PQ Bypass Systems for Femoropopliteal Bypass II

PQB 4 FP II Protocol

Signature Page

CLINICAL PROTOCOL NUMBER

STP 115 Rev F

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Approved by: _____ Date: _____

Ziad Rouag
Vice-President, Clinical and Regulatory Affairs
PQ Bypass, Inc.

The trial will be performed in accordance with the relevant parts of Title 21 CFR Parts 812, 50,54, 56 and ISO 14155:2011:01; the ICH Guidelines for Good Clinical Practices (E6), the Declaration of Helsinki, and any regional and/or national regulations.

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Appendix II: Guidewire Delivery System, Stent Graft System and Balloon Dilator Instructions for Use (English Version)

1.0 PRIMARY CONTACTS

Sponsor and Data Management	**PQ Bypass, Inc.** 269 N. Mathilda Avenue Sunnyvale, CA 94085 Phone: +1 (408) 940-3520 Fax: +1 (408) 735-7420 Ziad Rouag Vice- President Clinical and Regulatory Affairs PQ Bypass, Inc. Phone: +1-415-531-46472 Email: zrouag@pqbypass.com
Global Monitor / CRO **Authorized EU Representative**	Claire van den Nieuwenhof Quality Manager HealthLink Europe BV HealthLink International Inc. De Tweeling 20-22 5215 MC 'S Hertogenbosch The Netherlands Phone General: +31-(0)13-5479300 Fax: +31-(0)13-5479300 E-mail: claire.vandennieuwenhof@healthlinkeurope.com Web:www.healthlinkeurope.com
Legal Representative - Chile	**Bioscience Consulting Inc.** Ruben Carnero Encomenderos 113 - 2do Piso Las Condes, Santiago, Chile Phone: +56. 2.2570.3702 Email: rcarnero@biosciencewеb.com
Core Lab	**Vascular Ultrasound Core Lab** Gail Hadley RN, RVT, FSVU, Technical Director One Bowdoin Sq. 10th floor | Boston | MA | 02114 Business Office: 617-726-5552 Mobile: 941-321-4523 | Fax: 617-726-1977 gshadley@partners.org http://vascore.org

PQ BYPASS	**PROTOCOL SUMMARY**

Title:	PQ Bypass Systems for Femoropopliteal Bypass II (PQB 4 FP II)
Protocol Number	STP 115
Study Design:	Prospective, single-arm, multi-center, international, non-randomized, pre-market, safety and effectiveness clinical investigation evaluating the PQ Bypass Systems to access, deliver guidewires and implant stent grafts for a percutaneous femoropopliteal (fem-pop) bypass.
Study Objective:	To assess the safety and performance of the PQ Bypass Systemto access,deliver guidewires and implant stent grafts for a percutaneous fem-pop bypass.
Enrollment:	Up to **100** subjects will undergo a percutaneous fem-pop bypass, including up to **30** subjects in Germany.
Number of Sites	Up to 17 international sites (non U.S. sites).
Study Enrollment	24-month enrollment period: • Initial enrollment: Q1, 2015 • Last enrollment: Q1, 2017
Study Duration	60 months (24-month enrollment and 36-month follow-up)
Primary Safety Endpoint:	Major Adverse Events (MAE) at 1 month. MAE is a composite endpoint defined as: • Death • Target Vessel revascularization (TVR) • Target limb amputation
Primary Performance Endpoint:	The rate of primary patency at 6 months defined as: no evidence of clinically significant stenosis (≥50%) within the stent graft or immediately above or below the treated arterial segment based on duplex ultrasound (systolic velocity ratio of >2.5), with no clinically-driven re-intervention within the stented segment. The primary performance endpoint will be assessed by an independent Core Lab.
Secondary Safety Endpoints:	• Major Adverse Events (MAE) through follow-up. • Major adverse vascular event (MAVE) through follow-up defined as stent thrombosis, target limb amputation, clinically apparent distal embolization, defined as causing end-organ damage (e.g. lower extremity ulceration, tissue necrosis, or gangrene), procedure related arterial rupture, acute limb ischemia or bleeding event requiring transfusion. • Major Blood Loss defined as transfusion of >2 units packed red blood cells (PRBC)) through discharge. • The combined rate of death of target vessel revascularization (TVR), index limb amputation, and an increase in Rutherford-Becker Classification by 2 classes (comparing pre- to post-procedural assessments) through follow-up. • Deep Vein Thrombosis (DVT) on ipsilateral limb defined as a symptomatic blood clot (thrombus) in the targeted deep vein (e.g. posterior tibial) through follow-up. • Venous Clinical Severity Score (VCSS) and Villalta Scale through follow-up. • Venous Assessment (Miller Scale) through follow-up. • Stent fracture identified via X-ray through follow-up. Optional per standard practice. Not applicable if Radiological Safety Committee approval is required (e.g. BFS Germany)
Secondary Performance Endpoints:	• Technical Success defined as successful delivery of the investigational devices to the identified area and removal of delivery system. • Procedural Success defined as successful delivery of the investigational devices to the

	identified area and removal of delivery system in the absence of in-hospital MAEs. • Clinical Success defined as Limb ischemia improvement by Rutherford-Becker (improvement in scale by ≥ 1) through follow-up. • Limb ischemia by Rutherford-Becker Classification through follow-up. • Primary Patency through follow-up. • Primary assisted patency defined as revascularization of non-occlusive (<99%) stenosis within the stent graft or immediately above or below the treated arterial segment with less than 50% residual stenosis through follow-up. • Secondary patency defined as: revascularization of occlusion (100%) within the stent graft or immediately above or below the treated arterial segment with less than 50% residual stenosis through follow-up. • Ankle-Brachial Index (ABI) through follow-up. • Target vessel revascularization (TVR) through follow-up. • Number of any type of index limb amputations through follow-up. • Number of vessel run-offs through follow-up.
DSMB	A Data Safety Monitoring Board (DSMB) consisting of non-Investigator experts, will review safety data from the study and establish stopping rules for early termination of the trial. The DSMB will make recommendations based upon the safety analysis of adverse events, protocol deviations, and device failures. The DSMB will function in accordance with SOPs and applicable regulatory guidelines.
Inclusion Criteria:	• Willing and able to provide informed consent. • Age 18 or older. • Willing to comply with the specified follow-up evaluation schedule. • Women of child bearing potential must have a negative pregnancy test within 7 days prior to the index procedure. • Severe claudication or rest pain or ischemic ulceration not exceeding ulcer of the digits of the foot (Rutherford Becker scale 3-5) with a resting ABI < 0.9. Resting TBI is utilized only if unable to reliably assess ABI. TBI must be <0.7. • Subject is not morbidly obese (BMI<40). • Venous Clinical Severity Score <3. • Serum creatinine level < 2.0 mg/dL. • BUN ≤20 mg/dL. • Patent iliac and femoral arteries/veins and access vessels, of sufficient size and morphology (including tortuosity), to allow endovascular access with 8 Fr. introducer sheath. • Femoro-popliteal lesions ≥10 cm (TASC C and D) in length considered to be: o Chronic total occlusion (100% stenosis) o Diffuse stenosis (>50% stenosis) with moderate to heavy calcification o In-stent restenosis (>50% stenosis) • Reference vessel diameter (RVD) ≥ 5.0 mm and ≤ 6.7 mm, as measured via pre-screening CTA/MRA using 3D RPR reconstruction. • Orifice and proximal SFA is patent (approximately 1 cm stump). • Patent popliteal artery 3 cm proximal to tibial plateau. • At least 1 patent tibial artery to the foot. • Patient has the ability to comply with the necessary follow-up examinations and tests in accordance with protocol. • Patent femoral vein ≥ 10 mm in diameter or duplicate femoral vein. • Subject has > 2 year life expectancy.

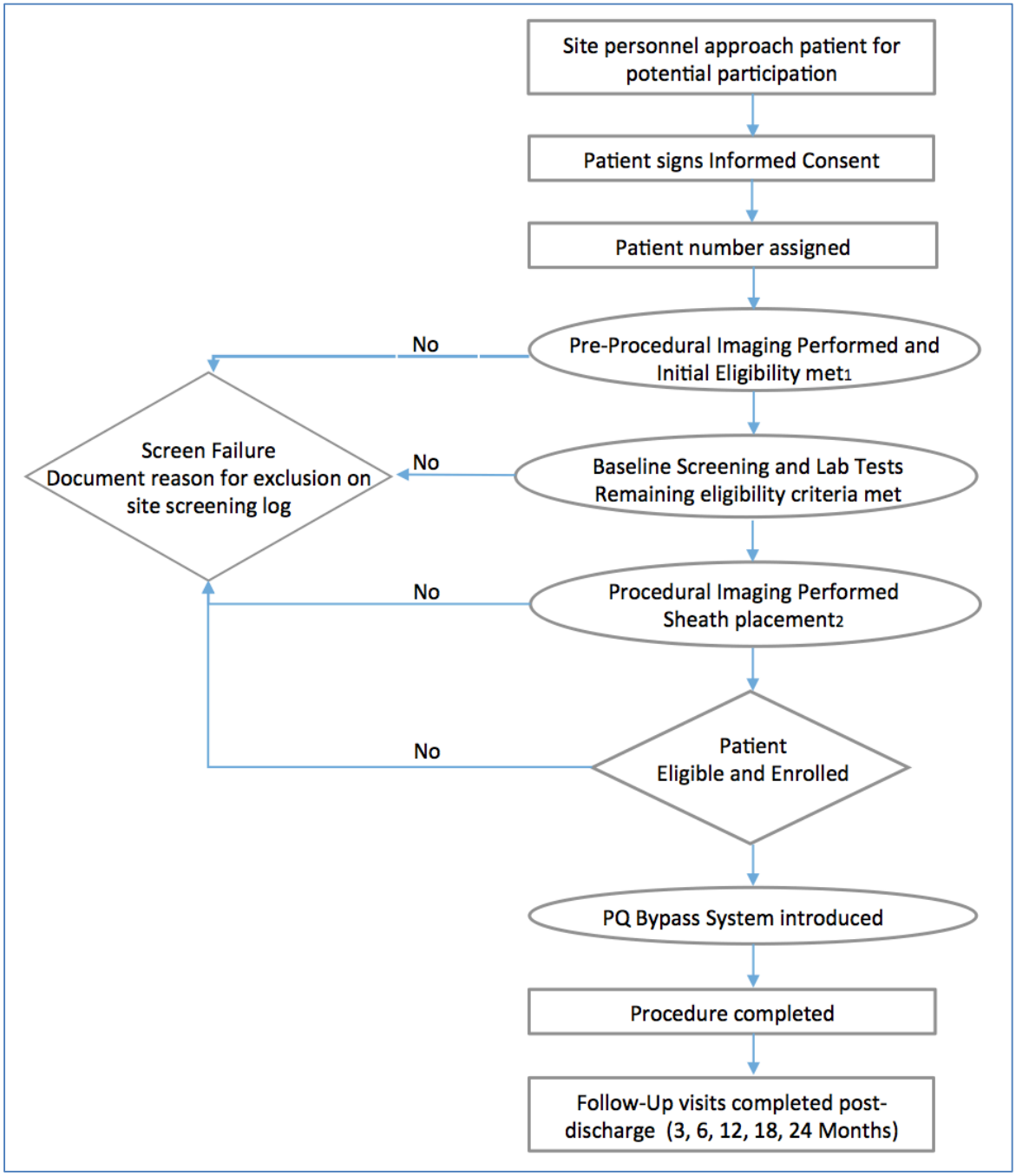
Exclusion Criteria:	• Age greater than 90. • History of deep vein thrombosis. • Has known hypersensitivities, allergies or contraindications to: nitinol, PTFE; aspirin, heparin, antiplatelet, anticoagulant or thrombolytic therapy; or anticoagulation or contrast media. • Has a known history of intracranial bleeding or aneurysm, myocardial infarction or stroke within the last 3 months. • Pregnant or nursing. • Untreated flow-limiting aortoiliac occlusive disease. • Has renal failure (eGFR < 30mL/min). • Major distal amputation (above the transmetatarsal) in the study or non-study limb. • Patient has had a revascularization procedure on the target limb within 7 days of the planned index procedure. • Known or suspected active infection at the time of the procedure. • Requires a coronary intervention 30 days or less prior to or 30 days post the treatment of the target lesion. • Thrombophlebitis, within the previous 30 days. • Thrombolysis of the target vessel within 72 hours prior to the index procedure, where complete resolution of the thrombus was not achieved. • Receiving dialysis or immunosuppressant therapy within the previous 30 days. • Stroke within the previous 90 days. • Ipsilateral femoral aneurysm or aneurysm in the SFA or popliteal artery. • Planned amputation of the target limb. • Previous bypass surgery on the target limb. • Participating in another clinical study for which follow-up may impact the current study. • Congestive heart failure, COPD (Stage IV, FEV1 <30% normal, or <50% normal with chronic respiratory failure present), metastatic malignancy, dementia, or other major co-morbidities that would prevent the post-interventional movement. • A condition that in the view of the investigator precludes participation in this study.
Follow-Up:	• Discharge • 1 month ± 7 days • 3 months ± 14 days • 6 months ± 30 days • 12 months ± 45 days • 18 months ± 45 days • 24 months ± 60 days • 30 months ± 60 days • 36 months ± 60 days

Schedule of Assessments

Activity	Initial Eligibility	Pre Procedural Baseline Screening	Procedure	Discharge	Follow-up 1M± 7D 3M ± 14D 6M ± 30D 18M ± 45D 24M ± 60D 30M ± 60D 36M ± 60D	Follow-up 12M ± 45D
Informed Consent	X					
Review of Inclusion/Exclusion Criteria	X					
Pre-Procedural CTA /MRA	X					
Pre-Procedural Venous Ultrasound	X					
Medical History/Demographics		X				
Ankle-Brachial Index		X		X	X	X
Rutherford Assessments		X		X	X	X
Serum Pregnancy Test		X				
VCCS and Villalta Scale		X		X	X	X
BUN and Creatinine		X				
Final eligibility Angiogram/Venogram			X			
Venous Ultrasound				X	X	X
Arterial Ultrasound				X	X	X
Stent Graft X-Ray *						X
Adverse Event Assessment			X	X	X	X
Concomitant Medications		X	X	X	X	X

*Optional per standard practice. Not applicable if Radiological Safety Committee approval is required (e.g. BFS Germany).

