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INtima Versus Adventitia Drug Delivery to Elucidate Mechanisms of Restenosis: Magnetic Resonance Imaging

INVADER MRI

CLINICAL RESEARCH PROTOCOL

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CHANGE LOG

Version	Release Date	Description of Changes
1.0	10 AUGUST 2015	New Release
1.1	21 DECEMBER 2015	Changed name of protocol Revised Background to provide more specific information about study context and for style. Revised Study Rationale for grammar. Revised Primary and Secondary Objectives for consistency with grant. Revised language related to "Investigational Product", Dispensing and Storage Instruction to clarify DEX is not an investigational product. Changed wording of Secondary Aim #3 (K^{trans}) to specify measurement at 6 months Sec. 9.10 "Research MRI" - removed K^{trans} at 24 hours and 12 months Changed Sec 9.2, Research lab measurements to include assessment of inflammatory markers at 12 months to match Secondary Aim #2.

		Updated screening exclusion criteria to the patient is expected to live 1-year or longer. Added exceptions to known active malignancy. Revised Procedural Inclusion/Exclusion Criteria to better define eligible lesions, concomitant procedures and medications. Changed maximum lesion length from < 20 cm to entire superficial femoral/popliteal artery Updated Treatment Segment Registration procedure to clarify when the investigator has discretion for choosing an index lesion. Updated Treatment Segment Registration to include origin of profunda femoris artery as key landmark Changed Sec. 9.8.2 “Order of Operations” to clarify the Core Lab will grade infusion success Removed Sec. 9.9 Clinical MRA due to differences in clinical practices between sites Added Sec. 9.10.2 Research MRI Protocol with specific language about processing modalities Added language to “Research MRI” procedure description regarding blind reading of MRI studies. Changed window for 12 month visit from 28 d to 30 d Amended Data Safety Monitoring section, removing two members and specifying expected procedure-related conditions Updated Primary Analysis Plan to include linear splines at 6 mo Changes wording of Assessments Visit 1 to include Rutherford & ABI as part of vascular exam Change to Appendix 1 – clarified appropriate tube type for MCP-1 Added Appendix 6: Lutonix DCB IFU Added Appendix 7: INPACT Admiral DCB IFU Added Appendix 8: Walking Impairment Questionnaire (WIQ)
1.2	1 JUN 2017	Change in PI Revised List of Abbreviations Revised grammar of inclusion/exclusion criteria, for clarity

		Standardized terminology throughout protocol Changed Sec 9.8 Order of Operations, items no.4 & no.7, to reflect modification of Sec 9.9.2 Changed Sec 9.9.2 to clarify the method used for determining the MRI scan location Added Sec 9.9.3 Pre-Reintervention MRI to specify conditions for imaging in the event of an unplanned visit for index leg reintervention Revised Sec 10 Schedule of Assessments for accuracy, including Inclusion/Exclusion criteria, Rutherford Category, Index Lesion Registration & PTX Treatment Changed Sec 11.2 Visit 2: Procedure (Day 0) to match Sec 9.1.4 Concomitant Medications and Sec 10 Schedule of Assessments by removing concomitant medications from Day 0 assessments Added Sec 11.8 Unplanned Visit for Index Leg Reintervention Change in Data Management team To eliminate possible confusion, all instances of the term “study drug” have been substituted with more accurate terminology. This trial uses FDA approved drugs and devices in accordance with their IFUs. For more information, please refer to Section 8.2 Formulation of Treatment
1.3	13 OCT 2017	Include eGFR criteria in Protocol Synopsis for Subject Screening Inclusion and Exclusion Addition of ILLUMENATE PIVOTAL studies to Section 1.1 under Drug Coated Balloon Addition of literature references for new studies in Section 1.2 regarding New Drug Coated Balloon Addition of Stellarex DCB Risk in Section 2.1.3.3 Inlcude eGFR criteria in section 6.2 and 6.3 Subject Screening Inclusion and Exclusion Criteria Add Stellarex DBC to Section 8.2 Add Stellarex DCB PTX Dosage to Section 8.3.1 Add DCE Research MRI protocol to section 9.9.2 Added an Appendix 8. Stellarex DCB Catheter IFU
1.4	26 OCT 2017	Correction of DEX Infusion Volume in Section 8.3.1

1.5	21 FEB 2018	Added eGFR will be assessed at Month 12 to Section 9.2.2 Added CE-MRA and post MERGE/DASH at 12 months on Table 3, Section 9.9.2 Added Clinical Lab eGFR to Visit 6 in Schedule of Assessments Table Section 10 Changed footnote in Section 10 to "Research and Clinical labs must be drawn between POD #1-7" Removed Ktrans assessment to Statistical Methods 2b in Section 16 Amended the Glow N' Tell tape protocol in Section 9.5 Treated Segment Registration and 11.2 Visit 2 Procedure
1.6	12 JUN 2018	Added under subheading 5.2 Secondary Endpoints: 5. Change in subject study status based on subjects receiving reintervention on < or >75% of treated segment." Added subheading Section 5.4 under Completion Endpoints: Subject Status and Study Completion under Section 5 Study Endpoints Added Unplanned Visit to the Schedule of Assessments in Section 10 Added under subheading 11.8 Unplanned Visit for Index Leg Reintervention, a protocol for subject follow up after reintervention. Added subheading 11.9 Study Completion under Section 11 Evaluation By Visit Added under subheading 13.1 Early Discontinuation/Withdrawals after Adverse Event an example, "(i.e index segment restenosis or occlusion <30 days of index segment treatment)

1.7	30 AUG 2019	Substitution of PTX treatment with POBA treatment moving forward, due to safety concerns (changes made to List of Abbreviations, Protocol Synopsis, Sections 1.1, 2.1.3.3, 5.1, 8.1, 9.6, 9.8, 10, 11.2, 11.7, 11.8, 16.2, and 16.4) Reduction of Number of Subjects to 54 overall, 27 per site (changes made to Protocol Synopsis, Section 16.4) Duration of Subject Participation has been extended to 36 months, with the addition of two telephone follow up visits (changes made to Protocol Synopsis, Sections 4.1, 5.4, 9.1.7, 10, 11.8, 11.11, and 15) Mercator MedSystems location revised to Emeryville, CA (Section 1.1) Section 1.2 (Literature References) includes two new references, Nos.74 (Katsanos et. al.) & 75 (FDA Letter from August 7th 2019) Section 11.11 (Study Completion) – 1-month is defined as ≥ 30 days. ≥75% of treated segment Section 16.4 (Sample Size and Randomization) – added calculations determining sample size
1.8	10 OCT 2019	Section 5.2 (Secondary Endpoints) – "5. Change in subject study status based on subjects receiving reintervention on < 75% or ≥ 75% of treated segment." Section 5.4 (Completion Endpoints) – "2. Subject develops restenosis after the 1-month study follow-up, requiring reintervention of ≥ 75% of treated segment." Section 5.4 (Completion Endpoints) – "If subject develops restenosis after the 1-month study follow-up, requiring reintervention of <75% of the treated segment, please see section 11.10 for specifics on recording Unplanned Visits for Index Leg Reintervention and continuing follow-up."

		Section 11.10 (Unplanned Visit for Index Leg Reintervention) – "For further specifics on study completion, please see section 11.11 Study Completion." Section 11.11 (Study Completion) – "2. Subject develops restenosis after the 1-month study follow-up, requiring reintervention of ≥ 75% of treated segment." Section 11.11 (Study Completion) – "If subject develops restenosis after the 1-month study follow-up, requiring reintervention of <75% of the treated segment, please see section 11.10 for specifics on recording Unplanned Visits for Index Leg Reintervention and continuing follow-up." Section 13.1 (Early Discontinuation/Withdrawal) – "(i.e. treated segment restenosis/occlusion occurring between index procedure date and the 1-month study follow-up date)"

Clinical Research Protocol

INtima Versus Adventitia Drug Delivery to Elucidate Mechanisms of Restenosis: Magnetic Resonance Imaging

INVADER MRI

Protocol Number:	1.8
Version Date:	10 OCT 2019
Investigational Product:	none
IND Number:	n/a
Funding Organization:	National Institutes of Health National Heart, Lung, and Blood Institute (NHLBI)
Principal Investigator:	Name: David Saloner, Ph.D. Telephone: 415-750-2238 E-mail: David.Saloner@ucsf.edu

Approval:

_____ _____

PI or Sponsor Signature (Name and Title) *Date*

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PROTOCOL AGREEMENT

I have read the protocol specified below. In my formal capacity as Investigator, my duties include ensuring the safety of the study subjects enrolled under my supervision and providing the University of California, San Francisco Committee on Human Research (CHR) with complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted GCP principles and to abide by the terms of this protocol.

Protocol Number:	1.8
Protocol Title:	*INtima Versus Adventitia Drug Delivery to Elucidate Mechanisms of Restenosis: Magnetic Resonance Imaging* *INVADER MRI*
Protocol Date:	10 OCT 2019

Investigator Signature *Date*

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LIST OF ABBREVIATIONS

ABI	Ankle-Brachial Index
AE	Adverse Event
AUC	Area Under the Curve
CFA	Common Femoral Artery
CFD	Computational Flow Dynamics
CFR	Code of Federal Regulations
CRF	Case Report Form
CRP	C-Reactive Protein
DCB	Drug Coated Balloon
DMC	Data Monitoring Committee
DEX	Dexamethasone
eGFR	estimated Glomerular Filtration Rate
FDA	Food and Drug Administration
GBCA	Gadolinium Based Contrast Agent
GCP	Good Clinical Practice
GR	Glucocorticoid Receptor
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFU	Instructions For Use
IL-1β	Interleukin 1 Beta
IRB	Institutional Review Board
ITT	Intention-To-Treat
LRNC	Lipid Rich Necrotic Core
LV	Lumen Volume
MCP-1	Monocyte Chemotactic Protein 1
MERGE	Motion sensitized driven Equilibrium prepared Rapid Gradient Echo
MRA	Magnetic Resonance Angiogram
MRI	Magnetic Resonance Imaging
NIH	National Institutes of Health
NHLBI	National Heart, Lung, and Blood Institute
NSF	Nephrogenic Systemic Fibrosis
OSI	Oscillatory Shear Stress
PI	Principal Investigator
PAD	Peripheral Artery Disease
POBA	Plain Old Balloon Angioplasty
PTA	Percutaneous Transluminal Angioplasty

PWA	Percent Wall Area
PTX	Paclitaxel
PWV	Percent Wall Volume
SAE	Serious Adverse Event
SFA	Superficial Femoral Artery
SMC	Smooth Muscle Cell
TOF	Time-of-Flight
TVA	Total Vessel Area
TVV	Total Vessel Volume
WA	Wall Area
WV	Wall Volume
WIQ	Walking Impairment Questionnaire
WSS	Wall Shear Stress
WSSG	Wall Shear Stress Gradient

PROTOCOL SYNOPSIS

TITLE	INtima Versus Adventitia Drug Delivery to Elucidate Mechanisms of Restenosis: Magnetic Resonance Imaging (INVADER MRI)
SPONSOR	National Institutes of Health National Heart, Lung, and Blood Institute (NIH NHLBI)
FUNDING ORGANIZATION	NIH NHLBI
NUMBER OF SITES	2
RATIONALE	Peripheral artery disease (PAD) affects at least 12 million Americans annually with more than half a million patients undergoing an endovascular or surgical revascularization procedure for treatment of the disease. Unfortunately, about two-thirds of patients still have blockages in the leg arteries, even after these procedures. Advances in Magnetic resonance imaging (MRI) offer promise for understanding the mechanism of failure through insights into vessel wall composition, remodeling, and inflammation. Restenosis has a known relationship to inflammation. Advances in micro-catheter technologies offer the ability to deliver anti-inflammatory medications such as dexamethasone (DEX) directly to the adventitia. This study aims to investigate if patient-specific parameters affect angioplasty outcomes, if DEX has a biological effect on the vessel wall, and if this effect is through the reduction of inflammation.
STUDY DESIGN	Prospective, multi-center randomized Phase IV trial.
PRIMARY OBJECTIVE	The primary objective is to assess the mechanisms of vascular healing following balloon angioplasty treatment to stenotic arteries from atherosclerosis. Vascular healing will be assessed by MRI determined percent wall volume change (PWV) from 24 hours post-angioplasty to 12 months
SECONDARY OBJECTIVES	1. To determine whether DEX infusion will result in less inflammation as measured by blood (MCP-1, CRP, and IL-1β) and tissue imaging (K^{trans}) markers of inflammation 2. To determine whether patient-specific physiological factors correlate with vascular healing
NUMBER OF SUBJECTS	54 overall 27 per site

SUBJECT SELECTION CRITERIA	Screening Inclusion Criteria: 1. Male or non-pregnant female ≥ 35 years of age 2. Atherosclerotic, infrainguinal PAD 3. Rutherford Clinical Category 2-6 4. Stenosis detected by radiology that in the clinician's opinion is the reason for the PAD symptoms 5. Patient is willing to provide informed consent and comply with the required follow up visits, testing schedule, and medication regimen 6. eGFR ≥ 30 and/or threshold established by the local Institutional Review Board or Committee of Human Research Procedural Inclusion Criteria: 1. De novo atherosclerotic lesion qualifying for angioplasty 2. A patent artery proximal to the index lesion. Concomitant inflow procedures, including open femoral artery endarterectomy and/or stenting of the iliac arteries, are permissible. 3. >50% diameter stenosis of the superficial femoral artery and/or popliteal artery (between the profunda and tibioperoneal trunk) 4. Reference vessel diameter ≥3 mm and ≤ 8mm 5. Successful wire crossing of lesion 6. Successful angioplasty of the index lesion or part of the index lesion, defined as ≤30% residual lumen stenosis compared with adjacent non-diseased lumen diameter, without flow-limiting dissection Screening Exclusion Criteria: 1. Any contraindication to receiving an MRI 2. Pregnant, nursing, or planning on becoming pregnant in < 2yrs 3. Life expectancy of < 1 yr 4. History of solid organ transplantation 5. Patient actively participating in another investigational device or drug study 6. History of hemorrhagic stroke within 3 months of index procedure 7. Previous or planned surgical or interventional procedure within 30 days of index procedure

	8. Chronic renal insufficiency with eGFR < 30 9. Prior bypass surgery, stenting, atherectomy or angioplasty of the index lesion 10. Inability to take required study medications 11. Contra-indication or known hypersensitivity to dexamethasone sodium phosphate, contrast media, gadolinium, aspirin or Plavix 12. Systemic fungal infection 13. Acute limb ischemia 14. Prior participation of the index limb in the current study (contralateral treatment is allowed) 15. Patient is being treated with long-term steroids (not including treatment of a bronchial condition with inhaled steroids) <u>Procedural Exclusion Criteria</u>: 1. Index lesions extending into the tibial trifurcation or above the profunda. Note: the outflow tibial artery can be treated concomitantly. Similarly, the common femoral artery can be treated concomitantly, either with open endarterectomy and patch angioplasty or with endovascular methods. However, the index lesion cannot be contiguous with either the CFA or the tibial trifurcation. 2. Circumferential calcification at index lesion, which in the judgment of the investigator would prevent penetration of the Micro-Infusion catheter needle through the vessel wall 3. Inadequate distal outflow defined as no patent tibial arteries (>50% stenosis). The outflow vessel can be established at the time of primary treatment 4. Use of adjunctive therapies other than angioplasty. Chocolate balloons and/or scoring balloons are allowed, if used below reference diameter.
DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	Subjects will be on study for up to 36 months **Screening:** up to 30 days **Follow-up:** 36 months The total duration of the study is expected to be 60 months. 3.5 years for subject recruitment, twelve months for final subject follow-up, and six months for final data clean-up.
PRIMARY ENDPOINT	The primary endpoint for this study will be percent wall volume (PWV) change of the treated segment from the 24-hour post-intervention MRI scan to 12 months between DEX treated and non-DEX (PTX or POBA) treated patients.

