplasty. Secondary clinical endpoints trended in favor of the LUTONIX<sup>®</sup> Drug Coated Balloon arm, particularly TLR (12.8% vs. 22.2% in PTA arm) and target vessel revascularization (TVR) (12.8% vs. 32.6%).

#### ***1.1.1.2 THE LEVANT 2 TRIAL AND CONTINUED ACCESS REGISTRY***

As a continuation of the LEVANT I study, the LEVANT 2 clinical study was designed to demonstrate improved results over current standard of care in a larger patient population at expanded clinical sites. Similar to LEVANT I, this study randomized treatment of patients with a symptomatic lesion in the SFA or popliteal artery to either the LUTONIX<sup>®</sup> Drug Coated Balloon or standard balloon angioplasty. Enrollment of 535 subjects (476 randomized- 2:1 DCB:POBA)) was completed in July of 2012 and follow up is currently ongoing.

Levant 2 met both pre-specified primary endpoints. Primary patency for Lutonix DCB (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%,  $p = 0.005$ ).

Several secondary endpoints were also analyzed but not hypothesis tested. Procedural success ( $< 30\%$  residual stenosis without SAE) was similar for Lutonix DCB and control PTA (88.9% vs. 86.8%), demonstrating effectiveness at acute restoration of patency. Freedom from TLR was 87.7% for DCB compared to 83.2% for control PTA. 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.

Secondary safety endpoints were generally similar for Lutonix DCB 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

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<sup>10</sup> Laird, J. R., & Yeo, K. K. (2012). The treatment of femoropopliteal in-stent restenosis: back to the future. *J Am Coll Cardiol*, 59(1), 24-25. doi: 10.1016/j.jacc.2011.09.037

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 DCB compared to control PTA.

Levant 2 Continued Access (NCT01628159) and Safety (NCT01790243) registries were initiated for collection of additional safety data after completion of Levant 2 enrollment. Enrollment was completed on September 27, 2013. A total of 657 subjects were enrolled at 63 sites across the United States (US) and Europe (EU). Clinical follow-up, monitoring, and CEC adjudications are ongoing.

Together with the randomized study, n = 1029 patients have been treated with Lutonix DCB and followed for a mean duration of 438 days. There are no unanticipated device- or drug-related adverse events, the primary endpoint, as of this reporting date.

Overall freedom from TLR for the all DCB-treated patients was 97.0% (914/942) at 6 months and 92.5% (719/777) at 12 months. Rutherford Class was improved at all time points compared to baseline; through 12 months, 87% of patients had an improvement in Rutherford Class, 72% by 2 or more grades. Sustained improvement in Rutherford Class without TVR was observed in 79% of patients. These clinical endpoints compare favourably to historic results and provide further support for the clinical benefit of Lutonix DCB.

Taken as a whole, the Levant 2 randomized and registry studies demonstrate that treatment of native femoropopliteal lesions with Lutonix DCB provides more durable patency than standard PTA through 12 months with comparable safety and provides a reasonable assurance of safety and effectiveness.

Further information on the LUTONIX<sup>®</sup> Drug Coated Balloon can be found in the Investigator Brochure.

## **1.2 DEVICE AND STUDY RATIONALE**

The drug coating on the LUTONIX<sup>®</sup> Drug Coated Balloon contains paclitaxel and drug carrier (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<sup>®</sup> Drug Coated Balloon 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 oncology<sup>11</sup> and drug-eluting stents (DES).<sup>12</sup>

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<sup>11</sup> Pacific Yew: Draft Environmental Impact Statement. Appendices. U.S. Departments of Agriculture, Interior, and Health and Human Services. January 1993.

## **2 STUDY OBJECTIVES AND ENDPOINTS**

### **2.1 PRIMARY OBJECTIVE**

The primary objective of the Lutonix SFA ISR Study is to demonstrate superior efficacy and non-inferior safety of the LUTONIX<sup>®</sup> Drug Coated Balloon for treatment of SFA ISR by direct comparison to an objective performance goal (OPG).

### **2.2 PRIMARY ENDPOINTS**

#### **2.2.1 SAFETY**

Freedom from all-cause perioperative ( $\leq 30$  day) death and freedom at 1 year from index limb amputation (above and below the ankle) index limb re-intervention, and index-limb-related death.

#### **2.2.2 EFFICACY**

The primary efficacy endpoint is primary patency at 12 months.

Primary Patency is defined as Freedom from Clinically-Driven TLR and from Binary Restenosis. Binary restenosis is adjudicated by the independent, core laboratory based on threshold Doppler PSVR  $\geq 2.5$  (together with waveform analysis & color mosaic appearance) or based on angiographic  $\geq 50\%$  diameter stenosis (if angiography is performed although not required per protocol). Clinically-Driven TLR is adjudicated by the CEC. The core labs and CEC will remain blinded to the treatment arm of subjects randomized and enrolled under previous versions of the protocol.

### **2.3 SECONDARY ENDPOINTS**

#### **2.3.1 SECONDARY EFFICACY ENDPOINTS**

Efficacy measurements of Device, Technical and Procedural Success will be assessed following the procedure.

Efficacy measurements of the following endpoints will be reported at 6, 12 and 24 Months:

- Primary and Secondary Patency (DUS PSVR  $< 2.5$ )
- Target Lesion Revascularization (TLR)
  - Clinically-driven
  - All TLR
- Sustained Clinical Benefit (improvement in Rutherford Class compared to baseline AND freedom from target vessel revascularization)
- Change of Rutherford classification from baseline
- Change of resting Ankle Brachial Index (ABI) from baseline
- Change in Walking Impairment Questionnaire from baseline
- Change in quality of life from baseline, as measured by EQ-5D

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<sup>12</sup> Lasala J, et.al. An Overview of the TAXUS<sup>®</sup> Express<sup>®</sup>, Paclitaxel-Eluting Stent Clinical Trial Program. Journal of Interventional Cardiology. 2006, Vol 19: 5 pp431-442

### 2.3.2 SECONDARY SAFETY ENDPOINTS

The following secondary safety endpoints will be reported:

- Major vascular complications ( $\leq 30$  day)

The following endpoints will be reported at 1, 6, 12, 24, and 36 Months:

- Composite Safety (criteria of the primary safety endpoint)
- Death
- Amputation (major and minor separately)
- Target Vessel Revascularization (TVR)
- Target limb Reintervention

## 3 DEVICE DESCRIPTION

The LUTONIX<sup>®</sup> Drug Coated Balloon (Figure 1) is a standard PTA catheter with a drug coating on the balloon portion of the catheter. The LUTONIX<sup>®</sup> Drug Coated Balloon is an over-the-wire type design with working lengths of 100 and 130 cm and is compatible with 0.035" guidewires. Marker bands are located at the proximal and distal ends of the balloons to assist in 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  $2\mu\text{g}/\text{mm}^2$ .

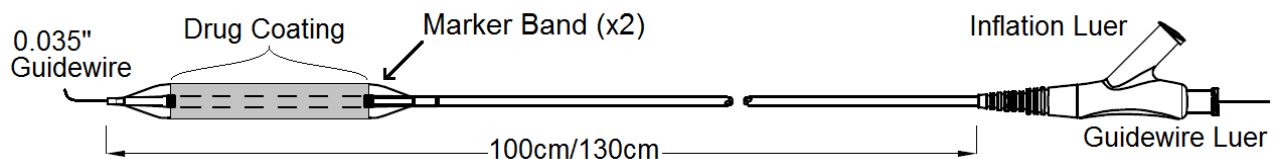


FIGURE 1: LUTONIX<sup>®</sup> DRUG COATED BALLOON

All devices are provided sterile and for single-use only.

### 3.1 INTENDED USE FOR TRIAL

The LUTONIX<sup>®</sup> Drug Coated Balloon is intended for use in percutaneous transluminal angioplasty of restenotic lesions in stented femoropopliteal arteries that are  $\geq 4.0$  to  $\leq 6.0$ 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 µg for devices that treat restenosis, such as coronary stents. Please refer to the Investigator's Brochure for a more detailed review of paclitaxel.

