Supplementary Online Content

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eAppendix. VISSIT: Vitesse Intracranial Stent Study on Ischemic Therapy Protocol Statistical Analysis Plan

This supplementary material has been provided by the authors to give readers additional information about their work.

VISSIT: VITESSE INTRACRANIAL STENT STUDY FOR ISCHEMIC THERAPY

PROTOCOL CA2007-01

IDE#: G080051

STUDY SPONSOR:

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SAN JOSE, CA 95131
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Acronyms

ACT	activated clotting time
AVM	arteriovenous malformation
BA	basilar artery
BES	balloon expandable stent
C4	level of the 4th cervical vertebrae
DSMB	Data Safety Monitoring Board
ECASS II	Second European Australasian Acute Stroke Study
iCRFs	internet-based Case Report Forms (see Appendix VIII)
CFR	U.S. Code of Federal Regulations
CT scan	computed tomography scan of the head
D_{normal}	diameter of the proximal normal artery
$D_{stenosis}$	diameter of artery at the site of most severe degree of stenosis
DSA	digital subtraction angiography
EC	Ethics Committee
EF	ejection fraction
EQ-5D	EuroQol general health status questionnaire (Appendix III)
HDE	Humanitarian Device Exemption
HI1	hemorrhagic infarction 1
HI2	hemorrhagic infarction 2
HUD	Humanitarian Use Device
ICA	internal carotid artery
ICF	Informed Consent Form (see sample ICF, Appendix VII)
IDE	Investigational Device Exemption
IRB	Institutional Review Board
ITT	Intention-to-Treat
MCA	middle cerebral artery
MI	myocardial infarction
mRS	modified Rankin Scale (Appendix I)
NIHSS	National Institute of Health Stroke Scale (Appendix II)
PCA	posterior cerebral artery
PH1	parenchymal hemorrhage 1
PH2	parenchymal hemorrhage 2
PTA	percutaneous transluminal angioplasty
RCT	randomized controlled trial
SAH	subarachnoid hemorrhage
SES	self-expanding stent
TIA	Transient Ischemic Attack
TMB	Transient Monocular Blindness
TVR	Target Vessel Revascularization
tPA	tissue plasminogen activator
VA	vertebral artery
VASP test	a test of the therapeutic efficacy of anticoagulation regimen
VBA	Vertebrobasilar Artery

Definitions

Bleeding: Loss of > 50cc of blood

Dissection: A flow-limiting tear or flap in the arterial wall requiring intervention to correct

Dyna CT: An X-ray imaging software option which allows the reconstruction of 2-dimensional images acquired with an angiographic C-arm into 3-dimensional image format

Fever: Documented temperature > 38˚C

Groin hematoma: An accumulation of blood at the puncture site requiring evacuation, transfusion, or extended hospital stay

Hard TIA: A transient episode of neurological dysfunction caused by focal brain or retinal ischemia that lasts for at least 10 minutes but resolves within 24 hours. Specifically, focal weakness or language disturbance (other than isolated slurred speech), transient monocular blindness, or required assistance in walking. [Johnston SC, et al; JAMA 2000]

Headache: Cerebral pain requiring medication

Hemorrhage: Acute loss of blood requiring transfusion

Hemorrhagic conversion: Cerebral hemorrhage that develops in ischemic tissue distal to the stent within 30 days after stent placement

HI1: Hemorrhagic infarction 1 was defined by ECASS II as small petechiae along the margins of the infarct

HI2: Confluent petechiae within the infarcted area but no space occupying effect [Hacke W, Lancet 1998]

Neurological Deterioration: An increase from baseline NIHSS score of ≥ 4 points

Non-Target Ischemia: Neurological signs or symptoms not attributable to the same territory as the target stenosis

PH1: Parenchymal hemorrhage 1 defined in ECASS II as blood clots in 30% or less of the infarcted area with some slight space-occupying effect

PH2: Blood clots in more than 30% of the infarcted area with substantial space-occupying effect [Hacke W, Lancet 1998]

Restenosis: Symptomatic in-stent narrowing of the arterial lumen ≥ 70% confirmed by angiogram

Stroke: Signs of focal cerebral or retinal ischemia persisting for 24 hours or more. A stroke is considered disabling if the modified Rankin score is 3 or greater

Subarachnoid Hemorrhage: Bleeding from a ruptured intracranial blood vessel, confined to the subarachnoid space

Target Ischemia: Neurological signs or symptoms attributable to the same territory or distal to the target stenosis

Transient Monocular Blindness: The abrupt onset of unilateral decreased visual acuity involving a portion or the entirety of the visual field that resolved within 24 hours

1.0 Protocol Synopsis

STUDY OBJECTIVES	Evaluation of the safety, probable benefit, and effectiveness of the PHAROS™ Vitesse™ Neurovascular Stent System
STUDY DESIGN	Randomized, prospective, controlled, multicenter trial
DEVICE	PHAROS™ Vitesse™ Neurovascular Stent System
TREATMENT POPULATION	Adults with cerebral or retinal ischemia due to neurovascular stenosis
ESTIMATED TRIAL SIZE	Up to 250 randomized Subjects
NUMBER OF SITES	Up to 30 sites inside and outside of the U.S.
PRIMARY ENDPOINTS FOR EFFECTIVENESS	Composite of: • Stroke in the same territory (distal to the target lesion) as the presenting event within 12 months of randomization • Hard TIA in the same territory (distal to the target lesion) as the presenting event from day 2 through month 12 post-randomization
SAFETY OUTCOMES	• Stroke in any territory within 30 days of randomization • Death from any cause within 30 days of randomization • Hard TIA in any territory occurring after a 24 hour post-procedure stabilization period (days 2-30) • Intracranial hemorrhage within 30 days of randomization
OTHER OUTCOMES	• Successful deployment of PHAROS Vitesse stent across target lesion with residual stenosis 0-20% • Percentage of Stent Group Subjects with symptomatic in-stent restenosis ≥ 70% confirmed by angiogram at 12 months • Comparison of NIHSS scores between Treatment arms • Comparison of mRS scores between Treatment arms • Comparison of quality of life between Treatment arms as assessed by the EQ-5D
VISIT SCHEDULE	Baseline, Procedure, Discharge, 30-Days, 3-Months, 6-Months, and 12-Months

2.0 Introduction and Background on Intracranial Atherosclerotic Disease

In western countries, stenoses caused by intracranial atherosclerotic disease (ICAD) are responsible for approximately 8 to 10% of all strokes [Sacco et al, 1995]. ICAD is characterized by deposition of atheromatous plaque in the endothelial lining of intracranial arteries causing narrowed lumen size leading to ischemic symptoms (NICE 2007). The epidemiology of intracranial arterial stenosis includes racial/ethnic variance; 6-10% of ischemic strokes are in whites, 6-29% in blacks, 11% in Hispanics, and 22-26% in Asians (Derdeyn 2007).

2.1 Medical Therapy

Patients with high grade symptomatic stenosis with luminal narrowing of more than 70% have a stroke risk of approximately 20% despite medical treatment with antiplatelet or anticoagulant [Chimowitz et al, 2005, Kasner et al, 2006]. Comparison of medical therapies (i.e., aspirin vs. warfarin, ticlopidine vs. aspirin, and evaluation of low dose vitamins vs. high dose vitamin administration), did not seem to substantially affect the stroke recurrence rates between treatment arms. The stroke recurrence rates in medically treated patients appeared to be comparable to the natural history of stroke recurrence. Importantly, warfarin was associated with significantly higher AE rates and provided no benefit over aspirin, leading to the conclusion that aspirin rather than warfarin should be used in patients with intracranial stenosis (Table 1).

Table 1: WASID Outcomes

Study Design	Randomized, double-blind, multicenter	
Enrollment	N=569 randomized to aspirin or warfarin; enrollment stopped prematurely due to safety concerns associated with warfarin	
Follow-up	Mean 1.8 ±1.3 yrs	
Results	**Aspirin**	**Warfarin**
Primary	22.1%	21.8%
Ischemic Stroke	**20.4%**	**17.0%**
Ischemic Stroke in territory of stenosis	15.0%	12.1%
Disabling/fatal stroke	8.9%	6.2%
Death	**4.3%**	**9.7%**
Vascular death	3.2%	5.9%
Non-vascular death	1.1%	3.8%
Major Hemorrhage	3.2%	8.3%

2.2 Neurovascular Angioplasty and Stenting

Angioplasty as a treatment for intracranial stenosis was first reported in 1980 by the Mayo Clinic, and since then the technology of balloons and stent design continues to evolve. There are, to date, no prospective published studies on the clinical outcomes of angioplasty alone without stenting for the treatment of neurovascular stenosis. Retrospective angioplasty studies report a wide range in 30-day stroke/death rate (4-40% stroke/death composite; restenosis rates 24-40%). Limitations of angioplasty alone without stenting include immediate elastic recoil, residual stenosis >50%, dissection, acute vessel closure, and high restenosis rates (Derdeyn 2007).

