A Prospective, Global, Multicenter, Randomized, Controlled Study Comparing Lutonix® 035 AV Drug Coated Balloon PTA Catheter vs. Standard Balloon PTA Catheter for the Treatment of Dysfunctional AV Fistulae (Lutonix AV)

CLINICAL INVESTIGATION PLAN
CL0023-01
Version: 2.0
November 30, 2015

Sponsor:

Lutonix, Inc.
9409 Science Center Drive
New Hope, MN 55428 USA

Investigational Device: Lutonix® 035 AV Drug Coated Balloon PTA Catheter

NCT Number: 02440022*
*NCT Number added post-approval per CT.gov requirement

This study will be conducted in compliance with the clinical investigational plan (CIP) and all other applicable regulatory requirements including the archiving of essential documents.

Confidential Information
No use or disclosure of this document outside Lutonix, Inc. is permitted without prior written authorization from Lutonix. Shred to dispose of document.

CIP Signature Page

A Prospective, Global Multicenter, Randomized, Controlled Study Comparing Lutonix® 035 AV Drug Coated Balloon PTA Catheter vs. Standard Balloon PTA Catheter for the Treatment of Dysfunctional AV Fistulae (Lutonix AV)

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), applicable privacy laws such as HIPAA, Declaration of Helsinki, applicable Health Canada regulations, 21CFR parts 50, 54, 56 and 812 and any local regulations.

_____

Clinical Site Name

Site Principal Investigator (Print Name)	Site Principal Investigator (Signature)	Date
Sponsor (Print Name)	Sponsor (Signature)	Date

TABLE OF CONTENTS

TABLES AND FIGURES

1.0 CIP SUMMARY

Title	A Prospective, Global, Multicenter, Randomized, Controlled Study Comparing Lutonix® 035 AV Drug Coated Balloon PTA Catheter vs. Standard Balloon PTA Catheter for the Treatment of Dysfunctional AV Fistulae (Lutonix AV)
Study Device	Lutonix 035 AV Drug Coated Balloon PTA Catheter, Model 9010
Overview	This prospective, global, multicenter, randomized, controlled study is designed to evaluate the safety and effectiveness of the Lutonix 035 AV Drug Coated Balloon PTA Catheter compared to a standard PTA Catheter in treating subjects presenting with clinical and hemodynamic abnormalities in native arteriovenous (AV) fistulae located in the upper extremity.
Objective	To assess the safety and effectiveness of the Lutonix 035 AV Drug Coated Balloon PTA Catheter in the treatment of dysfunctional AV Fistulae.
Study Design	Prospective, Global, Multicenter, Randomized, Safety and Effectiveness
Enrollment	Approximately 284 randomized subjects at up to 35 global clinical sites.
Primary Endpoint	*Effectiveness*: Target Lesion Primary Patency (TLPP) through 6 months. *Safety:* Freedom from any serious adverse event(s) involving the AV access circuit through 30 days.
Secondary Endpoints	*Key Secondary:* • TLPP evaluated at 12 months • Number of interventions, required to maintain target lesion patency at 12 months • Access Circuit Primary Patency (ACPP) evaluated at 6 months • ACPP evaluated at 12 months *Effectiveness:* • TLPP evaluated at 3, 9, 18 and 24 months • ACPP evaluated at 3, 9, 18 and 24 months • Device, Procedural and Clinical Success • TLPP evaluated at 6 months for subjects in whom a fiber pre-dilation balloon was used before the Lutonix AV DCB as compared to those in whom a non-fiber pre-dilation balloon. • Abandonment of permanent access in the index extremity at 3, 6, 9, 12, 18 and 24 months • Number of interventions, required to maintain access circuit patency at 3, 6, 9, 12, 18 and 24 months • Number of interventions, required to maintain target lesion patency at 3, 6, 9, 18 and 24 months *Safety:* • Rate of device and procedure related adverse events assessed at 1, 3, 6, 9, 12, 18 and 24 months

Inclusion Criteria	1. Age ≥21 years; 2. The subject is legally competent, has been informed of the nature, the scope and the relevance of the study, voluntarily agrees to participation and the study's provisions, and has duly signed the informed consent form (ICF); 3. Arteriovenous fistula located in the arm presenting with any clinical, physiological or hemodynamic abnormalities warranting angiographic imaging as defined in the K/DOQI guidelines; 4. Native AV fistula was created ≥30 days prior to the index procedure and has undergone one or more hemodialysis sessions utilizing two needles and the catheter has been removed for ≥30 days (immature fistulae are not allowed); 5. Venous stenosis of an AV fistula meeting the following criteria: a) Target lesion is located from the anastomosis to the axillosubclavian junction, as defined by insertion of the cephalic vein; b) Length ≤10cm; c) Reference vessel diameter 4-12mm; d) ≥50% stenosis by angiographic measurement; e) At least one clinical, physiological or hemodynamic abnormality directly attributable to the stenosis as defined in the K/DOQI guidelines; 6. Successful pre-dilation of the target lesion with a percutaneous transluminal angioplasty (PTA) balloon defined as: a) No clinically significant dissection; b) No extravasation requiring treatment; c) Residual stenosis ≤30% by angiographic measurement; d) Ability to completely efface the waist using the pre-dilation balloon 7. Intended target lesion or if a tandem lesion (≤2cm apart) can be treated with ≤120 mm of DCBs in length;
Exclusion Criteria	1. Women who are pregnant, lactating, or planning on becoming pregnant during the study; 2. Hemodialysis access is located in the leg; 3. Subject has more than two lesions in the access circuit (can only treat one target lesion and one secondary non-target lesion); 4. Subject has a secondary non-target lesion that cannot be successfully treated *(Successful treatment defined as ≤30% residual stenosis by angiographic measurement without procedural complications);* 5. Target lesion is located central to the axillosubclavian junction; 6. The subject has a secondary lesion located in the central venous system (central to the axillosubclavian junction) which, in the opinion of the Investigator, is clinically significant; (treatment of an asymptomatic lesion is not allowed) 7. A thrombosed access or an access with a thrombosis treated ≤30 days prior to the index procedure; 8. Surgical revision of the access site planned or expected ≤6 months after the index procedure;

	9. Prior surgical interventions of the access site ≤30 days before the index procedure. 10. Planned concomitant procedure (e.g. coil embolization) during the index procedure. 11. Known contraindication (including allergic reaction) or sensitivity to iodinated contrast media, that cannot be adequately managed with pre-and post-procedure medication; 12. Known contraindication (including allergic reaction) or sensitivity to paclitaxel. 13. Subjects who are taking immunosuppressive therapy or are routinely taking ≥10mg of prednisone per day; 14. Subject has another medical condition, which, in the opinion of the Investigator, may cause him/her to be noncompliant with the protocol or confound the data interpretation; 15. Subject has a life expectancy <12 months; 16. Anticipated for a kidney transplant via a living donor; 17. Anticipated conversion to peritoneal dialysis in the next 6 months; 18. Subject has one of the following: a) Bare metal stent in the target or secondary non-target lesion; b) Covered stent in the target or secondary non-target lesion; ***NOTE:*** *Patent stents within the access circuit at locations not treated as the target or a secondary non-target lesion are allowed.* 19. Subject has an infected AV access or systemic infection; 20. Currently participating in an investigational drug, biologic, or device study, or previous enrollment in this study. ***NOTE:*** *Enrollment in another investigational drug, biologic, or device study during the follow up period that would confound this study data is not allowed*.
Sponsor Contact	Lutonix, Inc. 9409 Science Center Drive New Hope, MN 55428 USA Tel: +1 763-445-2352
National Principal Investigator	[redacted]
Angiographic Core Lab	[redacted]

2.0 INTRODUCTION

The purpose of this investigation is to evaluate the safety and effectiveness of the Lutonix® 035 AV Drug Coated Balloon PTA Catheter (Lutonix® AV DCB Catheter) compared to a standard Percutaneous Transluminal Angioplasty (PTA) catheter, for the treatment of dysfunctional native AV fistulae located in the arm.

2.1 BACKGROUND

2.1.1 VASCULAR ACCESS DYSFUNCTION IN HEMODIALYSIS SUBJECTS

In 2009, nearly 400,000 patients in the United States underwent hemodialysis as a method of renal replacement therapy [1]. Reliable and durable vascular access is essential for the maintenance of therapy for these patients. The Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines for vascular access [2] recommend the primary placement of autogenous hemodialysis arteriovenous fistulae (AVF) in preference to expanded polytetrafluoroethylene (ePTFE) arteriovenous grafts (AVG) and central venous catheters as the AVF has fewer complications and longer durability. Yet both AVF and AVG are subject to dysfunction and eventual failure.

Vascular access dysfunction in hemodialysis is a leading cause of morbidity and hospitalization in the hemodialysis population. As many as 25% of hospital admissions have been attributed to vascular access problems, including fistula malfunctions and thrombosis [3].

Less than 15% of dialysis fistulae remain patent and can function without problems during the entire period of a subject's dependence on hemodialysis. For AVF the mean problem-free patency period is about 3 years, whereas AVG last 1-2 years before signs of failure or thrombosis are noted. After several interventions to treat underlying stenosis and thrombosis, the long-term secondary patency rates for AVF are 7 years for fistulae in the forearm and 3-5 years for fistulae in the upper arm; AVG remain patent for up to 2 years [3].

The primary underlying pathophysiologic mechanism responsible for failure is intimal hyperplasia at the anastomotic site. Additional causes include surgical and iatrogenic trauma, such as repeated venipunctures. Stenoses along the venous outflow tract and in intragraft locations (for AVG) are also common and require appropriate treatment [3,2]. Histologically, intimal hyperplasia is characterized by proliferation of smooth muscle cells, fibroblasts and myofibroblasts and microvessel formation (angiogenesis) [4,5]. Thus, interventions targeting this process may be useful to reduce the significant human and economic costs for vascular dysfunction.

2.1.2 PTA FOR THE TREATMENT OF HEMODIALYSIS ACCESS STENOSIS

Hemodialysis vascular access dysfunction as related to stenoses in AVF and AVG in the venous outflow circuit is a clinical problem for which there is currently no long lasting durable therapy [6,7]. According to K/DOQI guidelines [3], PTA with balloon angioplasty is the standard of care treatment versus surgical revision for hemodialysis access-related venous stenoses and occlusions. However, the patency rates in follow up periods are low because of high restenosis rates due to neointimal hyperplasia; this necessitates multiple repeat angioplasty sessions in the same circuit. Improving primary patency rates could reduce the number of PTAs required and thereby increase durability of hemodialysis access life span. The primary patency rate after PTA at 6 months in AVF

is approximately 50% (0% - 83% reported) while the primary patency observed in AVG is approximately 40% (23% - 63%).

Standard balloon PTA is currently the most widely used approach to preserve dialysis access patency. To improve immediate technical success, several methods have been applied such as cutting balloons, bare metal stents, and stent grafts. However, the outcomes have been controversial for cutting balloon and bare metal stents and a clear benefit over conventional PTA could not be shown [8-12]. Stent graft placement has been shown to result in better patency at the graft-vein anastomosis of synthetic AV grafts [42], however the benefit of stent grafts in AV fistulae has only been determined in in-stent restenotic lesions [42].

2.1.3 DRUG COATED BALLOONS

Vascular access patency may be optimized by an approach that would both block negative vessel wall remodeling and inhibit fibromuscular hyperplasia formation after standard balloon angioplasty. Paclitaxel, a chemotherapeutic agent, has been shown to effectively inhibit intimal hyperplasia [13], and paclitaxel eluting stents have been successfully used to treat coronary artery in-stent restenosis [14].

In recent years drug coated balloons (DCBs) have emerged as a therapeutic alternative in the interventional field. This approach allows short-term transfer of antiproliferative drugs to the arterial wall (during balloon inflation) with subsequent absorption and long-term retention (up to 30 days and longer). Compared to conventional drug-eluting stents (DES), DCBs provide a greater and more homogenous drug delivery per square millimeter due to the homogenous contact between the balloon surface instead of only delivering the drug from the struts. This may translate to greater therapeutic efficacy [15, 16].

Several pre-clinical studies showed that drug delivery by DCB is homogenous, safe and effectively inhibits neointimal proliferation [17-21]. In addition, a variety of clinical studies have confirmed the safety and efficacy of DCB in both peripheral vascular [22-25] and coronary beds [26-36, 38]. A summary of the publications relating to DCB use in AV Access can found below:

- The Katsanos study was a randomized, controlled trial comparing DCB dilation (N=20) with standard PTA (N=20) to treat stenosed AVF and AVG venous outflow lesions. At 6 months, cumulative target lesion primary patency was significantly higher after DCB application (70% in DCB group vs 25% in PTA group, p=0.001; HR 0.30, 95% CI 0.12 to 0.71, p <0.006) [39].
- The Patane study, a single-center, non-randomized first-in-man study, reported efficacy of a DCB in both de novo and recurrent juxta-anastomotic stenotic lesions of AVF (N=25). Primary patency at 9 months was markedly higher in this study compared to previous experience with PTA at the study site (92% vs 59%). No major or minor complications were reported [40].
- In a prospective pilot study conducted by Lai et al, subjects with two short (< 2cm) and separate lesions in the juxta-anastomotic portion of a radiocephalic AVF circuit (within 8cm of the anastomosis) had their lesions randomized to treatment with either PTA using DCB or PTA using a standard balloon. A total of 20 lesions were treated in 10 subjects. TLR-free duration was significantly longer in lesions treated with DCB (251.2 days versus 103.2 days; P <0.01). Target lesion patency was statistically higher in lesions treated with DCB at 6 months (70% versus 0%; P <0.01) but not at 12 months (20% versus 0%, P >0.47) [41].