### **3.3 EXCIPIENT (DRUG CARRIER)**

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

### **3.4 STUDY DEVICES AND INSTRUCTIONS**

LUTONIX<sup>®</sup> Drug Coated Balloons will be made available to all activated study sites. Always confirm current site inventory supply prior to enrolling subjects into the study. Please refer to the most current IFU for complete details on procedural use and preparation of the device selected for patient treatment.

## **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<sup>®</sup> Drug Coated Balloon and standard uncoated percutaneous angioplasty catheters used for pre-dilatation are intended to be the only devices used for treatment of the target lesion.

Due to the high similarity of the LUTONIX<sup>®</sup> Drug Coated Balloon 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 femoropopliteal disease.

#### ***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:

- Additional intervention
- Allergic reaction to drugs or contrast medium
- Aneurysm or pseudoaneurysm
- Arrhythmias
- Embolization
- Hematoma
- Hemorrhage, including bleeding at the puncture site
- Hypotension/hypertension
- Inflammation
- Occlusion
- Pain or tenderness



- Pneumothorax or hemothorax
- Sepsis/infection
- Shock
- Thrombosis
- Vessel dissection, perforation, rupture, or spasm

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 (drug carrier) that are approved by the Food and Drug Administration (FDA) as inactive ingredients in drug products for intravenous (IV) drug delivery. The anti-proliferative drug paclitaxel is a well understood API with extensive history of human use in oncology and drug-eluting stents (DES). The maximum total dose on the largest peripheral Lutonix PTA Catheter is less than 2% of the typical dose infused during a single course of cancer therapy (300mg). Adverse events that may be associated with the paclitaxel drug coating on the LUTONIX® Drug Coated Balloon:

- Allergic/immunologic reaction

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 in the studied device. Therefore women who are pregnant or intend to become pregnant and men intending to father children will be excluded from the trial.

## **4.2 RISK MANAGEMENT PROCEDURES**

The investigational plan is specifically designed to manage and minimize risks through careful subject selection, thorough training of investigators, adherence to the pre-determined time points

to assess subject clinical status and regular clinical monitoring visits by Sponsor appointed monitoring personnel.

Follow-up exams including duplex ultrasound will be performed to assess the target vessel patency and assess overall patient status. A Clinical Events Committee (CEC) and an independent Data Safety Monitoring Board (DSMB) will monitor safety of the subjects throughout the trial.

### **4.3 POTENTIAL BENEFITS**

There are no guaranteed benefits from participation in this study; however, it is possible that treatment with the LUTONIX<sup>®</sup> Drug Coated Balloon may reduce the potential for restenosis of the stented lesion, 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<sup>®</sup> Drug Coated Balloon are not known at the present time. Alternatives to the use of the LUTONIX<sup>®</sup> Drug Coated Balloon for ISR include standard or cutting balloon angioplasty, laser, atherectomy, cryoplasty, restenting or surgery (vessel bypass with native or synthetic vessel). Lutonix believes that the risk for significant injury or death due to the LUTONIX<sup>®</sup> Drug Coated Balloon is extremely low, and the potential benefits of 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 CEC 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
- Conditions of approval imposed by the reviewing IRB 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.

In the event of study suspension or termination, the Sponsor will send a report outlining the circumstances to the Institutional Review Board (IRB) and all Investigators and Regulatory



Authorities as required by regulation. A suspended or terminated study may not be reinitiated without approval of the reviewing IRB and Regulatory Authorities, as required by regulation.

The Investigator must notify the IRB 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 127 subjects presenting with an angiographically significant ( $\geq 50\%$ ) restenosis of previous bare or drug eluting nitinol stent(s) in the superficial femoral or popliteal artery. Drug-eluting stents must have been placed  $\geq 6$  months prior to study index procedure.

Subjects will have ultrasound and clinical follow-up through 2 years and telephone follow-up through 3 years. A table highlighting schedule of assessments can be found in Section 7.3.

### **5.1 SCREENING PROCEDURES**

All patients admitted for a percutaneous revascularization of a previously stented femoropopliteal artery should be screened for study eligibility. If inclusion criteria are met and no exclusion criteria are present at the time of screening, the Investigator will discuss the study and ask the patient to participate. Prior to enrollment, the patient must sign the informed consent form approved for use by the IRB or other appropriate committee. A copy of the signed and dated Informed Consent 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.

If not already performed as standard practice, the following 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
- Relevant medical history
- Rutherford Classification
- Pregnancy Test (blood or urine; if female of child bearing potential)
- Resting Ankle-Brachial Index (ABI) (within 90 days)
- Walking Impairment Questionnaire
- EQ5D Questionnaire

### **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 to be enrolled in the study.

#### Clinical Criteria

1. Male or non-pregnant female  $\geq 18$  years of age;
2. Rutherford Clinical Category 2-4;
3. Patient is willing to provide informed consent, is geographically stable and willing to comply with the required follow up visits, testing schedule and medication regimen;

#### Angiographic Criteria

4. Significant ( $\geq 50\%$ ) restenosis of a previous bare or drug-eluting nitinol stent(s) in the femoropopliteal artery. Drug-eluting stents must have been placed  $\geq 6$  months prior to study index procedure.  
*NOTE:* Discrete or composite lesions allowed within a continuous single or overlapped stented segment.  
*NOTE:* Edge restenosis allowed  $\leq 3$  cm beyond stent margin (confirmed after pre-dilatation).
5. The intended target lesion measures between 4 and 22 cm and can be treated with single or multiple balloons of cumulative balloon length  $\leq 26$  cm  
*NOTE:* This balloon length requirement ( $\leq 26$  cm) applies to the total length of all devices intended for use, not the length of the treated segment (which is less, since 5mm balloon overlap is required for treatment);
6. Target vessel diameter between  $\geq 4$  and  $\leq 6$  mm and able to be treated with available device size matrix;
7. A patent inflow artery free from significant lesion ( $\geq 50\%$  stenosis) as confirmed by angiography (treatment of target lesion acceptable after successful treatment of iliac inflow artery lesions);  
*NOTE:* Successful inflow treatment is defined as attainment of residual diameter stenosis  $\leq 30\%$  without death or major vascular complication.
8. Successful crossing with a guidewire and pre-dilatation of the target lesion;  
*NOTE:* Successful pre-dilatation is defined as attainment of residual diameter stenosis  $< 50\%$ .
9. At least one patent native outflow artery to the ankle, free from significant ( $\geq 50\%$ ) stenosis as confirmed by angiography that has not previously been (nor planned to be) revascularized;

10. No other prior vascular or surgical interventions within 2 weeks before and/or planned 30 days after the protocol treatment, except for contralateral iliac treatment.

### 5.3.2 **EXCLUSION CRITERIA**

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

1. Pregnant or planning on becoming pregnant or men intending to father children;
2. Life expectancy of <1 year;
3. Patient is currently participating in an investigational drug or other device study which could, in the opinion of the investigator, affect the results of this study, or previously enrolled in this study;  
*NOTE:* Enrollment in another drug or device clinical trial during the follow up period is not allowed.
4. History of stroke within 3 months;
5. History of MI, thrombolysis or angina within 2 weeks of enrollment;
6. Prior vascular surgery of the index limb, with the exception of remote common femoral patch angioplasty separated by at least 2 cm from the target lesion;
7. SFA disease in the opposite leg that requires treatment at the time of index procedure (Note inclusion #10- no other planned procedure allowed for 30 days post index procedure);
8. Target lesion involves either a previously placed covered stent or drug-eluting stent. Treatment of drug-eluting stents is only allowed if stent was placed  $\geq 6$  months prior to study index procedure;
9. Grade 4 or 5 stent fracture (mal-aligned components or trans-axial spiral configuration) in the restenotic stent(s);
10. Inability to take study medications or allergy to contrast that cannot be adequately managed with pre- and post-procedure medication;
11. Significant distal aortic vessel or common femoral artery disease. Successful treatment of iliac disease allowed prior to target lesion treatment;
12. Known inadequate distal outflow (>50 % stenosis of distal popliteal and/or all three tibial vessels), or planned future treatment of vascular disease distal to the target lesion;
13. Sudden symptom onset, acute vessel occlusion, or acute or sub-acute thrombus in target vessel;
14. Intended use of adjunctive treatment modalities (i.e. laser, atherectomy, cryoplasty, scoring/cutting balloon, stents, etc.).