Clinical case series and non-randomized studies published in recent years suggest the technical feasibility of intracranial stent treatment of atherosclerotic lesions. Stenting of intracranial atherosclerotic lesions was first initiated with the use of balloon expandable microstents developed for neurovascular use. While it was postulated that the early self-expanding stents would represent an improvement over balloon-expandable devices [Fiorella et al, 2007], self-expanding stents flexible enough to be placed via microcatheter have limited expansion forces and predilatation of the stenosis with a separate balloon catheter is required for adequate stent deployment. Despite promising early results, long-term outcomes based on larger case series suggest an increased risk of restenosis and stroke during follow-up [Fiorella et al 2007]. Only a small number of studies have described the incidence of restenosis and stroke through one year of follow-up. A recent publication reported restenosis rates of approximately 30% for the Wingspan self-expanding stent (Boston Scientific), with complete occlusion observed in several patients (Levy 2007). Additionally, a wide range of acute complication rates have been reported, with 30-day stroke and death rates ranging from 4.5% to more than 25%, averaging approximately 10% [Cruz-Flores, 2006]. Thus, there remains insufficient data concerning long-term effectiveness of the procedure.

Tables 2 and 3 summarize the outcomes of published series of patients treated with PTCA balloon angioplasty and/or stenting. The conclusions that can be drawn from data reported in these case series and studies are limited by the lack of randomized, prospective, multicenter trials, however, these data provide a strong rationale for continued evaluation of intracranial stents in this high-risk patient population.

3.0 PHAROS™ Vitesse™ Neurovascular Stent System

The PHAROS™ Vitesse™ Neurovascular Stent System is a balloon expandable cobalt chromium stent coated with silicon carbide mounted on a rapid-exchange percutaneous transluminal angioplasty catheter specially designed for intracranial endovascular applications. The silicon carbide coating on the PHAROS Vitesse stent has been used in an FDA-approved coronary stent, the Rithron-XR (Biotronik AG, Switzerland), and thus is known to be safe in endovascular applications (P030037, 2005). The delivery catheter is compatible with a 0.014” (0.36 mm) guidewire. The minimum guiding catheter diameter for

introduction of the device is 5 French. The PHAROS™ Vitesse™ Neurovascular Stent System is provided "STERILE" and is labeled for single-use only.

The PHAROS Vitesse Neurovascular Stent System is intended for use in improving cerebral artery lumen in patients with stenosis in neurovascular arteries with a reference diameter of $\geq$ 2.0mm to $\leq$ 5.0 mm that are accessible to the system.

The two (2) key components of the PHAROS™ Vitesse™ Neurovascular Stent System are as follows:

- The PHAROS™ Vitesse™ balloon expandable neurovascular stent
- A rapid-exchange percutaneous transluminal angioplasty delivery catheter specially designed for intracranial applications.

The PHAROS™ Vitesse™ stent is provided mounted on the delivery catheter and is intended to be implanted by expanding with balloon inflation. The system is used in conjunction with appropriately sized guidewires, guiding catheters, and flushing devices, as indicated on the label and the Instructions for Use (IFU).

The PHAROS™ Vitesse™ Neurovascular Stent sizes range in length from 8 – 40 mm and expanded diameter from 2.0 – 5.0 mm.

3.1 Stent Delivery System

The PHAROS™ Vitesse™ stent is provided mounted on a semi-compliant balloon located at the distal end of a rapid-exchange percutaneous transluminal angioplasty catheter specially designed for neurovascular applications. The balloon of the delivery catheter is designed to have a length approximately 2 mm greater than the stent. The stent is positioned between two (2) radiopaque balloon markers. The delivery catheter working length is 147 cm and the crossing profile of the catheter tip with stent ranges from 1.0 mm for the smallest diameter stent to 1.3 mm for the 5.0 mm stent. The balloon has a nominal stent deployment pressure of 8-10 atmospheres (ATM), depending on stent size, and a rated burst pressure of 16 ATM.

3.2 Principle of Operation

The PHAROS™ Vitesse™ Stent is placed in the target neurological vessel by advancing the balloon catheter with mounted stent to the lesion site from the femoral or brachial artery, using an appropriate guide catheter and guidewire. The balloon is precisely positioned across the stenotic portion of the target vessel using the radiopaque balloon marker bands and the stent end markers. When properly positioned, the balloon is inflated to nominal inflation pressure. Balloon inflation expands the stent to the deployment diameter in apposition with the vessel neointima. The balloon is then deflated and withdrawn, leaving the stent implanted at the site of the stenotic lesion.

3.3 Previous Clinical Experience with PHAROS Stent

Clinical experience with the PHAROS stent is available from Europe and Latin America, where the stent is commercially available. The PHAROS stent is nearly identical to the PHAROS Vitesse stent, with the exception of the underlying stent material, i.e., stainless steel vs. cobalt/chromium, and strut design. The coating (human contact material) and delivery system for the PHAROS stent is the same as that of the PHAROS Vitesse, thus the available clinical information on the PHAROS stent represent data supporting conduct of this clinical study.

The post-market clinical experience with the PHAROS stent is summarized in the Investigator Brochure, with data presented for both indications registered in the European Union, i.e., stent-assisted coiling of aneurysms and symptomatic stenoses in the neurovasculature. Importantly, a lower rate of restenosis has been reported with the PHAROS stent to date. Freitas and colleagues reported outcomes of treatment of 33 lesions in 32 patients with ischemic stenosis; 18 were treated with the Lekton stent, and 15 treated with PHAROS. Two deaths were reported in the PHAROS cohort but neither event was attributed to the device. One patient stopped taking the prescribed anticoagulation medications post-procedure and had a major stroke on day 14. The other death in the PHAROS cohort was due to a hypertensive crisis with cardiorespiratory failure one week after an uneventful stent procedure; this patient was non-compliant with prescribed medication regimen.

These data support initiation of this prospective, randomized, multicenter clinical trial of the PHAROS Vitesse neurovascular stent system for use in improving cerebral artery lumen in patients with stenosis in neurovascular arteries with a reference diameter of $\geq$ 2.0mm to $\leq$ 5.0 mm that are accessible to the system.

4.0 Study Objectives

The main objective of this study is to prospectively evaluate the safety, probable benefit, and effectiveness of the PHAROS Vitesse Neurovascular Stent System in a multicenter, randomized clinical trial.

A secondary objective of this study is to evaluate the impact of stenting in the neurovasculature to treat cerebral ischemia on other outcomes such as hospital length of stay, charges, and costs.

In this trial, we attempt to add to the data of cost effectiveness of neurovascular stenting, whether it decreases hospital and ICU costs and length of stay in patients with cerebral ischemia due to stenosis.

After enrollment in the clinical trial, subjects' hospital records, including itemized hospital bills, will be obtained and reviewed for charge data. Charges will be converted to costs using institution-specific cost to charge ratios. Hospital and ICU admission and discharge dates will be obtained from the iCRFs. Costs will be imputed for patients with missing charge data according to established techniques.

4.1 Study Hypothesis

Treatment of cerebral or retinal ischemia due to plaque in the neurovasculature using the PHAROS Vitesse Stent System plus medical therapy will provide additional clinical benefit over medical therapy alone.

4.2 Primary Effectiveness Endpoint

The primary effectiveness endpoint consists of a composite of the two following outcomes:

- Stroke in the same territory (distal to the target lesion) as the presenting event within 12 months of randomization
- Hard TIA in the same territory (distal to the target lesion) as the presenting event from day 2 through month 12 post-randomization

4.3 Safety Outcomes

Safety outcomes to be collected and reported as part of the overall risk-to-benefit profile for this device are:

- Stroke in any territory within 30 days of randomization
- Death from any cause within 30 days of randomization
- Hard TIA in any territory occurring after a 24 hour post-procedure stabilization period (days 2-30) since the recovery from anesthesia can mask accurate assessment of possible TIA symptoms.
- Intracranial hemorrhage within 30 days of randomization

4.4 Other Outcomes

- Stent Success – PHAROS Vitesse stent deployed across target lesion with residual stenosis 0-20%
- Percentage of Stent Group Subjects with symptomatic in-stent restenosis ≥ 70% confirmed by angiogram at 12 months
- Comparison of NIHSS scores between treatment arms
- Comparison of mRS scores between treatment arms

5.0 Clinical Study Design

5.1 Study Design

This is a randomized, controlled, multicenter clinical trial to be conducted inside and outside the United States. Eligible Subjects with ischemic symptoms attributable to stenosis of an intracranial artery (including extracranial vertebral artery from C4-basilar artery), who consent to study participation will be randomly assigned 1:1 to either treatment with:

- Medical therapy + PHAROS Vitesse neurovascular stent ("Stent Group"), or
- Medical therapy alone ("Medical Therapy Group")

5.2 Medical Therapy Regimen – All Subjects

The "optimal medical therapy regimen" to be prescribed unless medically contraindicated is outlined below. Variations from this regimen based on local standard of care will be documented in the Subject's medication CRF. In addition, Investigators should assess and address Subject's stroke risk factors for teaching and management.

- Aspirin 81-325 mg daily for the duration of the study
- Clopidogrel 75 mg daily for first 3 months
- Manage Subject's individual risk factors as appropriate, e.g.:
  - Statin 20-80 mg daily, if indicated, to lower baseline LDL-C level to < 100 mg/dL
  - Antihypertensive regimen, if indicated, to maintain blood pressure control
  - Risk factor management specific to Subject (e.g., smoking cessation, nutritionist, diabetes management, etc.)

