Clinical Study Protocol

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

Below **T**he **K**nee Arteries

Using the Tack Endovascular System® (**TOBA II BTK**)

Study Device:	Tack Endovascular System®
Protocol Number:	CA 0137
Protocol Version:	Rev C
Effective Date:	14-Sep-2017
Study Sponsor:	Intact Vascular, Inc. 1285 Drummers Lane, Suite 200 Wayne, Pennsylvania 19087 United States of America
NCT No. 02942966	

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LIST OF ACRONYMS

ABI	Ankle Brachial Index
ADE	Adverse Device Effect
AE	Adverse Event
AFS	Amputation Free Survival
AT	Anterior Tibial Artery
ATM	Atmospheres
BTK	Below The Knee
CABG	Coronary Artery Bypass Graft
CD-TLR	Clinically-Driven Target Lesion Revascularization
CD-TVR	Clinically-Driven Target Vessel Revascularization
CEC	Clinical Events 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
DP	Dorsalis Pedis Artery
DSMB	Data Safety and Monitoring Board
DUS	Duplex Ultrasound
EC	Ethics Committee
eCRF	Electronic CRF
EDC	Electronic Data Capture
EQ-5D-3L	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
IRB	Institutional Review Board
IVUS	Intravascular Ultrasound
LLL	Late Lumen Loss
LTFU	Lost to Follow-up
MALE	Major Adverse Limb Events
NHLBI	National Heart, Lung, and Blood Institute
OPG	Objective Performance Goal
P1	Proximal Popliteal Artery

LIST OF ACRONYMS

P2	Mid Popliteal Artery
P3	Distal Popliteal Artery
PA	Peroneal Artery
PAD	Peripheral Arterial Disease
PCI	Percutaneous Coronary Intervention
PI	Principal Investigator
PIC	Patient Implant Card
POD	Perioperative Death
PLT	Platelets/platelet count
PT	Posterior Tibial Artery
PSVR	Peak Systolic Velocity Ratio
PT / INR	Prothrombin time / International Normalized Ratio
PTA	Percutaneous Transluminal Angioplasty
RMA	Returned Materials Authorization
RS	Residual Stenosis
RVD	Reference Vessel Diameter
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SFA	Superficial Femoral Artery
SVS	Society of Vascular Surgery
TBI	Toe Brachial Index
TMA	Transmetatarsal Amputation
TPT	Tibioperoneal Trunk
TASC	Trans-Atlantic Inter-Society Consensus
$TcPO_2$	Transcutaneous Oximetry
TIA	Transient Ischemic Attack
TP	Toe Pressure
TL	Target Lesion
TLR	Target Lesion Revascularization
TV	Target Vessel
TVR	Target Vessel Revascularization
UADE	Unanticipated Adverse Device Effect
WIfI	Wound, Ischemia, foot Infection Score
WIQ	Walking Impairment Questionnaire
% DS	Percentage Diameter Stenosis

1. INVESTIGATOR SIGNATURE PAGE

STUDY TITLE: **TACK OPTIMIZED BALLOON ANGIOPLASTY STUDY FOR THE BELOW THE KNEE ARTERIES USING THE TACK ENDOVASCULAR SYSTEM® (TOBA II - BTK)**

STUDY CENTER: _____

(Print name of study center)

I, the undersigned, have read and understand the protocol specified above. As an Investigator, I understand that I am responsible for adhering to the terms of this protocol by ensuring the safety of study subjects enrolled under my supervision and by providing the Sponsor with complete and timely information. In addition, I understand that all information pertaining to this study shall be held strictly confidential and I will ensure that the requirement for confidentiality is understood by all study staff involved in this study. I agree to abide by the terms of this protocol and to maintain the procedures required to conduct this study in accordance with the Investigator Agreement, Good Clinical Practice (GCP), Declaration of Helsinki, 21 CFR Parts 50, 54, 56 and 812, ISO 14155:2011, and any applicable local regulations.

_____
SITE INVESTIGATOR – Print Name

_____
SITE INVESTIGATOR – Signature

_____
DATE

2. STUDY SYNOPSIS

Study Title:	**T**ack **O**ptimized **B**alloon **A**ngioplasty Study for the Below The Knee Arteries Using the Tack Endovascular System® **(TOBA II - BTK)**
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 evaluate the safety and efficacy of the Tack Endovascular System in subjects with below the knee (BTK) peripheral artery disease (PAD) as compared to a pre-defined performance goal (PG) established from published, peer reviewed scientific literature related to below-the-knee (BTK) PAD.
Study Device:	4F Tack Endovascular System manufactured by Intact Vascular, Inc.
Intended Use:	The Tack Endovascular System is intended for use in the Mid/Distal Popliteal, Tibial, and Peroneal Arteries ranging in diameter from 1.5mm to 4.5mm for the treatment of post percutaneous transluminal balloon angioplasty (PTA) dissection(s) requiring repair.
Subject Population:	Subjects with BTK PAD who receive PTA in the Mid/Distal Popliteal, Tibial, and Peroneal Arteries and have a resulting dissection(s) that the Investigator would otherwise treat by means such as, but not limited to, additional angioplasty with extended inflation time or stenting, are eligible for enrollment. To be enrolled, subjects must meet all inclusion criteria and not meet any of the exclusion criteria.
Device Regulatory Status:	4F Tack Endovascular System is a Class III Investigational Device within the United States and Class IIb within the European Union and has been designed and is manufactured by Intact Vascular, Inc. under the control of Intact Vascular's Quality Management System. Intact Vascular is ISO 13485 certified.
Enrollment:	Up to 232 subjects will be enrolled at up to 60 U.S. and International clinical sites. Each clinical site can enroll a maximum of 46 patients, establishing an enrollment cap at 20% of the subject sample size. The follow-up period for enrolled subjects that receive at least one Tack® implant is 36 months.
Primary Endpoints:	**Safety:** Freedom from major adverse limb events (MALE) plus perioperative death (POD) at 30 days defined as a composite of all-cause death, above-ankle target limb amputation, or major re-intervention to the target lesion(s) (defined as new bypass graft, jump/interposition graft revision, or thrombectomy / thrombolysis) **Efficacy:** Freedom from MALE at 6 months + POD at 30 days
Secondary Efficacy Endpoints:	▪ Target lesion(s) tacked segment(s) patency at 6 months defined as the presence of blood flow using duplex ultrasound. If angiography is available within the 6-month follow-up visit window, it should be used in place of the duplex ultrasound. Evidence of no blood flow within the Tacked segment indicates restenosis/loss of patency. ▪ Target Limb Salvage defined as freedom from any above-ankle target limb amputation at 6 months.

Observational Endpoints:	▪ Device Success: Successful deployment of the Tack implant(s) at the intended target site(s) and successful withdrawal of the delivery catheter from the introducer sheath. ▪ Target Lesion Success: Demonstrated target lesion patency [<30% residual diameter stenosis (DS), by visual estimate] without the use of a bailout stent within the target lesion upon completion of the index procedure. This will be assessed for all lesions treated with a Tack implant. In addition, target lesion success will also be analyzed by lack of bailout stent to tacked segment only. Multiple target lesions treated as one lesion with PTA will be analyzed as one lesion. ▪ Procedural Success: Demonstrated target lesion patency (<30% residual DS, by visual estimate) without the use of a bailout stent within the target lesion and without the occurrence of MALE+POD upon completion of the index procedure ▪ Amputation-free survival (AFS): Freedom from above-ankle target limb amputation or all-cause death at 6 and 12 months ▪ Freedom from MALE at 12 months + POD at 30 days ▪ Target lesion(s) tacked segment(s) patency at 12 months defined as the presence of blood flow using duplex ultrasound. ▪ Target Limb Salvage defined as freedom from any above-ankle target limb amputation at 12 months ▪ Assisted primary target lesion Tacked segment patency (flow vs. no flow) at 6 and 12 months ▪ Secondary target lesion Tacked segment patency (flow vs. no flow) at 6 and 12 months ▪ PSVR patency at 6 and 12 months [Freedom from binary restenosis defined as Peak Systolic Velocity Ratio (PSVR) of ≥ 2.5 and/or angiographic percent diameter stenosis of ≥50%] assessed for the following: o Target Lesion(s), defined as the entire contiguous arterial segment treated with angioplasty, inclusive of an additional proximal and distal margin of 5 mm o Tacked Segment(s), defined as the Tack device and 5 mm of artery proximal and distal to each Tack. If Tacks are within 10 mm of each other, they will be considered as a single tacked segment for the purposes of this patency assessment. ▪ Clinically-driven target lesion revascularization (CD-TLR) through 6 and 12 months ▪ Clinically-driven target vessel revascularization (CD-TVR) through 6 and 12 months ▪ All-cause death through 6 and 12 months ▪ Any Target vessel revascularization (TVR) through 6 and 12 months

	▪ Any Target lesion revascularization (TLR) through 6 and 12 months In addition, the following observational endpoints will be assessed at various time points through 36 months (See Time and Events Schedule **Section 8.1**): ▪ Changes in Wound, Ischemia, and foot Infection (WIfI)[1] Classification ▪ Changes in ankle brachial index (ABI) and toe brachial index (TBI) ▪ Changes in Rutherford Classification ▪ Changes in the EQ-5D-3L quality of life questionnaire ▪ Changes in the Walking Impairment Questionnaire (WIQ) ▪ Tack implant Integrity via X-ray (only performed at 12-month visit) ▪ Progress of wound(s) present at study entry (healed, improved, unchanged, worsening, amputated) ▪ Appearance of new wound(s) after study entry ▪ Unplanned below-ankle target limb amputation(s): digit or transmetatarsal
Inclusion Criteria:	1. Males or non-pregnant females ≥ 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. 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 informed consent form (ICF), an impartial witness may sign on behalf of the subject 4. Willing to comply with all required follow-up visits 5. Rutherford Classification 4 or 5 6. WIfI Wound grade of 0, 1 or modified 2 7. WIfI Foot Infection grade of 0 or 1 8. Estimated life expectancy ≥1 year
Angiographic Inclusion Criteria:	1. Reference vessel diameter is between 1.5 mm and 4.5 mm, inclusive (by visual estimate) 2. Only one limb requires treatment during the Index Procedure **Note:** If the subject has bilateral BTK disease, the Investigator should choose the limb that most closely meets eligibility criteria. If the chosen limb does not meet final eligibility after PTA treatment, the subject should not be enrolled at that time. This subject may be brought back for potential study device treatment to the contralateral limb per the

[1] Joseph L. Mills, Sr, MD, Michael S. Conte, MD, David G. Armstrong, DPM, MD, PhD, Frank B. Pomposelli, MD, Andres Schanzer, MD, Anton N. Sidawy, MD, MPH, and George Andros, MD, on behalf of the Society for Vascular Surgery Lower Extremity Guidelines Committee, The Society for Vascular Surgery Lower Extremity Threatened Limb Classification System: Risk stratification based on Wound, Ischemia, and foot Infection (WIfI). J Vasc Surg. 2014; Volume 59, Issue 1, Pages 220–234.e2

protocol requirements. Only one limb may receive study device treatment.

3. Ability to cross study device(s) antegrade through target lesion
4. Has de novo or restenotic target lesion(s) with pre-PTA stenosis of ≥70% or is occluded (by visual estimate) and is indicated for PTA treatment with a standard balloon catheter

   Note: Diseased segments with >30 mm of healthy vessel between them are considered separate target lesions

   Note: If any part of the lesion is restenotic, no part of the lesion should have more than 1 prior failure (by plain balloon angioplasty only), which must have occurred greater than 1 year (360 days) prior to the index procedure

   Note: After PTA treatment, the target lesion is defined as the entire contiguous arterial segment length treated with angioplasty

5. Target lesion(s) located in the mid popliteal (P2), distal popliteal (P3), tibioperoneal trunk, peroneal, anterior tibial, or posterior tibial arteries

   Note: The mid popliteal artery (P2) begins at the superior aspect of the patella. The most distal location of the tibial and/or peroneal artery(ies) ends at the beginning of the dorsalis pedis artery (DP). Tacks may not be implanted within 1 cm above radiographic tibiotalar joint.

6. Target vessel(s) reconstitute(s) at or above the ankle or displays normal terminal branching

   - If the target vessel is the peroneal artery, the artery must display normal terminal branching.
   - If the target vessel is the anterior tibial (AT) artery or the posterior tibial (PT) artery, the artery(ies) must display reconstitution at least 1cm proximal to the radiographic tibiotalar joint line, and continue into an intact runoff vessel (AT/ dorsalis pedis or PT/plantar artery).
   - If the target vessel is the P2 and/or P3, any 1 of the 3 distal arteries must show respective outflow.
   - If the target vessel is the TPT, then respective outflow for either the peroneal artery or posterior tibial artery must be confirmed.

   Note: Normal terminal branching and/or reconstitution of run-off vessels as described above should be confirmed prior to PTA treatment of the target lesion(s) as well as after PTA treatment to the target lesion(s) (prior to Tack deployment)

	7. Patent (<50% DS by visual estimate) arterial inflow from aortic bifurcation to the distal edge of the proximal popliteal artery (P1) at the superior end of the patella. **Note:** Treatment of inflow artery lesions within the iliac (ipsilateral or contralateral), common femoral, superficial femoral, and/or the proximal popliteal (P1) artery(ies) is allowed during the index procedure but must have documented success (<30% residual DS and no major vascular complications) prior to target lesion treatment. **Note:** If an inflow lesion requires treatment with atherectomy or requires surgical intervention, the patient should not be enrolled 8. After PTA treatment, the target lesion has <30% residual DS and presence of at least one post-PTA dissection (by visual estimate) that the Investigator would otherwise treat by means such as but not limited to additional angioplasty, with longer inflation time or stenting 9. No evidence of aneurysm or acute thrombus in target vessel
Exclusion Criteria:	1. Is pregnant or refuses to use contraception through the duration of the study 2. Previous bypass graft in the target limb 3. Acute limb ischemia, defined as symptom onset occurring less than 14 days prior to the index procedure 4. Prior or planned above-ankle amputation or complete transmetatarsal amputation to the target limb (this does not apply to ray amputation of ≤2 digits, simple digital amputations or ulcer debridements) 5. WIfI Foot Infection grade 2 or 3 6. Any systemic infection or immunocompromised state. Patients with an ascending infection/deep foot infection or abscess/white blood count (WBC)≥12,000/or febrile state 7. Endovascular or surgical procedure (not including diagnostic procedures, planned simple digital amputation or wound debridement) to the target limb less than 30 days prior to or planned for less than 30 days after the index procedure 8. Existing stent implant in the target vessel 9. Any other endovascular or surgical procedure (not including diagnostic procedures, planned simple digital amputation or wound debridement) less than 14 days prior to the index procedure or planned procedure less than 30 days after the index procedure 10. Known coagulopathy, hypercoagulable state, bleeding diathesis, other blood disorder, or a platelet count less than 80,000/microliter or greater than 500,000/microliter 11. WIfI Wound grade of 2 or 3.