Patient Screening, Enrollment and Follow-Up



1: Performed through CTA/MRA (artery) and Doppler ultrasound (vein)

2: Investigators will access the target lesion and the corresponding ipsilateral vein using standard percutaneous techniques and devices. Patient eligibility will be confirmed prior to insertion of the study device, based on procedural angiogram and sheath placement.

Revision Letter	Change Description
A	• Initial Release
B	• Increased sample size and number of sites • Updated inclusion exclusion criteria • Clarified schedule of assessment • Added reference to Core Lab • Added patient screening enrollment and follow-up flowchart • Added section for discharge evaluation. • Removed vital signs as a requirement after baseline evaluation • Clarified statistical plan
C	• Added Pre-Procedural Venous Ultrasound to Initial Eligibility • Updated signature pages • Clarified venous inclusion/exclusion criteria • Clarified statistical plan
C1	• Updated Per BFARM request
C2	• Updated Per BFARM request
D	• Updated per BfArM request
D1	• Updated per Austrian CA Request • Typographical corrections
E	• Increased enrollment to 100 patients • Updated statistical rational to account for surgical comparison • Updated primary safety endpoint to be in line with other SFA studies • Added additional secondary endpoints for analysis • Added Core Lab contact information • Clarified event reporting requirement, inclusive of Austria • Add all potential product adverse events per IFUs • Updated product images • Updates clinical outcome data to date • Added x-ray at 12-month follow-up • Added detailed listing of definitions
E1	• Minor typographical corrections, and other minor editorial changes/clarifications • Added Section 18 Publications per Latvian Regulations
F	• 12-month X-ray for Stent Graft as Optional per standard practice. Not applicable if Radiological Safety Committee approval is required (e.g. BFS Germany) • Added Definition for Malignant Tumor • Added Appendix III: Justification for the Safety and Primary Performance Endpoints • Updated EU Rep • Updated Reporting SAE (Changed to 7 Days) • Updated Patient Follow up to include 30month FU Visit and 36 month FU Visit • Updated CoreLab Information

2.0 INTRODUCTION

2.1 Peripheral Artery Disease Background

Atherosclerosis is a systemic disease process of plaque build-up within arterial vessels.[1] This plaque consists of fat deposits, cholesterol, calcium and other substances, and when plaque continues to accumulate, the vessel can become hardened, narrowed and/or completely occluded. The subsequent manifestation of narrowed arteries is a reduction of oxygen-rich blood flow to organs and other parts of the body.[2] In peripheral arterial disease (PAD), the accumulation of plaque blocks or reduces the flow of oxygen-rich blood to the arms, legs and pelvis, which can lead to numbness, pain and dangerous infections.[2] Removal of these narrowings or obstructions is critical to restoring adequate blood flow, maintaining healthy vessels, tissues and organs.

The most common risk factors for developing PAD are diabetes mellitus, cigarette smoking, advanced age, hyperlipidemia and hypertension.[3] In 2003, it was estimated that more than 27 million people in North America and Europe were affected by PAD,[4] and in 2007, it was estimated that PAD affects more than one in five people over the age of 70.[5] Despite the risk factors, less than 50 percent of patients with PAD know that they have the condition.[5] Patients suffering from PAD may also have symptomatic or asymptomatic coronary and/or carotid arterial disease and are three to six times more likely to experience a heart attack or stroke than patients without PAD.[5]

2.2 Current Treatment Options

The gold standard for treating lesions in the infrainguinal segment is surgical bypass using an autologous vein. Unfortunately, adequate vein is often unavailable and the long-term results of surgical bypasses using synthetic material are less satisfactory.[6] Over the past three decades, advances in endovascular technology, which is less invasive than surgery, have led to increasing use of endovascular tools in lieu of surgical options. Today, treatments are recommended based on specific lesion characteristics. The Trans-Atlantic Inter-Society Consensus (TASC) group recommends treatment using their Type A-D classification system, which incorporates lesion length and lesion type (stenosis vs. occlusion, denovo vs. re-stenosis, etc.). In 2000, the first TASC meeting recommended that TASC A lesions be treated endovascularly, TASC D lesions be treated surgically and had no recommendation for TASC B and C lesions due to lack of evidence.[7] In 2007, updated recommendations were published that both modified the classifications and recommended endovascular therapy for TASC B lesions and surgery for TASC C lesions in “good-risk” patients.[8] Many in the community felt the TASC II recommendations were not representative of the latest data on novel endovascular methods, prompting critiques in favor of an “endovascular first” approach for all femoropopliteal lesion types.[9,10,11] These critiques were consistent with the market, which increased use of endovascular therapies by 3x

while reducing surgical and amputation rates from 1996-2006.[12] (**Figure 2-1**).

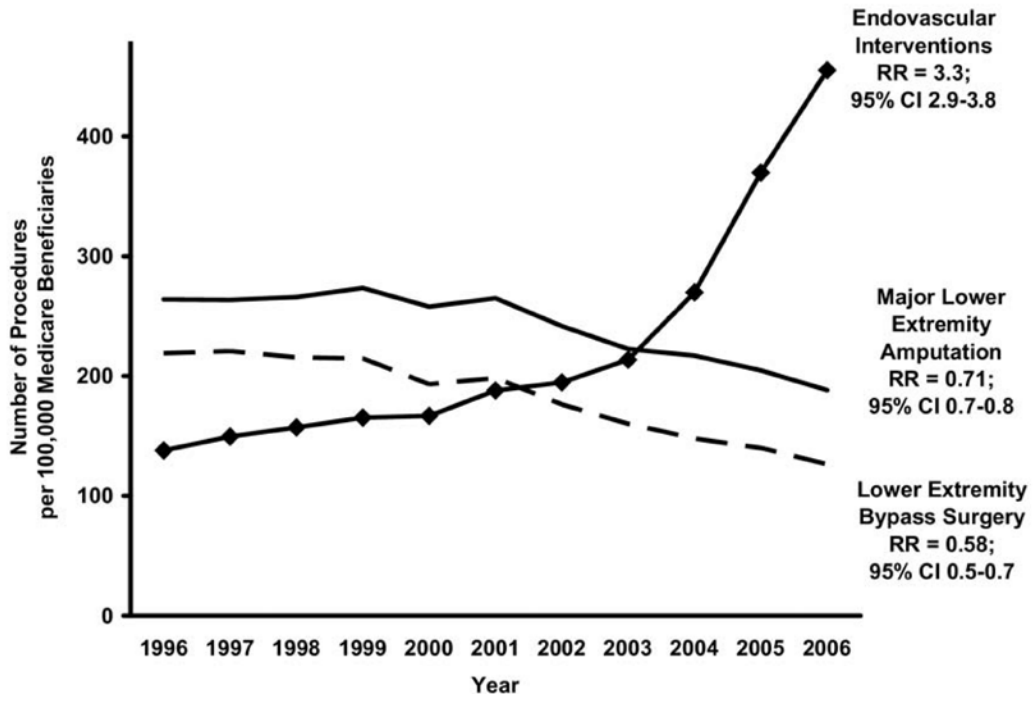


Figure 2-1: Trends in endovascular interventions, major amputation and lower extremity bypass surgery

The increasing trend of the "endovascular first" approach is supported by current research on endovascular and surgical outcomes. Which endovascular method to use for which lesion type, however, continues to be a research topic of interest. Percutaneous transluminal angioplasty (PTA) appears most effective in treating relatively short (<5 cm) femoropopliteal lesions with an average 12-month primary patency of 74% (61-84%).[13,14,15,16,17,18,19] With lesions longer than 5 cm, however, PTA primary patency drops to 35% (13- 56%).[20,21,22,23,24,25,26,27,28] Stenting after PTA improves primary patency in lesions longer than 5 cm (mean 72%, 54-87%), but PTA and stenting for lesions >10 cm long is less effective (mean 43%, 22-55%).[13-16,18,20,24,29,30,31,32,33] In terms of TASC categories, PTA and/or stenting have outcomes equal to or better than surgery for TASC A and B lesions, but fail to match surgery's patency rates in TASC C or D lesions (**Figure 2-2**).[34]

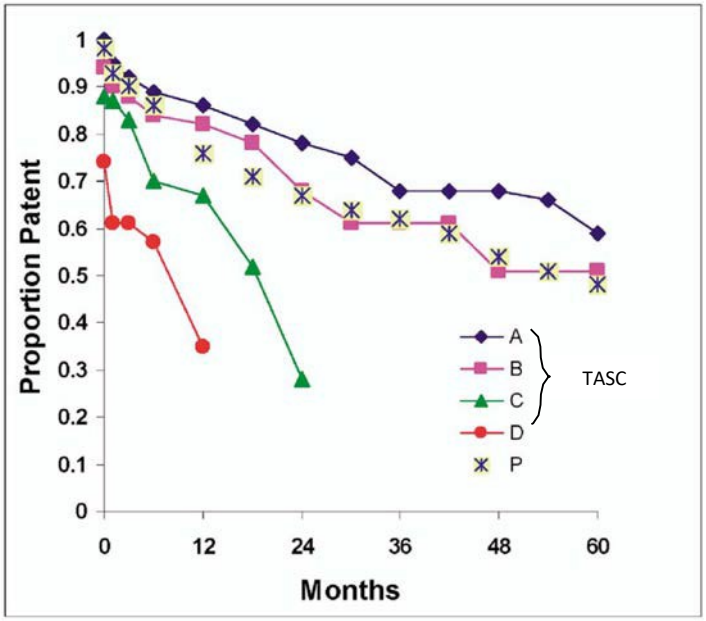


Figure 2-2: Primary Patency of SFA PTA and/or Stenting (letters indicate TASC lesion types [A-D] and prosthetic bypass surgery [P])

Despite lower patency in endovascular-treated TASC C/D groups, investigators are divided on whether to recommend surgery as the primary treatment for long-segment disease.[25,27,28,32,33,35,36] While some cite the superior primary patency of surgical grafts as the principle metric for recommendation, others cite the overall patient experience with surgical and endovascular means and conclude that endovascular methods should be attempted prior to subjecting a patient to the risks of open surgical repair.

New evidence using "covered stents"/stent grafts may provide another useful variable to consider in treating TASC C/D lesions, or long-segment disease. Like bare metal stents, covered stents/stent grafts are preceded by PTA. Unlike traditional stents, however, these devices are covered with a synthetic material; most commonly polytetrafluoroethylene (PTFE) or Dacron (knitted polyester), the same materials used for prosthetic surgical bypass. Much like investigators who theorized that a sub-intimal approach to long-segment angioplasty would lead to better outcomes by precluding the existing atheroma from the new lumen, covered stents eliminate the previously atherosclerotic vessel from direct communication with the blood which may eliminate some of the limitations experienced by other endovascular therapies in longer lesions.[27,37] Some of the earliest work reported in the literature began in the mid-1990's and found 79% patency at 12 months in lesions averaging 13.1cm in length (5-40cm).[37] These initial results compare very favorably to stents and PTA, both of which fail to reach 50% patency at 12 months in lesions longer than 10 cm. Since that time, a number of additional studies using stent grafts have been conducted supporting their effectiveness in long lesions; average 12- month patency is 73% in lesions between 10-15 cm and 71% in lesions between 15-
26 cm.[26,38,39,40,41,42,43,44,45,46] In terms of TASC Classification, stent grafts continue to demonstrate excellent patency in more complex lesions (**Figure 2-3**).[38]

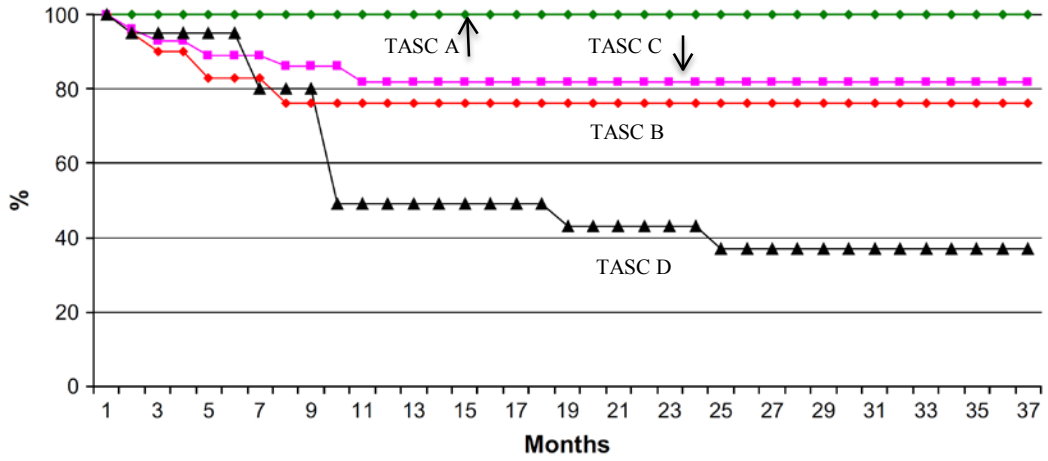


Figure 2-3: Primary Patency of SFA Stent Grafting

While TASC D patients continue to have poor prognosis compared to TASC A-C, the patency rates for all lesion types are improved relative to stenting and PTA. These apparent improvements in patency have also been confirmed in prospective comparisons. One study identified 12-month patency of 75% and 28% for stent grafts and PTA, respectively, in the treatment of long-segment lesions (>15 cm).[26] Another study found an equally dramatic difference with 12-month patency of 87% at 2 years in the stent graft group versus 23% with PTA in relatively short lesions (6.9 cm).[22] The leading stent graft on the market obtained FDA approval demonstrating a more modest difference in 12-month primary patency (stent grafts – 62%, PTA – 40%).[21] In the same study, the difference was more striking in long lesions (>13 cm) where the stent graft group maintained patency at a rate of 54% where the PTA group fell to 17% at 12 months. Stent grafts also fare well when compared to synthetic bypass grafting in femoropopliteal occlusive disease. A recently published four-year randomized study found no difference between the stent graft and synthetic surgical bypass groups at any follow-up period from 1 to 4 years in patients with an average lesion length of 25 +/- 15 cm (SD) and TASC scores distributed equally among A through D.[47]

While these findings are very promising, reports do exist that suggest stent grafts may not have an advantage over more conventional therapy. In a randomized evaluation of stent-grafts and bare metal stents in long-segment femoropopliteal disease (18-19 cm), no difference was identified between the two treatment groups over three years; primary patency at 3 years was 24.2% and 25.9% for the stent graft and bare metal stents, respectively.[48] While this report highlights the difficulty in treating long lesions with either endovascular method, the collective evidence supports using stent grafts in long lesions over traditional PTA and stenting.