## 6 **STUDY/TREATMENT PROCEDURES**

### 6.1 **ENROLLMENT**

After signing the informed consent document, a subject is considered enrolled in the study after baseline angiographic results and pre-dilatation confirm that the target lesion meets all appropriate inclusion/exclusion criteria.

Subjects that meet baseline angiographic criteria but do not meet post-pre-dilatation criteria will not be enrolled in the study.

## **6.2 LUTONIX® DRUG COATED BALLOON INSTRUCTIONS FOR USE (IFU)**

Always follow the current IFU for procedural information, preparation and use of the LUTONIX® Drug Coated Balloon. 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 (i.e. ~ 30 seconds).
- The DCB should be immediately inflated to appropriate pressure to ensure full wall apposition (balloon to artery ratio of  $\geq 1:1$ ).
- If the deployment of the DCB exceeds 3 minutes, the catheter requires replacement with a new unit.
- 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® Drug Coated Balloon 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 and, at the same time, reduce unnecessary vessel dilatation. Per protocol, cumulative balloon length must be  $\leq 26$  cm. The IFU also contains detailed information on lesion coverage and minimal inflation times.

## **6.3 BASELINE ANGIOGRAM**

Digital Subtraction Angiography (DSA)- or Cine- angiograms should be obtained per core lab guideline. Standard off-line Quantitative Vascular Angiography (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. Please refer to the trial specific Angiographic Acquisition Guidelines provided by the core laboratory for specific procedural imaging and submission instructions.

## **6.4 IN-FLOW LESION TREATMENT**

Absence of inflow disease ( $\geq 50\%$  stenosis) as confirmed by angiography is required for enrollment in the study. Enrollment is allowed following complete successful treatment per

standard practice of inflow iliac artery lesions, with successful treatment defined as attainment of a residual diameter stenosis  $\leq 30\%$  without death or major vascular complication. Treatment of aortic and common femoral inflow lesions is not allowed.

## **6.5 PRE-DILATATION**

Always refer to the current IFU packaged with the device for complete pre-dilatation requirements.

Lesion(s) pre-dilatation(s) is required for all patients. The pre-dilatation balloon should be a standard PTA balloon inflated to a diameter approximately 1 mm less than the reference vessel diameter (RVD). Successful pre-dilatation is defined as attainment of residual diameter stenosis  $< 50\%$ . 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<sup>®</sup> Drug Coated Balloon.

## **6.6 TREATMENT WITH LUTONIX<sup>®</sup> DRUG COATED BALLOON**

If after pre-dilatation(s) patients are determined to meet the criteria for enrollment, they will be treated with the LUTONIX<sup>®</sup> Drug Coated Balloon. A stented segment with multiple stents may be treated per this protocol; however, the stented area must be continuous.

The Investigator should determine the appropriate size of the balloon(s) to be used by online QVA (if possible) or by visual estimate. Inflate approximately to RVD for as long as necessary to achieve an optimal procedural result. Post-dilatations are allowed.

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 (i.e. ~ 30 seconds).
- The DCB should be immediately inflated to appropriate pressure to ensure full wall apposition (balloon to artery ratio of  $\geq 1:1$ ).
- If the deployment of the DCB exceeds 3 minutes, the catheter requires replacement with a new unit.
- 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%.

Please refer to the current LUTONIX<sup>®</sup> Drug Coated Balloon IFU for detailed information on device use.

## **6.7 POST TREATMENT AND PROVISIONAL (BAILOUT) STENTING**

There is no consensus or established objective criteria that are validated regarding the appropriate threshold for provisional SFA stenting for ISR treatment. In the absence of an

established threshold, the determination to bailout has previously been based on criteria that are either subjective or largely left to the discretion of the individual operator and his/her judgment.

The current trial design is intended to minimize the need for bailout stenting. Due to the need within the medical community to establish validated criteria for provisional stenting, this trial will utilize more rigorous criteria for bailout stenting. Specifically, the trial will employ the additional requirement of a pressure gradient measurement to document an unsatisfactory balloon-only outcome (obtained by measuring pressures proximal and distal to the lesion simultaneously).

If immediate procedural results are not satisfactory, e.g., residual stenosis >30% or flow-limiting dissection, then prolonged balloon dilations are recommended. Post dilatation may be performed using either the used Drug Coated Balloon (note that drug delivery occurs during the first inflation ONLY) or another plain angioplasty catheter, taking great care to avoid injury of a segment to which drug is not delivered. Stenting is allowed only in cases with flow-limiting dissection or stenosis >50% and documented pressure gradient refractory to postdilatation and nitroglycerine administration.

**Table 1: Bailout Criteria**

<b>Bailout Prevention</b>
Treatment requirement prior to bailout stenting: <ul style="list-style-type: none"><li>• Prolonged (&gt;2 minutes) balloon inflation(s)</li><li>• Vasodilators and/or thrombolytic agents per investigator discretion</li></ul>
<b>Bailout Criteria</b>
<ul style="list-style-type: none"><li>• Residual stenosis of &gt;50% (based on careful in-lab review of angiograms including QVA if available) <i>or</i> major flow-limiting dissection (Record angiography in 2 orthogonal views) <i>and</i></li><li>• Documented translesional pressure gradient of &gt;20mmHg (using ≤4F end-hole catheter) or &gt;10mmHg (pressure wire) measured immediately distal to the target lesion</li></ul>

These criteria are set as the minimum baseline pressure gradient requirement for allowing bailout stenting; however, bailout stenting is not required for pressures equal to or exceeding these thresholds (i.e. presence of a gradient at/above these thresholds does not require that the operator place a stent). Rather, these thresholds are seen as minimum requirements for bailout stenting; below these thresholds, bailout stenting is not allowed.

If the criteria for bailout stenting are fulfilled, placement of a bare nitinol stent (not DES) is permissible at the physician's discretion.

The angiographic core lab will be monitoring cases of bailout stenting throughout the course of enrollment for compliance to provisional (bailout) criteria listed in this section.

## **6.8 UNSCHEDULED ANGIOGRAPHY/REVASCLARIZATION**

A DUS is required prior to any subsequent angiography of the index limb, and the images must be submitted to the DUS Core Lab. A DUS at any time point post index procedure but prior to the re-intervention will suffice. Clinical status should be evaluated prior to angiography, including physical exam, Rutherford classification and ABI. In the event that a subject undergoes repeat angiography after the index procedure is complete, all subsequent angiograms for the index limb or, in the event of an index limb revascularization, all procedural angiograms must 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.

## **7 TREATMENT OF SUBJECT**

Lutonix (or its designee) reserves the right to attend index or DUS 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 for subjects randomized under protocol versions 2.0 and 3.0. All Duplex Ultrasound operators, core lab evaluators, and members of the Clinical Events Committee (CEC) will be blinded to the subject's treatment assignment. The study subject will be blinded to treatment until the completion of the 12 month visit.

All subjects enrolled under protocol version 4.0 or later will be treated with the LUTONIX<sup>®</sup> Drug-Coated Balloon; therefore a blinding plan is not applicable.

### **7.2 MEDICATIONS**

Subjects should be given standard dual antiplatelet loading and treatment doses per institution standard of care for at least one month post procedure. These medications will be captured on the eCRFs for each subject enrolled.

