Clinical Study Protocol

Tack **O**ptimized **B**alloon **A**ngioplasty Study for the

Superficial Femoral and Proximal Popliteal Arteries

Using the Tack Endovascular System™ (**TOBA II**)

Study Device:	Tack Endovascular System™
Protocol Number:	CA 0119
Protocol Version:	Rev B
Effective Date:	02/10/16
Study Sponsor:	Intact Vascular, Inc. 150 Strafford Avenue, Suite 303 Wayne, Pennsylvania 19087 United States of America

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TABLE OF CONTENTS

1. Investigator Signature Page 8
2. Study Synopsis 9
3. Study Management Contact List 14
4. Introduction 15
4.1. Background and Rationale 15
5. Investigational Device 19
5.1. Description 19
5.2. Principles of Operation 21
5.3. Intended Use 22
6. Clinical Study Objectives 22
6.1. Primary Endpoints 22
6.2. Observational Endpoints 22
7. Clinical Study Design 23
7.1. Investigational Sites 23
7.2. Subject Population 23
7.3. Anticipated Number of Subjects 23
7.4. Clinical Study Duration & Follow-up 23
7.5. Subject Selection 23
7.5.1. Inclusion Criteria 23
7.5.2. Angiographic Inclusion Criteria 24
7.5.3. Exclusion Criteria 25
7.5.4. Angiographic Exclusion Criteria 26
8. Treatment Plan 26
8.1. Time and Events Schedule 26
8.2. Pre-Screening 28
8.3. Obtaining Informed Consent 28
8.4. Screening Success and Failure Criteria 28
9. Baseline Evaluation 29
9.1. Baseline Assessments 29
9.2. Study medications 30
10. Index Procedure 30

10.1. Index Baseline Angiogram 30
10.1.1. Preparation 30
10.1.2. Baseline Angiographic Requirements 31
10.2. Pre-Enrollment Balloon Angioplasty 32
10.2.1. Post-Angioplasty Angiographic Requirements 32
10.3. Study Device Treatment 33
10.3.1. Enrollment (Intent-to-Treat) 33
10.3.2. Treatment Recommendations 33
10.3.3. Post-Study Device Treatment Measurements 33
10.4. Post-Dilatation of Treated Lesion (Post-Study Device) 34
10.4.1. Recommendations 34
10.4.2. Final Treatment Results 34
10.5. Bailout Stenting of Target Lesion (Post-Study Device) 34
11. Post-Procedure/Pre-Discharge 35
11.1. Required Assessments 35
12. Required Follow-up Visits and Assessments 35
12.1. 30-day Follow-up Visit (-2 days / +14 days post-Index Procedure) 35
12.2. 6 Month Follow-up Visit (±30 days post-Index Procedure) 35
12.3. 12 Month Follow-up Visit (±30 days post-Index Procedure) 36
12.4. 24 Month Follow-up Visit (±30 days post-Index Procedure) 36
12.5. 36 Month Follow-up Visit (±30 days post-Index Procedure) 36
12.6. Review of concomitant medications (antiplatelets/anticoagulants)Duplex Ultrasound (DUS) Assessment 37
12.7. X-Ray Assessment 37
12.8. Unscheduled Visits 38
12.9. Follow-up Visit Compliance 38
12.10. Subject Discontinuation and Replacement 38
13. Risk/Benefit Assessment 39
13.1. Risks 39
13.2. Potential Benefits 40
13.3. Justification for Clinical Study 40
14. Adverse Event Reporting 40
14.1. Adverse Events (AE) 41

14.1.1. AE Reporting 42
14.2. Adverse Device Effects (ADE) 42
14.2.1. ADE Reporting 42
14.3. Serious Adverse Events (SAE) 42
14.3.1. SAE Reporting 43
14.4. Major Adverse Events (MAE) 43
14.4.1. MAE Reporting 43
14.5. Serious Adverse Device Effects (SADE) 43
14.5.1. SADE Reporting 43
14.6. Unanticipated Adverse Device Effects (UADE) 43
14.6.1. UADE Reporting 44
15. Study Device Event Reporting 44
15.1. Device Deficiency 44
15.2. Device Malfunction 44
16. Statistical Considerations 44
16.1. Introduction 44
16.2. Analysis Groups 44
16.3. Enrollment Sample Size 45
16.4. Administrative Reports 45
16.5. Justification for Pooling 45
16.6. Handling of Missing Data 45
16.7. Summary of Baseline Demographics, Index Procedure Measurements, Tack Endovascular System Treatment Results, and Subject Compliance 46
16.8. Primary Safety Objective 46
16.9. Primary Efficacy Objective 47
16.10. Subgroup Summaries for Primary Endpoints 49
16.11. Observational Endpoints 49
17. Regulatory and Ethical Obligations 50
17.1. Institutional Review Board (IRB) / Ethics Committee (EC) Approval 50
17.2. Informed Consent 50
17.3. Protocol Amendment and Emergency Deviations 50
17.4. Subject Confidentiality 51
18. Clinical Study Conduct 51

18.1. Principal Investigator and Site Qualification 51
18.2. Principal Investigator and Site Training 51
18.3. Clinical Monitoring 52
18.4. Device Accountability 52
18.5. Investigator Reports 53
18.6. Data Management 53
18.7. Safety Monitoring 54
18.7.1. Data Safety Monitoring Board (DSMB) 54
18.7.2. Clinical Events Committee (CEC) 54
18.8. Medical Monitoring 55
18.9. Central Core Laboratories 55
18.10. Record Retention 55
18.11. Audits/Inspections 56
18.12. Study Termination (Stopping Rules) 57
18.13. Coverage of Subject Expenses 57
18.14. Clinical Study Reports 57
18.15. Publication Policies 58
18.16. Medicare Study Criteria 58
19. Study Definitions 59

LIST OF ACRONYMS

ABI	Ankle Brachial Index
ADE	Adverse Device Effect
AE	Adverse Event
CD-TLR	Clinically-driven Target Lesion Revascularization
CD-TVR	Clinically-driven Target Vessel Revascularization
CEC	Clinical Event Committee
CLI	Critical Limb Ischemia
CRF	Case Report Form
CTO	Chronic Total Occlusion
DCB	Drug-coated Balloon
DEB	Drug Eluting Balloon
DES	Drug Eluting Stent
DSMB	Data Safety and Monitoring Board
DUS	Duplex Ultrasound
EC	Ethics Committee
eCRF	Electronic CRF
EDC	Electronic Data Capture
EQ5D	EuroQol Group 5-Dimension Self-Report Questionnaire
FDA	Food and Drug Administration
FU	Follow Up
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IFU	Instructions For Use
INR	International Normalized Ratio
IRB	Institutional Review Board
IVUS	Intravascular Ultrasound
LLL	Late Lumen Loss
LTFU	Lost to Follow-up
MAE	Major Adverse Events
NHLBI	National Heart, Lung, and Blood Institute
PAD	Peripheral Arterial Disease
PAQ	Peripheral Artery Questionnaire
PI	Principal Investigator
PIC	Patient Implant Card
PLT	Platelets/platelet count

PPA	Proximal Popliteal Artery
PSVR	Peak Systolic Velocity Ratio
PT	Prothrombin time
PTA	Percutaneous Transluminal Angioplasty
RS	Residual Stenosis
RVD	Reference Vessel Diameter
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SFA	Superficial Femoral Artery
TASC	Trans-Atlantic Inter-Society Consensus
TL	Target Lesion
TLR	Target Lesion Revascularization
TV	Target Vessel
TVR	Target Vessel Revascularization
UADE	Unanticipated Adverse Device Effect
WIQ	Walking Impairment Questionnaire
% DS	Percentage Diameter Stenosis

1. INVESTIGATOR SIGNATURE PAGE

STUDY TITLE: **TACK OPTIMIZED BALLOON ANGIOPLASTY STUDY FOR THE SUPERFICIAL FEMORAL AND PROXIMAL POPLITEAL ARTERIES USING THE TACK ENDOVASCULAR SYSTEM™ (TOBA II)**

STUDY CENTER: _____

(Print name of study center)

I, the undersigned, have read and understand the protocol specified above and agree to abide by its content. I agree to perform and conduct the study as described in the protocol. In addition, when applicable, I agree to enlist sub-investigators who also agree to perform and conduct the study as described in the protocol and I acknowledge it is my responsibility to ensure that is carried out.

_____
SITE PI – Print Name

_____
SITE PI – Signature

_____
DATE

2. STUDY SYNOPSIS

Study Title:	**T**ack **O**ptimized **B**alloon **A**ngioplasty Study for the Superficial Femoral and Proximal Popliteal Arteries Using the Tack Endovascular System™ **(TOBA II)**
Study Design:	This is a prospective, multi-center, single-arm, non-blinded study designed to investigate the safety and efficacy of the Tack Endovascular System.
Study Objective:	To compare the safety and efficacy of the Tack Endovascular System in subjects with peripheral artery disease (PAD) to a pre-defined performance goal (PG).
Study Device:	Tack Endovascular System™ manufactured by Intact Vascular, Inc.
Intended Use:	The Tack Endovascular System is intended for use in the superficial femoral and proximal popliteal arteries ranging in diameter from 2.5mm to 6.0mm for the repair of post percutaneous transluminal balloon angioplasty (PTA) dissection(s) type(s) A through F.
Subject Population:	Subjects with PAD who receive PTA (with a standard or FDA-approved Lutonix drug-coated balloon) in the SFA and proximal popliteal (P1) arteries and have a resulting dissection(s) type(s) A through F are eligible for enrollment. To be enrolled, subjects must meet all inclusion criteria and not meet any of the exclusion criteria.
Enrollment:	Approximately 210 subjects will be enrolled at up to 40 clinical sites throughout the U.S. and Europe (up to 5 European sites will participate)
Primary Endpoints:	**Safety:** Freedom from the occurrence of any new-onset major adverse event(s) (MAEs) defined as index limb amputation (above the ankle), CEC adjudicated clinically-driven target lesion revascularization (CD-TLR), or all-cause death at 30 days. **Efficacy:** Primary patency defined as freedom from CEC adjudicated clinically-driven target lesion revascularization (CD-TLR) and freedom from core lab adjudicated duplex ultrasound derived binary restenosis at 12 months (defined as PSVR $\geq$2.5).
Observational Endpoints:	Device Success: Successful deployment of the Tack(s) at the intended target site(s) and successful withdrawal of the delivery catheter from the introducer sheath. If the study device is introduced but the subject does not receive a Tack due to user error and not a device malfunction, this device will not be included in the device success assessment. Procedural Success: Demonstrated vessel patency (<30% residual DS, by visual estimate) without the use of a bailout stent or the occurrence of MAE upon completion of the index procedure.

	In addition, the following observational endpoints will be assessed at various time points through 36 months (See **Section 8.1** Time and Events Schedule): ▪ All-cause death ▪ Amputation of the target limb (above the ankle) ▪ Clinically-driven target vessel revascularization (CD-TVR) ▪ Clinically-driven target lesion revascularization (CD-TLR) ▪ Target vessel revascularization (TVR) ▪ Target lesion revascularization (TLR) ▪ Changes from Baseline in Rutherford Classification ▪ Changes from Baseline in Ankle Brachial Index (ABI) measurement ▪ Changes from Baseline in the Peripheral Artery Questionnaire (PAQ) ▪ Changes from Baseline in the EQ-5D-3L quality of life questionnaire ▪ Changes from Baseline in the Walking Impairment Questionnaire (WIQ) ▪ Tack Integrity via X-ray (only performed at 12 month visit) ▪ Duplex Ultrasound (DUS) derived lesion and vessel patency (performed at each visit through 12 months)
Inclusion Criteria:	Subject must meet all of the following inclusion criteria to be eligible for enrollment: 1. Male or non-pregnant Female ≥ 18 years of age at the time of consent 2. Female subjects of childbearing potential must have a negative pregnancy test prior to treatment and must use some form of contraception (abstinence is acceptable) through the duration of the study 3. Target limb requires no additional treatment aside from the target lesion and the iliac artery(ies) during the index procedure 4. Subject has been informed of and understands the nature of the study and provides signed informed consent to participate in the study. If the subject possesses the ability to understand and provide informed consent but due to physical inability, the subject cannot sign the ICF, an impartial witness may sign on behalf of the subject 5. Willing to comply with all required follow-up visits 6. Rutherford Classification 2, 3 or 4 7. Estimated life expectancy >1 year 8. Eligible for standard surgical repair, if necessary 9. Subject is ambulatory (assistive devices such as a cane or walker is acceptable).
Angiographic Inclusion Criteria:	1. Reference vessel diameter is between 2.5 mm and 6.0 mm, inclusive (by visual estimate), and able to be treated with the Study Device implant

	2. Ability to cross a guidewire (antegrade) through target lesion 3. Has a de novo or non-stented restenotic target lesion indicated for PTA treatment with a standard or FDA-approved Lutonix drug-coated balloon catheter that meets the following criteria below: a. 70% to 99% stenosis with a total lesion length of ≥20mm and ≤150mm in length (by visual estimate) or; b. 100% occluded with a total lesion length ≤100mm (by visual estimate) Notes: A tandem lesion, defined as a lesion comprised of diseased and healthy segments, is eligible if the healthy segments are each not more than 30mm in length and all other criteria, including 3a and 3b above, are met A combination lesion, defined as a continuous lesion with both non-occluded and 100% occluded segments, is eligible if the lesion can be treated as a single lesion and all other criteria, including 3a and 3b above, are met c. A non-stented restenotic lesion must meet the following criteria: i. Meets criteria 3a and 3b ii. No part of the target lesion has been previously treated with a drug-coated balloon iii. No part of the target lesion has had more than 2 previous PTA failures iv. >90 days from most recent angioplasty treatment 4. Target lesion is in the superficial femoral artery (SFA) and/or proximal popliteal artery (above the knee), located ≥1 cm below the common femoral artery (CFA) bifurcation to the distal segment of the proximal popliteal (P1) artery at the superior end of the patella 5. Presence of at least one patent (<50% DS) infrapopliteal vessel that has not been revascularized prior to index procedure 6. After PTA treatment, the target lesion has <30% residual DS *and* presence of at least one post-PTA dissection (Type A-F) (by visual estimate) 7. No evidence of aneurysm or acute thrombus in target vessel
Exclusion Criteria:	Subject must NOT meet any of the following exclusion criteria to be eligible for enrollment: 1. Rutherford Classification 0, 1, 5 or 6 2. Is pregnant or refuses to use contraception through the duration of the study 3. Previous infrainguinal bypass graft in the target limb 4. Planned amputation on the target limb

	5. Systemic infection or Infection within the target limb and/or immunocompromised 6. Endovascular or surgical procedure (not including diagnostic procedures) on the target limb within 30 days prior to or within 30 days after the index procedure 7. Endovascular or surgical procedure (not including diagnostic procedures) on the non-target limb within 14 days prior to the index procedure or planned procedure within 30 days after the index procedure 8. Prior coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI) procedure within 30 days prior to the index procedure or planned CABG/PCI within 30 days after the index procedure 9. Any other previous or planned surgical or endovascular procedure (not including diagnostic procedures) within 14 days prior to or 30 days post index procedure 10. Planned atherectomy, cryoplasty, stenting or any other treatment (with the exception of a crossing device) of the target lesion other than PTA during the index procedure 11. Known coagulopathy, hypercoagulable state, bleeding diathesis, other blood disorder, or a platelet count less than 80,000/microliter or greater than 500,000/microliter. 12. Known hypersensitivity or allergy to antiplatelet or anticoagulant therapy 13. Myocardial infarction within 30 days prior to enrollment 14. History of stroke within 90 days prior to enrollment 15. Serum creatinine of >2.5 mg/dL 16. Requires treatment of tibial or outflow vessels at the index procedure, which include the P2 and P3 segments of the popliteal artery and the tibioperoneal vessels. 17. Known hypersensitivity or contraindication to nickel-titanium alloy (Nitinol) 18. Participating in another ongoing investigational clinical trial that has not completed its primary endpoint 19. Has other comorbidities that, in the opinion of the investigator, would preclude them from receiving this treatment and/or participating in study-required follow-up assessments 20. Known hypersensitivity or allergy to contrast agents that cannot be medically managed 21. Thrombolysis of the target vessel within 72 hours prior to the index procedure, where complete resolution of the thrombus was not achieved