The PQ Bypass approach to treating long-segment disease builds on the concept of stent grafting by implementing the use of a stent graft in a manner similar to surgical bypass. Where standard stent grafts are placed across lesions intra-arterially, the PQ Bypass stent grafts exit the artery proximal to the lesion and re-

enter the arterial lumen at the distal reconstitution site, leaving only a small portion of a stented graft inside of the native artery and bypassing the heavily diseased area. Using the same synthetic materials to surgically bypass lesions yields an average 12-month primary patency of 80%.[39, 45,49,50,51,52,53,54,55]

The PQ Bypass approach to treating long-segment disease also takes advantage of the reduced risk associated with endovascular repair compared with surgery. In reviewing the literature on traditional endovascular techniques (e.g., PTA, stents and stent grafts), very little information on co-morbidities can be identified. The majority of the safety concerns cited are related to the need for re-intervention. In fact, one recent study looking at the safety of stent graft use at one study center looked specifically for the use of thrombolysis (for occlusions) and the need for amputation and bypass surgery as their primary endpoint.[56] Restenosis or thrombosis of the target lesion/stent/stent graft requires the patient be exposed to another interventional procedure which carries some degree of safety concerns. These include, but are not limited to: access site hemorrhage or hematoma, access site pain, acute vessel closure, embolism, infection, and renal insufficiency/failure due to excessive contrast load.

Patients undergoing endovascular repair are often discharged from the hospital the next day whereas surgically treated patients may stay in the hospital for up to 7 days. Endovascularly treated patients can often go back to normal activities within the first week following the procedure. Surgically treated patients can take 6 weeks or longer to fully recover[56,57]. These extended recovery times combined with increasingly positive patency findings, are the principle reasons behind the previously cited decline in surgery and rise of endovascular repairs in recent years.

PQ Bypass seeks to place stent grafts in bypass conduit via a percutaneous method to evaluate the bypass concept as it compares to standard stent graft placement.

2.3 Previous Clinical Experience

Over the past decade, the founders of PQ Bypass have pioneered the percutaneous femoro-popliteal bypass approach using off-the-shelf devices. Dr. James Joye was referred patients with long-segment femoropopliteal disease that were destined for either bypass surgery or below the knee amputation. A retrospective review of patients treated by Dr. Joye was conducted in order to collect data and assess the safety and performance of this novel technique. This study was called “A Review of Patients Undergoing Percutaneous Femoropopliteal Bypass for the Treatment of Superficial Femoral Artery Occlusive Disease”. This study is henceforth referred to as the El Camino Hospital (ECH) Study. The following are the results of that retrospective review. From 2003 to 2012, Dr. Joye treated 25 limbs in 21 patients for whom data are currently available. Two patients in this group experienced graft failures due to extraneous circumstances. One patient was involved in an automobile accident that required a tourniquet on his bypassed limb, leading to an occlusion, and the other patient had upstream iliac disease from which an embolus originated and caused a downstream graft thrombosis. With these two exclusions, there are 23 limbs from 19 patients available for review. Average lesion length was 32 cm and all but 3 were TASC D lesions (19/22) involving the SFA and popliteal

arteries. Using a commercially available re-entry tool and stent graft, Dr. Joye successfully bypassed each of these patient's lesions percutaneously. At 6 and 12-months, 91% and 82% of the bypass grafts, respectively, remained widely patent without the need for re-intervention (**Figure 2-4**).

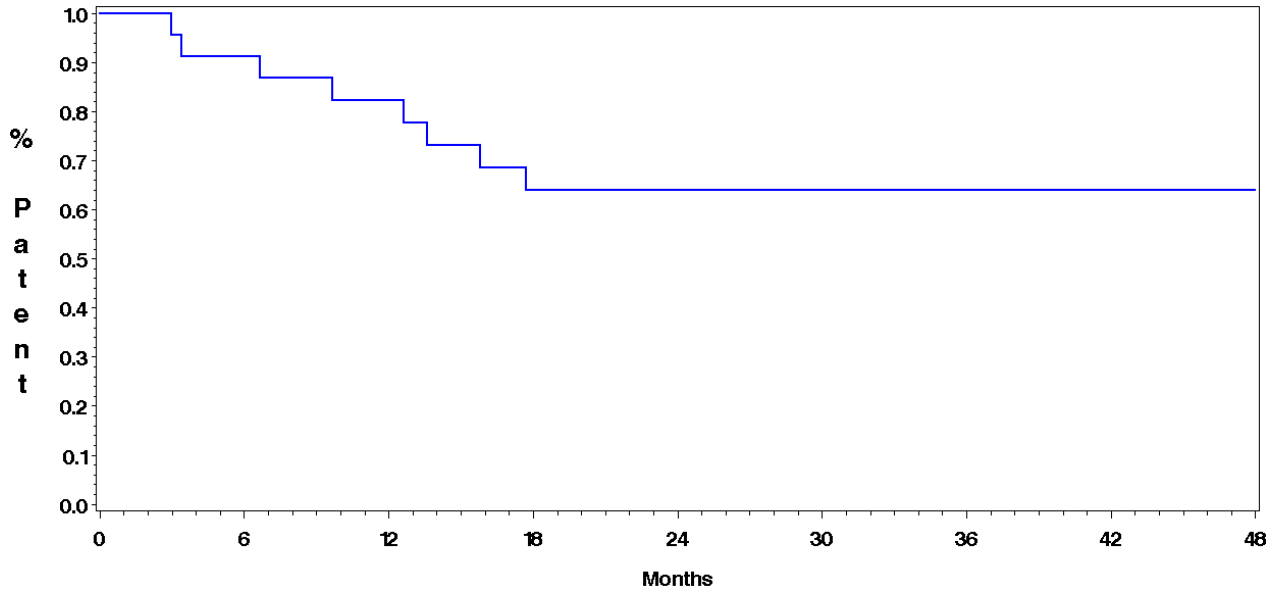


Figure 2-4 – Primary Patency

These results compare favorably with competitive endovascular procedures, all of which fail to reach 50% primary patency in this patient cohort. More importantly, none of the 23 limbs has been amputated a 100% limb survival rate.

In addition to excellent patency outcomes, as previously stated, all treated limbs survived and no venous sequelae have been identified. To further evaluate the use of the femoral vein as a conduit for the bypass, all patients that were available for follow-up were contacted, and a prospective evaluation of their lower extremity veins was conducted. Recently, 16 subjects (20 limbs) treated between 2003 and 2012 have returned for a duplex ultrasound of each treated limb. There were no venous sequelae identified in this patient cohort; all patients exhibited normal reflux and no evidence of deep vein thrombosis, thrombophlebitis or chronic edema. Only one vein out of the 20 limbs was occluded; however, the patient was not experiencing any venous related health concerns as a result. The patient underwent the percutaneous femoro-popliteal bypass in August 2011 and had a venous and arterial ultrasound performed in July 2013. This patient's arterial bypass graft remains widely patent without the need for re-intervention.

While this initial report is based on "off-the-shelf" devices that were not originally designed for this procedure the success rate proves the concept of the percutaneous bypass approach and supports the safety of using the femoral vein as a conduit for the bypass. PQ Bypass has designed and developed a kit of devices specific for this percutaneous procedure and is in the process of generating additional evidence supporting this novel therapeutic approach through the current CE Mark study.

2.4 Ongoing Clinical Experience (CE Mark Study)

The ongoing CE Mark study commenced in January 2015, in Riga, Latvia (Site 01), where the first two patients were enrolled. As of May 2016, 60 subjects have been treated at 7 sites. Enrollment and follow-up is ongoing. Table 2 below is a summary of the protocol. As noted in the inclusion exclusion criteria the population being treated involves TASC C/D long lesions (avg. = 28 cm) including CTOs. The results from the CE Mark study, showing high patency and low morbidity in TASC D lesions, may serve to support the safety profile of the Stent Graft. Core lab adjudicated outcomes through 6 months for 30 subjects are provided in **Figure 2-5** and **Figure 2-6** below. With an average lesion length of 28 cm and a primary patency of 90% at 6 months, results are encouraging.

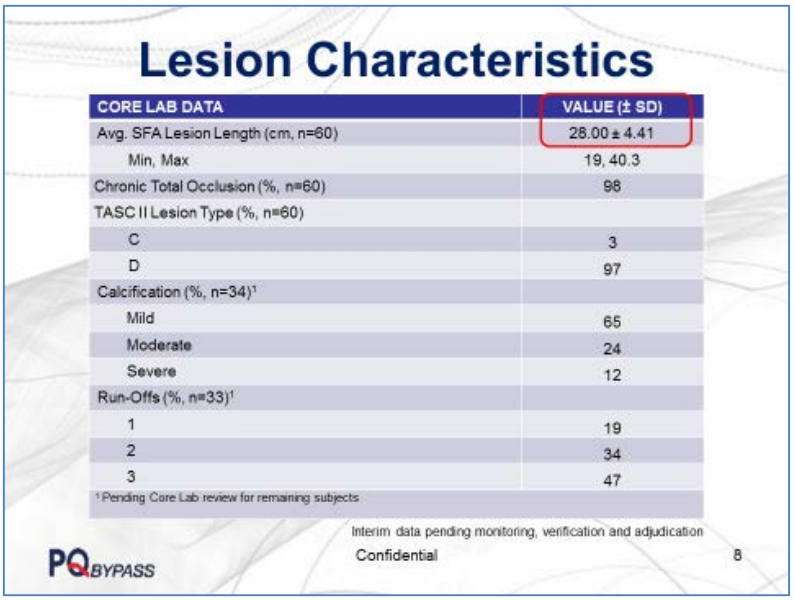


Figure 2-5 –Lesion Characteristics

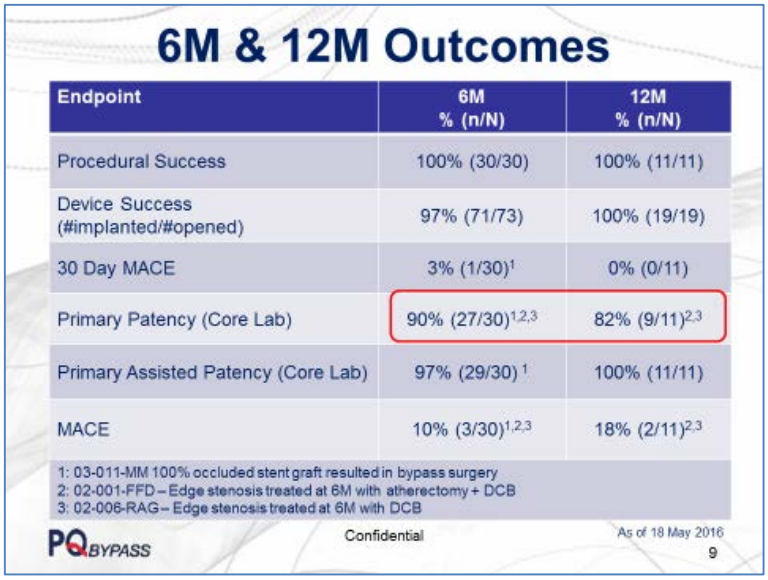


Figure 2-6 –Core Lab Assessed Outcomes to Date

3.0 DEVICE / TECHNOLOGY DESCRIPTION

PQ Bypass designs and manufactures the PQ Bypass Guidewire Delivery System (GWDS) and the PQ Bypass Stent Graft System (SGS) and purchases the PQ Bypass Balloon Dilator (BD) from an Original Equipment Manufacturer (OEM). The GWDS is comprised of the Percutaneous Anastomotic Device (PAD) and the Venous Locator (VL) and is intended to support the delivery of guidewires in the peripheral vasculature. The SGS is comprised of a Stent Graft and a Stent Graft Delivery System and is intended to place stent grafts in the peripheral vasculature to improve blood flow. The BD is a standard percutaneous transluminal angioplasty (PTA) balloon used to dilate arterio-venous anastomoses. When used together, the GWDS, SGS and BD allow for a percutaneous bypass procedure in the peripheral vasculature.

3.1 Guidewire Delivery System (GWDS) – Percutaneous Anastomotic Device (PAD)

The PAD (**Figure 3-1**) is a spring-loaded dual guidewire delivery tool that utilizes a 0.025” Nitinol Needle with a 15 mm throw that exits approximately 45° to the PAD shaft. The PAD is an 8Fr compatible device with 135 cm working length with dual 0.014” guidewire (GW) ports; an Rx GW Port and a Needle GW Port. The Rx GW Port is a back-loaded, rapid-exchange (Rx) design used for initial device placement. The Needle GW Port is the central lumen that exits through the Needle and is used to deliver guidewires to the desired location. The PAD also incorporates an intra-luminal Stabilizer and a Platinum-Iridium Marker Band used to support and direct needle deployment, respectively. The PAD features are controlled using the Outer Handle and the Button on the PAD Handle.

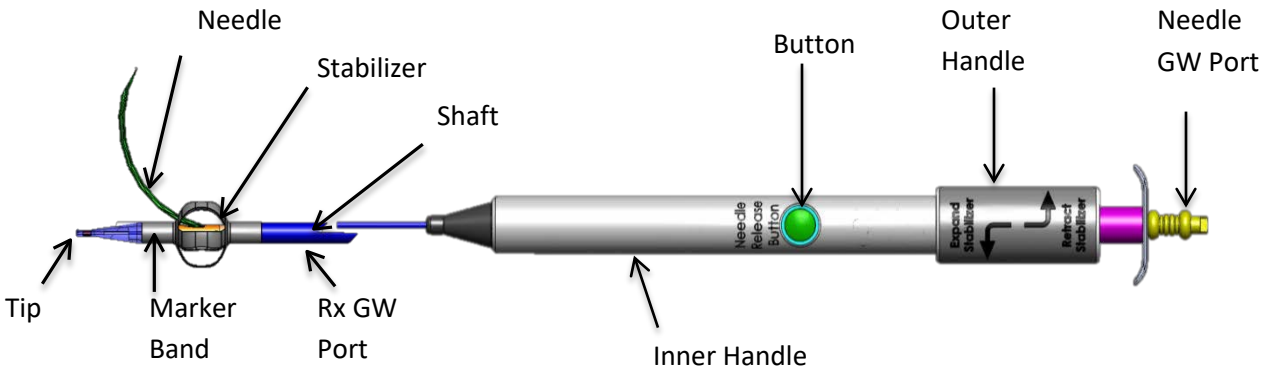


Figure 3-1: Percutaneous Anastomotic Device (PAD)

The Outer Handle controls spring loading, Stabilizer deployment and Needle activation. The user rotates the Outer Handle counter-clockwise and moves it proximal to distal to load the spring, deploy the Stabilizer and activate the Needle for deployment in a single motion. The PAD Shaft is keyed to ensure that the Needle cannot be deployed without first loading the spring and deploying the Stabilizer. Subsequent depression of the Button deploys the Needle in the direction indicated by the Marker Band.