### **7.3 STANDARD TESTS, PROCEDURES, AND FOLLOW-UP**

**Table 2** displays the required schedule 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.

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

**Table 2: Follow Up Schedule and Testing Requirements for Subjects**



EVENT	Pre-Procedure	Procedure	Post-Procedure	1 Month <sup>1</sup>	6 Month	12 Month	24 Month	36 months <sup>1</sup>	Repeat Angio/Revasc
Visit Window	30 Days	-		±14 days	±30 days	±30 days	±60 days	±60 days	-
Inc/Exc Criteria	√	√							
Inf. Consent	√								
Med Hx	√								
Pregnancy Test <sup>2</sup>	√								
Physical Exam	√		√	√ <sup>3</sup>	√	√	√		√ <sup>5</sup>
Medication Compliance	√			√	√	√	√	√	√
Resting ABI	√ <sup>4</sup>		√ <sup>5</sup>	√ <sup>3</sup>	√	√	√		√ <sup>5</sup>
Rutherford Classification	√				√	√	√		√ <sup>5</sup>
WIQ & EQ5D Questionnaires	√				√	√	√		
Angiogram		√							√
Adverse Event Monitoring		√	√	√	√	√	√	√	√
Duplex Ultrasound <sup>6</sup>				√ <sup>7</sup>	√	√	√		√

<sup>1</sup>Follow-up can be by telephone or clinical visit

<sup>2</sup>For females of childbearing potential

<sup>3</sup>Required only if clinical visit occurs

<sup>4</sup>Resting ABI is required within 90 days prior to index procedure.

<sup>5</sup>Not required, but encouraged to capture if possible

<sup>6</sup>DUS to be performed after Clinical Assessment

<sup>7</sup>DUS may be capture anytime 0-6 weeks post procedure

### 7.3.1 TESTING

#### 7.3.1.1 PREGNANCY TESTING

For women of childbearing potential, a pre-procedure pregnancy test must be done (blood or urine). Pre-procedure samples may be taken up to 30 days prior to the index procedure.

#### 7.3.1.2 ANKLE-BRACHIAL INDEX (ABI)

A resting ABI must be performed per local hospital standard, and consistently among subjects over the lifespan of the study (within 90 days prior to index procedure).

#### 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.

#### 7.3.1.4 WALKING IMPAIRMENT QUESTIONNAIRE

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



See Appendix B for a sample questionnaire form.

#### **7.3.1.5 *QUALITY OF LIFE QUESTIONNAIRE***

The EQ5D survey will be completed at pre-procedure and at 6, 12 and 24 months.

See Appendix C for a sample questionnaire form.

#### **7.3.1.6 *DUPLEX ULTRASOUND AND ANGIOGRAPHY GUIDELINES***

The initial baseline DUS must be performed after the index procedure (or at anytime up to 6 weeks post-procedure), and again at 6, 12 and 24 months. Since DUS and angiography are critical to assessing study endpoints, the quality of these tests are extremely important. 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 and Angiography Guidelines Manual of Operations for the most current version of the documentation requirements.

#### **7.3.2 *FOLLOW-UP PROCEDURES***

The Investigator or Research Coordinator will contact subjects via phone (or via clinical visit if preferred or as part of a regular follow-up) at 30 days, and 36 months (and possibly longer if required) in order to assess for any adverse events and medication compliance.

All subjects will return for follow-up at 6, 12 and 24 months post procedure for required testing at each follow-up visit time point. If DUS was not performed post index procedure, a clinic visit will be required within 6 weeks of initial treatment to obtain images.

All subjects are required to complete all assigned follow-up visits and procedures. During the duration of the study, all events need to be reported in the web-based eCRF. Subjects will be instructed to report adverse events to their study physician between evaluation visits.

## **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. See Appendix A for detailed AE definitions.

The following adverse events are required to be reported in this study:

- All SAEs
- All protocol defined Major Vascular Complications (MVC) occurring  $\leq 30$  days of the index procedure (See Appendix A for definition of MVC)
- Non-serious adverse events involving the target limb

## **8.1 ADVERSE EVENT REPORTING**

All adverse events occurring since the start of the study procedure must be recorded in the eCRF for enrolled subjects that meet all criteria after pre-dilatation. All adverse events occurring in this study will be classified in accordance with the adverse event signs or symptoms. The CEC will review and adjudicate all deaths, all index limb reinterventions, all index limb amputations, Unanticipated Adverse Device Effects (UADEs) and device related SAEs. Any Serious Adverse Event must be reported in the EDC within 5 working days of knowledge. Adverse events will be reported to the IRB 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.

## **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. Site and subject numbers will be used to track subject information throughout the study.

The eCRF is designed to accommodate the specific features of the study design. Modification of the eCRF will only be made if deemed necessary by Lutonix and/or the appropriate regulatory body.

#### ***10.1.2 ANGIOGRAMS AND DUPLEX ULTRASOUNDS***

All core lab raw data will be sent to the independent Core Lab for analysis. All Core Lab evaluators will be blinded to the randomized treatment of subjects enrolled under protocol versions 2.0 and 3.0.

### **10.2 MONITORING**

Each site will have an initiation visit performed by a Study Monitor and/or 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.

Sites will be monitored according to the approved monitoring plan. Monitoring personnel will monitor for accuracy and timely submission of data forms and core lab images, and compliance

with the study protocol, meeting enrollment commitments, applicable regulations, the signed Investigator Agreement and any conditions of approval imposed by the reviewing IRB and/or regulatory agencies.

The Study Monitors will maintain personal contact with the Investigator and staff throughout the study by phone, mail, and on-site visits. The Study Monitors will compile and submit to Lutonix a monitoring report after each visit that will include any findings, conclusions, and actions taken to correct deficiencies.

At the close of the study at an investigational site, appropriately trained personnel appointed by Lutonix will make a final on-site visit or a remote (i.e. telephone) visit if no subjects were enrolled at a site. The purpose of this visit is to collect all outstanding study data documents, ensure that the Investigator's files are accurate and complete, review record retention requirements with the Investigator, make a final accounting of all study supplies shipped to the Investigator, provide for appropriate disposition of any remaining supplies, and ensure that all applicable requirements are met for the study.

### **10.3 SOURCE DOCUMENTATION**

Auditors, monitors, the study Sponsor 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. (No source documentation will be recorded directly on an eCRF). The Investigator will permit study-related monitoring, audits, IRB review and authority inspections by allowing direct access to the source data.

In case of electronic source data, access will be allowed or dated print-outs will be available prior to the monitoring visits. Print-outs should not be limited to the vascular data only, but should include all available data related to the identified subject(s).

### **10.4 RECORD RETENTION**

The Sponsor 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.

## **11 DEVICE ACCOUNTABILITY**

The Investigator must ensure that the study devices are used only in accordance with the protocol and current IFU. The Investigator must maintain records that adequately document the device(s) the subject received. In the case where a Lutonix device has failed, the Investigator must make every possible effort to return the device to Lutonix; instructions for this procedure will be provided in the Investigator Site Binder.

## **11.1 DEVICE SUPPLY**

Investigational LUTONIX® Drug Coated Balloon will be utilized for this study.

## **12 STUDY MANAGEMENT**

### **12.1 DATA SAFETY MONITORING BOARD**

The Data Safety Monitoring Board (DSMB) is responsible for the oversight and safety monitoring of the study. The DSMB 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 DSMB members are 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 DSMB will review accumulating safety data to monitor for incidence of serious vascular events that would warrant modification or termination of the trial.

Any DSMB recommendations for study modification or termination because of concerns over subject safety or issues relating to data monitoring or quality control will be submitted in writing to the Study PI and sponsor for consideration and final decision.

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

### **12.2 CLINICAL EVENTS COMMITTEE**

The Clinical Events Committee (CEC) is made up of a minimum of three clinicians with expertise in vascular intervention and who are not participants in the study. The CEC is charged with the development of specific criteria used for the categorization of clinical events and clinical endpoints in the study that are based on the protocol.