2.1.4 THE LUTONIX CATHETER

The Lutonix Catheter (manufactured by Lutonix, Inc.) has been evaluated in two completed clinical trials in the femoropopliteal arteries, LEVANT 1 and LEVANT 2.

The LEVANT 1 trial (NCT00930813) compared treatment of femoropopliteal lesions with the Lutonix Catheter to a standard PTA catheter (with and without stenting) with a primary endpoint of late lumen loss. One hundred-one randomized subjects were enrolled at 9 European centers. After a defined pre-dilation, subjects were stratified to the balloon strata or stent strata and then randomized to treatment with the Lutonix Catheter or standard PTA. Subject inclusion and exclusion criteria were similar to previous femoropopliteal studies, with a lesion length range of 4-15 cm and vessel diameter range of 4-6 mm. Subject demographics, baseline lesion characteristics, Rutherford Category, and device and procedural successes were similar between arms.

The Lutonix Catheter demonstrated safety comparable to conventional PTA in the LEVANT 1 Trial, with similar adverse event (AE) and serious adverse event (SAE) rates through 24 months. The primary endpoint of the study, angiographic late lumen loss in the treatment segment at 6 months, was 58% lower for Lutonix Catheter (0.46 ± 1.13 mm) than for the control (1.09 ± 1.07 mm; p=0.016). There were no unanticipated adverse device effects in the DCB arm, and overall adverse event rates were similar to conventional uncoated balloon angioplasty.

The LEVANT 2 study (NCT01412541) was a prospective, multi-center, single-blind, randomized, controlled trial in subjects suffering from obstructive de novo or non-stented restenotic lesions in native femoropopliteal arteries. Four hundred seventy-six (476) subjects were randomized (316 Lutonix Catheter, 160 PTA) at 54 sites in both the United States and Europe. After a defined pre-dilation, subjects were randomized 2:1 to treatment with the Lutonix Catheter or standard PTA. Subject inclusion and exclusion criteria were similar to LEVANT 1, with a lesion length range of 4-15 cm and vessel diameter range of 4-6 mm. Subject demographics, baseline lesion characteristics, Rutherford Category, and device and procedural successes were similar between arms.

At 12 months, the Lutonix Catheter was shown to be non-inferior to PTA in freedom from safety events, defined as freedom from all-cause perioperative (≤30 day) death and freedom at 1 year from the following: index limb amputation (above or below the ankle), index limb re-intervention, and index limb-related death (p = 0.005). The Lutonix Catheter also showed superiority over PTA in primary patency, defined as absence of target lesion restenosis (as adjudicated by a blinded core lab) and freedom from target lesion revascularization (65.2% versus 52.6%, p = 0.015). There were no unanticipated adverse device effects in the DCB arm, and overall adverse event rates were similar in the two treatment arms.

2.2 STUDY RATIONALE

Based on the results of pre-clinical and clinical studies for the treatment of vascular stenosis using paclitaxel coated balloons, reducing intimal hyperplasia and restenosis rates, this study is designed to evaluate the safety and effectiveness of the Lutonix AV DCB Catheter versus Standard PTA in the treatment of subjects with clinically significant hemodialysis access stenosis or occlusion. Vascular access dysfunction in hemodialysis is still a significant health problem and reducing restenosis by limiting intimal hyperplasia could reduce the significant human and economic costs for vascular dysfunction.

2.3 DEVICE DESCRIPTION

The Lutonix AV DCB Catheter (manufactured by Lutonix, Inc.) is a standard PTA catheter with a drug coating on the balloon portion of the catheter. The Lutonix AV DCB Catheter is an over-the-wire (OTW) design with a working length of 75cm 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 2µg/mm^2. See **Figure 1** below.

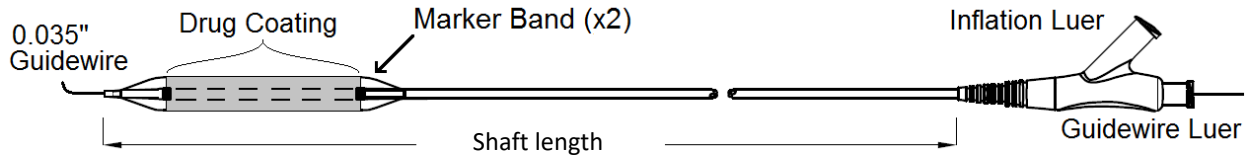


Figure 1: Lutonix 035 AV Drug Coated Balloon PTA Catheter

2.3.1 INTENDED USE/INDICATIONS FOR USE

The Lutonix AV DCB Catheter is intended for use in percutaneous transluminal angioplasty, after pre-dilation, for the treatment of stenotic lesions of native arteriovenous dialysis fistulae that are up to 10cm in length and 4mm to 12mm in diameter.

2.3.2 ACTIVE PHARMACEUTICAL INGREDIENT

Paclitaxel is a cytotoxic anticancer drug, which is originally a naturally occurring product obtained by extraction and successive purifications from yew tree species (Taxus brevifolia, Taxus yunnanensis, etc). [redacted] Paclitaxel drug is described in the United States Pharmacopoeia (*Paclitaxel*).

2.3.3 EXCIPIENT (DRUG CARRIER)

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

3.0 STUDY OBJECTIVES AND ENDPOINTS

3.1 PRIMARY OBJECTIVE

The primary objective of the Lutonix AV study is to demonstrate superior effectiveness and non-inferior safety of the Lutonix AV DCB Catheter, for treatment of dysfunctional AV fistulae located in the upper extremity, by direct comparison to uncoated PTA catheter.

3.2 PRIMARY ENDPOINTS

3.2.1 PRIMARY EFFECTIVENESS ENDPOINT

Target Lesion Primary Patency (TLPP) through 6 months

The primary effectiveness endpoint is to show superiority of the Lutonix AV DCB Catheter versus PTA through six months in the treatment of stenotic lesions.

Target Lesion Primary Patency (TLPP) is defined as the interval following index procedure intervention until clinically driven reintervention of the target lesion or access thrombosis, through 6 months.

Clinically driven reintervention is defined as a lesion that is ≥50% stenosed and the presence of at least one clinical, physiological or hemodynamic abnormality attributable to the stenosis defined in the K/DOQI guidelines. These are:

- Decreased access blood flow (<500ml/min, 25% decrease in flow)
- Elevated venous pressures
- Decreased dialysis dose (Kt/V)
- Abnormal physical exam:
    - Diminished or abnormal thrill (focal, systolic only, etc)
    - Pulsatility
    - Flaccid access
    - Abnormal bruit
    - Arm or hand swelling
- Prolonged bleeding
- Difficult puncture
- Infiltration
- Recirculation
- Pulling clots

3.2.2 PRIMARY SAFETY ENDPOINT

Freedom from serious adverse event(s) involving the AV access circuit through 30 days.

The primary safety endpoint is to show non-inferiority of Lutonix AV DCB Catheter versus PTA through 30 days in the treatment of stenotic lesions.

Safety is defined as freedom from any serious adverse event(s), directly involving the AV access circuit, through 30 days.

3.3 SECONDARY ENDPOINTS

Key Secondary:

- TLPP evaluated at 12 months
- Number of interventions, required to maintain target lesion patency at 12 months
- Access Circuit Primary Patency (ACPP) evaluated at 6 months
- ACPP evaluated at 12 months

Effectiveness

- TLPP evaluated at 3, 9, 18, and 24 months
- ACPP evaluated at 3, 9, 18, and 24 months
- Device, Procedural, and Clinical Success
- TLPP evaluated at 6 months for subjects in whom a fiber pre-dilation balloon was used before the Lutonix AV DCB as compared to those in whom a non-fiber pre-dilation balloon.
- Abandonment of permanent access in the index extremity at 3, 6, 9, 12, 18 and 24 months
- Number of interventions required to maintain access circuit patency at 3, 6, 9, 12, 18 and 24 months
- Number of interventions required to maintain target lesion patency at 3, 6, 9, 18 and 24 months

Safety

- Rate of device and procedure related adverse events assessed at 1, 3, 6, 9, 12, 18, and 24 months

The following relevant definitions can also be found in **Appendix B**:

- **Device Success**: Successful delivery to the target lesion, deployment, and retrieval at index procedure. 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.
- **Procedural Success**: At least one indicator of hemodynamic success (e.g., physical examination with restoration of a thrill, direct measurement of flow) in the absence of peri-procedural (index procedure and through hospital stay) Serious Adverse Device Effects (SADEs).
- **Clinical Success:** The resumption of dialysis for at least one session after the index procedure.
- **Access Circuit Primary Patency (ACPP)**: Interval following intervention until the next access circuit thrombosis or repeated intervention. Ends with treatment of a lesion anywhere within the access circuit.

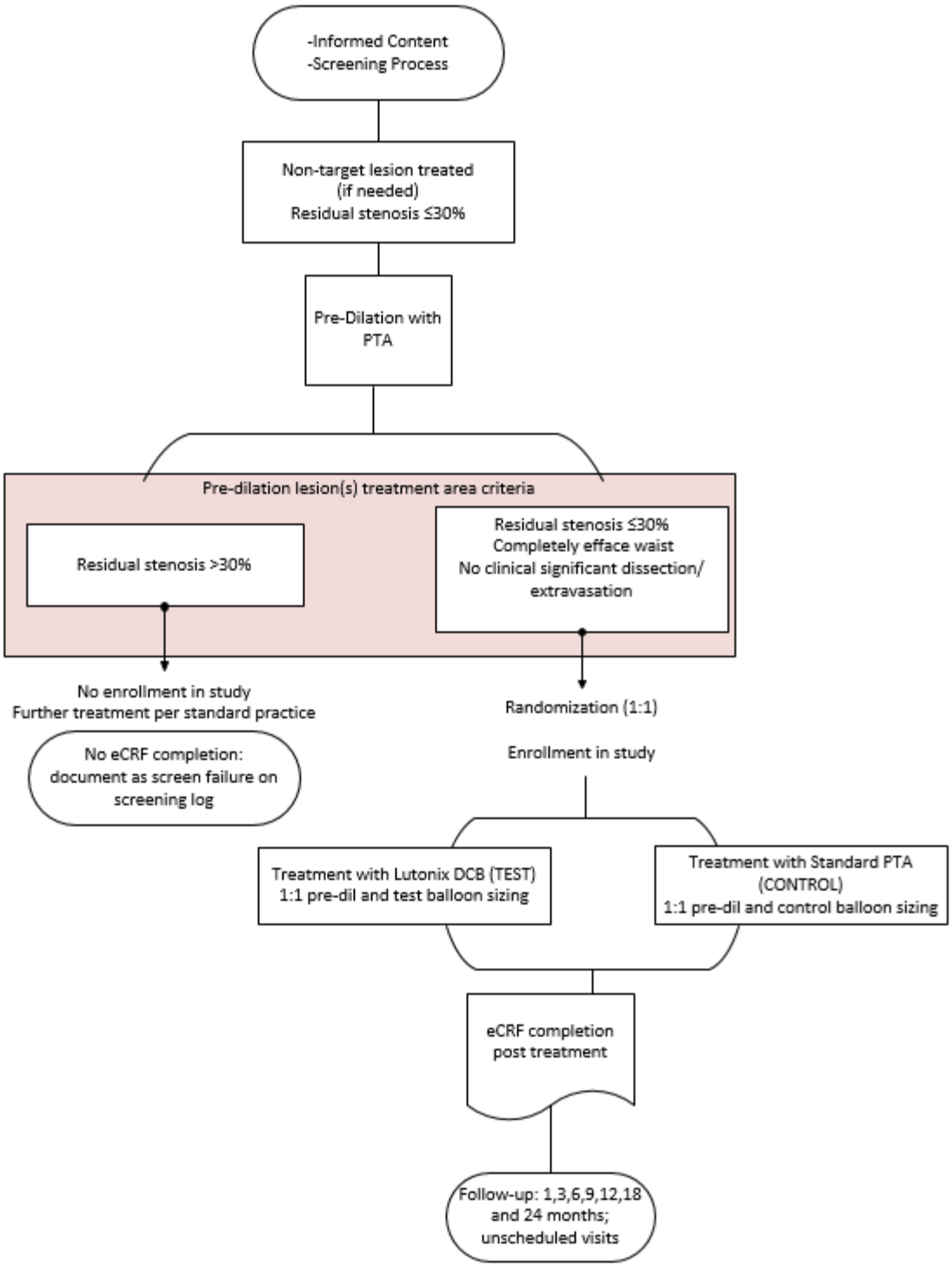
4.0 STUDY DESIGN

Potential subjects will be screened against the eligibility criteria outlined in Sections 5.1 and 5.2. After the target lesion size and stenosis is confirmed by angiography, pre-dilation will occur per standard treatment. After successful pre-dilation, subjects with angiographic documentation of residual stenosis ≤30% will be enrolled and randomized 1:1 to Lutonix AV DCB Catheter (TEST) or Standard PTA (CONTROL).