The Distal Tip of the PAD is inserted into the Distal Tip of the Venous Locator to dock the devices in the vein when creating the distal anastomosis.

Stabilizer

The Stabilizer is intended to stabilize the PAD during Needle deployment in the intra-luminal space. The Stabilizer is made of laser-cut Polyimide tubing laminated on the outer PAD Shaft. The Stabilizer is 8 mm in diameter in a deployed state (**Figure 3-2**).

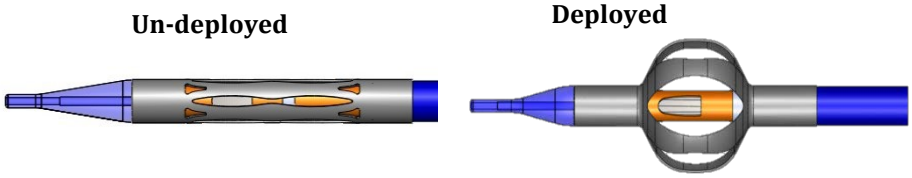


Figure 3-2: Stabilizer

Needle

The Needle utilizes a lancet-point to access discrete regions of the peripheral vasculature and allow guidewire delivery. The Needle is a 0.014" guidewire compatible nickel-titanium (NiTi) tube that is heat-set with a 15 mm throw. The Needle's lancet-point design enables penetration of calcified vessels (**Figure 3-3**).

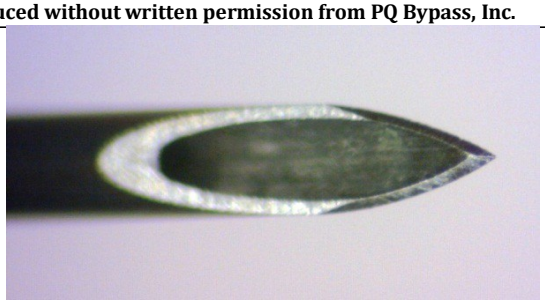


Figure 3-3: Needle Tip

Marker Band

The PAD uses a proprietary radiopaque Crown Marker Band System to orient the device prior to Needle deployment under fluoroscopy. The Crown Marker Band System (Crown System) indicates Needle direction and allows approximate adjustments in the Anterior/Posterior plane (**Figure 3-4, Figure 3-5 and Figure 3-6**).

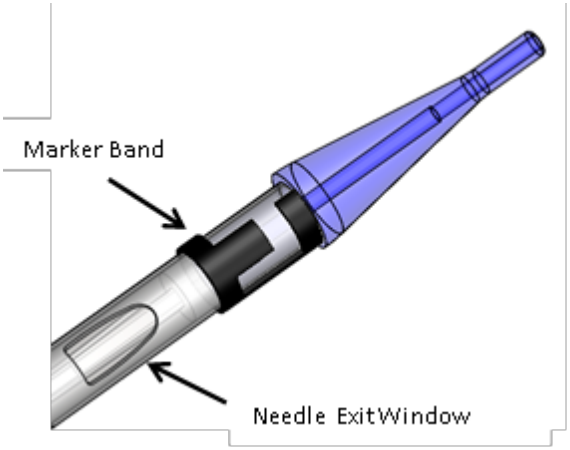


Figure 3-4: PAD Distal Tip Assembly

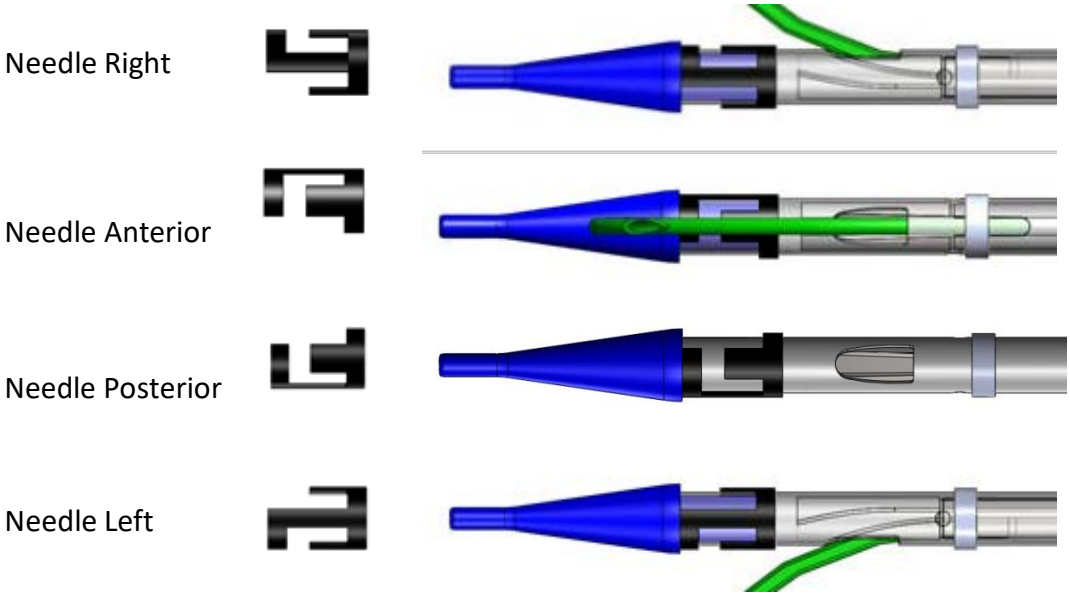


Figure 3-5: Crown Marker Band System Needle Direction (directions are noted from the perspective of the device in a supine patient)

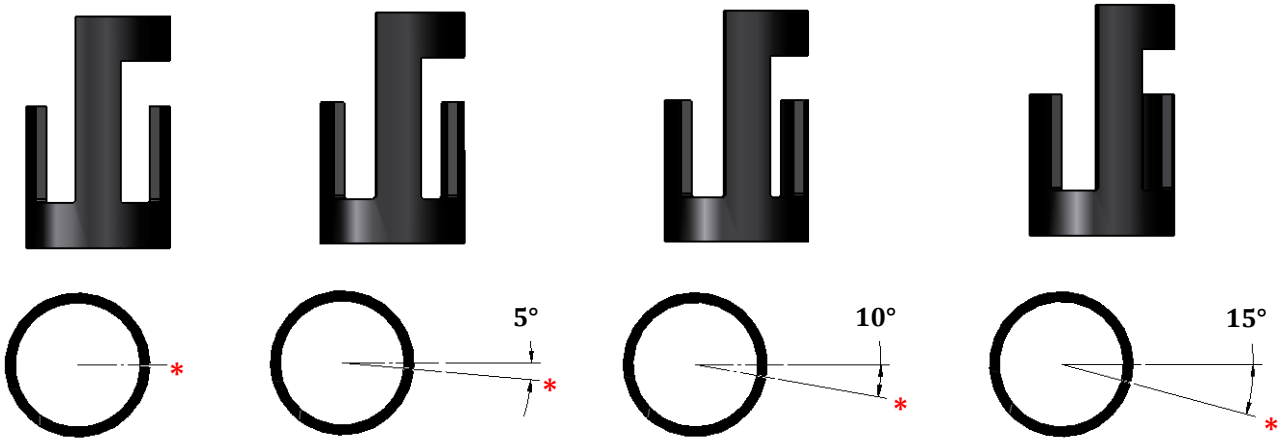
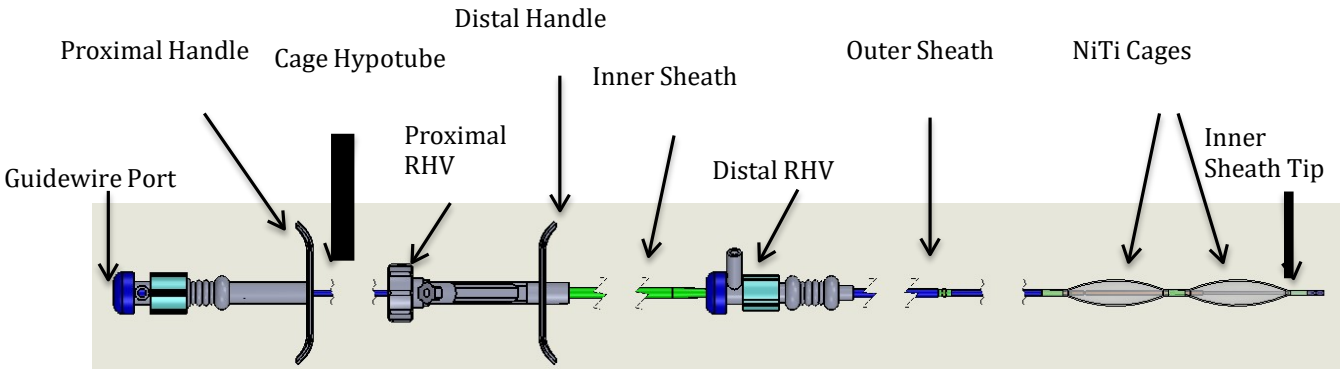


Figure 3-6: Crown Marker Band System: Direction Adjustment (Needle Direction indicated by *)

3.2 Guidewire Delivery System (GWDS) – Venous Locator (VL)

The VL (**Figure 3-7**) is an over-the-wire endovascular snare that utilizes dual, radiopaque NiTi cages to provide scaffold support to the femoral vein and to snare guidewires. The VL is 85 cm in length and is compatible with 7Fr sheaths and 0.014" guidewires. The dual NiTi cages deploy to a maximum of 11 mm at the apex and can be secured at a fixed diameter at any point during expansion (**Figure 3-8**).

Figure 3-7: Venous Locator (VL)



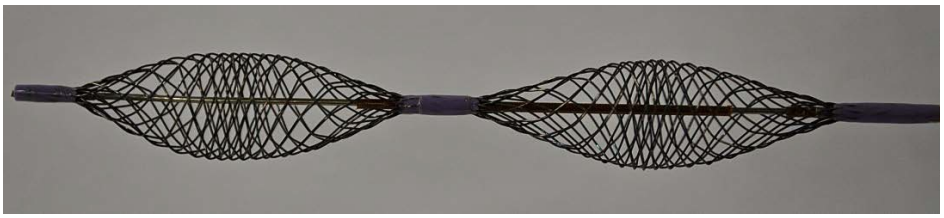


Figure 3-8: VL Cages Deployed

The VL is controlled using two rotating hemostasis valves (RHVs) and two handles. The Proximal Handle is connected to the Cage Hypotube which controls the retraction/deployment of the NiTi Cages. The Distal Handle allows the user to apply tension while manipulating the Proximal Handle. The Cage Hypotube runs through the Proximal RHV which is loosened to deploy/retract the NiTi Cages or tightened to lock the NiTi Cages in the desired position. The Distal RHV is connected to the Outer Shaft which slides over the retracted NiTi Cages for access, snaring and removal. The Inner Sheath defines the length of the device and provides a lumen through which the Cage Hypotube moves to allow NiTi Cage manipulation. The Inner Sheath Tip enables docking to the PAD when creating the distal anastomosis. The VL also has radiopaque markers at the proximal and distal ends of the NiTi Cages, between the NiTi Cages and at the distal tip to aide visualization during placement and deployment. The NiTi Cages are also radiopaque to enable visualization during use.

VL and PAD Docking

The Inner Sheath Tip of the VL (**Figure 3-9**) is shaped like a cone to allow docking to the PAD when creating the distal anastomosis. The user advances the PAD and VL on the same 0.014" guidewire to dock the PAD to the VL when creating a vein-to- artery anastomosis. Just as the Stabilizer is used to stabilize the PAD during Needle deployment in the intra-arterial space, docking the PAD to the VL stabilizes the PAD during Needle deployment in the intra-venous space.

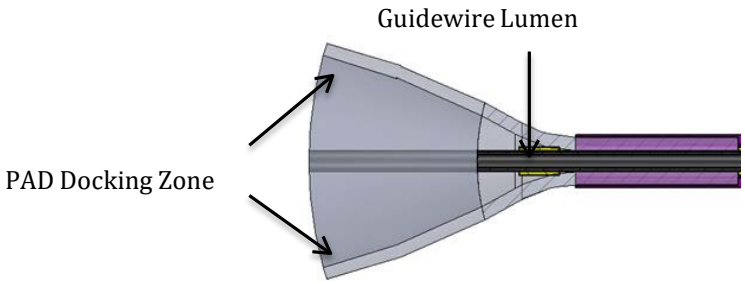


Figure 3-9: Inner Sheath Tip

3.3 Stent Graft System (SGS) – Stent Graft (SG)

The PQ Bypass Stent Graft (SG) is a flexible, self-expanding composite structure made of a NiTi-wire frame encapsulated in an expanded Polytetrafluorethylene (ePTFE) film.

The SG comes in a terminally sterile package pre-loaded on the Stent Graft Delivery System (SGDS). The SG uses a standard, crowned wire frame design that exhibits approximately twice the radial strength of commercially available stent grafts and comparable bending capability without kinking (**Figure 3-10**). The enhanced radial force helps maintain an open lumen through the proximal and distal anastomotic sites. The SG can be used either for standard intra-arterial placement or for a percutaneous bypass procedure.

Figure 3-10: PQ Bypass Stent Graft encapsulated in ePTFE

NiTi Frame:

The SG frame is a nitinol (NiTi) wire formed structure. It is made from a single 0.008" diameter NiTi wire which is shape-set and electropolished (**Figure 3-11**). The NiTi frame is a helically wrapped sinusoidal pattern with seven (7) crowns per revolution. To maintain flexibility when covered, the frame has a compression gap between adjacent helical wraps to achieve the required flexibility. Each crown has a radius with varying crown length based on the diameter of the stent graft.

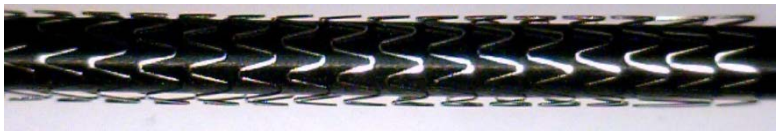


Figure 3-11: NiTi Wire Frame (pictured on a process mandrel)

Stent Graft Cover:

The NiTi wire frame is completely encapsulated by the ePTFE material. The ePTFE material is made from the same base material and manufacturing processes as the ePTFE used in AAA stent grafts. It has high tensile strength and low strain and maintains excellent abrasion resistance. Due to the frame design, the cover can be applied to both the inner and outer lumen while maintaining flexibility and compressibility. The inner and outer layers of the Cover are thermally laminated together.