All members of the CEC will be blinded to the primary results of the trial. The CEC will meet regularly to review and adjudicate all subject deaths, index limb reinterventions and device related SAEs.

## **13 REGULATORY RESPONSIBILITIES**

### **13.1 ETHICS APPROVAL**

Investigators must submit the study protocol to their IRB and obtain written approval before being allowed to conduct and participate in the study. The Investigator is also responsible for fulfilling any conditions of approval imposed by the IRB, 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 and written approval obtained prior to implementation.

## **13.2 INFORMED CONSENT**

Part of the IRB approval must include approval of an Informed Consent Form (ICF) that is specific to the study. 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. Lutonix or designee must pre-approve each ICF prior to initial submission to the IRB. The Investigator will provide Lutonix or designee with a copy of the approved ICF for his/her site.

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.

## **13.3 SELECTION OF CLINICAL SITES AND INVESTIGATORS**

The Sponsor will select Investigators who are qualified and experienced to participate in this study. Sites will be selected based upon a review of site assessments or questionnaires and the overall qualifications of the site.

Any site that becomes deactivated prior to initial enrollment, either by the sponsor or by the individual site itself, may be replaced.

## **13.4 INVESTIGATOR'S RESPONSIBILITIES**

Each Investigator is responsible for ensuring the study 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.

### ***13.4.1 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 main contact person at the site for all aspects of study administration.

## **13.5 LUTONIX RESPONSIBILITIES**

A 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.

## **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](http://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 will be submitted to a reputable scientific journal.

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

## **15 STATISTICAL ANALYSIS PLAN**

### **15.1 OVERVIEW OF STUDY DESIGN**

The SFA ISR study is a multi-center, single-arm trial comparing the LUTONIX<sup>®</sup> Drug Coated Balloon to safety and effectiveness performance goals based on standard balloon angioplasty for the treatment of femoropopliteal in-stent restenosis. The study will enroll patients presenting with claudication or ischemic rest pain (Rutherford Category 2-4) and occlusion or  $\geq 50\%$  stenosis of a previously deployed bare nitinol stent(s) or drug-eluting stent if placed  $\geq 6$  months prior to the index procedure in the femoropopliteal artery that is appropriate for angioplasty. After successful protocol-defined pre-dilatation, subjects are treated with the LUTONIX<sup>®</sup> Drug Coated Balloon.

The objective of the study is to demonstrate the effectiveness and safety of the LUTONIX<sup>®</sup> Drug Coated Balloon for treatment of SFA ISR by comparison to objective performance goals (OPGs). Both primary endpoint criteria must be met in order for the study to be considered successful.

### **15.2 ANALYSIS POPULATIONS**

Intent-To-Treat (ITT) population: All subjects who have signed the Informed Consent Form and are determined by the site to be suitable to receive treatment with the LUTONIX<sup>®</sup> Drug Coated Balloon or standard PTA.

As-treated (AT) population: All ITT subjects that were treated with the LUTONIX<sup>®</sup> Drug Coated Balloon. This may also be referred to as the Modified Intent-to-Treat (mITT) population.

Per-Protocol population (PP): All AT (mITT) subjects characterized by appropriate exposure to treatment (procedurally correct as pre-specified) and the absence of major protocol violations (including violations of entry criteria) that if not met for a given patient may obscure the evaluation of efficacy in that patient.



All baseline analyses will be completed using the mITT population. All effectiveness and safety analyses will be completed with the AT (mITT) population. .

PTA Population: The set of subjects originally randomized to and treated with PTA under the previous versions of the protocol.

The results of the PTA population will be listed or summarized separately from the Lutonix DCB subjects using descriptive statistics.

### **15.3 HANDLING MISSING DATA**

Endpoints may be missing because subjects have died, have uninterpretable 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 results for the primary endpoints will be reported. The primary safety and effectiveness endpoints will also be supportively analyzed using Kaplan-Meier survival analysis techniques as sensitivity analyses. In survival analyses, unobserved endpoints are a standard part of the analysis and, as long as the missing data is unrelated to the treatment or the actual (unobserved) outcome, the Kaplan-Meier method will produce unbiased estimates of the freedom-from-event rates. A tipping-point analysis will also be performed for the binary primary patency endpoint, 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 conclusion of the analysis. These analyses will constitute sensitivity analyses of the effect of missing data on the study results.

### **15.4 ASSESSMENT OF POOLABILITY OF SITES AND SECONDARY ANALYSIS**

All primary endpoints will also be presented by site and sites with 3 or fewer AT subjects will be combined for this purpose. In addition, the endpoints will also be summarized by site without pooling though no test of homogeneity will be performed.

An analysis will be performed to examine the potential for homogeneity of response rates across pooled sites. A logistic regression model will be fit for site. If the p-value for the site effect is  $<0.15$ , it will be considered evidence of a potential lack of homogeneity across the study sites, 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. A non-significant site effect or a significant effect that is only quantitative and not qualitative on nature will be taken to support the pooling sites for the primary analysis. Analyses may include testing for differences between sites for the covariates listed later in this section and the use of modeling involving the covariates along with study site to determine if they potentially explain any lack of homogeneity across the study sites.

In addition, a descriptive analysis that examines the impact of important covariates on study results will be performed. Baseline covariates are age, gender, smoking, obesity, hypercholesterolemia, diabetes mellitus, total target lesion length (sum of core lab-reported lesion lengths of more than one), and maximum percent stenosis of subject target lesion(s) (via

core lab analysis), previous target lesion intervention, ABI of the target limb, and Rutherford grade. Additional variables may be identified in the statistical analysis plan and will be identified prior to the completion of the study. The covariates will be included in a logistic regression model in order to understand their potential impact on study results.

An additional supportive analysis of patients without bailout stenting will also be performed based on descriptive statistics, and data will further be presented for subjects without bailout stenting.

## 15.5 PRIMARY ENDPOINTS

### 15.5.1 PRIMARY EFFICACY ENDPOINT: BACKGROUND

The primary efficacy endpoint is primary patency at 12 months. Primary Patency is defined as Freedom from CEC-adjudicated Clinically-Driven TLR and from Core laboratory-adjudicated Binary Restenosis. Binary restenosis is based on threshold Doppler PSVR  $\geq 2.5$  (together with waveform analysis & color mosaic appearance) or based on angiographic  $\geq 50\%$  diameter stenosis (if angiography is performed although not required per protocol).

In order to establish an objective performance goal (OPG) for primary patency for this uncontrolled study, results from three sources were considered: a meta-analysis of published results, the LEVANT 2 randomized primary patency result, and the Lutonix SFA Global Registry primary patency findings. Based on the evaluation of the data sources, an OPG of 45% for primary patency was proposed for this study and the rationale is provided below.

#### Meta-analysis results

Estimated 12-month primary patency response rates for PTA were 34.2% (95% CI = 29.5%, 39.0%) and for DCB were 84.5% (95% CI = 78.2%, 90.7%). These results would indicate a large treatment effect in ISR subjects and low expectations for PTA alone. The large range of responses in controlled studies may be explained by the use of additional therapies. Nonetheless, the results indicate the clear potential for an unmet need in treating ISR lesions with significant benefit in the use of DCB therapies.

The performance of PTA from six publications is shown below. **Table 3** provides a meta-analysis of reported outcomes after standard of care treatment of SFA ISR. A very high restenosis rate is observed, with only 34% patency at 12 months.