Subjects should be advised of the importance of not stopping their medical therapy regimen without consulting with the study center.

5.3 Medical Therapy Regimen – Stenting Procedure

All patients will either begin or continue to receive the standard of care medication regimen at the time of presenting to the stroke center for diagnosis and treatment of the qualifying event. In most instances, it is expected that all consenting Subjects will be on the optimal medication regimen for 3 or more days prior to the baseline angiogram and/or stenting procedure. In urgent cases, a loading dose may be given at least 4 hours before the procedure per hospital standard of care (e.g., 300 mg clopidogrel and 325 mg aspirin).

Conscious sedation is generally expected to suffice for the angiograms, while general anesthesia is recommended for all intradural stenoses. If baseline angiogram reveals thrombus in the territory of the target lesion, postpone the procedure to treat with Abciximab (or equivalent formulary drug) to avoid distal embolization of thrombus. A VASP test (or

similar test to check efficacy of anticoagulation regimen) is recommended pre-procedure. At the beginning of the procedure, administration of heparin bolus is recommended (e.g., 100 I.U./kg; ACT: 300 seconds before placement of guiding catheters or long sheaths). Nimodipine (4 cc in 500 cc flushing solution) may be used for prevention of vasospasm.

5.4 Study Duration and Enrollment

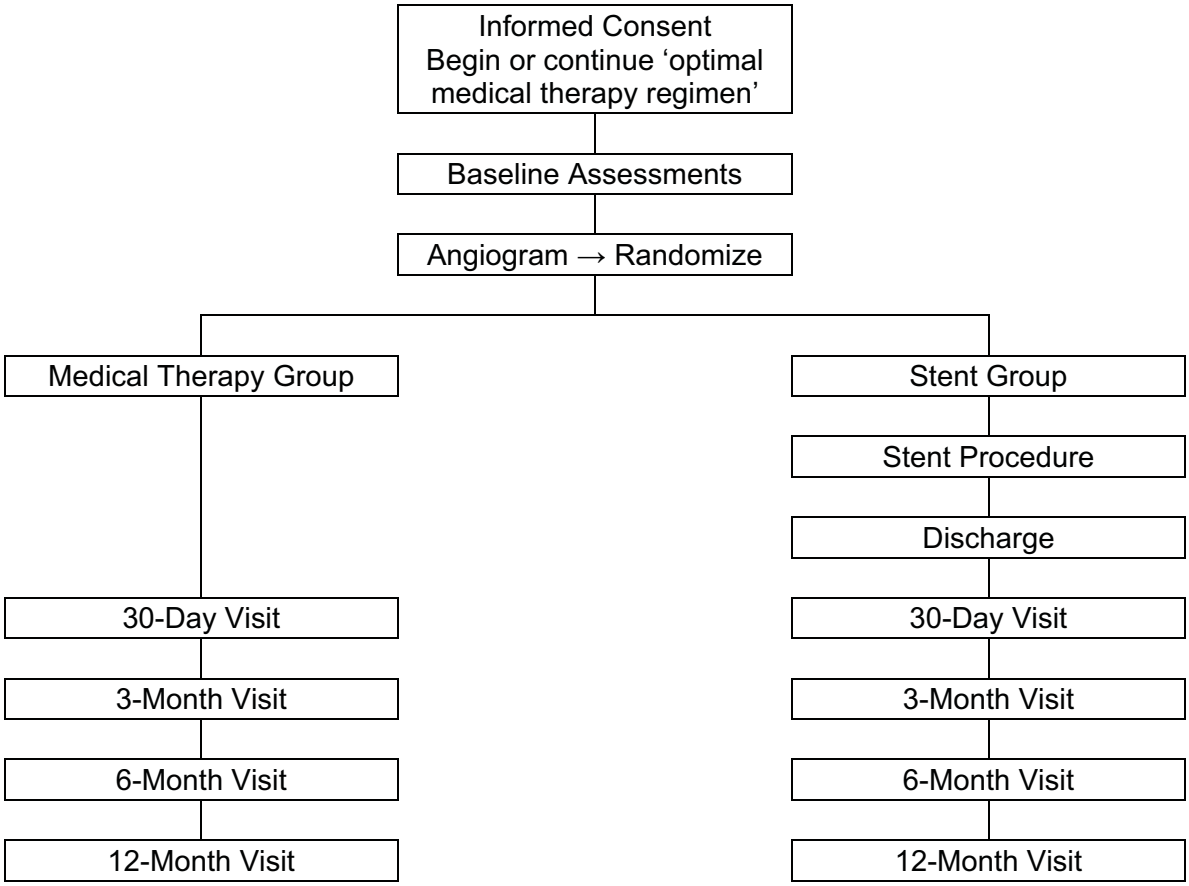
The duration of the study is expected to be approximately 30 months. This includes a start-up phase (up to 6 months), a full enrollment phase of 12-15 months, and a post randomization follow-up evaluation of each group for 12 months.

The number of Subjects to be enrolled, and subsequently randomized, in the study is up to 250. This sample size is estimated to be sufficient to yield acceptable safety and effectiveness data for comparison between treatment arms. It is anticipated that up to 30 centers inside and outside the United States will be needed to enroll this study in a timely fashion. Each Investigational Site will be expected to enroll at least 5 and up to 40 Subjects.

Qualified study centers will be expected to work in research teams that include a neurointerventionalist experienced in intracranial stenting, a neurologist, and a study Coordinator. Qualified neurointerventionalists will have successfully performed intracranial stent placement in at least ten (10) patients.

Each site must provide written approval from their reviewing Institutional Review Board / Ethics Committee (IRB/EC) and all other documentation required by the Sponsor's Site Initiation procedure (e.g., Financial Disclosure, see Appendix VI), prior to consenting and enrolling the first Subject.

Figure 1: Study Design Overview



5.5 Training

The PHAROS Vitesse Neurovascular Stent System should only be used by interventionalists with expertise in the navigation of neurovascular catheter systems and stenting procedures. Qualified potential Investigators for this clinical trial will have successfully placed intracranial stents in at least 10 patients in the 12 months prior to Site Initiation.

All Investigators and those to whom the investigator delegates study responsibilities (see Investigator Agreement and Investigator Responsibilities, Appendix V), will be trained on the protocol by a representative of the Sponsor. Interventional Investigators using the investigational device will be trained on the Instructions For Use of the PHAROS Vitesse Neurovascular Stent System. Additional training such as preparation and tabletop deployment of a demonstration device, animal lab, and/or case support will be offered by Sponsor as appropriate to meet the needs of the Site Investigators. In addition, training will be conducted at Investigator meetings and during site visits such as, Medical Imaging Laboratory Guidelines ("Core Lab", Appendix IV), internet-based CRF (iCRF) data entry procedures, and investigational device inventory management. All training completed will be documented as appropriate. Research staff responsible for assessing neurological

status using the NIHSS must be certified in the proper administration of this assessment tool. Training and Certification on administration of the NIHSS, if such documentation is not already available, can be obtained by taking a web-based accredited course such as:

http://nihss-english.trainingcampus.net/uas/modules/trees/windex.aspx .

5.6 Selection and Screening of Subjects

The study population for this clinical trial will be comprised of adult patients who have been diagnosed with symptomatic stenotic lesions in the neurovasculature. In addition, these patients must satisfy the inclusion and exclusion criteria. The trial will prospectively enroll and randomize up to 250 Subjects in a 1:1 ratio within two stratification factors: site and age (18-55 years versus 56-85 years). Patients presenting within the past 30 days with hard TIA or non-disabling stroke should be screened for study eligibility. Clinical site personnel will review the patient's medical history for eligibility. Potential candidates will be fully informed by a member of the research team as to the purpose of the study and the nature of the stenting procedure. The stenting procedure will be described and its potential risks and benefits will be explained in detail. Patients who voluntarily agree to participate in the trial will be asked to sign and date the written Informed Consent Form (ICF). If approved by the reviewing IRB/EC, Subjects may indicate verbal, witnessed consent with the signature of a patient representative not associated with the study team if cognition is intact but the Subject is unable to sign (e.g., hand function or visual disturbance). Internet-based Case Report Forms (iCRFs) must be completed for each Subject who consents to study participation.

5.6.1 Informed Consent

Prior to Subject participation in this study, the study team must obtain written IRB/EC approval for the protocol and the ICF. Once the patient's potential eligibility has been determined, the Investigator will discuss the study and ask the patient if they are interested in participating in the study. The study will be explained to the patient in lay terms. The approved ICF must be signed for study enrollment prior to performing study related assessments. A copy of the signed and dated ICF should be provided to the Subject. Failure to obtain a signed ICF prior to the procedure constitutes a major protocol deviation. Subjects must be informed that they may withdraw from the study at any time, and for any reason, and will continue to receive therapy as indicated by their physician.