After successful treatment with either the Lutonix AV DCB Catheter or a standard PTA catheter, the procedure will be completed per standard of care. Subjects and the dialysis clinic will be contacted at 1 month, 3 months, 6 months, 9 months, 12 months, 18 months and 24 months post-procedure for evaluation of access circuit patency and safety endpoints.

The study treatment flow-chart is shown below in **Figure 2**.

Figure 2: Study Flowchart



5.0 STUDY POPULATION

This study will enroll approximately 284 randomized subjects at up to 35 global clinical sites. The following describes the clinical eligibility (inclusion and exclusion) criteria for this study.

5.1 INCLUSION CRITERIA

A subject must meet the following criteria to be enrolled in the study:

1. Age ≥21 years;
2. The subject is legally competent, has been informed of the nature, the scope and the relevance of the study, voluntarily agrees to participation and the study's provisions, and has duly signed the informed consent form (ICF);
3. Arteriovenous fistula located in the arm presenting with any clinical, physiological or hemodynamic abnormalities warranting angiographic imaging as defined in the K/DOQI guidelines;
4. Native AV fistula was created ≥30 days prior to the index procedure and has undergone one or more hemodialysis sessions utilizing two needles and the catheter has been removed for ≥30 days (immature fistulae are not allowed);
5. Venous stenosis of an AV fistula meeting the following criteria:
    a) Target lesion is located from the anastomosis to the axillosubclavian junction, as defined by insertion of the cephalic vein
    b) Length ≤10cm
    c) Reference vessel diameter 4-12mm
    d) ≥50% stenosis by angiographic measurement
    e) At least one clinical, physiological or hemodynamic abnormality attributable to the stenosis as defined in the K/DOQI guidelines;
6. Successful pre-dilation of the target lesion with a percutaneous transluminal angioplasty (PTA) balloon defined as:
    a) No clinically significant dissection
    b) No extravasation requiring treatment
    c) Residual stenosis ≤30% by angiographic measurement
    d) Ability to completely efface the waist using the pre-dilation balloon
7. Intended target lesion or if a tandem lesion (≤2cm apart) can be treated with ≤120 mm of DCBs in length;

5.2 EXCLUSION CRITERIA

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

1. Women who are pregnant, lactating, or planning on becoming pregnant during the study;
2. Hemodialysis access is located in the leg;
3. Subject has more than two lesions in the access circuit (can only treat one target lesion and one secondary non-target lesion);
4. Subject has a secondary non-target lesion that cannot be successfully treated *(Successful treatment defined as ≤30% residual stenosis by angiographic measurement without procedural complications);*
5. Target lesion is located central to the axillosubclavian junction;

6. The subject has a secondary lesion located in the central venous system (central to the axillosubclavian junction) which, in the opinion of the investigator, is clinically significant; (treatment of an asymptomatic lesion is not allowed)
7. A thrombosed access or an access with a thrombosis treated ≤30 days prior to the index procedure;
8. Surgical revision of the access site planned or expected ≤6 months after the index procedure;
9. Prior surgical interventions of the access site ≤30 days before the index procedure;
10. Planned concomitant procedure (e.g. coil embolization) during the index procedure;
11. Known contraindication (including allergic reaction) or sensitivity to iodinated contrast media, that cannot be adequately managed with pre-and post-procedure medication;
12. Known contraindication (including allergic reaction) or sensitivity to paclitaxel.
13. Subjects who are taking immunosuppressive therapy or are routinely taking ≥10 mg of prednisone per day;
14. Subject has another medical condition, which, in the opinion of the Investigator, may cause him/her to be noncompliant with the protocol or confound the data interpretation;
15. Subject has a life expectancy <12 months;
16. Anticipated for a kidney transplant via a living donor;
17. Anticipated conversion to peritoneal dialysis in the next 6 months;
18. Subject has one of the following:
    a) Bare metal stent in the target or secondary non-target lesion
    b) Covered stent in the target or secondary non-target lesion

    NOTE: *Patent stents within the access circuit at locations not treated as the target or a secondary non-target lesion are allowed.*
19. Subject has an infected AV access or systemic infection;
20. Currently participating in an investigational drug, biologic, or device study, or previous enrollment in this study.

    NOTE: *Enrollment in another investigational drug, biologic, or device study during the follow-up period that would confound this study data is not allowed.*

6.0 STUDY / TREATMENT PROCEDURES

Table 1 displays the required schedule for subject treatment and evaluation.

Table 1. Procedure and Follow-Up Schedule

Visits	Screening/Baseline	Index Procedure	Post- Procedure/ Discharge	Month 1 (30 day) (Call[5])	Month 3 (90 days) (Call[5])	Month 6 (180 days) (Visit[6])	Month 9 (270 days) (Call[5])	Month 12 (365 days) (Call[5])	Month 18 (545 days) (Call[5])	Month 24 (730 days) (Call[5])	Un-scheduled Revascularization
Visit window (days)				± 7	± 30	± 30	± 30	± 30	± 60	± 60	
Informed Consent	√										
Inclusion/Exclusion Criteria	√	√									
Demographics, Medical History	√										
AVF Assessment (physical exam)[1]	√		√			√					√
Pregnancy Test[2]	√										
Angiography[3]		√									√[4]
AV Access Status	√			√	√	√	√	√	√	√	√
Collection of Kt/V values[7]	√			√	√	√	√	√	√	√	√
Collection of flow rates[8]	√			√	√	√	√	√	√	√	√
Adverse Event Assessment		√	√	√	√	√	√	√	√	√	√

1 AVF assessment must be performed by a medical doctor at follow-up if completed as an office visit
2 Pregnancy test for females of childbearing potential
3 Submit angiogram to core lab if performed during a follow up visit
4 Angiography is required when a revascularization of the access circuit is performed
5 Phone call includes calls with both subject and dialysis center. Visit may be performed as an office visit, though not required.
6 The office visit must have a phone call to the dialysis unit to obtain required information.
7 Kt/V values will be collected on a monthly basis and reported according to the follow up time points.
8 Flow rates can be obtained via the dialysis machine or Transonic. The most recent dialysis session flow rate will be collected.

6.1 SUBJECT SCREENING AND BASELINE EVALUATION

During the screening and recruitment process, the Investigators will be responsible for describing the nature of the clinical study, verifying that the eligibility criteria have been met, and obtaining informed consent. If inclusion criteria are met and no exclusion criteria are present at the time of screening, the Investigator will discuss the study and invite the patient to participate. 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.

6.1.1 INFORMED CONSENT FORM

All subjects or legally authorized representatives must sign the Informed Consent Form (ICF) approved by the IRB/EC for the study prior to collection of study data or performance of study-specific procedures. A copy of the ICF will be provided to the subject. Subjects will be assured that they may withdraw from the study at any time and for any reason. Evidence about the consent process must be recorded in the medical notes.

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.

6.1.2 ELIGIBILITY

Subjects must meet all the clinical eligibility criteria, voluntarily agree to participate, and provide written 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 occurs at the specified time and that all applicable data are reviewed and entered into the electronic case report form (eCRF) system in a timely fashion.

The following assessments must be performed after obtaining informed consent and prior to the index procedure to verify and complete eligibility and for baseline data:

- Subject demographics
- Relevant medical history including:
  - Current AV access status
  - History of AV access dysfunction
  - Previous AV access interventions
- Physical examination
- Collection of Kt/V values and flow rates
- Pregnancy test or surrogate, see below (for women of childbearing potential only)

6.2 PREGNANCY TEST

Patients undergoing hemodialysis may have issues with their kidneys that would preclude the ability to complete a urine pregnancy test. However the effects of the study device on a fetus are not known, therefore an absence of pregnancy still needs to be confirmed. The method of confirmation will be left to the investigator's discretion (e.g. ultrasound, urine or blood test, sexual abstinence in the last 90 days, partner is sterilized).

6.3 PRE-DILATION

Refer to the current IFU for complete pre-dilation requirements. Treatment of the secondary non-target lesion (if applicable) and successful pre-dilation of the target lesion must be completed prior to randomization. Lesion pre-dilation is required for all (test and control) subjects.

Successful pre-dilation of the target lesion defined as**:**

a) No clinically significant dissection

b) No extravasation requiring treatment

c) Residual stenosis ≤30% by angiographic measurement

d) Ability to completely efface the waist using the pre-dilation balloon.

Pre-dilation balloons with an external wire support, cutting/scoring component or other similar modifications are not permitted. Multiple balloons and/or inflations, as well as prolonged inflation, may be used.

6.4 TARGET LESION

Only one (1) target lesion may be treated with the study device in a single access circuit. If there is a tandem lesion (≤2cm apart), the length is measured as the sum of the treated areas (including the space between the lesions) and must be ≤10cm to be treated with ≤120mm of DCB length. The entire treated area will be considered the target lesion.

The target lesion must be located from the anastomosis to the axillosubclavian junction, as defined by insertion of the cephalic vein. If two lesions are present that meet the target lesion inclusion/exclusion criteria, the lesion **closest** to the anastomosis will be the target lesion.

Subjects who have a previously failed AV access may be included in the study. Subjects who have a pre-existing patent stent or stent-graft, not at the site of the target lesion or non-target lesion, in the AV access circuit may also be included.

6.5 SECONDARY NON-TARGET LESION TREATMENT

If a second stenotic lesion is present, the lesion **closest** to the anastomosis will be the target lesion. Successful treatment of the secondary non-target lesion must be completed prior to attempted pre-dilation of the target lesion. Successful treatment is defined as attainment of residual stenosis ≤30% by angiographic measurement without procedural complications.

During treatment of the secondary non-target lesion, placement of bare metal stents or stent grafts is not allowed. If clinically significant dissection or extravasation occurs that is not treatable with prolonged balloon inflation (balloon tamponade) and placement of a stent or stent graft is deemed medically necessary, these subjects will not be randomized and will be considered screen failures.

6.6 SCREENING AND ENROLLMENT

Study subjects will be considered enrolled at the time of randomization. All subjects will be recorded on the screening log.

Refer to the following situations for guidance on enrollment and screen failures:

- Subjects with a lesion that, after baseline angiography, does not meet all inclusion/exclusion criteria and is not pre-dilated per protocol are considered screen failures and will not be considered enrolled in the study.
- Subjects that do not meet post pre-dilation criteria and are **not** randomized are treated per standard practice and will not continue in the study. No follow up is required.

- All randomized subjects will be followed for the entire duration of the study and included in the primary and secondary analyses.
- Subjects that do meet the post -pre-dilation criteria **and** are randomized but have an adjunct procedure will be followed for the entire duration of the study.

6.7 RANDOMIZATION AND BLINDING

Upon study enrollment, subjects will be randomized 1:1 to treatment with either the Lutonix AV DCB Catheter (TEST) or a standard PTA Catheter (CONTROL).

Each site will receive one set of randomization envelopes that are numbered in sequential order. Within each randomization envelope, a treatment assignment card will be enclosed. To further minimize potential bias associated with the Investigator's PTA techniques due to knowledge of treatment assignment, the Investigator will not open the randomization envelope (i.e., remain blinded to the treatment assignment) until ***after*** all successful pre-dilation inflations are complete (when the last PTA balloon is deflated and fistulogram confirms success as defined above). All subjects who are randomized in the study will participate in the ITT analysis. The treatment assignment card will be filed in the subject's medical record to serve as documentation.

To minimize bias both the subject and the dialysis unit will be blinded to the treatment until one year, the length of time for all hypothesis tested secondary endpoints to be collected. The Investigator and members of the investigator's study team who are of necessity privy to randomization group will not be blinded.

6.8 INDEX PROCEDURE

After the lesion(s) is successfully pre-dilated and subject eligibility has been confirmed the subject will be randomized. Regardless of treatment arm, each subject will have the index procedure performed. At a minimum, the index procedure device (test or control balloon) must be inflated to nominal pressure.

Refer to the most current IFU for complete details on preparation and procedural use of the Lutonix AV DCB Catheter.

CONTROL Arm

PTA will be performed using a commercially available uncoated PTA balloon with characteristics similar to the Lutonix AV DCB (i.e semi-compliant, standard pressure). The PTA balloon must be the same diameter as the balloon used for successful pre-dilation of the target lesion. At a minimum, the control balloon must be inflated to nominal pressure.

Balloons with an external wire support, cutting/scoring component or other similar modifications are not permitted. Multiple balloons, inflations and/or prolonged inflation may be used.

Treatment modalities to be captured for each balloon used, are (but not limited to):

- Balloon brand and manufacturer
- Maximum balloon pressure achieved for each inflation
- Maximum duration of inflation for each inflation

- Number of inflations
- Balloon diameter and length
- Procedural information

TEST Arm

Please refer to the current Lutonix AV DCB Catheter IFU for detailed information on device use. Multiple balloons and/or balloon inflations may be used. The DCB must be the same diameter as the balloon used for successful pre-dilation of the target lesion. At a minimum, the DCB must be inflated to nominal pressure.

Treatment modalities to be captured for each balloon used, are (but not limited to):

- Maximum balloon pressure for each inflation
- Maximum duration of inflation of each inflation (must be at least 30 seconds)
- Number of inflations
- Balloon diameter and length
- Procedural information

6.8.1 ADJUNCT PROCEDURES AFTER RANDOMIZATION

Subjects who are randomized and have an adjunct procedure will be followed for the entire duration of the study. Any adjunct procedures shall be done according to standard of care and will be captured in the eCRF.

