Venous Sinus Stenting to Treat Intractable Pulsatile Tinnitus Caused By Venous Sinus Stenosis

Updated IDE G150164 Protocol

May 12, 2017

NCT02734576

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Sponsor/ Primary Investigator: Athos Patsalides MD MPH
Department of Neurological Surgery
Division of Interventional Neuroradiology
Weill Cornell Medical College
525 East 68th Street, Box 99
New York, NY 10065
Tel: 212-746-2821
Fax: 212-746-8111
Email: atp9002@med.cornell.edu

REPORT OF PRIOR INVESTIGATIONS

We seek permission to use the **Cordis Precise Pro Rx Nitinol Stent System** to treat intracranial dural venous sinus stenosis in patients with severe venous pulsatile tinnitus and severe lateral venous sinus stenosis.

The sponsor of this application has performed prior use of the device to treat symptomatic stenosis of dural venous sinuses in a series of more than 20 patients in the United States. Specifically, we have IDE approval to use this same device in a prospective clinical trial titled "Venous sinus stenting for Idiopathic Intracranial Hypertension refractory to medical therapy" (IDE# G090050), and 10 patients have been enrolled in this trial (last annual report attached). The anatomic location and the procedure of stent placement are identical in this protocol and IDE# G090050. Moreover, 10 additional patients with symptomatic venous sinus stenosis were treated outside the trial. There were no significant neurological or device related complications. Recently, a paper was published (Baomin et al. 2014) reporting on the results of 46 cases of pulsatile tinnitus and lateral (transverse and sigmoid) venous sinus stenosis treated with stenting using the Cordis Precise Pro Rx Nitinol Stent System. The procedure was successful in all 46 patients, resulting in resolution of tinnitus in all patients. There were no neurological or device related complications. Therefore, there are at least 66 cases of the Cordis Precise Pro Rx Nitinol Stent System used to treat stenosis of the lateral (transverse and sigmoid) venous sinus without severe procedural or neurological adverse events.

The Cordis Precise Pro Rx Nitinol Stent System Cordis is approved by the FDA under Premarket Approval (PMA) for carotid revascularization in patients at high-risk for adverse events from carotid endarterectomy and:

1. ≥ 50% common or internal carotid artery stenosis with associated neurological symptoms, or ≥ 80% common or internal carotid artery stenosis without associated neurological symptoms, and
2. Vessel diameter 4-9 mm at the target lesion.

INVESTIGATIONAL PLAN

HYPOTHESIS AND OBJECTIVES

Papers published during the last seven years show that in patients with venous pulsatile tinnitus and significant venous sinus stenosis, tinnitus improves or resolves after stenting in the vast majority of patients. There have been 100 patients with venous sinus stenosis and venous pulsatile tinnitus reported in the literature (Table 1, attached document). Fifty-four of these patients had Idiopathic Intracranial Hypertension and venous pulsatile tinnitus and the rest had isolated venous pulsatile tinnitus. After stenting, the venous pulsatile tinnitus resolved in 93/100, improved in 4/100 and remained unchanged in 3/100. This corroborates our experience at Cornell; out of 18 patients with venous sinus stenosis and venous pulsatile tinnitus treated by the PI with stenting, 17 had immediate resolution of the tinnitus. In one patient the tinnitus remained unchanged (anecdotal evidence; paper submitted for publication).

Our hypothesis is that venous pulsatile tinnitus is caused by the venous sinus stenosis and stenting would offer effective and long-term resolution of these symptoms. Our project aims to evaluate the long-term efficacy of venous sinus stenting in patients with severe intractable venous pulsatile tinnitus.

Primary Outcome:

- The primary outcome will be complete or near-complete resolution of tinnitus at 12 months in more than 75% of treated patients.
- Primary Outcome Measure: No, slight, mild, or moderate tinnitus (grades 1, 2, and 3) on Tinnitus Handicap Inventory at 1, 6, 12, and 24 months

Secondary Outcomes:

- Long-term success of treatment (clinical recurrence rates over 24 months)
- Long-term patency of the stent (stent patency 12 months after treatment)
- Rate and severity of adverse events probably or possibly related to the treatment within a 24-month period

BACKGROUND AND SIGNIFICANCE

Introduction

Tinnitus is the conscious perception of sound that seems to arise from the ear when no external acoustic stimulus is present. It is a complex symptom rather than a syndrome or disease and can present itself as many possible sounds, including whooshing, ringing, whistling, buzzing, or clicking. These abnormal noises can either be perceived in one or both ears, and can occur intermittently or constantly. It is estimated that tinnitus affects about 25.3% in the general population in the United States which corresponds to an estimate of 80 million adults (Shargorodsky, 2010).

Tinnitus has many variants and can be categorized by its level of audibility, rhythm, and etiology. In terms of audibility, tinnitus which can be heard by a physician, either with a stethoscope or listening closely to the ear, is termed objective tinnitus. Subjective tinnitus, on the other hand, is audible only to the patient. Tinnitus can also be categorized by its rhythm. Pulsatile tinnitus sound synchronizes with the rhythm of the patient's heartbeat, in contrast to non-pulsatile tinnitus, which includes all other noises. Contributing to their different rhythm patterns, the source of sound for pulsatile and non-pulsatile tinnitus are also different. Pulsatile tinnitus usually has a physical source of sound in the tissues of the ear, in particular, due to turbulence of blood flow surrounding the ear. This disturbance can occur in either arterial or venous locations. Non-pulsatile tinnitus, on the other hand, typically results from a problem with the nerves.