5.6.2 Inclusion Criteria

Candidates for this study must meet the following criteria to be enrolled in the study:

1. Subject has at least one neurovascular lesion (70-99%) stenosis [internal carotid, middle cerebral, vertebral artery (C4-BA), and/or basilar artery] symptomatic with a hard TIA or stroke attributable to the territory of the lesion within the past 30 days. An intracranial tandem lesion (50-99%) stenosis may be treated if normal artery segment is sufficient length to avoid overlapping stents.

2. Target vessel diameter / lesion length measurements are within one of the below per angiogram:
    - Vessel diameter is ≥ 2.0 mm and < 2.5 mm / lesion length is ≤ 16 mm, or
    - Vessel diameter is ≥ 2.5 mm and < 3.0 mm / lesion length is ≤ 18 mm, or
    - Vessel diameter is ≥ 3.0 mm and < 4.5 mm / lesion length is ≤ 26 mm, or
    - Vessel diameter is ≥ 4.5 mm and ≤ 5.0 mm / lesion length is ≤ 36 mm
3. Subject has normal artery adjacent to each stenosis; diameter 2.0 mm - 5.0 mm
4. Subject age is 18-85 years
5. Life expectancy is at least 2 years
6. Subject 's mRS score is ≤ 3
7. Subject is available for study follow-up visits (e.g., lives within 3 hours of research center)
8. Subject is willing and cognitively able to provide Informed Consent (consent may be indicated verbally and signed by neutral witness if stroke has impaired hand or visual function)

5.6.3 Exclusion Criteria

Candidates will be ineligible for enrollment in the study if any of the following conditions apply:

1. Subject has contraindications for balloon expandable stent, e.g.
    - Extreme tortuosity at, or proximal to, target lesion,
    - More than 2 lesions with > 50% stenosis (including vertebral ostia and common carotid disease),
    - Carotid or vertebral dissection
2. CT scan or MRI evidence of any of the following:
    - Intracranial hemorrhage of type PH1 or PH2[1]
    - Subdural or epidural hemorrhage
    - Mass effect, or
    - Intracranial tumor (except small meningioma)
3. Subject has a previous stent in the territory of the target lesion(s)
4. Subject has a previous coil or clip placed in the territory of the target lesion within 6 months
5. Subject has a potential source of cardiac embolism requiring anticoagulation therapy (e.g., atrial fibrillation, intracardiac thrombus or vegetation, significant mitral stenosis, mechanical heart valve, congestive heart failure with EF <30%, or endocarditis)

[1] Hacke, et al; Lancet 1998; 352:1245-1251

6. Subject has concurrent intracranial pathology, e.g.
    a. Moyamoya
    b. Vasculitis documented by biopsy results
    c. Ruptured Aneurysm
    d. Unruptured aneurysm > 7mm
7. Subject has uncontrolled hypertension (systolic >185 mmHg or diastolic >110 mmHg)
8. Hemoglobin < 10 g/dL; platelet count < 100,000; INR > 1.5 (e.g., use of warfarin)
9. Subject has an uncorrectable bleeding diathesis
10. Subject's neurological status is unstable and rapidly declining (NIHSS score increased > 4 points within 48 hours prior to randomization)
11. Subject has a contraindication for combination antithrombotic treatment (e.g., clopidogrel and aspirin) such as peptic ulcer disease
12. Subject history indicates high risk of non-compliance (e.g., substance abuse, psychosocial issues, etc.)
13. Subject has a known history contraindicating contrast dye or iodine (vs. sensitivity which can be safely controlled by antihistamine)
14. Subject is pregnant or plans to become pregnant in the next 12 months
15. Myocardial infarction within past 3 months
16. Treatment with tPA or other thrombolytic agent within 48 hours prior to randomization
17. Major surgery or trauma within 2 weeks prior to randomization
18. Enrollment in another investigational device or drug study that may confound the results

6.0 Method for Measuring % Stenosis

The WASID method defines the equation to measure percent stenosis as follows:

$$[\ 1 - (\ D_{stenosis} / D_{normal}\ )\ ] \times 100 = \%\ \text{Stenosis}$$

$D_{stenosis}$ = the diameter of the intracranial or extracranial vertebral artery at the site of the greatest narrowing

D_{normal} = the diameter of the proximal normal artery.

For D_{normal}

- First Choice – The diameter of the proximal part of the artery at its widest, non-tortuous, normal segment
- Second Choice – If the proximal artery is diseased, the diameter of the distal portion of the artery at its widest, parallel, non-tortuous, normal segment

- Third Choice – If the entire arterial segment is diseased, the most distal, parallel, non-tortuous normal segment of the feeding artery is measured [Samuels, AJNR 2000].

7.0 Subject Enrollment, Procedures, and Follow-Up

7.1 Screening and Consent

All Subjects who meet the eligibility criteria and give written informed consent are considered enrolled in the study and must be entered into the electronic database for assignment of Subject identification number. This unique number identifies each iCRF and should be used on all source documents so that study data is reported in anonymous form to protect Subject confidentiality.

A screen failed Subject refers to a Subject who signed the approved ICF but failed to meet all the eligibility criteria. There are no follow-up requirements for Subjects who electively withdraw from the study prior to randomization. The original ICF and a screening log will be maintained in the clinical site's study files.

If the Investigator is unable to place a PHAROS Vitesse Stent in a Subject randomized to the Stent Group, the Subject should continue on the Medical Therapy regimen and return for all follow-up assessments. The reason(s) for failure to place the stent will be documented on the Procedure iCRF.

7.2 Baseline Assessments

The following information will be assessed and the documentation will be maintained as source records at the study site:

- Neurological assessment of the Subject and evaluation of symptoms is done by an experienced neurologist. The severity of ischemic symptoms is classified by NIHSS (to be administered by research staff certified in the administration of the NIHSS).
- The Subject's mRS score will also be collected for the iCRF to reflect baseline functional status.
- EQ-5D questionnaire to assess general quality of life
- Medical History
- Current medications history including anti-platelet and anti-coagulation drugs
- Physical Examination
- Laboratory values to include hemoglobin (Hg), sedimentation rate, platelet count (Plt), prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR), high-density lipoprotein (HDL), low-density lipoprotein (LDL-C), creatinine (Cr), glucose, and pregnancy test (if Subject is a female with child-bearing potential).

- Chest X-ray
- Electrocardiogram
- CT scan or MRI to assess exclusion criteria (not sent to Core Lab)

7.3 Imaging

Any neurological imaging done relevant to a Serious Adverse Event shall be read by the Investigational site and the report provided to the clinical monitor as well as the data safety monitoring board (DSMB).[2] The DSMB may request redacted images for direct assessment if indicated by the nature of the SAE. Clinical adjudication of stroke, hard TIA, intracranial hemorrhage, and death events will be reported as determined by the DSMB (see Section 7.3).

7.3.1 Baseline Angiogram – All Subjects

After consent, all Subjects should complete the baseline assessments outlined in Section 7.2 and the Schedule of Assessments (Table 2). Subjects who meet all Inclusion/Exclusion criteria should then undergo angiogram according to Core medical imaging laboratory guidelines (Appendix IV) to measure and check the remaining inclusion and exclusion criteria.

Check for resistance to aspirin and clopidogrel prior to stent procedure. In order to avoid unnecessary exposure to radiation and contrast dye, angiograms done under standard of care within 30 days of randomization may be used if they were done in a manner consistent with the Core Lab protocol (see Appendix IV).

Perform four vessel angiograms (left and right vertebral arteries and left and right internal carotid arteries) prior to crossing the target lesion to evaluate other potential clinically significant and exclusionary issues in the baseline cerebral circulation unless the inclusion/exclusion criteria can be adequately assessed from non-invasive imaging (e.g., CTA or MRA ordered under standard-of-care). Orthogonal and working projections should be selected and documented for evaluation which must be reproduced during post-interventional and/or follow-up for precise comparisons. Measurement of stenosis must be done according to WASID criteria. Include specifics to determine a local percentage of stenosis with reference diameter in a normal vessel segment with parallel vessel walls proximal to the plaque or distal to the plaque outside post-stenotic dilatation or more proximally in the cavernous ICA-segment in cases with involvement of the tapered intradural ICA (see Section 7.2).

[2] The members of the DSMB have been selected from Institutions not participating as Investigational sites.

7.4 Randomization

Subjects meeting the final enrollment criteria after angiogram should then be randomly assigned to a treatment group by telephone (Phoenix Data Systems). Baseline data will have to be entered into the iCRF for this to occur including Investigator sign-off on Inclusion/Exclusion criteria. Subjects randomized to the Medical Therapy Group may be discharged after performing a CT or MR perfusion scan[3] and recovery from the angiogram.

Due to the logistics of scheduling anaesthesiology to support the Stent Group procedures without advance knowledge of which cases will require such support, these Subjects should undergo the stenting procedure within 24 hours of randomization.

Any Subject randomized to the medical therapy group who is treated with a stent at any point during the study will be counted as a major protocol deviation. Similarly, Subjects randomized to the stenting arm who receive another type of stent (not the PHAROS Vitesse) will also be counted as a protocol deviation. Subjects who crossover from medical therapy to the stenting arm and stent-assigned Subjects who do receive a PHAROS Vitesse stent will not be replaced in the trial.

7.5 Procedure – Stent Group

General anesthesia is recommended to ensure the Subject does not move during the precise measurements and stent placement procedures.