	12. Any subject in which antiplatelet, anticoagulant, or thrombolytic therapy is contraindicated 13. Myocardial infarction, coronary thrombolysis or angina less than 30 days prior to the Index Procedure 14. History of stroke or transient ischemic attack (TIA) less than 90 days prior to the Index Procedure 15. Currently on dialysis 16. Known hypersensitivity or contraindication to nickel-titanium alloy (Nitinol) 17. Participating in another ongoing investigational clinical trial in which the subject has not completed the primary endpoint(s) 18. 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 19. Known hypersensitivity or allergy to contrast agents that cannot be medically managed 20. Subject already enrolled into this study 21. Restenotic target lesion previously treated by means other than plain balloon angioplasty and/or less than 1 year prior to index procedure.
Angiographic Exclusion Criteria:	1. Acute vessel occlusion or acute or sub-acute thrombosis in target lesion 2. Subject has significant stenosis (≥50% DS) or occlusion of inflow arteries (including the iliac, superficial femoral and proximal popliteal arteries) not successfully treated (<30% residual DS and without major complication) prior to PTA of target lesion 3. The target lesion shows no dissections after PTA or dissections of a lesser grade for which the operator would normally not pursue additional treatment 4. If parallel non-target vessel (anterior tibial, peroneal, or posterior tibial) is treated during index procedure and is not successful (<30% residual DS and without major complication) prior to PTA of target lesion/vessel 5. Below the ankle lesion requiring treatment 6. Use of atherectomy, cryoplasty, cutting/scoring/contoured balloon angioplasty, stenting or any other treatment (with the exception of a crossing device) of the target lesion/vessel other than plain balloon angioplasty PTA during the index procedure **Note:** Use of atherectomy in a parallel, non-target vessel is allowed during the index procedure but must have documented success (<30% residual DS and no major vascular complications) prior to target lesion/vessel treatment

3. Study Management Contact List

Please see **APPENDIX A – Study Management Contact List** located at the end of this document.

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.[2] 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.[3, 4] CLI has a yearly incidence of approximately 220 new cases per million population.[5]

Critical limb ischemia remains a significant problem associated with morbidity and mortality. Per, Conte, et al, one year mortality ranges from 10% to 40% and with no revascularization interventions, up to 40% of those affected will suffer limb loss within 6 months.[6] According to a publication by Iida, et al, CLI is associated with a high mortality rate (19%-54% at one year) and a high amputation rate (≥25%) at 6 months after failure of primary revascularization.[7]

Infrapopliteal arterial occlusive disease is a leading source of CLI.[8] The treatment approach for these patients ranges from medical management to surgical management which can consist of either revascularization or amputation.[9] Critical limb ischemia is attributed to severe compromise of the blood flow to the affected extremity which manifests as significant limb pain at rest. It results from a chronic lack of blood supply. Per Varu, et al. the international consensus on the definition of CLI is "any patient with chronic ischemic rest pain, ulcers, or gangrene attributable to objectively proven arterial occlusive disease." Many of these patients, have extended diffuse three-vessel disease and only 20-30% present with a simple focal lesion and good runoff.[10] The primary goal of the treatment of CLI is relief of ischemic rest pain, healing of

[2] Davies MG, El-Sayed HF. Objective performance goals after endovascular intervention for critical limb ischemia. J Vasc Surg. 2015;621555-63.
[3] 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.
[4] McDaniel MD, Cronenwett JL. Basic data related to the natural history of intermittent claudication. Ann Vasc Surg. 1989;3:273-277.
[5] Van Overhagen, Spiliopoulus S, Tsetis D. Below-the-Knee Interventions. Cardiovasc Intervent Radiol. 2013; 36:302-11.
[6] Conte MS, Geraghty PJ, Bradbury AW, Hevelone ND, Lipsitz SR, Moneta GL, Nehler MR, Powell RJ, Sidawy AN. Suggested objective performance goals and clinical trial design for evaluating catheter-based treatment of critical limb ischemia. J Vasc Surg. 2009;50:1462-73.
[7] Iida O, Nakamura M, Yamauchi Y, Kawasaki D, Yokoi Y, Yokoi H, Soga Y, Zen K, Hirano K, Suematsu N, Inoue N, Suzuki K, Shintani Y, Miyashita Y, Urasawa K, Kitano I, Yamaoka T, Murakami T, Uesugi M, Tsuchiya T, Shinke T, Oba Y, Ohura N, Hakasaki T, Nanto S, OLIVE Investigators. Endovascular treatment for infrainguinal vessels in patients with critical limb ischemia: OLIVE registry, a prospective, multicenter study in Japan with 12-month follow-up. Circ Cardiovasc Interv. 2013;6:68-76.
[8] Van Overhagen, Spiliopoulus S, Tsetis D. Below-the-Knee Interventions. Cardiovasc Intervent Radiol. 2013; 36:302-11.
[9] Varu VN, Hogg ME, Kibbe MR. Critical Limb Ischemia. J Vasc Surg. 2010; 51:230-41.
[10] Randon C, Jacobs B, De Ryck F, Vermassen F. Angioplasty or primary stenting for infrapopliteal lesions: results of a prospective randomized trial. Cardiovasc Intervent Radiol. 2010 Apr;33(2):260-9.

ulcers or gangrene, and prevention of limb loss.[11,12] While tibial bypass is often utilized, it is associated with a 1.8%-6% perioperative mortality.[13] As a result, less invasive endovascular treatments have been utilized to achieve revascularization.

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 below the knee (BTK) arteries. The goal in treating patients with PAD is to provide relief of symptoms and to restore at least one straight line of blood flow to the distal foot.[14] In the more advanced cases, the goal is to preserve tissue or limb salvage. Percutaneous transluminal angioplasty (PTA) alone is the most common method of endovascular therapy for BTK arteries.[15] Percutaneous transluminal angioplasty, however, is limited by recoil, dissection, thrombosis and early restenosis. Recently, Trans-Atlantic Inter-Society Consensus (TASC) guidelines were updated with lesion characterization guidelines for the infrapopliteal segment; however no treatment guidelines have been presented to date.[16]

The Tack Endovascular System has been designed to provide a treatment solution for post-PTA dissection in the BTK arteries. To assist in both developing a comparative baseline and to assist in clinical protocol development for the Tack Endovascular System, a project was initiated to research the peer-reviewed clinical literature to outline the clinical results of the use of PTA in the BTK/infrapopliteal arteries and the associated treatment of dissections. Elements of that review are summarized below.

As stated previously, the primary clinical goal of infrapopliteal arterial interventions for CLI is to restore at least one unobstructed line of blood flow to the distal foot with the intention of preventing major amputation. There are several endovascular treatment options that are utilized to accomplish this including PTA with traditional balloons, PTA with drug-eluting balloons (DEB) or the placement of bare metal stents (BMS) or drug-eluting stents (DES). To develop a comprehensive overview of these interventions, clinical data was obtained and evaluated from the literature for all of these technologies.[17]

After analysis of the peer-reviewed literature, it was determined to focus on PTA. The Intact Vascular Tack Endovascular System is a first of its kind device where no such FDA approved device for treatment of post-PTA vessel dissections exists. As a consequence, a direct comparator is not available. Under current treatment protocols, dissections that occur following PTA would typically be treated with the off-label placement of a stent. When the intent is to treat a lesion

[11] Randon C, Jacobs B, De Ryck F, Vermassen F. Angioplasty or primary stenting for infrapopliteal lesions: results of a prospective randomized trial. Cardiovasc Intervent Radiol. 2010 Apr;33(2):260-9.
[12] Van Overhagen, Spiliopoulus S, Tsetis D. Below-the-Knee Interventions. Cardiovasc Intervent Radiol. 2013; 36:302-11.
[13] Randon C, Jacobs B, De Ryck F, Vermassen F. Angioplasty or primary stenting for infrapopliteal lesions: results of a prospective randomized trial. Cardiovasc Intervent Radiol. 2010 Apr;33(2):260-9.
[14] Karnabatidis D, Katsanos K, Siablis D. Infrapopliteal stents: Overview and unresolved issues. J Endovasc Ther. 2009;16(Suppl I):I153-I162.
[15] Razavi MK, Mustapha JA, Miller LE. Contemporary systematic review and meta-analysis of early outcomes with percutaneous treatment for infrapopliteal atherosclerotic disease. J Vasc Interv Radiol. 2014 Oct;25(10):1489-96.
[16] TASC Steering Committee, Jaff MR, White CJ, Hiatt WR, Fowkes GR, Dormandy J, Razavi M, Reekers J, Norgren L. An Update on Methods for Revascularization and Expansion of the TASC Lesion Classification to Include Below-the-Knee Arteries: A Supplement to the Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). J Endovasc Ther. 2015;22(5):663-77.
[17] Intact Vascular Document EXT-17-0069 (Clinical review of scientific literature for the endovascular treatment of CLI and treatment of post-PTA dissections in the peripheral vasculature: Below-the-Knee Arteries).

with only balloon angioplasty, the use of a Tack device to treat a vessel wall dissection is more consistent with the plan to leave as little metal behind as possible, in contrast to placement of a stent. With this in mind, PTA results were concluded to be the most appropriate treatment to provide clinical data on endovascular interventions in the BTK arteries for the TOBA clinical trial design.

One outcome of the review was the conclusion that often the clinical results demonstrate a discrepancy between patency and clinical success measures such as limb salvage and patient survival. Based on the literature review, the primary patency rate following PTA treatment for below knee lesions varied from 18% to 82%. This wide range in reported patency is due in large part to variability in key patient and procedural characteristics across studies, such as treated lesions (lesion lengths, number of treated lesions/vessels, stenotic vs occluded), the method of lesion treatment (PTA only, PTA with stents, pre-treatment with atherectomy or laser), allowance for associated treatment of inflow and outflow lesions, definition and method of measuring lesion/vessel patency (clinical, duplex ultrasound, magnetic resonance angiography, angiography, computed tomographic angiography), as well as composition of patient types (studies that focused CLI vs below knee lesions, or on diabetics, or on patients with chronic renal failure). Due to the fact that the Tack device is a first of its kind device and there exists no known comparator, the use of relevant PTA outcome data is a reasonable approach in establishing the current state of the art in the peer-reviewed clinical literature. While data are limited, this assessment identified information that was successful in identifying literature results on per patient and per lesion patency that could be used for this purpose. This analysis resulted in an overall patency range per limb of 18%-82% and per patient of 38%-66% at one year. Where reported at 6 months, patency rates per limb/lesion of 35.1%-91% and per patient of 65%-76% were observed. When Kaplan-Meier curves were presented, 6 month rates were estimated unless otherwise specifically reported. The corresponding limb salvage range at one-year was 84%-100% and the patient survival range at one-year was 68.4%-94.8%. The clinical data summary did demonstrate that there are clinical benefits associated with the use of endovascular interventions in the BTK arteries. While there is variability in the data reported, the review indicated that the most commonly reported outcomes are limb salvage (and/or amputation free survival/amputation rate) and patient survival. Patency is reported less consistently. All clinical endpoints were associated with large ranges for the reported data.

Due to the variability in the generally reported clinical data, several outcome measures for below-the-knee interventions were identified utilizing the guidance provided in publications that have been focused on developing objective performance goals for endovascular treatment of CLI. These objective performance goals (OPGs) and associated classification systems were developed by the Society of Vascular Surgery (SVS)[18,19,20] and published by Conte, et al. and serve to provide a consistent framework for the evaluation of new catheter-based treatments in CLI based on evidence from historical controls. They consist of both safety (30 days) and efficacy profiles (1

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

[19] Goodney PP, Schanzer A, Demartino RR, Nolan BW, Hevelone ND, Conte MS, Powell RJ, Cronenwett JL; Vascular Study Group of New England. Validation of the Society for Vascular Surgery's objective performance goals for critical limb ischemia in everyday vascular surgery practice. J Vasc Surg. 2011 Jul;54(1):100-108.

[20] Mills JL, Conte MS, Armstrong DG, Pomposelli FB, Schanzer A, Sidawy AN, Andros G, Vascular Surgery Lower Extremity Guidelines Committee. The Society for Vascular Surgery Lower Extremity Threatened Limb Classification System: Risk stratification based on Wound, Ischemia, and foot Infection (WIfI). J Vasc Surg. 2014:59:220-34.

year). The SVS OPG values that were reviewed were those for the "Anatomical High Risk Group" as defined by Conte. Data from recent studies that have reported on the use of OPGs are summarized in **Table 1** and **Table 2**.[21,22,23]

Table 1. OPG Summary—Safety (30 Days)—Anatomical High Risk Group (Infrapopliteal)

Measure	OPG		PTA (Literature Reported)	
	30 Day	1 Year	30 Day	1 Year
MACE	10%		0.0%-5.0%	
MALE	9%		2.5%-13.0%	
Amputation	4%		1.7%-5.0%	

MACE: Major Adverse Cardiovascular Event—MI, Stroke, All Cause Death
MALE: Major Adverse Limb Event—Above-Ankle Amputation, Major Intervention

Table 2. OPG Summary—Efficacy (1 Year)—Anatomical High Risk Group (Infrapopliteal)

Measure	OPG		PTA (Literature Reported)	
	30 Day	1 Year	30 Day	1 Year
Freedom from MALE+POD		67%		76.0%-86.0%
AFS		68%		67.0%-78.7%
Limb Salvage		81%		83.0%-87.0%
Survival		80%		83.0%-87.0%

MALE: Major Adverse Limb Event—Above-Ankle Amputation, Major Intervention
POD: Perioperative Death
AFS: Amputation Free Survival

This analysis of the relationship of patency with the clinical outcomes of limb salvage and survival correlates with information reported elsewhere in the clinical literature. From the literature, the most suitable clinical outcome measures to assess clinical success in BTK CLI interventions are safety as assessed by perioperative death (POD) and major adverse limb events (MALE) coupled with the clinical efficacy measure associated with limb salvage and survival. These align with the objective performance goals proposed by Conte, et al. For the proposed clinical study, OPG measurements are proposed with a focus on freedom from all cause of death and MALE at 30 days, freedom from MALE+POD at 6 months and amputation-free survival at 6 months (Limb

[21] Davies MG, El-Sayed HF. Outcomes of Isolated Tibial Endovascular Interventions for Tissue Loss in CLI Patients on Hemodialysis. J Endovasc Ther. 2015;22(5):681-9
[22]Nakano M, Hirano K, Iida O, Yamauchi Y, Soga Y, Kawasaki D, Tazaki J, Suzuki K, Fujiwara M, Yamaoka T. Clinical efficacy of infrapopliteal endovascular procedures for hemodialysis patients with critical limb ischemia. Ann Vasc Surg. 2015;29(6):1225-34
[23] Varela C, Acin F, de Maturana IL, de Haro J, Bleda S, Paz B, Esparza L. Safety and efficacy outcomes of infrapopliteal endovascular procedures performed in patients with critical limb ischemia according to the Society for Vascular Surgery Objective Performance Goals. Annals Vasc Surg. 2014; 28:284-294

Salvage). The OPG for 6 months is extrapolated directly from the data provided in Conte, et. al. as noted above using identical methodology.

A review of post-PTA dissections and their impact was also conducted. Few articles reported any data related to dissections in the BTK arteries; however, summaries from those that did is presented below.