Angiographic Exclusion Criteria:	1. Retrograde crossing through target lesion 2. Acute vessel occlusion or acute or sub-acute thrombosis in target lesion 3. Subject has significant stenosis (≥50% stenosis) or occlusion of ipsilateral inflow iliac artery not successfully treated (<30% residual DS and without complication) prior to PTA of target vessel 4. Angiographic evidence of calcification severe enough that it renders the target lesion non-dilatable and/or has ≥5cm (visual estimate) of circumferential calcification 5. The target lesion shows no dissections after PTA 6. Presence of residual diameter stenosis ≥30% after PTA (based on visual estimate) 7. Non-target limb requiring any vascular treatment at time of index procedure 8. Previously implanted stent in the target vessel

3. STUDY MANAGEMENT CONTACT LIST

Sponsor:	Intact Vascular. Inc. 150 Strafford Avenue #303 Wayne, PA 19087 USA Fax: 1 (484) 253-1047 Marc Penna, VP of Clinical Affairs Mobile : 1 (978) 760-0311 E-mail : mpenna@intactvascular.com Catherine Seme, Project Manager Mobile : 1 (732) 330-3843 E-mail : cseme@intactvascular.com
Medical Monitor:	Dennis Donohoe, M.D. Telephone: 1 (215) 499-4458 Email: ddonohoe@intactvascular.com
Medical Research Organization (MRO) / Data Management:	NAMSA (Clinical Research Services) 4050 Olson Memorial Highway, Suite 450 Minneapolis, Minnesota 55422 1 (866)-666-9455
Principal Investigator (US):	William A. Gray, MD System Chief, Division of Cardiovascular Services, Main Line Health President, Lankenau Heart InstituteLankenau MOB East Suite 356 100 Lancaster Avenue Wynnewood, PA 19096 Telephone: 484-476-2684 Email: GrayW@mlhs.org
Angiographic / X-Ray Core Lab, DSMB, CEC:	Yale Cardiovascular Research Group One Church Street, Suite 330 New Haven, CT 06510 Tel: 203-737-3427 Fax: 203-737-7457
Duplex Ultrasound Core Lab:	VasCore Massachusetts General Hospital One Bowdoin Square, 10th Floor Boston, MA 02114 Office: (617) 726-5552 Fax: (617) 726-1977

4. INTRODUCTION

4.1. BACKGROUND AND RATIONALE

Peripheral artery disease (PAD) is a chronic occlusive artery disease caused by plaque buildup in the arterial lumen which leads to diminished blood flow. Clinical symptoms include pain while walking or in more severe cases rest pain or tissue loss. In the most extreme cases amputations can occur. Lower extremity PAD remains one of the most unrecognized manifestations of systemic arteriosclerosis estimated to affect between 3% and 7% of the population and up to one in five patients above the age of 75.[1] Approximately 15-30% of patients with lower extremity PAD will progress from intermittent claudication to critical limb ischemia (CLI) over the course of their disease.[2,3] Critical limb ischemia remains a significant problem associated with morbidity and mortality. As a result, physicians continue to explore revascularization strategies that include endovascular therapies and arterial bypass surgery.

Endovascular therapies for lower extremity treatment are well accepted by both patients and physicians due to the less invasive approach. However, there is uncertainty regarding the best endovascular treatment strategy for symptomatic patients with atherosclerotic disease of the superficial femoral (SFA) and popliteal arteries.[4] The goal in treating patients with PAD is to provide relief of symptoms. In the more advanced cases, the goal is to preserve tissue or limb salvage. Surgery has long been considered the gold standard treatment when medical therapy and behavior modification has failed. Advances over the last decade in both interventional techniques and improvement of medical device technology have led to acute treatment success and durability of less invasive endovascular therapy. With these improvements, endovascular therapy is becoming a first-line therapy to treat patients with PAD.[5]

Per the current TASC guidelines (TASC II)[6] balloon angioplasty (Percutaneous Transluminal Angioplasty or PTA) is recommended as the primary option for endovascular treatment of symptomatic femoropopliteal lesions (TASC II A and B lesions). Generally, angioplasty (PTA) is the preferred initial treatment in patients with disabling claudication or femoropopliteal stenosis or occlusion and in those with chronic critical ischemia and a stenosis.[7] This is primarily because PTA is less invasive and has lower morbidity and mortality risks than bypass surgery. The use of stents is reserved for salvage therapy when balloon dilations is suboptimal or fails.[8]

[1] Davies M, Waldman D, Peterson T. Comprehensive Endovascular Therapy for Femoropopiteal Arterial Atherosclerotic Occlusive Disease. J Am Coll Surg. 2005;201(2):275-96.
[2] Dormandy J, Mahir M, Ascady G., Balsano F, De Leeuw P, Blomberg P, Bousser MG, Clement D, Coffman J, Deutschinoff A, et al. Fate of the patient with chronic leg ischemia: a review article. J Cardiovasc (Torino). 1989;30:50-57.
[3] McDaniel MD, Cronenwett JL. Basic data related to the natural history of intermittent claudication. Ann Vasc Surg. 1989;3:273-277.
[4] Laird JR, Katzen BT, Scheinert D, Lammer J, Carpenter J, Buchbinder M, Dave R, Ansel G, Lansky A, Cristea E, Collins TJ, Goldstein J, Jaff MR; RESILIENT Investigators. Nitinol stent implantation versus balloon angioplasty for lesions in the superficial femoral artery and proximal popliteal artery: twelve-month results from the RESILIENT randomized trial. Circ Cardiovasc Interv. 2010;3:267-76.
[5] Zeller T. Current State of Endovascular Treatment of Femoro-Poplital Artery Disease. Vasc Med. 2008;12:223-34.
[6] Zeller T. Current State of Endovascular Treatment of Femoro-Poplital Artery Disease. Vasc Med. 2008;12:223-34.
[7] Hunink MG, Wong JB, Donaldson MC, Meyerovitz MF, de Vries JA, Harrington DP. Revascularization for femoropopliteal disease: a decision and cost-effectiveness analysis. JAMA. 1995;274(2):165-171.
[8] Tepe G, Zeller T, Schnorr B, Claussen CD, Beschorner U, Brechtel K, Scheller B, Speck U. High-Grade, Non-Flow-Limiting Dissections Do Not Negatively Impact Long-Term Outcome After Paclitaxel-Coated Balloon Angioplasty: An Additional Analysis From the THUNDER Study. J Endovasc Ther. 2013;20:792-800.

To understand the effectiveness of PTA alone, a full literature review was conducted by Intact Vascular. Information was compiled from review articles, meta-analyses and more recent randomized controlled trials where PTA was often the control group in peripheral stent device trials. While there was great inconsistency in the type of data reported and the outcomes measured, typically primary patency was reported. Primary patency was considered reported when at a minimum the study defined it as maintenance of hemodynamic and symptomatic improvement after angioplasty without further intervention. The review of PTA results determined that while primary patency at early time periods was high (71%-91% at 6 months) the longer term results decreased progressively over time beginning at one year (0%-87%) through five years (38%-62%). A similar review was conducted on PTA completed with drug-coated balloons (DCBs). This assessment determined that there are improved patency rates with the use of DCBs which were most pronounced at the 6 month time point (72% vs 49%; DCB vs PTA), but were maintained through one year (65.2%-67% vs 52.6%-55%; DCB vs PTA) and two years (57% vs 40%; DCB vs PTA).

As with all medical interventions, there are risks associated with the use of PTA in the femoropopliteal arteries that may lead to sub-optimal results and likely contribute to the large range associated with efficacy results. The guidelines and clinical research do not provide a clear definition of angioplasty failure, however one cause of suboptimal results is post-PTA arterial dissection. Limited information is available on the effect of dissection on angiographic and clinical outcomes after peripheral artery interventions. One reason for the lack of reported data in peripheral studies is that much of the methodology and approaches for treating dissections were initially developed within the practice of coronary angioplasty. The techniques and practices developed in the coronary field were adopted over to peripheral PTA. At this time, there is no peripheral specific system available for classification of post-PTA dissections and no defined treatment paradigms.

In order to determine the incidence and characteristics of peripheral dissections, the associated literature related to femoropopliteal PTA was investigated in detail. The reported rates for dissection as assessed either through angiographic assessment or IVUS was 7.4%-88%. In some instances, the approach to treat dissections is use of "Bailout" stents. Reported rationale for their use in the femoropopliteal segments are for suboptimal angiographic result or flow-limiting dissection and their reported use ranges from 6%-72.9%. In an additional analysis comparing the use of DCB to standard PTA, similar results were noted. The rate of dissection in comparative trials reported ranged from 19%-63.7% in DCB cases and 18%-73.5% of PTA cases and bail-out stenting for dissection was performed at a rate of 2.5%-8.9% for DCB and 6.9%-14.3% for PTA. Bailout stenting was typically performed with bare metal nitinol stents; however the type was generally not defined.

Two studies were identified that discussed the incidence of dissections and associated clinical implications in the peripheral vasculature in more detail. First is the EPISODE study.[9,10] The first preliminary study in this series indicated that IVUS data obtained following PTA may predict whether a patient is likely—or not—to have a long-term, event-free outcome. Per the

[9] Gussenhoven EJ, van der Lugt A, Pasterkamp G, van den Berg FG, Sie LH, Vischjager M, The SHK, Li W, Pieterman H, can Urk H. Intravascular Ultrasound Predictors of Outcomes After Peripheral Balloon Angioplasty. Eur J Endovasc Surg. 1995;10:279-288.
[10] van der Lugt, Gussenhoven EJ, Mali WPTM, Reekers JA, Seelen JL, Tielbeek AV, Pieterman H. Effect of Balloon Angioplasty in Femoropopliteal Arteries Assessed by Intravascular Ultrasound. Eur J Endovasc Surg. 1997; 13:549-556

authors "Failure is more likely to occur in the presence of a large dissection and a small residual free lumen area and diameter evidenced following PTA."[11] A follow-up study investigated the potential role of intravascular ultrasound (IVUS) in assessing the outcome in patients undergoing percutaneous transluminal angioplasty (PTA) of the superficial femoral artery. After PTA, vascular damage was seen at the target site in 72% of arteries, plaque rupture in 26%, dissection in 57%(45% of all cross sections and 88% in all dilated segments) and media rupture in 17%.

The second study to be discussed in detail is the THUNDER trial.[12] The THUNDER trial was a prospective, randomized double-blinded controlled German multicenter study on the efficacy of local paclitaxel delivered by a drug coated balloon for prevention of restenosis in the superficial femoral and popliteal arteries. The study performed an analysis of outcomes after dissection. Within the study, the overall rate of dissection with PTA intervention was 56%. Note that stents were to be used in cases of residual stenosis (>50%) or in the case of flow-limiting dissection. There were two cases of flow limiting dissection and in each case stents were placed. In all other cases of non-flow-limiting dissections, no additional interventions were performed.

For analysis of outcomes after dissection, the THUNDER data were reviewed by a blinded and independent core lab. The lab used the National Heart, Lung and Blood Institute (NHBLI) classification system for intimal tears (applies to angiographic assessments). This system which was developed by the Coronary Angioplasty Registry grades intimal disruption as A to F based on angiographic appearance. The dissection rates by type for the normal PTA arm of the study are presented below in **Table 1**.

Table 1: Femoropopliteal Dissection-THUNDER Trial Reported Rates

Dissection Type	Percentage
A[13]	12%
B	52%
C	6%
D	28%
E	2%
F[14]	0%

Similar results were observed in a clinical trial conducted by Intact Vascular. The TOBA study was conducted in Europe to collect confirmatory data in support of the safety and performance of the Intact Vascular Tack Endovascular System™. In the study, operators routinely underestimated the severity of dissections. In each instance, dissections were reported by site through post-treatment documentation. Each angiogram underwent a post-procedure review by an independent core lab. A comparison of the site reported data and the core lab reported data for dissections is presented in **Table 2**.

[11] Gussenhoven EJ, van der Lugt A, Pasterkamp G, van den Berg FG, Sie LH, Vischjager M, The SHK, Li W, Pieterman H, can Urk H. Intravascular Ultrasound Predictors of Outcomes After Peripheral Balloon Angioplasty. Eur J Endovasc Surg. 1995;10:279-288.
[12] Tepe G, Zeller T, Schnorr B, Claussen CD, Beschorner U, Brechtel K, Scheller B, Speck U. High-Grade, Non-Flow-Limiting Dissections Do Not Negatively Impact Long-Term Outcome After Paclitaxel-Coated Balloon Angioplasty: An Additional Analysis From the THUNDER Study. J Endovasc Ther. 2013;20:792-800.
[13] Approximated from study tables
[14] There were two cases of flow-limiting dissection in the study population; however they were not included in the assessment as in each case they were treated with a stent

Table 2: Femoropopliteal Dissections—TOBA Reported Results				
Dissection Type	**Site Reported (n=128)**		**Core Lab Reported (n=127)**	
	Number	**Percentage**	**Number**	**Percentage**
A	56	43.8%	6	4.7%
B	38	29.7%	24	18.9%
C	21	16.4%	79	62.2%
D	9	7.0%	15	11.8%
E	3	2.3%	0	0.0%
None	1	0.8%	3	2.4%

The findings were consistent with the THUNDER study and demonstrate, that dissections are often worse than they are observed at the time of the intervention. In this instance, the majority of site reported dissections were Grade A or B; however after Core Lab evaluation, they were often higher grade. In fact, the operator reported data only reported 25.7% grade C or higher dissections in contrast to the 74% value determined by the core lab.

To fully understand the impact of post-PTA dissections, investigation is required on their associated potential clinical implications. Because of higher incidence of complications due to dissections, their impact on clinical outcome has been an important issue in percutaneous coronary interventions. More severe dissections seem to be associated with higher restenosis rates and early occlusions.[15] The most comprehensive assessment of clinical implications in the peripheral vasculature was the previously discussed in the THUNDER study. Angiographic analysis of study patients included angiograms from before and after the intervention and from the 6-month follow-up. The primary clinical outcome was TLR at 6- and 24- month time points. The parameters assessment were late lumen loss (LLL), minimum lumen diameter (MLD) and an area analysis to evaluate the entire longitudinal luminal area of the vessel dilated. There were no significant differences in the post-procedure angiographic parameters between patients with grades A or B dissection vs. grade C, D, or E (although the degree of residual stenosis (Narrowing) tended to be larger with higher grade dissections).

The THUNDER study concluded that untreated dissections were observed to be correlated with increased complications and with decreased long-term patency. For all dissection grades, clinical implications were noted in patients with observed dissections. To further understand the implications, the literature results were reviewed and compiled to compare to the extent possible the clinical/angiographic results of PTA with no post-procedure dissections (from general literature references) to those of post-PTA dissection (from the THUNDER Trial) in the femoropopliteal arteries. Only one time period had defined data for both subsets (6 months). These results are summarized in **Table 3**.