3.4 Stent Graft System (SGS) – Stent Graft Delivery System (SGDS)

The Stent Graft Delivery System (SGDS) is an 8Fr system. It is 0.035" guidewire compatible and has a 135 cm working length. The handle of the delivery system consists of an internal pulley mechanism activated through turning an external knob. The handle also features the fluid flush insertion point for the inner lumen. The SGDS is a familiar design which uses an outer sheath to maintain the SG in a compressed state. Once at the target site, the user can slide the outer sheath proximally by turning the knob to expose the SG which is self-expanding. The SGDS has radiopaque markers on both the proximal and distal ends of the SG landing zone (area where SG is located), as well as a marker band on the outer sheath to allow visualization of the sheath during deployment. The SGDS is shown below (**Figure 3-12**).

Figure 3-12: Stent Graft Delivery System

The outer sheath of the SGDS consists of PTFE liner, braid, and pebax layers laminated together. The proximal area of the outer sheath (area behind the SG) consists of a second layer of extrusion to reduce stretching during SG deployment.

The inner shaft of the SGDS consists of a guidewire lumen, which has a section where the SG is compressed to minimize movement during deployment. Proximal to this section, the inner shaft has a proximal stop bushing, followed by a solid wound coil, which runs the entire length of the inner shaft to the handle. The proximal stop bushing reacts to the compressive load on the inner shaft created during stent graft deployment. The coil reacts to this same load, but transfers it to the handle section, which is rigid.

The outermost sheath of the SGDS, or the tri-axial layer, isolates the outer shaft from friction induced by the valve of the introducer sheath, the vessel walls, and other sources of interference. This allows the outer shaft to be retracted with a lower deployment force, and for the SG to be deployed more accurately.

3.5 Balloon Dilator (BD)

The BD is a 4 mm by 40 mm PTA balloon used to dilate arterio-venous anastomoses during a percutaneous bypass procedure. The BD is 4Fr compatible with an OTW 0.014” guidewire port. PQ Bypass purchases the BD as a finished product from ClearStream Technologies, who designed and manufactures the BD. ClearStream Technologies commercially markets the BD as the Bantam Alpha Catheter which received its initial CE Mark in 2008 as a PTA balloon (0344). PQ bypass does not modify the device upon receipt except to label the product as the BD and provide instructions for how to utilize the product during a percutaneous bypass procedure.

4.0 PROPOSED INTENDED USE

The PQ Bypass Guidewire Delivery System is intended to support the delivery of guidewires in the peripheral vasculature.

The PQ Bypass Stent Graft System is intended to improve blood flow in patients with peripheral artery disease.

The PQ Bypass Balloon dilator is intended to dilate arterio-venous anastomoses in the peripheral vasculature.

5.0 STUDY DESIGN

5.1 Study Design

Prospective, multi-center, non-randomized study evaluating the safety and performance of the PQ Bypass Systems to access, deliver guidewires and implant stent grafts for a percutaneous femoropopliteal (fem-pop) bypass.

5.2 Study Endpoints

Primary Safety Endpoint:
Major Adverse Clinical Events (MAE) at 1 month, defined as death, target vessel revascularization (TVR), target limb amputation.

Primary Performance Endpoint:
Primary Patency at 6 month, defined as no evidence of clinically significant stenosis (≥50%) within the stent graft or immediately above or below the treated arterial segment based on duplex ultrasound (systolic velocity ratio of >2.5), with no clinically-driven re-intervention within the stented segment.

Secondary Safety Endpoints:

- Major Adverse Events (MAE) through follow-up.
- Major adverse vascular event (MAVE) through follow-up defined as stent thrombosis, target limb amputation, clinically apparent distal embolization, defined as causing end-organ damage (e.g. lower extremity ulceration, tissue necrosis, or gangrene), procedure related arterial rupture, acute limb ischemia or bleeding event requiring transfusion.
- Major Blood Loss defined as transfusion of >2 units packed red blood cells (PRBC)) through discharge.
- The combined rate of death of target vessel revascularization (TVR), index limb amputation, and an increase in Rutherford-Becker Classification by 2 classes (comparing pre- to post-procedural assessments) through follow-up.
- Deep Vein Thrombosis (DVT) on ipsilateral limb defined as a symptomatic blood clot (thrombus) in the targeted deep vein (e.g. posterior tibial) through follow-up.
- VCSS and Villalta Scale through follow-up.
- Venous Assessment (Miller Scale) through follow-up.

- Stent fracture identified via X-ray through follow-up. (Optional per standard practice. Not applicable if radiological Safety Committee approval is required e.g. BFS Germany).

Secondary Performance Endpoints:

- Technical Success defined as successful delivery of the investigational devices to the identified area and removal of delivery system.
- Procedural Success defined as successful delivery of the investigational devices to the identified area and removal of delivery system in the absence of in-hospital MAEs.
- Clinical Success defined as Limb ischemia improvement by Rutherford-Becker (improvement in scale by ≥ 1) through follow-up.
- Limb ischemia by Rutherford-Becker Classification through follow-up.
- Primary Patency through follow-up.
- Primary assisted patency defined as revascularization of non-occlusive (<99%) stenosis within the stent graft or immediately above or below the treated arterial segment with less than 50% residual stenosis through follow-up.
- Secondary patency defined as: revascularization of occlusion (100%) within the stent graft or immediately above or below the treated arterial segment with less than 50% residual stenosis through follow-up.
- Ankle-Brachial Index (ABI) through follow-up.
- Target vessel revascularization (TVR) through follow-up.
- Number of any type of index limb amputations through follow-up.
- Number of vessel run-offs through follow-up.

5.3 Study Duration

This study is expected to commence enrollment in the fourth quarter of 2014. Enrollment of all subjects is expected to be completed in the first quarter of 2017. Clinical follow-up will occur at 3 months (±14 days), 6 months (±30 days), 12 months (±45 days), 18 months (±45 days) 24 months (±60 days), 30 months (±60 days), 36 months (±60 days) following the procedure.

5.4 Number of Subjects and Sites

Up to **60** subjects meeting all inclusion criteria and absent all exclusion criteria, and who are willing to sign informed consent will be enrolled in the **first phase** of the study including:

- Up to 30 subjects in Germany

Up to **100** subjects will be enrolled in the **second phase** of the study (additional 40 subjects) including:

- Up to 30 subjects in Germany

5.5 Inclusion Criteria

Subjects must meet <u>all</u> of the following criteria to be eligible for enrollment in this trial:

- Age 18 or older.

- Willing to comply with the specified follow-up evaluation schedule.
- Women of child bearing potential must have a negative pregnancy test within 7 days prior to the index procedure.
- Severe claudication or rest pain or ischemic ulceration not exceeding ulcer of the digits of the foot (Rutherford Becker scale 3-5) with a resting ABI < 0.9. Resting TBI is utilized only if unable to reliably assess ABI. TBI must be <0.7.
- Subject is not morbidly obese (BMI<40).
- Venous Clinical Severity Score <3.
- Serum creatinine level < 2.0 mg/dL.
- BUN < 20 mg/dL.
- Patent iliac and femoral arteries/veins and access vessels, of sufficient size and morphology (including tortuosity), to allow endovascular access with 8 Fr. introducer sheath.
- Femoro-popliteal lesions ≥10 cm (TASC C and D) in length considered to be:
    - Chronic total occlusion (100% stenosis)
    - Diffuse stenosis (>50% stenosis) with moderate to heavy calcification
    - In-stent restenosis (>50% stenosis)
- Reference vessel diameter (RVD) ≥ 5.0 mm and ≤ 6.7 mm, as measured via pre-screening CTA/MRA using 3D RPR reconstruction.
- Orifice and proximal 1 cm of SFA is patent (approximately 1 cm stump).
- Patent popliteal artery 3 cm proximal to tibial plateau.
- At least 1 patent tibial artery to the foot.
- Patient has the ability to comply with the necessary follow-up examinations and tests in accordance with protocol.
- Patent femoral vein ≥ 10 mm in diameter or duplicate femoral vein.
- Subject has > 2 year life expectancy.

5.6 Exclusion Criteria

Subjects will be excluded from this trial if <u>any</u> of the following criteria are met:

- Age greater than 90.
- History of deep vein thrombosis.
- Has known hypersensitivities, allergies or contraindications to: nitinol, PTFE; aspirin, heparin, antiplatelet, anticoagulant or thrombolytic therapy; or anticoagulation or contrast media.
- Has a known history of intracranial bleeding or aneurysm, myocardial infarction or stroke within the last 3 months.
- Pregnant or nursing.
- Untreated flow-limiting aortoiliac occlusive disease.
- Has renal failure (eGFR < 30mL/min).
- Major distal amputation (above the transmetatarsal) in the study or non-study limb.
- Patient has had a revascularization procedure on the target limb within 7 days of the planned index procedure.
- Known or suspected active infection at the time of the procedure.
- Requires a coronary intervention 30 days or less prior to or 30 days post the treatment of the target lesion.

- Thrombophlebitis, within the previous 30 days.
- Thrombolysis of the target vessel within 72 hours prior to the index procedure, where complete resolution of the thrombus was not achieved.
- Receiving dialysis or immunosuppressant therapy within the previous 30 days.
- Stroke within the previous 90 days.
- Ipsilateral femoral aneurysm or aneurysm in the SFA or popliteal artery.
- Planned amputation of the target limb.
- Previous bypass surgery on the target limb.
- Participating in another clinical study for which follow-up is currently on going which may impact the current study.
- Congestive heart failure, COPD (Stage IV, FEV1 <30% normal, or <50% normal with chronic respiratory failure present), metastatic malignancy, dementia, or other major co-morbidities that would prevent the post-interventional movement.
- A condition that in the view of the investigator precludes participation in this study.

6.0 SUBJECT ENROLLMENT INFORMATION

6.1 Written Informed Consent

Subjects who meet general entry criteria will be asked to sign the study specific Ethics Committee (EC) approved Informed Consent form before any study-specific tests or procedures are performed. Study personnel should explain that even if a subject agrees to participate in the study and signs an Informed Consent Form, the subject may not be eligible to participate if he/she fails screening criteria.

A Screening/Enrollment Log will be maintained to document select information about candidates who fail to meet the entry criteria.

6.2 Enrollment

Subjects will be considered enrolled into the study once informed consent has been signed and all eligibility criteria confirmed. Investigators will access the target artery and the corresponding ipsilateral vein using standard percutaneous techniques and devices. Patient eligibility will be confirmed prior to insertion of the study device, based on procedural angiogram and sheath placement.

6.3 Duration of Subject Participation

Subjects enrolled in the trial will participate for approximately 24 months.

6.4 Withdrawal of Subjects

Each subject may voluntarily withdraw his/her participation from the study at any time. Investigators may discontinue a subject's participation in the study as deemed appropriate per safety measures and/or if the subject's medical condition contraindicates further study participation. All enrolled subjects will undergo the complete study follow-up for safety evaluation.

6.5 Loss to Follow-Up

A subject will be considered lost to follow-up and terminated from the study when all of the following criteria have been met:

- Documentation of three unsuccessful attempts on three different days over a period of three (3) months by the Investigator or his/her designee to contact the subject or next of kin, one of which should be by certified mail with signature confirmation
- Prior agreement of the Sponsor to remove the subject from the clinical investigation

6.6 Subject Confidentiality

All information concerning subjects or their participation in this trial will be considered confidential. Only authorized PQ Bypass personnel and designated consultants and regulatory agencies will have access to these confidential files. Enrolled subjects will be assigned a unique identifier that will be used to maintain confidentiality of each subject's medical information. Subject names and other protected health information will not be captured on the case report forms. In addition, angiographic and ultrasonic images submitted from the participating site to the Sponsor or angiographic reviewers for analysis should be redacted from all patient identifiers.

7.0 RISK-BENEFIT ASSESSMENT

7.1 Risks

There are standard risks associated with any interventional procedure or stent graft placement as well as risks specific to the PQ Bypass devices and procedure. Risks associated with any interventional procedure include access site hemorrhage or hematoma, access site pain, acute vessel closure, infection, renal insufficiency/failure due to excessive contrast load, and death. The risks stated below concern each system manufactured by PQ Bypass and their use in the PQ Bypass procedure.

Possible risks related to the PQ Bypass Guidewire Delivery System include, but are not limited to, the following: vessel dissection, perforation or wall trauma, embolism, infection, bruising or hemorrhage at the procedural access site, deep vein thrombosis, bleeding or infection.

Possible risks related to the PQ Bypass Stent Graft System include, but are not limited to, the following: thrombosis, stenosis or occlusion, aneurysm or pseudoaneurysm formation, vessel dissection, perforation or wall trauma, embolism, venous flow disruption (including deep vein thrombosis, edema or phlebitis), arteriovenous fistula formation, bleeding infection or side branch occlusion.

Additionally, subjects will be exposed to risks associated with conscious sedation, use of radiographic contrast and procedural medications. Subjects will be asked to take anti-platelet medication for this study, such as aspirin for life and Plavix

(clopidogrel) or Ticlid (ticlopidine) for length of follow-up. These medications have been approved to reduce the risk of cardiovascular events. An Investigator will discuss with each subject the standard risks associated with these medications.

Risk will be mitigated by working with Investigators who are experienced and skilled in endovascular techniques including use of re-entry tools and stent graft placement. Additionally, each Investigator will be thoroughly trained on proper device operation prior to device use. Risks will also be minimized in this study by adhering to the inclusion/exclusion criteria. For example, subjects with known allergies or contraindications to study medications (contrast, anti-platelet, heparin) will be excluded. Risks associated with device malfunctions or failures will be minimized through bench and in-vivo animal verification and validation testing prior to use in this study.

7.2 Benefits

Patients included in this study have lesions that are challenging to treat with conventional endovascular means. Based on previous treatments using commercially available devices and PQ Bypass's bench and animal testing, it is expected that the participants in this study will have their lesions successfully treated without the need for surgery. Bypassing lesions with the PQ Bypass Systems may allow physicians to treat challenging lesions in the femoral artery percutaneously, thereby avoiding the risks and morbidity of more invasive procedures such as surgical bypass or amputation.

8.0 STUDY PROCEDURE

8.1 Vascular Access and Guidewire Delivery

Investigators will access the target lesion and the corresponding ipsilateral vein using standard percutaneous techniques and devices. Patient eligibility will be confirmed prior to insertion of the study device, based on procedural imaging and sheath placement.