Note: Diabetic Subjects taking drugs containing metformin should be switched to insulin management the night before the stent procedure and not be restarted on metformin until 48 hours after the last injection of contrast dye.

Heparin is given during the angiogram and stenting procedures (100 I.U./kg). ACT and/or measurement of platelet function is recommended according to local protocols.

A stable vascular access with a long sheath and a coaxial 5 or 6 Fr guiding catheter, which should be placed as distal as possible, are strongly recommended to provide adequate support to navigate the stent delivery catheter around vascular curves.

The stent delivery catheter is prepared and introduced over a 0.014” guidewire. The stenosis is passed by the guidewire followed by the stent delivery catheter. Primary stenting is the procedure of choice. Predilatation is only recommended in cases with partly calcified stenosis using an undersized balloon (diameter (at least 0.5 mm below measured normal arterial diameter at angioplasty site). To select an appropriate stent length, select as short as possible for ease of navigation and good vessel wall apposition but long enough to cover the entire lesion plus 2 mm on each side of the target lesion.

Precise placement of the stent across the stenosis is required and should be controlled by road map or contrast injections. All tension and slack should be pulled out of the delivery

[3] If CT perfusion is used at procedure, the same should be performed at month 6. If MR perfusion is the chosen assessment at procedure, then MR perfusion should be repeated at month 6 for consistency and comparability.

catheter. Stent delivery is performed by very slow balloon inflation with increasing pressure over a period of about one minute or more. Over dilatation must be strictly avoided. Slight under dilatation according to the pressure-diameter table of the semi-compliant balloon is acceptable. After slow balloon deflation, post angiograms and CT or MR perfusion should be performed to evaluate proper stent positioning, apposition, and restoration of the vessel lumen. Careful retrieval of the delivery catheter is necessary to avoid dislodging the stent. Completion angiograms should display the stented site and the dependent intracranial territory in at least two orthogonal planes. Percent residual stenosis will be measured and reported on iCRF; pre and post angiograms must be provided to the Core Lab for independent assessment.

7.5.1 Post-Procedure Care

Following the angiogram, procedure, and CT or MR perfusion study, the Subjects will be asked to lie flat with a pressure bandage over the groin or radial puncture site according to the local standard of care (e.g., assess for bleeding, hematoma, pedal/radial pulses). The Subject will be monitored closely for significant change in neurological status (peri-procedural adverse events).

Stent Group Subjects should be monitored in an intensive care or intermediate care unit. Specifically treatment of hemodynamically relevant stenosis in the anterior circulation demands strict blood pressure monitoring for prevention of hyperperfusion injury, for the first 24-48 hours. Target maintenance of BP < 130/80 is desired to avoid post-stent hyperperfusion syndrome.[4] Aggressive use of protamine sulfate to antagonize the total dose of heparin should be avoided due to risk of stent thrombosis. Enter hourly vital signs X 3 in the post-procedure iCRF.

If new neurological deficit or a significant change in neurological status is identified by NIHSS/mRS during post-procedure monitoring, assess for intracranial thrombus or hemorrhage using CT scan or MRI if deemed appropriate by the Investigator under standard of care and treat accordingly.

Investigate fever >38˚C guided by standard of medical care (e.g., blood cultures, urinalysis, chest X-ray, phlebitis source), and treat as appropriate.

Enter any Serious Adverse Events into the electronic database promptly for Sponsor notification and to comply with local IRB/EC rules regarding reportable adverse events. Treat any adverse events according to the local standard of medical care.

[4] Please refer to the *Seventh report of the Joint National Committee (JNC7)* for guidelines on the management of blood pressure in the target population.
http://www.nhlbi.nih.gov/guidelines/hypertension/jnc7full.pdf

7.6 Discharge – Stent Group

On the day of discharge post stenting procedure, clinical and neurological assessment of the Subject is done. The severity of ischemic symptoms is classified by NIHSS and mRS. Assess for any new or unresolved adverse events, and record any changes in medication regimen as appropriate.

7.7 30-Day Follow-up Visit (+7 / -3 days)

During the 30-Day visit after the angiogram / stenting procedure, clinical assessment of the Subject and evaluation of neurological symptoms are done by an experienced neurologist. The neurological examination and severity of ischemic symptoms are classified by NIHSS and mRS. Assess for any new or unresolved adverse events, and record any changes in medication regimen.

7.8 3-Month Follow-up Visit (+/- 4 weeks)

During the 3-Month visit after the angiogram / stenting procedure, clinical assessment of the Subject and evaluation of neurological symptoms are done by an experienced neurologist. The neurological examination and severity of ischemic symptoms are classified by NIHSS and mRS. Assess for any new or unresolved adverse events, and record any changes in medication regimen.

7.9 6-Month Follow-up Visit (+/- 4 weeks)

During the 6-Month visit, clinical assessment of the Subject and evaluation of neurological symptoms are done by an experienced neurologist. The neurological examination and severity of ischemic symptoms are classified by NIHSS and mRS. A CT or MR perfusion scan, whichever was performed at procedure visit, will be done. The Subject's general quality of life will be measured using the EQ-5D questionnaire. Assess for any new or unresolved adverse events, and record any changes in medication regimen.

7.10 12-Month Follow-up Visit (+/- 6 weeks)

During the 12-Month visit, an angiogram is done for Stent Group Subjects to reassess the target lesion measurements and assess for in-stent restenosis. Follow the Core Lab guidelines in Appendix IV and submit the uncompressed DICOM images to Bio-Imaging as directed (MRA/CTA/Doppler US is not considered an acceptable substitute). Clinical assessment of all Subjects and evaluation of neurological symptoms is done by an experienced neurologist. The neurological examination and severity of ischemic symptoms are classified by NIHSS and mRS. The Subject's general quality of life will be measured using the EQ-5D questionnaire. Assess for any new or unresolved adverse events, and record any changes in medication regimen. Complete a Termination iCRF for study completion for all Subjects.

7.11 Unscheduled Follow-up Visit

If an unscheduled follow-up visit occurs post-procedure at the investigational site, assess for new or unresolved adverse events. If the visit is due to a change in neurological status, complete NIHSS and mRS iCRFs. Document any imaging ordered and, if related to stroke or neurovascular death, send redacted images to Core Lab for DSMB adjudication. Change of medications, diagnostic test results, or interventions completed should be documented in the web-based iCRF.

7.12 Schedule of Assessments

A summary of the study related assessments as outlined above is described in Table 2.

Table 2: Schedule of Assessments

Assessment	Baseline	Angiogram and Stent Procedure	Discharge (Stent Group)	30 Days +7 / -3 Days	3 Months +/- 4 Weeks	6 Months +/- 4 Weeks	12 Months +/- 4 Weeks
Informed Consent	✓						
History & Physical Exam	✓						
Medications Review	✓		✓	✓	✓	✓	✓
mRS	✓		✓	✓	✓	✓	✓
NIHSS (neuro exam)	✓		✓	✓	✓	✓	✓
EQ-5D questionnaire	✓					✓	✓
Blood Labs	✓	✓					
Chest X-ray	✓						
ECG	✓						
CT scan or MRI	✓						
CT or MR perfusion study[3]		✓				**Stent Group**	
Angiogram		**All Subjects**					**Stent Group**
Adverse Events		✓	✓	✓	✓	✓	✓

Notes:

1) *Baseline angiogram should be 4 vessels (right and left internal carotid and vertebral arteries) to assess stenosis measurements and other potential cerebral circulation pathology* unless the inclusion/exclusion criteria can be adequately assessed from non-invasive imaging (e.g., CTA or MRA ordered under standard-of-care). *All study angiograms are to be provided to Bio-Imaging (see Appendix IV).*
2) *For unscheduled visits to study site, assess for adverse events. If visit is due to a change in neurological status, complete NIHSS and mRS stroke scale iCRFs.*

3) Be consistent. If CT perfusion is done at procedure, then CT perfusion should be repeated at month 6. Likewise, if MR perfusion was done at procedure, MR perfusion should be repeated at month 6.

7.13 Study Completion

After the Subject has completed the 12-month follow-up examination, a Subject Termination iCRF must be completed. During the course of the study, it is possible that Subjects will be withdrawn from the study early. Factors leading to Subject withdrawal may include, but are not limited to the following:

- **Subject Withdrawal** - A Subject may voluntarily withdraw from the study at any time without affecting their future medical treatment or benefits. In addition, the Investigator may withdraw a Subject from the study if the Subject refuses further testing or follow-up evaluations, or for any other reason as determined by the Investigator.
- **Subject Lost to Follow-Up** – If the Investigator has attempted to contact a Subject at least three times and receives no response, the Subject may be lost to follow-up. The research staff should document at minimum three attempts to contact the Subject prior to terminating a Subject from the trial.
- **Subject Death** - When a Subject expires, the SERIOUS ADVERSE EVENT and SUBJECT TERMINATION iCRFs must be completed promptly. Source documents such as death summary, autopsy report (if done), and a copy of the death certificate should be redacted of personal identifiers and provided to the designated clinical monitor and DSMB to describe the cause of the Subject's death. The Investigator will notify the IRB/EC and Sponsor within 48 hours upon leaning of the event.