Table 3: Comparison of 6 month Angiographic Data				
	PTA[16]	**Dissection Grade A/B**	**Dissection Grade C/D/E**	**All Dissection**

[15] Tepe G, Zeller T, Schnorr B, Claussen CD, Beschorner U, Brechtel K, Scheller B, Speck U. High-Grade, Non-Flow-Limiting Dissections Do Not Negatively Impact Long-Term Outcome After Paclitaxel-Coated Balloon Angioplasty: An Additional Analysis From the THUNDER Study. J Endovasc Ther. 2013;20:792-800.
[16] PTA without noted dissection per literature references

Binary restenosis[17]	43%[18]	50%	62%	55%
Patency (extrapolated from restenosis data)	71%-91%	50%	38%	45%
Late Lumen Loss (mm)	NA	1.6±1.7	2.4±1.78	1.9±1.7
Target Lesion Revascularization	10.5%	33%	44%	37%

The results in **Table 3** suggest that even with low grade dissections (Type A/B) clinical implications may be observed with lower patency rates than those observed for PTA and higher rates of TLR when compared to PTA without dissections. While these results are more pronounced for C/D/E dissections, the clinical impact of all dissections is notable. Primary patency was lower and target lesion revascularization higher for the patient population with observed dissections.

Based on the clinical and literature reported data indicative of an under-reporting of higher grade dissections and the clinical links to observed lower patency rates, there exists a clinical need to provide for focal treatment of post-PTA non-flow-limiting dissections in addition to those that are flow-limiting. The Tack Endovascular System is designed to provide a treatment option for all grade dissections.

5. INVESTIGATIONAL DEVICE

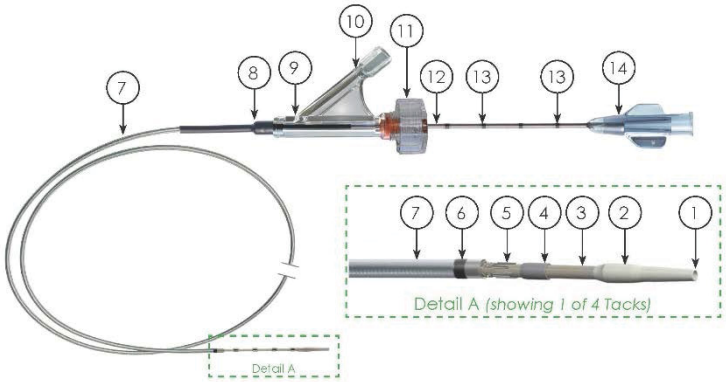
5.1. DESCRIPTION

The Tack Endovascular System is an endovascular device system designed to treat vascular dissections with Tack implants following angioplasty in the superficial femoral and proximal popliteal arteries, ranging 2.5 mm to 6.0 mm in diameter. The 6F (2.0 mm) catheter contains 6 independent self-expanding Tacks made of a nickel titanium alloy (Nitinol). When deployed, the Tack implants are designed to treat acute dissections of the inner wall or lining of an artery by Tacking the damaged tissue to the inner luminal surface through a low outward radial force.

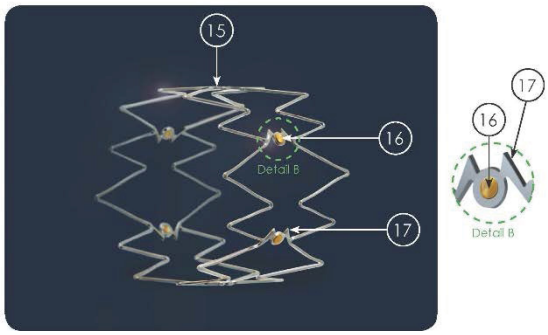
The Tack Endovascular System consists of 6 self-expanding Nitinol Tacks and a 6F Delivery Catheter (See **Figure 1**). The numbers in parentheses in the following section refer those in **Figure 1** below.

Figure 1. The Tack Endovascular System

[17] ≥50%
[18] For the one PTA that reported restenosis at 6 months, all patients were Rutherford Class 4-6 which would likely correlate with a higher restenosis rate



1. Guidewire Lumen
2. Distal Tip
3. Inner Core Shaft
4. Distal Inner Core Marker
5. Crimped Tack
6. Target Band (Outer Sheath RO Marker)
7. Outer Braided Sheath
8. Strain Relief
9. Bifurcation Luer
10. Side port
11. Hemostatic Valve
12. Inner Core Shaft
13. Proximal Inner Core Markers
14. Guidewire Port
15. Unconstrained Tack
16. Middle RO Marker
17. Anchor



The Tacks are approximately 6mm in length and expand to an unconstrained diameter of 7.3 mm (See **Table 4** below). The Tack implants are designed with a relatively flat chronic outward force curve and may be used across all reference vessel diameters (RVDs) ranging from 2.5 to 6.0mm. Six Radiopaque (RO) Markers (16) as well as six pairs of Anchors (17) are located around the centerline of each Tack implant. The anchors assist in maintaining proper Tack implant position.

Table 4. Tack Length at Various Diameters

Diameter	Length
1.8 mm (Constrained Tack)	6.5 mm
2.5 mm RVD (Deployed Tack)	6.4 mm
6.0 mm RVD (Deployed Tack)	6.2 mm
7.3 mm (Unconstrained Tack)	6.1 mm

The delivery catheter has an effective length of 120cm. The 6F Outer Braided Sheath (7), which constrains the Tack implants, is bonded proximally to the Bifurcation Luer (9) within the Strain Relief (8). The Hemostatic Valve (11) is integrated proximally to the Bifurcation Luer. The Inner Core Shaft (3) slides within the Hemostatic Valve and has seven Proximal Inner Core Markers (13). The number of visible reference marks corresponds to the number of undeployed Tack implants remaining in the distal end of the delivery system. A soft, tapered Distal Tip (2) is bonded to the distal end of the Inner Core Shaft for ease of advancement in the blood vessel. Constrained within the Outer Braided Sheath, each self-expanding Tack implant is positioned on the Inner Core Shaft (3) between two radiopaque Distal Inner Core Markers (4) spaced approximately 7mm apart. A 1mm radiopaque Target Band (6) is located on the distal end of the Outer Braided Sheath.

The catheter is flushed prior to the procedure through the side port of the Bifurcation Luer and the Guidewire Port. Tack implant positioning is achieved prior to deployment by using as reference the Middle RO Markers on the Tack implant and the Target Band on the outer sheath. During Tack implant deployment; the Hemostatic Valve is unlocked by rotating the valve counter-clockwise. The Tack implants are individually unsheathed by pinning the Proximal Inner Core Shaft and pulling back on the outer sheath the distance between proximal inner core markers. After each deployment, the Hemostatic Valve is locked by rotating the valve clockwise, ensuring that the proximal edge of the Target Band is secured directly over a Distal Inner Core Marker. Between deployments, both the proximal inner core markers and the distal inner core markers serve to visually represent the number of remaining Tack implants in the delivery catheter.

5.2. PRINCIPLES OF OPERATION

A peripheral intervention of the lower extremity arteries, such as balloon angioplasty to treat stenotic or occluded arteries is performed, which would include dilatation of the artery at the target site to its full intended arterial diameter. A post-PTA angiogram is done to assess the results of the angioplasty. If optimal angioplasty results are not achieved due to one or more dissections in a lesion with less than 30% residual diameter stenosis (DS), the patient may be a candidate for treatment with the Tack Endovascular System.

Once a treatment area has been identified for the Tack Endovascular System, a 0.035" guidewire is inserted into the 6F percutaneous angiographic sheath and advanced to the targeted treatment site. The delivery catheter is then advanced to the treatment site using fluoroscopic guidance. Each Tack is deployed independently at the desired location by retracting the distal sheath which contains the constrained Tacks.

Note: For a full device and procedural description, please refer to the Instructions for Use (IFU).

5.3. INTENDED USE

The Tack Endovascular System is intended for use in the superficial femoral and proximal popliteal arteries ranging in diameter from 2.5mm to 6.0mm for the repair of post percutaneous transluminal balloon angioplasty dissection(s) type(s) A through F.

6. CLINICAL STUDY OBJECTIVES

6.1. PRIMARY ENDPOINTS

Safety: Freedom from the occurrence of any new-onset major adverse event(s) (MAEs) defined as index limb amputation (above the ankle), CEC adjudicated clinically-driven target lesion revascularization (CD-TLR), or all-cause death at 30 days.

Efficacy**:** Primary patency defined as freedom from CEC adjudicated clinically-driven target lesion revascularization (CD-TLR) and freedom from core lab adjudicated duplex ultrasound derived binary restenosis at 12 months (defined as PSVR ≥2.5).

6.2. OBSERVATIONAL ENDPOINTS

Device Success: Successful deployment of the Tack(s) at the intended target site(s) and successful withdrawal of the delivery catheter. If the study device is introduced but the subject does not receive a Tack due to user error and not a device malfunction, this device will not be included in the device success assessment.

Procedural Success: Demonstrated vessel patency (<30% residual DS, by visual estimate) without the use of a bailout stent or the occurrence of MAE upon completion of the index procedure.

The following will be assessed through 36 months:

- All-cause death
- Amputation of the target limb (above the ankle)
- Clinically-driven target vessel revascularization (CD-TVR)
- Clinically-driven target lesion revascularization (CD-TLR)
- Target vessel revascularization (TVR)
- Target lesion revascularization (TLR)
- Changes from Baseline in Rutherford Classification
- Changes from Baseline in Ankle Brachial Index (ABI) measurement
- Changes from Baseline in the Peripheral Artery Questionnaire (PAQ)
- Changes from Baseline in the EQ-5D-3L quality of life questionnaire
- Changes from Baseline in the Walking Impairment Questionnaire (WIQ)
- Tack Integrity via X-ray (only performed at 12 month visit)
- Duplex Ultrasound (DUS) derived lesion and vessel patency (performed at each visit through 12 months)

7. CLINICAL STUDY DESIGN

This is a prospective, multi-center, single-arm, non-blinded study designed to investigate the safety and efficacy of the Tack Endovascular System in subjects with post-balloon angioplasty (post-PTA) dissection(s) type(s) A through F in the superficial femoral and proximal popliteal arteries ranging in diameter from 2.5mm to 6.0mm.

7.1. INVESTIGATIONAL SITES

Subjects will be enrolled at up to 40 clinical sites throughout the United States and Europe (up to 5 European sites will participate).

7.2. SUBJECT POPULATION

Subjects with PAD who receive PTA (with a standard or FDA-approved Lutonix drug-coated balloon) in the SFA and proximal popliteal (P1) arteries and have a resulting dissection(s) type(s) A through F are eligible for enrollment. To be enrolled, subjects must meet all inclusion criteria and not meet any of the exclusion criteria.

7.3. ANTICIPATED NUMBER OF SUBJECTS

It is anticipated that up to 210 subjects will be enrolled. Each clinical site can enroll a maximum of 53 patients, establishing an enrollment cap at 25% of the subject sample size.

Intact Vascular will continuously monitor each enrolled subject receiving study device treatment following PTA with a standard balloon or the FDA-approved Lutonix drug-coated balloon (DCB). Treatment with a Tack following PTA with a DCB shall not exceed 60% of subjects enrolled.

7.4. CLINICAL STUDY DURATION & FOLLOW-UP

The follow-up duration for each enrolled subject is 36 months. Any subject who is enrolled but does not receive at least one Tack implant will be followed for 12 months and then exited from the study (see **Section 10.3.1**).

7.5. SUBJECT SELECTION

7.5.1. INCLUSION CRITERIA

Subjects must meet all the following Inclusion Criteria. The response for each criterion below must be "Yes":

1. Male or non-pregnant Female ≥ 18 years of age at the time of consent
2. Female subjects of childbearing potential must have a negative pregnancy test prior to treatment and must use some form of contraception (abstinence is acceptable) through the duration of the study
3. Target limb requires no additional treatment aside from the target lesion and the iliac artery(ies) during the index procedure
4. Subject has been informed of and understands the nature of the study and provides signed informed consent to participate in the study. If the subject possesses the ability to understand and provide informed consent but due to physical inability, the subject cannot sign the ICF, an impartial witness may sign on behalf of the subject

5. Willing to comply with all required follow-up visits
6. Rutherford Classification 2, 3 or 4
7. Estimated life expectancy >1 year
8. Eligible for standard surgical repair, if necessary
9. Subject is ambulatory (assistive devices such as a cane or walker is acceptable).

7.5.2. ANGIOGRAPHIC INCLUSION CRITERIA

Subjects must meet all the following Angiographic Inclusion Criteria. The response for each criterion below must be "Yes":

1. Reference vessel diameter is between 2.5 mm and 6.0 mm, inclusive (by visual estimate), and able to be treated with the Study Device implant
2. Ability to cross a guidewire (antegrade) through target lesion
3. Has a de novo or non-stented restenotic target lesion indicated for PTA treatment with a standard or FDA-approved Lutonix drug-coated balloon catheter that meets the following criteria below:
    a. 70% to 99% stenosis with a total lesion length of ≥20mm and ≤150mm in length (by visual estimate) or;
    b. 100% occluded with a total lesion length ≤100mm (by visual estimate)

       Notes:

       A tandem lesion, defined as a lesion comprised of diseased and healthy segments, is eligible if the healthy segments are each not more than 30mm in length and all other criteria, including 3a and 3b above, are met

       A combination lesion, defined as a continuous lesion with both non-occluded and 100% occluded segments, is eligible if the lesion can be treated as a single lesion and all other criteria, including 3a and 3b above, are met
    c. A non-stented restenotic lesion must meet the following criteria:
        i. Meets criteria 3a and 3b
        ii. No part of the target lesion has been previously treated with a drug-coated balloon
        iii. No part of the target lesion has had more than 2 previous PTA failures
        iv. >90 days from most recent angioplasty treatment
4. Target lesion is in the superficial femoral artery (SFA) and/or proximal popliteal artery (above the knee), located ≥1 cm below the common femoral artery (CFA) bifurcation to the distal segment of the proximal popliteal (P1) artery at the superior end of the patella
5. Presence of at least one patent (<50% DS) infrapopliteal vessel that has not been revascularized prior to index procedure
6. After PTA treatment, the target lesion has <30% residual DS *and* presence of at least one post-PTA dissection (Type A-F) (by visual estimate)
7. No evidence of aneurysm or acute thrombus in target vessel

7.5.3. EXCLUSION CRITERIA

Subjects must not meet any of the following Exclusion Criteria. The response for each criterion below must be "No":

1. Rutherford Classification 0, 1, 5 or 6
2. Is pregnant or refuses to use contraception through the duration of the study
3. Previous infrainguinal bypass graft in the target limb
4. Planned amputation on the target limb
5. Systemic infection or Infection within the target limb and/or immunocompromised
6. Endovascular or surgical procedure (not including diagnostic procedures) on the target limb within 30 days prior to or within 30 days after the index procedure
7. Endovascular or surgical procedure (not including diagnostic procedures) on the non-target limb within 14 days prior to the index procedure or planned procedure within 30 days after the index procedure
8. Prior coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI) procedure within 30 days prior to the index procedure or planned CABG/PCI within 30 days after the index procedure
9. Any other previous or planned surgical or endovascular procedure (not including diagnostic procedures) within 14 days prior to or 30 days post index procedure
10. Planned atherectomy, cryoplasty, stenting or any other treatment (with the exception of a crossing device) of the target lesion other than PTA during the index procedure
11. Known coagulopathy, hypercoagulable state, bleeding diathesis, other blood disorder, or a platelet count less than 80,000/microliter or greater than 500,000/microliter.
12. Known hypersensitivity or allergy to antiplatelet or anticoagulant therapy
13. Myocardial infarction within 30 days prior to enrollment
14. History of stroke within 90 days prior to enrollment
15. Serum creatinine of >2.5 mg/dL
16. Requires treatment of tibial or outflow vessels at the index procedure, which include the P2 and P3 segments of the popliteal artery and the tibioperoneal vessels.
17. Known hypersensitivity or contraindication to nickel-titanium alloy (Nitinol)
18. Participating in another ongoing investigational clinical trial that has not completed its primary endpoint
19. Has other comorbidities that, in the opinion of the investigator, would preclude them from receiving this treatment and/or participating in study-required follow-up assessments
20. Known hypersensitivity or allergy to contrast agents that cannot be medically managed
21. Thrombolysis of the target vessel within 72 hours prior to the index procedure, where complete resolution of the thrombus was not achieved

7.5.4. ANGIOGRAPHIC EXCLUSION CRITERIA

Subjects must not meet any of the following Angiographic Exclusion Criteria. The response for each criterion below must be "No":

1. Retrograde crossing through target lesion
2. Acute vessel occlusion or acute or sub-acute thrombosis in target lesion
3. Subject has significant stenosis (≥50% stenosis) or occlusion of ipsilateral inflow iliac artery not successfully treated (<30% residual DS and without complication) prior to PTA of target vessel
4. Angiographic evidence of calcification severe enough that it renders the target lesion non-dilatable and/or has ≥5cm (visual estimate) of circumferential calcification
5. The target lesion shows no dissections after PTA
6. Presence of residual diameter stenosis ≥30% after PTA (based on visual estimate)
7. Non-target limb requiring any vascular treatment at time of index procedure
8. Previously implanted stent in the target vessel

8. TREATMENT PLAN

8.1. TIME AND EVENTS SCHEDULE

All subjects will receive the assessments at specific time points as listed in **Table 5** below.