**Table 3: Primary Patency for Standard of Care Treatment for SFR ISR**

Source	Design	Cohort	CTO%	Length (mm)	N	n patent	p	w = n/p(1-p)	w*p
<sup>13</sup> Tosaka	Retrospect Observ	CTO (III)	100.0%	198	44	10	22.73%	250.541	56.941
<sup>13</sup> Tosaka	Retrospect Observ	stenosis (I&II)	0.0%	91	89	61	68.54%	412.745	282.893

<sup>13</sup> Tosaka, A., Soga, Y., Iida, O., Ishihara, T., Hirano, K., Suzuki, K., . . . Nobuyoshi, M. (2012). Classification and clinical impact of restenosis after femoropopliteal stenting. *J Am Coll Cardiol*, 59(1), 16-23. doi: 10.1016/j.jacc.2011.09.036



<sup>4</sup> Yeo-Laird	Retrospect Observ	combined	40.9%	132	21	10	47.62%	84.191	40.091
<sup>14</sup> Liistro	RCT-DEBATE ISR	POBA	NA	138	39	11	28.21%	192.594	54.321
<sup>2</sup> Dick	RCT-PTA v. cutting	POBA (6m)	9.1%	80	22	6	27.27%	110.917	30.250
<sup>15</sup> Dippel	RCT – EXCITE ISR	POBA	36.8%	193	51	6	11.8%	491.300	57.800
<sup>16</sup> Krankenber	RCT - FAIR Trial	POBA	33.3%	81	40	15	37.5%	170.667	64.000
<sup>17</sup> D'Agostino meta ->								1712.966	586.30
Standard-of-Care Rate ->								<b>0.342</b>	
95% CI [LL UL]->								<b>0.295</b>	<b>0.390</b>

The above analysis is confounded by sporadic adjunctive use of laser, atherectomy, and stents in the observational standard-of-care studies, which may result in an overestimated primary patency rate for on label therapy – POBA – for which only 12% to 38% patency was observed in the RCT control arms.

Preliminary data is available for drug-coated balloons. The promising results from another manufacturer's DCB (Medtronic In.Pact) suggest that DCB may provide a much more durable solution. Available data for DCB and meta-analytic patency rate are provided in **Table 4**.

**Table 4: Primary Patency for Drug Coated Balloon Treatment for SFR ISR**

Source	Design	Cohort	CTO%	Length (mm)	N	n patent	p	w = n/p(1-p)	w*p
<sup>9</sup> Stabile	Prosp Registry	In.Pact DCB	20.50	83	38	35	92.11%	522.591	481.333
<sup>14</sup> Liistro	RCT-DEBATE ISR	In.Pact DCB	NA	131	41	33	80.49%	261.064	210.125
<sup>16</sup> Krankenber	RCT - FAIR Trial	In.Pact DCB	24.2	82	44	31	70.50%	211.375	148.923
<sup>17</sup> D'Agostino meta ->								995.030	840.381
DCB Rate ->								<b>84.5%</b>	
95% CI [LL UL]->								<b>78.2%</b>	<b>90.7%</b>

The primary patency rate of 84.5% reported above for DCB (**Table 4**) cannot be assumed, given the limited number of subjects treated in only three studies. Furthermore, the test device of the present study differs from the Lutonix DCB.

#### Randomized Comparison of PTA and Lutonix DCB

<sup>14</sup> Liistro F, et al, JACC Vol 60/17/Suppl B | October 22–26, 2012 | TCT Abstracts/POSTER/Diabetic Patients

<sup>15</sup> Dippel E, et al, Randomized Controlled Study of Excimer Laser Atherectomy for Treatment of Femoropopliteal In-Stent Restenosis, JACC Vol 8(1), Jan 2015:92-101

<sup>16</sup> Krankenberg H, et al, Drug-Coated Balloon Versus Standard Balloon for Superficial Femoral Artery In-Stent Restenosis: The Randomized Femoral Artery In-Stent Restenosis (FAIR) Trial; DOI:10.1161/CIRCULATION.AHA.115.017364

<sup>17</sup> D'Agostino, R. B. et al, Meta-analysis: A method for synthesizing research. Clinical Pharmacology & Therapeutics, 58: 605–616. doi: 10.1016/0009-9236(95)90016-0

The LEVANT 2 pivotal study included a randomized comparison of the primary patency at 12 months in the PTA and DCB subjects. The subjects were not ISR subjects, but LEVANT 2 provides reference rates based on the primary patency methodology proposed for this study. Response rates for primary patency were 52.6% (71/135) for PTA subjects and 65.2% (172/264) in DCB subjects. These indicate a potential higher primary patency rate in PTA subjects and a potentially more model effect for primary patency in DCB subjects.

#### Lutonix SFA Global Registry Results

The SFA Global Registry was an open-label registry containing 691 subjects. This study included a subset of subjects with one or more ISR lesions. Overall site based primary patency response at 12 month was 80.5% (62/77) in ISR subjects and 82.7% (416/503) in non-ISR subjects. A similar trend was observed in the TLR-Free response rate at 12 months which was 91.5% (75/82) in ISR subjects and 94.6% (524/554) in non-ISR subjects.

#### Selection of an Objective Performance Goal

The poor PTA alone results in the meta-analysis suggest that the ISR subjects may do very poorly with regard to primary patency. However, given the wide range response rates, the pooled response rate of 34.2% may be overly pessimistic even though the total number of treated subjects is 306. A proposed OPG based for this study is 45% (this is slightly above the average of the LEVANT 2 PTA response rate and the meta-analysis estimate). This OPG balances the poor response in ISR subjects observed in the meta-analysis with the higher PTA response from LEVANT 2.

For sample size purposes, the DCB response rate is assumed to be 63.0% which reflects a small adjustment to the DCB reduction in the 65.2% response rate observed in the LEVANT 2 study in line with the 2.2% difference in response rates for primary patency in ISR subjects in the SFA Global Registry.

#### ***15.5.2 EFFICACY ENDPOINT: HYPOTHESIS TEST AND SAMPLE SIZE CALCULATION***

The primary efficacy endpoint is primary patency at 12 months. Primary Patency is defined as Freedom from Clinically-Driven TLR and from Binary Restenosis. Binary restenosis is adjudicated by the independent, blinded core laboratory based on threshold Doppler PSVR  $\geq 2.5$  (together with waveform analysis & color mosaic appearance) or based on angiographic  $\geq 50\%$  diameter stenosis (if angiography is performed although not required per protocol). Clinically-Driven TLR is adjudicated by the CEC.

Objective: To assess whether the proportion of subjects with Primary Patency ( $\pi$ ) in DCB subjects is less than or equal to or greater than the primary patency OPG (45.0%) through 12-months post-index procedure.

**H<sub>0</sub>:** The proportion of Lutonix DCB subjects with Primary Patency is less than or equal to the OPG to 0.45 (45.0%) at 12 months ( $H_0: \pi \leq 0.45$ ).

**H<sub>1</sub>:** The proportion of Lutonix DCB subjects with Primary Patency is greater than the OPG of 0.45 (45.0%) at 12 months ( $H_1: \pi > 0.45$ ).

The statistical analysis will be performed using an exact binomial test with one-sided  $\alpha=0.025$  based on the AT (mITT) population. The response variable in each subject will be the presence or absence of at least one efficacy event (core-lab adjudicated binary restenosis or CEC-adjudicated clinically-driven TLR) from the time following the index procedure through 12 months. A significant rejection of the null hypothesis will be based on a one-sided p-value less than or equal to 0.025. The proportions at 12-months post-index procedure and the exact 95% confidence intervals will also be reported.

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

- The true 12-month proportion in the Lutonix DCB subjects is 63%
- The Type 1 error,  $\alpha = 0.025$  (one-sided).
- The Type 2 error,  $\beta = 0.10$  (Power =  $1 - \beta = 90\%$ ).
- Based on exact binomial test

The study evaluable sample size required for 90% power is 83 subjects. Allowing for up to 15% of subjects with missing 12 month efficacy endpoint data, the required enrolled sample size is 98 DCB subjects in order to obtain 83 subjects with 12 month follow-up. The total study sample size of 127 includes 98 DCB subjects and 29 subjects previously treated with PTA.