	The treated segment is defined as the length of vessel, encompassing the index lesion, that has undergone primary revascularization, from normal back to normal artery.
STATISTICS **Primary Analysis Plan**	The primary analysis will be an intention-to-treat (ITT) comparison of observed change in mean ΔPWV between treatment groups at 12 months using a t-test. Because ΔPWV may be nonlinear in time, linear splines with knots at 24 hours, 1 month,6 months, and 12 months will be used to fit the model. Multivariable regression models will be constructed to determine independent variables associated with ΔPWV controlling for demographic and anatomical variables, statin use, inflammatory markers, and smoking. We will also investigate effects by treatment received by constructing generalized linear models controlling for demographic, clinical, and anatomic variables. Predictors of PWV will be evaluated via univariate and multivariate regression analysis.
Rationale for Number of Subjects	The sample size for this study is based on the statistical hypothesis for the primary endpoint, observed change in mean ΔPWV between groups at 12 months. While there are no predicate serial studies of PWV changes in femoral artery restenosis following angioplasty to estimate the sample size, previous work on the progression of de novo atherosclerosis in similar sized peripheral arteries (carotids) forms the basis of this estimation. Based on the power calculations outlined in Sec 16.4, we estimate the need for 22 subjects per treatment assignment to detect a 2.7% difference in PWV at a power level of 80%. Assigning a 20% attrition rate due to loss to follow up and/or index lesion revascularization, 27 subjects will be enrolled per arm. Calculation is based on an unpaired t-test at a 5% significance level.

1 BACKGROUND

Population to be studied

This is a randomized trial designed to explore the mechanisms of restenosis following balloon angioplasty. This trial will evaluate subjects with peripheral artery disease who require an endovascular intervention of the femoropopliteal arterial segment (SFA/Popliteal) to restore blood flow to the leg. Peripheral artery disease (PAD) is a condition defined by extensive accumulation of atherosclerotic plaque below the distal aorta that reduces lower limb arterial perfusion and results in ischemia on demand noted as intermittent claudication or ischemic rest pain or ulceration known as critical limb ischemia. The SFA is the most common peripheral artery affected in patients with PAD and percutaneous transluminal angioplasty (PTA) is the most common mode of treatment. PTA may be used alone or in combination with another treatment modality such as a stent or debulking device but it serves as the primary treatment platform for restoring blood flow to the leg. There is an estimated 800,000 SFA procedures performed worldwide annually, representing a market of approximately $1.5 billion. Roughly 450,000 of those cases are performed in the United States with an overall market growth estimated in the mid-single digits.

The Current Treatment of PAD and the Epidemic of Restenosis

Balloon angioplasty (PTA) is the cornerstone of endovascular treatment of arteries. A balloon is used to deploy, or used for post-dilation of, vascular stents (balloon expandable). PTA is also used in conjunction with debulking therapy. However, until recently PTA was rarely used as a single modality to treat arterial stenosis except in the short lesions, (TASC II A, < 5 cm), due to the high rate of binary restenosis 67% (primary patency 33%, Krisna Rocha Singh). This high rate of failure for PTA was also noted in the control arm of the Zilver PTX study which evaluated a paclitaxel covered stent compared to balloon angioplasty alone. More recently, better PTA techniques have resulted in decreased restenosis rates of PTA to about 50%. This improvement occurred as a result of 1) sequential dilation of the stenosis with progressively larger balloons, 2) slower inflation of each balloon to reach nominal dilation, and 3) longer inflation times of each balloon at nominal pressure often exceeding 2 minutes, and limiting the inflation atmospheres and barotrauma. Further improvement was attained by adding a proprietary matrix to the balloon surface to allow paclitaxel (PTX) to be delivered into the artery wall. These are known as drug-coated balloons (DCB) and there are 3 approved by the FDA: the INPACT Admiral DCB (Medtronic Inc, Minneapolis MN), the Lutonix 035 DCB (C. R. Bard Inc, Covington GA) and the Stellarex DCB (Spectranetics Corp, Colorado Springs CO). In general, the effectiveness and safety profiles of these devices are not substantially different. Primary patency rates in selected lesions can approach 75% with these devices under trial conditions (<10cm lesions, claudication patients) and they are reported to attain clinically-driven target lesion revascularization (cd-TLR), similar to stents. One concern about DCBs is that the depot drug delivery is at the intima surface. To reach the deeper layers of the arterial wall the drug must diffuse down its concentration gradient in accordance with Fick's Law $\frac{\partial \varphi}{\partial t}$=-D$\nabla^2\varphi$, where $\frac{\partial \varphi}{\partial t}$ is the diffusion flux, D is the diffusion coefficient, ∇^2 is the Laplacian operator, and φ is the amount if drug in dimensions mol/mm^3. $\varphi=\varphi(x,t)$ is a function which depends on location x and time, t, in seconds. Therefore, the initial concentration of the drug will be highest in the intima until, over time, the drug diffuses evenly through the vessel wall. This potentially could inhibit re-endothelialization of the treated area and cause increased restenosis after the drug is no longer retained in the wall. This would be referred to as late catch up where the treatment arm would catch up to the control arm after a specified period of time. In the

coronaries first generation paclitaxel stents have been known to cause late stent thrombosis due to delinquent endothelialization over the stent struts. This phenomenon necessitates prolonged dual antiplatelet therapy (DAPT). Because of these reasons and others, as will be explained below, the adventitia is an alternative to the intima in drug delivery.
It is desirable to avoid stents in leg arteries if possible as vascular stents are susceptible to micro-abrasion, friction, and fatigue.[1] Constant micro-forces associated with daily ambulation lead to stent fractures and restenosis. Once restenosis occurs within a stent, it is very difficult to regain and maintain patency of the artery.[2] Further, future therapy options such as bypass surgery become limited due to the stent implant and many consider this to "burn bridges" for future revascularization options. In fact, more bypass surgery is now being performed after failed stenting than for de novo lesions, and studies show that bypass surgery performed after failed stenting have worse outcomes.[3] This truly is an epidemic of restenosis.[4]

The Tunica Adventitia is an Active Participant in Arterial Restenosis

Once thought to be a passive layer of the arterial wall, the tunica adventitia is now known to be extremely metabolically active and capable of regulating vascular hemostasis.[8, 9] The adventitia contains a rich variety of immune cells, including T cells, B cells, dendritic cells, progenitor cells, and fibroblasts that can differentiate into myofibroblasts.[10-13] There is extensive microvascular architecture, which can traffic inflammatory cells into the vessel wall following injury.[14] Balloon angioplasty experiments in pig coronary arteries demonstrate that the adventitia is the primary site for acute inflammation after mechanical vascular injury.[15] The hypothesis that these cells contribute to intimal hyperplasia and restenosis is supported by several lines of evidence in animals. In porcine models of angioplasty, injections with 5-bromo-2-deoxyuridine (BrDU) have identified proliferating cells located in the adventitia as early as two days following injury which appear to migrate into the inner vessel in subsequent time points.[16, 17] Shi et al. noted that adventitial myofibroblasts contribute to increases in wall volumes via synthesis of extracellular matrix and collagen and migration to the intima following balloon injury.[18, 19] Finally, utilizing in vivo reporter gene transfer studies into adventitial cells, Siow et al. demonstrated adventitial myofibroblast migration into the media and intima following balloon injury.[20] *Collectively, these studies support an "outside-in" hypothesis of vascular inflammation and provide important biological rationale to target the adventitia to reduce restenosis.*

Restenosis is an Inflammatory Process

Balloon angioplasty produces a barotraumatic (8-15 atmospheres) mechanical injury, resulting in stress signals and homing of inflammatory cells into the artery.[15, 21, 22] We have shown in a porcine balloon injury model that inflammatory cells peak in the adventitia early after injury and then slowly decline over the next 28 days.[23] P-selectin and vascular cell adhesion molecule-1 (VCAM-1) is up-regulated in vasa vasorum endothelial cells soon after balloon injury thus providing a means for increased inflammatory cell trafficking.[15] Vasa vasorum expansion occurs in de novo atherosclerosis and following balloon injury, and drugs targeting neoangiogenesis are potential therapies to reduce restenosis.[24-26] Microcomputed tomography imaging demonstrates a direct correlation between the computed tomography-determined extent of adventitial angiogenesis and the extent of intimal hyperplasia.[27-29] In addition to an increase in microvascular density, vascular inflammation is also associated with increased adventitial microvasculature permeability. Examination of atherosclerotic coronary arteries from autopsy specimens show that vasa vasorum invading the media from the adventitia lack mural coverage and inter-endothelial contact at endothelial junctions is either incomplete or absent in 76% of the vessels.[24, 30, 31] These histological factors make them inherently more permeable.[30] *MRI employing dynamic contrast techniques with kinetic modeling can measure adventitial perfusion*

which is a function of both the permeability and the surface area of the adventitial vasculature. This highly validated technology forms the basis of in vivo assessment of vascular inflammation and the therapeutic response of mitigating drugs.

Glucocorticoid Receptor as a Therapeutic Target for Vascular Injury

The glucocorticoid receptor (GR) is a member of the nuclear hormone receptor superfamily of ligand-activated transcription factors. Activation of GR results in binding of receptor homodimers to glucocorticoid response elements in target genes, leading to initiation or repression of transcription. Cortisol is the naturally occurring ligand to the GR and unbound fraction of cortisol can diffuse through the cell wall to interact with the cytosolic receptor. DEX is a synthetic glucocorticoid with 25-fold higher binding affinity to GR than cortisol and no mineralocorticoid activity.[32] GRs are present in vascular smooth muscle and endothelial cells.

DEX may inhibit restenosis in several possible ways as it is known to repress angioplasty-induced immune response programs by inhibiting inflammatory transcription factors, NFκB and AP-1, and their downstream mediators.[33, 34] In vitro and preclinical studies have demonstrated that DEX down-regulates monocyte chemoattractant protein-1 (MCP-1), tumor necrosis factor α (TNF-α), and interleukin 1β in nano- and micromolar concentrations in vascular SMCs.[35, 36] IL-1β is known to stimulate SMC proliferation and to induce basic fibroblast growth factor in vascular SMCs. Intra-muscular DEX treatment demonstrated decreased macrophages present in atherosclerotic lesions and inhibition of macrophage accumulation following balloon angioplasty in cholesterol fed rabbits.[37] DEX has been shown to inhibit the proliferation and migration of smooth muscle and inflammatory cells as well as adventitial myofibroblasts through effects on thymidine kinase, matrix metalloproteinases, and retinoblastoma protein.[38-40] DEX inhibits the autocrine induction of PDGF-α chains – a known potent SMC mitogen. DEX induces the anti-inflammatory proteins annexin 1 and mitogen activated kinase phosphatase 1, while repressing the transcription of pro-inflammatory molecules such as cyclooxygenase 2.[32] DEX also markedly inhibits the production of ROS by inflammatory cells in vivo. DEX increases the immune-modulatory cytokine IL-10, which is known to inhibit the pro-inflammatory TH1 cells.[41] DEX also inhibits collagen production and extracellular matrix synthesis, which is responsible for late lumen loss following PTA[42, 43] and thought to be due to negative (shrinkage) arterial remodeling.[44] The latter is pertinent to the present application as Derksen et al., noted that fibrotic plaques rich in collagen and SMCs were associated with more constrictive remodeling following PTA.[45]

Clinical studies demonstrate that DEX treatment has shown an ability to mitigate the initial inflammatory response to vascular injury. For example, patients with unstable angina treated with DEX-eluting stents had lower plasma concentrations of CRP, ICAM- 1, and VCAM-1 post-intervention compared to patients treated with a bare metal stent.[46, 47] Two coronary studies independently tested the use of the BiodivYsio Matrix Lo stent loaded with DEX versus the same stent platform without drug as control. Han et al. randomly assigned a total of 92 patients to the DEX or control group.[48] The use of DEX-eluting stents was the only independent predictor for the major adverse cardiac event at 12 months (relative risk 0.20, 95% CI 0.06-0.68, P = .009) and binary restenosis at 6 months (relative risk 0.17, 95% CI 0.05-0.60, P = .006) by multivariate analysis. In a similar study, Konig et al. randomly assigned 120 patients with acute coronary syndrome to revascularization using the Dexamet stent or BMS.[49] The target lesion revascularization rate was lower in the Dexamet group (16.67% vs 33.33% patients; P = .031) and angiography revealed improved lumen restoration in the Dexamet stent group (late lumen loss, 0.55 ± 0.65 vs. 1.07 ± 0.92 mm P = .001).

1.1 Overview of Clinical Studies

Pharmacokinetic Studies of Dexamethasone In Porcine Carotid Arteries

The DEX pharmacokinetic (PK) profile has been demonstrated in a study of the Micro-Infusion catheter delivery into the adventitial tissue of porcine carotid arteries, Figure 1. In this study, therapeutic levels in the range of 10 to 100 nM were seen at 7 days after infusion of 1 mg.

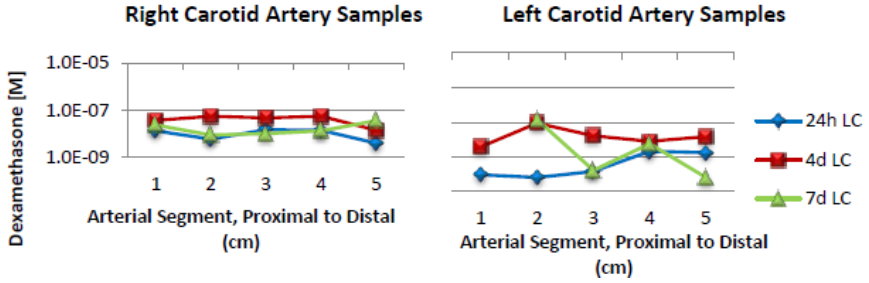

Figure 1. Dexamethasone levels measured in pig carotid arteries 1, 4, and 7 days after confirmed delivery of 1 mg dexamethasone sodium phosphate in 3 ml volume to the carotid artery adventitia with the Bullfrog Micro-Infusion catheter. Each line represents a single artery.

While the exact duration of the therapeutic window to treat vascular inflammation is unknown, based on preclinical PTA models, the optimal time frame is 7-30 days. This is supported by another porcine preclinical study employing femoral artery balloon injury model,[23] where it was determined that the adventitial leukocyte infiltration is decreased by 60% of peak value within 28 days, Figure 2. Clinical experience with steroids also support this time frame as a pulsed, intensive therapy for 3-7 days is sufficient to treat most soft tissue inflammatory processes.