Table 5. Time and Events Schedule

Assessment	Baseline[1]	Implant Procedure	Pre-Discharge	30-day (-2 days/ +14 Days)	6 Month (±30 Days)	12 Month (± 30 Days)	24 Month (± 30 Days)	36 Month (± 30 Days)	Unscheduled[7]
Informed Consent	X[2]								
Medical History / Physical Exam	X								
Serum Creatinine	X								
PT/ INR[3]	X								
Urine pregnancy test if female[4]	X								
Ankle Brachial Index (ABI)	X		X[10]	X	X	X	X	X	X
Rutherford Classification	X			X	X	X	X	X	X
Pre-procedural Medications		X							
Angiogram		X							X[9]
Study Medications		X	X	X	X	X	X	X	X
Duplex Ultrasound (DUS)[5]				X	X	X			X[9]
X-ray of Implanted Tacks[6]						X[8]			X[9]
Adverse Event Assessment		X	X	X	X	X	X	X	X
Peripheral Artery Questionnaire (PAQ)	X			X	X	X	X	X	X
EQ-5D-3L	X			X	X	X	X	X	X
Walking Impairment Questionnaire (WIQ)	X			X	X	X	X	X	X

[1] Assessments may be done up to 30 days before the procedure, with the exception of a pregnancy test

[2] Consent to be obtained within 30 days prior to enrollment.

[3] PT/INR to be obtained only if subject is on chronic warfarin therapy.

[4] Negative urine pregnancy test within 7 days of the Index Procedure is required for women of childbearing potential.

[5] All scheduled DUS exams should be performed per the protocol established by the core lab. If a DUS is non-diagnostic (per the imaging protocol), the site should make every effort to obtain a repeat exam within the visit window.

[6] Assessment of Tack Integrity. All required and unscheduled X-ray exams should be performed in accordance with the core lab protocol.

[7] Unscheduled visit data should be captured for a target limb related adverse event or intervention to target limb. If intervention to the target limb occurs, the data for assessments performed prior to the interventional procedure should be recorded in the eCRF.

[8] Only required for subjects in whom at least one Tack was placed during the index procedure.

[9] If clinically indicated or per standard of care.

[10] Pre-discharge ABI may be assessed up to 72 hours post-index procedure.

NOTE: All imaging of the target limb acquired during scheduled and unscheduled visits (such as Angiogram, DUS or X-Ray) should be submitted to the respective core lab within 3 days of occurrence.

8.2. PRE-SCREENING

All subjects presenting to the institution with known superficial femoral and/or proximal popliteal artery disease requiring balloon angioplasty (standard or drug-coated balloon) will be screened for initial eligibility. A trained member of the research team shall perform a preliminary evaluation of the potential subject's medical history and screen for initial eligibility. If during the pre-screening the subject is found to meet one or more exclusion criteria, the subject would be considered a "pre-screen failure". No further action would be taken for pre-screen failure subjects. If determined eligible per initial inclusion criteria, the subject will be approached by qualified research staff and informed about this study through the informed consent process.

8.3. OBTAINING INFORMED CONSENT

All sites shall comply with 21 CFR 50, provisions of ICH Good Clinical Practices (GCPs), local IRB/EC policy and all applicable local regulations for obtaining Informed Consent. Written informed consent using the most current IRB/EC-approved informed consent form (ICF) at the time of consent will be obtained for all subjects **prior** to any study-specific screening/baseline tests or procedures are performed. This does not include those procedures or tests that are obtained in the normal course of the subject's non-study related care and prior to undergoing the study procedure, but shall include previously performed tests that may need to be repeated in order to determine eligibility.

All subjects shall possess the ability to understand the information contained in the informed consent form. Subjects will have the study procedures explained in a manner as non-technical as possible, including the risks, benefits and follow-up requirements. If the subject agrees to participate in this study, the subject will personally sign and date the ICF. In the event that a subject possesses the ability to understand the informed consent process and participation in study, but due to physical inability cannot sign the ICF, an impartial witness may sign the ICF on behalf of the subject. Non-English speaking subjects may only be enrolled if they sign an IRB/EC approved and certified translated informed consent form document reflective of his/her spoken language.

Once all required parties have signed the ICF, subjects will receive copies of their signed informed consent documentation.

8.4. SCREENING SUCCESS AND FAILURE CRITERIA

Final eligibility of a subject will occur during the Index Procedure. Subjects undergoing an angiographic screen must provide prior informed consent. Every effort will be made to ensure eligibility of the participants prior to enrollment. If no angiographic exclusion criteria are met after pre-enrollment angioplasty, subjects will be considered eligible for enrollment. If at any point prior to or just after pre-enrollment angioplasty, an angiographic exclusion criteria is met, subjects will not be considered eligible for enrollment and will be documented as

"angiographic screen failures". No further follow-up will be required of these subjects, however; reason for angiographic failure shall be documented by the site into a screening log.

9. BASELINE EVALUATION

9.1. BASELINE ASSESSMENTS

The following assessments will be performed during baseline evaluation. These examinations and tests will be used both to screen eligible subjects and provide baseline information for those subjects that meet study criteria. All assessments must be completed within the 30 days prior to undergoing the index procedure, except for the urine pregnancy test which must be completed within 7 days of the index procedure with a negative result prior to receiving treatment.

- Demographic information and medical history including risk factors
- Physical examination
  - Height and weight
- Target Limb Resting Ankle Brachial Index (ABI)
- Rutherford Classification
- Serum creatinine (≤2.5 mg/dL for inclusion)
- PT & INR (if on chronic warfarin therapy), PLT count
- Urine pregnancy test if female of child-bearing age (within **7** days of procedure)
- Peripheral Artery Questionnaire (PAQ)
- EQ-5D-3L
- Walking Impairment Questionnaire (WIQ)
- Concomitant medications (antiplatelet/anticoagulants)

9.2. STUDY MEDICATIONS

See **Table 6** below for Study Medications

Table 6. Recommended Study Medications

Medication	Pre-Procedure	During Procedure	Post-Procedure
Aspirin	Loading dose if required, per institutional standard of care if not on chronic antiplatelet therapy	N/A	81-325 mg/QD indefinitely is recommended
Thienopyridine Class Agent[1]	Loading dose if required, per institutional standard of care if not on chronic antiplatelet therapy	N/A	75 mg/QD for a minimum of one month recommended[2]
Heparin	Dosage per institutional standard of care.	Achieve anticoagulation per hospital / institution standard of care[3]	N/A

[1] *Recommended Thienopyridine class agents include Clopidogrel, Ticlopidine or Prasugrel.*

[2] *Recommended daily dose for Clopidogrel. Respective regimen should be prescribed for other thienopyridine agents per Investigator discretion.*

[3] *An Activated Clotting Time (ACT) of ≥250s is recommended.*

10. INDEX PROCEDURE

10.1. INDEX BASELINE ANGIOGRAM

The Index Baseline Angiogram will be performed before Pre-Enrollment Balloon Angioplasty in order to assess baseline angiographic eligibility for inclusion as described in **Section 10.1.2** below. The angiogram is to be performed as per guidelines established by the independent core laboratory. Index procedure angiograms performed for all enrolled subjects will be reviewed by the core lab for specified data points (including identification of post-PTA dissections and associated type), as outlined in the angiographic core lab protocol.

10.1.1. PREPARATION

Procedural techniques will be in accordance with the institutional standard of care for balloon angioplasty of the superficial femoral and proximal popliteal arteries.

All subjects should receive the appropriate antiplatelet therapy per Table 6. Study Medications above (**Section 9.2**).

All sites will receive study devices containing a 120cm length delivery catheter to facilitate either contralateral or ipsilateral vascular access, per operator discretion.

Ruler Placement: A radiopaque ruler is placed directly on the subject's target limb under the sterile drapes. The end of the ruler should be placed at the tibial plateau. In any later assessments, including follow-up duplex and X-Ray evaluations, the process will be repeated

to identify the treatment location. All other measurements are referenced back to this angiographic measurement.

Refer to the Instructions for Use (IFU) for a description of the procedure.

10.1.2. Baseline Angiographic Requirements

Baseline angiographic measurements of the target lesion (visual estimate) shall be captured to determine eligibility and include, but are not limited to the following:

- Target Lesion Location (Prox. SFA, Mid SFA, Distal SFA, Prox. Popliteal [P1])
- Baseline Lesion Length
- Lesion type (Single, Combination or Tandem / De novo or Non-stented restenotic
- Reference Vessel Diameter (proximal and distal)
- Calcification Severity (None, Mild, Moderate or Severe)
- Baseline Diameter Stenosis (%)
    - Note: The number of subjects with total occlusions (100% occluded target lesion at baseline) will be closely monitored by the sponsor so as not to exceed 20% of subjects enrolled in the study. Once this rate has been reached, sites will be appropriately notified by the sponsor.
- Number of patent (<50% DS) infrapopliteal vessels to the ankle (must have at least one patent vessel that has not been revascularized to qualify for this study)
- Presence of thrombus

Subjects that are eligible for enrollment and present with bilateral stenosis (qualifying lesions in both limbs) may be enrolled under the following conditions:

- The more severe stenosis, per operator discretion, that is intended to be treated with only balloon angioplasty should be considered for enrollment.
- Per operator discretion, the non-target limb lesion can be treated by any appropriate clinical means other than the study device no less than 14 days prior to or 30 days after enrollment (Note: If the PI documents the need for planned intervention on contralateral limb at the time of the index procedure, it would not be considered an adverse event at time of occurrence if treated after enrollment, but this should not be less than 30 days post index procedure).

If subjects that are eligible for enrollment and present with bilateral stenosis are determined by the PI to require intervention during the same procedure, the subject should not be enrolled.

10.2. PRE-ENROLLMENT BALLOON ANGIOPLASTY

All consented subjects undergoing balloon angioplasty for possible enrollment into this study shall receive PTA treatment with a standard balloon or FDA-approved Lutonix drug-coated balloon.

Note: Requirements for pre-dilatation with a standard balloon (non-drug coated) preceding treatment with a DCB should be performed in accordance with the respective IFU. Once the DCB is introduced, inflations should be performed according to recommendations below for balloon angioplasty. Operators should follow these recommendations unless patient safety concerns present.

The recommendations for balloon inflation are as follows:

- The operator should select a balloon diameter that can be inflated to a ratio of 1.1:1 relative to the target lesion proximal RVD.
- The length of the balloon should be appropriate for the lesion length. When possible, a single balloon should be selected that extends across the entire lesion. If a DCB is being used, then the relevant instructions for use should be referenced for lesion lengths requiring multiple balloons.
- Balloon Inflation: Inflate the balloon and maintain inflation at the specified 1.1:1 diameter for a minimum of 60 seconds total (180 seconds is recommended).

Please refer to the Instructions for Use (IFU) for detailed instructions regarding Pre-Enrollment Balloon Angioplasty inflation recommendations.

10.2.1. POST-ANGIOPLASTY ANGIOGRAPHIC REQUIREMENTS

Final angiographic eligibility of subjects for study device treatment will be determined post pre-enrollment balloon angioplasty and include the following target lesion measurements (by visual estimate):

- Target lesion residual diameter stenosis <30%
- Presence of dissection(s)
- Presence of thrombus

In addition, other lesion measurements and balloon details will be recorded during Pre-Enrollment Balloon Angioplasty and include but are not limited to the following:

- Total number of dissection(s) visualized
- Dissection characteristics (by visual estimate) for each dissection visualized including;
    - Dissection Type (A through F)
    - Dissection Length
- Balloon Type (standard or drug-coated), Length, Diameter
- For each balloon inflation:
    - Inflation Duration(s) at Max Pressure

- Max Pressure (ATM)

10.3. STUDY DEVICE TREATMENT

Subjects that meet all inclusion and angiographic inclusion criteria, and do not meet any exclusion or angiographic exclusion criteria will be deemed eligible for Study Device Treatment.

10.3.1. ENROLLMENT (INTENT-TO-TREAT)

A subject is defined as an intent-to-treat (ITT) patient and officially enrolled in the study once the Tack Endovascular System is advanced through the introducer sheath. Subjects in whom at least one Tack is not placed, will be exited after 12 months. Subjects in whom at least one Tack is placed will be followed for 36 months.

In addition, the per-protocol (PP) population will be defined as ITT subjects with evaluable data that have met the definition for device success, excluding subjects with major deviations such as:

- A major inclusion/exclusion criterion deviation; or
- A major procedural deviation

The criteria for deviations meeting the classification of "major" will be defined before study endpoint data is available for statistical analysis. All major deviations will be adjudicated by an independent designee without visibility to study results.

10.3.2. TREATMENT RECOMMENDATIONS

The lesion considered for Tack placement is assessed with a minimum of two angiographic views, an anterior-posterior view and a 45 degree oblique view, for optimal visualization of the dissections. All dissections identified for treatment with the Tack will be categorized by type by the operator as described in **Section 10.2.1**. If there are no dissections present, the subject may not be enrolled and Tacks should not be placed.

Intact Vascular recommends deployment of a Tack to the distal edge of the target dissection. If additional Tack implants are required, the operator should continue proximally to the next planned deployment site. A minimum gap distance of 4.0mm between Tacks (end to end) is recommended. Overlapping Tack implants is not permitted.

Please refer to the Instructions for Use (IFU) for detailed instructions regarding recommended criteria for Tack Endovascular System placement.

10.3.3. POST-STUDY DEVICE TREATMENT MEASUREMENTS

The following information should be recorded Post-Study Device Treatment:

- Device Success
- Number of Device Systems used to treat subject and associated lot numbers
- Number of Tacks Deployed
    - Ruler location of each deployed Tack (From distal to proximal to measure distance between Tacks)

- Number of Tacks deployed to treat each dissection identified in **Section 10.2.1**

10.4. POST-DILATATION OF TREATED LESION (POST-STUDY DEVICE)

Post-dilatation of the target lesion is required in order to seat the anchors of the Tack.

10.4.1. RECOMMENDATIONS

After Tack placement, it is recommended that post-dilatation of all deployed Tacks be performed using the following criteria.

- The balloon size for post-dilatation should use the largest balloon diameter used during angioplasty prior to Tack placement.
- Post-Dilatation Duration at Max Pressure: A minimum 120 seconds.
- Post-dilatation balloon angioplasty should be performed with a new standard balloon catheter (non-drug coated) to reduce the risk of contact with deployed Tacks while advancing the balloon catheter into place.