#### ***15.5.3 PRIMARY SAFETY ENDPOINT: BACKGROUND***

The primary safety endpoint is a composite of freedom from all-cause perioperative ( $\leq 30$  day) death and freedom at 1 year from the following: index limb amputation (above and below the ankle) index limb re-intervention, and index-limb-related death. These events are called “safety events” in the following text.

Data for this endpoint was not reported in the SFA ISR studies cited above (**Table 3** and **Table 4**). However, safety outcomes reported to date for DCB-treated in-stent and native femoropopliteal lesions appear similar in general. It is therefore assumed that safety outcomes after DCB treatment of SFA ISR are similar to those observed in the LEVANT2 clinical study, 84.9% for DCB compared to 79.0% for control PTA.

Restenosis is common after use of currently available devices. A safety OPG target of 69.0% is proposed for the safety endpoint by applying a 10% margin to the PTA event rates from the LEVANT 2 study. This is intended to reflect that these subjects may be at somewhat greater risk of previous need for stent placement.

#### ***15.5.4 SAFETY ENDPOINT: HYPOTHESIS TEST AND SAMPLE SIZE CALCULATION***

The primary safety endpoint is a composite of freedom from all-cause perioperative ( $\leq 30$  day) death and freedom at 1 year from the following: index limb amputation (above and below the ankle) index limb re-intervention, and index-limb-related death.

Objective: To assess whether the proportion of Lutonix DCB subjects free from any safety event\* is greater than the OPG target of 69% through 12 months post-index procedure.

$H_0$ : The proportion of Lutonix DCB subjects free from safety events post-index procedure is less than or equal to the OPG of 0.69 (69%) at 12 months ( $H_0: \phi_{DCB} \leq 0.69$ ).

$H_1$ : The proportion of Lutonix DCB subjects free from safety events post-index procedure is greater than then OPG of 0.69 (69%) at 12 months ( $H_1: \phi_{DCB} > 0.69$ ).

\* All-cause perioperative ( $\leq 30$  day) death, index limb amputation (above or below the ankle), target limb reintervention, and target limb related death are safety events.

The statistical analysis will be a one-sided exact binomial test assessed using a one-sided  $\alpha=0.05$  based on the AT population. 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 12 months. A significant rejection of the null hypothesis with one-sided p-value less than 0.05 indicates success for this endpoint.

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

- The true 12 month proportion in the Test group is 84.9%
- The Type 1 error,  $\alpha = 0.05$  (one-sided).
- The Type 2 error,  $\beta = 0.10$  (Power =  $1 - \beta = 90\%$ ).

The evaluable sample size required for 90% power is 79 DCB subjects. While almost no missing data is expected for this endpoint, allowing for censoring of 10% of subjects, at least 88 DCB subjects would be required. Hence, the primary safety endpoint is not the sample size driver of the study.

## **15.6 SECONDARY ENDPOINTS**

### ***15.6.1 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 binary outcomes, the exact 95% confidence intervals for the rates will be provided for the 12 month endpoint. In addition, descriptive statistics will also be estimated for the subsets of subjects with and without bailout stenting.

Efficacy measurements of Device, Technical and Procedural Success will be assessed following the procedure.

Efficacy measurements of the following endpoints will be reported at 6, 12 and 24 Months:

- Primary and Secondary Patency
- Target Lesion Revascularization (TLR)
  - Clinically-driven
  - All TLR
- Sustained Clinical Benefit (improvement in Rutherford Class compared to baseline AND freedom from target vessel revascularization)
- Change of Rutherford classification from baseline
- Change of resting Ankle Brachial Index (ABI) from baseline
- Change in Walking Impairment Questionnaire from baseline
- Change in quality of life from baseline, as measured by EQ-5D

The following secondary safety endpoints will be reported:

- Major vascular complications ( $\leq 30$  day)

The following endpoints will be reported at 1, 6, 12, 24, and 36 Months:

- Composite Safety (criteria of the primary safety endpoint)
- Death
- Amputation (major and minor separately)
- Target Vessel Revascularization (TVR)
- Target Limb Reintervention

Secondary Kaplan-Meier analyses may also be conducted. These analyses will only be performed with the mITT population.

## **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)**

A SAE is an adverse event that:

- led to death or led to a serious deterioration in the health of the subject
- resulted in a life-threatening illness or injury,
- resulted in a permanent impairment of a body structure or a body function,
- required in-subject hospitalization or prolongation of existing hospitalization or
- resulted in medical or surgical intervention to prevent permanent impairment to body structure or a body function

#### **Serious Adverse Device Effect (SADE)**

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

#### **Unanticipated Adverse Device Effect (UADE)**

A UADE is “any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects” (21 CFR 812.3(s)).

### **Adverse Event Severity Stratification**

The Investigator will use the following definitions to rate the severity of each adverse event:

<b>Mild</b>	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.
<b>Moderate</b>	Interferes with the subject's usual activity and/or requires symptomatic treatment.
<b>Severe</b>	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:

<b>Not Related</b>	The event is definitely not associated with device application. The adverse event is due to an underlying or concurrent illness or effect of another device or drug.
<b>Unlikely</b>	An adverse event has little or no temporal relationship to the study device and/or a more likely alternative etiology exists.
<b>Possible</b>	The temporal sequence between device application and the event is such that the relationship is not unlikely or subject's condition or concomitant therapy could have caused the AE.
<b>Probable</b>	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.
<b>Highly Probable</b>	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:

<b>Not Related</b>	The event is definitely not associated with procedure. The adverse event is due to an underlying or concurrent illness or effect of another procedure.
<b>Unlikely</b>	An adverse event has little or no temporal relationship to the procedure and/or a more likely alternative etiology exists.
<b>Possible</b>	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.
<b>Probable</b>	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.
<b>Highly Probable</b>	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.

### **All Cause Perioperative Death**

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

### **Amputation of the Index Limb**

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

### **Ankle Brachial Index 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.

### **As-Treated**

All ITT subjects that were treated with the LUTONIX<sup>®</sup> Drug Coated Balloon. This may also be referred to as the Modified Intent-to-Treat (mITT) population.

### **Binary Restenosis Rate**

The presence of a hemodynamically significant restenosis (>50%) as determined by angiography or by duplex ultrasound (defined by systolic velocity ratio  $\geq 2.5$ ).



## Bleeding Complications

Bleeding will be classified per the TIMI definitions<sup>18</sup>

Major	Intracranial Hemorrhage  ≥ 5 g/dl decrease in the hemoglobin concentration  ≥ 15% absolute decrease in hematocrit
Minor	Observed blood loss:  ≥ 3 g/dl decrease in the hemoglobin concentration  ≥ 10% decrease in the hematocrit  No observed blood loss:  ≥ 4 g/dl decrease in the hemoglobin concentration  ≥ 12% decrease in the hematocrit
Minimal	Any clinically overt sign of hemorrhage associated with a <3 g/dl decrease in the hemoglobin concentration or < 9% decrease in the hematocrit

## Clinically Driven Target Lesion Revascularization

Revascularization at the target lesion with evidence of target lesion diameter stenosis >50% determined by duplex ultrasound or angiography and new distal ischemic signs (worsening ABI or worsening Rutherford Category associated with the target limb or due to clinical symptoms), OR revascularization of a target lesion with an in-lesion diameter stenosis of >70% by angiography, in the absence of the previously mentioned ischemic signs or symptoms.

## Clinically Driven Target Vessel Revascularization

Revascularization of the target vessel with evidence of target vessel diameter stenosis >50% determined by duplex ultrasound or angiography and new distal ischemic signs (worsening ABI or worsening Rutherford Category associated with the target limb or due to clinical symptoms), OR revascularization of a target vessel with an in-lesion diameter stenosis of >70% by angiography, in the absence of the previously mentioned ischemic signs or symptoms.

## DUS Clinical Patency

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<sup>18</sup> Chesebro JH, Knatterud G, Roberts R et al.: Thrombolysis in Myocardial Infarction (TIMI) Trial, Phase I: a comparison between intravenous tissue plasminogen activator and intravenous streptokinase. Clinical findings through hospital discharge. *Circulation* 76,142–154 (1987).