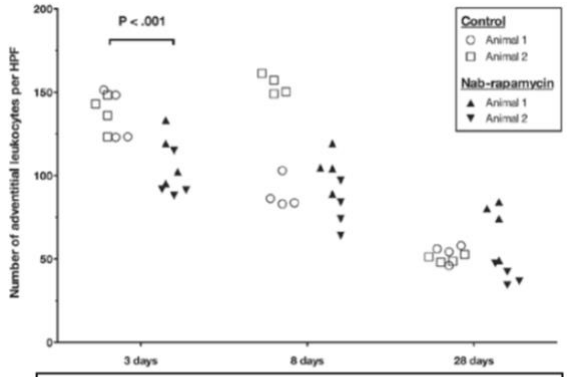

Figure 2. *Time course of adventitial leukocyte infiltration in control (two pigs per time point and nab-rapamycin-treated) femoral arteries. HPF indicates high powered field, from reference 23.*

Results of the safety and feasibility study

We conducted a Phase 1, first-in-man safety and feasibility study of DEX delivery to femoral and popliteal adventitia (NCT 01507558) with the Bullfrog Micro-Infusion catheter (Mercator MedSystems, Emeryville, CA).[7] Patients with SFA stenosis or occlusions up to 15 cm were eligible for this study. Mean lesion length was 8.9±5.3 cm, N=20 with 80% located in the distal SFA/popliteal artery, which has traditionally been considered a no stent zone. The mean number of infusions required to completely treat each lesion was 3.0 ± 1.3, minimum 1 and maximum 6. The mean volume injected was 3.8 ± 1.9 ml which contained a mean of 12.1 ± 6.1

mg of DEX and .80 ± .4 ml of contrast. This equated to a mean of 1.6 ± 1.1 mg of DEX per centimeter of lesion length. The minimal dose was 3.2 mg and the maximal dose a patient received was 24 mg of DEX. Accordingly, there was a positive linear correlation between the amount of DEX received and length of lesion treated, R2=.27, P=.019.

Procedural safety was seen in 100% of patients, with a lack of drug-related or device-related serious adverse events or major adverse limb events within 30 days of the procedure. At the 6 month follow up, two subjects had experienced a target lesion restenosis, as defined by a peak systolic velocity ratio ($PSV_{lesion}/PSV_{reference}$) > 2.4 or occlusion noted by ultrasound for a 90% patency rate. The ankle-brachial index improved from 0.67 ± 0.17 pre-op to 0.88 ± 0.18 at 6 months (P<0.003) and Rutherford classification scores decreased from 3.1 ±. 71 to 0.5 ± .70, p<.001 indicating improved hemodynamic and clinical benefit with DEX.

Update on the DANCE single arm multi-institutional study

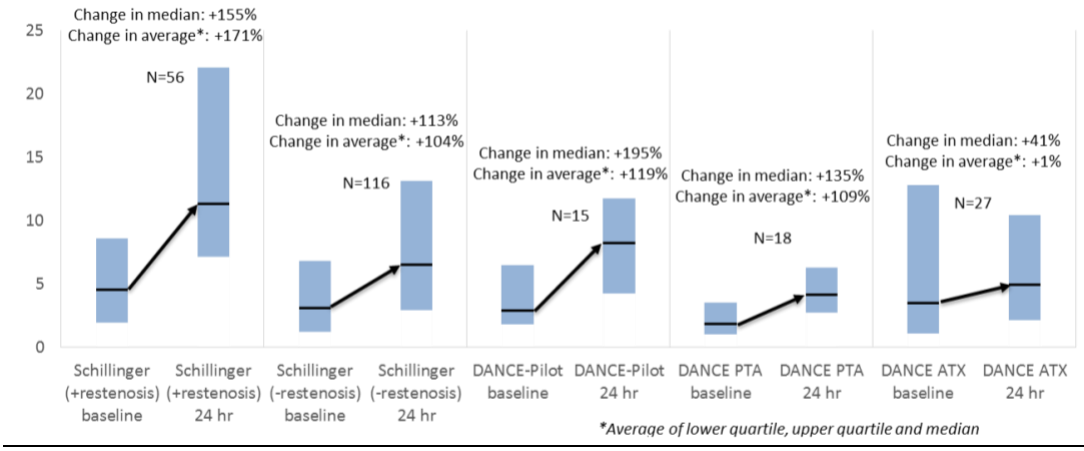

Figure 3. Data from the ongoing DANCE trial. Baseline and 24 hours blood markers of inflammation were built in as a surrogate endpoint. From left to right, Schillinger CRP levels in patients undergoing peripheral artery endovascular treatment, data generated from the DANCE-Pilot, and DANCE PTA and DANCE ATX arms. CRP- C reactive protein, ATX-atherectomy

Markers of technical success using the Micro-Infusion catheter

The Micro-Infusion catheter (Mercator MedSystems, Emeryville, CA), a FDA 510K-cleared device, is a rapid- exchange, wire-guided catheter with a balloon-sheathed 1.5 mm long, 35-gauge (140 µm diameter) needle that delivers infusions to adventitial and perivascular tissues. Using standard angioplasty inflation equipment, the balloon is inflated exposing the needle. When the balloon contacts the arterial wall opposite the needle tip, contact pressure forces the needle through the vessel wall and into the adventitia and perivascular tissues.

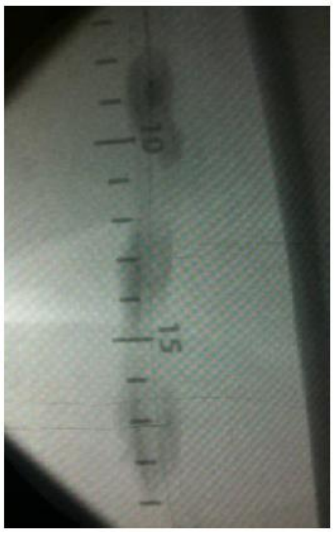

Figure 4. The fluoroscopy picture to the left demonstrates three separate infusions of DEX and contrast along the artery wall. A .014 wire can be seen within the lumen of the artery and the Glow 'N Tell tape provides a reference. After about three minutes, further longitudinal diffusion within the adventitia obscures the border between the separate infusions.

The contact pressure of the balloon against the artery wall is limited to 2 atmospheres by a pressure release valve, which prevents damage to the artery wall. A mixture of infusate and contrast (4:1) is then delivered under fluoroscopic guidance at a rate of 1 ml/min to the adventitia and perivascular tissues. When the infusion is complete, the balloon is deflated, sheathing the needle, and allowing the catheter to be withdrawn. The drug contrast admixture can be seen as "staining" along the blood vessel providing visual confirmation of successful drug delivery, Figure 4 (left). It is our experience that a single injection produces 360° delivery of drug around the circumference of the vessel coverage and extends approximately 1-2 cm proximally and distally from the point of injection. Thus, a single injection circumferentially treats 3-4 cm of artery. This catheter has been shown to be one of the most efficient modes of drug delivery as it maximizes tissue concentration while minimizing off-target drug deliver.[50] The micro-infusion catheter has been used to deliver stem cells into the adventitia of coronary arteries to improve myocardial function following infarction.[51]

Drug Coated Balloon

In this study, angioplasty must be carried out with an FDA-approved DCB balloon catheter for treatment of arteries and veins according to the manufacturer's instructions for use. The INPACT SFA, LEVANT 2, ILLUMENATE PIVOTAL and ILLUMENATE EU trials were paramount Investigational Device Exemption (IDE) safety and effectiveness trials.

The LEVANT 2 study was a prospective, multicenter, single-blind, randomized, safety and efficacy study which randomized in a 2:1 assignment of 316 subjects treated with Lutonix DCB and 160 subjects treated with POBA. Balloon angioplasty had to be successful prior to enrollment. Only 11 patients were excluded due to unsuccessful balloon angioplasty. Physicians evaluating the patients in follow up were blinded to the treatment assignment of the patient. The study population consisted mostly of Rutherford 2 and 3 patients. Freedom from the primary safety endpoint (composite all cause 30 day death, device related death at 365 days, index limb amputation, target vessel revascularization) evaluated graphically by Kaplan-Meier analysis (ITT) was 86.7% in the test DCB arm and 81.5% in the control arm. The primary effectiveness endpoint was freedom from binary restenosis or target lesion revascularization was 73.5% in the DCB text arm and 56.8% in the control arm.

The INPACT SFA study was a multicenter, single-blind, randomized controlled safety and efficacy study with a 2:1 randomization scheme that included 220 subjects treated with INPACT DCB and 111 subjects treated with POBA. Randomization occurred once the lesion was crossed and successful initial balloon angioplasty was performed. It is not known how many subjects were excluded due to unsuccessful balloon angioplasty. Freedom from the primary safety endpoint, freedom from device or procedural related death at 30 days or index limb amputation or target vessel revascularization, occurred in 95.6% in the test DCB group and 76.6% in the control group. Primary patency was 78.4% in the DCB test group and 49.5% in the control group. Although the subject was blinded to the treatment provided, the local research team was not. All primary endpoint events were adjudicated by a core laboratory and Clinical Events Committee, both of whom were blinded to the treatment provided.

The ILLLUMENATE PIVOTAL study was a multicenter, single-blind, randomized controlled safety and efficacy study with a 2:1 randomization scheme that included 200 subjects treated with Stellarex DCB and 100 subjects treated with POBA. Randomization occurred after successful lesion crossing and initial balloon angioplasty with 11 subjects excluded due to unsuccessful initial balloon angioplasty. Although the subject was blinded to the treatment provided, the local research team was not. All primary endpoint events were adjudicated by a core laboratory and Clinical Events Committee, both of whom were blinded to the treatment provided. Freedom from the primary safety endpoint (composite of 30-day freedom from device and procedure-related death and 1 year freedom from target limb major amputation and CD-TLR) was 92.1% in the DCB group and 83.2% in the control group. Freedom from primary effectiveness endpoint (restenosis or CD-TLR at 1 year) was 76.3% in the DCB group and 57.6% in the control group.

All DCBs lose paclitaxel during the delivery and inflation of the balloon. The ILLLUMENATE PIVOTAL trial included a 25 subject pharmacokinetic substudy that found plasma paclitaxel was measurable in all subjects at 24 hours after Stellarex DCB treatment and was no longer detectable in all but 1 subject at 7 days. It appears that the proprietary paclitaxel formulation and excipient combination for each brand of DCB determines the nature of the shed paclitaxel. In a comparison of healthy swine femoral arteries treated with INPACT or Lutonix DCBs, there was measurable paclitaxel in the downstream (non-target) tissues at 90 days, with significantly higher levels measured after INPACT DCB. In addition, embolized “crystalline-like material” was seen in the downstream tissue after treatment with INPACT but not Lutonix DCB.

In December 2018, a meta-analysis of published randomized clinical trials demonstrated a significantly increased late (3-5 year) mortality rate in subjects treated with paclitaxel-coated devices for femoropopliteal peripheral artery disease. In response to this meta-analysis, the FDA has issued 3 letters advising health care practitioners and convened a "public meeting of the Circulatory System Devices Panel of the Medical Devices Advisory Committee" from June 19-20, 2019. An FDA "Letter to Healthcare Providers" from August 9, 2019 summarized the FDA's analysis of available trial data with the conclusion that "the crude mortality rate at 5 years was 19.8% (range 15.9% - 23.4%) in patients treated with paclitaxel-coated devices compared to 12.7% (range 11.2% - 14.0%) in subjects treated with uncoated devices. The relative risk for increased mortality at 5 years was 1.57 (95% confidence interval 1.16 – 2.13), which corresponds to a 57% relative increase in mortality in patients treated with paclitaxel-coated devices. A meta-analysis performed by VIVA (Vascular InterVentional Advances) Physicians of patient-level data provided by manufacturers reported similar findings with a hazard ratio of 1.38 (95% confidence interval 1.06 - 1.80)."

Dynamic Contrast Enhanced-MRI Measurement of Adventitial Inflammation

The tunica adventitia thickness of human peripheral arteries can be visualized with imaging modalities with sub-millimeter spatial resolution. For example, MRI can detect this layer following contrast injection due its ring-like enhancement. We have demonstrated the feasibility of applying dynamic contrast-enhanced MRI (DCE-MRI) with kinetic modeling to study adventitial perfusion, which generates physiological parameters of vasa vasorum.[52] Characterization of microvessel density is pertinent to the present application as adventitial inflammation and restenosis is associated with increased microvessel density necessary to support the increase in wall volume. We have shown in a porcine balloon injury model that microvessels were associated with restenosis.[23] In validation studies in individuals with carotid stenosis, K^{trans} was positively and significantly correlated with plasma CRP, thus providing an in vivo link between vascular wall inflammation and a blood marker of inflammation. Human validation histologic studies were also completed in patients having DCE-MRI scans prior to carotid endarterectomy. These studies demonstrated correlation of K^{trans} and endarterectomy specimen neovasculature (R=0.41, P=.04) and macrophages (R=0.49, P=.01) supplied by vasa vasorum.[53]

DCE-MRI has also been used to provide information on the therapeutic effect of drugs on the vascular wall. In a study evaluating the effects of intensive lipid therapy targeting low density lipoprotein to below 60 mg/dl in subjects with extant cardiovascular disease, there were significant differences in adventitial K^{trans} at 12 months after lipid therapy (0.067 ± 0.028 min^{-1}) compared with baseline (0.085 ± 0.037 min^{-1}, p=.02).

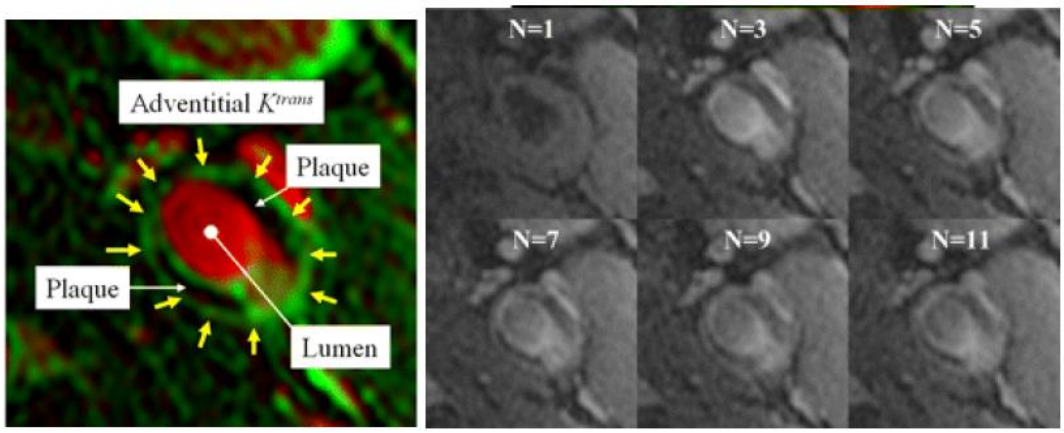

Figure 5. *Left*: Kinetic analysis of dynamic contrast enhanced MRI of carotid atherosclerosis yields a parametric image "vasa vasorum" displaying the value of fractional blood volume (v_p) in red and transfer constant (K^{trans}) in green. The rapid transfer in the vessel adventitia is indicated using yellow arrows. *Right:* Image is derived from kinetic modeling of changing intensity in serial images coinciding with contrast agent.