Please refer to the Instructions for Use (IFU) for detailed instructions regarding post-Tack placement balloon angioplasty recommendations.

10.4.2. FINAL TREATMENT RESULTS

The following information should be recorded after post-dilatation and upon completion of index procedure:

- Details for balloon used for post-dilatation:
  - Type (standard or drug-coated), Length, Diameter
  - For each balloon inflation:
    - Inflation Duration(s) at Max Pressure
    - Max Pressure (ATM)
- Final residual diameter stenosis of target lesion treated with Tacks
- Bailout stent occurrence (post-study device treatment)
  - If applicable, bailout stent device details will be recorded
- Procedure time (defined as the time of insertion of introducer sheath to the time of withdrawal of last post-Tack dilatation PTA balloon catheter)
- Adverse event occurrence
- Procedural Success

10.5. BAILOUT STENTING OF TARGET LESION (POST-STUDY DEVICE)

The use of a bailout stent may occur in the event of persistent flow-limiting dissection not able to be treated with the Tack (or as otherwise required for safety of the subject). All enrolled subjects in whom at least one Tack is placed and receive a bailout stent will be followed for the duration of the study.

11. POST-PROCEDURE/PRE-DISCHARGE

All subjects will be assessed prior to discharge (Pre-Discharge) and shall receive a medical regimen for the medications required post-procedure per **Table 6** in **Section 9.2**. All concomitant medications (antiplatelet/anticoagulant) shall be captured in the CRF.

11.1. REQUIRED ASSESSMENTS

Assessments required at pre-discharge include the following:

- Target limb resting ABI Measurement (within 72 hours post-index procedure)
- Adverse event occurrence
- Study medication assessment

All subjects receiving treatment with a Tack should be provided with the Tack Endovascular System Patient Implant Card (PIC). The PIC is designed for the patient to carry along with their insurance cards. This PIC is to be completed by the designated research personnel to include information pertaining to the Tack device(s) including the model, lot number and location of the implanted Tack(s) and the date of the index procedure. The card also provides manufacturing information and MRI Compatibility.

12. REQUIRED FOLLOW-UP VISITS AND ASSESSMENTS

All subjects will be required to return for clinic follow-up visits as outlined in **Table 5** of **Section 8.1** and in the sections below.

12.1. 30-DAY FOLLOW-UP VISIT (-2 DAYS / +14 DAYS POST-INDEX PROCEDURE)

The following assessments are required to be performed at the 30-day follow-up visit:

- Rutherford Classification
- Target limb resting ABI
- Duplex ultrasound
- Peripheral Artery Questionnaire (PAQ)
- EQ-5D-3L
- Walking Impairment Questionnaire (WIQ)
- Major adverse event (MAE) occurrence
- Adverse event occurrence
- Review of concomitant medications (antiplatelets/anticoagulants)

12.2. 6 MONTH FOLLOW-UP VISIT (±30 DAYS POST-INDEX PROCEDURE)

The following assessments are required to be performed at the 6 month follow-up visit:

- Rutherford Classification
- Target limb resting ABI
- Duplex ultrasound
- Peripheral Artery Questionnaire (PAQ)
- EQ-5D-3L
- Walking Impairment Questionnaire (WIQ)
- Major adverse event (MAE) occurrence
- Adverse event occurrence
- Review of concomitant medications (antiplatelets/anticoagulants)

12.3. 12 Month Follow-up Visit (±30 days post-Index Procedure)

The following assessments are required to be performed at the 12 month follow-up visit:

- Rutherford Classification
- Target limb resting ABI
- Duplex ultrasound
- X-Ray assessment
- Peripheral Artery Questionnaire (PAQ)
- EQ-5D-3L
- Walking Impairment Questionnaire (WIQ)
- Major adverse event (MAE) occurrence
- Adverse event occurrence
- Review of concomitant medications (antiplatelets/anticoagulants)

12.4. 24 Month Follow-up Visit (±30 days post-Index Procedure)

The following assessments are required to be performed at the 24 month follow-up visit:

- Rutherford Classification
- Target limb resting ABI
- Peripheral Artery Questionnaire (PAQ)
- EQ-5D-3L
- Walking Impairment Questionnaire (WIQ)
- Major adverse event (MAE) occurrence
- Adverse event occurrence
- Review of concomitant medications (antiplatelets/anticoagulants)

12.5. 36 Month Follow-up Visit (±30 days post-Index Procedure)

- The following assessments are required to be performed at the 36 month follow-up visit: Rutherford Classification
- Target limb resting ABI
- Peripheral Artery Questionnaire (PAQ)
- EQ-5D-3L
- Walking Impairment Questionnaire (WIQ)
- Major adverse event (MAE) occurrence
- Adverse event occurrence

12.6. Review of concomitant medications (antiplatelets/anticoagulants)Duplex Ultrasound (DUS) Assessment

Lower extremity arterial duplex ultrasonography is widely accepted as a method of determining arterial stenosis. Duplex ultrasonography combines spectral Doppler Technology in addition to B-mode imaging to allow the visualization of blood flow patterns within the arteries and veins. This spectral Doppler also provides a method to measure the velocity of the blood flow at specific locations.

The peak systolic blood flow velocity within the Tacks as well as the target vessel will be taken to determine the peak systolic velocity ratio (PSVR). All scheduled and unscheduled DUS exams shall be reviewed by an independent core laboratory for analysis.

The DUS exam should be performed on all subjects at the 30-day, 6, and 12 month follow-up visits. Duplex ultrasonography and/or angiography should be performed prior to any endovascular intervention during the follow-up period in order to assess the treated vessel patency. Operators should have experience with DUS and the specific methods for calculating the blood flow velocities. Operators will be trained on the DUS protocol provided by the respective core laboratory. Each operator is required to submit a test case DUS exam to the core lab prior to performing any study-required DUS exams.

A comprehensive overview for DUS acquisition requirements can be found in the core laboratory manual.

12.7. X-Ray Assessment

An X-Ray assessment will be required at the 12 month follow-up visit to assess Tack integrity for all subjects in whom at least one Tack was placed during the index procedure.

- Acquire all x-rays as a high resolution image
  - Exposure < 80 kVp
  - Magnification of 1.5 image intensifier/receptor magnification
  - Avoid overlying bone and image entire Tacked segment(s)
- Make certain the radiopaque ruler is placed perpendicular to the imaging plane, flat on the patient. The ruler must be present in all film sequences to be analyzed. Once placed, the ruler should not be moved during the entire procedure.
- Use multiple acquisition views as defined in the x-ray protocol established by the core lab.

A comprehensive overview of procedural requirements for X-Ray assessments can be found in the core laboratory manual.

12.8. Unscheduled Visits

A subject who presents to the investigational site between scheduled study-required follow-up visits for a target limb related adverse event or intervention to target limb is considered to have an "unscheduled visit". Every effort should be made to gather data from the same clinical assessments required at the 12 month follow-up visit, including angiographic (if Target limb revascularization occurs), DUS and X-ray imaging (if clinically indicated or per standard of care). At the very least, target limb resting ABI measurement and Rutherford Classification should be assessed prior to any intervention to the target limb. In any case, if a Target limb intervention occurs, all the data from any assessment (clinical or imaging) performed prior to the intervention should be recorded in the Unscheduled Visit eCRF.

In the event a subject receives an intervention on the target vessel and/or lesion, all associated media (angiographic, DUS and X-Ray) shall be performed in accordance with imaging protocols and should be provided to the respective core labs. If a subject presents for target limb intervention that does not involve the target vessel/lesion, but the imaging performed captures the target lesion and Tacked portion vessel, such imaging should be sent to the respective core lab.

12.9. Follow-up Visit Compliance

As part of the informed consent process, all reasonable efforts will be made to obtain complete data for all subjects according to the follow-up visit schedule. Investigators and research staff will be expected to maintain continuous and open communication with study subjects regarding their participation in this study.

Three attempts via telephone will be made to contact subjects who do not present for study follow-up visits. If after three telephone attempts, the subjects cannot be contacted, a certified letter should be sent by the PI or designated study coordinator to the subject's last known address. If possible, public records should be searched to ascertain survival status. If efforts to reach the subject are unsuccessful after three telephone contacts and a certified letter and there is no evidence of subject expiration, the sites will complete a Protocol Deviation for a Visit Not Done. A detailed record of all contact attempts should be maintained in the subject's file. This process should be repeated for every subsequent follow-up visit and documented accordingly. These subjects will not be considered lost-to-follow-up (LTFU) and exited from the study until the end of the final follow-up visit window, unless it becomes known to the site that the subject has expired or wishes to withdraw consent.

12.10. Subject Discontinuation and Replacement

A subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. In addition, a subject may be discontinued if in the investigator's opinion it is in the subject's best interest. If a subject prematurely discontinues from the study, the reason will be recorded in the eCRF with supporting documentation. These results will be tabulated by number and percent for each category for discontinuation.

Subjects who prematurely exit the study after treatment will have their data maintained and evaluated up until the time of withdrawal. Subjects who are voluntarily or involuntarily (per PI discretion) withdrawn cannot re-enter the study. These subjects will not be replaced.

13. Risk/Benefit Assessment

13.1. Risks

The use of the Tack Endovascular System in percutaneous transluminal balloon angioplasty (PTA) may result in anticipated potential risks or complications similar to other available endovascular implant devices (such as stents) used in PTA procedures. Such risks are included in the Tack Endovascular System Instructions for Use (IFU) and are listed below:

- Access failure or abrupt closure
- Allergic / anaphylactoid reaction to anticoagulant and/or antithrombotic therapy or contrast medium
- Allergic reaction to nitinol
- Amputation of lower extremity
- Anemia
- Angina / coronary ischemia / myocardial infarction
- Arrhythmia
- Arterial occlusion / (re) stenosis / dissection / thrombus
- Arterial spasm
- Arteriovenous fistula
- Blue toe syndrome
- Claudication or rest pain, worsened
- Death
- Disseminated intravascular coagulation
- Edema, peripheral
- Embolism
- Emergent repeat hospital intervention
- Fever
- Gangrene
- Gastrointestinal bleed from anticoagulation / antiplatelet medication
- Hematoma / hemorrhage
- Hypotension / hypertension
- Inadvertent venipuncture
- Infection / abscess at insertion site
- Inflammation
- Multi-organ failure
- Pain
- Pseudoaneurysm
- Renal insufficiency or failure
- Respiratory distress or failure
- Septicemia / bacteremia (sepsis)
- Tack implant embolization
- Tack implant migration (device moves over time)
- Tack implant occlusion / restenosis

- Tissue necrosis
- Trauma to adjacent structures
- Stroke / TIA (hemorrhagic / embolic)
- Vascular complications which may require surgical repair

These risks are present in any endovascular treatment procedure for which the study subjects would be indicated because of their disease and will be reviewed with all subjects during the informed consent process.

13.2. Potential Benefits

Prior human studies validated that the Tack Endovascular System can safely and effectively appose dissected tissue in subjects with post-PTA dissections, thereby resulting in acute dissection repair and long term luminal patency.

13.3. Justification for Clinical Study

The safety and performance of the Tack Endovascular System has been established through extensive design verification and validation testing, including prior human use, and through a detailed risk analysis process per ISO 14971. The results of non-clinical and clinical testing have demonstrated safety and benefit and therefore, it is anticipated that the assessment of risk and benefit is appropriate for the intended use of the study device and the initiation of this study.

This trial is being conducted in order to collect additional safety and effectiveness data on the Tack Endovascular System device to support a Premarket Approval (PMA) application. All efforts will be made to minimize the occurrence of risk to study subjects through investigator/institution qualification, investigator training on the safe and proper use of the device in accordance with the IFU, investigator/site training on the protocol, and clearly defining subject eligibility requirements (inclusion/exclusion criteria) and contraindications as described in the IFU.

14. Adverse Event Reporting

The adverse event (AE) reporting period will begin at the time of enrollment into the study (See **Section 10.3.1**) and will continue through study completion.

The Principal Investigator at each participating site is ultimately responsible for the timely review and reporting of adverse events per respective IRB/EC policy and in accordance with FDA requirements. All Adverse Events during the safety observation period should be followed until the event is resolved or judged to be chronically stable. Follow-up information will be submitted to the Medical Monitor and/or the Sponsor as it becomes available.

All adverse events must be recorded on the Adverse Event CRF by the Investigator (or designee). The report should include: severity, duration, action taken, treatment outcome and relationship of the adverse experience to the study device, procedure, concomitant medications, pre-existing condition, (i.e., unrelated, related or relationship unknown).

All events will be made accessible to the Sponsor and/or designee to review the need for FDA regulatory reporting. All AE's will be reviewed for their relationship to the study device(s) and/or procedure and severity of the event.

Severity of adverse events will be classified according to the following criteria:

Mild: A mild adverse event is an AE usually transient in nature and generally not interfering with normal activities.

Moderate: A moderate adverse event is an AE that is sufficiently discomforting to interfere with normal activities.

Severe: A severe adverse event is an AE that is incapacitation and prevents normal activities.

The relationship of the AE to the device or procedure will be classified according to the following criteria:

Unrelated: No relationship to the study device or study procedure.

Possibly: Signs or symptoms are the study device or study procedure *and* the natural disease process or other injury/illness.

Definitely: Clearly related to the study device and/or study procedure. Signs and symptoms not related to natural disease process or other injury/illness.

Unknown: Unable to determine relationship between study device, study procedure, natural disease process and/or other injury/illness.

14.1. ADVERSE EVENTS (AE)

An adverse event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational device/procedure.

For purposes of this study, the following events are not considered adverse events because they are normally expected to occur in conjunction with endovascular procedures / post-procedure, 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 from baseline not associated with hemodynamic changes, remaining above 30% and not requiring transfusion
- Electrolyte imbalance without clinical sequelae following PTA/Tack procedure, even if requiring correction
- Low grade temperature increase (≤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
- Any pre-planned (planned prior to enrollment) surgical/endovascular procedures

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.

14.1.1. AE Reporting

All AEs will be evaluated to determine whether the event further meets the criteria for ADE, SAE, MAE, SADE, or UADE and will be subject to the respective reporting requirements as outlined in the sections below. Non-serious and non-device related AEs must be reported to the Sponsor in a timely manner and must also be submitted to the IRB/EC per policy.

14.2. Adverse Device Effects (ADE)

An adverse device effect is defined as any untoward adverse event related to the use of an investigational or unintended response to a medical device.

Note 1: This definition includes adverse events resulting from insufficient or inadequate Instructions for Use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. This definition includes any event resulting from insufficiencies or inadequacies in the Instructions for Use or the deployment of the device or any event that is a result of user error (See **Section 15**).

Note 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device (See **Section 15**).

A list of events that may be associated with the study device and/or the index procedure is provided in **Section 13.1**.

14.2.1. ADE Reporting

All ADEs must be evaluated to determine whether the event further meets criteria for an SADE (See **Section 14.5**) and would be subject to respective reporting requirements. Non-serious, anticipated ADEs must be reported by the Investigator (or designee) to the Sponsor in a timely manner and must also be submitted to the IRB/EC per policy. If the event occurred as a result of a device event, respective reporting requirements must be followed as outlined in **Section 15**.

14.3. Serious Adverse Events (SAE)

A serious adverse event (SAE) is defined an adverse event that:

- led to death,
- led to a serious deterioration in the health of the subject, that either resulted in:
- a life-threatening illness or injury, or
- resulted in a permanent impairment of a body structure or a body function, or

- required in-patient hospitalization or prolongation of existing hospitalization, or
- resulted in medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to body structure or a body function, or,
- led to fetal distress, fetal death or a congenital abnormality or birth defect.

Note: Planned hospitalization for a pre-existing condition, or a procedure required by the investigational plan without serious deterioration in health, is not considered a serious adverse event.