6.8.2 ANGIOGRAPHY

Angiography is required during the index procedure and when a revascularization of the access circuit is performed.

Target lesion criteria/characteristics to be documented include, but may not be limited to:

- Lesion location
- Lesion length
- Lesion reference vessel diameter
- Determination if AV access or target lesion is thrombosed*

Note *the subject is excluded from participating in the study if the target lesion has a corresponding thrombosis in the access circuit or if the target lesion has had a thrombosis treated within the previous thirty days prior to the index procedure (exclusion criteria #7)*

The following procedure will be used to evaluate the target lesion criteria and the target lesion post-procedure:

1. The target lesion will be imaged in two views that are ≥30 degrees apart using magnification angiography prior to or at the beginning of the index procedure to determine study eligibility.

2. During angiography, a measuring device (e.g., radiopaque object of known size) will be placed in the imaging field close to the target lesion and in a manner that permits the most accurate measurement with the least amount of distortion. The following images should be collected:
    a) Before any therapeutic intervention;
    b) During pre-dilation balloon inflation;
    c) Post pre-dilation balloon inflation;
    d) During treatment balloon inflation; and
    e) The final result of the procedure/intervention.
3. Reinterventions for dysfunction: should the subject have an intervention post-index procedure the angiogram should be collected in this same manner.

Standard angiography measurement techniques shall be used to determine:

- the reference vessel diameter (RVD),
- minimum lumen diameter (MLD),
- initial percent diameter stenosis (%DS),
- residual stenosis after pre-dilation, and
- final residual stenosis after the procedure.

For non-target secondary lesions, angiographic measurement technique shall also be used to determine RVD, MLD, initial %DS and final percent residual stenosis.

All angiograms of the access circuit must be sent by the study sites to the angiographic core lab for analysis. This will be done either by electronic upload via a secured website or via shipment of CD-ROMs.

Standard off-line Quantitative Vascular Angiography (QVA) acquisition procedures shall be followed for analysis at the independent angiographic core laboratory. All angiography procedures (both index and un-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 study specific angiographic guidelines provided by the core laboratory for additional procedural imaging and submission instructions.

6.8.3 DISCHARGE

Medication therapy and medical treatment will be conducted at the discretion of the Investigator per the investigational site's standard of care. Subjects will be treated and discharged according to the investigational site's standard of care. AV access hemodynamic functionality must be determined prior to the subject being discharged. The following assessments will take place to determine such functionality:

- Conduct a physical exam to assess access patency

- Determination of whether the subject has experienced any per protocol reportable adverse events

6.9 FOLLOW-UP.

Refer to **Table 1** for a summary of the required follow-up schedule.

Office Visits

An office visit is defined as a subject encounter with the Investigator or delegated site personnel at the investigational site. A physical exam is required at each office visit. A phone call to the dialysis unit is required to obtain information from the subject's medical record.

Access function will be measured by physical exam in order to detect any abrnomailites per K/DOQI, in accordance with each investigational site's standard of care.

The following will be collected:

- Determination of subject's ability to dialyze and date of last dialysis session,
- Determination of whether the subject has undergone any interventions,
- Collection of Kt/V values and flow rates,
- Determine whether the subject has experienced any per protocol reportable adverse events.

Phone Calls

The investigational site will place phone calls directly to the subject and the subject's dialysis unit to obtain information from the subject's medical record. Phone calls will be documented in the subject's medical record at the investigational site.

The following will be collected:

- Determination of subject's ability to dialyze and date of last dialysis session,
- Collection of Kt/V values and flow rates,
- Determination of whether the subject has undergone any interventions,
- Determine whether the subject has experienced any per protocol reportable adverse events.

Angiographic Examinations

Angiographic examinations will only be conducted during the Index procedure and if there is revascularization due to a clinical, physiological or hemodynamic abnormality within the access circuit.

Follow-up: 30 Days (1 month) Post-procedure Follow-Up (± 7 days)

This follow up should occur via phone calls to both the dialysis unit and the subject. Information to be obtained should include:

- Status: Determine whether the subject continues to be successfully dialyzed through the current AV fistula and document the date of the subject's last dialysis session,
- Collection of Kt/V values and flow rates,

- Interventions: Determine whether the subject has undergone any interventions to the AV access circuit since the index procedure,
- Determine whether the subject has experienced any per protocol reportable adverse events since the index procedure.

Follow-up: 3 Months Post-procedure Follow-up (±30 days)

This follow up should occur via phone calls to both the dialysis unit and the subject. Information to be obtained should include:

- Status: Determine whether the subject continues to be successfully dialyzed through the current AV fistula and document the date of the subject's last dialysis session,
- Collection of Kt/V values and flow rates,
- Interventions: Determine whether the subject has undergone any interventions to the AV access circuit since the previous visit,
- Determine whether the subject has experienced any per protocol reportable adverse events since the previous visit.

Follow-up: 6 Months Post-procedure Follow-up (±30 days)

This follow up should occur via an office visit to the investigational site and a phone call to the dialysis unit. Information to be obtained should include:

- Office visit: conduct a physical exam at the investigational site to assess access patency in accordance with the Investigator's standard of care,
- Collection of Kt/V values and flow rates,
- Status: Determine whether the subject continues to be successfully dialyzed through the current AV fistula and document the date of the subject's last dialysis session,
- Interventions: Determine whether the subject has undergone any interventions to the AV access circuit since the previous visit,
- Determine whether the subject has experienced any per protocol reportable adverse events since the previous visit.

Follow-up: 9 Months (±30 days), 12 Months (1 year) (± 30 days), 18 Months (1.5 years) and 24 Months (2 year) Post-procedure Follow-Up (± 60 days)

This follow up should occur via phone calls to both the dialysis unit and the subject. Information to be obtained should include:

- Status: Determine whether the subject continues to be successfully dialyzed through the current AV fistula and document the date of the subject's last dialysis session,
- Collection of Kt/V values and flow rates,
- Interventions: Determine whether the subject has undergone any interventions to the AV access circuit since the previous visit,

- Determine whether the subject has experienced any per protocol reportable adverse events since the previous visit.

6.10 UNSCHEDULED VISITS

An unscheduled visit follow up form must also be completed for subjects who return for additional non-scheduled follow-up examinations relevant to the index access circuit at times other than CIP-defined intervals. If the subject requires reintervention on the target lesion, the site will treat per standard of care. The Lutonix AV DCB Catheter cannot be used for revascularizations post index procedure.

In the event that a subject undergoes repeat angiography and/or revascularization after the index procedure is complete, all subsequent angiograms for the access circuit must be forwarded to the angiographic core lab for review and analysis. Attempts will be made to record the same views and angles as from the index procedure. The core lab will analyze all revascularizations involving the target lesion. The analysis will determine if the revascularization met the angiographic definition of clinically driven as defined in this protocol.

Information to be obtained during an unscheduled visit should include:

- Status: Determine whether the subject continues to be successfully dialyzed through the current AV fistula and document the date of the subject's last dialysis session,
- Angiographic evaluation if a reintervention of the access circut occurs at this visit,
- Collection of Kt/V values and flow rates,
- Interventions: Determine whether the subject has undergone any interventions to the AV access circuit since the previous visit,
- Determine whether the subject has experienced any per protocol reportable adverse events since the previous visit.

6.11 STUDY DEVICE SUPPLY AND ACCOUNTABILITY

Investigational devices are utilized for this study. Please refer to the most current IFU for complete details on procedural use and preparation of the device selected for patient treatment.

The Investigator must ensure that the selected device (test or control) is used only in accordance with the protocol and current IFU. The Investigator must maintain records that adequately document the device(s) the subject received.

Training and support will be provided on an ongoing basis by the Sponsor.

After use, this product may be a potential biohazard. Handle and dispose of in accordance with acceptable medical practices and applicable local, state and national laws and regulations.

In the case where a Lutonix device has failed, the Investigator must make every possible effort to return the device to the Sponsor. Sites shall return devices by following the Return Material Authorization (RMA) instructions. 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 in the eCRF system.

Investigational Devices

Study sites will receive a supply of the Lutonix AV DCB Catheters upon completion of the protocol requirements for study initiation. Training and support will be provided as needed on an ongoing basis. Any unused devices must be returned to the Sponsor at the time site enrollment stops or upon sponsor request. All investigational Lutonix AV DCB Catheters must be stored in a locked storage facility to which only the Investigator and/or designated study staff will have access. The Investigator is responsible for investigational device accountability at the trial site. The Investigator may assign the responsibility for the investigational device accountability to an appropriate study staff member, but remains the final responsible person. The Investigator must ensure that the investigational device is used only in accordance with the protocol and current IFU. The Investigator must maintain records that document investigational device delivery to the trial site, the inventory at the site, administration to each subject and the return to Sponsor, if applicable. These records must include dates, quantities, batch/serial numbers, expiration dates, and the unique code numbers assigned to the trial subjects.

6.12 WITHDRAWAL

Following the index procedure, every subject should remain in the study until completion of the required follow-up period; however a subject's participation may be discontinued. Should this occur, the reason for discontinuation must be written in the source documents. Potential reasons for discontinuation may include, but are not limited to the following:

- **Subject Withdrawal:** Subject participation in a clinical trial is voluntary, and the subject may discontinue participation (refuse all subsequent testing/follow-up) at any time without penalty or loss of benefits. Subjects who withdraw will not be replaced.
- **Investigator Termination:** The Investigator may terminate the subject's participation without regard to the subject's consent if the Investigator believes it is medically necessary. Subjects terminated by the Investigator will not be replaced.
- **Lost-to-Follow-up:** The subject does not respond to a scheduled follow-up but has not "officially" withdrawn from the study. This does not apply to missed visits, where the subject misses one of the follow-up contact time points, but completes a subsequent one. In order to consider a subject lost-to-follow-up, site personnel will make all reasonable efforts to locate and communicate with the subject. A minimum of 3 attempts (one attempt must be via a certified letter) to contact the subject will be recorded in source documentation, including date and name of site personnel trying to make contact. Subjects who are lost to follow up should have a study exit form completed. Subjects who are lost to follow up will not be replaced, however lost-to-follow-up has been considered for sample size statistics.

7.0 STATISTICAL ANALYSIS PLAN

7.1 OVERVIEW OF STUDY DESIGN

The clinical study will be a prospective, global, multi-center, single-blind, randomized safety and effectiveness study with the primary objective to demonstrate superior effectiveness and non-inferior safety of the Model 9010 Lutonix AV DCB Catheter by direct comparison to standard PTA for

treatment of recurrent lesions of native arteriovenous fistulae that are up to 10cm in length and 4mm to12mm in diameter.

The study will observe subjects presenting with clinical or hemodynamic abnormality in native AV fistulae located in the arm and clinical evidence of stenosis ≥50%.

Anticipated treatment is with up to 120mm Lutonix AV DCB Catheter length (allows for 5mm treatment margin beyond lesion length and total maximal systemic dose 9mg based on the largest balloon diameter). Based on the paclitaxel dose matrix listed in the Instructions for Use, the use of up to three 12 x 40mm balloons per treatment (9mg total) would be allowed.

For the study to be considered successful, superiority of Lutonix AV DCB Catheter must be demonstrated for the primary effectiveness endpoint, and non-inferiority of the Lutonix AV DCB Catheter must be demonstrated for the primary safety endpoint.

7.2 ANALYSIS POPULATIONS

- The ITT population will consist of all enrolled subjects who have signed the Informed Consent Form and have been randomized.
- The Modified ITT (MITT) population will consist of any subjects in the ITT population who are treated with Lutonix AV DCB Catheter or standard PTA.
- A Per-Protocol (PP) population may be created if there are subjects who have any major protocol deviations. The PP population will consist of any subjects in the MITT population who do not have any major protocol deviation. The protocol deviations that are considered to have a "major" grade will be defined a priori in the analysis plan.
- All analyses including the primary analyses will be primarily based on the MITT population. PP analyses may also be performed for the primary endpoints. They will only serve as sensitivity analyses for the primary analyses which are based on the MITT population. Additionally As-treated (AT) analysis may be performed in which subjects will be analyzed based on the actual treatment received instead of the randomized treatment, if there are subjects randomized but received the wrong treatment.

7.3 ASSESSMENT OF COMPARABILITY OF TREATMENT GROUPS AND POOLABILITY OF SITES

To demonstrate the comparability of the Control to Test subjects, the treatment groups will be compared with respect to demographics and baseline characteristics and other covariates using t-tests or Wilcoxon nonparametric tests for means and χ^2-tests for proportions.

Demographics, baseline characteristics and other covariates will also be compared between the treatment groups by sites using descriptive statistics. Both primary endpoints will also be summarized by treatment group and by site. This can help identify any confounding covariates that can potentially explain the variability of the treatment effect across sites.

US and non-US enrollment will be monitored throughout the study to ensure at least 50% of randomized subjects occur at US sites. The minimum number of US subjects is 142 and the maximum number of OUS subjects is 142. The same study protocol will be used across all geographies.

No site will be allowed to enroll more than 20% (~56 subjects) of the overall number of subjects to ensure the study to be reasonably well balanced, multicenter study. Each site should randomize at least 10 subjects. However, it's difficult to predict that all participating site will eventually have at least 10 subjects at the end of the study. The sites with less than 10 randomized subjects will be sorted by country and by site number and pooled by order to form pooled sites with at least 10 randomized subjects each.