After eligibility confirmation, the Venous Locator (VL), Percutaneous Anastomotic Device (PAD) and Balloon Dilator (BD) will be used to deliver a guidewire from the arterial segment proximal to the target lesion, through the femoral vein and back into the reconstituted artery distal to the target lesion. This procedure is described in detail in the Guidewire Delivery System and Balloon Dilator IFUs (**Appendix II**). The number of deployment attempts for guidewire placement access at each anastomosis will be recorded.

8.2 Stent Graft Placement

Stent Grafts (SGs) of appropriate dimension are selected based on the instructions provided in the Stent Graft System IFU (**Appendix II**). SGs are then deployed in series, starting distally, until the bypass is complete. After placement, the Investigator uses a standard balloon dilation catheter to complete stent deployment, ensuring that the balloon is only inflated within the SGs' lumen.

8.3 Follow-Up

Subjects will return to the study center at 1 month (±7 days), 3 months (±14 days), 6 months (±30 days), 12 months (±45 days), 18 months (±45 days) 24 months (±60 days),30months (±60 days) and 36 months (±60 days) following the procedure for a follow-up evaluation. The subject will undergo lower-extremity arterial and venous duplex ultrasounds, venous health questionnaires and examined for any post-procedural complications or adverse events.

9.0 MATERIALS AND METHODS

Safety and performance evaluations will be conducted throughout the study. Such evaluations will be conducted on the case report forms.

9.1 Initial Eligibility

After subjects have signed an informed consent form and before the scheduled interventional procedure, subjects will undergo an initial eligibility evaluation. This evaluation may be conducted from an office visit within the previous 90 days. The evaluation will consist of the following:

- Pre-procedural CTA or MRA
- Pre-procedural venous ultrasound
- Review of inclusion/exclusion criteria

9.2 Baseline Evaluation

After subjects have signed an informed consent form and before the scheduled interventional procedure, subjects will undergo a baseline evaluation. This evaluation may be conducted from an office visit within the previous 30 days. The evaluation will consist of the following:

- Subject's demographic data (sex and date of birth)
- Medical history
- Rutherford score and Ankle-Brachial Index (ABI)
- Serum pregnancy test
- Venous Clinical Severity Score
- Villalta scale
- BUN and Creatinine
- Medication history and review

9.3 Procedural Evaluation

Final eligibility will be determined based on imaging study and sheath placement. Information on the lesion being treated and the specific vasculature used in its treatment will be collected. The procedural evaluation will consist of the following:

- Lesion length
- Lesion calcification (TASC II Classification)
- Lesion type
- Procedure time

- Access sites used
- Number of attempts to create each anastomosis
- Complications or adverse events

9.4 Discharge Evaluation

The discharge evaluation will consist of:

- Rutherford score and Ankle-Brachial Index (ABI)
- Arterial and Venous duplex-ultrasound assessment
- Complications or adverse events
- Concomitant medications

9.5 Follow-Up Evaluation

The evaluations at 1 month (±7 days), 3 months (±14 days), 6 months (±30 days), 12 months (±45 days), 18 months (±45 days) 24 months (±60 days), 30 months (±60 days) and 36 months (±60 days) post-procedure or when a subject withdraws prematurely from the study will consist of:

- Rutherford score and Ankle-Brachial Index (ABI)
- Venous Clinical Severity Score[58]
- Villalta Scale[59]
- Arterial and Venous duplex-ultrasound assessment
- Complications and adverse events
- Concomitant medications

10.0 INVESTIGATIONAL DEVICE DISTRIBUTION AND ACCOUNTABILITY

10.1 Device Accountability

The Investigator shall maintain adequate records of the receipt and disposition of all investigational devices. The Investigator is responsible for ensuring that the investigational devices are used only under the Investigator's supervision and are only used according to this protocol and any approved amendments. The Investigator will not supply an investigational device to any person not authorized to participate in the study. The Investigator shall document in CRFs the lot numbers of the devices used during a case. In addition, the Investigator shall keep complete and accurate records of all devices used or unused that have been returned to PQ Bypass in a Device Accountability Log provided by PQ Bypass.

10.2 Return of Devices

All unused investigational devices will be returned to the study Sponsor upon completion of the clinical study. All used investigational devices will be properly disposed of, per institutional procedures. Any investigational device that fails to perform correctly will be returned to the study Sponsor for analysis. The Investigator or his/her designated representative is responsible for device accountability and disposition of all used and unused devices. The study Sponsor

or its designated representative will conduct device reconciliation at the completion of subject enrollment or at the conclusion of the study.

11.0 ENDPOINTS AND STATISTICAL ANALYSIS PLAN

11.1 Endpoints Analyses and Reporting of Results

The study objective is to assess the safety and performance of the PQ Bypass System to access, deliver guidewires and implant stent grafts for a percutaneous fem-pop bypass.

The study is a feasibility study with no formal hypothesis testing and therefore no required sample size. Study results will be presented using descriptive statistics. Results from this study will be used to design additional clinical studies.

All subjects will be followed on an intent-to-treat basis. The device performance will be assessed based on a per-protocol analysis of the primary safety and effectiveness endpoints. An Intent-to-treat analysis, along with other secondary analyses, will also be completed and reported.

Demographic, baseline clinical and disease characteristics, procedural results and primary, secondary and all additional endpoints will be summarized using descriptive statistics.

All statistical analyses will be performed using SAS for Windows version 9.1 or higher.

Primary Safety Endpoint Reporting:

Safety assessment is achieved by recording and measuring Major Complication rates/Serious Adverse Event rates associated with the PQ Bypass procedure. The number and percentage 6-month MAE will be presented using descriptive Statistics. Using the Score approximation, the one-sided upper 95% confidence bound will be calculated and presented.

Primary Performance Endpoint Reporting:

Descriptive statistics of the primary performance endpoint which includes total number of patent PQB grafts, number and percentage of patent PQB grafts, and the one-sided 95% CI of the percentage using the Score approximation will be presented. The lower bound of the one-sided 95% CI will be compared to the performance goal of 70% (80% historical control rate – 10% Delta.)

Secondary Endpoint Analysis:

The secondary endpoint of primary assisted and secondary patency will be summarized using Kaplan-Meier survival analysis. Life tables will be created and a Kaplan-Meier survival curve will be presented.

The secondary endpoints of Procedural Success, Clinical Success and Technical

Success will be summarized by providing point estimates, number of subjects, and 95% confidence bounds calculated using the Score approximation.

Demographic, procedural and safety data:

Demographic and baseline clinical and disease characteristics will be summarized in tables. For continuous variables the summary will include number, mean, and standard deviation and 95% confidence intervals. Summaries for categorical variables will include the number and percent of subjects in each category.

Imputation for Missing Data

Imputations for missing data in (e.g. withdrawn subjects, loss to follow-up, missing data) will not be performed. Analyses will be performed with all available data only.

11.2 Sample Size Justification

The sample size chosen for this study has been updated from 60 to 100 patients. The sample size was chosen to demonstrate statistically non-inferiority of the PQ Bypass Systems performance as compared to results previously reported in similar studies:

- for intravascular stent grafts (e.g. Gore Viabahn) – n=60
- for prosthetic surgical bypass - n=100

A larger sample size is required as prosthetic surgical bypass outcomes are superior to those of intravascular stent grafts.

Stent Graft Studies

Clinical data published on existing stent graft techniques for treating femoropopliteal disease have reported 6-month primary patency rates of approximately 80%.[37,40-42,45,60,61] This average success rate has been used as the historical control for the current study. The standard error reported in the cited studies range from 3% to 12%; the lower limit of one-sided 95% confidence intervals (CI) is approximately 68%.

In order to establish a sample size, a margin of non-inferiority, delta, was set at 10% for the current study to demonstrate non-inferiority of the PQ Bypass Systems to the historical control in terms of patency. This delta reflects the diversity of the lesions to be enrolled in this study and the range of reported performance using similar technology; 6-month primary patency in the studies cited above ranges from 27% to 92%, average lesion lengths range from 9-25cm and the percent occlusions included ranges from 50% to 100%. Due to this wide variety of lesions reported in the literature and the potential diversity of patients and lesion lengths that will be enrolled in this study, a 10% delta is adequate to accurately reflect non- inferiority. This delta sets up a comparison between the lower 95% CI of the PQ Bypass Systems performance to the lower 95% CI reported for the competitive products (~70%).

As such using as historical control rate of 80% and a non-inferiority margin of 10%,

the null and alternative hypotheses of the primary performance endpoint can be written as:

$$H_0: \pi_{PQB\_performance} \leq \pi_{PG\_performance}$$
$$H_A: \pi_{PQB\_performance} > \pi_{PG\_performance}$$

where,

$\pi_{PG\_performance}$ = 80% historical control rate – 10% Delta

$\pi_{PQB\_performance}$ = PQB Systems success rate

The hypotheses for the primary performance endpoint can be rewritten as:

$$H_0: \pi_{PQB\_performance} \leq 70\%$$
$$H_A: \pi_{PQB\_performance} > 70\%$$

In order to approximate the performance rates for this study, the results from the El Camino Hospital (ECH) Study were used. The PQB procedural approach was evaluated in the ECH Study. This study used a similar technique to the interventional approach utilized in the ECH Study. This study also used a stent graft that is very similar to the stent graft used in the ECH Study, the Gore Viabahn Stent Graft. Primary patency at 6 months was approximately 90% in the ECH Study. A more conservative estimate of 85% performance for the PQ Bypass Systems was utilized along with the aforementioned performance goal for the purpose of sample size estimation. To achieve 80% power using a one-sided alpha of 0.05, the sample size is 50. To adjust for lost to follow-up and to maintain consistency with current literature on the use of stent grafts, 60 subjects will be enrolled in this study ((**Table 11-1**).

Table 11-1: Non-Inferiority with PQ Bypass Performance of 85%

PG	NI Margin				
	5%	7.5%	10%	12.5%	15%
80%	103	69	50	38	30
85%	368	174	103	69	50
90%	-	1371	368	174	103
95%	-	-	-	1371	368

The sample size was also elected in order to observe the rate of major adverse events. The median number of patients enrolled in stent graft trials reported in the literature is 59 patients (range 15-144).

Surgical Bypass Studies

Clinical data published on existing surgical bypass studies for treating femoropopliteal disease is more limited quantitatively and qualitively. Most importantly, few studies involve doppler-ultrasound assessments of arterial velocity as a basis of assessing patency (e.g. peak systolic velocity ratio). However, one particular and recent randomized prospective study of the Gore Viabahn stent graft vs. prosthetic bypass surgery provides very reliable data set on surgical outcomes as illustrated in **Table 11-2**.

The randomized prospective study was designed to compare the effectiveness of treating superficial femoral artery occlusive disease percutaneously with expanded polytetrafluoroethylene (ePTFE)/nitinol self-expanding stent grafts vs surgical femoral-to-above knee (AK) popliteal artery bypass with synthetic graft material.
Methods: From March 2004 to May 2005, 100 limbs in 86 patients with femoral-popliteal arterial occlusive disease were identified. Patients had symptoms ranging from claudication to rest pain, with or without tissue loss, and were prospectively randomized for treatment into one of two groups. The limbs were treated percutaneously with angioplasty and one or more self-expanding stent grafts (n=50) or surgically with femoral-to-AK popliteal artery bypass using synthetic Dacron or ePTFE grafts (n=50).

The mean and SD total length of artery stented was 25.6 and 15 cm. Follow-up evaluation with ankle-brachial indices and color flow duplex sonography imaging were performed at 3, 6, 9, and 12 months after treatment.

Patients were monitored for a median of 18 months. No statistical difference was found in the primary patency (P=895) or secondary patency (P=.861) between the two treatment groups. Primary patency at 3, 6, 9, and 12 months of follow-up was 84%, 82%, 75.6%, and 73.5% for the stent graft group and 90%, 81.8%, 79.7%, and 74.2% for the femoral-popliteal surgical group. Thirteen patients in the stent graft group had 14 re-interventions, and 12 re-interventions occurred in the surgical group. This resulted in secondary patency rates of 83.9% for the stent graft group and 83.7% for the surgical group at the 12-month follow-up (**Table 11-2**).

Based on review of the limited literature and the recent long lesion stent graft vs prosthetic surgery randomized study 6-month surgical bypass primary patency rate of 82-85% can be extrapolated.

Table 11-2 Randomized Comparison of Viabahn Stent Graft vs. Prosthetic Surgery

Table IV. Primary patency in femoral-popliteal bypass group and stent graft group

Time post-treatment (months)	*N at risk at start of interval*	*N events during interval**	*N censored during interval**	*% Free from loss of patency*	*95% CI*
Operative (day 0-30)					
Fem-pop bypass	50	2 (2)	0 (0)	0.960	(0.849, 0.990)
Stent graft	50	2 (2)	0 (0)	0.960	(0.849, 0.990)
3 months (day 31-136)					
Fen-pop bypass	48	3 (5)	1 (1)	0.900	(0.776, 0.957)
Stent graft	48	6 (8)	1 (1)	0.840	(0.705, 0.917)
6 months (day 137-227)					
Fem-pop bypass	44	4 (9)	2 (3)	0.818	(0.680, 0.901)
Stent graft	41	1 (9)	1 (2)	0.820	(0.682, 0.902)
9 months (day 228-319)					
Fem-pop bypass	38	1 (10)	8 (11)	0.797	(0.655, 0.885)
Stent graft	39	3 (12)	1 (3)	0.756	(0.611, 0.854)
12 months (day 320-456)					
Fem-pop bypass	29	2 (12)	8 (19)	0.742	(0.587, 0.846)
Stent graft	35	1 (13)	7 (10)	0.735	(0.587, 0.837)

CI, Confidence interval.
Log-rank $P = .895$.
*Number in parenthesis represents cumulative events or censored observations through end of interval.