14.3.1. SAE Reporting

All SAEs must be evaluated to determine whether the event further meets criteria for an SADE (See **Section 14.5**) and would be subject to respective reporting requirements. All events that meet the criteria above for SAEs must be reported by the Investigator (or designee) to the Sponsor ***within 2 business days from first knowledge of event*** and must also be reported to the IRB/EC per policy.

14.4. Major Adverse Events (MAE)

For the purpose of this study, the definition of major adverse event(s)(MAEs) includes the following events that comprise safety and observational endpoints for this study:

- Index limb amputation (major)
- Clinically-driven target lesion revascularization (TLR)
- All-cause death

14.4.1. MAE Reporting

All events that meet the criteria above for an MAE must be reported by the Investigator (or designee) to the Sponsor ***within 2 business days from first knowledge of the event***, and must also be reported to the IRB/EC per policy.

14.5. Serious Adverse Device Effects (SADE)

A serious adverse device effect (SADE) is defined as an adverse device effect (ADE) that results in any of the consequences characteristics of a serious adverse event (SAE).

14.5.1. SADE Reporting

All events that meet the criteria above for an SADE must be reported by the Investigator (or designee) to the Sponsor ***within 2 business days from first knowledge of event*** and must also be reported to the IRB/EC per policy. If the event occurred as a result of a device event, respective reporting requirements must be followed as outlined in **Section 15**.

14.6. Unanticipated Adverse Device Effects (UADE)

An Unanticipated Adverse Device Effect (UADE) is any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan; or any other unanticipated problem associated with a device that relates to the rights, safety, or welfare of the subjects.

14.6.1. UADE Reporting

Any event that is suspected of meeting UADE criteria should be reported in the same manner as an SAE or SADE and must be reported by the Investigator (or designee) to the Sponsor ***within 2 business days from first knowledge of event*** and must also be reported to the IRB/EC per policy. All SAEs will be reviewed by the Sponsor (or designee) to determine if UADE criteria is met, and if so will immediately conduct an evaluation and report the results of the evaluation to FDA, all reviewing IRBs/ECs, and participating investigators within 10 business days after the Sponsor first receives notice of the effect.

15. Study Device Event Reporting

A Study Device Event refers to the performance of the study device and the occurrence of a deficiency or malfunction as defined in sub-sections below. Device events are to be reported on the Device Event eCRF and submitted to the sponsor as soon as possible and **within 2 business days of first knowledge of occurrence.** Any adverse event suspected of resulting from a device event must be reported per the required timelines as outlined in **Section 14**.

15.1. Device Deficiency

Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or user error, and inadequate labeling.

15.2. Device Malfunction

A malfunction is defined as a failure of a device to meet its performance specifications or otherwise to perform as intended.

16. Statistical Considerations

16.1. Introduction

Descriptive statistics for each variable will be calculated which will include the number of observations, mean, standard deviation, median, minimum and maximum for continuous variables and will include the number and percent of observations for categorical variables.

When the mean is found not to be an appropriate measure of central tendency, alternative statistics will be considered (e.g. median). When the distribution of a variable does not support the use of parametric statistics, nonparametric approaches or data transformations may be implemented. If data transformations are used they will be specified in the final clinical report.

16.2. Analysis Groups

Intent to Treat (ITT): A subject is defined as an intent-to-treat (ITT) patient once the subject has met all the inclusion and exclusion criteria including angiographic criteria and the Tack Endovascular System is advanced through the introducer sheath. See **Section 10.2.1 – 10.3.1** for details.

Per Protocol (PP): The per-protocol (PP) population is defined as the subset of the ITT population with evaluable data that have met the definition for Device Success, excluding subjects with major protocol deviations such as:

- A major inclusion/exclusion criterion violation; or
- A major procedural deviation

The criteria for deviations meeting the classification of "major" will be defined before study endpoint data is available for statistical analysis. All major deviations will be adjudicated by an independent designee without visibility to study results.

16.3. Enrollment Sample Size

The maximum sample size required for the primary objectives is 178 subjects meeting the ITT definition for primary efficacy that are evaluable for the primary patency endpoint measured at 12 months. The sample size was increased for 15% attrition over 12 months, resulting in 210 enrolled subjects. See Sample Size Rationale in **Section 16.7** and **Section 16.8** for sample size calculations specific to each primary endpoint.

16.4. Administrative Reports

The study will permit the use of either drug-coated or standard balloons in the angioplasty procedure that immediately precedes Tack placement. The performance goal for the primary efficacy objective depends on the proportion of subjects enrolled, i.e. ITT patients who were treated with standard or drug-coated balloons. Once the index procedure is completed for all enrolled subjects, the proportion of subjects treated with standard balloons and drug-coated balloons will be calculated. The proportions are the weights in the formula to calculate the performance goal. The calculation is described in **Section 16.8 Performance Goal.** The performance goal for primary efficacy will be fixed in advance of or prospectively to the primary efficacy analysis. There is no Type I error adjustment for this report given that no hypotheses will be tested.

16.5. Justification for Pooling

The investigational sites will be tested for differences in the primary safety and efficacy endpoints using Fisher's Exact test in the ITT sample. For the primary efficacy endpoint, sites will be additionally stratified by standard vs. drug-coated balloons to evaluate pooling. The Fisher's Exact test will be performed twice, once for subjects treated with drug-coated balloons and once for subjects treated with standard balloons. Investigational sites with fewer than 10 subjects will be combined for this purpose. If there are any investigational site effects (i.e., statistically significant results at two-sided $p < .10$), a random center effect will be included in a logistic regression model to assess the primary objective. If there are no differences, the data from all investigational sites will be pooled for the analyses.

Additionally, the primary safety and efficacy endpoints will be summarized by US and OUS centers in the ITT sample. The study was not powered to demonstrate the primary efficacy and safety endpoints within the subgroups defined by geography and therefore it is not an expectation that the primary safety and efficacy endpoint will be statistically significant within the subgroups determined by geography.

16.6. Handling of Missing Data

The primary statistical analysis will be conducted using the observed data with standard imputations used when the 12 month DUS determination is missing but an earlier or later DUS

or angiogram are available in the ITT sample (see Primary Statistical Analysis in **Section 16.8** for more detail).

Additionally, a sensitivity analysis to the missing data in the intent-to-treat sample will be conducted. The sensitivity analysis will include a best case, worst case and tipping point analysis. The best case analysis will impute successes for the missing data. The worst case analysis will impute failures for missing data. The tipping point analysis starts with the best case analysis and continues until the worst case analysis is completed, by increasing the number of missing cases imputed as failures by one in each analysis. The goal of the tipping point analysis is to determine at what point the imputation of failures causes the statistical evaluation of the endpoint to lose statistical significance. If the worst case analysis maintains statistical significance, the tipping point analysis is not necessary.

16.7. Summary of Baseline Demographics, Index Procedure Measurements, Tack Endovascular System Treatment Results, and Subject Compliance

Baseline demographics including at a minimum, gender, age and selected medical history will be summarized for patients enrolled in the study. In addition, angiographic characteristics and measurements, as well as final treatment results captured during each phase of the Index Procedure (Baseline, Post-PTA, and Post-Study Device) as outlined in **Section 10** will also be summarized.

Patient follow-up and compliance with the protocol will be reported. The number and percent of patients enrolled, completing study required follow-ups and completing the study will be summarized. The patients who exit the study early will be summarized along with the reason for early study termination.

16.8. Primary Safety Objective

Subjects Included the Analysis: Subjects who meet the ITT definition as specified in **Section 16.2 and 10.3.1.**

Endpoint: Freedom from the occurrence of any new-onset major adverse event(s) (MAEs) defined as index limb amputation (above the ankle), CEC adjudicated clinically-driven target lesion revascularization (CD-TLR), or all-cause death at 30 days as specified in **Section 6.1.**

Hypothesis and Performance Goal: The VIVA performance goal of 88%[19] will be used as the performance goal for this endpoint.

H_0: Freedom from MAE (p_{MAE}) is less than or equal to 88% at 30 days, $p_{MAE} \leq 88\%$

H_1: Freedom from MAE is greater than 88% at 30 days, $p_{MAE} > 88\%$

Sample Size Rationale: Using PASS 2012, a one-sample Exact Test, power = 90%, one-sided Type I error controlled at 5.0%, a performance goal of 88% and an assumed freedom from MAE at 30 days in Group 1 of 95%, 138 subjects with 30 days of follow-up and/or an MAE prior to 30 days are required for the analysis.

[19] Rocha-Singh KJ, Jaff MR, Crabtree TR, Bloch DA, Ansel G on behalf of VIVA Physicians, Inc. Performance Goals and Endpoint Assessments for Clinical Trials of Femoropopliteal Bare Nitinol Stents in Patients with Symptomatic Peripheral Arterial Disease. Catheterization and Cardiovascular Interventions 69: 910 – 919 (2007).

Primary Statistical Analysis: The primary statistical analysis will be conducted in subjects who meet the ITT definition and have observed data for the primary safety endpoint. The primary statistical method is a one-sample exact test comparing the proportion of subjects free from a MAE to the performance goal using a one-sided $\alpha = 0.05$. The exact one-sided 95% confidence interval for the proportion of subjects free from MAE will be calculated.

The freedom from MAE proportion will be calculated such that the numerator is the number of subjects in whom a MAE did not occur within 30 days of the index procedure. The denominator is the number of subjects with 30 days of follow-up plus the number of subjects with an MAE prior to 30 days who exited the study early, if any.

Additional Analysis: If pooling is not justified per the methods outlined in **Section 16.5**, the additional analyses specified in that section will be completed. If there is missing data for the ITT subjects, the sensitivity to missing data analysis outlined in **Section 16.6** will be completed. Additionally, the primary statistical analysis will be conducted in the per protocol sample.

16.9. PRIMARY EFFICACY OBJECTIVE

Subjects Included the Analysis: Subjects who meet the ITT definition as specified in **Section 16.2** and **10.3.1.**

Endpoint: Primary patency defined as freedom from CEC adjudicated clinically-driven target lesion revascularization (CD-TLR) and freedom from core lab adjudicated duplex ultrasound derived binary restenosis at 12 months (defined as PSVR ≥2.5) as specified in **Section 6.1.**

Hypothesis:

H_0: Primary patency (p_{p_pat}) is less than or equal to performance goal (PG) at 12 months, $p_{p\_pat} \leq PG$

H_1: Primary patency is greater than the performance goal at 12 months, $p_{p\_pat} > PG$

Performance Goal: The performance goal is based upon the 12 month primary patency results from the recently completed Levant 2 IDE trial[20] that supported approval of the test DCB. The Levant 2 randomized controlled trial used the same primary efficacy endpoint as the TOBA II trial and represents current estimates for primary patency associated with PTA using standard and drug-coated balloons. The primary patency estimates for the ITT completer population from Levant 2 are provided in **Table 7.**

Table 7 - Primary Patency at 1 Year in LEVANT 2 for ITT Completers

Measure	**Test Drug-Coated Balloon (DCB) %(n/N) [95% CI]**	**Control PTA %(n/N) [95% CI]**
Primary Patency	65.2% (172/264) [59.4, 70.9]	52.6% (71/135) [44.2, 61.0]

The performance goal for TOBA II is derived from the lower limit of the 95% confidence interval for the Test DCB and Control PTA in Levant 2 given that the expectation is that the Tack

[20] Summary of Safety and Effectiveness Data (SSED) LUTONIX® 035 Drug Coated Balloon PTA Catheter

device will resolve dissections without negatively impacting primary patency at 12 months. The primary patency rate is dependent on the type of balloon used and therefore the performance goal will be calculated using the Levant 2 lower 95% confidence limits and the proportion of subjects enrolled and treated with DCB (p_{DCB}) and Control PTA (p_{PTA}) in the TOBA II Trial. The following formula will be used:

$$PG = p_{DCB} X\ 59\% + p_{PTA} X\ 44\%$$

For example, assuming the proportion of subjects meeting the ITT definition in TOBA II is 60% DCB and 40% Control PTA, the calculated performance goal will be 0.6*59% + 0.4*44% = 53%. The primary efficacy performance goal will be calculated upon completion of the index procedure for all enrolled subjects (see **Section 16.4**).

Sample Size Rationale: The sample size required to have data evaluable for the primary efficacy endpoint at 12 months, was calculated using PASS 2012, a one-sample Exact Test, power = 90%, one-sided Type I error controlled at 2.5%, and setting the maximum proportion of subjects treated with DCB enrolled at 60%. In this case, the performance goal for primary patency at 12 month is 53%. A current estimate for primary patency at 12 months in the TOBA European trial (POBA use only) is 75%. Conservatively, the primary patency for DCB + Tack and Control PTA + Tack was assumed to be 65% for the purpose of the sample size calculation. Using those assumptions, 178 subjects are required to have data evaluable for the primary efficacy endpoint at 12 months.

The power at N=178 subjects is provided in **Table 8** varying the assumed proportion of subjects treated with DCB + Tack. As can be seen in **Table 8**, the sample size calculation for the TOBA II trial has at least 90% power given the proportion of subjects treated with DCB + Tack is 60% or less.

Table 8 - Power for N=178 Subjects Varying the Proportion of Subjects Treated with DCB + Tack Meeting the ITT Definition with Data Available to Evaluate the Primary Efficacy Endpoint at 12 months

Proportion of Subjects Meeting ITT Definition with Tack +		Performance Goal[a]	Assumed Patency at 12M for TOBA II			Power at N=178
DCB	Control PTA		DCB + Tack	Control PTA + Tack	Pooled	
30%	70%	49%	65%	65%	65%	99.1%
40%	60%	50%				98.0%
50%	50%	52%				92.4%
60%	40%	53%				90.0%

[a]The performance goal, PG, is calculated as PG = proportion DCB + Tack*59 + proportion control PTA + Tack*44.

Primary Statistical Analysis: The primary statistical analysis will be conducted in subjects who meet the ITT definition and have data evaluable for the primary efficacy endpoint. Subjects with a missing DUS ultrasound at 12 months and a patent DUS ultrasound at a later visit with no intervening clinically driven TLR will be considered patent at 12 months. In the event an angiogram is available within the 12 month visit window, the angiographic core-lab determined stenosis using the 50% cutoff will be used instead of the DUS core-lab determined stenosis. The primary statistical method is a one-sample exact test comparing the proportion of subjects with

primary patency to the performance goal using a one-sided α= 0.025. The exact two-sided 95% confidence interval for the proportion of subjects with primary patency will be calculated.

The primary patency proportion will be calculated such that the numerator is the number of subjects who are patent at 12 months with no clinically-driven TLR by the close of the 12 month visit window. The denominator is the total number of subjects with a core-lab adjudicated DUS ultrasound finding of either patent or not patent at 12 months, clinically-driven TLR prior to the close of the 12 month visit window, or missing 12 month DUS with a patent DUS finding at a subsequent visit with no intervening clinically driven TLR.

Additional Analysis: If pooling is not justified per the methods outlined in **Section 16.5**, the additional analyses specified in that section will be completed. If there is missing data for the ITT subjects, the sensitivity to missing data analysis outlined in **Section 16.6** will be completed. Additionally, the primary statistical analysis will be conducted in the per protocol sample.

16.10. SUBGROUP SUMMARIES FOR PRIMARY ENDPOINTS

Summary statistics for the following subgroups will be summarized. The study was not powered to demonstrate the primary efficacy and safety endpoints within the subgroups and therefore it is not an expectation that the primary safety and efficacy endpoint will be statistically significant within the subgroups

- Gender
- Most severe post-PTA site reported dissection per lesion and the most severe post-PTA core-lab reported dissection per lesion. Additionally the dissection grade may be grouped into two categories defined by the most severe site and corelab reported post-PTA dissection grade reported, i.e. types A-C and types D-F. However, all dissection types per lesion will be recorded in the site and corelab CRFs.
    - The dissection distribution at baseline will be qualitatively compared against the dissection distribution reported in the Levant 2 trial for post-study treatment.
    - The primary efficacy and safety endpoints summarized by worst dissection grade will be qualitatively compared to any and all available relevant data in the literature on outcomes in post-PTA dissection.