Complete the Termination iCRF to record date and reason for early termination (if Subject does not complete the study) or at the final Visit (if Subject completes all study time points).

8.0 Management of Adverse Events

8.1 Definitions

An Adverse Event (AE) is any untoward medical occurrence in a Subject after study enrollment.

A Serious Adverse Event (SAE), per ISO 14155 (Clinical Investigation of Medical Devices for Human Subjects), is an adverse event that:

- Led to a death
- Led to a serious deterioration in the health of the Subject that –

o Resulted in a life-threatening illness or injury

o Resulted in a permanent impairment of a body structure or a body function

o Required hospitalization or prolongation of existing hospitalization

- Resulted in medical or surgical intervention to prevent permanent impairment to body structure or function

Note: The following hospitalizations are not considered SAEs:

- Diagnostic or elective surgical procedures for pre-existing condition, unless the condition becomes more severe or increases in frequency
- Therapy of the study target disease explicitly anticipated and defined in the protocol. For example, if a Subject is enrolled because of hard TIA symptoms and randomly assigned to the Medical Therapy Group and is kept in the hospital for observation overnight post uncomplicated angiogram per local standard of care, such hospitalization would not be considered an SAE. Similarly, the Stent Group Subjects would be expected to be in the hospital for close monitoring post-procedure. Report an SAE for post-procedure hospitalizations considered by the Investigator to be prolonged due to a complication.
- study effectiveness measures, as defined in the protocol (e.g., the 12-Month visit angiogram)

An Adverse Device Effect (ADE) is any untoward and unintended response to a medical device.

A Serious Adverse Device Effect (SADE) is an ADE that has resulted in any of the consequences characteristic of an SAE or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune.

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

8.2 Reporting of Adverse Events

An Investigator will submit to the Sponsor a report of any SAE, or SADE occurring during an investigation as soon as possible but in no event later than 5 working days after the Investigator first learns of the event. The report will be entered directly into the web-based electronic database, and email alerts will automatically notify the Sponsor of the occurrence of such events; the Sponsor will coordinate communications with the members of the DSMB. In addition, the reviewing IRB/EC rules defining reportable events must be followed by the Site's Principal Investigator or designee. Documentation of events reported to the IRB/EC, such as IRB/EC acknowledgement of receiving such reports, should be provided to the clinical monitor.

All adverse events will be recorded on the appropriate iCRF and in the Subject's medical records. The Investigator will also identify the date of onset, date of resolution, severity, seriousness, outcome, and the potential relationship to any Micrus device or procedure.

The relationship of the adverse event or procedural complication to any Micrus device will be rated and recorded on the iCRF as follows:

- ***Related –*** the adverse event had a direct relationship to the investigational device or procedure
- ***Possibly Related –*** the adverse event may have had a relationship to the investigational device or procedure
- ***Unrelated –*** the adverse event was due to underlying disease or to concomitant medication or therapy not related to the investigational device or procedure
- ***Unknown –*** the relationship of the adverse event to the investigational device or procedure cannot be determined

8.2.1 Severity of Adverse Events

In addition to seriousness, all adverse events will be categorized as follows:

- ***Mild –*** the adverse event did not interfere with functioning
- ***Moderate –*** the adverse event symptoms are severe enough to interfere with activities of daily living
- ***Severe –*** the adverse event symptoms are incapacitating requiring treatment

Appropriate treatment for AEs will be available for study Subjects.

8.3 Independent Adjudication of Clinical Outcome Events by DSMB

All potential stroke, hard TIA, and death outcome events will be reviewed and adjudicated by the DSMB (the members of which are not otherwise involved in the study). Clinical event summaries and relevant imaging studies will be reviewed by the DSMB which includes a neurointensivist, a vascular neurologist, an interventional neuroradiologist, and a biostatistician.

9.0 Risk / Benefit Analysis

9.1 Risks of Neurovascular Stenosis and Standard Medical Therapy

The average rate of ischemic events under antithrombotic treatment with daily aspirin or warfarin was reported as approximately 10% per year in the WASID study. A subgroup of patients with ≥ 70% stenoses showed even higher stroke risks of approximately 20% in the first year [Kasner, et al 2006]. Non-randomized studies give rise to the assumption that patients with recurrent symptoms despite optimized medical treatment, hemodynamic impairment, or progressive stenoses might also have increased stroke risks under medical therapy alone [Thijs et al 2000]. The risks of neurovascular stenosis and medical therapy include:

- Allergic reactions or sensitivities to medications (e.g., nausea, gastrointestinal distress, hives, respiratory distress)
- New or worsening stenotic plaques from underlying pathology
- Coronary artery disease (CAD)
- Cranial nerve deficit (from slurred speech or visual disturbances to paralysis)
- Death
- Hypertension
- Hypotension
- Myocardial Infarction
- Peripheral vascular disease (PVD)
- Stroke
- Transient Ischemic Attacks (TIA)

9.2 Risks of Angiogram

In addition to the above risks of neurovascular stenosis and medical therapy, there are risks associated with angiography due to the groin puncture, injection of contrast dye, and vessel trauma including:

- Allergic reaction or sensitivity to contrast dye, including anaphylaxis
- Bleeding / bruising
- Hematoma (including retroperitoneal)
- Hemorrhage (e.g., subarachnoid)
- Infection
- Pain / discomfort
- Phlebitis
- Vessel injury (e.g., perforation, dissection / puncture / rupture / thrombosis)

9.3 Risks of Intracranial Stenting

In addition to the above risks of neurovascular stenosis, medical therapy, and angiography, the review of the Cochrane database of intracranial stent studies, as well as published case series, reveals an average 30 day stroke and death rate of approximately 10% [Cruz-Flores 2006, SSYLVIA 2004, Berkefeld 2006, Levy 2007, and Jiang 2007]. However, high restenosis rates in up to 30% of Subjects may limit long-term effectiveness of intracranial stenting with prior approved stent technologies (SSYLVIA 2004, Levy 2007).

Although safety and probable benefit have been established for both balloon-expandable and self-expanding systems for neurovascular indications (H01004 NEUROLINK® System, H050001 Wingspan™ Stent System), effectiveness of these systems has not yet been studied in a prospective, randomized comparison to the standard of care (i.e., medical therapy). The HDE-approved self-expanding system (Wingspan Stent System) has been commercialized in the United States. The HDE-approved balloon-expandable system (NEUROLINK System) was never commercialized in the United States.

Early experience (bench, animal, and reported clinical outcomes from single center case series using the PHAROS Stent system under CE-Mark indications) with the PHAROS balloon-expandable stent system suggests favorable technical success and acceptable

safety. The goal of this Investigational Device Exemption study is to prospectively collect clinical data regarding safety, probable benefit, and effectiveness of this therapeutic option.

The risks of intracranial stenting include:

- Coagulopathy
- Death
- Decreased level of consciousness including coma
- Embolism
- Failure to deliver or properly position stent
- Fever
- Fistula
- Headache
- Hemorrhagic conversion post treatment of ischemic stroke
- Intracranial hemorrhage
- Ischemia
- Medication reaction
- Neurological deterioration
- Pseudoaneurysm
- Restenosis / occlusion
- Seizure
- Stent migration / misplacement
- Stroke involving previously uninvolved territory
- Syncope
- Thrombus
- Urinary tract infection
- Vasospasm

In addition to above risks, it is anticipated that adverse events associated with medical comorbidities and daily living over the course of the study will be captured on iCRF and categorized by organ system including:

- Angina
- Anxiety
- Depression
- Dysrrhythmias
- Edema
- Hematuria
- Hiatal hernia
- Hyperglycemia / hypoglycemia
- Laboratory abnormalities (capture if clinically significant change from baseline)
- Multi-organ system failure
- Myocardial infarction (MI)
- Pneumonia
- Pulmonary edema
- Renal insufficiency / failure
- Respiratory distress / failure
- Trauma (e.g., motor vehicle accidents, falls, fractures).

9.4 Potential Benefits of Intracranial Stenting

Although there is insufficient data to support any promise of clinical benefit from participating in this clinical trial, selected Subjects with symptomatic neurovascular stenoses may benefit from improved blood flow by widening the stenotic lumen with a neurovascular stent; thus, potentially lowering their risk of stroke to a rate that is comparable to or better than medical therapy alone. They may also benefit from the additional close monitoring and management provided by a research team of neurologists and neurointerventionalists. There is an opportunity for Subjects and their families to increase their knowledge about neurovascular disease, treatment options, and long-term management of their vascular disease and individual risk factors.

10.0 Ethics and Regulatory Considerations

10.1 Subject Information and Consent Procedures

The Investigator, or designee, will obtain written informed consent from the Subject prior to performing study assessments. The Subject will be informed that the Sponsor and regulatory authorities will have access to personally identifiable information for the purposes of monitoring data against source documentation. However, all data entered in the database, filed, and presented by the Sponsor will be in anonymous form.

The site customized ICF (see sample ICF provided by Sponsor), must be approved by Micrus and the IRB/EC before use. Each Investigational site will provide Micrus with a copy of the IRB/EC approved ICF and renewed approvals and consents as appropriate for the duration of the study.