The assessment determined that the occurrence of dissection in the BTK arteries ranges from 6.4%-30.7%.[24,25,26,27] Razavi, et al., states related to dissection, "*It is conceivable that the reported dissection rates in the BTK vessels may have been underestimated because they are harder to detect as a result of their smaller diameters and frequent interference with optimal visualization by osseous structures*."

In a study of DEBs versus PTA (in which 24.6% of the patients were treated in the BTK arteries), Fanelli, et al. noted that "*Another interesting result is correlated with dissections that occurred after angioplasty; in DEB group non-flow limiting dissection occurred in 9 over 57 treated lesions (15%) but none of them developed a significant restenosis (flow-limiting dissection) during the follow-up. In those lesions treated with non-coated balloons, a dissection not limiting the blood flow occurred in 20 cases (20/65, 30.7%) but 16 (16/65, 24%) of them developed a significant restenosis during follow-up*." They further go on to discuss that "*as reported in other articles[28] in case of dissections not limiting the blood flow, provisional stenting can be avoided."* The authors do highlight that this is a fairly recent trend in reporting and that further studies with larger populations are required to fully understand the implications.

One study that did address the rate of dissection in the BTK arteries was the IN.PACT clinical study (Zeller, et al.).[29] The study was designed to assess the efficacy and safety of a DEB compared to PTA. As an element of reporting on post-procedural complications, the freedom from post-procedural dissection was presented. The rate was higher in the DEB arm (87.7%) versus the PTA arm (80.8%). In each arm, most dissections were considered "mild" and non-flow limiting. The corresponding bailout stent rates were 2.3% and 2.8% in the DEB and PTA arms, respectively. This was the only study identified that discussed dissections in more detail that utilized independent core lab adjudication of the data.

[24] Fanelli F, Cannavale A, Boatta E, Corona M, Lucatelli P, Wlderk A, Cirelli C, Salvatori FM. Lower limb multilevel treatment with drug-eluting balloons: 6-month results from the DEBELLUM randomized trial. J Endovasc Ther. 2012 Oct;19(5):571-80

[25] Fanelli F, Cannavale A, Corona M, Lucatelli P, Wlderk A, Salvatori FM. The "DEBELLUM"--lower limb multilevel treatment with drug eluting balloon—randomized trial: 1-year results. J Cardiovasc Surg (Torino). 2014 Apr;55(2):207-16

[26] Randon C, Jacobs B, De Ryck F, Vermassen F. Angioplasty or primary stenting for infrapopliteal lesions: results of a prospective randomized trial. Cardiovasc Intervent Radiol. 2010 Apr;33(2):260-9

[27] Razavi MK, Mustapha JA, Miller LE. Contemporary systematic review and meta-analysis of early outcomes with percutaneous treatment for infrapopliteal atherosclerotic disease. J Vasc Interv Radiol. 2014 Oct;25(10):1489-96

[28] Fanelli F, Cannavale A, Gazzetti M, D'Adamo A. How Do We Deal With Dissection After Angioplasty? J Endovasc Ther. 2013;20:801-4; 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.

[29] Zeller T, Baumgartner I, Scheinert D, Brodmann M, Bosiers M, Micari A, Peeters P, Vermassen F, Landini M, Snead DB, Kent KC, Rocha-Singh KJ; IN.PACT DEEP Trial Investigators. Drug-eluting balloon versus standard balloon angioplasty for infrapopliteal arterial revascularization in critical limb ischemia: 12-month results from the IN.PACT DEEP randomized trial. J Am Coll Cardiol. 2014 Oct 14;64(15):1568-76.

An additional report that addressed dissection was a single study that reported dissections by grade for PTA.[30] In this study, the reported dissection rates by grade were 33% Type A, 33% Type B, 16.7% Type D and 16.7% Type F. Similar to previously compiled data for the superficial femoral artery (SFA) and popliteal artery, most dissections were lower grade (A/B).

There has been recent discussion in the literature about the clinical implications of dissections. While the direct impact remains unclear, there is interest in investigating the correlation between dissection and restenosis. The literature does highlight that there is a fairly recent trend in reporting dissections and that further studies with larger populations are required to fully understand the implications. It was also noted in the literature that as with other peripheral interventions, dissections are often under-reported. The Tack Endovascular System is designed to provide a treatment option for all grade dissections.

4.2. Report of Prior Investigations

Intact Vascular has developed the Tack Endovascular System, a system designed to provide apposition of dissected tissue with an implantable, cylindrical nitinol (nickel-titanium) Tack implant following percutaneous transluminal balloon angioplasty (PTA). Intact Vascular is currently conducting a clinical study in below-the-knee arteries (TOBA-BTK) and a United States pivotal investigation device exemption (IDE) study of the 6Fr device in the femoropopliteal arteries.

The TOBA-BTK Study (Prospective, Multicenter Tack Optimized Balloon Angioplasty Below the Knee (TOBA - BTK) Study for Infrapopliteal Arteries Using the *Tack Endovascular System® (Protocol# TD 0109 Rev D))* is a prospective, single arm, multi-center, first in man study designed to collect data in support of safety and performance of the Intact Vascular *Tack Endovascular System®* for tissue apposition in peripheral arteries with reference vessel diameters (RVD) ranging from 1.5-4.5mm. Specifically, the population for this study included subjects with critical limb ischemia (Rutherford Class 4-5) that had angiographic evidence of type A-F dissection following below the knee (BTK) percutaneous transluminal angioplasty (PTA). TOBA-BTK was a feasibility study designed to assess 30-day safety and ease of use. Long-term follow-up will be conducted through 24 months. Currently, data through 12 months is available.

The inclusion criteria for the TOBA-BTK study was:

- Rutherford 4 or 5
- RVD 1.5 – 4.5mm
- Lesion located between knee joint and ankle
- De novo lesion ≥70% stenotic or occluded
- Up to 2 tibial arteries can be treated with cumulative length of ≤15cm
- Presence of post PTA dissection

The exclusion criteria for the TOBA-BTK study was:

- Stenosis or occlusion of inflow vessels not successfully treated
- Previous inflow vessel treatment failure

[30] Shammas NW, Lam R, Mustapha J, Ellichman J, Aggarwala G, Rivera E, Niazi K, Balar N. Comparison of orbital atherectomy plus balloon angioplasty vs. balloon angioplasty alone in patients with critical limb ischemia: results of the CALCIUM 360 randomized pilot trial. J Endovasc Ther. 2012 Aug;19(4):480-8

- Previous below the knee bypass
- Lesion on plantar surface of heel or Achilles tendon or exposed calcaneus

Subjects with an optimal result (i.e. no dissections) following primary balloon angioplasty were screen failures. Subjects with suboptimal angioplasty results (i.e. the presence of post-PTA dissections) were enrolled and treatment with the Tack implant was attempted. If a Tack implant was attempted, but the Tack device(s) was not successfully deployed and implanted into the subject, the subject was followed for 1 month and then exited from the study. The protocol scheduled follow-up visits were to occur at 1, 3, 6, 12, and 24 months. The primary safety endpoint for this study included a safety composite of MALE and POD, which was assessed at 1-month post-procedure. Major adverse limb events included major amputation (amputation above the ankle) or re-intervention (surgical or endovascular) in the target limb. Additional primary endpoints included:

- Device success – successful delivery and deployment of the study implant(s) at the intended target site(s) and successful withdrawal of the delivery catheter.
- Procedure success – Demonstrated vessel patency as reported by the physician (visual estimate) without the occurrence of MALE + POD on the date of procedure.

Secondary endpoints included:

- All-cause mortality at 3, 6, 12, and 24 months
- Amputation of the limb (above the ankle) at 3, 6, 12, and 24 months
- Amputation free survival at 3, 6, 12, and 24 months
- Clinically driven target vessel revascularization (TVR) at 3, 6, 12, and 24 months
- Clinically driven target lesion revascularization (TLR) at 3, 6, 12, and 24 months
- Changes in Rutherford Clinical Category from baseline at 3, 6, 12, and 24 months
- Maintenance of luminal patency of the target lesion by toe brachial index (TBI) (≤0.15 decrease) as compared to the baseline TBI obtained prior to discharge at 1, 3, 6, 12, and 24 months
- Doppler Exam (presence of signal) at 1, 3, 6, 12, and 24 months

A total of 35 subjects were enrolled, all of which are included in the safety sample. Of these 35 subjects, 32 had at least one Tack implant placed. These 32 subjects are included in the performance sample. In the other three subjects, Tack implant(s) were attempted, but device catheters could not reach treatment site(s). These 3 subjects were followed for 30 days post-treatment for safety analysis. Three (3) additional subjects in the performance sample exited the study prior to the 12-month follow-up visit, one prior to 30 days and two prior to 12 months.

Demographics for the TOBA-BTK Trial subjects are summarized below in **Table 3**.

Table 3. TOBA-BTK Trial Subject Demographics

Parameter	Safety Sample N = 35	Performance Sample N = 32
Age at Procedure (mean ± stdev)	76.1 ± 9.3 (35)	76.1 ± 9.5 (32)
(minimum, median, maximum)	(55, 77.0, 91)	(55, 77.0, 91)
Gender		
Female	48.6% (17 / 35)	43.8% (14 / 32)
Male	51.4% (18 / 35)	56.3% (18 / 32)
Ethnicity		
Non-Hispanic or Latino	100.0% (35 / 35)	100.0% (32 / 32)
Race		
White	100.0% (35 / 35)	100.0% (32 / 32)
History of Hypertension	91.4% (32 / 35)	90.6% (29 / 32)
History of Smoking		
No	61.8% (21 / 34)	58.1% (18 / 31)
Yes - Current (within last 3 months)	5.9% (2 / 34)	6.5% (2 / 31)
Yes - Former (stopped > 3 months ago)	29.4% (10 / 34)	32.3% (10 / 31)
Yes - Not Specified	2.9% (1 / 34)	3.2% (1 / 31)
History of Diabetes Mellitus	77.1% (27 / 35)	81.3% (26 / 32)
Diet	11.4% (4 / 35)	12.5% (4 / 32)
Insulin	42.9% (15 / 35)	46.9% (15 / 32)
Oral Medications	34.3% (12 / 35	34.4% (11 / 32)
Previous Peripheral Vascular Revascularization	45.7% (16 / 35)	43.8% (14 / 32)
BMI (mean ± stdev)	28.2 ± 4.2 (34)	28.3 ± 4.2 (31)
(minimum, median, maximum)	(22, 27.6, 39)	(22, 27.6, 39)

Baseline clinical assessments of the target limb are summarized below in **Table 4**. Clinical assessments were used to measure the extent of peripheral artery disease in the target limb at baseline (pre-treatment) and at the 30-day follow up. The majority of the subjects (88.6% safety sample; 87.5% performance sample) were Rutherford category 5 with the remainder being category 4.

The ankle-brachial index (ABI) for the treated leg for the safety and performance samples were 0.95 ± 0.42 and 0.91 ± 0.41, respectively. In the safety sample, 48.6% of subjects report no leg pain, of the remaining subjects 28.6% and 28.6% reported pain at rest and pain on exercise, respectively.

Table 4. TOBA-BTK Trial Baseline Clinical Assessment of Target Limb

Parameter	Safety Sample N = 35	Performance Sample N = 32
Target Limb		
Left	40.0% (14 / 35)	34.4% (11 / 32)
Right	60.0% (21 / 35)	65.6% (21 / 32)
Number of Patent Tibial / Peroneal Vessels in the Target Limb		
1	42.9% (15 / 35)	46.9% (15 / 32)
2	42.9% (15 / 35)	37.5% (12 / 32)
3	14.3% (5 / 35)	15.6% (5 / 32)
ABI treated leg (mean ± stdev)	0.95 ± 0.42 (35)	0.91 ± 0.41 (32)
(minimum, median, maximum)	(0.0, 0.94, 1.9)	(0.0, 0.93, 1.9)
TBI treated leg (mean ± stdev)	0.49 ± 0.30 (24)	0.47 ± 0.28 (23)
(minimum, median, maximum)	(0.0, 0.47, 1.1)	(0.0, 0.46, 1.1)
Subject Pain Symptoms for Target Limb (check all that apply)		
No Leg Pain	48.6% (17 / 35)	46.9% (15 / 32)
Rest pain	28.6% (10 / 35)	28.1% (9 / 32)
Pain on exercise	28.6% (10 / 35)	31.3% (10 / 32)
Rutherford Clinical Category for Target Limb		
4	11.4% (4 / 35)	12.5% (4 / 32)
5	88.6% (31 / 35)	87.5% (28 / 32)

The mean pre-PTA percent diameter stenosis per lesion was 72.3%± 17.4 and 73.0%± 17.8, for the safety and performance samples, respectively. Total occlusion comprised eight of the lesions (22.2% safety sample, 24.2% performance sample). Of all dissections reported (Safety Sample), the most frequently reported worst dissection grade was B (40.5%) followed by A (35.7%), C (19.0%), and D (4.8%). The worst post-PTA dissection grades pre-Tack at Tack sites were A (21.2%), B (60.6%), and C (18.2%). The mean number of Tack implant(s) used in the Performance Sample was 2.8±2.0 with a range of 1 to 12 per lesion. Tack implant(s) were successfully delivered in 33/36 (91.7%) lesions. Three individual lesions in three subjects were not successfully treated as in each case, the catheter was not able to be advanced to the lesion location. Of the successfully placed Tack implant(s), the post-Tack implant dissection grade was 0 in 32/33 (97.0%) and B in 1/33 (3.0%). Tack implant locations to treat the dissections included anterior tibial artery (32.6%), tibio-peroneal trunk (30.4%), peroneal artery (20.7%), and posterior tibial artery (16.3%). In greater than 89.7% of the Performance Sample vessels, the Tack was placed on the proximal edge of the dissection being treated and in 76.9% of the vessels the Tack was placed on the distal edge of the dissection.

Device success, which was defined as the ability to successfully deliver and deploy the Tack implant(s) to the intended target sites was successfully achieved in 32/35 (91.4%; 95% CI 77.6, 97.0) subjects. In all three subjects where device success was not achieved, the physician was unable to advance the device to the desired position due to tortuous vessel anatomy and/or torque transmission in the delivery catheter. Procedure Success was defined as demonstrated

vessel patency as reported by the physician (visual estimate) without occurrence of MALE + POD on the date of procedure. Procedure success was achieved in 34/35 (97.1%; 95% CI 85.5, 99.5) subjects in the Safety Sample and 31/32 (96.9%; 95% CI 84.3, 99.5) in the Performance Sample. These data support that the Tack device performed as intended in this subject cohort.

ABI was significantly ($p<0.05$) improved at all time points. At all post-procedure time points there was a significant ($p<0.05$) in audible Doppler signal. Specifically, at 12 months, 10/34 lesions improved, 23/34 had no change, and 1/34 was worse.

Table 5 below summarizes amputation-free survival, survival, freedom from amputation, freedom from clinically driven TVR, and freedom from clinically driven TLR for all subjects. At 12 months, the amputation free-survival rate was 84.5% (95% CI; 66.6, 93.2) and freedom from clinically driven TVR and TLR was 93.5% (95% CI; 76.6, 98.3).