16.11. OBSERVATIONAL ENDPOINTS

The observational endpoints are listed in **Section 6.2** and are supportive in nature. Descriptive statistics will be calculated and may be provided in labeling if deemed informative for the user. Descriptive statistics for the purposes of labeling are defined as N, mean, standard deviation, median, interquartile range, minimum and maximum for continuous variables and number and percent of observations for categorical variables.

Standard statistical methods will be used and include the Kaplan-Meier product limit method for time to event endpoints and the Wilcoxon signed rank test for changes from baseline for endpoints compared to baseline. Statistical significance will be defined as two-sided $\square < 0.05$. Two sided 95% confidence intervals may be calculated for estimates. P-values and 95% confidence intervals are not intended for the labeling.

Safety endpoints will be evaluated in the sample of subjects meeting the ITT definition only. Efficacy endpoints will be evaluated in both the ITT and PP subjects.

17. REGULATORY AND ETHICAL OBLIGATIONS

As the study Sponsor, Intact Vascular is responsible for the overall conduct and quality of the study, including the assurance that the study complies with the regulations and guidance that apply to medical devices evaluated under an Investigational Device Exemption (IDE) and Good Clinical Practice (GCP) guidance (FDA Guidance and ICH E6). Additionally, Intact Vascular will ensure that qualified monitors and designated personnel are monitoring the study and that the Informed Consent process is followed per each site's local and national requirements.

17.1. INSTITUTIONAL REVIEW BOARD (IRB) / ETHICS COMMITTEE (EC) APPROVAL

The Principal Investigator at each participating site is responsible for securing IRB/EC approval for this study protocol and the Informed Consent documents. The IRB/EC for each specific institution must review and approve this study protocol, the specific Informed Consent form and any written materials for subjects to be used at that site **prior** to enrollment of the first subject. The Sponsor **must** also review and approve the final Informed Consent documents prior to their use. The Sponsor must receive a copy of any IRB/EC correspondence as well as the final approval letter and the final approved Informed Consent from each IRB/EC. The IRB/EC approval letter must be signed by the IRB/EC chair or designee, identify the IRB/EC name and address, the clinical study protocol by name or number, and the date the approval was granted.

The site investigator is also responsible for initiating and obtaining continuing review of the clinical study. Continuing IRB/EC review and approval should not exceed intervals over one year, but may occur at more frequent intervals as required by site specific IRB/EC policies. The investigator must also provide the Sponsor with all correspondence and documentation of continued IRB/EC approval of the clinical study.

17.2. INFORMED CONSENT

All sites shall comply with 21 CFR 50, provisions of ICH Good Clinical Practices (GCPs), local IRB/EC policy and all applicable local regulations for obtaining Informed Consent. Written, informed consent is to be obtained for all subjects prior to treatment as described in **Section 8.3**.

Informed Consent templates will be provided by the Sponsor to all participating clinical sites. Changes to this template made by the site based upon IRB/EC requirements must be provided to the Sponsor for review and approval prior to being submitted to the IRB/EC for review and approval. Any revisions required by a site's IRB/EC should also be provided to the Sponsor for review and approval prior to being submitted to the IRB/EC for final review and approval.

17.3. PROTOCOL AMENDMENT AND EMERGENCY DEVIATIONS

Changes to the research conducted under this protocol will be implemented with a formal protocol amendment. Amendments to the protocol may be initiated by the Sponsor or at the request of the Investigator. In either case, changes to the protocol must be approved by the Sponsor and submitted to the applicable regulatory agency as appropriate. A protocol

amendment cannot be implemented at the site without first being signed and acknowledged by the Investigator and approved by the IRB/EC.

Emergency deviations or modifications may be initiated without prior Sponsor or IRB/EC approval only in cases when the deviation is necessary to eliminate an immediate potential hazard to a subject. Emergency deviations or modifications implemented to protect the life or physical well-being of a subject must be reported to the Sponsor and site specific IRB/EC **within 5 business days of occurrence.**

17.4. Subject Confidentiality

Confidentiality of subjects will be maintained throughout the study. A unique identification code will be assigned to each subject enrolled into the study. Access to the subject's medical records will be limited to authorized personnel of the Sponsor, their designated monitors, clinical site study staff and authorized regulatory authorities as required by the IRB/EC and/or local or national agencies. Any data that may be published in abstracts or scientific journals and/or presented at medical meetings will reference a unique subject code and will not reveal the subject's identity. The Sponsor and their representatives will make every reasonable effort to protect the confidentiality of the subjects participating in the study.

All U.S. clinical study sites must comply with the provisions of the Health Insurance Portability and Accountability Act (HIPAA) and in accordance with all applicable federal, local and institutional requirements.

18. Clinical Study Conduct

18.1. Principal Investigator and Site Qualification

All Principal Investigator's (PI) and investigational sites will be selected by Intact Vascular through the PI and site qualification process. All selected PI's will be responsible for complying with all study-related and regulatory requirements and will be ultimately responsible for overseeing the conduct of the study at their respective investigational sites, per the Investigator Agreement.

All selected PI's will have the required training and expertise in performing peripheral vascular interventional procedures in a clinical research setting. The investigational sites where the study procedures and assessments are to be performed must have the adequate volume of the target subject population, experienced staff, as well as the appropriate facilities and equipment to meet the requirements of the study protocol and the expected enrollment time frames.

All PI's and research staff must be willing to undergo all study and device-related training and participate and assist with monitoring, audits and inspections initiated by either the Sponsor and/or regulatory authorities.

18.2. Principal Investigator and Site Training

Training of the Investigators and clinical study staff is the responsibility of the Sponsor and their designee. Investigators and study staff will undergo site initiation visit training on the use of the study device, the study protocol, eligibility criteria, and device accountability prior to participating in the study. Training will also include, but is not limited to, instructions on timely and accurate eCRF completion, safety reporting timelines, as well as procedures for acquiring study related images and associated timelines for submission to appropriate core laboratory.

All training of the Investigators and research staff must be documented on the training log before performing any study-related function.

18.3. Clinical Monitoring

Intact Vascular will designate qualified clinical monitor(s) and oversee the conduct of this study. The clinical monitors will evaluate compliance with the protocol, Good Clinical Practices (FDA Guidance and ICH E6), any specific recommendations made by the site's IRB/EC and the signed Investigator and Study Agreements.

The clinical monitor will conduct periodic monitoring visits to verify that the eCRFs are in agreement with the source documentation and other records, that the rights and well-being of the subjects, and that the trial is being conducted in accordance with the approved protocol/amendments and GCPs. Periodic phone contacts will also be conducted to ensure that the protocol is being followed and to assist the site with queries that may arise.

For record verification purposes during site monitoring visits, the clinical monitor and/or authorized Sponsor representative will be provided access to hospital records, original laboratory data, and other records and data as they relate to the study and as agreed to with the Investigator prior to the initiation of the trial. The Investigator will also make available to the clinical monitor all regulatory documents, all completed eCRFs, informed consent documents, source documentation and other relevant records for all enrolled subjects at the site. It is important that the Investigator and other relevant site personnel are available for consultation with the clinical monitors during the monitoring visits and that sufficient time is devoted at the site to the monitoring process.

If the Sponsor and/or their authorized representative become aware that an Investigator is not complying with the study protocol, the Investigator Agreement, the Declaration of Helsinki, GCPs, applicable privacy standards, or any condition of the study imposed by the IRB/EC, the Sponsor or their authorized representative may immediately secure compliance, discontinue further shipments of the study devices and/or seize unused devices on-site. An inability to secure compliance and/or to complete an investigation into the factors that are inhibiting compliance may result in the Investigator's termination from the study by the Sponsor.

Study close-out visits will be conducted after the final follow-up visit is completed at each site. Following the resolution of any outstanding data discrepancies and adverse events, the remaining study devices will be the collected and returned to the Sponsor. A final study report will be generated and submitted to the Investigator and the appropriate study oversight authorities. Study document retention requirements will be reviewed with each site during the close-out visit.

18.4. Device Accountability

All study devices will be provided to the Investigator by the Sponsor after being tested, released and shipped according to appropriate standards. The investigator and/or designee is responsible for the secure storage of and controlled access to the study devices and accountability. The study device shall not be dispensed to any person who is not a consented study subject under this protocol.

18.5. INVESTIGATOR REPORTS

All investigators will be responsible for preparing and submitting the following complete, accurate, and timely reports.

To the sponsor and the IRB/EC:

- Any unanticipated adverse device effect occurring during an investigation as soon as possible but no later than 2 working days after first learning of the effect.
- Assist sponsor in generating Progress reports on the investigation at regular intervals, but in no event less often than yearly. If there is a study monitor, a copy of the report will also be sent to the monitor.
- Any deviation from the investigational plan made to protect the life or physical well-being of a subject in an emergency, as soon as possible but no later than 5 working days after the emergency occurs. Except in emergency situations, a protocol deviation requires prior sponsor approval; and if the deviation may affect the scientific soundness of the plan or the rights, safety, or welfare of subjects, prior FDA and IRB/EC approval are required.
- Any use of the device without obtaining informed consent, must be reported within **5 working days after such use.**
- Assist sponsor in generating a final report within 3 months following termination or completion of the investigation or an individual investigator's part of the investigation.
- Any further information requested by FDA or the IRB/EC about any aspect of the investigation.

To the Sponsor:

- Withdrawal of IRB/EC approval of the investigator's part of an investigation. (Due within 5 working days of such action). If the Investigator's IRB/EC withdraws their approval to conduct this study for any reason, the Investigator must notify the Sponsor as soon as possible, but in no event later than five working days after the withdrawal of the approval.

In addition, the Investigator is responsible for the reporting of all clinical and device events per the timelines specified in **Section 14** and **Section 15**.

18.6. DATA MANAGEMENT

Standardized electronic Case Report Forms (eCRF) will be used to collect complete and accurate records of the clinical data required by the study in accordance with Good Clinical Practices (GCP) principles. The Investigator and/or study staff under his/her direction is responsible for accurately recording the clinical data for this study within five (5) days after each visit.

18.7. SAFETY MONITORING

18.7.1. DATA SAFETY MONITORING BOARD (DSMB)

To meet the ethical responsibilities and standards for research subjects, an independent board of multi-disciplinary physicians and subject matter experts shall serve as the Data Safety and Monitoring Board (DSMB) for the study. In order to enhance objectivity and reduce the potential for bias, the DSMB shall be independent of the Sponsor as well as the investigational sites/ investigators.

The DSMB shall serve as an independent body conducting a review and oversight of all key safety events to monitor the rate of occurrence (both site reported and CEC adjudicated events) as part of their mission to protect the rights and safety of research subjects. The DSMB will define the types of events that may require real time reporting and the format and frequency of interim data reviews for aggregate event rates. The DSMB will conduct systematic interim safety reviews at pre-specified intervals as outlined in the DSMB charter. The committee will be responsible for making any recommendations to the Sponsor it deems necessary to protect subjects enrolled in the trial.

At the close of each meeting, deliberation will occur and each DSMB member will vote in favor of continuation of the study as designed, or modification of the study to protect the welfare of subjects enrolled into the study. The result of this vote will be recorded in the meeting minutes. A summary of the meeting output and voting decision will be prepared by the DSMB liaison and this will be distributed to all participating clinical sites for IRB/EC continuing review.

The methodology for performing these responsibilities shall be developed and outlined in the DSMB Charter.

18.7.2. CLINICAL EVENTS COMMITTEE (CEC)

An independent Clinical Events Committee consisting of a team of clinical experts with experience in the conduct of clinical trials shall be formed to review clinical events reported by the investigators, or at the request of the Sponsor to determine if they meet the pre-specified endpoint definitions. The CEC may also be called upon to review relevant Serious Adverse Events to make an assessment of relationship to study device and/or study procedure. The CEC's determination of whether a clinical event meets the study defined endpoint will be considered the primary determination for the purpose of reporting study results with the exception of endpoints derived from Core Laboratory analysis.

Operational provisions shall be established to minimize potential bias (i.e., the physicians serving on the CEC shall be blinded to the clinical site to the extent possible during adverse event review and adjudication). The methodology for performing these responsibilities will be outlined in the CEC Charter. The CEC will define the minimum required information necessary to facilitate their review of an event. This may include information from original source documentation and imaging media.

18.8. MEDICAL MONITORING

The sponsor will be responsible for identifying a Medical Monitor who possesses the appropriate expertise and medical knowledge to oversee all adverse events reported during the study. All adverse event reports will be directed to the Sponsor as well as the Medical Monitor. The Medical Monitor will be responsible for the first-line and timely review of all adverse events in order to identify seriousness, severity, and causality and expectedness (anticipated vs. unanticipated) of the event to the study device and/or study procedure. The Medical Monitor will also have responsibilities including but not limited to:

- Reviewing all AEs for UADE potential and notifying the Sponsor of the need for regulatory reporting
- Determining the need for additional information or supporting documentation from the site regarding an adverse event to facilitate complete assessment
- May help determine if an adverse event meets the criteria for DSMB/CEC review and adjudication, as outlined in the charter
- Providing thorough review and assistance (if needed) for generating documents (i.e., subject event narratives) subject to CEC review and adjudication.
- Providing answers to the sites, IRBs/ECs, and/or Sponsor to questions requiring medical expertise that pertain to the protocol (i.e., subject eligibility) or any other medical aspect of the study
- Reviewing protocol and procedural deviations
- Identifying potential need for an amendment to the protocol
- Provide a review of safety information included in regulatory reporting

The Medical Monitor will review all adverse events throughout the duration of the study until study completion.

18.9. CENTRAL CORE LABORATORIES

To ensure that the clinical data and images are analyzed in a controlled, non-biased manner and that the results are analyzed using a standardized process, all angiograms, duplex ultrasound studies and x-ray obtained during this study will be submitted to a respective central core lab for analysis.

The core labs will be responsible for analyzing the angiograms, duplex ultrasound and x-ray images according to the study eligibility criteria, the study endpoints and requirement measurements according to this study protocol. Feedback will be provided to the sites and Sponsor regarding the quality of the tracings and images and for providing a written summary report of all angiogram, duplex ultrasound and X-ray results to the study Sponsor.

18.10. RECORD RETENTION

The Principal Investigator is responsible for maintaining the following accurate, complete, and current records relating to his/her participation in this investigational study:

- Correspondence with another investigator, an IRB/EC, the Sponsor, a monitor, or FDA;

- Records of receipt, use or disposition of a device that relate to:
    - The type and quantity of the device, dates of receipt, and batch numbers or code marks
    - Names of all persons who received, used, or disposed of each device
    - The number of units of the device returned to the sponsor, repaired, or otherwise disposed of, and the reason(s) therefore;
- Records of each subject's case history and exposure to the device, including:
    - Documents evidencing informed consent and, for any use of a device without informed consent, any written concurrence of a licensed physician and a brief description of the circumstances justifying the failure to obtain informed consent
    - All relevant observations, including records concerning adverse device effects (whether anticipated or not), information and data on the condition of each subject upon entering, and during the course of, the investigation, including information about relevant previous medical history and the results of all diagnostic tests;
    - A record of the exposure of each subject to the investigational device, including the date and time of each use, and any other therapy.
- The protocol, with documents showing the dates of and reasons for each deviation from the protocol; and
- Any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigations or a particular investigation.