Defined as patency of the target limb (based on a PSVR threshold  $< 2.5$ ) without prior Clinically Driven TLR.

### **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**

Device success is defined as, on 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**

A patient is considered enrolled in the study after they have provided consent and have been treated or attempted to be treated with the study device.

### **Intent-To-Treat (ITT)**

The principle of including outcomes of all subjects in the analysis who have signed the Informed Consent Form and are determined by the site to be suitable to receive treatment with the LUTONIX<sup>®</sup> Drug Coated Balloon or standard PTA.

### **Index Limb Related Death**

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

### **Major Adverse Event (MAE)**

Events of death, amputation of the target limb, or target lesion revascularization (surgical or percutaneous

### **Major Vascular Complications**

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 Amputation**

Amputation of the lower limb above the ankle

### **Minor Amputation**

Amputation of a part of the foot below the ankle.

### **Patent Run-off**

At least one patent native outflow artery from the popliteal to the ankle, free from significant ( $\geq 50\%$ ) stenosis as confirmed by angiography or ultrasound that has not previously been revascularized.

### **Per-Protocol (PP)**

All AT (mITT) subjects characterized by appropriate exposure to treatment (procedurally correct as pre-specified) and the absence of major protocol violations (including violations of entry criteria) that if not met for a given patient may obscure the evaluation of efficacy in that patient.

### **Primary Patency**

Primary Patency is defined as Freedom from Clinically-Driven TLR and from Binary Restenosis. Binary restenosis is adjudicated by the independent, blinded core laboratory based on threshold Doppler PSVR  $\geq 2.5$  (together with waveform analysis & color mosaic appearance) or based on angiographic  $\geq 50\%$  diameter stenosis (if angiography is performed although not required per protocol). Clinically-Driven TLR is adjudicated by the CEC.

### **Procedural success**

Attainment of  $\leq 30\%$  residual stenosis in the treatment area by independent core lab analysis without major adverse events (defined as occurrence of death, amputation of the target limb or repeat revascularization of the target lesion) during the index procedure and through the hospital stay

### **Popliteal Artery**

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

### **PSVR**

Peak Systolic Velocity Ratio

### **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**

Either  $\geq 50\%$  restenosis of the diameter of the reference-vessel segment by QVA or peak systolic velocity ratio of  $\geq 2.5$ , determined by blinded ultrasound and independent core lab analysis.

### **Restenotic Lesion**

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

### **Rutherford Categories**

<b>Category</b>	<b>Clinical Description</b>
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 Binary Restenosis as adjudicated by the blinded, independent core laboratory, independent of whether or not patency is re-established via an endovascular procedure. Binary restenosis is based on threshold Doppler

PSVR  $\geq 2.5$  (together with waveform analysis & color mosaic appearance) or based on angiographic  $\geq 50\%$  diameter stenosis (if angiography is performed although not required per protocol).

### **Stroke**

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

### **Target Lesion**

Lesion that is to be treated during the index procedure.

### **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.

### **Technical Success**

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.

### **Treatment Area**

The entire treated vessel segment in which angioplasty balloons were inflated (the injury segment) including the target lesion.

### **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.

### **Transient Ischemic Attack (TIA)**

Clinical signs/symptoms of focal neurological deficit lasting up to 24 hours

### **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 of Ankle Brachial Index**

A deterioration in the Ankle Brachial Index (ABI) by more than 0.15 from the maximum early post-procedural level.

### **Worsening Rutherford Clinical Category**

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

## APPENDIX B: SAMPLE WALKING IMPAIRMENT QUESTIONNAIRE

### WALKING IMPAIRMENT QUESTIONNAIRE (WIQ)

**Walking impairment:** These questions ask about the reasons why you have difficulty walking. We would like to know how much difficulty you had walking during the past week. By difficulty, we mean how hard it was or how much physical effort it took to walk because of each of these problems.

#### PAD SPECIFIC QUESTIONS

#### DEGREE OF DIFFICULTY

	None	Slight	Some	Much	Very
Pain, aching or cramps in your calves (or buttocks)?					
RIGHT LEG	4	3	2	1	0
LEFT LEG	4	3	2	1	0
BOTH LEGS	4	3	2	1	0

#### DIFFERENTIAL DIAGNOSIS

#### DEGREE OF DIFFICULTY

	None	Slight	Some	Much	Very
1. Pain, stiffness or aching in your joints (ankles, knees or hips)?	4	3	2	1	0
2. Weakness in one or both of your legs?	4	3	2	1	0
3. Pain or discomfort in your chest?	4	3	2	1	0
4. Shortness of breath?	4	3	2	1	0
5. Heart palpitations?	4	3	2	1	0
6. Other problems? (please list)	4	3	2	1	0

**Walking distance:** Report the degree of physical difficulty that best describes how hard it was for you to walk on level ground without stopping to rest for each of the following distances during the last week:

#### DISTANCE

#### DEGREE OF DIFFICULTY

	None	Slight	Some	Much	Unable
1. Walking indoors such as around your home?	4	3	2	1	0
2. Walking 50 feet?	4	3	2	1	0
3. Walking 150 feet (1/2 block)?	4	3	2	1	0
4. Walking 300 feet (1 block)?	4	3	2	1	0
5. Walking 600 feet (2 blocks)?	4	3	2	1	0
6. Walking 900 feet (3 blocks)?	4	3	2	1	0
7. Walking 1500 feet (5 blocks)?					



**Walking speed:** Report the degree of difficulty that best describes how hard it was for you to walk one city block on level ground at each of these speeds without stopping to rest during the last week:

<b><i>SPEED</i></b>	<b><i>DEGREE OF DIFFICULTY</i></b>				
	None	Slight	Some	Much	Unable
1. Walking one block slowly?	4	3	2	1	0
2. Walking one block at an average speed?	4	3	2	1	0
3. Walking one block quickly?	4	3	2	1	0
4. Walking or jogging one block?	4	3	2	1	0

**Stair climbing:** For each of these questions, report the degree of physical difficulty that best describes how hard it was for you to climb stairs without stopping to rest during the past week:

<b><i>STAIRS</i></b>	<b><i>DEGREE OF DIFFICULTY</i></b>				
	None	Slight	Some	Much	Unable
1. Climbing one flight of stairs?	4	3	2	1	0
2. Climbing two flights of stairs?	4	3	2	1	0
3. Climbing three flights of stairs?	4	3	2	1	0

## APPENDIX C: SAMPLE EQ5D QUESTIONNAIRE

By Placing a tick in one box in each group below, please indicate which statements best describe your own health state today

### Mobility

- I have no problems walking about ☐
- I have some problems walking about ☐
- I am confined to bed ☐

### Self-Care

- I have no problems with self-care ☐
- I have some problems with self-care ☐
- I am unable to wash or dress myself ☐

### Usual activities (*e.g. work, study, housework, family or leisure activities*)

- I have no problems with performing my usual activities ☐
- I have some problems with performing my usual activities ☐
- I am unable to perform my usual activities ☐

### Pain/Discomfort

- I have no pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have extreme pain or discomfort ☐

### Anxiety/Depression

- I am not anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am extremely anxious or depressed ☐
- Patients own health state today ☐

To help people say how good or bad a health state is, we  
Have drawn a scale (rather like a thermometer) on which  
The best state you can imagine is marked 100 and the worst  
State you can imagine is marked 0

We would like you to indicate on this scale how good  
Or bad your own health is today, in your opinion. Please  
Do this by drawing a line from the box below to whichever  
Point on the scale indicates how good or bad your health is  
today.

**Your own  
health state  
today**

Best  
imaginable  
health state

100

90

80

70

60

50

40

30

20

10

0

Worst  
imaginable  
health state

## **APPENDIX D: SAMPLE INFORMED CONSENT FORM**