Table 5. Summary for Amputation-Free Survival, Survival and Freedom from Amputation, Clinically Driven Target Vessel Revascularization and Clinically Driven Target Lesion Revascularization in All Enrolled Patients

Parameter	30 Days	3 Month	6 Month	12 Month
Amputation-free survival, composite of death/amputation	100%	93.8%	93.8%	84.5%
Survival	100%	97%	97%	97%
Freedom from amputation of the limb (above the ankle)	100%	96.8%	96.8%	87.1%
Freedom from clinically driven target vessel revascularization (TVR)	100%	100%	93.5%	93.5%
Freedom from clinically driven target lesion revascularization (TLR)	100%	100%	93.5%	93.5%

Primary patency was defined post-hoc as presence of a Doppler signal, freedom from clinically driven target lesion revascularization (CD-TLR) and major amputation (above the knee). Primary patency was determined per patient and per vessel. Primary patency is lost at the first occurrence of CD-TLR, major amputation or lack of an audible signal observed at the 1, 3, 6 or 12 month follow-up.

Table 6 below summarizes the estimates for primary patency by vessel and by patient. At the close of the 6 and 12 month visit windows, the primary patency per patient was 80.6% and 66.4%, respectively.

Table 6. Comparison of Per Vessel and Per Patient Estimates for Primary Patency in TOBA-BTK Study at 6 and 12 months

Time Frame in Months	Kaplan Meier Day	Per Vessel	Per Patient
6	180	86.5% (70.5, 94.1)	87.1% (69.2, 95)
	210*	81.1% (64.4, 90.5)	80.6% (61.9, 90.8)
12	360	78.4% (61.4, 88.5)	77.4% (58.4, 88.5)
	390*	67.2% (38.6, 84.7)	66.4% (37.5, 84.2)

*Close of 6 or 12 month visit window.

Twenty-six (26) subjects experienced a total of 111 adverse events (AEs). Overall, there were 55 serious adverse events (SAEs). Of these serious adverse events, one was serious and considered to be probably related to the device. The device-related SAE was a high grade re-obstruction of

the target lesion 107 days post-procedure requiring target lesion revascularization. Five (5) AEs were serious and considered to be possibly related or related to the procedure. The procedure-related SAEs were:

- Hematoma of the right groin spreading into the abdominal wall on the day of the procedure that required prolonged hospitalization. The subject recovered without sequelae.
- Restenosis of Tack-treated segment at 115 days post-procedure that required PTA and prolonged hospitalization. The subject recovered without sequelae.
- Patient presented to the emergency department complaining of a 1 week history of left leg swelling. The symptoms started 4 days post-procedure and the subject was admitted to the hospital and worked up to eliminate deep vein thrombosis, which was ruled out by ultrasound. The subject recovered without sequelae.
- Access site complication on the day of the procedure requiring intervention. Subject had an unresolved right SFA stenosis requiring femoral endarterectomy and patch. The subject recovered with sequelae.
- Residual stenosis of right common iliac artery at 102 days post-procedure. Residual stenosis was revealed on ultrasound and repeat angioplasty with an 8 mm Omnilink stent placed. The subject recovered without sequelae.

Forty-nine (49) additional events were serious, but did not have a causal relationship to the device or the procedure. The most common SAEs not related to the procedure or the device were local infection requiring treatment (11 events; 5 subjects), minor amputation (7 events; 4 subjects), and systemic infection (4 events; 2 subjects). There were no reports of Unanticipated AEs or Unanticipated Adverse Device Effects (UADEs).

Overall, the Tack Endovascular System demonstrated encouraging clinical results both for safety and efficacy. When comparing these results to the literature-derived values for PTA alone, the use of the Tack device demonstrates a potential clinical benefit for patients who have post-PTA BTK dissections.

5. INVESTIGATIONAL DEVICE

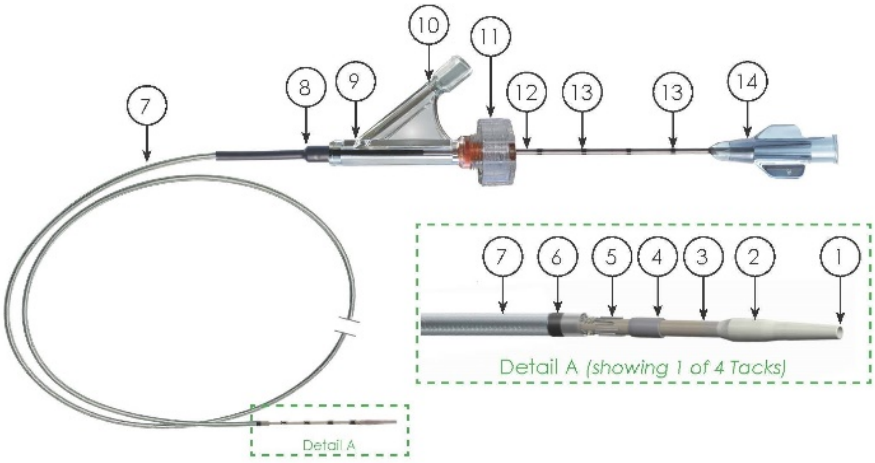
5.1. DESCRIPTION

The *Tack Endovascular System* is designed to treat vascular dissections with *Tack* implant(s) following angioplasty in the mid/distal popliteal, tibial and peroneal arteries, ranging 1.5 mm to 4.5 mm in diameter. The 4F (1.33 mm) catheter contains 4 independent self-expanding *Tack* implants 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.

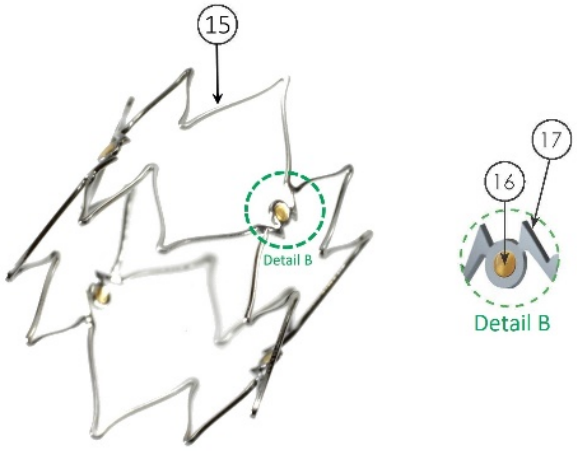
5.2. PRINCIPLES OF OPERATION

The *Tack Endovascular System* consists of 4 self-expanding Nitinol implants and a 4F (1.33 mm) Delivery Catheter (See **Figure 1** below). The numbers in parentheses in the following section refer to those in **Figure 1**.

Figure 1. The *Tack Endovascular System* (representative image)



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 *Tack* implants are approximately 6mm in length and expand to an unconstrained diameter of 5.7 mm (See **Table 7** 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 1.5 to 4.5mm. Four RO Markers (16) as well as four pairs of Anchors (17) are located around the centerline of each *Tack* implant. The anchors assist in maintaining proper *Tack* implant position.

Table 7. Tack Implant Length at Various Diameters

Diameter	Length
1.1 mm (Constrained implant)	6.50
1.5 mm (Deployed implant)	6.48
4.5 mm (Deployed implant)	6.24
5.7 mm (Unconstrained implant)	5.90

The delivery catheter has an effective length of 90cm and 150cm. The 4F 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 five 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.

5.3. INTENDED USE

The Tack Endovascular System is intended for use in the Mid/Distal Popliteal, Tibial, and Peroneal Arteries ranging in diameter from 1.5 mm to 4.5 mm for the treatment of post percutaneous transluminal balloon angioplasty (PTA) dissection(s) requiring repair.

6. Clinical Study Objectives

6.1. Primary Endpoints

Safety: Freedom from major adverse limb events (MALE) plus perioperative death (POD) at 30 days defined as a composite of all-cause death, above-ankle target limb amputation, or major re-intervention to the target lesion(s) (defined as new bypass graft, jump/interposition graft revision, or thrombectomy / thrombolysis).

Efficacy: Freedom from MALE at 6 months + POD at 30 days.

6.2. Secondary Endpoints

- Target lesion(s) tacked segment(s) patency at 6 months defined as the presence of blood flow using duplex ultrasound. If angiography is available within the 6-month follow-up visit window, it should be used in place of the duplex ultrasound. Evidence of no blood flow within the Tacked segment indicates restenosis/loss of patency.
- Target Limb Salvage defined as freedom from any above-ankle target limb amputation at 6 months.

6.3. Observational Endpoints

- Device Success: Successful deployment of the Tack implant(s) at the intended target site(s) and successful withdrawal of the delivery catheter from the introducer sheath.
- Target Lesion Success: Demonstrated target lesion patency [<30% residual diameter stenosis (DS), by visual estimate] without the use of a bailout stent within the target lesion upon completion of the index procedure. This will be assessed for all lesions treated with a Tack implant. In addition, target lesion success will also be analyzed by lack of bailout stent to tacked segment only. Multiple target lesions treated as one lesion with PTA will be analyzed as one lesion.
- Procedural Success: Demonstrated target lesion patency (<30% residual DS, by visual estimate) without the use of a bailout stent within the target lesion and without the occurrence of MALE+POD upon completion of the index procedure
- Amputation-free survival (AFS): Freedom from above-ankle target limb amputation or all-cause death at 6 and 12 months
- Freedom from MALE at 12 months + POD at 30 days
- Target lesion(s) tacked segment(s) patency at 12 months defined as the presence of blood flow using duplex ultrasound.
- Target Limb Salvage defined as freedom from any above-ankle target limb amputation at 12 months
- Assisted primary target lesion Tacked segment patency (flow vs. no flow) at 6 and 12 months
- Secondary target lesion Tacked segment patency (flow vs. no flow) at 6 and 12 months
- PSVR patency at 6 and 12 months [Freedom from binary restenosis defined as Peak Systolic Velocity Ratio (PSVR) of ≥ 2.5 and/or angiographic percent diameter stenosis of ≥50%] assessed for the following:
    - Target Lesion(s), defined as the entire contiguous arterial segment treated with angioplasty, inclusive of an additional proximal and distal margin of 5 mm

- Tacked Segment(s), defined as the Tack device and 5 mm of artery proximal and distal to each Tack. If Tacks are within 10 mm of each other, they will be considered as a single tacked segment for the purposes of this patency assessment.

- Clinically-driven target lesion revascularization (CD-TLR) through 12 months
- Clinically-driven target vessel revascularization (CD-TVR) through 12 months
- All-cause death through 12 months
- Any Target vessel revascularization (TVR) through 12 months
- Any Target lesion revascularization (TLR) through 12 months

In addition, the following observational endpoints will be assessed at various time points through 36 months (See Time and Events Schedule **Section 8.1**):

- Changes in Wound, Ischemia, and foot Infection (WIfI)[31] Classification
- Changes in ankle brachial index (ABI) and toe brachial index (TBI)
- Changes in Rutherford Classification
- Changes in the EQ-5D-3L quality of life questionnaire
- Changes in the Walking Impairment Questionnaire (WIQ)
- Tack implant Integrity via X-ray (only performed at 12-month visit)
- Progress of wound(s) present at study entry (healed, improved, unchanged, worsening, amputated)
- Appearance of new wound(s) after study entry
- Unplanned below-ankle target limb amputation(s): digit or transmetatarsal

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 as compared to a pre-defined performance goal (PG) established from published, peer reviewed scientific literature.

7.1. Anticipated Number of Subjects and Investigational Sites

It is anticipated that up to 232 subjects will be enrolled at up to 60 US and International clinical sites. No single clinical site can enroll more than 46 patients, establishing an enrollment cap at 20% of the subject sample size.

7.2. Subject Population

Subjects with PAD who receive PTA in the Mid/Distal Popliteal, Tibial, and Peroneal Arteries and have a resulting dissection(s) that an operator would attempt to treat by means such as additional angioplasty with extended inflation time or stenting, are eligible for enrollment. To be enrolled, subjects must meet all general and angiographic inclusion criteria and not meet any of the general or angiographic exclusion criteria.

[31] Joseph L. Mills, Sr, MD, Michael S. Conte, MD, David G. Armstrong, DPM, MD, PhD, Frank B. Pomposelli, MD, Andres Schanzer, MD, Anton N. Sidawy, MD, MPH, and George Andros, MD, on behalf of the Society for Vascular Surgery Lower Extremity Guidelines Committee, The Society for Vascular Surgery Lower Extremity Threatened Limb Classification System: Risk stratification based on Wound, Ischemia, and foot Infection (WIfI). J Vasc Surg. 2014; Volume 59, Issue 1, Pages 220–234.e2

7.3. 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 30 days and then exited from the study (see **Section 13.3.1**).

7.4. Subject Selection

7.4.1. Inclusion Criteria

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

1. Males or non-pregnant females ≥ 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. 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 informed consent form (ICF), an impartial witness may sign on behalf of the subject
4. Willing to comply with all required follow-up visits
5. Rutherford Classification 4 or 5
6. WIfI Wound grade of 0, 1 or modified 2
7. WIfI Foot Infection grade of 0 or 1
8. Estimated life expectancy ≥1 year

7.4.2. 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 1.5 mm and 4.5 mm, inclusive (by visual estimate)
2. Only one limb requires treatment during the Index Procedure

   Note: If the subject has bilateral BTK disease, the Investigator should choose the limb that most closely meets eligibility criteria. If the chosen limb does not meet final eligibility after PTA treatment, the subject should not be enrolled at that time. This subject may be brought back for potential study device treatment to the contralateral limb per the protocol requirements. Only one limb may receive study device treatment.
3. Ability to cross study device(s) antegrade through target lesion
4. Has de novo or restenotic target lesion(s) with pre-PTA stenosis of ≥70% or is occluded (by visual estimate) and is indicated for PTA treatment with a standard balloon catheter

   Note: Diseased segments with >30 mm of healthy vessel between them are considered separate target lesions

Note: If any part of the lesion is restenotic, no part of the lesion should have more than 1 prior failure (by plain balloon angioplasty only), which must have occurred greater than 1 year (360 days) prior to the index procedure

Note: After PTA treatment, the target lesion is defined as the entire contiguous arterial segment length treated with angioplasty

5. Target lesion(s) located in the mid popliteal (P2), distal popliteal (P3), tibioperoneal trunk, peroneal, anterior tibial, or posterior tibial arteries

   Note: The mid popliteal artery (P2) begins at the superior aspect of the patella. The most distal location of the tibial and/or peroneal artery(ies) ends at the beginning of the dorsalis pedis artery (DP). Tacks may not be implanted within 1 cm above the radiographic tibiotalar joint.

6. Target vessel(s) reconstitute(s) at or above the ankle or displays normal terminal branching

   - If the target vessel is the peroneal artery, the artery must display normal terminal branching.
   - If the target vessel is the anterior tibial (AT) artery or the posterior tibial (PT) artery, the artery(ies) must display reconstitution at least 1 cm proximal to the radiographic tibiotalar joint line, and continue into an intact runoff vessel (AT/ dorsalis pedis or PT/plantar artery).
   - If the target vessel is the P2 and/or P3, any 1 of the 3 distal arteries must show respective outflow.
   - If the target vessel is the TPT, then respective outflow for either the peroneal artery or posterior tibial artery must be confirmed.