For the primary effectiveness endpoint, an analysis will be performed to examine the potential for interaction of site and treatment group. A Cox regression model will be fit that includes fixed effect for treatment group, site and the interaction of treatment group and site. If the p-value for the interaction term is <0.15, it will be considered evidence of a possible significant interaction effect, and additional analyses will be performed to explore the differences between sites to assess their potential causes and whether or not they are clinically meaningful.

For the primary safety endpoint, an analysis will be performed as well to examine the potential for interaction of site and treatment group. A logistic regression model will be fit that includes fixed effect for treatment group, site and the interaction of treatment group and site. If the p-value for the interaction term is <0.15, it will be considered evidence of a possible significant interaction effect, and additional analyses will be performed to explore the differences between sites to assess their potential causes and whether or not they are clinically meaningful.

Both primary endpoints will also be presented by geography (US versus OUS). Similar analyses will be performed to examine the potential for interaction of geography and treatment group for both endpoints. A Cox regression model for the primary effectiveness endpoint and a logistic regression model for the primary safety endpoint will be fit that includes fixed effect for treatment group, geography and the interaction of treatment group and geography. If the p-value for the interaction term is <0.15, it will be considered evidence of a possible significant interaction effect, and additional analyses will be performed to explore the differences between geographies to assess their potential causes and whether or not they are clinically meaningful.

7.4 HANDLING OF MISSING DATA

Endpoints may be missing because subjects have died or withdrawn from the study prior to the time the endpoint is measured. Missing data, particularly when the reason for missing is related to the treatment and causes imbalances across treatment groups or there is a large amount of missing data, makes the interpretation of study result difficult. It is important to minimize missing data by all means and always record the reason for missing data.

The primary analysis of the primary effectiveness endpoint is a survival analysis. As a supportive analysis, the primary safety endpoint will also be analyzed using survival analysis techniques. In survival analyses, unobserved endpoints are a standard part of the analysis; they are known as "censored observations". As long as the censoring is unrelated to the treatment, this method of handling missing endpoints produces unbiased estimates of the freedom-from-event rates.

In addition, as a supportive analysis, the primary effectiveness endpoint will be analyzed as a proportion-based binomial rate.

For both primary endpoints, the reason for the censoring of all subjects with missing endpoints will be reported; a worst-case analysis will be performed for each primary endpoint, in addition to the

standard analysis. For the primary effectiveness endpoint, the worst case analysis will be based on a survival analysis. For the primary safety endpoint, it will be based on a binary analysis. In a worst-case analysis, an event will be assumed to have occurred at the time the subject discontinued participation in the study for all such subjects in the Test group. In the Control group, all subjects with missing data will be assumed *not* to have had an event.

In addition, a tipping-point analysis will also be performed for both primary endpoints using a proportion-based binary analysis, in which assumptions about missing data are varied from worst-case to best-case to examine at what point the missing data would alter the results of the analysis. These analyses will constitute sensitivity analyses of the effect of missing data on the study results.

7.5 PRIMARY ENDPOINTS AND SAMPLE SIZE

7.5.1 PRIMARY EFFECTIVENESS ENDPOINT

The Primary Endpoint is Target Lesion Primary Patency (TLPP) evaluated at 6 months. TLPP ends with the next clinically driven reintervention of the target lesion or access thrombosis. In order to demonstrate clinically acceptable effectiveness, this randomized study will assess superiority of the rate of TLPP at 6 months of the Lutonix AV DCB Catheter by direct comparison to standard PTA for treatment of AV fistulae.

7.5.2 PRIMARY EFFECTIVENESS ENDPOINT HYPOTHESIS TEST

The primary effectiveness endpoint is TLPP at 6 months. Objective: To assess if the 6 months TLPP for Lutonix AV DCB Catheter is superior to the primary patency rate for standard uncoated balloon, by direct comparison:

H_0: The (survival) rate $S_1(t)$ of subjects in the DCB treatment group with TLPP through $t \leq 6$ month post index procedure is less than or equal to that $S_2(t)$ of PTA treatment group. (i.e. $S_1(t) \leq S_2(t)$, for $t \leq 6$ months)

H_1: The (survival) rate $S_1(t)$ of subjects in the DCB treatment group with TLPP through $t \leq 6$ month post index procedure is greater than that $S_2(t)$ of PTA treatment group. (i.e. $S_1(t) > S_2(t)$, for $t \leq 6$ months

Rejection of the null hypothesis will signify that the 6 month TLPP of Lutonix AV DCB Catheter is superior to the 6 month TLPP of standard uncoated balloon.

A Kaplan-Meier analysis will be used to estimate the survival rate of TLPP in the DCB and PTA groups. A log-rank test comparing DCB and PTA will be used to test the primary hypothesis to determine if DCB is superior to PTA. The test is successful if the one-sided p-value is less than 0.025 and the result is in favor of DCB. In addition to the p-value of the test, the confidence intervals of the rate in each group will be provided.

Based on a review of the literature regarding the use of DCB in arteriovenous access, Lutonix expects a 6 month primary patency rate of approximately 70% for lesions treated with the Lutonix AV DCB Catheter. Patency rates reported in literature for DCB treated lesions in the AV circuit range between 50%-96%. The literature reported 6-month primary patency rates for standard PTA in

fistulae are varied, ranging from 0-77%. The K/DOQI guidelines suggest one should expect a 6-month patency rate of 50% for AV access stenoses treated with PTA. The assumed treatment effect of 20% increase in 6-month patency for DCB vs. PTA is consistent with the reported differences seen in literature for DCB in AV access.

The sample size estimation assumes the following:

- Target Lesion Primary Patency rate at 6 months in DCB treated subjects is 70%;
- Target Lesion Primary Patency rate at 6 months in PTA treated subjects is 50%;
- Allocation ratio: 1:1
- The Type 1 error, $\alpha = 0.025$ (one-sided);
- The Type 2 error, $\beta = 0.10$ (Power = 1 - β = 90%).

A sample size of 256 evaluable subjects allocated 1:1, for 128 subjects in the Lutonix AV DCB Catheter arm and 128 subjects in the standard PTA arm, achieves a greater than 90% power at a one-sided alpha level of 0.025 to reject the null hypothesis and to demonstrate superiority of the Lutonix AV DCB Catheter (nQuery 7.0 based on log-rank test of survival curves). Accounting for approximately 10% censoring, 284 subjects are required to be enrolled and treated with either Lutonix AV DCB Catheter or PTA.

7.5.3 PRIMARY SAFETY ENDPOINT

The primary safety endpoint is freedom from localized or systemic serious adverse events through 30 days that reasonably suggests the involvement of the AV access circuit.

Objective: To assess if the 30-day primary safety rate for Lutonix AV DCB Catheter is non-inferior to that of standard uncoated balloon, by direct comparison:

H_0: The primary safety rate p_1 in the DCB treatment group through 30 days post index procedure is inferior to that p_2 of the PTA treatment group. (i.e. $p_1 \leq p_2 - \delta$)

H_1: The primary safety rate p_1 in the DCB treatment group through 30 days post index procedure is non-inferior to that p_2 of the PTA treatment group. (i.e. $p_1 > p_2 - \delta$)

Where $\delta = 10\%$ is the non-inferiority margin, which is the range of difference that is considered not clinically important.

A non-inferiority Farrington and Manning Exact Test will be used to test the primary safety hypothesis. The test is successful if the one-sided p-value is less than 0.025. In addition to the p-value of the test, the confidence intervals of the rate in each group and the difference between the two groups will be provided.

The sample size estimation assumes the following:

- The Primary Safety rate through 30 days in DCB treated subjects is 95%;
- The Primary Safety rate through 30 days in PTA treated subjects is 95%;
- Non-inferiority margin $\delta = 10\%$
- Allocation ratio: 1:1
- The Type 1 error, $\alpha = 0.05$ (one-sided);

With a sample size of 284 subjects allocated 1:1, 142 subjects in the Lutonix AV DCB Catheter arm and 142 subjects in the standard PTA arm, the test has 96% power at a one-sided alpha level of 0.05 to reject the null hypothesis and to demonstrate non-inferiority of the Lutonix AV DCB Catheter with 270 evaluable subjects after accounting for approximately 5% censoring.

7.6 SECONDARY ENDPOINTS

7.6.1 SECONDARY ENDPOINTS WITH HYPOTHESIS TEST

The following secondary endpoints will have hypothesis tests. No secondary endpoints will be tested unless both primary hypotheses are successful. The testing of the secondary objectives will be performed in a hierarchical fashion in the order in which they are listed below. This means that as soon as a null hypothesis is *not rejected*, no further hypotheses will be tested. This hierarchical testing scheme ensures that the study-wide Type 1 error rate remains at 0.025 one-sided when all of the secondary endpoints are tested at two-sided α=0.05 or equivalently at one-sided α=0.025.

7.6.1.1 KEY SECONDARY ENDPOINT: TLPP AT 12 MONTHS

Objective: To assess if the 12 months TLPP for Lutonix AV DCB Catheter is superior to the 12 month TLPP for standard uncoated balloon, by direct comparison.

The key secondary endpoint will be evaluated by the following hypothesis:

H_0: The (survival) rate $w_1(t)$ of subjects in the DCB treatment group with TLPP through $t \leq$ 12 month post index procedure is less than or equal to that $w_2(t)$ of PTA treatment group. (i.e. $w_1(t) \leq w_2(t)$, for $t \leq$ 12 months)

H_1: The (survival) rate $w_1(t)$ of subjects in the DCB treatment group with TLPP through $t \leq$ 12 month post index procedure is greater than that $w_2(t)$ of PTA treatment group. (i.e. $w_1(t) > w_2(t)$, for $t \leq$ 12 months)

Rejection of the null hypothesis will signify that the 12 month TLPP of Lutonix AV DCB Catheter is superior to the 12 month patency rate of standard uncoated balloon.

A Kaplan-Meier analysis will be used to estimate the survival rate of TLPP in the DCB and PTA groups. A log-rank test comparing DCB and PTA will be used to test the key secondary hypothesis to determine if DCB is superior to PTA. The test is successful if the one-sided p-value is less than 0.025 and the result is in favor of DCB. In addition to the p-value, the confidence intervals of the rate in each group will be provided.

7.6.1.2 SECONDARY ENDPOINT: NUMBER OF INTERVENTIONS REQUIRED TO MAINTAIN TARGET LESION PATENCY AT 12 MONTHS

Objective: To assess if the median number of interventions by 12 months required for Lutonix AV DCB Catheter is less than that for standard uncoated balloon, by direct comparison:

H_0: The median number of interventions μ_1 by 12 months required for Lutonix AV DCB Catheter is less than or equal to that μ_2 of PTA treatment group. (i.e. $\mu_1 \leq \mu_2$)

H_1: The median number of interventions μ_1 by 12 months required for Lutonix AV DCB Catheter is greater than that μ_2 of PTA treatment group. (i.e. $\mu_1 > \mu_2$)

A Wilcoxon rank sum test comparing DCB and PTA will be used to test the secondary hypothesis to determine if DCB is superior to PTA. The test is successful if the one-sided p-value is less than 0.025 and the result is in favor of DCB. In addition to the p-value, the median number of interventions required by 12 months for both treatment groups will be presented along with its 95% confidence intervals.

7.6.1.3 SECONDARY ENDPOINT: ACPP AT 6 MONTHS

Objective: To assess if the 6 month ACPP for Lutonix AV DCB Catheter is superior to the 6 month ACPP for standard uncoated balloon, by direct comparison:

The key secondary endpoint will be evaluated by the following hypothesis:

H_0: The (survival) rate $h_1(t)$ of subjects in the DCB treatment group with ACPP through $t \leq 6$ months post index procedure is less than or equal to that $h_2(t)$ of PTA treatment group. (i.e. $h_1(t) \leq h_2(t)$, for $t \leq 6$ months)

H_1: The (survival) rate $h_1(t)$ of subjects in the DCB treatment group with ACPP through $t \leq 6$ month post index procedure is greater than that $h_2(t)$ of PTA treatment group. (i.e. $h_1(t) > h_2(t)$, for $t \leq 6$ months)

Rejection of the null hypothesis will signify that the 6 month ACPP rate of Lutonix AV DCB Catheter is superior to the 6 month ACPP rate of standard uncoated balloon.

A Kaplan-Meier analysis will be used to estimate the survival rate of ACPP in the DCB and PTA groups. A log-rank test comparing DCB and PTA will be used to test the primary hypothesis to determine if DCB is superior to PTA. The test is successful if the one-sided p-value is less than 0.025 and the result is in favor of DCB. In addition to the p-value of the test, the confidence intervals of the rate in each group will be provided.

7.6.1.4 SECONDARY ENDPOINT: ACPP AT 12 MONTHS

Objective: To assess if the 12 month ACPP for Lutonix AV DCB Catheter is superior to the 12 month ACPP for standard uncoated balloon, by direct comparison:

The key secondary endpoint will be evaluated by the following hypothesis:

H_0: The (survival) rate $h_1(t)$ of subjects in the DCB treatment group with ACPP through $t \leq 12$ months post index procedure is less than or equal to that $h_2(t)$ of PTA treatment group. (i.e. $h_1(t) \leq h_2(t)$, for $t \leq 12$ months)

H_1: The (survival) rate $h_1(t)$ of subjects in the DCB treatment group with ACPP through $t \leq 12$ month post index procedure is greater than that $h_2(t)$ of PTA treatment group. (i.e. $h_1(t) > h_2(t)$, for $t \leq 12$ months)

Rejection of the null hypothesis will signify that the 12 month ACPP rate of Lutonix AV DCB Catheter is superior to the 12 month ACPP rate of standard uncoated balloon.