Computational Fluid Dynamics

Balloon angioplasty induces barotrauma (8-16 atmospheres) to the artery to redistribute the arterial wall mass, expand the arterial volume, with the goal to increase the lumen volume of the treated segment. This results in luminal irregularities, dissections, and residual stenosis within the artery. We propose that the resulting flow disturbances and shear stress gradients predispose to areas of restenosis due to increased wall thickening or negative remodeling. Surprisingly, there has been relatively little attention given to serial changes in blood flow and shear stress following angioplasty in the leg. CFD methodologies developed by our group are

pertinent to the present application.[54-56] To examine the relationship between arteriovenous fistula remodeling and flow parameters, we have conducted serial CFD-derived flow analysis that was carried out at three time points: 5 days, 30 days, and 90 days following creation of the anastomosis. Non-contrast enhanced time-of-flight (TOF) magnetic resonance angiogram (MRA) datasets were used to acquire patient-specific geometries at each time point. Phase contrast magnetic resonance velocimetry (PC-MRV) measurements were obtained at each imaging session and used to prescribe time- dependent velocity boundary conditions for the computational models. CFD simulations were carried out using the methodology described below. Velocity fields and wall shear stress (WSS) distributions obtained at each time point were then compared. The computational results in Figure 5 show that the size of the vessels increased and the WSS values substantially reduced with the maturation of the fistula.

Plaque compositional analysis and arterial remodeling assessment with MRI

It is unlikely that one specific type of therapy will be suited for every SFA plaque type. For example, Derksen et al. determined that femoral plaques with more fibrous tissue had higher rates of restenosis. Therefore, knowledge of plaque composition and adventitial perfusion by MRI may help guide the type of therapy. MRI has been shown to provide an accurate virtual histological map of vascular plaques in femoral and carotid arteries based on pixel signal intensity (see section below) using multicontrast MRI.[57,58] In prior studies, we have matched carotid endarterectomy histology sections via landmarks to MRI images obtained in vivo prior to surgery to ascertain the sensitivity and specificity of MRI tissue characterization.[59,60] For plaques > 2 mm^2, in vivo assessment of plaque composition can be accomplished with high sensitivity (79% to 95%) and moderate to high specificity (76% to 91%).[61] We have also examined the inter- and intra- reader reproducibility for detecting tissue areas with respect to total vessel area. The interclass correlation coefficient (ICC) for lipid rich necrotic core (LRNC), calcification, and fibrous tissue was between .88 and .95.[62,63] In this application, we will characterize SFA plaque composition and associate each with response to DEX or PTX (control) treatment.

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2 STUDY RATIONALE

The fundamental hypothesis of this trial is that inhibition of inflammation at the site of injury will result in improved vascular healing and a sustained patent artery.

This trial is designed to explore the mechanism of restenosis by using two alternative approaches to drug delivery, intimal-based antiproliferative (paclitaxel) and adventitial-based anti-inflammatory (Dexamethasone). Safety concerns about paclitaxel have halted that treatment arm in favor of plain balloon angioplasty. Angioplasty creates a mechanical injury to the atherosclerotic vascular wall resulting in an inflammatory response as a multitude of growth factors and cytokines, catalysts for cellular proliferation and restenosis, are released. Subsequent restenosis is related to the magnitude of the inflammatory response which is more pronounced in the femoral artery than in other vascular beds. Clinical trials of therapies to suppress vascular inflammation were initially successful, but were not fully developed in favor of anti-proliferative drugs, which have been highly successful in the coronary arteries, but not in leg arteries. Hence, the hypothesis that inhibition of vascular inflammation at the time of treatment can improve outcomes remains to be tested. Information on the healing response of the vessel wall following treatment is limited. Duplex ultrasound and quantitative angiography are sensitive to changes in the vessel lumen but provide no information on the vessel wall or remodeling. Recent advances in magnetic resonance imaging (MRI) with black-blood and multi-contrast imaging techniques now offer a non-invasive means to evaluate the geometric and compositional morphology of the vessel wall at sub-millimeter resolution. Further insights into the vascular wall can be obtained with dynamic-contrast imaging techniques, which is capable of providing information on vessel wall perfusion arising from adventitial vasa vasorum. Thus, modern MRI affords deep structural and physiological insights into the vasculature and is ideally suited for serial in vivo studies to monitor the biologic response to therapy.

2.1 Risk / Benefit Assessment

2.1.1 Anticipated Clinical Benefits

In this trial, balloon angioplasty of the superficial femoral or popliteal artery will be followed with either:

1. an adventitial infusion of dexamethasone sodium phosphate (USB, 4mg/mL)

   or

2. no further treatment.

There are no guaranteed benefits for subjects participating in the trial.

2.1.2 Anticipated Adverse Events to balloon angioplasty of the SFA

- Additional intervention
- Allergic reaction to drugs or contrast

- Aneurysm or pseudoaneurysm
- Arrhythmias
- Embolization
- Hematoma
- Hemorrhage including at the puncture site
- Hypotension/hypertension
- Inflammation
- Occlusion
- Pain or tenderness
- Pneumothorax or hemothorax
- Sepsis/infection
- Shock
- Stroke
- Thrombosis
- Vessel dissection, perforation, or rupture

2.1.3 Possible Risks of Participation in this Clinical Trial

2.1.3.1 Procedural Risks of Adventitial Infusion

Likely: (likelihood >5%)

- Irritation or extravasation of blood at the perivascular injection site – typically mild and self-limited. Less damage than balloon angioplasty or atherectomy.
- Perivascular air injection – due to incorrect preparation of catheter for injection; harmless, involves a volume of <1.5mL and is typically self-limited (air is reabsorbed).
- Device balloon rupture – due to incorrect preparation of the device balloon; low frequency event in prior device use and testing as there is a pressure relief valve to prevent over-inflation of the device balloon; there are no adverse effects due to simple balloon rupture (device is discarded after removal from the patient).

Rare: (likelihood <1%)

- Vessel spasm – due to incorrect catheter sizing for target vessel; usually self-limited, but may require further treatment (balloon angioplasty) if severe.
- Vessel dissection – due to incorrect catheter sizing for target vessel, excessive vessel wall thickness or mis-administration of medication; may require further treatment (balloon angioplasty or stent) if severe.
- Vessel thrombosis – due to incorrect catheter sizing for target vessel or prolonged inflation of catheter balloon; may require further treatment (balloon angioplasty, stent, embolectomy, thrombolysis) if severe.
- Distal emboli – due to incorrect catheter sizing for target vessel or disruption of vessel wall plaque; may require further treatment (embolectomy, thrombolysis) if severe.

Extremely Rare: (likelihood <0.1%)

- Arteriovenous fistula – complication of perivascular injection; extremely rare given needle length and diameter; may require further treatment (stent) if severe.
- Pseudoaneurysm – bleeding complication at site of perivascular injection, extremely rare given needle length and diameter; may require further treatment if severe.
- Device balloon fragmentation with emboli – device failure, extremely rare event in prior device use and testing as there is a pressure relief valve to prevent over-inflation of the device balloon; may require further treatment (embolectomy, thrombolysis) if severe.
- Device component separation - due to incorrect use of the device or manufacturing failure; rare event in prior device use testing as there is a pressure relief valve to prevent over-inflation of the device balloon; may require further treatment (embolectomy) if components embolize.

2.1.3.2 Risks of Dexamethasone

The Contraindications, Warnings, Precautions, Adverse Reactions and Overdosage sections of the Dexamethasone Sodium Phosphate Injection, USP, package insert should be consulted prior to administration of the drug.

We plan to administer a single dose of dexamethasone in the perivascular space. Therefore, we expect the risk of systemic adverse effects typically associated with repeated, long-term, supra-physiologic doses of dexamethasone will be very low. This expectation is based on the following data:

1. Delivery of dexamethasone (DEX) will be localized to the perivascular tissues. Thus we expect the pharmacokinetics to be similar to the local administration of dexamethasone in soft tissue. A study comparing adventitial drug delivery of DEX vs. a drug-infusion balloon vs. intravenous administration of DEX in swine coronary arteries found that adventitial delivery was the only method with a high-concentration of study drug in the target tissue (myocardium) and negligible levels in liver, lungs, blood or urine [50].
2. Each infusion of dexamethasone in the range of 2 to 7.5 mL (1.6 mg dexamethasone per 1 cm of target artery, with a total dose of 6.4 to 24 mg for expected treated segment lengths of approximately 4-15 cm) is within the common dose range of dexamethasone for adults per the manufacturer's dosing instructions.

Likely: (likelihood >5%)

- None

Less Likely: (likelihood <5%)

- Hyperglycemia, particularly in patients with diabetes - effect is likely transient (<24hrs), possible need for increased insulin or oral hypoglycemic agents.

Rare: (likelihood <1%)

- Hypertension - likely transient, possible need for increased antihypertensive therapy.

Extremely Rare: (likelihood <0.1%)

- Allergic reaction - typically in response to preservatives in the medication. Can range from allergic dermatitis to severe, life-threatening anaphylactic reactions supportive care and monitoring. Dexamethasone will be administered in the OR with the patient under observation by both the surgeon and anesthesiologist.

- Vessel wall necrosis - multiple studies with dexamethasone eluting stents in lab animals and humans have not found evidence of vessel wall necrosis (see background studies) but this is a theoretical risk that would require further intervention (stenting) to treat.
- Fluid and electrolyte disturbances: sodium retention, fluid retention, congestive heart failure in susceptible patients, potassium loss, hypokalemic alkalosis, or hypertension.
- Musculoskeletal: muscle weakness, steroid myopathy, loss of muscle mass, osteoporosis, vertebral compression fractures, aseptic necrosis of femoral and humeral heads, pathologic fracture of long bones, or tendon rupture.
- Gastrointestinal: peptic ulcer with possible subsequent perforation and hemorrhage, perforation of the small and large bowel, particularly in patients with inflammatory bowel disease, pancreatitis, abdominal distention, or ulcerative esophagitis.
- Dermatologic: impaired wound healing, thin fragile skin, petechiae and ecchymosis, erythema, increased sweating, may suppress reactions to skin tests, burning or tingling, especially in the perineal area (after I.V. injection), or other cutaneous reactions, such as allergic dermatitis, urticaria, angioneurotic edema.
- Neurologic: convulsions, increased intracranial pressure with papilledema (pseudotumor cerebri) usually after treatment, vertigo, headache, or psychic disturbances.
- Endocrine: menstrual irregularities, development of cushingoid state, suppression of growth in children, secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery, or illness, decreased carbohydrate tolerance, manifestations of latent diabetes mellitus, increased requirements for insulin or oral hypoglycemic agents in diabetics, or hirsutism.
- Ophthalmic: posterior subcapsular cataracts, increased intraocular pressure, glaucoma, or exophthalmos.
- Metabolic: negative nitrogen balance due to protein catabolism.
- Cardiovascular, myocardial rupture following recent myocardial infarction (see WARNINGS in drug labeling).
- Other: anaphylactoid or hypersensitivity reactions, thromboembolism, weight gain, increased appetite, nausea, malaise, or hiccups.
- The following additional adverse reactions are related to parenteral corticosteroid therapy: rare instances of blindness associated with intralesional therapy around the face and head, hyperpigmentation or hypopigmentation, subcutaneous and cutaneous atrophy, sterile abscess, infection, postinjection flare (following intra-articular use), or charcot-like arthropathy

2.1.3.3 Risks of Paclitaxel

Paclitaxel is the active agent on FDA approved DCBs. Paclitaxel inhibits smooth muscle cell (SMC) and fibroblast proliferation, migration, and matrix synthesis by modulating microtubule polymerization (stabilizes). Because SMCs and fibroblasts are the primary cellular components of the neointimal hyperplastic response, they are thought to be the mechanism by which paclitaxel improves the patency of arteries. Other agents that are known as excipients are carried on the balloon to allow the paclitaxel to be delivered to the target artery and then to partition into the artery when the balloon contacts the arterial wall. INPACT Admiral DCB uses

urea as the excipient, the Lutonix 035 DCB uses sorbitol and polysorbate and the Stellarex uses polyethylene glycol, a polymer excipient. Urea is a natural occurring product of protein metabolism and carried in the blood stream as blood urea nitrogen. The urea released from a DCB is about 20,000 fold lower than what is normally produced in the body. Both sorbitol and polysorbate are FDA approved and regulated and are ubiquitous in many household products such as toothpaste, cough syrup, hard candy, diabetic sweeteners (sorbitol), and shampoo, lubricants, cosmetics (polysorbate). Similarly, polyethylene glycol is used in household products like creams, lubricants, toothpaste, gum and has several industrial and biologic uses as well. The combination of [paclitaxel + urea], [paclitaxel + sorbitol and polysorbate] and [crystalline paclitaxel + polyethylene glycol] are known as the matrix on the balloon surface.

The pharmacokinetics of paclitaxel release following treatment with a balloon catheter has been studied. The time to maximal plasma concentration following DCB inflation is about 10 minutes and the Cmax is less than 8 ng/ml in each balloon. Typical infusions of paclitaxel for cancer treatment are 135 – 175 mg/m^2, yielding a C_{max} that is 2170-3650 ng/ml. Hence maximal plasma levels of paclitaxel are over 200-fold less than typical levels used to treat cancer. Plasma levels fall to less than 3 ng/ml within one hour's time. The pharmacokinetics of paclitaxel demonstrated a bi-exponential decay characterized by a rapid redistribution and then and log-linear elimination phase. The half-life is 72 hours. The metabolism of paclitaxel is catalyzed by cytochrome P450 enzymes CYP2C8 and CYP3A4 as well as being a substrate for P-glycoprotein. No formal drug-drug interactions studies have been performed but drugs metabolized by the same enzymes may interfere with paclitaxel metabolism.

Concerns about the safety of paclitaxel (PTX) coated devices have led to recommendations by the FDA that "for many patients, alternative treatment options for paclitaxel-coated balloons and paclitaxel-eluting stents provide a more favorable benefit-risk profile." Subjects are no longer treated with paclitaxel DCBs. In this study, those subjects already treated with PTX will be monitored for adverse events.

Potential adverse events

Likely: (likelihood >5%)

- None

Less Likely: (likelihood <5%)

- increased risk of death

Rare: (likelihood <1%)

- none

Extremely Rare: (likelihood <0.1%)

- Hypersensitivity reaction to paclitaxel manifested as a cutaneous rash
- Emboli of the matrix INPACT balloon
- Peripheral neuropathy

2.1.3.4 Risks of MRI and Gadolidium Contrast Agent

Gadolinium reactions may occur but they are extremely rare. The incidence of adverse reactions ranges from 1-1.4% and may consist of nausea and vomiting to anaphylaxis. Life-threatening reactions to gadolinium are extremely rare. Mild reactions are also rare and usually self-limited. In patients who have compromised kidney function, the use of gadolinium agents has also been associated with a rare but serious condition, called Nephrogenic Systemic

Fibrosis (NSF). Kidney function is measured by a value termed eGFR (estimated Glomerular Filtration Rate) in units of ml/min/1.73m^2. There have been no reported cases of NSF in individuals with eGFR > 60 ml/min/1.73m^2. Following the guidelines of the MR Safety Committee at UCSF/SFVAMC and UW, we will measure creatinine levels and determine the eGFR in all patients in this study as part of their preoperative assessment. If eGFR is < 30 ml/min/1.73m^2 then subjects are excluded from participation in this research study. If eGFR is < 60 ml/min/1.73m^2 but > 30 ml/min/1.73m^2 the minimal dose of gadolinium necessary will be used after consultation with a radiologist.