   Note: Normal terminal branching and/or reconstitution of run-off vessels as described above should be confirmed prior to PTA treatment of the target lesion(s) as well as after PTA treatment to the target lesion(s) (prior to Tack deployment)

7. Patent (<50% DS by visual estimate) arterial inflow from aortic bifurcation to the distal edge of the proximal popliteal artery (P1) at the superior end of the patella.

   Note: Treatment of inflow artery lesions within the iliac (ipsilateral or contralateral), common femoral, superficial femoral, and/or the proximal popliteal (P1) artery(ies) is allowed during the index procedure but must have documented success (<30% residual DS and no major vascular complications) prior to target lesion treatment.

   Note: If an inflow lesion requires treatment with atherectomy or requires surgical intervention, the patient should not be enrolled

8. After PTA treatment, the target lesion has <30% residual DS and presence of at least one post-PTA dissection (by visual estimate) that the Investigator would otherwise treat by means such as but not limited to additional angioplasty, with longer inflation time or stenting

9. No evidence of aneurysm or acute thrombus in target vessel

7.4.3. EXCLUSION CRITERIA

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

1. Is pregnant or refuses to use contraception through the duration of the study
2. Previous bypass graft in the target limb
3. Acute limb ischemia, defined as symptom onset occurring less than 14 days prior to the index procedure
4. Prior or planned above-ankle amputation or complete transmetatarsal amputation to the target limb (this does not apply to ray amputation of ≤2 digits, simple digital amputations or ulcer debridements)
5. WIfI Foot Infection grade 2 or 3.
6. Any systemic infection or immunocompromised state. Patients with an ascending infection/deep foot infection or abscess/white blood count (WBC)≥12,000/or febrile state
7. Endovascular or surgical procedure (not including diagnostic procedures, planned simple digital amputation or wound debridement) to the target limb less than 30 days prior to or planned for less than 30 days after the index procedure
8. Existing stent implant in the target vessel
9. Any other endovascular or surgical procedure (not including diagnostic procedures, planned simple digital amputation or wound debridement) less than 14 days prior to the index procedure or planned procedure less than 30 days after the index procedure
10. Known coagulopathy, hypercoagulable state, bleeding diathesis, other blood disorder, or a platelet count less than 80,000/microliter or greater than 500,000/microliter
11. WIfI Wound grade of 2 or 3.
12. Any subject in which antiplatelet, anticoagulant, or thrombolytic therapy is contraindicated
13. Myocardial infarction, coronary thrombolysis or angina less than 30 days prior to the Index Procedure
14. History of stroke or transient ischemic attack (TIA) less than 90 days prior to the Index Procedure
15. Currently on dialysis
16. Known hypersensitivity or contraindication to nickel-titanium alloy (Nitinol)
17. Participating in another ongoing investigational clinical trial in which the subject has not completed the primary endpoint(s), as well as subjects who are already enrolled into this study, as only one limb may be treated with the 4F study device.
18. 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
19. Known hypersensitivity or allergy to contrast agents that cannot be medically managed

20. Subject already enrolled into this study
21. Restenotic target lesion previously treated by means other than plain balloon angioplasty and/or less than 1 year prior to index procedure.

7.4.4. ANGIOGRAPHIC EXCLUSION CRITERIA

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

1. Acute vessel occlusion or acute or sub-acute thrombosis in target lesion
2. Subject has significant stenosis (≥50% DS) or occlusion of inflow arteries (including the iliac, superficial femoral and proximal popliteal arteries) not successfully treated (<30% residual DS and without major complication) prior to PTA of target lesion
3. The target lesion shows no dissections after PTA or dissections of a lessor grade for which the operator would normally not pursue additional treatment
4. If parallel non-target vessel (anterior tibial, peroneal, or posterior tibial) is treated during index procedure and is not successful (<30% residual DS and without major complication) prior to PTA of target lesion/vessel
5. Below the ankle lesion requiring treatment
6. Use of atherectomy, cryoplasty, cutting/scoring/contoured balloon angioplasty, stenting or any other treatment (with the exception of a crossing device) of the target lesion/vessel other than plain balloon angioplasty PTA during the index procedure

   Note: Use of atherectomy in a parallel, non-target vessel is allowed during the index procedure but must have documented success (<30% residual DS and no major vascular complications) prior to target lesion/vessel treatment

8. TREATMENT PLAN

8.1. TIME AND EVENTS SCHEDULE

All subjects will receive the assessments at specific time points as listed in **Table 8** below.

Table 8. Time and Events Schedule

Assessment[12]	Baseline[1]	Index 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 / Brief Physical	X								
White Blood Count / Platelet Count	X								
Prothrombin Time (PT) / International Normalized Ratio (INR)[3]	X								
Urine pregnancy test if female[4]	X								
Ankle Brachial Index (ABI)/ Toe Brachial Index (TBI)[10]	X			X	X	X	X	X	X
$TcPO_2$[10]	X			X	X	X	X	X	X
Rutherford Classification	X			X	X	X	X	X	X
WIfI Classification	X			X	X	X	X	X	X
Wound Assessment[9]	X			X	X	X	X	X	X
Pre-procedural Medications		X							
Angiogram		X							X[8]
Study Medications	X	X	X	X	X	X	X	X	X
Duplex Ultrasound (DUS)[5]				X	X	X			X[8]
X-ray of Implanted Tacks[6]						X			X[8]
Adverse Event (AE) Assessment[11]		X	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 prior to the index procedure, with the exception of a pregnancy test
[2] Consent may be obtained up to 30 days prior to index procedure.
[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] X-ray assessment of Tack Integrity is only required for subjects in whom at least one Tack was placed during the index procedure. All required and unscheduled X-ray exams should be performed in accordance with the core lab protocol.
[7] Unscheduled data should be captured prior to any intervention to target limb; Rutherford classification and wound assessment should be documented prior to re-intervention to the target limb.
[8] If clinically indicated. All imaging of the target limb acquired during scheduled visits or a target limb intervention (such as Angiogram, DUS or X-Ray) should be submitted to the respective core lab within 3 days of occurrence.
[9] Wound assessment is required and all efforts should be made to acquire photographs of the wound to support the assessment for healed, improved, unchanged, worsening, amputated or new (if applicable).
[10] Both ABI and TBI are required at baseline and throughout follow-up. If during baseline, an ABI or TBI is not attainable, due to non-compressible arteries or prior digital amputation, this shall be noted on the electronic case report form

(eCRF). If ABI, ankle pressure or toe pressure cannot be acquired, $TcPO_2$ may be recorded, if possible, to confirm a WIfI Ischemia Grade.

[11] Only the following types of adverse events (AEs) shall be recorded in the eCRF: Serious adverse events (SAEs), or any AE that is classified as 'possibly' or' definitely' related to the study device and/or study device procedure by the investigator. Assessments of MALE+POD will also be part of the AE assessment.

[12] Follow-up assessments (required at the 30-day visit and beyond) that cannot be performed due to a subject's medical condition (i.e., amputation) will not be considered a deviation if it is fully documented in source records.

9. Required Tests and Assessments

The required tests and assessments described in this section are required at baseline and/or at various follow-up visits according the Time and Event Schedule in **Section 8.1**.

9.1. Laboratory Testing

Laboratory blood samples must be drawn pre-procedure but may not exceed 30 days prior to the index procedure.

Laboratory samples include:

- WBC
- Platelet count
- PT/INR (only if subject is on chronic warfarin)
- Pregnancy test (if female of childbearing potential) within 7 days of index procedure

9.2. Angiographic Assessment & Imaging

The index baseline angiogram is performed during the index procedure. If the subject is enrolled, all imaging and accompanying worksheets shall be submitted to the angiographic core laboratory for analysis within 3 days. The imaging for the baseline angiogram must follow the most current requirements set forth by the core laboratory. Failure to acquire/provide all required index procedural sequences and images will result in a protocol deviation. In addition, any subsequent angiographic assessments performed on the target limb (due to recurrent or worsening symptoms) shall also be provided to the respective core laboratory for analysis per the instructions established by the core laboratory.

9.3. Ankle and Toe Brachial Indices (ABI and TBI)

Target limb resting ABI and TBI should be performed per hospital standard of care and consistently among all enrolled subjects through completion of the study. Both target limb resting ABI and TBI are required at baseline and follow-up. ABI and TBI values, including respective individual systolic pressure values must be documented in source and recorded on the appropriate electronic case report forms (eCRFs).

To confirm the WIfI Ischemia grade, Transcutaneous oxygen ($TcPO_2$) may be assessed and recorded only if reliable ABI, ankle pressure, or toe pressure are not attainable. However, if $TcPO_2$ cannot be conducted, it will not be considered a protocol deviation.

9.4. DUPLEX ULTRASOUND (DUS) ASSESSMENT

Lower extremity arterial duplex ultrasound (DUS) assessments will be used to determine arterial stenosis as well as Tacked segment patency (Flow/No Flow). The peak systolic blood flow velocity within the Tacks as well as the target lesion will be taken to determine the PSVR.

The DUS exam should be performed per the Time and Events Schedule in **Section 8.1**. DUS exams performed outside of window or not at all will result in a protocol deviation. Duplex ultrasonography and/or angiography should be performed prior to any endovascular intervention during the follow-up period to assess the treated lesion patency. Operators should have experience with DUS and follow the DUS core laboratory acquisition guidelines and specific methods for measuring the blood flow velocities. All scheduled DUS assessments shall be submitted to the respective DUS core laboratory for analysis, in addition to any DUS performed prior to or after any events meeting MALE criteria.

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

9.5. QUESTIONNAIRES

Both the WIQ and the EQ-5D-3L will be used to assess changes in the patient's quality of life throughout the duration of this clinical study.

9.6. RUTHERFORD CLASSIFICATION

Rutherford Classification should be assessed for the target limb and consistently among all patients throughout the duration of this clinical study.

See **Section 24** for a description of Rutherford Classifications.

9.7. WIFI CLASSIFICATION

The WIfI Classification is a grading system created by the Society of Vascular Surgery (SVS). This system focuses on the three main factors that impact amputation risk and clinical management: Wound, Ischemia, and foot Infection (WIfI). Each of the three factors are graded on a scale from 0 to 3. The 0 represents none, 1-mild, 2-moderate and 3-severe.[32]

The Wound portion of the WIfI classification is required for all subjects. For inclusion into the study, the subject must have a Wound Grade 0, 1, or "modified 2". For the purpose of this study only, an additional Wound grade of modified 2 has been added to the SVS Wound table in **Section 23**. The Wound grade "modified 2" permits a deeper ulcer without exposed bone, joint or tendon; or shallow or superficial heel ulcer, without deep tissue involvement or exposed calcaneus. It also permits gangrenous changes limited to digits. In addition, for the purpose of this study, subjects without

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presence of wound and gangrene should be given a WIfI Wound grade of 0, regardless of their WIfI Ischemia grade.

The Ischemia portion of the WIfI classification is required for all subjects and uses hemodynamic/perfusion criteria (ABI, Ankle Pressure, Toe Pressure or $TcPO_2$) to determine its grade. Subjects are eligible for inclusion regardless of their WIfI Ischemia Grade. The Ischemia Grade should reflect the value obtained using the following hierarchy: Toe Pressure (or $TcPO_2$) being the first, then the highest Ankle Pressure (if TP or $TcPO_2$ is not attained), then ABI (if ankle pressure is not documented). Therefore, it is crucial to follow requirements for these assessments per **Table 8. Time and Events Schedule Section 8.1**.

The Infection portion of the WIfI classification is required for all subjects and is determined by clinical observations of infection. Subjects must have an Infection Grade of 0 or 1 to be eligible for enrollment.

See **Section 23** for WIfI classification tables.

9.8. Wound Assessment

An assessment of existing and/or new wound(s) is to be performed per **Table 8. Time and Events Schedule Section 8.1.** Wounds should be classified as: Healed, Improved, Unchanged, Worsening, Amputated or New (If applicable). If, at the time of any follow-up visit, a patients wound is dressed and per PI discretion the dressing should not be removed, this should be documented and will not be considered a deviation.

All assessments shall be accompanied by a photograph of the wound(s) that includes a ruler. These photographs shall be part of the subject's study file.

9.9. X-Ray Assessment

An X-Ray assessment will be performed at the 12-month follow-up visit to assess Tack implant integrity for all subjects in whom at least one Tack implant was placed during the index procedure. If an X-ray is performed prior to the 12-month visit and is within the 12-month visit window and all Tacks are imaged, this may be used in lieu of the X-ray required at the 12-month visit.

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

10. Screening Procedures

All subjects presenting to the institution with PAD and/or known popliteal (P2 and P3) and/or below-the-knee artery disease requiring balloon angioplasty 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. Only assessments consistent with the institutions standard of care may be performed prior to obtaining a signed consent form. 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 shall be taken for pre-screen failure subjects. If determined eligible per initial inclusion criteria, the subject will be approached by qualified and trained research staff and informed about this study through the informed consent process.

10.1. Obtaining Informed Consent

All sites shall comply with 21 CFR 50, provisions of ICH E6 Good Clinical Practices (GCPs), local institutional review board (IRB)/ethics committee (EC) policy and all applicable local regulations for obtaining Informed Consent. Written informed consent using the most current IRB/EC-approved 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 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. If 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.

10.2. Screening Success and Failure Criteria

Final eligibility of a subject will occur during the Index Procedure. Subjects must provide prior informed consent no greater than 30 days prior to the index procedure. 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 criterion 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 for these subjects, however; reason for angiographic failure shall be documented by the site into a screening log. Both limbs may be considered for enrollment if all study-required timeframes per the inclusion/exclusion criteria are met. If 30 days have passed since the subject signed an informed consent form, the subject should be re-consented.

11. Baseline Evaluation

11.1. Baseline Assessments

The following assessments will be performed during baseline evaluation. These examinations and tests will be used both to screen for eligible subjects and provide baseline information for those subjects who meet study criteria. All assessments must be completed no more than 30 days prior to undergoing the index procedure, except for the urine pregnancy test which must be completed no more than 7 days prior to the index procedure with a negative result prior to receiving treatment.

- Demographic information and medical history including risk factors

- Brief physical examination
  - Including height and weight
- Target Limb Resting ABI
- Target Limb Resting TBI
- Target Limb $TcPO_2$ (to confirm WIfI Ischemia score only if ABI, ankle pressure, or toe pressure cannot be attained)
- Rutherford Classification
- WIfI Classification
- Wound Assessment
- WBC, Platelet count
- PT & INR (if on chronic warfarin therapy)
- Urine pregnancy test if female of child-bearing age (within **7** days of procedure)
- EQ-5D-3L
- Walking Impairment Questionnaire (WIQ)
- Study medications (antiplatelet/anticoagulants)

12. STUDY MEDICATIONS

See **Table 9** below for Study Medications. Pre-procedural, intra-procedural and post-procedural medications will be recorded in the eCRF.