The original, signed and dated ICF should be retained in the Subject's study records, and a copy provided to the Subject. The consent completion will be monitored by the Sponsor or designee.

10.2 IRB/EC Approval

The Investigator, or designee, is responsible to submit the clinical protocol and any Amendments to the IRB/EC for approval prior to any Subject being enrolled and to obtain renewals at periods determined by the IRB/EC for the duration of the study.

11.0 Statistical Methods

Kasner SE et al; (*Circulation* 2006; 113:555-563, Table 3), report that the 1-year risk of ipsilateral stroke in WASID increases with the degree of intracranial artery stenosis. It is interesting to note that the results from WASID are surprisingly congruent with the results from the largest trial of extracranial artery stenosis, assessing the efficacy of carotid

endarterectomy (Table 6, personal communication M. Eliasziw). The trial was named North American Symptomatic Carotid Endarterectomy Trial (NASCET; Barnett 1998). The NASCET surgical results are also congruent with the periprocedural results from Marks MP et al. (*Stroke* 2006;37:1016-1020) and Fiorella D et al. (*Stroke* 2007;38:881-887) (5.8% and 6.1%, respectively), and with the 1-year risk of ipsilateral stroke (9%, Marks MP et al.).

Table 3: One-Year Risk of Ipsilateral Stroke by Degree of Stenosis

	Intracranial Medical WASID		**Extracranial Medical NASCET**		**Extracranial Surgical NASCET**		
Percent Stenosis	**Number Patients**	**Risk (%)**	**Number Patients**	**Risk (%)**	**Number Patients**	**Risk (%)**	**Periop (%)**
50-59	134	7	238	10.3	239	8.5	7.6
60-69	151	8	190	10.7	191	8.5	5.8
70-99	203	18	331	16.9	328	7.0	5.5
Overall	488	12	759	13.1	758	7.9	6.2

Using the congruency of results between WASID and NASCET, as well as, methodological concepts from another trial of carotid endarterectomy by the Veterans Administration (Mayberg et al., *Journal of the American Medical Association* 1991;266:3289-3294), a composite outcome of stroke and hard TIA in the same territory as the target stenosis was used to define the primary endpoint for effectiveness in the present trial. The 1-year NASCET results, supporting this choice of composite outcome appear in Table 7 (personal communication M. Eliasziw).

Table 4: One-Year Risk of Ipsilateral Stroke or Hard TIA by Degree of Stenosis

	Extracranial Medical NASCET		Extracranial Surgical NASCET		
Percent Stenosis	**Number Patients**	**Risk (%)**	**Number Patients**	**Risk (%)**	**Periop (%)**
50-59	238	18.7	239	11.9	8.9
60-69	190	21.3	191	12.2	7.4
70-99	331	31.7	328	10.4	7.3
Overall	759	24.8	758	11.3	7.8

11.1 Sample Size Estimation: Based upon Composite of Stroke and Hard TIA in the Same Territory as the Target 70-99% Stenosis

For the stent arm, the 30-day composite periprocedural rate of stroke or hard TIA in any territory and death from any cause is assumed to be 8%. From 31 days to 1 year, the risk of primary outcome is assumed to be 3%. Summing these two percentages yields a 1-year risk of outcome of 11% in the stenting arm. Extrapolating from the NASCET trial to intracranial disease, the 1-year risk of primary composite outcome (including stroke or hard TIA in any territory or death from any cause within 30 days of randomization) is estimated to be 31%. To detect an absolute difference of 20% (a 65% relative risk reduction) with 90% power at a two-sided 5% level of significance, a total of 172 Subjects need to have evaluable data at the 12-month visit. Allowing for a combined 30% crossover, stent failure, withdrawal, and lost-to-follow-up rate, up to 250 Subjects will be enrolled.

11.2 Statistical Analysis Plan

- Kaplan-Meier event-free survival analysis will be used to compare the two treatment arms for the primary endpoint of effectiveness, and tested for statistical significance using the logrank test. Standard errors of the absolute risk reduction at 12 months and corresponding 95% confidence intervals will be calculated with the use of Greenwood's formula.
- A chi-square test will be used to compare the two treatment arms for the primary safety outcome, namely percentage of Subjects with pre-defined clinical outcomes within the first 30 days of randomization. A corresponding 95% confidence interval about the difference in percentages will be calculated using the normal approximation formula.
- The percentage of Subjects with successful deployment of a PHAROS Vitesse stent will be calculated and an exact 95% confidence interval will be calculated using the

binomial distribution. An identical approach will be used to calculate the percentage of Stent Group Subjects with symptomatic in-stent restenosis ≥ 70% confirmed by angiogram at 12 months.

- As both the NIHSS and mRS are ordinal, the treatment arms will be compared by selecting clinically meaningful cutpoints to create binary variables. For the NIHSS, an increase of 4 or more points from baseline to 12 months is considered to represent neurological worsening. For the mRS, a score of 3 or greater at 12 months will be considered to be functionally disabled; however, since Subjects may enroll with a mRS score of 3, a negative outcome will be counted if Subjects with a baseline mRS score of 2 or 3 increase their mRS by at least one point. For both these binary variables, the chi-square test will be used to assess statistical significance. For Subjects who die or become lost to follow-up during the 12-month period since randomization, the last-observation-carried-forward (LOCF) approach will be used to impute the score at 12 months. The Sponsor believes that the LOCF approach represents a conservative analysis in this Subject population.
- The EQ-5D is a generic health-related quality of life measure that defines health status in terms of 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has three levels of response corresponding to 'no health problems,' 'moderate health problems,' and 'extreme health problems.' A dimension for which there are no problems is said to be at level 1, while a dimension for which there are extreme problems is said to be at level 3. Although it's common practice to calculate a mean EQ-5D score using weighted health states, the present trial will use an equally common practice of comparing the percentage of patients reporting any health problems (moderate or severe) in the two arms for each of the 5 dimensions, using a chi-square test.
- The percentage of Subjects who crossover from medical therapy and receive a stent will be calculated and an exact 95% confidence interval will be calculated using the binomial distribution. For Subjects assigned to the stent arm, an identical statistical approach will be used to report the percentage of stent failures and percentage who received a non-trial stent.
- All clinical outcome analyses will be intention-to-treat, defined as enrolled Subjects who meet all Inclusion/Exclusion criteria and are randomized post angiogram. Clinical outcomes among medically-randomized Subjects who subsequently receive a stent will be analyzed as part of the medical arm. Clinical outcomes among Subjects assigned to the investigational stent arm who require intervention with a non-study stent, (e.g., if neurointerventionalist is unable to access target stenosis after attempting to place a PHAROS Vitesse), will be analyzed as part of the stent arm. P-values will be two-tailed, and results with p-values < 0.05 will be considered statistically significant.
- Per-protocol analyses will also be conducted, consisting of all enrolled Subjects who meet all Inclusion/Exclusion criteria, are randomized post angiogram, and stay within their assigned treatment arm (medical therapy or PHAROS Vitesse stent only) for the entire duration of the 12-month follow-up.
- Adverse events will be categorized and summarized according to organ system and time point so that analyses can be performed for each study period (within 30 days or the procedure or randomization, and follow-up period). Of specific note, all TIAs occurring within the first 5 days after randomization will be recorded and analyzed as adverse events.

- Three subgroup analyses are planned. The primary outcome will be required to yield a p-value < 0.05 prior to analyzing these subgroups. Cox proportional hazards regression will be used to assess the statistical significance of the interaction between treatment arm and each of the three subgroup factors individually. To adjust the three interaction p-values for multiplicity, and to control the familywise error rate at 5%, Holm's stepdown Bonferroni method will be used to assess statistical significance.
    1. Time from presenting symptoms to randomization $\leq$14 days versus > 14 days;
    2. Type of presenting event stroke versus TIA. Both factors have been reported in the literature as modifying effects of benefits for extracranial disease;
    3. Subjects $\leq$ age 55 years with supraclinoid lesions as it's been reported they have a higher rate of in-stent restenosis [Fiorella, ASITN 2007].

11.3 Analysis for HDE Application

For the purpose of supporting a possible Humanitarian Device Exemption (HDE) application, data only from the stenting arm will extracted when 75 eligible Subjects have been enrolled in the stenting arm and followed for 6 months. The number 75 was chosen because by the time this cohort reaches their 6-month follow-up visit, all 250 Subjects are expected to be enrolled into the trial. To protect the integrity of the final randomized comparisons, only the first 75 eligible Subjects in the stenting arm will be used for an HDE application to compare the safety profile and outcome events to historical controls. The analyses will consist of the 30-day and 6-month safety outcomes and other 6-month clinical outcome measures to include neurological status. Adverse events, occurring within 6 months of randomization, for the cohort of 75 Subjects will also be reported.

Except for the single extraction of 75 stented Subjects followed for 6 months, no further data looks are planned.