Table V. Secondary patency in femoropopliteal bypass group and stent graft group

Time post-treatment (months)	*N at risk at start of interval*	*N events during interval**	*N censored during interval**	*% Free from loss of patency*	*95% CI*
Operative (day 0-30)					
Fem-pop bypass	50	2 (2)	0 (0)	0.960	(0.849, 0.990)
Stent graft	50	0 (0)	0 (0)	1.000	(1.000, 1.000)
3 months (day 31-136)					
Fem-pop bypass	48	2 (4)	1 (1)	0.920	(0.801, 0.969)
Stent graft	50	6 (6)	1 (1)	0.880	(0.752, 0.944)
6 months (day 137-227)					
Fem-pop bypass	45	3 (7)	2 (3)	0.859	(0.726, 0.930)
Stent graft	43	1 (7)	1 (2)	0.860	(0.728, 0.930)
9 months (day 228-319)					
Fem-pop bypass	40	1 (8)	8 (11)	0.837	(0.701, 0.915)
Stent graft	41	1 (8)	1 (3)	0.839	(0.703, 0.916)
12 months (day 320-456)					
Fem-pop bypass	31	0 (8)	11 (22)	0.837	(0.701, 0.915)
Stent graft	39	0 (8)	9 (12)	0.839	(0.703, 0.916)

CI, Confidence interval.
Log-rank P value = .861.
*Number in parenthesis represents cumulative events or censored observations through end of interval.

Kedora et al J Vasc Surg 2007;45:10-16
McQuade et al J Vasc Surg. 2009 Jan,49(1):109-15

In order to establish a sample size, a margin of non-inferiority, delta, was set at 10% for the current study to demonstrate non-inferiority of the PQ Bypass Systems to the historical control in terms of patency. This delta reflects the limited quantitative and qualitative availability of fem-pop bypass studies in the literature. Therefore, a 10% delta is adequate to accurately reflect non-inferiority. This delta sets up a comparison between the lower 95% CI of the PQ Bypass Systems performance to the lower 95% CI reported for the competitive products (~70%).

As such using as historical control rate of 80-85% and a non-inferiority margin of 10%, the null and alternative hypotheses of the primary performance endpoint can be written as:

H_0: $\pi_{PQB\_performance} \leq \pi_{PG\_performance}$

H_A: $\pi_{PQB\_performance} > \pi_{PG\_performance}$

where,

$\pi_{PG\_performance}$ = 85% historical control rate – 10% Delta

$\pi_{PQB\_performance}$ = PQB Systems success rate

The hypotheses for the primary performance endpoint can be rewritten as:

H_0: $\pi_{PQB\_performance} \leq 70\%$

H_A: $\pi_{PQB\_performance} > 70\%$

A conservative estimate of 85% performance for the PQ Bypass Systems was utilized along with the aforementioned performance goal for the purpose of sample size estimation. To achieve 80% power using a one-sided alpha of 0.05, the maximum sample size required is 103 subjects. As the surgical patency rate is extrapolated to be between 82% and 85% and since no loss to follow-up is expected in the study, a sample size of 100 subjects should be sufficient and enrolled in this study (**Table 11-3**).

Table 11-3: Non-Inferiority with PQ Bypass Performance of 85%

PG	NI Margin				
	5%	7.5%	10%	12.5%	15%
80%	103	69	50	38	30
85%	368	174	103	69	50
90%	-	1371	368	174	103
95%	-	-	-	1371	368

12.0 ADVERSE EVENTS

The occurrence of Adverse Events will be monitored during this study. All Adverse Events will be recorded on the Complication/Adverse Event Form at onset and at each follow-up visit until resolved.

Potential adverse events associated with use of the Stent Graft System (SGS) SGS include, but are not limited to the following:

• Access site hemorrhage or hematoma • Access site pain/infection • Acute vessel closure • Aneurysm or pseudoaneurysm formation • Arteriovenous (AV) fistula	• Inflammation • Malposition • Myocardial infarction • Radiation injury • Renal insufficiency/failure due to excessive

• Death • Device failure • Embolism • Fever/pain in absence of infection • Infection	contrast load • Sepsis • Shock • Side branch occlusion • Stenosis or Occlusion • Thrombosis • Vessel dissection, perforation or wall trauma

Potential adverse events associated with use of the Guidewire Delivery System (GWDS) include, but are not limited to the following:

• Access site hemorrhage or hematoma • Access site pain • Acute vessel closure • Bleeding complications • Vessel dissection, perforation or wall trauma	• Death • Embolism • Infection • Renal insufficiency/failure due to excessive contrast load

Potential adverse events associated with use of the Balloon Dilator (BD) include, but are not limited to the following:

• Hemorrhage or hematoma • Hypotension • Pain • Arrhythmias • Systemic embolization • Endocarditis • Pyrogenic reaction • Acute vessel closure • Vascular Thrombosis • Bleeding complications • Sepsis/Infection	• Short term hemodynamic deterioration • Drug reactions, allergic reaction to contrast media • Aneurysm or pseudoaneurysm formation • Death • Renal insufficiency/failure due to excessive contrast load • Vessel dissection, perforation or wall trauma • Potential balloon separation following rupture or abuse and subsequent need to use a snare or other medical interventional techniques to retrieve the pieces

To meet the objectives of this study, the following definitions will apply. (Definitions reference ISO 14155:2011-01)

12.1 Adverse Event (AE)

Adverse Event (AE): Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the medical device. This includes events related to the device or events related to the procedures involved.

Adverse Device Effect: An adverse event related to the use of a medical device, including adverse events resulting from insufficient or inadequate Instructions for Use, deployment, implantation, installation or operation, or any malfunction of the medical device or any event resulting from user error or intentional misuse of the medical device.

The Investigator is responsible for assessing the severity of the AE, the causal relationship between any events and the clinical study procedure, activities or device. Additionally, the Investigator is responsible for providing appropriate treatment for the event and for adequately following the event until resolution. The following categories of adverse event severity are to be used:

- Mild: Awareness of a sign or symptom that does not interfere with the subject's usual activity or is transient, resolved without treatment and with no clinical sequelae.
- Moderate: Interferes with the subject's usual activity.
- Serious: Any fatal or immediately life-threatening clinical experience that requires a subject to be hospitalized, or hospitalization is unduly prolonged because of potential disability or danger to life or because an intervention has been necessitated. This includes any permanently disabling event.

12.2 Serious Adverse Event (SAE)

Serious Adverse Event (SAE): A serious adverse event is any problem or unwanted event encountered in a clinical trial or a performance evaluation that has led, or could have led, directly or indirectly to death or to a serious deterioration in the health of a subject or user or any other person, without regard to whether the event was caused by a medical product. (§ 2 no. 5 MPSV). The following events (including laboratory results and outcome events) will be considered to be SAEs and must immediately (within 24 hours) be reported to the study Sponsor by telephone, fax and/or email. These events must be reported whether or not the Investigator believes they are related to study procedures, activities or device:

- Death
- Serious deterioration in the health of the subject, that either resulted in
    - a life-threatening illness or injury, or
    - a permanent impairment of a body structure or a body function, or
    - in-patient or prolonged hospitalization, or
    - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
    - Malignant Tumor (Austrian Medical Device Act, § 3 Abs.16 MPG as amended)

Serious Adverse Device Effect: An adverse device effect that has resulted in any of the consequences of a Serious Adverse Event.

Note: Planned hospitalization for a pre-existing condition, a condition unrelated to the treatment or a procedure required by this study, that is without serious deterioration in health, is not considered a serious adverse event.

12.3 Adverse Device Effect (UADE)

Unanticipated Serious Adverse Device Effect (USADE): Serious adverse device

effect which, by its nature, incidence, severity or outcome has not been identified in the risk analysis report.

Anticipated Serious Adverse Device Effect (ASADE): An effect, which by its nature, incidence, severity or outcome has been identified in the risk analysis report. UADEs must be reported to the study Sponsor by telephone, fax and/or email within 24 hours.

Unanticipated Adverse Device Effect (UADE): An adverse device effect which by its nature, incidence, severity or outcome has not been identified in the risk analysis report.

12.4 Reporting of Adverse Events

All incidents will be captured as a part of this clinical study. At each contact with the subject, the investigator will seek information on adverse device effects by specific questioning and, as appropriate, by examination. Information on all adverse device effects will be recorded immediately in the source document, and also in the appropriate adverse effect case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document. All SAEs, UADEs and possible device and/or procedure-related adverse events must be recorded on the Adverse Event CRF by the Investigator (or his/her designee) and reported to the Sponsor within 24 hours. The report should include: severity, duration, action taken, treatment outcome and relationship to the adverse event to the study device, procedure, concomitant medications, pre-existing condition, etc. (i.e., unrelated, relation or relationship unknown).

In the case of serious adverse events (SAE), procedure and/or device failures and malfunctions, medical record documentation (e.g., procedure notes, operative notes, discharge summary, relevant progress notes, imaging or lab studies) must be provided to PQ Bypass or its designee, if requested. All SAEs shall be recorded in the CRF and this information shall be faxed to the Study Monitor/PQ Bypass. If appropriate, PQ Bypass shall inform the Competent Authority and the relevant Ethics Committee about the event within the appropriate timelines. In accordance with MEDDEV 2.7 / 3 rev.3 (May 2015), the sponsor must report:

- all reportable events as described in section 4 which indicate an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it,
- to the National Competent Authorities where the clinical investigation has commenced,
- Immediately, but not later than 2 calendar days after awareness by sponsor of a new reportable event or of new information in relation with an already reported event.

Reporting of SAEs to the Austrian competent authority (BASG) occurring e occurred in Austria will be done performed using form F-I208 which is provided on the homepage:

http://www.basg.gv.at/medizinprodukte/klinische-pruefung-von-medizinprodukten/.

For all SAEs occurring outside of Austria, a rolling registration form has to be used (tabular listing = line listing): FI287. In addition, the reporting requirements pursuant to § 70 MPG as amended, will be observed.

12.5 Reporting of Device Failures and Malfunctions

All reported device malfunctions or failures of the PQ Bypass Systems are required to be documented in the CRF and must be immediately reported to the study sponsor by telephone, fax and/or within 24 hours. Device failures and malfunctions should also be documented in the subject's medical record. Instructions for returning the investigational device will be provided.

NOTE: Device failures or malfunctions are NOT to be reported as adverse events. However, if there is an adverse event that results from a device failure or malfunction, that specific event would be recorded in the usual way.

12.6 Documentation, Evaluation and Notification of Serious Adverse Events

The Investigator shall report all serious adverse events (anticipated or unanticipated) to Sponsor or Sponsor's representative within 24 hours upon becoming aware of events.

Sponsor Representative Contact
Claire van den Nieuwenhof
Quality Manager

HealthLink Europe BV
HealthLink International Inc.
De Tweeling 20-22
5215 MC 'S Hertogenbosch
The Netherlands

Phone General: +31-(0)13-5479300
Fax: +31-(0)13-5479300
E-mail: claire.vandennieuwenhof@healthlinkeurope.com

The Sponsor will ensure compliance with all country-specific reporting requirements to the appropriate Ethical Committees and Competent Authorities. In Germany, the Sponsor shall use form 'Meldeformular_Klinishe_Pruef_SAE.pdf' as specified by German Medical Device Safety Regulation. The e-mail to be used when submitting the SAE notification form is MPSAE@BFARM.de. SAEs should be reported immediately and no later than 30 days from the Sponsor's first knowledge of the event.

13.0 MONITORING

The Sponsor or its designated representative, qualified by training and experience, will be responsible for monitoring and overseeing the conduct of the trial. The accuracy of all collected data will be verified (100% monitoring) for:

- Eligibility criteria
- Baseline characteristics

- Primary safety and performance endpoints
- Adverse events
- Secondary endpoints

with source documents including, but not limited to, medical records, office/clinic notes, procedure reports, laboratory results, physician and nursing progress notes. Verification and quality of data, monitoring of clinical study progress and Investigator compliance with the approved protocol will be conducted by the study Sponsor or its designated representative.

The study Sponsor or its designated representative must be allowed to visit the clinical site and have direct access to all study records throughout the duration of the study. The monitor will review all source data and compare them to the data documented in the case report forms, in addition to performing a review of the Regulatory Binder, and conducting device accountability. The Investigator and/or institution will provide direct access to source data/documents for trial-related monitoring, audits, EC review and regulatory inspection.

It is important that the Investigator and relevant study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

Additionally, telephone and/or e-mail contact will be conducted on a regular basis with the Investigator and the site staff to ensure that the protocol is being followed and to address any issues that may occur during the course of the trial.

If a deficiency is noted during the course of the trial the clinical monitor is required to discuss the situation with the site and the Sponsor (if required) to secure compliance.

14.0 STUDY ADMINISTRATION

PQ Bypass will make necessary efforts to ensure that this study is conducted in compliance with Good Clinical Practices (GCPs) and all applicable regulatory requirements.

14.1 Source Documentation

The Investigator must maintain detailed source documents on all trial subjects who are enrolled in the trial or who undergo screening. Source documents include subject medical records, hospital charts, clinic charts, Investigator's subject trial

files, as well as the results of diagnostic tests (e.g., laboratory tests).

The following minimum information should be recorded in the subject's medical records:

- The date the subject entered the trial and the subject number
- The trial protocol number and the name of the Sponsor
- The date that informed consent was obtained
- Evidence that the subject meets trial eligibility requirements (e.g., medical history, trial procedures and/or evaluations)
- The dates of all trial related subject visits
- Evidence that required procedures and/or evaluations were completed
- Use of any concomitant medications
- Documentation of specific device used, if any
- Occurrence and status of any Adverse Events
- The date the subject exited the trial, and a notation as to whether the subject completed the trial or was discontinued, including the reason for discontinuation

14.2 Criteria for Terminating Study

PQ Bypass reserves the right to terminate the study at any time, but intends only to exercise this right for valid scientific or administrative reasons related to protection of subjects. Investigators and associated EC and CA will be notified in writing in the event of termination.

Possible reasons for study termination include:

- The discovery of an unexpected, significant, or unacceptable risk to the subjects enrolled in the study
- A decision on the part of PQ Bypass to suspend or discontinue development of the device

14.3 Criteria for Suspending/Terminating a Study Center

PQ Bypass reserves the right to stop the screening of subjects at a study center at any time after the study initiation visit if no subjects have been enrolled or if the center has multiple or severe protocol violations without justification or fails to follow remedial actions.

Possible reasons for suspending/terminating a study center include, but are not limited to:

- Repeated failure to complete case report forms prior to scheduled monitoring visits
- Failure to obtain written Informed Consent
- Failure to report SAEs/UADEs to PQ Bypass within 24 hours of knowledge
- Loss of (or unaccounted for) investigational product inventory

14.4 Data Safety Monitoring Board (DSMB)

A Data Safety Monitoring Board (DSMB) consisting of non-Investigator experts, will review safety data from the study and establish stopping rules for early termination of the trial. The composition of the DSMB will include at least one statistician and at least two clinicians with expertise in the treatment interventional peripheral disease. Names of the actual members will not be announced. The frequency of the DSMB meetings will be determined in conjunction with the Sponsor. However, the DSMB may call a meeting at any time if there is reason to suspect safety is an issue.