The FDA is investigating the risk of brain deposits following the repeated use of gadolinium based contrast agents (GBCAs) for MRI. Recent publications in the medical literature have reported that deposits of GBCAs remain in the brains of some patients who undergo four or more contrast MRI scans, long after the last administration. It is unknown whether these gadolinium deposits are harmful or can lead to adverse health effects. These effects have only been seen in the linear chelates of Gd. For this reasons, the protocol will avoid the use of linear chelates.

The additional risk of magnetic resonance imaging (MRI) requires that the subject be placed in a small and confined space for periods of time, and this can lead to claustrophobia in some patients. Electric implants, such as cardiac pacemakers, may be susceptible to interference from the magnet and RF fields produced by the MR instrument. Persons with cardiac pacemakers or other implanted electronic devices are prohibited from entering a zone where the magnetic field exceeds five gauss. The magnetic field of the MR instrument is strong enough to forcefully attract ferromagnetic objects. The inadvertent introduction of ferromagnetic materials in the proximity to the magnet may result in such objects becoming projectiles, which could present a risk to subjects and other persons. This force can cause a ferromagnetic implant, such as an aneurysm clip, surgical clip, or prosthesis, to move or be dislodged. Entry to the magnet area is possible only through a single door beside the operator's console, which is guarded by the technologist during the study. A technologist screens all persons before they enter the magnet area. In addition, warning signs are posted.

The Bureau of Radiologic Health has issued guidelines for the amount of radiofrequency energy which may be employed in imaging subjects in order to ensure that the procedure does not entail more than minimal risk. If energy beyond this value is used, some subjects may undergo an evaluation in body temperature. If energy which grossly exceeds this guideline is used, the subject may receive soft tissue burns. Both the Siemens and the GE MR System includes both software and hardware limits, which prevent selection of imaging sequences from exceeding the energy deposition guidelines of the Bureau of Radiologic Health. All studies will be conducted below this energy limit.

2.1.3.5 Other Risks

The following study activities involve only minimal risk to participants:

- **Blood Draw** - Phlebotomy involved in this study poses minimal risk to the subject; however, bruising may be expected around the venipuncture site. Occasional, dizziness and vasovagal episodes occur.
- **Ankle Brachial Index (ABI)** - May involve minor discomfort similar to a standard brachial blood pressure measurement.

3 STUDY OBJECTIVES

3.1 Primary Objective

The primary objective is to assess the mechanisms of vascular healing following balloon angioplasty treatment to stenotic arteries from atherosclerosis. Vascular healing will be assessed by MRI determined percent wall volume change (PWV) from 24 hours post-angioplasty to 12 months

3.2 Secondary Objectives

Secondary objectives include:

1. To determine whether DEX infusion will result in less inflammation as measured by blood (MCP-1, CRP, and IL-1β) and tissue imaging (K^{trans}) markers of inflammation
2. To determine whether patient-specific physiological factors correlate with vascular healing

4 STUDY DESIGN

4.1 Study Overview

This is a prospective, multicenter, randomized trial to determine the mechanisms of vascular healing. The study will evaluate subjects with peripheral artery disease (PAD) who require an endovascular intervention of the femoropopliteal arterial segment (SFA/Popliteal) to restore blood flow to the leg.

The total duration of subject participation will be 36 months. Total duration of the study is expected to be five years.

4.2 Specific Aims

1. **To determine whether adventitial DEX infusion will result in improved vascular healing following femoral artery angioplasty**, with the following Statistical Hypotheses:
    a. Adventitial DEX infusion will result in reduced change in percent wall volume (ΔPWV) within the treated segment.
    b. Adventitial DEX infusion will result in improved vascular remodeling of the treated segment.
2. **To determine whether DEX infusion will result in less inflammation** as measured by blood (MCP-1, CRP, and IL-1β) and imaging (K^{trans}) markers of inflammation, with the following Statistical Hypotheses:
    a. Adventitial DEX infusion will result in reduced peri-operative inflammatory profile.
    b. Adventitial DEX infusion will result in less adventitial perfusion (a surrogate of inflammation) as measured by kinetic modeling of dynamic contrast-enhanced MRI.
    c. Peri-operative inflammatory profile will be associated with ΔPWV.
3. **To determine whether patient-specific physiological factors correlate with vascular healing**, with the following Statistical Hypotheses:
    a. Treated segment remodeling will be associated with the fibrous volume in plaques.

b. Treated segment remodeling will be associated with wall shear stress provided by MRI determined, patient-specific, geometry and computational fluid dynamics.

5 STUDY ENDPOINTS

5.1 Primary Endpoint

The primary endpoint for this study will be PWV change of the treated segment from the 24 hour post- intervention MRI scan to 12 months between DEX treated and non-DEX (PTX or POBA) treated patients.

The treated segment is defined as the length of vessel, encompassing the index lesion, that has undergone successful revascularization, from normal back to normal artery.

5.2 Secondary Endpoints

Secondary endpoints include:

1. Change in wall volume (WV) without a change in total vessel volume (TVV) at 12 months
2. Change in perioperative inflammatory profile (MCP-1, CRP, IL-1β) at 12 months
3. Change in K^{trans} from 1 month to 6 months
4. Change in lumen volume (LV) relative to total vessel volume (TVV) at 12 month
5. Change in subject study status based on subjects receiving reintervention on < 75% or $\geq$ 75% of treated segment.

5.3 Safety Endpoints

The incidence of adverse events will be the primary metric for the evaluation of safety. A Data Safety Monitoring Committee will meet on a regular, semi-annual basis to review the trial and address all safety issues (See Sec. 15 Data Safety Monitoring)

5.4 Completion Endpoints

Subject Status & Study Completion:

For subject to complete their participation in this study they must:

1. Undergo follow-up for 36-month period after index procedure, completing all assessments in the Schedule of Assessments.

2. Subject develops restenosis after the 1-month study follow-up, requiring reintervention of $\geq$ 75% of treated segment.

If subject does not complete the study following the above indications, please see section 13.1 for specifics on Early Discontinuation/Withdrawals.

If subject develops restenosis after the 1-month study follow-up, requiring reintervention of <75% of the treated segment, please see section 11.10 for specifics on recording Unplanned Visits for Index Leg Reintervention and continuing follow-up.

6 SUBJECT SELECTION

6.1 Study Population

Subjects with a diagnosis of peripheral artery disease who require an endovascular intervention of the femoropopliteal arterial segment (SFA/Popliteal) to restore blood flow to the leg may be eligible for the study. Screening criteria will be used to identify subjects eligible for enrollment. Final eligibility and randomization will occur intra-operatively following adjudication of Procedural Inclusion/Exclusion criteria.

6.2 Inclusion Criteria

Screening Inclusion Criteria:

1. Male or non-pregnant female ≥ 35 years of age
2. Atherosclerotic, infrainguinal PAD
3. Rutherford Clinical Category 2-6
4. Stenosis detected by radiology that in the clinician's opinion is the reason for the PAD symptom
5. Patient is willing to provide informed consent and comply with the required follow up visits, testing schedule, and medication regimen
6. eGFR ≥ 30 or threshold established by the radiology safety committee of study site

Procedural Inclusion Criteria:

1. De novo atherosclerotic lesion qualifying for angioplasty
2. A patent artery proximal to the index lesion. Concomitant inflow procedures, including open femoral artery endarterectomy or stenting of the iliac arteries, are permissible.
3. >50% diameter stenosis of the superficial femoral artery and/or popliteal artery (between the profunda and tibioperoneal trunk)
4. Reference vessel diameter ≥3 mm and ≤ 8mm
5. Successful wire crossing of lesion
6. Successful angioplasty of the index lesion or part of the index lesion, defined as ≤30% residual lumen stenosis compared with adjacent non-diseased lumen diameter, without flow-limiting dissection

6.3 Exclusion Criteria

Screening Exclusion Criteria:

1. Any contraindication to receiving an MRI
2. Pregnant, nursing, or planning on becoming pregnant in < 2yrs
3. Life expectancy of <1 yr
4. History of solid organ transplantation
5. Patient actively participating in another investigational device or drug study
6. History of hemorrhagic stroke within 3 months of index procedure

7. Previous or planned surgical or interventional procedure within 30 days of index procedure
8. Chronic renal insufficiency of eGFR < 30
9. Prior bypass surgery, stenting, atherectomy or angioplasty of the index lesion
10. Inability to take required study medications
11. Contra-indication or known hypersensitivity to dexamethasone sodium phosphate, contrast media, gadolinium, aspirin or Plavix
12. Systemic fungal infection
13. Acute limb ischemia
14. Prior participation of the index limb in the current study (contralateral treatment is allowed)
15. Patient is being treated with long-term steroids (not including treatment of a bronchial condition with inhaled steroids)

Procedural Exclusion Criteria:

1. Index lesions extending into the tibial trifurcation or above the profunda. Note: the outflow tibial artery can be treated concomitantly. Similarly, the common femoral artery can be treated concomitantly, either with open endarterectomy and patch angioplasty or with endovascular methods. However, the index lesion cannot be contiguous with either the CFA or the tibial trifurcation.
2. Circumferential calcification at index lesion, which in the judgment of the investigator would prevent penetration of the Micro-Infusion catheter needle through the vessel wall
3. Inadequate distal outflow defined as no patent tibial arteries (>50% stenosis). The outflow vessel can be established at the time of primary treatment
4. Use of adjunctive therapies other than angioplasty. Chocolate balloons and/or scoring balloons are allowed, if used below reference diameter.

7 CONCURRENT MEDICATIONS

All subjects should be maintained on the same medications throughout the entire study period, as medically feasible, with no introduction of new chronic therapies.

7.1 Allowed Medications and Treatments

Standard therapies for pre-existing or emergent conditions are allowed except for treatments noted in the exclusion criteria described above.

8 STUDY TREATMENTS

8.1 Method of Assigning Subjects to Treatment Groups

Upon confirming eligibility, and after consultation with treating physicians, patients will be assigned to a treatment group (DEX infusion or POBA) using a block randomization scheme. A unique set of blocks will be created for each site.

8.2 Formulation of Treatment

This trial uses FDA approved drugs and devices and therefore there is no test product. This trial will use commercially available dexamethasone sodium phosphate USP and iodixanol contrast medium (320 mg I/ml). A copy of the dexamethasone sodium phosphate USP label is included as Appendix 4. The trial also uses a Micro-Infusion catheter, used in accordance with the IFU.

8.2.1 Packaging and Labeling

DEX is widely available throughout the hospital and carried in the hospital formulary. It is available in all anesthesia carts and is commonly used intravenously to treat allergic reactions during surgery.

8.3 Supply of DEX at the Site

Each site is responsible for obtaining DEX and maintaining inventory.

8.3.1 Dosage/Dosage Regimen

This protocol will utilize a 4 mg/ml preparation of Dexamethasone Sodium Phosphate Injection, USP. Each milliliter of the solution contains 4.37 mg of dexamethasone sodium phosphate equivalent to 4 mg of dexamethasone phosphate or 3.33 mg of dexamethasone. The Dexamethasone Sodium Phosphate Injection, USP will be mixed 80%:20% with iodinated contrast medium (iodixanol, 320 mg I/mL) to diagnose the distribution of injectate. This will result in a final concentration of 3.2 mg dexamethasone phosphate (3.5 mg dexamethasone sodium phosphate, or 2.67 mg dexamethasone) and 60-74 mg iodine in each mL of solution.

The dosage proposed for this clinical trial is 1.6 mg of Dexamethasone Sodium Phosphate per cm of lesion. The typical length of lesions range from 4 -15 cm in length so each infusion will range from 2 to 7.5 ml for a total one-time perivascular dosage in each patient of 6.4 to 24 mg. Multiple infusions are possible and thus allowance of up to 20% loss due to variability in anatomy, distribution pattern, or intravascular diagnostics. The 4 mg/ml dexamethasone solution will be diluted to 3.2 mg/ml with contrast medium to track infusions. Based on the distribution seen with similar infusions, each 0.5 mL of infusion would be intended to treat 1.0 cm of vessel segment, with multiple doses as needed to treat longer diseased regions.

8.3.2 Dispensing

This study is an open label study. The primary operator performing the angioplasty is not blinded to the treatment assignment of the patient. Therefore, DEX may be obtained from the clinical pharmacy. DEX will be diluted with contrast under sterile conditions in the OR and delivered to the tissue using the Bullfrog Micro-Infusion catheter device.

8.3.3 Administration Instructions

DEX, which will be mixed with contrast in the operating or the catheterization room, will be labelled with name, concentration, and date, in accordance with standard operating procedures per institutional policy.

8.3.4 Storage

DEX will be stored in accordance with the manufacturer's label or IFU. The expiration date will be noted prior to use and any expired drug or device will be discarded and will not be used in this study.

8.4 DEX Accountability

An accurate and current accounting of the dispensing of DEX for each subject will be maintained by study staff.

8.5 Supply of Devices at the Site

The intent of this trial is to study the mechanisms of angioplasty failure. Therefore, there are no investigational devices used in the trial. All devices and drugs used in the study are FDA approved and are being used as indicated. The site is responsible for buying angioplasty balloons and equipment including adventitial infusion catheters.

9 STUDY PROCEDURES AND GUIDELINES

A Schedule of Events representing the required testing procedures to be performed for the duration of the study is diagrammed in Section 10 “Schedule of Assessments”.

Prior to conducting any study-related activities, written informed consent and the Health Insurance Portability and Accountability Act (HIPAA) authorization must be signed and dated by the subject. If appropriate, assent must also be obtained prior to conducting any study-related activities.

9.1 Clinical Assessments

9.1.1 Pregnancy Test

Female subjects of childbearing potential will receive a serum βHCG pregnancy test. Only women who are surgically sterile or postmenopausal may be considered to not be of childbearing potential and thus are exempt from this test.

Postmenopausal is further defined:

1. If the woman is over 50 years of age and has experienced no menstruation for 12 consecutive months, she is “postmenopausal”.
2. If the woman is under 50 years of age, has experienced no menstruation for 12 consecutive months, and provides verification by an endocrinologist or gynecologist, then she is “postmenopausal”.

Assessment will occur at: Screening.

9.1.2 Demographics

Demographic information (date of birth, gender, race) will be recorded.

Assessment will occur at: Baseline.

9.1.3 Medical History

Relevant medical history, including history of current disease, other pertinent cardiovascular history, and information regarding underlying diseases will be recorded.

Assessment will occur at: Baseline.

9.1.4 Concomitant Medications

All concomitant medication and concurrent therapies will be recorded during the study visits described below and at early termination when applicable. Dosage, units, route, frequency of administration, and dates of medication will be captured.

Assessments will occur at: Baseline, Post-Op, Month 1, Month 6, and Month 12.

9.1.5 Vital Signs

Body temperature, blood pressure, pulse and respirations will be recorded as part of their standard clinical care. Results from these exams will be recorded by study staff.

Assessments will occur at: Baseline, Post-Op, Month 1, Month 6, and Month 12.