Table 9: Recommended Study Medications

Medication	Pre-Procedure	Intra-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.*

13. INDEX PROCEDURE

13.1. 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 13.1.2** 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 identification of post-PTA dissections and associated type, as outlined in the angiographic core lab protocol.

All data that is required to be recorded during the Index Procedure is reflected in the index procedure interval eCRFs within the EDC. Required measurements and data listed in following sections are not exhaustive of all data that is required. Therefore, the required data should be reviewed in advance of the procedure to ensure it is understood and captured appropriately. The CRF Completion Guidelines contain instructions for data entry and should be referenced as necessary.

13.1.1. PREPARATION

Procedural techniques will be in accordance with the institutional standard of care for balloon angioplasty of the popliteal (P2 and P3) and below-the-knee arteries.

All subjects should receive the appropriate antiplatelet and anticoagulant therapy per **Table 9**. Study Medications above (**Section 12**).

A radiopaque ruler is placed directly on the subject's target limb under the sterile drapes according to the angiographic core lab imaging protocol. In any later angiographic assessments, the same ruler placement should be used to identify the treatment location.

13.1.2. BASELINE ANGIOGRAPHIC REQUIREMENTS

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

- Target Lesion(s) details including Vessel location(s), Ruler location(s), Lesion length(s) (normal to normal), and pre-PTA %DS
- Lesion type(s) (De novo or restenotic)
- Reference Vessel Diameter(s) (proximal and distal)
- Inflow artery patency
- Normal artery branching and/or target vessel reconstitution
- Absence of thrombus

13.2. PRE-ENROLLMENT BALLOON ANGIOPLASTY (TREATMENT PTA)

All consented subjects undergoing balloon angioplasty for possible enrollment into this study shall receive PTA treatment with a standard balloon.

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 relative to the target lesion proximal RVD
- The length of the balloon should be appropriate for the lesion length, fully covering the lesion. When possible, a single balloon should be selected that extends across the entire lesion.

- Balloon Inflation: Inflate the balloon and maintain inflation at the specified 1:1 diameter for a minimum of 60 seconds total

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

13.2.1. Post-Angioplasty Angiographic Requirements

Final angiographic eligibility of subjects for study device treatment will be determined post pre-enrollment balloon angioplasty and include but are not limited to the following target lesion measurements (by visual estimate):

- Target lesion residual diameter stenosis <30%
- Presence of dissection(s)
- Absence of thrombus
- Normal artery branching and/or target vessel reconstitution

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
  - Vessel Location
  - Ruler Location
- For each vessel segment inflation:
  - Balloon name/Manufacturer, Length, Diameter
  - Vessel location
  - Ruler location
  - Max Pressure (atm) (across all inflations)
  - Inflation Duration at Max Pressure (across all inflations)
  - Max Inflation Diameter (across all inflations)

13.3. Study Device Treatment

Subjects who 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.

13.3.1. Enrollment (Intent-to-Treat)

A subject is defined as an intent-to-treat (ITT) and officially enrolled in the study once the Tack Endovascular System is advanced through the introducer sheath. Subjects in whom at

least one Tack implant is not placed, will be exited after 30 days. Subjects in whom at least one Tack implant 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 by an independent designee before study endpoint data is available for statistical analysis.

13.3.2. Treatment Recommendations

The lesion considered for Tack implant 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 implant will be categorized by type by the operator as described in **Section 13.2.1**. If there are no dissections present, the subject may not be enrolled and Tack implants should not be placed.

Intact Vascular recommends deployment of a Tack implant 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 Tack implants (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.

13.3.3. Post-Study Device Treatment Measurements

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

- Number of Device Systems used to treat subject and associated lot numbers
  - Number of Tacks deployed from Device
  - Whether device was successfully withdrawn
- Number of Tack implants deployed
  - Ruler and vessel location of each deployed Tack implant
  - Number of Tack implants deployed to treat each dissection and whether it was successful in treating respective dissection identified in **Section 13.2.1**

13.4. Post- Tack Dilation

Post-dilation of all deployed Tack implants is required to seat the anchors of the Tack implant. Use of a new standard balloon catheter is required to reduce the risk of contact with deployed Tack implants while advancing the balloon catheter into place.

13.4.1. RECOMMENDATIONS

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

- The balloon diameter for post-dilation should use the same balloon diameter and pressure used during angioplasty prior to Tack implant placement and should be the shortest length possible
- Post-Dilation Duration at Max Pressure: A minimum of 120 seconds.

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

13.4.2. FINAL TREATMENT RESULTS

The following information should be recorded after post-dilation and upon completion of index procedure and includes but is not limited to:

- For each vessel segment receiving post-Tack inflation:
  - Balloon name/Manufacturer, Length, Diameter
  - Vessel location
  - Ruler location
  - Max Pressure (atm) (across all inflations)
  - Inflation Duration at Max Pressure (across all inflations)
  - Max Inflation Diameter (across all inflations)
  - Final residual diameter stenosis of target lesion(s) treated with Tacks
- Bailout stent occurrence (post-study device treatment)
  - If applicable, bailout stent device details will be recorded
- Study Device Procedure time (defined as the time the first Tack Endovascular System is advanced through the introducer sheath to the time of withdrawal of last post-Tack dilation PTA balloon catheter)
- Adverse event occurrence
- Device event occurrence

13.5. 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 implant (or as otherwise required for safety of the subject). All enrolled subjects in whom at least one Tack implant is placed and receive a bailout stent to any deployed Tack within the target lesion will be followed for the duration of the study. Details around the use of a bailout stent will be captured in the eCRF including but not limited to; name/manufacturer, reason for stenting, length diameter, ruler and vessel location(s).

14. 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 9** "Recommended Study Medications" in **Section 12**. All concomitant medications (antiplatelet/anticoagulant) shall be captured in the eCRF.

14.1. REQUIRED ASSESSMENTS

Assessments required at pre-discharge include the following:

- Adverse event occurrence
- Study medication assessment (antiplatelet agents/anticoagulants)

All subjects receiving treatment with a Tack implant 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 vessel location of the implanted Tack(s) and the date of the index procedure. The card also provides manufacturing information and MRI Compatibility.

15. REQUIRED FOLLOW-UP VISITS AND ASSESSMENTS

All subjects will be required to return for clinic follow-up visits as outlined in **Table 8** of **Section 8.1** and in the sections below.

15.1. 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
- WIfI Classification
- Wound Assessment
- Target limb resting ABI
- Target limb resting TBI
- Target Limb $TcPO_2$ (if ABI, ankle pressure or toe pressure cannot be acquired)
- Duplex ultrasound (DUS)
- EQ-5D-3L
- Walking Impairment Questionnaire (WIQ)
- Adverse event occurrence
- Review of study medications (antiplatelets/anticoagulants)

15.2. 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
- WIfI Classification

- Wound Assessment
- Target limb resting ABI
- Target limb resting TBI
- $TcPO_2$ (if ABI, ankle pressure or toe pressure cannot be acquired)
- Duplex ultrasound (DUS)
- EQ-5D-3L
- Walking Impairment Questionnaire (WIQ)
- Adverse event occurrence
- Review of study medications (antiplatelet agents/anticoagulants)

15.3. 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
- WIfI Classification
- Wound Assessment
- Target limb resting ABI
- Target limb resting TBI
- $TcPO_2$ (if ABI, ankle pressure or toe pressure cannot be acquired)
- Duplex ultrasound (DUS)
- X-Ray assessment

  Note: If an X-ray of all Tack implant(s) is performed before the 12-month visit and is within the 12-month visit window, this may be used in lieu of the x-ray required at the 12-month visit.
- EQ-5D-3L
- Walking Impairment Questionnaire (WIQ)
- Adverse event occurrence
- Review of study medications (antiplatelet agents/anticoagulants)

15.4. 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
- WIfI Classification
- Wound Assessment
- Target limb resting ABI
- Target limb resting TBI

- $TcPO_2$ (if ABI, ankle pressure or toe pressure cannot be acquired)
- EQ-5D-3L
- Walking Impairment Questionnaire (WIQ)
- Adverse event occurrence
- Review of study medications (antiplatelet agents/anticoagulants)

15.5. 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
- WIfI Classification
- Wound Assessment
- Target limb resting ABI
- Target limb resting TBI
- $TcPO_2$ (if ABI, ankle pressure or toe pressure cannot be acquired)
- EQ-5D-3L
- Walking Impairment Questionnaire (WIQ)
- Adverse event occurrence
- Review of study medications (antiplatelet agents/anticoagulants)

15.6. UNSCHEDULED TARGET LIMB ANGIOGRAPHY/REVASCULARIZATION

If a subject presents between study-required follow-up visits for an intervention to the target limb, the assessments below should be performed prior to the interventional procedure. In addition, all imaging studies performed should follow the guidelines set forth by the respective core laboratory. This imaging should be submitted to the respective core laboratories within 3 business days for review and analysis.

- Rutherford Classification
- WIfI Classification
- Wound Assessment
- Target limb resting ABI
- Target limb resting TBI
- $TcPO_2$ (if ABI, ankle pressure or toe pressure cannot be acquired)
- Duplex ultrasound (DUS) (if clinically indicated)
- X-Ray assessment (if clinically indicated)

  Note: If an X-ray of all Tack implant(s) is performed before the 12-month visit and is within the 12-month visit window, this may be used in lieu of the x-ray required at the 12-month visit.

- EQ-5D-3L
- Walking Impairment Questionnaire (WIQ)
- Review of study medications (antiplatelet agents/anticoagulants)

  Note: Any change in study medication, including any loading dose provided during the unscheduled procedure, should be recorded in the eCRF.

15.7. 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 a study follow-up visit. 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, or the site has not been notified of a subject's wish to withdraw consent, a Protocol Deviation for a visit not done must be documented in the EDC. 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 visits and documented accordingly. After required contact attempts are unsuccessful for at least 2 consecutive visits and the 12-month visit window (or any later subsequent visit window) has passed, only then should a subject be considered lost-to-follow-up (LTFU) and exited from the study.

15.8. 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 or if LTFU) withdrawn cannot re-enter the study. These subjects will not be replaced.

16. Risk/Benefit Assessment

16.1. 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.

16.2. Potential Benefits

Prior human studies validated that the Tack Endovascular System can appose dissected tissue in subjects with post-PTA dissections, thereby resulting in acute dissection repair.

16.3. Justification for Clinical Study

The safety 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 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 study is being conducted in order to collect 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.

17. SAFETY REPORTING

The Principal Investigator at each participating site is ultimately responsible for the timely review and reporting of AEs per respective IRB/EC policy and in accordance with FDA and ISO (European sites) requirements.

The safety reporting period will begin at the time of enrollment into the study (See **Section 13.3.1**) and will continue through study completion.

All protocol reportable AEs will be monitored from the time of enrollment through the follow-up period for this study. A description of the event, including the start date, resolution (or date of final outcome assessment) date, action taken, and the outcome should be provided, along with the Investigator's assessment of the relationship between the event and the study device or study device procedure. Pain, neurological status and functional impairment should be considered AEs when a subject's complaint for any of these symptoms is outside the normal pattern for the illness treated.

All protocol reportable events reported 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.

The Sponsor or its designee will report all applicable serious adverse events as vigilance reports per MEDDEV 2.12.1, Rev 8 (2013) "Guidelines on a Medical Devices Vigilance System" and as clinical study reportable events per MEDDEV 2.7/3 "Clinical Investigations: Serious Adverse Event Reporting". The Sponsor will determine whether all of the local Investigators need to be informed immediately of an SAE or UADE, or whether this can be postponed until the next regularly scheduled study update.

17.1. PROTOCOL REPORTABLE SAFETY EVENTS

The following types of adverse events must be recorded on the Adverse Event eCRF by the Investigator (or designee):

- Serious Adverse Events
- Any event that is "possibly" or "definitely" related to the study device
- Any event that is "possible" or "definitely" related to the study device procedure

The report will include: the AE term, seriousness, severity, action taken, treatment outcome and relationship of the adverse event to the study device and/or study device procedure and status.

All events will be made accessible to the Sponsor and/or designee to review the need for FDA regulatory reporting. All reported safety events will be reviewed by the Sponsor or designee for any events that meet criteria for regulatory reporting.

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 study device procedure will be classified according to the following criteria:

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

Possibly: Signs or symptoms may be related to the study device or study device procedure *and* the natural disease process or other injury/illness.

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

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

17.2. ADVERSE EVENTS (AE)

An 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, AE's that are not considered 'serious' or not considered at least 'possibly' related to the study device and/or study device procedure are not required to be reported on the AE eCRF.

All protocol reportable AEs will be evaluated by the Investigator using his/her clinical judgement to determine whether the event further meets the criteria for ADE, SAE, serious adverse device effect (SADE), or UADE and will be subject to the respective reporting requirements as outlined in the sections below. Investigator or designee is also responsible for informing their IRB / EC of adverse events as required by their IRB / EC procedures and in conformance with FDA and local regulatory requirements. In addition, the investigator shall provide documentation of the IRB / EC report to Intact Vascular or its designee.

17.3. 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 not observing the IFU (See **Section 18**).

Note 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device (See **Section 18**).

A list of events that may be associated with the study device and/or the study device procedure is provided in **Section 16.1**.

17.3.1. ADE Reporting

All ADEs must be evaluated to determine whether the event further meets criteria for an SADE (See **Section 17.6**) 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 18**.

17.4. 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.

17.4.1. SAE Reporting

All SAEs must be evaluated to determine whether the event further meets criteria for an SADE (See **Section 17.6**) 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 the respective policy.

17.5. Major Adverse Limb Events (MALE) + Perioperative Death (POD)

For the purpose of this study, the definition of major limb adverse event(s)(MALEs)+POD include the following outcomes:

- All-cause death less than 30 days after the Index Procedure
- Above-ankle target limb amputation
- Major re-intervention to the target lesion (defined as new bypass graft, jump/interposition graft revision, or thrombectomy / thrombolysis)

17.5.1. MALE+POD Reporting

All events that lead to any of the outcomes meeting criteria above for an MALE+POD 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 the respective policy.

17.6. 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).

17.6.1. 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 18**.

17.7. Unanticipated Adverse Device Effects (UADE)

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

17.7.1. 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 the respective 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.

18. 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 17**.

18.1. Device Deficiency

Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or not observing the IFU, and inadequate labeling.

18.2. Device Malfunction

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

18.3. Device Returns

In the event that a device is suspected of deficiency or malfunction, the Investigator should make every effort to return the device to the manufacturer, Intact Vascular. The Investigator or designee shall contact Intact Vascular for a return manufacturer authorization (RMA) number and for additional instructions for the return of potentially biohazardous material.

19. Statistical Methods and Considerations

19.1. 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.

19.2. Analysis Populations

Subjects with BTK PAD who receive PTA in the Mid/Distal Popliteal, Tibial, and Peroneal Arteries and have a resulting dissection(s) that an Investigator would otherwise treat by means such as additional angioplasty with extended inflation time or stenting, are eligible for enrollment. To be enrolled, subjects must meet all inclusion criteria and not meet any of the exclusion criteria

The intent to treat (ITT) population will consist of all subjects who had the Tack Endovascular System advanced through the introducer sheath. ITT subjects are included in both primary and secondary endpoint analyses.