In addition, all Principal Investigators and Sub-Investigators (Sub-I) shall disclose to the sponsor sufficient and accurate financial information to allow the sponsor to submit certification or disclosure of financial interests under 21 CFR 54. All PI(s) and Sub-I(s) shall update the information if any relevant changes occur during the course of the investigation and for one year following completion of the study.

The Sponsor, Core Laboratories and clinical sites will maintain the study records until two (2) years after the last marketing application and until there are no pending or contemplated marketing applications or at least two (2) years have elapsed since formal discontinuation of clinical development of investigational product. These records may be retained for a longer period of time if required by applicable regulatory agencies. The Sponsor will notify each site regarding the regulatory requirements for record retention during the study close-out visit.

18.11. AUDITS/INSPECTIONS

In accordance with GCP requirements, the Sponsor and/or Designee may request access to all study records, including source documents, for inspection and duplication. In the event that an Investigator is contacted by an applicable regulatory body in relation to this study, the Investigator will notify the Sponsor as soon as possible.

The Investigator and/or designees must be available to respond to reasonable requests by authorized Sponsor, CRO and regulatory agency representatives during the monitoring and inspection process. The Investigator must provide the Sponsor with copies of all correspondence that may affect the review of the current study (i.e. Inspection Observations) or their qualification as an Investigator in clinical studies conducted by the Sponsor. The Sponsor will provide any needed assistance to the clinical site for regulatory audits, if any.

18.12. Study Termination (Stopping Rules)

The Sponsor, IRBs/ECs, or regulatory authorities may terminate the study if the safety and well-being of study subjects is in jeopardy. If the Investigator terminates the study at his/her site without prior approval by the Sponsor, all details must be provided promptly to the Sponsor and IRB/EC.

The Sponsor reserves the right to terminate or reevaluate a site for continued participation in the study for any of the following reasons:

- Unsatisfactory enrollment with respect to eligibility criteria
- Failure to obtain Informed Consent
- Failure to report Serious Adverse Events within 2 business days of knowledge
- Loss of or unaccountable device inventory
- Repeated protocol violations or safety concerns
- Repeated failure to complete Case Report Forms (or inaccurate/incomplete eCRF completion)
- Failure to enroll an adequate number of subjects
- The potential benefits are unlikely to outweigh the risks (Futility)

If the study is terminated by the Sponsor, the investigator(s) will be promptly informed, who must then promptly inform the IRB/EC. If the IRB/EC terminates the study, the Investigator will promptly notify the Sponsor providing an explanation.

18.13. Coverage of Subject Expenses

The treated subjects will not be compensated for their time during the trial. The Sponsor may provide reimbursement for reasonable out-of-pocket costs to the subject associated with travel, parking, or other expenses associated strictly with completing the protocol requirements of this study that would not normally be covered under routine medical coverage for the subject's underlying medical condition. This will be provided on a case-by-case basis and will require Sponsor (and/or Designee) approval.

18.14. Clinical Study Reports

All information and data generated in association with the study will be held in strict confidence and remains the sole property of the Sponsor. The Investigator agrees to use this information for the sole purpose of completing the study and for no other purpose without prior approval of the Sponsor.

All progress reports will be generated and submitted to FDA by the Sponsor in compliance with periodic reporting requirements. If requested, all participating Investigators and clinical sites

should provide assistance to the Sponsor regarding the data and any other pertinent information to be included in the study reports. All progress reports submitted to FDA will be summarized by the Sponsor and distributed to each site for IRB/EC review, which shall include all relevant feedback and/or approval provided by FDA.

Upon receipt of the final study data and the final reports from each center, the Sponsor will complete a final study report. Copies of the final report will be provided to each Investigator.

18.15. PUBLICATION POLICIES

At the conclusion of the study, a multi-center manuscript led by the national study Principal Investigator will be prepared with the assistance of Intact Vascular for publication in a reputable scientific journal. The publication of the principal results from any single center experience within the trial is not allowed until the preparation and publication of the multi-center results as indicated in the Clinical Trial Agreement. Exceptions to this rule require the prior approval of National PI and Intact Vascular. For the purposes of timely abstract presentation and publication, secondary publications will be delegated to the appropriate principal authors, and final analyses and manuscript review for all multi-center data and/or single-center experience reports will require review from Intact Vascular.

This study will be registered with clinicaltrials.gov.

18.16. 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, 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 status. Lower extremity peripheral artery disease remains one of the most unrecognized manifestations of systemic arteriosclerosis estimated to affect between 3% and 7% of the population and up to one in five patients above the age of 75.[1] While the overall prevalence of PAD ranges from 3% to 10%, PAD affects 12% to 20% of Americans aged 65 years and older.[21,22] Because the prevalence of PAD increases with age, the results of this study are expected to be generalizable to the Medicare eligible population primarily due to program eligibility due to age (E.g., 65 years or older).

[21]Norgren L, Hiatt WR, Dormandy JA, et al. Inter-Society consensus for the management of peripheral arterial disease (TASC II). J Vasc Surg. 2007;45:S5-S67.
[22] Becker GJ, McClenny TE, Kovacs ME, et al. The importance of increasing public and physician awareness of peripheral arterial disease. J Vasc Interv Radiol. 2002;13:7-11.

19. STUDY DEFINITIONS

Term	Definition
Activated Clotting Time (ACT)	Clotting test for high-dose heparin anticoagulation.
Acute Renal Failure	Acute post-operative renal insufficiency resulting in one or more of the following (a) increase of > 1.0 mg/dl in serum creatinine from most recent prior measured level, and current measured absolute value is > 2.5 mg/dl; (b) a new requirement for dialysis.
Adverse Device Effect (ADE)	An adverse device effect is defined as any untoward adverse event related to the use of an investigational or unintended response to a medical device. ▪ Note 1: This definition includes adverse events resulting from insufficient or inadequate Instructions for Use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. This definition includes any event resulting from insufficiencies or inadequacies in the Instructions for Use or the deployment of the device or any event that is a result of user error (See **Section 15**). ▪ Note 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device (See **Section 15**).
Adverse Event (AE)	An adverse event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational device/procedure.
Allergic Reaction	An allergic reaction characterized by rash, nausea, vomiting, upper respiratory congestion, urticarial, shortness-of-breath, vasovagal reaction, or general collapse (anaphylaxis).
Ankle / Brachial Index (ABI)	The ratio of systolic blood pressure measured at the ankle to systolic blood pressure measured at the brachial artery. The ABI is calculated by dividing the ankle pressure [the higher of the dorsalis pedis (DP) or posterior tibial (PT) artery] by the brachial systolic pressure (the higher of two arm pressures). Resting ABI is performed after a patient has been resting supine for a minimum of 10 minutes.
Bailout Stenting	The use of a bailout stent may occur in the event of persistent flow-limiting dissection not able to be treated with the Tack (or as otherwise required for safety of the subject).
Balloon Angioplasty	A catheter containing an inflatable balloon (standard or drug-coated) is advanced through a narrowed or occluded portion of an artery and inflated in order to open the artery and restore blood flow. Also referred to as "PTA" (percutaneous transluminal angioplasty).
Binary Restenosis	Greater than 50% restenosis in the treated segment as determined by duplex ultrasound derived peak systolic velocity ratio (PSVR) of ≥2.5:1.
De Novo Lesion	A lesion in the artery that has not been previously treated.

Device Deficiency	Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or user error and inadequate labeling.
Device Malfunction	A malfunction of a device to perform in accordance with its intended purpose when used in accordance with the Instructions for Use.
Device Success	Successful deployment of the Tack(s) at the intended target site(s) and successful withdrawal of the delivery catheter from the introducer sheath. If the study device is introduced but the subject does not receive a Tack due to user error and not a device malfunction, this device will not be included in the device success assessment.
Dissection	Disruption of an arterial wall resulting in separation of the intimal layer. May or may not be flow limiting.
	Dissection Types (National Heart, Lung and Blood Institute – NHLBI)
Type A	Small radiolucent area within the lumen of the vessel disappearing with the passage of the contrast material.
Type B	Appearance of contrast medium parallel to the lumen of the vessel disappearing within a few cardiac cycles.
Type C	Dissection protruding outside the lumen of the vessel persisting after passage of the contrast material.
Type D	Spiral shaped filling defect with our without delayed run-off of the contrast material in the antegrade flow.
Type E	Persistent luminal filling defect with delayed run-off of the contrast material in the distal lumen.
Type F	Filling defect accompanied by total occlusion.
Drug-Coated Balloon (DCB)	FDA-approved Lutonix drug-coated balloon catheter used for percutaneous transluminal (balloon) angioplasty.
Duplex Ultrasound (DUS)	A form of medical ultrasonography that includes the following elements on the same screen ("duplex") to facilitate interpretation 1) B-mode, pulsed Doppler display to visualize the structure within a vessel and 2) Color-Doppler display to visualize the blood flow and hemodynamics within a vessel.
Index Procedure	The interventional procedure during which treatment with the Study Device occurs.
Intent-to-treat (ITT) subjects	A subject is defined as an intent-to-treat (ITT) patient and officially enrolled in the study once the Tack Endovascular System is advanced through the introducer sheath.
Luminal Patency	Restenosis <50% as determined by angiography or duplex ultrasound.
Major Adverse Event (MAE)	Index limb amputation (above the ankle), Clinically-driven target lesion revascularization, or All-cause death
Myocardial Infarction (MI)	Q wave MI (QWMI): requires one of the following criteria: • Chest pain or other acute symptoms consistent with myocardial ischemia and new pathological Q waves in two or more contiguous ECG leads • New pathologic Q waves in two or more contiguous ECG leads and elevation of cardiac enzymes above normal.

	Non-Q Wave MI (NQWMI): defined as either: elevated CK = 2X the laboratory upper limit of normal with the presence of an elevated CK-MB (any amount above the laboratory upper limit of normal) in the absence of new pathological Q waves or elevated CK-MB = 3X the laboratory upper limit of normal in the absence of new pathological Q waves.
Peak Systolic Velocity Ratio (PSVR)	A measurement (using Duplex Ultrasonography) of peak velocity of blood (cm/sec) within a lesion or stented vessel segment that is divided by the peak velocity of blood (cm/sec) proximal to the lesion of stented segment.
Per-protocol (PP) subjects	The per-protocol (PP) population is defined as ITT subjects with evaluable data that have met the definition for device success, excluding subjects with major protocol deviations such as: ▪ A major inclusion/exclusion criterion violation; or ▪ A major procedural deviation The criteria for deviations meeting the classification of "major" will be defined before study endpoint data is available for statistical analysis. All major deviations will be adjudicated by an independent designee without visibility to study results.
Primary Efficacy Endpoint	Primary patency defined as freedom from CEC adjudicated clinically-driven target lesion revascularization (CD-TLR) and freedom from core lab adjudicated duplex ultrasound derived binary restenosis at 12 months (defined as PSVR $\geq$2.5)
Primary Safety Endpoint	Freedom from the occurrence of any new-onset major adverse event(s) (MAEs) defined as index limb amputation (above the ankle), CEC adjudicated clinically-driven target lesion revascularization (CD-TLR), or all-cause death at 30 days.
Procedure Start/End Time	Start: The time of insertion of introducer sheath End: The time of withdrawal of last post-Tack PTA balloon catheter
Procedural Success	Demonstrated vessel patency (<30% residual DS, by visual estimate) without the use of a bailout stent or the occurrence of MAE upon completion of the index procedure.
Renal Insufficiency	An increase in serum creatinine of ≥ 1.0 mg/dL over previous value requiring medical treatment but which does not require dialysis to resolve, or a serum creatinine level >2.5 mg/dL at baseline (subject should not be enrolled)
Restenosis	Reoccurrence of narrowing or blockage or target lesion.

Rutherford Classification	Clinical scale identifying three grades of claudication and three grades of critical limb ischemia ranging from rest pain alone to minor and major tissue loss. (ACC/AHA PAD Practice Guidelines – Hirsch et al. 2005)
Class	*Clinical Description*
0	Asymptomatic
1	Mild claudication
2	Moderate claudication
3	Severe claudication
4	Ischemic rest pain
5	Minor tissue loss
6	Ulceration or gangrene
Serious Adverse Device Event (SADE)	A serious adverse device effect (SADE) is defined as an adverse device effect (ADE) that results in any of the consequences characteristics of a serious adverse event (SAE). (See ADE)
Serious Adverse Event (SAE)	A serious adverse event (SAE) is defined an adverse event that: ▪ led to death ▪ led to a serious deterioration in the health of the subject, that either resulted in: ▪ a life-threatening illness or injury, or ▪ resulted in a permanent impairment of a body structure or a body function, or ▪ required in-patient hospitalization or prolongation of existing hospitalization, or ▪ resulted in medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to body structure or a body function, or ▪ led to fetal distress, fetal death or a congenital abnormality or birth defect. Note: Planned hospitalization for a pre-existing condition, or a procedure required by the investigational plan without serious deterioration in health, is not considered a serious adverse event.
Standard Balloon Angioplasty	A standard balloon catheter (non-drug-coated) used to perform percutaneous transluminal (balloon) angioplasty. Also referred to as Plain Old Balloon Angioplasty (POBA)
Stroke	A neurological deficit lasting more than 24 hours with a brain imaging study (if performed) showing infarction or hemorrhage.

Target Lesion	Has a de novo or non-stented restenotic target lesion indicated for PTA treatment with a standard or FDA-approved Lutonix drug-coated balloon catheter that meets the following criteria below: a. 70% to 99% stenosis with a total lesion length of ≥20mm and ≤150mm in length (by visual estimate) or; b. 100% occluded with a total lesion length ≤100mm (by visual estimate) Notes: A tandem lesion, defined as a lesion comprised of diseased and healthy segments, is eligible if the healthy segments are each not more than 30mm in length and all other criteria, including 3a and 3b above, are met A combination lesion, defined as a continuous lesion with both non-occluded and 100% occluded segments, is eligible if the lesion can be treated as a single lesion and all other criteria, including 3a and 3b above, are met c. A non-stented restenotic lesion must meet the following criteria: i. Meets criteria 3a and 3b ii. No part of the target lesion has been previously treated with a drug-coated balloon iii. No part of the target lesion has had more than 2 previous PTA failures iv. >90 days from most recent angioplasty treatment
Target Lesion Revascularization, Clinically-driven (CD-TLR)	Any re-intervention within the target lesion having angiographic evidence of >50% diameter stenosis and the presence of symptoms associated with the target limb (defined as an increase in Rutherford Classification and a decrease in ABI >0.15 from pre-discharge).
Target Lesion Revascularization (TLR)	A repeat revascularization procedure (percutaneous or surgical) of the original target lesion site.
Target Vessel	The superficial femoral artery (SFA) and/or proximal popliteal artery (above the knee), located ≥1 cm below the common femoral artery (CFA) bifurcation to the distal segment of the proximal popliteal (P1) artery at the superior end of the patella.
Target Vessel Revascularization, Clinically-driven non-TLR (TVR-non TLR),	Any re-intervention within the target vessel (excluding the target lesion) having angiographic evidence of >50% diameter stenosis and the presence of symptoms associated with the target limb (defined as an increase in Rutherford Classification and a decrease in ABI >0.15 from pre-discharge).
Target Vessel Revascularization, Clinically-driven (CD-TVR)	Any re-intervention within the target vessel having angiographic evidence of >50% diameter stenosis and the presence of symptoms associated with the target limb (defined as an increase in Rutherford Classification and a decrease in ABI >0.15 from pre-discharge).
Target Vessel Revascularization (TVR)	A repeat revascularization procedure (percutaneous or surgical) of the original target vessel.
Unanticipated Adverse Device Event (UADE)	An Unanticipated Adverse Device Effect (UADE) is any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan; or any other unanticipated problem associated with a device that relates to the rights, safety, or welfare of the subjects.