9.1.6 Physical Examination

An appropriate physical examination will be performed by qualified clinical staff (MD, NP, PA, RN or trained research assistant) as part of their standard clinical care. Results from these exams will be recorded by study staff.

Assessments will occur at: Baseline, Post-Op, Month 1, Month 6, and Month 12.

9.1.7 Vascular Examination

A complete vascular pulse examination, Ankle-Brachial Index (ABI), and Rutherford Categorization will be performed by qualified clinical staff (MD, NP, RN, or PA) or research staff under the supervision of a study investigator. Results of the exam will be recorded by study staff.

The Ankle-Brachial Index (ABI) examination will be performed according to current, accepted guidelines. Subjects will rest 10 minutes in a supine position prior to the exam. The ABI will be defined as the ratio between the higher of the two pedal systolic blood pressures (dorsalis pedis and posterior tibialis) and the higher of the two systolic brachial pressures. A continuous wave Doppler, between 5 and 12 MHz, will be used to measure the systolic pressures in both the dorsalis pedis and posterior tibial arteries in each leg, as well as the brachial arteries in each arm. The ABI will be calculated for both legs. In the event the pedal / tibial vessels are noncompressible, a toe brachial index may be used.

Rutherford Categories will be defined by patient-reported pain-free walking distance. Table 1 related Rutherford Categories to objective criteria and to common patient-reported distances.

Table 1. Rutherford Categories

Category	Clinical description	Objective criteria
0	Asymptomatic—no hemodynamically significant occlusive disease	Normal treadmill or reactive hyperemia test
1	Mild claudication	Completes treadmill exercise†; AP after exercise >50 mm Hg but at least 20 mm Hg lower than resting value
2	Moderate claudication	Between categories 1 and 3
3	Severe claudication	Cannot complete standard treadmill exercise† and AP after exercise <50 mm Hg
4	Ischemic rest pain	Resting AP <40 mm Hg, flat or barely pulsatile ankle or metatarsal PVR; TP <30 mm Hg
5	Minor tissue loss—nonhealing ulcer, focal gangrene with diffuse pedal ischemia	Resting AP <60 mm Hg, ankle or metatarsal PVR flat or barely pulsatile; TP <40 mm Hg
6	Major tissue loss—extending above TM level, functional foot no longer salvageable	Same as category 5

*Grades II and II, categories 4, 5, and 6 are embraced by the term chronic critical ischemia.

†Five minutes at 2 mph on a 12% incline.

Assessments will occur at: Baseline, Post-Op, Month 1, Month 6, and Month 12.

Telephone assessment of changes in medical history (medications, cardiovascular events, hospitalizations, etc.) will occur at 24 and 36 months.

9.2 Laboratory Measurements

9.2.1 Research Laboratory Measurements

Research laboratory assessments include:

1. Serum C-Reactive Protein (CRP)
2. Monocyte Chemotactic Protein 1 (MCP-1)
3. Interleukin-1 Beta (IL-1β).

A complete description of the collection requirements are outlined in Appendix 2. Briefly, a 20 ml sample will be obtained (1x10 ml EDTA and 1x10 ml SST tubes). The samples will be centrifuged, aliquoted, and stored at -80°C.

Assessment will occur at: Baseline, Post-Operative Day #1, Month 1, and Month 12.

9.2.2 Clinical Laboratory Measurements

Clinical labs performed as part of routine clinical care will be extracted from the subject's chart by study staff.

Assessment of clinical labs for baseline will occur within 30 days prior to the index procedure (Day 0)

Analyses recorded at baseline include:

1. Serum chemistry
2. Complete blood count (hemoglobin, hematocrit, white blood cell count, white blood cell differential, and platelet count)
3. Lipid panel
4. Coagulation studies.

Following a successful index procedure at Day 0, only eGFR will be collected for clinical labs.

Assessments of eGFR will occur at: POD Day #1, Month 1, Month 6, and Month 12.

9.3 Adverse Events

Information regarding occurrence of adverse events will be captured throughout the study. Duration (start and stop dates), severity/grade, outcome, treatment and relation to the index procedure will be recorded on the case report form (CRF).

9.4 Walking Impairment Questionnaire

The Walking Impairment Questionnaire may be administered by study staff or self-administered by the subject.

Please refer to Appendix 8. Walking Impairment Questionnaire for more details

Assessments will occur at: Baseline, Month 1, Month 6, and Month 12.

9.5 Treated Segment Registration

During the index procedure, the investigator will identify an “index lesion”, which is a segment of the SFA and/or popliteal artery that meets the procedural inclusion/exclusion criteria (see Section 6). The index lesion will fall within the following constraints:

1. The index lesion will be between the femoral bifurcation and the infrapopliteal trifurcation (specifically, the take-off of the anterior tibial artery).
2. If the femoropopliteal arterial segment has diffuse disease, there must be at least 2 cm of “normal” vessel proximal and distal to the index lesion. A “normal” vessel is defined as having < 20% stenosis.
3. If a subject has multiple lesions that meet the procedural inclusion/exclusion criteria, the investigator may choose any qualified lesion as the index lesion.

A Glow ‘N Tell radiopaque tape (LaMaitre Vascular, Burlingame MA) will be placed at the subject’s medial tibial spine as the “0 cm” mark, topographically overlying the knee cap and the numbers increase proximally. The lesion length, location, and degree of stenosis/occlusion will be documented.

Following a successful revascularization, the treated segment will be registered to the nearest millimeter on the tape, including 5 mm proximal and 5 mm distal to the actual treated lesion.

9.6 Randomization

An opaque envelope scheme will be used to reveal the allocation intra-operatively. Prior to the procedure, study staff will identify the next sequential Randomization ID and bring this envelope to the OR. Once Procedural Criteria have been assessed and the subject passes, study staff will record the Randomization ID on procedural CRFs, open the envelope, and reveal the assignment (DEX vs POBA).

A full description of the Randomization process is given in Sec. 16.4 “Sample Size & Randomization”.

9.7 DEX Infusion

Patients randomized to the DEX group will receive dexamethasone infusion after the primary revascularization procedure and before any provisional stenting. The equipment, order of operations, and dosing instructions are described below.

9.7.1 Equipment

A micro-infusion catheter (Mercator Cricket, Bullfrog, or Bullfrog XL) will be used to deliver FDA-approved Dexamethasone Sodium Phosphate Injection, USP, 4 mg/ml, mixed with FDA-approved non-ionic contrast medium to the index lesion

9.8 Order of Operations

Research procedures will be performed in between steps of a clinical procedure. In general, the order of operations is as follows:

1. Establish vascular access
2. Initial angiogram
3. Place Glow ‘N Tell tape
4. Index lesion registration with respect to knee joint

5. Primary revascularization
6. Assessment of Procedural Inclusion/Exclusion Criteria
7. Treated segment registration with respect to knee joint
8. Randomization
9. DEX infusion or POBA
10. Provisional stenting
11. Completion angiography

Primary Revascularization: A balloon shall be selected such that the diameter is 1 mm less than the vessel reference diameter. To secure good results, slow inflation, prolonged inflation (3 min) at nominal pressure should be used. One additional inflation may be used to ensure good results. If there is > 30% residual stenosis, that portion of the stenosis is ineligible to be included and a stent will be placed. However, if there is a portion of the lesion that has adequate results and there is no anticipation of a stent, then the successfully PTA treated, but non-stented, segment can be registered as the treated segment.

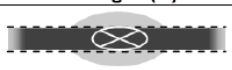
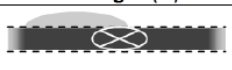
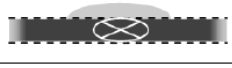
For subjects randomized to POBA, If the patient is randomized to POBA, then an appropriate sized device may be used according to the IFU, at a 1:1 artery:balloon size ratio. The Investigator will complete the clinical portions of the procedure (e.g. completion angiograms) per standard of care, Provisional stenting of the treated segment is allowed if clinically indicated.

For subjects randomized to DEX, the Investigator will infuse dexamethasone (1.6 mg / cm lesion length). The investigator may administer DEX at multiple sites along the treated segment and may reposition the Micro-Infusion Catheter as needed to establish successful distribution of the drug along the treated segment.

Imaging will be saved for the Core Lab (UCSF VipeRx Lab) to assess the technical success of drug administration, the extent of circumferential (or lateral using 2-dimensional X-ray fluoroscopic guidance) and longitudinal coverage of the artery by the contrast. The following scale will be used to grade the pattern of distribution:

Technical success is defined as grades A, B or C

Table 2: Diffusion grades and distribution patterns

Diffusion Grade	Characteristics	Appearance relative to target (X)	Diffusion Grade	Characteristics	Appearance relative to target (X)
A	*complete* circumferential, *complete* longitudinal coverage of target		C	*partial* circumferential, *partial* longitudinal coverage	
B1	*complete* circumferential, *partial* longitudinal coverage		D	perivascular, but no target overlap	
B2	*partial* circumferential, *complete* longitudinal coverage		F	No detectable perivascular infusion	

Provisional stenting of the treated segment is allowed if clinically indicated.

9.9 Research MRI

A research MRI will be performed to assess change in Percent Wall Volume (ΔPWV) and transfer constant (K^{trans}) following the procedure. Specific details of the protocol are discussed below.

Assessments of ΔPWV will occur: at Post-Op, Month 6, and Month 12.

Assessments of K^{trans} will occur at: Month 1 and Month 6.

9.9.1 Equipment

A research MRI will be obtained on either a 3T Siemens Skyra MRI (Erlangen Germany) (SFVAMC/UCSF) or a 3T Philips Achieva MRI (Philips Healthcare, Netherlands) (UW) using a phased-array coil wrapped around the leg at the level of the region of interest.

9.9.2 Protocol

Patients will be scanned with a phased array coil placed such that the anterior portion covers the femoral segment and the posterior section coverage includes the popliteal segment of the artery. The scan landmark will be positioned at a point approximately 20 cm proximal to the knee joint, and that location will be advanced to the center of the magnet. The 3D black blood study will be performed centered with zero offset in the head-foot direction. The superior tip of the medial tibial spine will be identified on the 3D black blood images. The targeted 2D T1, T2 and DCE sequences will be centered 20 centimeters proximal to the medial tibial spine landmark, in the adductor canal, as this is considered to be the most likely location of the treated segment.

After the location of the treated segment is identified, a specific set of MRA sequences will be performed. The sequences vary by study visit. A description of the sequences and requirements is provided in Table 3.

Table 3: Research MRI Sequences

Sequence	Baseline (-30 days)	Within 7 days Post-Op	1 Mo	6 Mo	12 Mo	Immediately pre re-intervention
Pre MERGE /DASH	**X**	**X**	**X**	**X**	**X**	**X**
2D-T1	**X**	**X**	**X**	**X**	**X**	**X**
2D-T2	**X**	**X**	**X**	**X**	**X**	**X**
MP RAGE	**X**	**X**	**X**	**X**	**X**	**X**
DCE	**X**		**X**	**X**		**X**
CE-MRA		**X**			**X**	
Post MERGE /DASH	**X**	**X**	**X**	**X**	**X**	**X**
PC-MRI		**X**				

Pre MERGE/DASH (DANTE prepared-FLASH): These sequences are high-resolution, 3D black-blood imaging of the vessel wall, which are achieved by using a preparation pulse to null the signal from flowing blood. MERGE uses an MSDE (Motion Sensitive Driving Equilibrium) prep-pulse, with a Rapid Gradient Echo acquisition. DASH uses a DANTE prep-pulse (Delay Alternating with Nutation for Tailored Excitation) with a FLASH sequence (Flash Low Angle Shot). These sequences are essentially different implementations to achieve the same goal of vessel wall imaging, and they both contain a motion-sensitive preparation (to null the signal from the blood) coupled to a fast gradient echo acquisition.

2D-T1: This is a 2D, high-resolution, T1 weighted sequence. T1 image weighting measures the spin-lattice relaxation time of hydrogen protons in a tissue.

2D-T2: This is a 2D, high-resolution, T2 weighted sequence. T2 image weighting measures the spin-spin relaxation time of hydrogen protons in a tissue.

MP RAGE: This is a 3D, T1-weighted, Magnetization Prepared Rapid Acquisition Gradient Echo sequence and provides information about blood degradation products in tissues.

DCE: Dynamic Contrast Enhanced MRI is a T1-weighted sequence with high temporal resolution, acquired after the injection of a gadolinium-based contrast agent (e.g. Omniscan, Gadavist, or ProHance). This sequence allows for measurement of the passage of contrast agent, which gives information about physiological tissue characteristics such as the integrity and perfusion/permeability of the vessel wall. This imaging sequence is used to calculate K^{trans}.

The protocol for the Delayed Contrast Enhancement for this study requires an injection of Gd contrast agent:

A half dose of Gadolinium is injected. For Magnevist this corresponds to (0.1ml of Magnevist)/(kg patient weight) and for Gadavist this corresponds to (0.05ml of Gadavist)/(kg patient weight of Gadavist). If Gadavist is used it is diluted 50:50 with saline. This ensures that the total volume injected is the same independent of whether Magnevist or Gadavist is used.

Injection timing:

The DCE scan is first started. The contrast should then be injected at the end of the first dynamic run, at an injection rate of 1cc/sec, and immediately followed by a saline flush of 15 cc saline also at 1cc/sec. Dynamic scanning should not be not interrupted during the injection delivery.

CE-MRA: Contrast-Enhanced Magnetic Resonance Angiography is a pulse sequence acquired with the simultaneous intravenous injection of a gadolinium-based contrast agent. Gadolinium shortens the T1 relaxation time of blood. This allows for fast image acquisition, with high signal intensity in the lumen of vessels (where gadolinium is present), and low signal in extravascular territories (where gadolinium is not present). This sequence will give the geometry of the lumen used for CFD simulations.

This sequence is usually acquired after using a timing bolus in order to evaluate the time it takes from injection to the arrival of the contrast bolus to the vessel of interest (scan delay). Contrast

agent is generally delivered at 2mL/second.) Typically, the timing bolus is 2mL, 1:1 gadolinium:saline while the full bolus for CE-MRA is 20mL, also 1:1 gadolinium/saline.

Post MERGE/DASH: These 3D black blood sequences are acquired shortly after contrast administration to evaluate for contrast enhancement (uptake of gadolinium in the vessel wall).

PC-MRI: Phase Contrast Magnetic Resonance Imaging is a technique that allows for the measurement of blood flow. This is accomplished by placing a bipolar gradient along a vessel of interest. As hydrogen protons of blood flow along this vessel of interest, they accumulate a phase shift that is proportional to their speed. In this way, we are able to non-invasively measure the velocity and flow of blood. This sequence will allow description of the inlet flow conditions which will be used to generate CFD models.

The acquisitions parameters are provided in Appendix 3.

Data files from SFVAMC research MRIs will be sent to the University of Washington for analysis. Data files from University of Washington will be sent to SFVAMC for CFD modelling.

Study staff performing the analysis of MRIs will be blinded as to the subject ID and study visit.

9.9.3 Pre-Reintervention MRI

If the patient proceeds to a reintervention during the study period, and it has been longer than 30 days since the last research MRI study, an additional MRI study of the treated segment will be performed prior to the reintervention.

9.10 Clinical Ultrasound

A standard-of-care clinical ultrasound will be obtained at follow-up visits. The exam will cover the iliac, femoropopliteal, and infrapopliteal arterial segments and will include Doppler pulse wave velocities and B-mode diameter measurements of each segment.