The DSMB will make recommendations based upon the safety analysis of adverse events, protocol deviations, and device failures. The DSMB will function in accordance with SOPs and applicable regulatory guidelines.

The DSMB chairperson will notify PQ Bypass by confidential memo, of any safety or compliance issues. They will also provide confidential recommendations, when necessary, of study termination based upon the safety stopping rules determined at study onset, or because a clinically significant result was identified in safety analyses of the data. All DSMB reports will remain strictly confidential, but will be made available to regulatory authorities upon request.

15.0 PROTOCOL DEVIATIONS

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

Investigators shall be required to obtain prior approval from PQ Bypass Clinical Director before knowingly deviating from the protocol, except where necessary to protect the life or physical well-being of a subject in an emergency. Such approval shall be documented in writing and maintained in clinical study management and Investigator files. Prior approval is generally not expected in situations where unforeseen circumstances are beyond the Investigator's control, (e.g., subject was not available for scheduled follow-up office visit, blood sample lost by laboratory, etc.); however, the event is still considered a deviation and will be reported via the appropriate CRF.

Deviations must be reported to PQ Bypass regardless of whether medically justifiable, pre-approved by PQ Bypass or taken to protect the subject in an emergency. Subject specific deviations will be reported on the Protocol Deviation case report form. Non-subject specific deviations, (e.g., unauthorized use of an investigational device outside the study, unauthorized use of an investigational device by a physician who has not signed an Investigator agreement or not been trained in the use of the device, etc.), will be reported to PQ Bypass. Investigators will also adhere to procedures for reporting study deviations to their EC and CA, where required, in accordance with their specific reporting policies and procedures.

Regulations require that Investigators maintain accurate, complete and current records, including documents showing the dates of and reasons for each deviation from the protocol.

16.0 REGULATORY CONSIDERATIONS

16.1 Maintaining Records

The Sponsor will maintain copies of correspondence, data, shipment of devices, serious adverse device effects and other records related to the clinical trial.

16.2 Site Record Retention Policy

The Sponsor and clinical sites will maintain all records pertaining to this study for a period of seven years following the date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a regulatory submission. If the reviewing Ethics Committee or Competent Authority retention policy is longer than seven years, record retention will be mandated under those respective policies. Record retention dates will be provided to all concerned by the Sponsor.

16.3 Ethics Committee (EC) and Competent Authority (CA) Approval

The trial will only be started in a center after written approval of the protocol and Patient Informed Consent has been obtained from the appropriate Ethics Committee. Any amendment to the final protocol should be submitted to the Ethics Committee for either notification or approval.

Regulatory approvals must be obtained prior to enrolment of the first patient. The Sponsor will arrange regulatory and local approvals for the study. The Sponsor or its designated CRO (HealthLink, Inc) will require a copy of any EC and CA correspondence, as well as the final approval letter from the EC and CA, where applicable.

An Investigator may not make protocol changes without prior approval by Sponsor. All significant protocol changes that may affect the following must be submitted and approved by the EC and CA before initiating the change:

- Validity of the data or information resulting from the completion of the approved protocol
- Relationship of the likely subject risk to benefit relied upon to approve the protocol
- Scientific soundness of the investigational plan
- Rights, safety, or welfare of the human subjects involved in the investigation

The change must be approved by the relevant EC and CA. The sponsor will submit a copy of the protocol amendment to all Investigators for their EC to review and ensure the study continues to be conducted consistently across all sites. The investigative sites must send the Sponsor a copy of the approval letter for the protocol amendment.

The Sponsor may make certain administrative changes to the protocol without prior approval of the relevant EC and CA. The Sponsor will notify all investigative sites of

such changes to ensure the study continues to be conducted consistently across all sites. The site EC will be notified of these changes

17.0 INVESTIGATOR RESPONSIBILITIES, RECORDS AND REPORTS

17.1 Investigator Responsibilities

The Investigator is responsible for ensuring that this trial is conducted according to this protocol and that signed Informed Consent is obtained from each subject prior to his or her inclusion in this trial.

It is the Investigator's responsibility to ensure that all staff assisting with this trial have the appropriate qualifications and are fully instructed on the trial procedures and respect subject confidentiality, as specified in the Investigator Agreement with the Sponsor.

The Investigator is responsible for ensuring that the conduct of the trial conforms to the EC and CA requirements and provides all necessary communication with the EC and CA including, but not limited to, annual trial reports and required adverse event notifications.

17.2 Investigator Records

Case Report Forms

The standardized Case Report Forms (CRFs) will be used to collect complete and accurate records of the clinical data from the trial according to the International Conference on Harmonization (ICH)/WHO Good Clinical Practice (GCP) standards. The Investigator is responsible for collecting and accurately recording the data generated for this trial.

Screening Log

Investigators will maintain a screening log that will record the date of informed consent, the date of screening, the enrollment status (enrolled/excluded) and the reason for exclusion for all screen failures.

17.3 Investigator Report

The final clinical report will be prepared and provided to each Principal Investigator for submission to their respective IEC after conclusion of the trial.

18.0 PUBLICATIONS

The PQ Bypass publications policy for this Study is as follows. Following the earliest of a) publication of the multi-center Study results, b) receipt of a notice from PQ Bypass stating that the multi-center Study has been terminated or, c) twenty-four (24) months after completion or termination of the Study at all Investigative sites, Investigators shall have the right to publish, in appropriate scientific journals or other professional publications, information and data collected or produced as a result of their participation in the Study, provided that drafts of the publications

have been delivered to PQ Bypass for purposes of review and comment at least sixty (60) days prior to the first submission for publication or public release, to which Investigating Parties shall give due consideration. PQ Bypass shall return comments to the Investigator within forty-five (45) days receipt of the draft. In addition, the Investigator shall delay any proposed publication/presentation in the event PQ Bypass so requests to enable PQ Bypass to secure patent or other proprietary protection. In all such publications, credit shall be given to PQ Bypass its sponsorship of the Study. Similarly, in publications by PQ Bypass regarding the Study, appropriate recognition will be given of the contribution made by the Institution and Principal Investigator, as applicable. PQ Bypass may use, refer to, and disseminate reprints of scientific, medical, and other published articles relating to the Study, including such reprints that disclose the name of Investigators and/or Institution.

A description of this clinical trial is available on http://www.ClinicalTrials.gov. The ClinicalTrials.gov identifier is NCT02471638.

19.0 DEFINITIONS

Adverse Device Effect
An adverse event related to the use of an investigational medical device. 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 also includes any event resulting from use error or from intentional misuse of the investigational medical device.

Adverse Event (AE)
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 medical device or index procedure. Adverse events are captured throughout the course of the study.

Allergic Reaction to contrast, polyester, nickel compound of the device and/or anesthesia
An overreaction of the body's immune system to a component of an investigational device (e.g., nitinol metal, polyester, plastics), contrast agents and/or anesthesia medication given to the subject for completion of a study related procedure (e.g., MSCT, angiogram, investigational device), which requires medical intervention to treat the allergic reaction.

Anesthesia Type
Type of anesthesia administered. Categorized as either general, local, or epidural/spinal.

Anticipated Adverse Device Effect (AADE)
An expected effect associated with endovascular treatment of the SFA and may occur during the procedure or during the course of the study. These anticipated effects have been previously identified in the risk analysis report.

Blood Loss

- **Major Blood Loss** - Defined as transfusion of >2 units packed red blood cells (PRBC)).
- **Estimated Procedural Blood Loss -** Defined as the total estimated blood loss (mL) during the index procedure. Includes blood loss resulting from adjunctive procedures performed during the index-procedure.

Clinical Success
Improvement of at least one category using the Rutherford Clinical Severity Scale.

Contrast Volume
Total volume of contrast (mL) administered during the index procedure. Includes contrast administered for adjunctive procedures performed during the index procedure.

Death
Death is divided into two categories and will be reported anytime in a subject's study participation.

- **Device or procedure related death -** Death related to the Study Device or to any procedure (index or subsequent) intended to treat the target vessel.
- **Non-device or procedure related death –** Death NOT related to any procedure (index or subsequent) intended to treat the target vessel or death not related to the Study Device.

Deep Vein Thrombosis (DVT) on Ipsilateral Limb
A blood clot (thrombus) in the targeted deep vein (e.g. posterior tibial). A deep vein thrombosis is symptomatic. A deep vein thrombosis is distinct from the presence of mild fibrin/thrombus with no hemodynamic impact or the intentional l occupancy of the vein by the graft or asymptomatic occlusive thrombus (see **Venous Classification** below)

Device Deficiency
Inadequacy of the Study Device with respect to its identity, quality, durability, reliability, safety or performance. Device deficiencies include malfunctions, use errors, and inadequate labeling.

Device Time
Number of minutes from initial Study Device insertion to final Study Device removal. It does not include time needed to perform adjunctive procedures.

Explant
Removal of the Study Device implant for any reason.

Fluoroscopy Time
Total fluoroscopy time (minutes) used during the index procedure and includes time utilized for adjunctive procedures performed during the index procedure.

Intensive Care Unit Time
See post-procedure ICU time

Life Expectancy > 2 Year
The duration of time the test subject is expected survive post procedure. Subjects must not have a concurrent medical condition that would cause expected survival to be less than 2 years.

Malignant Tumor[1]
A tumor that invades surrounding tissues, is usually capable of producing metastases, may recur after attempted removal, and is likely to cause death of the host unless adequately treated.

Major Adverse Event (MAE)

[1] http://www.medilexicon.com

Composite endpoint of death, target vessel revascularization (TVR) or any amputation of the index limb. See individual events for detailed definitions.

Major Adverse Vascular Event (MAVE)

Composite endpoint of stent thrombosis, target limb amputation, clinically apparent distal embolization, defined as causing end-organ damage (e.g. lower extremity ulceration, tissue necrosis, or gangrene), procedure related arterial rupture, acute limb ischemia or bleeding event requiring transfusion.

Myocardial Infarction (MI) [2]

Typical chest pain and either a Q-wave or non Q-wave MI as described below. Myocardial infarction is a component of MAE.

- **Q-Wave Myocardial Infarction –** Development of new, pathological Q waves in two or more contiguous leads V1-V3 or Q Wave ≥ 3 ms in width in leads I, II, aVL, AVF, V4, V5 or V6 and ≥ 1 mm in depth on at least two serial ECGs.
- **Non-Q-Wave Myocardial Infarction –** (1) Non-procedural (pre-procedural or > 30 days post-index procedure, endovascular or surgical intervention) – CK-MB elevation ≥ 2 times the upper limit of normal in the absence of new pathological Q waves, (2) post-index procedure or endovascular re-intervention (≤ 30 days) – CK-MB elevation ≥ 3 times the upper limit of normal in the absence of new pathological Q waves, or (3) post-Surgical intervention (< 30 days) – CK-MB elevation ≥ 5 times the upper limit of normal in the absence of new pathological Q waves.

Post-Procedure ICU Time

Number of hours a patient is in an intensive care unit prior to discharge or moving to a step down or standard care unit.

Primary Assisted Patency

Revascularization of non-occlusive (<99%) stenosis within the stent graft or immediately above or below the treated arterial segment with less than 50% residual stenosis.

Primary Patency

No evidence of clinically significant stenosis (≥50%) within the stent graft or immediately above or below the treated arterial segment based on duplex ultrasound (systolic velocity ratio of >2.5).

Post-Procedure Length of Hospital Stay

Number of days from the end of the procedure until the patient is discharged from the hospital. This does not include time spent in a skilled care facility.

Procedural Success

Successful delivery of the investigational devices to the identified area and removal of delivery system. in the absence of in-hospital MAEs.

Procedure Time

Number of minutes needed to perform the index procedure from time of initial vessel cut down time to time of final guidewire removal. Also referred to as skin-to-skin time.

[2] Myocardial infarction redefined--a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. Eur Heart J. 2000 Sep;21(18):1502-13. Review.

Renal Failure
Need for dialysis or a laboratory finding of serum creatinine > 3.5 mg/dL.

Respiratory Failure
The need for mechanical ventilation beyond the first 24 hours post-index procedure (and/or re-intervention) or the need for re-intubation or ventilator support after the first 24 hours (unless the subject was ventilator dependent pre-procedure).

Secondary intervention
Any visit to the operating room or catheterization laboratory subsequent to the PQ Bypass procedure to treat an adverse event related to the disease, the index procedure or the study device.

Secondary Patency
revascularization of occlusion (100%) within the stent graft or immediately above or below the treated arterial segment with less than 50% residual stenosis

Serious Adverse Event (SAE)
Any undesirable event occurring which led, could have led or might lead either directly or indirectly to the death or serious deterioration in the health of a subject, user or another person, regardless of whether the event was caused by the medical device.

Stroke or Transient Ischemic Attack (TIA)

- **Stroke -** A new neurological deficit lasting more than 24 hours, or lasting 24 hours or less with a brain imaging study showing infarction.
- **TIA -** A neurological deficit lasting less than 24 hours and, if an imaging study is performed, shows no evidence of infarction. These events may occur anytime throughout a subject's study participation and may or may not require intervention.

Stent Graft Occlusion
Complete blockage of blood flow through the Stent Graft as determined by traditional imaging (e.g. DUS, CTA, MRA or Angiography).

Stent Graft Placement Accuracy
Estimated distance (mm) from the operator's intended target as compared to the actual position placed as assessed via angiography during the index procedure.

Target Lesion Revascularization (TLR)
A re-intervention on the index lesion site.

Target Vessel Revascularization (TVR)
Treatment of another lesion at the target vessel site.

Technical Success
Successful delivery of the investigational devices to the identified area and removal of delivery system.

Unanticipated Adverse Device Effect (UADE)
An adverse device effect which by its nature, incidence, severity or outcome has not been identified in the risk analysis report.

Vascular Access Type

Method of entry into the vascular system. Categorized as either surgical cut down or percutaneous.

Venous Classification (Miller Scale)

A means of classifying observations in the deep vein in which the stent graft is implanted:

- 0: Patent, no presence of fibrin or thrombus
- 1: Patent, thin film fibrin sheath
- 2: Patent, presence of mild fibrin/thrombus without hemodynamic impact
  - a) located in gutter adjacent to anastomosis
  - b) located in body of graft
- 3: Intentional occupation of vein with no anticipated flow
- 4: Asymptomatic Occlusive thrombosis

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APPENDIX I: SAMPLE INFORMED CONSENT (ENGLISH VERSION)

(Attached as separate document)

APPENDIX II: INSTRUCTIONS FOR USE

(Attached as separate documents)