The PP population will be the subset of the ITT population that have met the definition of device success and have not had any major protocol deviations. Major protocol deviations include:

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

The criteria for deviations meeting the classification of “major” will be defined by an independent designee before study endpoint data is available for statistical analysis.

19.3. Primary Endpoints

19.3.1. Safety

Freedom from major adverse limb events (MALE) plus peri-operative death (POD) at 30 days defined as a composite of all-cause death, above-ankle target limb amputation, or major re-intervention to the target lesion(s) (defined as new bypass graft, jump/interposition graft revision, or thrombectomy / thrombolysis)

19.3.2. EFFICACY

The primary efficacy endpoint is freedom from MALE at 6 months + POD at 30 days.

19.4. SECONDARY ENDPOINTS

- Target lesion(s) tacked segment(s) patency at 6 months defined as the presence of blood flow using duplex ultrasound. If angiography is available within the 6-month follow-up visit window, it should be used in place of the duplex ultrasound. Evidence of no blood flow within the Tacked segment indicates restenosis/loss of patency.
- Target Limb Salvage defined as freedom from any above-ankle target limb amputation at 6 months.

19.5. OBSERVATIONAL ENDPOINTS

- Device Success: Successful deployment of the Tack implant(s) at the intended target site(s) and successful withdrawal of the delivery catheter from the introducer sheath.
- Target Lesion Success: Demonstrated target lesion patency [<30% residual diameter stenosis (DS), by visual estimate] without the use of a bailout stent within the target lesion upon completion of the index procedure. This will be assessed for all lesions treated with a Tack implant. In addition, target lesion success will also be analyzed by lack of bailout stent to tacked segment only. Multiple target lesions treated as one lesion with PTA will be analyzed as one lesion.
- Procedural Success: Demonstrated target lesion patency (<30% residual DS, by visual estimate) without the use of a bailout stent within the target lesion and without the occurrence of MALE+POD upon completion of the index procedure
- Amputation-free survival (AFS): Freedom from above-ankle target limb amputation or all-cause death at 6 and 12 months
- Freedom from MALE at 12 months + POD at 30 days
- Target lesion(s) tacked segment(s) patency at 12 months defined as the presence of blood flow using duplex ultrasound.
- Target Limb Salvage defined as freedom from any above-ankle target limb amputation at 12 months
- Assisted primary target lesion Tacked segment patency (flow vs. no flow) at 6 and 12 months
- Secondary target lesion Tacked segment patency (flow vs. no flow) at 6 and 12 months
- PSVR patency at 6 and 12 months [Freedom from binary restenosis defined as Peak Systolic Velocity Ratio (PSVR) of ≥ 2.5 and/or angiographic percent diameter stenosis of ≥50%] assessed for the following:
    - Target Lesion(s), defined as the entire contiguous arterial segment treated with angioplasty, inclusive of an additional proximal and distal margin of 5 mm
    - Tacked Segment(s), defined as the Tack device and 5 mm of artery proximal and distal to each Tack. If Tacks are within 10 mm of each other, they will be considered as a single tacked segment for the purposes of this patency assessment.
- Clinically-driven target lesion revascularization (CD-TLR) through 6 and 12 months
- Clinically-driven target vessel revascularization (CD-TVR) through 6 and 12 months

- All-cause death through 6 and 12 months
- Any Target vessel revascularization (TVR) through 6 and 12 months
- Any Target lesion revascularization (TLR) through 6 and 12 months

In addition, the following observational endpoints will be assessed at various time points through 36 months (See Time and Events Schedule **Section 8.1**):

- Changes in Wound, Ischemia, and foot Infection (WIfI)[33] Classification
- Changes in ankle brachial index (ABI) and toe brachial index (TBI)
- Changes in Rutherford Classification
- Changes in the EQ-5D-3L quality of life questionnaire
- Changes in the Walking Impairment Questionnaire (WIQ)
- Tack implant Integrity via X-ray (only performed at 12-month visit)
- Progress of wound(s) present at study entry (healed, improved, unchanged, worsening, amputated)
- Appearance of new wound(s) after study entry
- Unplanned below-ankle target limb amputation(s): digit or transmetatarsal

19.6. SAMPLE SIZE

The sample size for the primary efficacy endpoint of freedom from MALE at 6 months plus POD at 30 days was calculated using a one-sided, single group, normal approximation test of a proportion (with continuity correction) against a performance goal. The performance goal for this endpoint is 74% developed based on the information reported in table VIIb and figure 2A of Conte (2009). From figure 2A, the estimated 6-month rate of freedom from MALE + POD in the infra-popliteal group is 80.5% with 95% confidence interval calculated to be (77%, 84%). Applying the recommended 3% margin to the lower bound of the confidence interval yields the 74% OPG. Assuming the observed freedom from MALE+POD is 84% and a one-sided Type I error rate of 0.025, a sample size of 186 subjects provides 90% power to detect this difference between observed freedom from MALE+POD and the performance goal of 74%.

The sample size for the primary safety endpoint of MALE+POD at 30 days was calculated using the exact binomial distribution. This is also a one-sided, single group test of a proportion against a performance goal. The performance goal for this endpoint was established at 12%. This performance goal was derived from the information reported in table VIIa of Conte (2009). In that table, MALE+POD was not reported, however MALE and 30-day death were reported separately. The sum of those two estimates (8.9%) was used for sample size calculation. Conte (2009) established performance goals for safety endpoints by constructing a 95% confidence interval and using the upper bound of that interval as the performance goal. With some algebraic manipulation, a similar 95% confidence interval was established for the 8.9%point estimate of 30day MALE+POD which resulted in an upper bound of 11.9%. Therefore 12% is used as the performance goal for this endpoint. Assuming an observed MALE+POD rate of 5%

[33] Joseph L. Mills, Sr, MD, Michael S. Conte, MD, David G. Armstrong, DPM, MD, PhD, Frank B. Pomposelli, MD, Andres Schanzer, MD, Anton N. Sidawy, MD, MPH, and George Andros, MD, on behalf of the Society for Vascular Surgery Lower Extremity Guidelines Committee, The Society for Vascular Surgery Lower Extremity Threatened Limb Classification System: Risk stratification based on Wound, Ischemia, and foot Infection (WIfI). J Vasc Surg. 2014; Volume 59, Issue 1, Pages 220–234.e2

and a one-sided Type I error rate of 2.5%, a sample size of 171 subjects provides 90% power to demonstrate that the observed 30-day MALE+POD rate is below the performance goal of 12%.

Since the required sample size for the primary efficacy endpoint (186), is larger than the required sample size for the primary safety endpoint (171), an effective sample size of 186 subjects meeting the ITT definition will be assumed. Assuming approximately 20% loss to follow-up, total enrollment will be 186/0.80 or 232 subjects.

The secondary endpoint of primary patency of the tacked segment of the treated lesion at 6 months will also be formally tested against a performance goal of 64%. The performance goal of 64% was chosen as a result of a meta-analysis combining 13 papers that reported 6-month patency for standard PTA or from which the 6-month patency rate could be derived. These papers covered several patient populations, however all these populations are target populations for use of the Tack. A meta-analysis was performed on the results reported in these papers and the random effects estimate of 6-month patency was 63.5%. Therefore, 64% was chosen as the performance goal. Assuming an observed 6-month patency rate of 81% and a one-sided Type I error rate of 2.5%, the effective sample size given above for the primary efficacy endpoint of 175 would provide greater than 90% power to detect the difference between an observed 6-month patency of 81% and the performance goal of 64%.

19.7. Baseline Variables

Baseline variables will be summarized for those subjects enrolled in this trial. Continuous variables will be presented as means, standard deviations, and sample size (N). Discrete variables will be presented as a percent along with the number of subjects displaying the characteristic and the total number of subjects. The types of baseline variables summarized will be demographics, medical history and lesion characteristics.

19.8. Statistical Analysis

19.8.1. Primary Safety

The primary safety endpoint of MALE+POD at 30 days will be analyzed by constructing a one-sided upper 97.5% confidence interval using the exact binomial distribution. This upper bound will be compared to the performance goal of 12%. The hypotheses being tested are:

$$Ho: P_{MALE+POD} \geq 12\%$$
$$Ha: P_{MALE+POD} < 12\%$$

where $P_{MALE+POD}$ is the proportion of subjects experiencing a MALE+POD event within 30 days of the procedure. All subjects that meet the ITT definition are included in this analysis.

19.8.2. Primary Efficacy

The primary efficacy endpoint of freedom from MALE at 6 months plus POD at 30 days will be analyzed using a one-sided, single group, Z-test comparing the observed proportion of subjects free of MALE and POD to the performance goal of 74%. The hypotheses are:

$$Ho: P_{MALE\_6+POD} \leq 74\%$$
$$Ha: P_{MALE\_6+POD} > 74\%$$

where P_{MALE_6+POD} is the proportion of subjects free of MALE at 6 months + POD at 30 days. The p-value associated with the standard Z-test will be provided along with a one-sided 97.5% lower confidence bound on the point estimate observed. All subjects that meet the ITT definition are included in this analysis.

The Z-test that will be used for analysis is the continuity corrected Z under the estimated P_{MALE_6+POD}. That is:

$$Z = \frac{\hat{p} - P0 + c}{\sqrt{\hat{p}\,(1-\hat{p})/\,n}},$$

where$\hat{p}$ is the estimate of P_{MALE_6+POD}, P0 is the performance goal of 74% under the null hypothesis, and

$$c = \begin{cases} -\frac{1}{2n} & if\ \hat{p} > P0 \\ \frac{1}{2n} & if\ \hat{p} < P0 \\ 0 & if\ |\hat{p} - P0| < \frac{1}{2n}. \end{cases}$$

19.8.3. Secondary Efficacy Endpoints

The secondary efficacy endpoint of 6-month patency will be estimated as the proportion of tacked segments of the lesion(s) that are still patent at 6 months. A one-sided lower 97.5% confidence bound will be calculated for this estimate using the standard normal approximation. This lower bound will be compared to the performance goal of 64%. The hypotheses being tested are:

$$Ho: P_{Patency\_6month} \leq 64\%$$
$$Ha: P_{Patency\_6month} > 64\%$$

where $P_{Patency\_6month}$ is the proportion of subjects whose tacked portion of the vessel is still patent 6 months post procedure. Patency will also be displayed using a Kaplan-Meier curve.

The secondary efficacy endpoint of target limb salvage at 6 months will be summarized using the Kaplan-Meier method to estimate freedom from above-ankle target limb amputation. The final 6-month estimate will be presented along with 95% confidence intervals. All subjects that meet the ITT definition are included in this analysis.

19.8.4. Observational Endpoints

All observational endpoints will be summarized descriptively.

19.9. Subgroup Analysis

The primary safety and efficacy endpoints will be re-analyzed stratifying by gender and by US versus OUS. Point estimates and 95% confidence intervals will be displayed for each endpoint. No formal testing will be done since the reduced sample sizes would result in underpowered tests.

19.10. Site Pooling Analysis

For both the primary safety endpoint and the primary efficacy endpoint, a pooling analysis will be completed demonstrating that the information on the primary endpoints can be pooled across site. For each endpoint, the site specific estimate of the endpoint will be calculated. These site specific rates will then be compared using a standard Pearson chi-square statistic. A p-value greater than 0.15 will indicate poolability of site information. Low enrolling sites (enrollment ≤ 5) will be pooled into an "other site" category for the purposes of this analysis. If differences between sites exist at the alpha=0.15 level, summary statistics will be presented for each site and any differences by study site will be discussed in the study report. In this case, a meta-analytic modeling approach will be used to combine the estimates across sites using the random effects estimate based on the inverse variance to account for the heterogeneity of sites. Specifically, each of the binary primary endpoints will be modeled as a function of the random effect of site and the estimates and resulting confidence intervals used to compare the estimate to the performance goal. The DerSimonian-Liard estimator of the variance with inverse variance weights will be used to adjust for the random effect of site in the final analysis. Additionally, a sensitivity analysis of the primary outcomes will be performed by excluding outlying sites one at a time until a statistically significant difference between sites (at alpha=0.15) no longer exists. Then, the pooled results for the remaining sites will be used for the sensitivity analysis.

19.11. Handling of Missing Data

For the primary analysis, only complete data will be used. Data will be considered "complete" if the subject had the event of interest at or prior to the time point for analysis and/or if the subject's status is known at any time beyond the analysis window. Subjects without sufficient follow-up based on the lower end of the visit window will be excluded from the analysis (that is, subjects must have at least 28 days of follow-up for the 30 day endpoints, 6 months minus 30 days for the 6 month endpoints and 12 months minus 30 days for endpoints defined at 1 year). Thus, subjects without events but whom are known to be event free at a later visit will have their data imputed backward but not forward for the primary analysis.

As a sensitivity analysis, missing values for the primary endpoints will be replaced by regression imputations based on a multivariate logistic regression analysis of completed cases (those that have follow-up at the required time point or experienced the endpoint in question prior to final follow-up visit). Covariates to consider for inclusion in the logistic regression include but are not limited to: age, sex, history of hypertension, diabetes, previous peripheral vascular intervention, BMI, dissection location (mid popliteal (P2), distal popliteal (P3), tibioperoneal trunk, peroneal, anterior tibial, or posterior tibial), and baseline Rutherford class. Backward selection will be used to identify predictors. In the event there are no significant predictors in the logistic regression model at alpha=0.1, a "hot deck" method will be employed where a random selection of the outcome from a group of completed cases with similar baseline characteristics will be used as the imputed value using simple random sampling with replacement. The baseline characteristics to be used for the hot deck method will include but are not limited to age (<> median), sex, dissection location (mid popliteal (P2), distal popliteal (P3), tibioperoneal trunk, peroneal, anterior tibial, or posterior tibial), use of statin medication, current smoker status and baseline Rutherford class.

With either method of imputation, five complete datasets will be constructed. Each dataset will be analyzed separately and then combined in an overall analysis across the five complete datasets.

In addition, a tipping point analysis will be conducted whereby all subjects missing data for the endpoint of interest will be imputed as a failure one at a time until the point of tipping the analysis has been determined. That is, the tipping point analysis starts with the best case analysis (all missing subjects are a success) and continues until the worst case analysis is completed (all missing subjects are failures), 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.

19.12. Study Success Definition

The trial will be considered a success if both the primary safety and primary efficacy endpoints are met.

19.13. Multiplicity

There is no correction to alpha in controlling type I error for the primary endpoints as both endpoints must be met in order to declare study success. Additionally, the type I error will be controlled by testing the secondary endpoint hierarchically. That is, the secondary endpoint of 6-month patency will be formally tested if and only if the primary study endpoints are met. If the 6-month patency endpoint is met then the two-sided 95% confidence interval for the secondary endpoint of target limb salvage at 6 months will be reported. There is no formal hypothesis for this endpoint. There are no additional formal hypothesis tests and thus no further adjustments are necessary.

20. 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.

20.1. Institutional Review Board (IRB) / Ethics Committee (EC) Approval

21 CFR Parts 50 & 56; ISO 14155: 2011 Section 4

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.