10 SCHEDULE OF ASSESSMENTS

	VISIT 1 SCREENING & BASELINE (S & B) (-30 days)	VISIT 2 PROCEDURE (Day 0)	VISIT 3 POST-OP (Day 1-7)	VISIT 4 MONTH 1 (Day 30±7)	VISIT 5 MONTH 6 (Day 180±14)	VISIT 6 MONTH 12 (Day 365±30)	VISIT 7 MONTH 24 (BY PHONE) (Day 730±30)	VISIT 8 MONTH 36 (BY PHONE) (Day 1095±30)	UNPLANNED VISIT (UV)
Informed Consent	X								
Inclusion Criteria	X								
Exclusion Criteria	X								
Pregnancy Test	X								
Demographics	X								
Medical History	X								
Concomitant medications	X		X	X	X	X	X	X	X
Vital Signs	X		X	X	X	X			X
Physical Exam	X		X	X	X	X			X
Vascular Exam[1]	X		X	X	X	X			X
Rutherford Category	X		X	X	X	X			X
Research Labs[2]	X		X[3]	X		X			X
Clinical Labs	X[4]		X[3] [5]	X[5]	X[5]	X[5]			X
Walking Impairment Questionnaire	X			X	X	X			
Research MRI	X		X	X	X	X			X[8]
Clinical Ultrasound				X	X	X			X
Index Lesion Registration		X							

Schedule of Assessments continues on the next page

Schedule of Assessments, continued.

(Continued)	VISIT 1 S & B (-30 days)	VISIT 2 PROCEDURE (Day 0)	VISIT 3 POST-OP (Day 1-7)	VISIT 4 MONTH 1 (Day 30±7)	VISIT 5 MONTH 6 (Day 180±14)	VISIT 6 MONTH 12 (Day 365±30)	VISIT 7 MONTH 24 (BY PHONE) (Day 730±30)	VISIT 8 MONTH 36 (BY PHONE) (Day 1095±30)	UV
Procedural Inclusion & Exclusion Criteria		X							
Primary Revascularization		X							
Treated Segment Registration									
Randomization (after successful angioplasty)		X							
DEX Infusion[6] or POBA[7]		X							
Telephone follow-up							X	X	
Adverse Event Assessment		X	X	X	X	X	X	X	

[1]Vascular exam CRF includes ABI's

[2]Research labs include CRP, MCP-1, and IL-1β

[3]For Visit 3 Post-Op, Research & Clinical Labs must be drawn POD #1-7

[4]Clinical labs for Visit 1 include Serum chemistry, CBC, lipid panel, coagulation studies

[5]eGFR only

[6]For subjects randomized to DEX

[7]For subjects randomized to POBA (formerly PTX)

[8]Perform research MRI, if >30 days since last study MRI

11 EVALUATIONS BY VISIT

11.1 Visit 1: Screening & Baseline (Day -30 to Day -1)

1. Review the study with the subject and obtain written informed consent and HIPAA authorization and assent, if appropriate
2. Assign the subject a unique study ID number
3. Evaluate Inclusion & Exclusion Criteria
4. Assess childbearing potential of female patients, administer serum βHCG pregnancy test if indicated
5. Record demographics data
6. Record medical history
7. Record concomitant medications
8. Perform and record vital signs
9. Perform a general physical examination
10. Perform a focused vascular exam including Ankle-Brachial Index & Rutherford Categorization
11. Collect blood for research laboratory tests (CRP, MCP-1, IL-1β)
12. Record results from standard-of-care clinical laboratory tests (results obtained within 30 days may be recorded): serum chemistry, CBC, lipid panel, coagulation studies
13. Administer Walking Impairment Questionnaire (WIQ)
14. Schedule baseline research MRI prior to procedure (up to -30 days allowed)

11.2 Visit 2: Procedure (Day 0)

1. Define index lesion after initial angiogram. Using Glow 'N Tell tape, starting at the medical tibial spine, the index lesion is registered according to its location and length.
2. If subject is eligible, perform Primary Revascularization (angioplasty of index lesion)
3. Register the treated segment, location and length using Glow 'N Tell tape.
4. Assess Procedural Inclusion/Exclusion Criteria
5. Randomize subject (see Sec. 9.7" Randomization" & Sec. 16.4 "Sample Size and Randomization")
6. For subjects Randomized to DEX, infuse dexamethasone
7. For subjects Randomized to POBA (formerly PTX), perform no further treatment
8. Perform provisional stenting if indicated clinically
9. Record any procedural Adverse Events
10. Record any interim Adverse Events

11.3 Visit 3: Post-Operative Assessments (Day 1-7)

1. **Obtain research labs (CRP, MCP-1, IL-1β) on Post-Operative Day #1 (POD #1)**
2. Obtain clinical labs (eGFR only) **on Post-Operative Day #1 (POD #1)**
3. Record any changes to medications
4. Record vital signs
5. Perform physical exam

6. Perform vascular exam including Ankle-Brachial Index & Rutherford Categorization
7. Perform research MRI (up to POD #7 allowed)
8. Record any interim Adverse Events

11.4 Visit 4: 1 Month Follow-up (Day 30±7)

1. Record any changes to medications
2. Record vital signs
3. Perform physical exam
4. Perform vascular exam including Ankle-Brachial Index & Rutherford Categorization
5. Obtain research labs (CRP, MCP-1, IL-1β)
6. Obtain clinical labs (eGFR only)
7. Administer Walking Impairment Questionnaire
8. Perform research MRI
9. Record results of clinical ultrasound
10. Record any interim Adverse Events

11.5 Visit 5: 6 Month Follow-up (Day 180±14)

1. Record any changes to medications
2. Record vital signs
3. Perform physical exam
4. Perform vascular exam including Ankle-Brachial Index & Rutherford Categorization
5. Obtain clinical labs (eGFR only)
6. Administer Walking Impairment Questionnaire
7. Perform research MRI
8. Record results of clinical ultrasound
9. Record any interim Adverse Events

11.6 Visit 6: 12 Month Follow-up (Day 365±30)

1. Record any changes to medications
2. Record vital signs
3. Perform physical exam
4. Perform vascular exam including Ankle-Brachial Index & Rutherford Categorization
5. Obtain research labs (CRP, MCP-1, IL-1β)
6. Administer Walking Impairment Questionnaire
7. Perform research MRI
8. Record results of clinical ultrasound
9. Record any interim Adverse Events

11.7 Visit 7: 24 Month Telephone Follow-up (Day 730±30)

10. Record any changes to medications
11. Record any interim Adverse Events

11.8 Visit 8: 36 Month Telephone Follow-up (Day 1095±30)

12. Record any changes to medications
13. Record any interim Adverse Events

11.9 Early Withdrawal Visit

In the event of early withdrawal, the Principal Investigator or Co-Investigator will contact the subject and arrange a follow-up clinical appointment. If the subject is unable or unwilling to return, the investigator may perform a telephone interview.

The following information will be recorded at a final clinical appointment:

1. Record changes to concomitant medications
2. Perform vascular exam including Ankle-Brachial Index & Rutherford Categorization
3. Collect blood for research laboratory tests (CRP, MCP-1, IL-1β) and safety (eGFR)
4. Record any interim Adverse Events

The following steps will be performed during a telephone interview:

1. Record any interim Adverse Events
2. Arrange for release of records from outside hospitals/providers
3. Record reason for withdrawal

11.10 Unplanned Visit for Index Leg Reintervention

If the investigator determines that a subject requires reintervention of the index leg, a study visit will be performed prior to the reintervention.

If the need for reintervention is determined within the window of a study visit, all procedures for that study visit will be performed.

If the need for reintervention is determined outside of a study visit window, the following will be performed:

1. Record any changes to medications
2. Record vital signs
3. Perform physical exam
4. Perform vascular exam including Ankle-Brachial Index & Rutherford Categorization
5. Obtain clinical labs (eGFR only)
6. Administer Walking Impairment Questionnaire
7. Perform research MRI, if >30 days since last study MRI
8. Record results of clinical ultrasound
9. Record procedural details of the reintervention
10. Record any interim Adverse Events

If subject is receiving reintervention on <75% of the treated segment, please continue to follow subject until they have completed the study. For further specifics on study completion, please see section 11.11 Study Completion.

11.11 Study Completion

For subject to complete their participation in this study they must:

1. Undergo follow-up for 36-month period after index procedure, completing all assessments in the Schedule of Assessments.

2. Subject develops restenosis after the 1-month study follow-up, requiring reintervention of ≥75% of treated segment.

If subject does not complete the study following the above indications, please see section 13.1 for specifics on Early Discontinuation/Withdrawals.

If subject develops restenosis after the 1-month study follow-up, requiring reintervention of <75% of the treated segment, please see section 11.10 for specifics on recording Unplanned Visits for Index Leg Reintervention and continuing follow-up.

12 ADVERSE EVENT REPORTING AND DOCUMENTATION

12.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical investigation of a patient administered a pharmaceutical product and that does not necessarily have a causal relationship with the treatment. An AE is therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the administration of an investigational product, whether related to that investigational product or not. An unexpected AE is one of a type not identified in nature, severity, or frequency in the current Investigator's Brochure or of greater severity or frequency than expected based on the information in the Investigator's Brochure.

The Investigator will probe, via discussion with the subject, for the occurrence of AEs during each subject visit and record the information in the site's source documents. Adverse events will be recorded in the patient CRF. Adverse events will be described by duration (start and stop dates and times), severity, outcome, treatment and relation to the index procedure, or if unrelated, the cause.

AE Severity

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 should be used to assess and grade AE severity, including laboratory abnormalities judged to be clinically significant. The modified criteria can be found in the study manual. If the experience is not covered in the modified criteria, the guidelines shown below, in Table 1, should be used to grade severity. It should be pointed out that the term "severe" is a measure of intensity and that a severe AE is not necessarily serious.

Table 1. AE Severity Grading

Severity (Toxicity Grade)	Description
Mild (1)	Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required. The subject may be aware of the sign or symptom but tolerates it reasonably well.
Moderate (2)	Mild to moderate limitation in activity, no or minimal medical intervention/therapy required.
Severe (3)	Marked limitation in activity, medical intervention/therapy required, hospitalizations possible.

Life-threatening (4)	The subject is at risk of death due to the adverse experience as it occurred. This does not refer to an experience that hypothetically might have caused death if it were more severe.

12.2 Serious Adverse Events (SAE)

An SAE is defined as any AE occurring at any dose that results in any of the following outcomes:

- death
- a life-threatening adverse experience
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant disability/incapacity
- a congenital anomaly/birth defect

Other important medical events may also be considered an SAE when, based on appropriate medical judgment, they jeopardize the subject or require intervention to prevent one of the outcomes listed.

12.2.1 Serious Adverse Event Reporting

Study sites will document and report all SAEs that occur (whether or not related to index procedure) within 5 business days of investigator awareness, as per UCSF IRB Guidelines. The collection period for all SAEs will begin after informed consent is obtained and end after procedures for the final study visit have been completed.

In accordance with the standard operating procedures and policies of the local Institutional Review Board (IRB)/Independent Ethics Committee (IEC), the site investigator will report SAEs to the IRB/IEC.

13 DISCONTINUATION AND REPLACEMENT OF SUBJECTS

13.1 Early Discontinuation/Withdrawal

A subject may be discontinued from study treatment at any time if the subject, the investigator, or the Sponsor feels that it is not in the subject's best interest to continue. The following is a list of possible reasons for study treatment discontinuation:

- Subject withdrawal of consent (or assent)
- Subject is not compliant with study procedures
- Adverse event that in the opinion of the investigator would be in the best interest of the subject to discontinue study treatment (i.e. treated segment restenosis/occlusion occurring between index procedure date and the 1-month study follow-up date)
- Protocol violation requiring discontinuation of study treatment
- Positive pregnancy test (females)
- Lost to follow-up
- Death

If a subject is withdrawn from treatment due to an adverse event, the subject will be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized.

All subjects who decide to withdraw or discontinue study treatment should come in for an early discontinuation visit as soon as possible.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents.

13.2 Replacement of Subjects

Subjects who withdraw from the study treatment will not be replaced.

14 PROTOCOL VIOLATIONS

A protocol violation occurs when the subject or investigator fails to adhere to significant protocol requirements affecting the inclusion, exclusion, subject safety and primary endpoint criteria. Protocol violations for this study include, but are not limited to, the following:

- Failure to meet inclusion/exclusion criteria
- Use of a prohibited concomitant medication
- Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a protocol violation. The Investigator will determine if a protocol violation will result in withdrawal of a subject.

When a protocol violation occurs, it will be discussed with the investigator and a Protocol Violation Form detailing the violation will be generated. This form will be signed by the Investigator. A copy of the form will be filed in the site's regulatory binder and in the Sponsor's files.

15 DATA SAFETY MONITORING

Since this is a multi-institutional study, a Data Monitoring Committee (DMC) comprised of the principal investigator, two co-investigators (Drs. Hatsukami and Gasper) will meet on a regular semi-annual basis to review the progress of the trial and address all safety issues. The minutes of the meetings will be submitted to the UCSF institutional review board.

All Serious Adverse Events (SAEs) will be reported to the IRB within 5 business days of investigator awareness (or as per local IRB policy), followed to resolution and adjudicated. Adverse Events will also be grouped and analyzed in the following three distinct periods:

1. From intervention through discharge from hospital;
2. From hospital discharge until the 1-month evaluation; and
3. Beyond the 1-month evaluation and through 36 months and completion of study participation.

Adverse events will be documented on the AE Case Report Form. Those SAEs that are possibly related to the treatment (angioplasty, infusion or drug), the procedure (angiogram, access vessel, etc.), or the disease state being treated (PAD) may be reviewed and adjudicated

by an Independent Reviewer. All Serious Adverse Events and/or Unanticipated Adverse Device Effects will be reported to the IRB per the IRB's specific policies and guidelines.

16 STATISTICAL METHODS AND CONSIDERATIONS

16.1 Data Sets Analyzed

All eligible patients who are randomized into the study will be included in the safety analysis and descriptive statistics of the study population.

Descriptive statistics will be used to characterize the parametric and nonparametric data with means and standard deviation or median and interquartile range where appropriate. Proportions will be used for categorical data.

16.2 Analysis of Primary Endpoint

The primary endpoint for this study will be PWV change of the treated segment from the post-operative (1-7 days after intervention) MRI scan to 12 months between DEX treated and non-DEX (PTX or POBA) treated patients.

Statistical hypothesis 1a: Adventitial DEX infusion will result in reduced change in percent wall volume (PWV) within the treated segment.

Statistical Methods: The primary analysis will be an intention-to-treat (ITT) comparison of observed change in mean ΔPWV between treatment groups at 12 months using a *t*-test. Because ΔPWV may be nonlinear in time, linear splines with knots at 24 hours, 1 month, 6 months, and 12 months will be used to fit the model. Multivariable regression models will be constructed to determine independent variables associated with ΔPWV controlling for demographic and anatomical variables, statin use, inflammatory markers, and smoking. We will also investigate effects by treatment received by constructing generalized linear models controlling for demographic, clinical, and anatomic variables. Predictors of PWV will be evaluated via univariate and multivariate regression analysis.