A Kaplan-Meier analysis will be used to estimate the survival rate of ACPP in the DCB and PTA groups. A log-rank test comparing DCB and PTA will be used to test the primary hypothesis to determine if DCB is superior to PTA. The test is successful if the one-sided p-value is less than 0.025 and the result is in favor of DCB. In addition to the p-value of the test, the confidence intervals of the rate in each group will be provided.

7.6.2 SECONDARY ENDPOINTS WITH DESCRIPTIVE STATISTICS

The following secondary endpoints will be summarized with descriptive statistics and confidence intervals using the MITT population. For categorical variables summary statistics will include frequency counts and percentages. In addition, 95% CI for the percentages may be provided. For continuous variables, summary statistics will include mean, standard deviation, minimum, median, and maximum. Ninety-five percent (95%) confidence intervals may be provided for the mean.

Effectiveness

- Device, Procedural, and Clinical Success
- ACPP evaluated at 3, 9, 18 and 24 months
- TLPP evaluated at 3, 9, 18, and 24 months
- Abandonment of permanent access in the index extremity at 3, 6, 9, 12, 18 and 24 months
- Number of interventions required to maintain target lesion patency at 3, 6, 9, 18 and 24 months
- Number of interventions required to maintain access circuit patency at 3, 6, 9, 12, 18 and 24 months

Safety

- Rate of device and procedure related adverse events assessed at 1, 3, 6, 9, 12, 18 and 24 months

7.6.3 EXPLORATORY AND SUBGROUP ANALYSIS

Primary endpoint and key secondary endpoints may be explored in subgroups (use of a stent, gender, geography, lesion length, lesion location, whether a fiber pre-dilation balloon was used, etc.) if needed.

8.0 ADVERSE EVENTS AND DEVICE DEFICIENCIES

8.1 ADVERSE EVENTS

The Principal Investigator is responsible for the detection, documentation and reporting to the Sponsor of events meeting the criteria and definitions of an Adverse Event (AE), as provided in this CIP. Refer to the appendices for detailed AE, Serious Adverse Event (SAE), Adverse Device Effect (ADE), Serious Adverse Device Effect (SADE), and Unanticipated Adverse Device Effects (UADE) definitions.

For purposes of this study, the following events are not considered adverse events because they are expected to occur in conjunction with endovascular procedures / post-procedure timeframe, or are associated with customary, standard care of subjects undergoing these procedures:

- Early post-operative pain (within 24 hours post-index procedure) at the access site and/or related to position on procedure table
- Minor, localized tenderness, swelling, induration, bruising, oozing, hematoma <5 cm at vascular access site
- Post-anesthesia/conscious sedation emesis, nausea, or headache (within 24 hours post-index procedure)
- Chest pain without associated ECG changes
- Hematocrit decrease of 30% from baseline not associated with hemodynamic changes, and not requiring transfusion
- Electrolyte imbalance without clinical sequelae following PTA, even if requiring correction
- Low grade fever (≤38°C/≤101.4°F)
- Sinus bradycardia/tachycardia that does not require treatment or intervention
- Systolic or diastolic blood pressure changes that do not require treatment or intervention
- Dissections occurring during index procedure unless it exists at the end of the procedure and requires treatment above and beyond usual care/medical practice due to acute flow limitation.

This listing of events is intended to provide guidance to the investigational sites for purposes of adverse event reporting. The Investigator at the investigational site should utilize his/her own clinical judgment in evaluating adverse experiences, and may decide that the above events should be reported as adverse events.

Non-serious adverse events (AEs) should only be reported if the event requires medical treatment or intervention. AEs that are observational will not be required to be reported (stubbed toes, paper cuts, etc.).

8.1.1 RELATIONSHIP TO STUDY DEVICE AND PROCEDURE

Each AE will be assessed by the Investigator for its relationship to the use of the study device or study procedure as outlined below.

- **Device**: Restricted to the study device; used even if there was no malfunction, failure, or defect of the study device (i.e., if any similar device could have caused, contributed, or been associated with the event). "User error" will be grouped in the device related category if the "error" occurred during the use of the study device.
- **Procedure**: Includes any activity that supports the use of the device, including drugs, diagnostic agents, and non-study devices.
- **Access Circuit**: The area from the AV access anastomosis to the superior vena cava-right atrial junction

Not Related	The event is definitely not associated with procedure. The adverse event is due to an underlying or concurrent illness or effect of another procedure.
Possibly Related	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.
Definitely Related	It is obvious, certain, or there is little doubt regarding the relationship.

8.1.2 SEVERITY

Each AE will be assessed by the Investigator for its severity or intensity experienced by the subject according to the criteria listed below.

Mild	Awareness of a sign or symptom that does not interfere with the patient's usual activity or is transient, resolved without treatment and no sequelae.
Moderate	Interferes with the patient's usual activity and/or requires symptomatic treatment.
Severe	Symptom(s) causing severe discomfort and significant impact of the subject's usual activity and requires treatment.

8.2 SERIOUS ADVERSE EVENTS (SAES)

Adverse event that:

- Results in death,
- Is life-threatening.
- Requires inpatient hospitalization or prolongation of existing hospitalization (>24 hrs),
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect, or
- Requires intervention to prevent permanent impairment or damage.

8.3 DEVICE DEFICIENCIES

The following definitions relate to device deficiencies (DDs) and can be found in **Appendix B**.

- **Device Deficiency**: Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance and may include malfunctions, use errors, and inadequate labeling.
- **Device Malfunction**: 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.

8.4 DOCUMENTATION AND REPORTING

AEs will be documented in the medical records and in the eCRF. AEs experienced by the subject will be collected from the time point of randomization until the subject's end of study participation.

All AEs must be reported to the Sponsor at the time the Investigator becomes aware of the event (e.g. at the follow up evaluations). All SAEs/SADEs will be reported to the Sponsor within 5 working days of being made aware of the event. All SAEs/SADEs will be reported to the Investigational Review Boards/Ethics Committees as per applicable regulations. Refer to **Table 2** for reporting requirements.

All UADEs must be reported to the Sponsor as soon as possible but no later than 48 hours of being made aware of the event.

Lutonix may request additional information such as angio lab reports, operative reports, discharge summaries, histopathology reports and a physician's summary of the event, be provided to Lutonix as supporting documentation of any reported adverse event.

All Device Deficiencies occurring during the conduct of this study will be recorded on the Device Deficiency eCRF page, and reported by the Investigator to the Sponsor in a timely manner. Deficient devices shall be returned to the Sponsor. The further management of device deficiencies by the Investigator and the Sponsor/manufacturer will adhere to the appropriate national laws and regulations.

8.5 SAFETY MANAGEMENT

8.5.1 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 AV access and biostatistics who are not participating in the trial.

During the enrollment phase of the trial, the DSMB will review aggregate safety data to monitor for incidence of serious 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 National 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.

8.5.2 CLINICAL EVENTS COMMITTEE

The Clinical Events Committee (CEC) is made up of a minimum of three clinicians with expertise in AV access and who are not Investigators 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, reinterventions, device related and SAEs involving the access circuit.

9.0 DATA COLLECTION AND MANAGEMENT

The Investigator (or designated study staff) will assure primary data collection based on source-documented hospital chart reviews.

9.1 CASE REPORT FORMS

The Investigator is responsible for ensuring the accuracy and completeness of all study documentation.

All required clinical data for this trial will be collected in web-based standardized electronic case report forms (eCRF). FDA 21 CFR 11 will be followed as well as other applicable legislation on the handling of electronic data. Subject personal information will be pseudonymized. Site numbers 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 the Sponsor and/or the appropriate regulatory body.

9.2 SOURCE DOCUMENTATION

Auditors, monitors, the 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 the eCRF.

The Investigator will permit study-related monitoring, audits, IRB/EC review and authority inspections by allowing direct access to the source data. In case of electronic source data, access must be allowed or dated print-outs must be available prior to the monitoring visits. Print-outs will not be limited to the treatment data only, but will include all available data related to the identified subject(s).

9.3 DATA MANAGEMENT

A Data Management Plan (DMP) will be developed outlining the procedures used for data review, database cleaning and issuing and resolving data queries. Procedures for validations and data storage will also be contained within the DMP.

9.4 RECORD RETENTION

The Investigator will retain all study records for a minimum of two years after the market approval or termination of the study, or when it is no longer needed to support a marketing application, whichever is later. The data for some of these records may be available in computerized form but the final responsibility for maintaining study records remains with the Investigator. Further information on record retention and later destruction can be found in the signed CSA. All investigators must contact the Sponsor prior to destroying or archiving any records or reports pertaining to the study off-suite, to ensure that they no longer need to be retained on-site.

Outside US (OUS), Investigators will retain all study records as required per regulatory requirements in the local of the study site or as per the regulatory requirements in the market(s) where approval is sought, whichever is longer (if both are undefined then 2 years from approval in the study site's market).

Additionally, the Sponsor must be contacted if the Investigator plans to leave the investigational site to ensure that arrangements for a new Investigator or records transfer are made prior to the Investigator's departure.

10.0 MONITORING

Each site will have an initiation visit performed by a Study Monitor and/or a member of the Sponsor 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. The Monitoring Plan will contain specifications on all monitoring activities to be performed, including the extent of source data verification, frequency and timing of monitoring visits, and reporting. This may include but is not limited to accuracy and timely submission of data forms and core lab images, and compliance with the study CIP, meeting enrollment commitments, applicable regulations, the signed CSA and any conditions of approval imposed by the reviewing IRB/EC and/or regulatory agencies.

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

At the completion of the study, the Study Monitor will conduct a final close-out visit. The purpose of this visit may include but is not limited to collecting all outstanding study data documents, confirming that the Investigator's files are accurate and complete, reviewing the record retention requirements with the Investigator, and assuring that all applicable requirements for closure of the study are met. The actions and observations made at this visit will be recorded and filed.

11.0 RISK/BENEFIT ANALYSIS

11.1 POTENTIAL RISKS

Due to the high similarity of the Lutonix AV DCB Catheter to other marketed balloon catheters, procedural use is not expected to significantly change or increase risks during the initial procedure. Complications and AEs associated with use of the Lutonix AV DCB Catheter are listed in the IFU.

Potential adverse events which may be associated with a peripheral balloon dilation procedure include:

- 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
- Stroke
- Thrombosis
- Vessel dissection, perforation, rupture, or spasm

Potential adverse events that may be unique to the Lutonix DCB paclitaxel drug coating:

- Allergic reaction to drug coating

11.2 RISK MANAGEMENT PROCEDURES

The Lutonix AV DCB Catheter is being evaluated for use as intended in maintaining target lesion primary patency in native AV fistulae. The CIP 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 the Sponsor appointed monitoring personnel. Adverse Events will be reviewed by independent physicians throughout the study.

11.3 POTENTIAL BENEFITS

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

Additionally, information gained from the conduct of this study may be of benefit to others with the same medical condition. As with all investigational medical devices, the long-term results of using the Lutonix AV DCB Catheter are not known at the present time. Alternatives to the use of the Lutonix AV DCB Catheter include standard or cutting balloon angioplasty, vascular stenting, and surgical revision of the access. Lutonix believes that the risk for significant injury or death due to the Lutonix AV DCB Catheter is extremely low, and the potential benefits of decreased restenosis and decreased need for reinterventions are likely.

12.0 REGULATORY AND ETHICAL CONSIDERATIONS

This clinical study will be conducted in accordance with 21CFR parts 812, 50, 54 and 56, the Declaration of Helsinki, ICH Good Clinical Practices (GCP), Health Canada and the conditions of approval imposed by the reviewing IRB/EC.

12.1 IRB/EC APPROVAL

Investigators or designees must submit the study CIP together with all locally required documentation to their IRB/EC and obtain study-specific written favorable opinion before being allowed to conduct and participate in the study. Annual re-approval must also be obtained, as per local regulation. The Investigator or designee is also responsible for fulfilling any conditions of approval imposed by the IRB/EC, such as regular safety reporting, study timing, etc. The Investigator or designee will provide the Sponsor with copies of such approvals and reports.

The IRB and EC will be notified of any amendments to the CIP, as well as possible associated information and consent form changes, where applicable, and written favorable opinion / approval will be obtained prior to implementation, if required.

12.2 REGULATORY APPROVAL

In the US an Investigational Device Exemption (IDE) application must be submitted to the FDA. IDE approval must be received prior to the inclusion of the first US subject.

In Canada, an application for Investigational Testing Authorization must be submitted to Health Canada and the Therapeutic Products Directorate (TPD). ITA approval must be received prior to the inclusion of the first Canadian subject.

12.3 INFORMED CONSENT FORM

Part of the IRB/EC 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 prior to submission to the IRB/EC. An ICF template is provided in **Appendix C**. The Sponsor or designee must pre-approve each ICF prior to initial submission to the IRB/EC. The Investigator will provide the Sponsor 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 CIP and this decision will not influence his/her relationship with the Investigator and/or study staff. After this explanation and before entering the study, the subject (or legally authorized representative) must voluntarily sign and date the IRB/EC approved ICF.