20.2. 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 (i.e. ISO 14155 for European Sites) for obtaining Informed Consent. Written, informed consent is to be obtained for all subjects prior to treatment as described in **Section 10.1**.

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.

20.3. 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.**

20.4. 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.

21. CLINICAL STUDY CONDUCT

21.1. PRINCIPAL INVESTIGATOR AND SITE QUALIFICATION

21 CFR 812.43; ISO 14155:2011 Section 8.2.1

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.

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

21.3. CLINICAL MONITORING

21 CFR 812.46; ISO 14155:2011 Section 8.2.4.2

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.

21.4. 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.

21.5. Investigator Reports

21CFR Parts 50 & 56; ISO 14155:2011 Section 4

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 may require a 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 safety and device events per the timelines specified in **Section 17** and **Section 18**.

21.6. 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.

21.7. SAFETY MONITORING

21.7.1. 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.

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

21.7.2. 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.

21.8. 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 reported 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;
- 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.

21.9. 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-rays 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.

21.10. 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.

21.11. 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.

21.12. 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.

21.13. 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.

21.14. 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.

21.15. 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 is registered with clinicaltrials.gov (NCT02942966).

21.16. 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 that the device under investigation will treat a Medicare population different than the demographics found in 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.[2] While the overall prevalence of PAD ranges from 3% to 10%, PAD affects 12% to 20% of Americans aged 65 years and older.[34,35] 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).

22. ECONOMIC ANALYSIS

Intact Vascular will collect procedural and reimbursement data (if available) from multiple sources including but not limited to hospital billing forms and Medicare claims data. These data will be used to perform an economic analysis for the Tack Endovascular System.

[34]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.
[35] 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.

23. WIfI Classification Tables

Table 10, Table 11, and Table 12 below provide the criteria that is shall be used to determine WIfI classification.

Table 10: Wound Grading

W: WOUND	*SVS grades for rest pain and wounds/tissue loss (ulcers and gangrene):*			
	0 (ischemic rest pain, ischemia grade 3; no ulcer) 1 (mild) 2 (moderate) 3 (severe)			
Eligible to Enroll	**Wound Grade**	**Clinical Description**	**Ulcer**	**Gangrene**
Yes	0	Ischemic rest pain (requires typical symptoms AND ischemia grade 3); no wound*	No Ulcer	No Gangrene
Yes	1	Minor tissue loss. Salvageable with simple digital amputation (1 or 2 digits) or skin coverage.	Small, shallow ulcer(s) on distal leg or foot; no exposed bone, unless limited to distal phalanx	No Gangrene
Yes	Modified 2	Tissue loss salvageable with simple digital amputation (1 or 2 digits) or skin coverage.	Deeper ulcer without exposed bone, joint or tendon; shallow or superficial heel ulcer, without deep tissue involvement or exposed calcaneus	Gangrenous changes limited to digits
No	2	Major tissue loss salvageable with multiple (≥3) digital amputations or standard TMA ± skin coverage.	Deeper ulcer with exposed bone, joint or tendon; generally not involving the heel; shallow heel ulcer, without calcaneal involvement	Gangrenous changes limited to digits
No	3	Extensive tissue loss salvageable only with a complex foot reconstruction or nontraditional TMA (Chopart or Lisfranc); flap coverage or complex wound management needed for large soft tissue defect	Extensive, deep ulcer involving forefoot and/or midfoot; deep, full thickness heel ulcer ± calcaneal involvement	Extensive gangrene involving forefoot and /or midfoot; full thickness heel necrosis ± calcaneal involvement

TMA, Transmetatarsal amputation.
*Sponsor note: For the purpose of this study, subjects without presence of wound and gangrene should be classified as a Wound Grade of 0, regardless of their Ischemia grade.

Table 11. Ischemia Grading

I: Ischemia	*Hemodynamics/perfusion: Measure TP or TcPO2 if ABI incompressible (>1.3)*			
	SVS grades 0 (none), 1 (mild), 2 (moderate), and 3 (severe).			
Eligible to Enroll	**Ischemia Grade**	**ABI**	**Ankle Systolic Pressure**	**TP,$TcPO_2$**
Yes	0	≥0.80	>100 mm Hg	≥60 mm Hg
Yes	1	0.60 - 0.79	70-100 mm Hg	40-59 mm Hg
Yes	2	0.40 - 0.59	50-70 mm Hg	30-39 mm Hg
Yes	3	≤0.39	<50 mm Hg	<30 mm Hg
ABI, Ankle-brachial index; PVR, pulse volume recording; SPP, skin perfusion pressure; TP, toe pressure; TcPO2, transcutaneous oximetry.				
Patients with diabetes should have TP measurements. If arterial calcification precludes reliable ABI or TP measurements, ischemia should be documented by TcPO2, SPP, or PVR. If TP and ABI measurements result in different grades, TP will be the primary determinant of ischemia grade.				
Flat or minimally pulsatile forefoot PVR = grade 3.				

Table 12: Foot Infection Grading

fI: Foot Infection	*SVS grades 0 (none), 1 (mild), 2 (moderate), and 3 (severe: limb and/or life-threatening)*		
	SVS adaptation of Infectious Diseases Society of America (IDSA) and International Working Group on the Diabetic Foot (IWGDF) perfusion, extent/size, depth/tissue loss, infection, sensation (PEDIS) classifications of diabetic foot infection		
Eligible to Enroll	**Foot Infection Grade**	**Clinical Manifestation of infection**	**IDSA/PEDIS infection severity**
Yes	0	No symptoms or signs of infection	Uninfected
Yes	1	Infection present, as defined by the presence of at least 2 of the following items:- ▪ Local swelling or induration ▪ Local warmth ▪ Erythema >0.5 to ≤2 cm around the ulcer ▪ Purulent discharge (thick, opaque to white, or sanguineous secretion) ▪ Local tenderness or pain Local infection (as described above) involving only the skin and the subcutaneous tissue (without involvement of deeper tissues and without systemic signs as described below). Exclude other causes of an inflammatory response of the skin (eg, trauma, gout, acute Charcot neuro-osteoarthropathy, fracture, thrombosis, venous stasis)	Mild
No	2	Local infection (as described above) with erythema >2 cm, or involving structures deeper than skin and subcutaneous tissues (eg, abscess, osteomyelitis, septic arthritis, fasciitis), and No systemic inflammatory response signs (as described below)	Moderate
No	3	Local infection (as described above) with the signs of SIRS, as manifested by two or more of the following: - Temperature >38° or <36° C - Heart rate >90 beats/min - Respiratory rate >20 breaths/min or $PaCO_2$ <32 mm Hg - White blood cell count >12,000 or <4000 cu/mm or 10% immature (band) forms	Severe[a]
$PACO_2$, Partial pressure of arterial carbon dioxide; SIRS, systemic inflammatory response syndrome.			
[a]Ischemia may complicate and increase the severity of any infection. Systemic infection may sometimes manifest with other clinical findings, such as hypotension, confusion, vomiting, or evidence of metabolic disturbances, such as acidosis, severe hyperglycemia, new-onset azotemia.			

24. 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) an increase of > 1.0 mg/dl in serum creatinine from most recent prior measured level, and current measured absolute value is > 2.2 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 not observing the IFU.
	▪ Note 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.
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, urticaria, shortness-of-breath, vasovagal reaction, or general collapse (anaphylaxis).
Amputation-free Survival	Freedom from above-ankle target limb amputation or all-cause death
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).
Assisted Primary Target Lesion Tacked Segment Patency	Assisted primary patency (freedom from total occlusion) achieved with the use of an additional or secondary surgical or endovascular procedures, as long as total occlusion of the Tacked segment has not occurred prior to such procedures. In all cases, freedom from total occlusion is confirmed by angiography or DUS (flow vs. no flow) if angiography was not performed.

Term	Definition
Bailout Stenting	Unplanned stenting to the target lesion and/or Tack implant(s). 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 uncoated) 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 or equal to 50% restenosis determined by angiography or 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 not observing the IFU 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.
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)	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.

Term	Definition
DUS Flow / No Flow	DUS Flow - Visualization of color Doppler and pulsed Doppler detectable flow within an arterial segment DUS No Flow – Absence of color Doppler and pulsed Doppler detectable flow within an arterial segment with evidence of flow within the corresponding venous segment
Index Procedure	The interventional procedure during which the study device is advanced through the introducer sheath and the subject is enrolled.
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.
Lesion Success	Demonstrated target lesion patency (<30% residual DS, by visual estimate) without the use of a bailout stent. This will be assessed for all lesions treated with a Tack. In addition, target lesion success will also be analyzed by lack of bailout stent to tacked segment only. Multiple target lesions treated as one lesion with PTA will be analyzed as one lesion.
Limb Salvage	Freedom from any above-ankle target limb amputation
Major Adverse Event (MALE)	Above-ankle target limb amputation or major re-intervention to the target lesion(s) (defined as new bypass graft, jump/interposition graft revision, or thrombectomy / thrombolysis)
Major Re-intervention	New bypass graft, jump/interposition graft revision, or thrombectomy / thrombolysis occurring after the index procedure
Major Amputation	Any above the ankle amputation to the target limb.
Minor Amputation	Any below the ankle amputation to the target limb (digital or transmetatarsal (ray or complete))
Minor Re-intervention	Endovascular procedures (PTA, atherectomy, stenting) without thrombectomy/thrombolysis, and minor surgical revisions (patch angioplasty) occurring after the index procedure
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.

Term	Definition
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 by an independent designee before study endpoint data is available for statistical analysis.
Perioperative Death (POD)	All-cause death occurring at 30 days after the Index Procedure
Primary Efficacy Endpoint	Freedom from major adverse limb events (MALE) at 6 months plus peri-operative death (POD) at 30 days defined as a composite of all-cause death, above-ankle target limb amputation, or major re-intervention to the target lesion(s) (defined as new bypass graft, jump/interposition graft revision, or thrombectomy / thrombolysis)
Primary Safety Endpoint	Freedom from BTK MALE+POD at 30 days. Composite of all-cause death, above-ankle target limb amputation or major re-intervention to the target lesion(s) (defined as new bypass graft, jump/interposition graft revision, or thrombectomy / thrombolysis)
Procedural Success	Demonstrated target lesion patency (<30% residual DS, by visual estimate) without the use of a bailout stent and without the occurrence of MALE+POD upon completion of the index procedure.
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.
Class	*Clinical Description*
0	Asymptomatic —no hemodynamically significant occlusive disease
1	Mild claudication
2	Moderate claudication
3	Severe claudication
4	Ischemic rest pain
5	Minor tissue loss—nonhealing ulcer, focal gangrene with diffuse pedal ischemia
6	Major tissue loss—extending above TM level, functional foot no longer salvageable

Term	Definition
Secondary Efficacy Endpoints:	▪ Target lesion(s) tacked segment(s) patency at 6 months defined as the presence of blood flow using duplex ultrasound. If angiography is available within the 6-month follow-up visit window, it should be used in place of the duplex ultrasound. Evidence of no blood flow within the Tacked segment indicates restenosis/loss of patency. ▪ Target Limb Salvage defined as freedom from any above-ankle target limb amputation at 6 months.
Secondary Target Lesion Tacked Segment Patency	Secondary patency (freedom from total occlusion) achieved with the use of an additional or secondary surgical or endovascular procedures. In all cases, freedom from total occlusion is confirmed by angiography or DUS (flow vs. no flow) if angiography was not performed.
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.
Study Device Procedure Start/End Time	Start: The time the first Tack Endovascular System is advanced through the introducer sheath End: The time of withdrawal of last post-Tack PTA balloon catheter

Term	Definition
Tacked Segment	Defined as the Tack device and 5 mm of artery proximal and distal to each Tack. If Tacks are within 10 mm of each other, they will be considered as a single tacked segment for the purposes of this patency assessment.
Target Lesion Tacked Segment Patency	Patency defined as the presence of blood flow using duplex ultrasound. If angiography is available within the follow-up visit window, it should be used in place of the duplex ultrasound. Evidence of no blood flow within the Tacked segment indicates restenosis/loss of patency.
Target Lesion	The lesion(s) that are assessed and if eligible, treated with the study device. After PTA treatment, the target lesion length is defined as the entire contiguous arterial segment treated with angioplasty and may also be referred to as the "treated lesion". The target lesion(s) may be de novo or non-stented restenotic with pre-PTA stenosis of ≥70% or is occluded (by visual estimate) and is indicated for PTA treatment with a standard balloon catheter **Note:** If the lesion is restenotic, no part of the lesion should have more than 1 prior failure (by plain balloon angioplasty only), which must have occurred greater than 1 year (360 days) prior to the index procedure **Note:** Diseased segments with >30mm between them are considered separate lesions **Note:** After PTA treatment, the target lesion is defined as the entire contiguous arterial segment treated with angioplasty
Target Lesion Revascularization, Clinically-driven (CD-TLR)	Any re-intervention (endovascular or surgical) to the target lesion(s) in subjects with recurrent clinical symptoms indicated by a worsening Rutherford classification (increase of one category or more) since earliest post-procedure classification or a new or worsening wound. The designation of CD-TLR should be corroborated by angiographic evidence of ≥50% DS at the time of repeat intervention and will be adjudicated by the CEC. This trial will evaluate CD-TLR based on a per lesion analysis as well as the Tack treated section of the target lesion.
Target Lesion Revascularization (TLR)	Any re-intervention (endovascular or surgical) to the target lesion(s) occurring after the index procedure.

Term	Definition
Target Vessel	The vessel location(s) of the target lesion(s). Lesions may be eligible for study device treatment if located within the following arteries: mid popliteal (P2), distal popliteal (P3), tibioperoneal trunk, peroneal, anterior tibial, or posterior tibial **Note:** The Mid Popliteal artery (P2) begins at the superior aspect of the patella. The most distal location of the tibial and/or peroneal artery(ies) ends at the beginning of the dorsalis pedis artery (DP). Tacks may not be implanted within 1cm of, or below, the radiographic tibiotalar joint
Target Vessel Revascularization, Clinically-driven (CD-TVR)	Any re-intervention (endovascular or surgical) to the target vessel(s) in subjects with recurrent clinical symptoms indicated by a worsening Rutherford classification (increase of one category or more) since earliest post-procedure classification or a new or worsening wound. The designation of CD-TVR should be corroborated by angiographic evidence of ≥50% DS at the time of repeat intervention and will be adjudicated by the CEC.
Target Vessel Revascularization (TVR)	Any re-intervention (endovascular or surgical) to the target vessel(s) occurring after the index procedure.
Toe/Brachial Index (TBI)	The ratio of systolic blood pressure measured at the toe to systolic blood pressure measured at the brachial artery. The TBI is calculated by dividing the toe pressure by the brachial systolic pressure (the higher of two arm pressures).
Transient Ischemic Attack (TIA)	Clinical signs/symptoms of focal neurological deficit lasting up to 24 hours
Treatment PTA	Refers to the PTA performed to the target lesion(s) prior to introduction of the study device
Unanticipated Adverse Device Event (UADE)	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.
Unplanned Procedure	A procedure that was not planned at the time of subject enrollment.