11.4 Demographics by race/ethnicity

Of the 30 sites, it is estimated that the countries will break down as follows:

- United States approximately 15 sites
- Europe approximately 7 sites (e.g., Austria, Germany)
- China approximately 4 sites
- Additional sites may include Brazil, Argentina, Canada, Australia

Because cerebral ischemia due to stenoses in the neurovasculature is more prevalent in the Native American, Alaskan native, black, and Hispanic patient population, it is anticipated that there will be a higher relative percentage of these patients represented in the study population (http://www.cdc.gov/mmwR/preview/mmwrhtml/mm5619a2.htm). In addition, it is expected that sites that see high numbers of the target population will enroll at a faster rate (e.g., some sites in China typically perform significantly more intracranial stenting procedures than experienced sites in the US and EU).

12.0 Records and Reports

12.1 Records

The investigational site will maintain iCRF and source study records for monitoring and/or audit purposes for the latter of:

- At least two years after study completion
- At least two years after Sponsor submits data to a regulatory authority
- For the period required by the local governing authority and reviewing IRB/EC

Sponsor is to be advised prior to destruction of study records and notified if study records are moved to an off-site location for archiving.

12.2 Reports

Investigators at participating sites are required to submit reports in conformance with all applicable regulations.

13.0 Data Management

All required data for this study will be collected on appropriate source medical records and study forms and entered into a secure, 21 CFR Part 11 compliant, web-based database (Phoenix Data Systems).

14.0 Monitoring of the study and Quality Control

14.1 Medical Monitoring by DSMB

All SAEs will be evaluated by the DSMB members for potential relationship to the investigational device or procedure. All AEs will be evaluated by Sponsor for significance and relevance with respect to trends that may represent a previously unknown or unanticipated risk that may relate to the investigational device or procedure.

14.2 Data Collection and Monitoring

The research Coordinator will collect and document data in hospital and clinic charts and on source document forms prepared for the study. iCRF data will be entered in anonymous form into the secure web-based, password protected database. Passwords will not be issued by the Sponsor until Site Initiation and database training has been conducted for all personnel to whom Investigator has delegated data entry responsibilities. Hardcopy blank CRFs may be reproduced as needed and may be used as source documents; these should

be signed and dated by the person collecting the data. Completed iCRFs in final form (with queries resolved) may be printed and filed in hardcopy for archiving if required by local governing authority. All data will be exported and stored on appropriate electronic media by Sponsor and to biostatistician for group analyses.

The Sponsor will designate and train monitors to review iCRF data against source documents for completeness and accuracy. Discrepant data will be queried; the electronic database will maintain audit trails of all queried and corrected data. The Investigator is responsible for data integrity at the site and will review and electronically sign all Inclusion/Exclusion, Adverse Event, Deviation, and Terminations iCRFs.

14.3 Source Documentation

Regulations require that Investigators maintain information in the study Subject's medical records that corroborate data reported in the iCRFs. In order to comply with these regulatory requirements, at minimum the following information should be maintained:

- Sufficient medical history/physical condition of the study Subject before involvement in the study to verify protocol entry criteria
- Dated and signed notes on the day of entry into the study including a statement regarding the consent process followed
- A log that maps the key to Subject identity for monitors and auditors showing Subject name and assigned identification number. This record will not be collected by Sponsor but should be maintained at the study site so that the appropriate medical records are compared to study iCRF data.
- Dated and signed progress notes, procedure reports, assessments, and diagnostic results as appropriate to each study Subject visit to confirm iCRF data
- Investigator / site radiologist assessment of medical imaging
- Evaluate clinical significance of abnormal lab results
- Records following adverse events reported, results of diagnostic tests ordered, treatment given, and clinical outcome at resolution or stabilization
- Dictated procedure report
- Dictated discharge summary;
- Notes regarding medications taken during the study
- Study Subject's condition upon completion of, or withdrawal from, the study.

14.4 Site Compliance / Deviations

The Sponsor requests that all iCRFs should be entered in the web-based database as indicated in Table 5.

Table 5: Electronic Data Entry Timelines

iCRF	Timeline
Serious Adverse Event iCRF	Complete SAE on web-based database within 48 hours of learning of event for Sponsor notification. Provide source documents to monitor as soon as available. Comply with local reviewing IRB/EC reporting rules.
All other iCRFs	Within 14 days of Subject discharge or follow-up

The clinical site will be monitored routinely for adequate enrollment, timeliness of data submission, and compliance with the investigational plan and local regulations. Consistent pattern of non-compliance with respect to the above will require a corrective action plan to be negotiated with the Investigator. If corrective actions are not effective in resolving site compliance, the clinical site may be withdrawn from the study by the Sponsor.

Significant deviation from the protocol will be reported to the Sponsor via the Deviation iCRF which may be completed by the site or the monitor. The Sponsor will categorize deviations as major (e.g., improper informed consent, inappropriate use of investigational device) or minor (e.g., visit outside window, assessment missed). Deviation reports will be submitted to the U.S. FDA by the Sponsor and should be submitted to the reviewing IRB/EC by the site.

In the event that the Investigator identifies a potential Subject that meets all but 1 Inclusion/Exclusion criterion and expresses a medical opinion regarding why it is appropriate to consider the patient for the study, this documentation may be submitted to the Sponsor for consideration. If the Sponsor agrees, then a prospective deviation may be approved to allow the Subject to be enrolled in the study.

15.0 References

1. Barnett HJM, et al; Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis; N Engl J Med, 1998; 339:1415-25
2. Berkefeld J, et al; Endovascular treatment for intracranial stenoses. A common statement by neurologists and neuroradiologists. Nervvnarazt, 2006 Dec;77 (12):1444-55
3. Chimowitz MI et al, Comparison of Warfarin and Aspirin for Symptomatic Intracranial Arterial Stenosis. NEJM 2005; 352:1305-1316
4. Cruz-Flores S and Diamond AL; Angioplasty for intracranial artery stenosis; Cochrane Database of Systematic Reviews, 2006; Issue 3. Art. No.: CD004133. DOI: 10.1002/14651858.CD004133.pub2 [Review]
5. Derdeyn CP and Chimowitz MI; Angioplasty and Stenting for Atherosclerotic Intracranial Stenosis: Rationale for a Randomized Clinical Trial; Neuroimaging Clinics of N Am 2007; :355-363
6. Fiorella D and Woo HH; Emerging Endovascular Therapies for Symptomatic Intracranial Atherosclerotic Disease; Stroke, 2007; 38:2391-2396
7. Fiorella D, et al; A 7-year Experience with Balloon-mounted Coronary Stents for the Treatment of Symptomatic Vertebrobasilar Intracranial Atheromatous Disease; Neurosurgery, August 2007; 61:236-243
8. Fiorella D., et al. US Multi-center Experience With the Wingspan Stent system for the Treatment of Intracranial Atheromatous Disease, Stroke, Mar 2007;38:881-887
9. Freitas JMM, et al; Intracranial arterial stenting for symptomatic stenosis: a Latin American experience. Surgical Neurology, October 2007; 68-4:378-386
10. Hacke W, et al; Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS-II). Second European-Australasian acute stroke study investigators. Lancet 1998;352:1245-1251
11. Jiang WJ, et al; Comparison of elective stenting of severe vs moderate intracranial atherosclerotic stenosis; Neurology 2007; 68:420-426
12. Jiang WJ, et al; Apollo stent for symptomatic atherosclerotic intracranial stenosis: study results. AJNR 2007 May;28(5):830-834
13. Johnston SC, Gress DR et al; Short-term Prognosis after Emergency Department Diagnosis of TIA ; JAMA 2000;284:2901-2906
14. Kasner SE, et al; Warfarin vs. aspirin for symptomatic intracranial stenosis: subgroup analyses from WASID. Neurology 2006 Oct 10;67(7):1275-8
15. Kasner SE, et al; Predictors of ischemic stroke in the territory of a symptomatic intracranial arterial stenosis. Circulation, 2006 Jan 31;113(4):555-563
16. Levy EI, et al; Wingspan In-stent restenosis: Incidence, clinical presentation, and management; Neurosurgery 2007, 61(3):644-651
17. Marks MP, et al; Angioplasty for Symptomatic Intracranial Stenosis: Clinical Outcome; Stroke 2006; 37:1016-1020

18. Mayberg MR et al; Carotid Endarterectomy and Prevention of Cerebral Ischemia in Symptomatic Carotid Stenosis; JAMA Dec 1991; 266:3289-3294

19. National Institute for Health and Clinical Excellence: Interventional Procedures Programme. Interventional procedures overview of endovascular stent insertion for intracranial atherosclerotic disease; March 2007; www.nice.org.uk/ip386overview

20. P030037; Summary of Safety and Effectiveness Data, Rithron-XR Coronary Stent System, April 29, 2005

21. Sacco RL, Kargman DE, Gu Q, Zamanillo MC: Race-ethnicity and determinants of intracranial atherosclerotic cerebral infarction. The Northern Manhattan Stroke study. Stroke 1995;26:14-20

22. Samuels OB, et al; A standardized method for measuring intracranial stenosis; Am J Neuroradiol 2000; 21:643-646

23. SSYLVIA study Investigators: Stenting of Symptomatic Atherosclerotic Lesions in the Vertebral or Intracranial Arteries (SSYLVIA): study results; Stroke 2004;35:1388-1392

24. Thijs VN and Albers GW, Symptomatic intracranial atherosclerosis: outcome of patients who fail antithrombotic therapy. Neurology. 2000 Aug 22;55(4):465-466