13.0 ADMINISTRATIVE REQUIREMENTS

13.1 PUBLICATION POLICY

The trial will be registered on the ClinicalTrials.gov website prior to the inclusion of the first study subject in order to meet the criteria of the International Committee of Medical Journal Editors (ICMJE).

After the conclusion and final analysis of the trial results, a formal abstract presentation may be made at a major vascular conference and the study results submitted to a reputable scientific journal.

Following the publication of the main manuscript, secondary analyses proposals shall be considered for publication from individual Investigators. All publications or presentations regarding this study must be submitted to the Sponsor for prior review and approval.

13.2 INVESTIGATOR AND SITE SELECTION

The Sponsor will select Investigators who are qualified and experienced to participate in this IDE study. Sites will be selected based upon a review of a recent site assessment and the 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. The curriculum vitae (CV) of the Investigator will be maintained in the Sponsor files as documentation of previous medical training, and federal databases will be searched to ensure that the Investigator is not prohibited from engaging in federally sponsored clinical research.

13.3 INVESTIGATOR RESPONSIBILITY

Each Investigator is responsible for ensuring the investigation is conducted according to all signed agreements, the Clinical Investigational Plan (CIP) and applicable laws and regulations. The site Principal Investigator may 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 or performing CIP required procedures. All Interventionalists performing procedures must be trained as Co-Investigators in the study.

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

- Complete Signed Investigator Agreement
- Financial Disclosure Forms for all participating Investigators
- IRB/EC Roster or General Assurance number
- IRB/EC Protocol and Informed Consent Approvals
- Investigators' and Co-Investigators' current curricula vitae (CV)
- Site Signature and Responsibility Form

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

13.4 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.

Lutonix will maintain the following records:

- All correspondence which pertains to the investigation
- Signed Investigator Agreements/Compensation Agreements, and Curriculum Vitaes
- Adverse effects and complaints
- All Case Report Forms (signed by the Investigator)
- Clinical Investigational Plan
- Qualification Visit Form
- Monitoring Reports

Although the Investigator and his/her staff may have contact with other key individuals at the Sponsor throughout the course of the study, all communications regarding the conduct of the study must be channeled through the Sponsor's clinical affairs personnel or their designees.

13.5 REPORTING REQUIREMENTS

Table 2 below displays a list of the reports that are the Investigator's responsibility to generate. The table also shows to whom the report is to be sent, and with what frequency or time constraints. While some of these reports will be developed by or with the assistance of the Sponsor or their designee, the final responsibility rests with the Investigator.

Table 2: Reports Required from Clinical Investigators

Report Type	Prepared For:	Time Constraints of Notification
Subject death during investigation	Lutonix/IRB/EC	To Lutonix: in eCRF within 24 hours of knowledge. To IRB/EC: Written documentation of the event within 10 working days or per local requirements.
SAE/SADE	Lutonix/IRB/EC	For US and Canada, within 5 working days of knowledge and to IRB/EC per local reporting requirements.
UADE	Lutonix/IRB/EC	As soon as possible, but in no event later than 48 hours after the Investigator first learns of the event.
Protocol Deviations due to emergency	Lutonix/IRB/EC	As soon as possible, but no later than 5 working days after emergency occurs.
Subject withdrawal	Lutonix	By eCRF within 5 working days.
Withdrawal of IRB/EC approval	Lutonix	Immediately by telephone followed by a copy of the notification within 5 working days.
Continuing IRB/EC re-approval	IRB/EC	Prior to continuing review date.
Progress report	Lutonix/IRB/EC	Submitted at regular intervals or annually.
Failure to obtain ICF	Lutonix	Within 5 working days.
Final summary report	Lutonix	Within 3 months.

13.6 DEVIATIONS

A CIP deviation is defined as an event where the clinical Investigator or site personnel did not conduct the study according to the CIP.

It is the Investigator's responsibility to ensure that there are no deviations from the CIP except where necessary to protect the life or physical well being of a subject in an emergency. Except in emergency situations, a protocol deviation requires prior Sponsor approval. If the deviation affects the scientific soundness of the plan or the rights, safety, or welfare of a subject, prior FDA and IRB approval is required. Continued CIP deviations may result in termination of enrollment in the study at the site.

Deviations must be reported within the eCRF regardless of whether medically justifiable, Sponsor approved or taken to protect the subject in an emergency. Investigators will also adhere to procedures for reporting study deviations to and obtaining approval from their IRB/EC in accordance with their specific IRB/EC reporting policies and procedures.

13.7 TERMINATION OF STUDY

The Sponsor reserves the right to suspend enrollment or terminate the study at any time as set forth in the Clinical Trial Agreement (CTA) and for reasons including, but not limited to, inadequate data collection, low subject enrollment rate, achievement of the total enrollment, conditions imposed by the reviewing IRB/EC and/or regulatory agencies, or non-compliance with the CIP or other clinical research requirements. Written notice will be submitted to the Investigator in advance of such termination.

In the event of study suspension or termination, the Sponsor will send a report outlining the circumstances to the IRB/EC, 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/EC and Regulatory Authorities, as required by regulation.

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

14.0 STATEMENT OF COMPLIANCE

This clinical investigation will be conducted in compliance with the CIP and the following regulatory requirements:

- 21 CFR parts 50, 54, 56 and 812
- ICH Good Clinical Practices (GCP)
- Health Canada regulations
- Declaration of Helsinki adopted by the 18th World Medical Assembly in Helsinki, Finland, in 1964, in its current revision
- Applicable sections of the national laws and regulations.

By acting in accordance with this CIP, the Sponsor, the Investigators and the study site personnel fulfill the requirements of 21CFR parts 50, 54, 56, 812 and GCP.

The clinical investigation will not commence at a clinical site until favorable opinion(s) from the respective IRB/EC has been received. All additional requirements imposed by the IRB/EC(s) will be followed. Involvement of the national competent authorities, e.g. by notification, seeking authorization, will be accomplished as required by national laws and regulations.

Insurance coverage for damages emerging from the clinical investigation will be provided according to applicable legal requirements.

15.0 MEDICARE STUDY CRITERIA

Access to clinical study data provides opportunities to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by research participants are used to maximum effect in the creation of knowledge and understanding. To this end, the study's results information on all pre-specified outcomes, including negative outcomes, will be submitted to ClinicalTrials.gov not later than one year after the study completion date of the study, where the completion date is defined as the date that the final subject was examined or received an intervention for purposes of data collection for the primary outcome measure. Results submission could be delayed if an extension is granted to the results submission deadline; however, the release of all results on pre-specified outcomes will be hastened if the study is terminated early.

It is not anticipated the device under investigation will treat a Medicare population different than the demographics found the investigators' general population for this same condition including populations eligible for Medicare due to age (e.g., 65 years or older), disability, or other eligibility (e.g., End Stage Renal Disease (ESRD)). The current treatment for the majority of dialysis patients is hemodialysis. Vascular access dysfunction in hemodialysis is still a significant health problem and reducing restenosis by limiting intimal hyperplasia could reduce the significant human and economic costs for vascular dysfunction. Interventions targeting the process of vascular access dysfunction, a significant health problem in the population of patients receiving hemodialysis, may be useful to reduce the significant human and economic costs for vascular dysfunction. According to the United States Renal Data System (USRDS) 2014 Annual Data Report* -- The number of prevalent ESRD patients continues to increase in all age groups, with a steeper increase among patients aged 45 and over than among younger patients. With the recent leveling off of the number of (a) Prevalent cases (b) Prevalence per million incident ESRD patients, the continuing rise in ESRD prevalence is presumably due to longer survival among ESRD patients in recent years. In 2012, the adjusted prevalence of ESRD per million was 83 for age 0-19, 938 for age 20-44, 3,550 for age 45-64, 6,302 for age 65-74, and 6,261 for age 75+. The prevalence per million continues to increase in all age groups, with the relative magnitude of increase greater in older age groups. Relative increases since 2000 are 14% at age 0-19, 16% at age 20-44, 23% at age 45-64, 30% at age 65-74, and 50% at age 75+. Thus, the results of this study are expected to be generalizable to the Medicare eligible population, both by age (65 years or older) and by other eligibility status (ESRD).

*Citation: *United States Renal Data System, 2014 USRDS annual data report: An overview of the epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2014*. Available at: http://www.usrds.org/2014/view/Default.aspx

16.0 REFERENCES

1. http://www.kidney.niddk.nih.gov/KUDiseases/pubs/kustats/index.aspx
2. Sofocleous, CT, Cerveira J, Cooper SG, Yudd M. Dialysis fistulae. Siskin, GP, Hartnell G, Cho KJ (eds). Drugs, Diseases Procedures. Medscape. 2013. [Online]. Available from: http://emedicine.medscape.com/article/419393-overview#showall.
3. National Kidney Foundation. K/DOQI Clinical Practice Guidelines and Clinical Practice Recommendations for 2006 Updates: Hemodialysis Adequacy, Peritoneal Dialysis Adequacy and Vascular Access. Am J Kidney Dis 48:S1-S322, 2006 (suppl 1).
4. Roy-Chaudhury P, Kelly BS, Miller MA, Reaves A, Armstrong J, Nanayakkara N et al. Venous neointimal hyperplasia in polytetrafluoroethylene dialysis grafts. Kidney Int 2001; 59(6):2325-2334.
5. Roy-Chaudhury P, Arend L, Zhang J, Krishnamoorthy M, Wang Y, Banerjee R et al. Neointimal hyperplasia in early arteriovenous fistula failure. Am J Kidney Dis 2007; 50(5):782-790.
6. Gray Richard J. MD, Subcommittee Chair, David Sacks, MD, Committee Chair, Louis G. Martin, MD, Scott O. Trerotola, MD, and the Members of the Society of Interventional Radiology Technology Assessment Committee. Reporting Standards for Percutaneous Interventions in Dialysis Access. J Vasc Interv Radiol 2003; 14:S433–S442.
7. Sidawy, Anton N. MD, Richard Gray, MD, Anatole Besarab, MD, Mitchell Henry, MD, Enrico Ascher, MD, Michael Silva, Jr, MD, Arnold Miller, MD, Larry Scher, MD, Scott Trerotola, MD, Roger T. Gregory, MD, Robert B. Rutherford, MD, and K. Craig Kent, MD. Recommended standards for reports dealing with arteriovenous hemodialysis accesses. J Vasc Surg 2002; 35:603-10.
8. Kariya S, Tanigawa N, Kojima H, Komemushi A, Shomura Y, Shiraishi T et al. Primary patency with cutting and conventional balloon angioplasty for different types of hemodialysis access stenosis. Radiology 2007; 243(2):578-587.
9. Turmel-Rodrigues L, Pengloan J, Baudin S, Testou D, Abaza M, Dahdah G et al. Treatment of stenosis and thrombosis in haemodialysis fistulas and grafts by interventional radiology. Nephrol Dial Transplant 2000; 15(12):2029-2036.
10. Clark TW. Nitinol stents in hemodialysis access. J Vasc Interv Radiol 2004; 15(10):1037-1040.
11. Maya ID, Allon M. Outcomes of thrombosed arteriovenous grafts: comparison of stents vs angioplasty. Kidney Int 2006; 69(5):934-937.
12. Sreenarasimhaiah VP, Margassery SK, Martin KJ, Bander SJ. Salvage of thrombosed dialysis access grafts with venous anastomosis stents. Kidney Int 2005; 67(2):678-684.
13. Liuzzo JP, Ambrose JA, Coppola JT. Sirolimus- and taxol-eluting stents differ towards intimal hyperplasia and re-endothelialization. J Invasive Cardiol 2005; 17(9):497-502.
14. Tepe G, Zeller T, Albrecht T, Heller S, Schwarzwalder U, Beregi JP et al. Local delivery of paclitaxel to inhibit restenosis during angioplasty of the leg. N Engl J Med 2008; 358(7):689-699.
15. Gray WA, Granada JF. Drug-coated balloons for the prevention of vascular restenosis. Circulation 2010; 121(24):2672-2680.
16. Rotmans J, Pattynama PM, Verhagen HJ, et al. Sirolimus-eluting stents to abolish intimal hyperplasia and improve flow in porcine arteriovenous grafts: a 4-week follow-up study. Circulation 2005; 111:1537-1542.