16.3 Analysis of Secondary Endpoints

Statistical hypothesis 1b: Adventitial DEX infusion will result in improved vascular remodeling of the treated segment.

Statistical Methods: ITT comparison of observed change in remodeling between treatment groups at 12 months using a *t*-test. Models will be constructed similar to ΔPWV with attention or hemodynamic descriptors, WSS and OSI, derived by CFD and plaque composition which have both been hypothesized to influence vessel remodeling.

Statistical hypothesis 2a: Adventitial DEX infusion will result in reduced peri-operative inflammatory profile.

Statistical Methods: Each biomarker will be tested for normality and log-transformed as necessary. Descriptive statistics will record the mean and standard deviation (or median and inter-quartile range) of each biomarker at each time point. Then, the area under the curve (AUC) will be calculated for each biomarker from baseline, 24 hours post-intervention, and the 1 month time point. ITT comparisons of the mean AUC between treatment assignments will be by a *t*-test.

Statistical hypothesis 2b: Adventitial DEX infusion will result in less adventitial perfusion (a surrogate of inflammation) as measured by kinetic modeling of dynamic contrast-enhanced MRI.

Statistical Methods: ITT Comparisons will be made between average K^{trans} values of the two treatment groups using the Wilcoxon signed rank test. Spearman rank correlation coefficient will be determined between VP and K^{trans} values, and other variables such as smoking status, statin use, plaque component, and biomarker levels. K^{trans} will also be assessed at baseline MRI visit as a parameter of plaque inflammation for descriptive purposes. K^{trans} will likely be difficult to assess in the freshly injured artery at the 24 hour MRI.

Statistical hypothesis 2c: Peri-operative inflammatory profile will be associated with ΔPWV.

Statistical Methods: Pearson correlation coefficients will be calculated between CRP, MCP-1, and IL-1β and confounding factors such as diabetes, foot ulcer, and treated segment length, etc. Multivariable linear regression models will be created with each inflammatory marker AUC as the dependent variable in order to determine the independent effect of inflammation on ΔPWV.

Statistical hypothesis 3a: Treated segment remodeling will be associated with the fibrous volume in the plaque.

Statistical Methods: Multi-contrast MRI will be used to determine the relative volumes of fibrous, calcification, and LRNC expressed as a percent of TVV for each treated segment in this study. Pearson's correlation coefficient will be used to determine if patient-related factors or markers of inflammation are associated with plaque composition. Then multivariable regression equations will be generated to determine if fibrous tissue content is associated with remodeling. Models will be constructed with and without DEX to determine if DEX will change the β-coefficient of the association between fibrous tissue content and remodeling.

Statistical hypothesis 3b: Treated segment remodeling/ΔPWV will be associated with wall shear stress provided by MRI-determined, patient-specific, geometry and computational fluid dynamics

Statistical Methods: Hemodynamic parameters WSS, WSSG, and OSI, derived from CFD will be calculated at each MRI time point. Multivariable regression models will be constructed to determine the independent contribution of these parameters on treated segment remodeling and ΔPWV.

Interim analyses will be made prior to DMC meetings and in preparation of publications.

16.4 Sample Size and Randomization

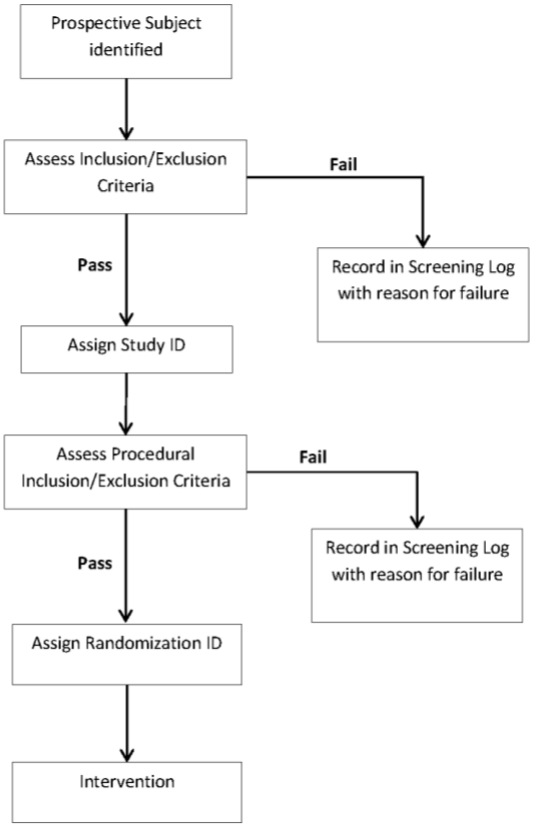
The sample size for this study is based on Statistical Hypothesis 1a. While there are no predicate serial studies of PWV changes in femoral artery restenosis following PTA to estimate the sample size, previous work on the progression of de novo atherosclerosis in similar sized peripheral arteries (carotids) forms the basis of this estimation (please refer to Section 1.2 reference numbers 70 and 71). Power calculations were performed based on an expected reproducibility variance of 8% (determined from evaluations performed on measurements performed on the untreated leg for studies at multiple time points). An effect size of 6.3% or 7% was assumed based on data from pilot studies. Based on power calculations, we estimate the need for 22 subjects/treatment assignment to detect a 7% difference in PWV at a power level of 80%. Assigning a 20% attrition rate due to loss to follow up or index lesion revascularization, 27

subjects will be enrolled per arm. Calculation is based on an unpaired t test at a 5% significance level.

Overall sample size providing 80% power in 2-sided 5% tests			
Between-group difference	**Measurement error**		
	7%	8%	9%
6.3%	42	54	68
7%	34	44	54

The Principal Investigator's staff will develop and maintain a block randomizations scheme for each site. The scheme will be developed using Stata 12.1 (StataCorp, College Station, TX, USA) with a 1:2 allocation of DEX:POBA because the 9 or 10 subjects treated with DEX to this point will be carried forward in the analysis. The block size will not be revealed to Investigators, to minimize bias. Allocation to treatment group will be tied to Randomization ID. The Randomization ID will be assigned to a subject once the Procedural Inclusion/Exclusion Criteria are assessed. Figure 6 illustrates the Study Enrollment and Randomization process.

Figure 6: Enrollment and Randomization process



17 DATA COLLECTION, RETENTION AND MONITORING

17.1 Data Collection Instruments

The Investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject treated with the index procedure.

Study personnel at each site will enter data from source documents corresponding to a subject's visit into the protocol-specific electronic Case Report Form (eCRF) when the information corresponding to that visit is available. Subjects will not be identified by name in the study database but will be identified by a subject number.

If a correction is required for an eCRF, the time and date stamps track the person entering or updating eCRF data and creates an electronic audit trail. If a correction is made on a paper source form, the study staff member will line through the incorrect data, write in the correct data and initial and date the change.

The Investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator. A copy of the CRF will remain at the Investigator's site at the completion of the study pursuant to institutional record retention guidelines.

17.2 Data Management Procedures

The data will be entered into a validated database. A staff member designated as the Data Manager will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

Data will be shared with collaborating investigators and contract laboratories as appropriate for analyses. Data will be coded or deidentified, according to the matrix in Appendix III – Data Management. The code will be maintained and kept secure by the Data Manager.

17.3 Data Quality Control and Reporting

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis. These checks will occur following the completion of each 10 study subjects. Ad hoc checks may be initiated by the Investigator. The study database will be updated in accordance with the resolved queries. All changes to the study database will be documented.

17.4 Archival of Data

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained. Databases are backed up by the database administrator in conjunction with any updates or changes to the database.

At critical junctures of the protocol (e.g., production of interim reports and final reports), data for analysis is locked and cleaned per established procedures.

17.5 Availability and Retention of Investigational Records

The Investigator must make study data accessible to the monitor, other authorized representatives of the Sponsor (or designee), IRB/IEC, and Regulatory Agency (e.g., FDA) inspectors upon request. A file for each subject must be maintained that includes the signed

Informed Consent, HIPAA Authorization and Assent Form and copies of all source documentation related to that subject. The Investigator must ensure the reliability and availability of source documents from which the information on the CRF was derived.

All study documents (patient files, signed informed consent forms, copies of CRFs, Study File Notebook, etc.) must be kept secured and retained according VA & UW IRB policies.

17.6 Subject Confidentiality

In order to maintain subject confidentiality, only a site number, subject number and subject initials will identify all study subjects on CRFs and other documentation submitted to the IRB and contract organizations.

18 ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312).

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number and initials only. All study records will be kept in a locked file cabinet and code sheets linking a patient's name to a patient identification number will be stored separately in another locked file cabinet. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the FDA. The Investigator must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

18.1 Protocol Amendments

Any amendment to the protocol will be written by the Investigator. Protocol amendments cannot be implemented without prior written IRB/IEC approval except as necessary to eliminate immediate safety hazards to patients. A protocol amendment intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRBs are notified within five working days.

18.2 Institutional Review Boards and Independent Ethics Committees

The protocol and consent form will be reviewed and approved by the IRB/IEC of each participating center prior to study initiation. Serious adverse experiences regardless of causality will be reported to the IRB/IEC in accordance with the standard operating procedures and policies of the IRB/IEC, and the Investigator will keep the IRB/IEC informed as to the progress of the study. The Investigator will obtain assurance of IRB/IEC compliance with regulations.

Any documents that the IRB/IEC may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB/IEC. The IRB/IECs written unconditional approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated. The IRB/IECs unconditional approval statement will be transmitted by the Investigator to designee prior to the shipment of study supplies to the site. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB/IEC approval except when necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the study. Such

modifications will be submitted to the IRB/IEC and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB/IEC must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

18.3 Informed Consent Form

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.

The Investigator will prepare the informed consent form, assent and HIPAA authorization and provide the documents to the Sponsor or designee for approval prior to submission to the IRB/IEC. The consent form generated by the Investigator must be acceptable to the Sponsor and be approved by the IRB/IEC. The written consent document will embody the elements of informed consent as described in the International Conference on Harmonisation and will also comply with local regulations. The Investigator will send an IRB/IEC-approved copy of the Informed Consent Form to the Sponsor (or designee) for the study file.

A properly executed, written, informed consent will be obtained from each subject prior to entering the subject into the trial. Information should be given in both oral and written form and subjects must be given ample opportunity to inquire about details of the study. If appropriate and required by the local IRB/IEC, assent from the subject will also be obtained. If a subject is unable to sign the informed consent form (ICF) and the HIPAA authorization, a legal representative may sign for the subject. A copy of the signed consent form (and assent) will be given to the subject and the original will be maintained with the subject's records.

18.4 Publications

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among the study Sponsor and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

18.5 Investigator Responsibilities

By signing the Agreement of Investigator form, the Investigator agrees to:

1. Conduct the study in accordance with the protocol and only make changes after notifying the Sponsor (or designee), except when to protect the safety, rights or welfare of subjects.
2. Personally conduct or supervise the study (or investigation).
3. Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in § 21 CFR, parts 50 and 56.
4. Report to the Sponsor or designee any AEs that occur in the course of the study, in accordance with §21 CFR 312.64.
5. Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.

6. Maintain adequate and accurate records in accordance with §21 CFR 312.62 and to make those records available for inspection with the Sponsor (or designee).
7. Ensure that an IRB that complies with the requirements of §21 CFR part 56 will be responsible for initial and continuing review and approval of the clinical study.
8. Promptly report to the IRB and the Sponsor (or designee) all changes in the research activity and all unanticipated problems involving risks to subjects or others (to include amendments and IND safety reports).
9. Seek IRB approval before any changes are made in the research study, except when necessary to eliminate hazards to the patients/subjects.
10. Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in § 21 CFR part 312.

APPENDIX 1. SAMPLE COLLECTION & PROCESSING GUIDELINES

Tube Matrix

Tube	Volume (ml)	Processing	Centrifuge	Aliquot to	Storage
Tiger Top SST	10	Allow to clot 30-60 min	4°C, 2800 RPM, 10 min	Serum, 4x2ml cryovials	-80°C
Lavender EDTA	10	Process immediately	4°C, 2800 RPM, 10 min	Plasma, 4x2ml cryovials	-80°C

Assay Matrix

Assay	Obtained from
CRP	10 ml Tiger Top SST
MCP-1	10 ml Tiger Top SST
IL-1β	10 ml Lavender EDTA

APPENDIX 2. DATA MANAGEMENT

Individual/Institution	Role	Role	Dataset	Coded	Deidentified
David Saloner, PhD	Principal-investigator	Analysis, manuscript preparation	Full dataset	As appropriate	No
Chun Yuan, PhD	Co-investigator	Analysis, manuscript preparation	Full dataset	As appropriate	No
Warren Gasper, MD	Co-investigator	Analysis, manuscript preparation	Full dataset	As appropriate	No
Thomas Hatsukami, MD	Co-investigator	Analysis, manuscript preparation	Full dataset	As appropriate	No
Michael Hope, MD	Co-investigator	Analysis, manuscript preparation	Full dataset	As appropriate	No
Balu Niranjan, PhD	Co-investigator	Analysis, manuscript preparation	Full dataset	As appropriate	No
Niten Singh, MD	Co-investigator	Analysis, manuscript preparation	Full dataset	As appropriate	No
DMC	Safety monitoring	Interim safety analyses	descriptive statistics, adverse event descriptions, prepared by DSMB coordinator	AE descriptions may contain coded information	No
Children's Hospital Boston: Dept. of Laboratory Medicine, CERLab	Contract lab	Inflammatory Marker analysis	Manifests containing subject IDs	Yes	No

APPENDIX 3. RESEARCH MRI ACQUISITION PARAMETERS

	Pre-post 3D-MERGE (3D Dash)	**MP-RAGE**	**2D T1w**	**2D T2w**	**DCE**	**CE-MRA**	**PC-MRI**
Mode	3D	3D	2D	2D	2D	3D	2D
Acquisition plane	Coronal	Coronal	Axial	Axial	Axial	Coronal	Axial
Black-blood prep	MSDE (DANTE)		MSDE	MSDE			
Resolution, mm^2	1.0 (0.8)	1.0	0.7	0.7	0.7	0.7	0.5
FOV, mm^2	300×360 (324x370)	300x360	120x300 (160x300)	120x300 (160x300)	120x300	300x360	160x300
Slice thickness , mm	0.7 (0.8)	0.7	3	3	4	0.7	5
# of slices	150 (104)	150	16	16	8	150	2
TR/TE, ms	8/4 (7/3.4)	8/5	800/10	4500/40	8/4	8/4	5/3
Flip angle, °	6 (8)	11			15		20
Turbo factor	25 (100)	100	14	10			
NSA	1	1	2	1	1	1	1
No of stations	1	1	1	1	1	1	2
Scan time (min)	3.5 (4.5)	4.5	12	6	5	2	2

APPENDIX 4. DEXAMETHASONE SODIUM PHOSPHATE MONOGRAPH

APPENDIX 5. BULLFROG MICRO-INFUSION CATHETER IFU

APPENDIX 6. LUTONIX 035 DCB CATHETER IFU

APPENDIX 7. INPACT ADMIRAL DCB CATHETER IFU

APPENDIX 8. STELLAREX DCB CATHETER IFU

APPENDIX 9. WALKING IMPAIRMENT QUESTIONNAIRE (WIQ)