17. Speck U, Scheller B, Abramjuk C, et al. Neointima inhibition: comparison of effectiveness of nonstent-based local drug delivery and a drug-eluting stent in porcine coronary arteries. Radiology. 2006;240:411– 418.
18. Scheller B, Speck U, Abramjuk C et al. Paclitaxel balloon coating, a novel method for prevention and therapy of restenosis. Circulation 2004; 110:810–4.
19. Cremers B, Kuehler M, Kaufels N et al. Paclitaxel-coated balloon catheter: influence of different dosages on neointimal proliferation in the porcine coronary restenosis model. Eur Heart J Suppl. 2008 Sept; 29 (Suppl. 1):338.
20. Lee BH, Nam HY, Kwon T, et al. Paclitaxel-coated expanded polytetrafluoroethylene haemodialysis grafts inhibit neointimal hyperplasia in porcine model of graft stenosis. Nephrol Dial Transplant 2006; 21:2432-2438.
21. Kohler TR, Toleikis PM, Gravett DM, Avelar RL. Inhibition of neointimal hyperplasia in a sheep model of dialysis access failure with the bioabsorbable Vascular Wrap paclitaxel eluting mesh. J Vasc Surg 2007; 45:1029-1037.
22. Tepe G, Zeller T, Albrecht T et al. Local delivery of paclitaxel to inhibit restenosis during angioplasty of the leg. N Engl J Med. 2008 Feb 14;358(7):689-99.
23. Werk M, Langner S, Reinkensmeier B et al. Inhibition of restenosis in femoropopliteal arteries: paclitaxel-coated versus uncoated balloon: femoral paclitaxel randomized pilot trial. Circulation. 2008 Sep 23;118(13):1358-65.
24. Liistro F, Grotti S, Proto I, Angioli P, and Ricci L et al. Drug-eluting balloon in peripheral intervention for the superficial femoral artery: the DEBATE-SFA randomized trial (drug eluting balloon in peripheral intervention for the superficial femoral artery). JACC Cardiovasc Interv. 2013 Dec;6(12):1295-302.
25. Siablis D, Kitrou PM, Spiliopoulos S, Katsanos K, and Karnabatidis D. Paclitaxel-coated balloon angioplasty versus drug-eluting stenting for the treatment of infrapopliteal long-segment arterial occlusive disease: the IDEAS randomized controlled trial. JACC Cardiovasc Interv. 2014 Sep; 7(9):1048-56.
26. Scheller B, Hehrlein C, Bocksch W et al. Treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter. N Engl J Med. 2006 Nov 16;355(20):2113-24.
27. Scheller B, Hehrlein C, Bocksch W et al. Two year follow-up after treatment of coronary instent restenosis with a paclitaxel-coated balloon catheter. Clin Res Cardiol. 2008 Oct;97(10):773-81.
28. Unverdorben M, Vallbracht C, Cremers B et al. Paclitaxel-Coated Balloon Catheter Versus Paclitaxel-Coated Stent for the Treatment of Coronary In-Stent Restenosis. Circulation. 2009;119:2986-2994.
29. Unverdorben M, Kleber FX, Heuer H, Figulla HR, Vallbracht C, Leschke M et al. Treatment of small coronary arteries with a paclitaxel-coated balloon catheter. Clin Res Cardiol 2010; 99(3):165-174.
30. Fanggiday JC, Stella PR, Guyomi SH, Doevendans PA. Safety and efficacy of drug-eluting balloons in percutaneous treatment of bifurcation lesions: the DEBIUT (drug-eluting balloon in bifurcation Utrecht) registry. Catheter Cardiovasc Interv. 2008;71:629-635.
31. Jim MH, Fung RC, Yiu KH, Ng AL, and Siu CW et al. Combined paclitaxel-eluting balloon and Genous cobalt-chromium alloy stent utilization in de novo coronary stenoses (PEGASUS). J Interv Cardiol. 2013 Dec;26(6):566-60

32. Liistro F, Porto I, Angioli P, Grotti S, and Ducci K et al. Elutax paclitaxel-eluting balloon followed by bare-metal stent compared with Xience V drug-eluting stent in the treatment of de novo coronary stenosis: a randomized trial. Am Heart J. 2013 Nov;166(5):920-6.
33. López Mínguez JR, Nogales Asensio JM, Doncel Vecino LJ, Sandoval J, and Romany S et al. A prospective randomized study of the paclitaxel-coated balloon catheter in bifurcated coronary lesions (BABILON trial): 24-month clinical and angiographic results.
34. Adriaenssens T, Dens J, Ughi G, Bennett J, Dubois C, and Sinnaeve P et al. Optical coherence tomography study of healing characteristics of paclitacel-eluting balloons vs. everolimus-eluting stents for in-stent restenosis: the SEDUCE (Safety and Efficacy of a Drug eluting balloon in Coronary artery rEstenosis) randomized clinical trial. Euro Interventions. 2014 Aug;10(4):439-48.
35. Alfonso F, Peréz-Vizcayno MJ, Cárdenas A, García Del Blanco B, and Seidelberger B et al. A randomized comparison of drug-eluting balloon versus everolimus-eluting stent in patients with bare-metal stent-in-stent restenosis: the RIBS V Clinical Trial (Restenosis Intra-stent of Bare Metal Stents: paclitaxel-eluting balloon vs everolimus-eluting stent). J Am Coll Cardiol 2014. Apr 15;63(14):1378-86.
36. Habara S, Iwabuchi M, Inoue N, Nakamura S, and Nanto S et al. A multicenter randomized comparison of paclitaxel-coated balloon catheter with convention al balloon angioplasty in patients with bare-metal stent restenosis and drug-eluting stent restenosis. Am Heart J. 2013 Sep;166(3):527-33.
37. Liistro F, Angioli P, Porto I, Ricci L, and Ducci K et al. Paclitaxel-eluting balloon vs. standard angioplasty to reduce recurrent restenosis in diabetic patients with in-stent restenosis of the superficial femoral and proximal popliteal arteries: the DEBATE-ISR study. J Endovasc Ther. 2014 Feb;21(1):1-8.
38. Xu B, Gao R, Wang J, Yang Y, and Chen S et al. A prospective, multicenter, randomized trial of paclitaxel-coated balloon versus paclitaxel-eluting stent for the treatment of drug-eluting stent in-stent restenosis: results from the PEPCAD China ISR trial. JACC Cardiovasc Interv. 2014 Feb;7(2):204-11.
39. Katsanos K, Karnabatidis D, Kitrou P, Spiliopoulos S, Christeas N, Siablis D. Paclitaxel-coated balloon angioplasty vs. plain balloon dilation for the treatment of failing dialysis access: 6-month interim results from a prospective randomized controlled trial. J Endovasc Ther 2012; 19(2):263-272.
40. Patane D. Drug eluting Balloon for stenotic arterial venous fistulas. 2011. [Online] Available from: http://www.massafmedical.com.br/pdf/hemodinamica/99cfeae425ec8ec3ffff80bfffffd502.pdf
41. Lai CC, Fang HC, Tseng CJ, Liu CP, and Mar GY. Percutaneous angioplasty use a paclitaxel-coated balloon improved target lesion restenosis on inflow lesions of autogenous radiocephalic distulas: a pilot study. J Vasc Interv Radiol. 2014 Apr;25(4):535-41.
42. Haskal ZV et. Al. Stent graft versus balloon angioplasty for failing dialysis-access grafts N Engl J Med. 2011;362:494-503.

17.0 APPENDICES

Appendix A. Abbreviations

Abbreviation	Term
AE	Adverse Event
ADE	Adverse Device Effect
API	Active Pharmaceutical Ingredient
AV	Arteriovenous
AVF	Arteriovenous Fistula
AVG	Arteriovenous Graft
CA	Competent Authority
CE	Conformité Européenne
CIP	Clinical Investigation Plan
CTA	Clinical Trial Agreement
CV	Curriculum Vitae
DCB	Drug Coated Balloon
DD	Device Deficiency
DES	Drug Eluting Stent
DMP	Data Management Plan
EC	Ethics Committee
eCRF	Electronic Case Report Forms
ePTFE	Expanded Polytetrafluoroethylene
FAS	Full Analysis Set
FDA	Food and Drug Administration
ICF	Informed Consent Form
IFU	Instructions For Use
IV	Intravenous
K/DOQI	Kidney Outcomes Quality Initiative
MLD	Minimum Lumen Diameter
NDA	Nondisclosure Agreement
OTW	Over The Wire
PP	Per Protocol
PTA	Percutaneous Transluminal (Balloon) Angioplasty
QVA	Quantitative Vascular Angiography
RMA	Return Material Authorization
RVD	Reference Vessel Diameter
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SD	Standard Deviation
SIR	Society of Interventional Radiology
TLPP	Target Lesion Primary Patency
TLR	Target Lesion Revascularization
UADE	Unanticipated Adverse Device Effect

Appendix B. Definitions

Term	Definition text
Access Circuit	The area from the AV access anastomosis to the superior vena cava-right atrial junction.
Access Circuit Primary Patency	Interval following intervention until the next access circuit thrombosis or repeated intervention. Ends with treatment of a lesion anywhere within the access circuit.
Adverse Event - AE	Any unfavorable and unintended sign, symptom, or disease temporally associate with the use of an investigational product, whether or not related to the investigational product.
Serious Adverse Event - SAE	An AE that: • Results in death, • Is life threatening, • Requires inpatient hospitalization or prolongation of existing hospitalization (>24hrs), • Results in persistent or significant disability/incapacity, or • Is a congenital anomaly/birth defect. • Requires intervention to prevent permanent impairment or damage
Anticipated Adverse Event	Any AE whether or not considered related to the investigational product(s) or drug regimen prescribed as part of the CIP, predefined in the CIP and/or IFU.
Adverse Device Effect -ADE	An AE related to the use of the study device.
Serious Adverse Device Effect - SADE	A SADE is an ADE that has resulted in any of the consequences characteristic of a SAE.
Unanticipated Adverse Device Effect - UADE	A UADE is an ADE which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.
Anastomosis	The site(s) of surgical connection between an AV access graft or artery (fistula) and venous structures.
Arteriovenous Fistula	Surgically created communications between the artery and vein in an extremity. Direct communications are called arteriovenous fistulae (AVFs).
Arteriovenous Graft	A natural or synthetic tube structure used for AV access.

Clinical or Physiological Abnormalities	Per K/DOQI guideline, stenoses should be treated in the presence of the following clinical or physical abnormalities.
	• Decreased access blood flow (<500ml/min, 25% decrease in flow)
	• Elevated venous pressures
	• Decreased dialysis dose (Kt/V)
	• Abnormal physical exam:
	  ○ Diminished or abnormal thrill (focal, systolic only, etc)
	  ○ Pulsatility
	  ○ Flaccid access
	  ○ Abnormal bruit
	  ○ Arm or hand swelling
	• Prolonged bleeding
	• Difficult puncture
	• Infiltration
	• Recirculation
	• Pulling clots

Clinical Success	The resumption of dialysis for at least one session after the index procedure.

Clinically driven reintervention	Clinically driven reintervention is defined as a lesion that is ≥50% stenosis and at least one clinical, physiological or hemodynamic abnormality attributable to the stenosis defined in the K/DOQI guidelines.
	• Decreased access blood flow (<500ml/min, 25% decrease in flow)
	• Elevated venous pressures
	• Decreased dialysis dose (Kt/V)
	• Abnormal physical exam:
	  ○ Diminished or abnormal thrill (focal, systolic only, etc)
	  ○ Pulsatility
	  ○ Flaccid access
	  ○ Abnormal bruit
	  ○ Arm or hand swelling
	• Prolonged bleeding
	• Difficult puncture
	• Infiltration
	• Recirculation
	• Pulling clots

Device Deficiency - DD	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance and may include malfunctions, use errors, and inadequate labeling.
Device Malfunction	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	Successful delivery to the target lesion, deployment, and retrieval at index procedure. 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 timepoint at which the subject was released from the admitting hospital or transferred to another facility.
Hemodynamic Success	Reduction of venous dialysis pressures, reduction of static intragraft/cuffed brachial static pressure ratios and increase in access volume flows.
Kidney Disease Outcomes Quality Initiative- K/DOQI	K/DOQI™ has provided evidence-based clinical practice guidelines for all stages of chronic kidney disease (CKD) and related complications since 1997.
Procedural Success	At least one indicator of hemodynamic success (e.g., physical examination with restoration of a thrill, direct measurement of flow) in the absence of peri-procedural (index procedure and through hospital stay) Serious Adverse Device Effects (SADEs).
Reference Vessel Diameter	According to K/DOQI guidelines "the diameter of the immediately upstream or downstream normal vessel", whichever is smallest. • Perianastomotic stenoses: If there is no usable adjacent normal vein to use, such as in stenosis beginning at the anastomosis and ending in an aneurysmal vein, the adjacent arterial diameter may be used as the RVD.
Screen Failures	Subjects screened and who have given their informed consent, but not meeting all study entry criteria and hence are not randomized, are considered screening failures and will be documented as such on the Screening Logs.
Secondary Non-Target Lesion	A secondary non-target lesion in the access circuit which may be treated as per the clinical protocol.
Society of Interventional Radiology	The Society of Interventional Radiology (SIR) is a national organization of physicians, scientists and allied health professionals dedicated to improving public health through disease management and minimally invasive, image-guided therapeutic interventions.
Stenosis	Narrowing of the vessel. Percent (%) stenosis or residual stenosis is measured in comparison to the reference vessel diameter (RVD).
Study Device	Lutonix 035 AV Drug Coated Balloon PTA Catheter, Model 9010
Target Lesion	Lesion(s) that are to be treated with a study device during the index procedure
Target Lesion Primary Patency	Target Lesion Primary Patency (TLPP) is defined as the interval following index procedure intervention until clinically driven reintervention of the target lesion or access thrombosis through 6 months.
Thrill	The vibration or tremble of blood flow in a graft or fistula.
Treatment Area	The entire treated vessel segment(s) in which the study device angioplasty balloons were inflated (the injury segment) in access circuit including the Target Lesion(s).

Appendix C1. Informed Consent Form – U.S. Investigational Sites

Appendix D2. Informed Consent Form – Canadian Investigational Sites