Pulsatile Tinnitus

Of the tinnitus population, 4% is estimated to have pulsatile tinnitus, which is roughly a population of 3.2 million (Liyanage et al. 2006). Although pulsatile tinnitus affects a small percentage of the population, it can be dangerous if left undiagnosed. Pulsatile tinnitus is mostly reported as an annoying rather than severe symptom, however there is a sub-set of patients who experience it to a debilitating degree. The perceived sounds can become so intense and frequent as to become incapacitating, cause difficulty sleeping or concentrating, seriously interfere with work, increase stress, and create feelings of depression or anxiousness. Some patients may even become diagnosed with psychological problems (Baomin et al. 2014). Furthermore, pulsatile tinnitus may be the

only presenting symptom of an underlying serious condition such as: arteriosclerosis, vascular tumor, idiopathic intracranial hypertension, arteriovenous malformation, or aneurysm.

The evaluation of pulsatile tinnitus is thus crucial to the detection of a potentially more serious disease. Evaluation of pulsatile tinnitus consists of a thorough physical examination paired with blood tests and radiological imaging. Careful examination must be done by the physician to confirm that the sound heard is in sync with the heartbeat and the rhythm increases with physical activity (Herraiz et al. 2007). Due to its lower pressure, though, pulsatile tinnitus of venous etiology may be more difficult to detect as the loudness of flow is much lower compared to arterial pulsatile tinnitus. As a result, pulsatile tinnitus of venous etiology may not be detected by auscultation and may be misdiagnosed as subjective tinnitus (Baomin et al. 2014). Pulsatile tinnitus, especially venous, can also be confirmed by the clinician through the compression of the internal jugular vein ipsilateral to the tinnitus. Doing so will often decrease or stop the perceived sound by the patient (Signorelli et al. 2011). Blood testing and radiological imaging is used after physical examination to confirm the cause of pulsatile tinnitus. Depending on the suspected etiology, various tests can be appropriate. Anemia or hyperthyroidism can be tested for with blood work. Magnetic Resonance Imaging (MRI/MRA/ MRV) can confirm a vascular malformation such as arteriovenous malformation and dural arteriovenous fistula, venous sinus thrombosis, venous sinus stenosis, venous sinus diverticulum, or idiopathic intracranial hypertension. Carotid arteriosclerosis, a tortuous carotid, and cardiac murmur can be confirmed with an eco-doppler electrocardiogram. Lastly, a CT scan can confirm presence of a tympanic/jugular glomus, aberrant carotid, or alteration of the jugular bulb (Herraiz et al. 2007).

Etiologies of Pulsatile Tinnitus

As mentioned previously, pulsatile tinnitus can have different etiologies: arterial, arteriovenous and venous origin. Possible arterial etiologies include atherosclerosis, carotid aneurysm, dissection of the carotid or vertebral artery, and fibromuscular dysplasia. Arteriovenous causes include arteriovenous malformation, dural arteriovenous fistula, paraganglioma, and Paget's Disease. Venous etiologies can include idiopathic

intracranial hypertension, venous diverticulum, venous stenosis (stenosis of the internal jugular vein, transverse sinus, sigmoid sinus, or jugular bulb), a high or dehiscent jugular bulb, and a dehiscent sigmoid plate (Mundada et al. 2014). A review of the current literature at the time by Hofmann et al. 2013 indicated that the majority of pulsatile tinnitus cases (486 total) were of venous origin; 28% were due to venous causes while 23% were arterial, 18% were arteriovenous, and 31% were due to other or unknown causes. More than half of the venous cases of pulsatile tinnitus were due to idiopathic intracranial hypertension, which is recently known to be associated with venous stenosis. A retrospective review of CTA and CTV scans in 30 patients further indicated that the prevalent venous cause for pulsatile tinnitus was stenosis of some kind (N=16), with stenosis of the internal jugular vein being the most common cause (N=13) (Mundada et al. 2014). Sismanis et al. 1998 reviewed 145 patients with pulsatile tinnitus and found that the greatest proportion of patients (39%) had idiopathic intracranial hypertension. Venous sinus stenosis may have a role in the pathogenesis of IIH with a high proportion of IIH patients also having venous stenosis (Farb et al. 2003).

Efficacy and safety of current therapeutic options

Possible treatments for non-severe tinnitus include masking therapies, hearing devices, tinnitus retraining therapies, and acoustic neural stimulation. However, for patients with severe tinnitus, more invasive methods are available, such as cochlear implants for patients with sensorineural hearing loss, stereotactic radiosurgery for patients with vestibular schwannomas, and deep brain stimulation for patients with concomitant movement disorders (Soleymani et al. 2011).

For patients with severe pulsatile tinnitus and venous etiology, surgical vein ligation and endovascular treatment represent possible treatment options. Although there have been documented immediate and long-term relief of pulsatile tinnitus from jugular vein ligation surgery (Golueke et al. 1987; Buckwalter et al. 1983; Nehru et al. 1993; Aikoye et al. 2012; Ott 1977; Duvillard et al. 2004), there have been mixed results (Zhang et al. 2010). Zhang et al. reported that out of 12 patients, 7 reported relief of tinnitus in less than one week after surgery while 5 reported no relief. However, during long-term follow-up of at least 1 year after surgery (to which 5 patients were lost), only 2

patients reported relief of tinnitus, 4 reported no relief, and 1 reported worsening. Furthermore, a warning was published by Jackler et al. 2001 regarding serious neurologic complaints after jugular vein ligation. These included headaches, vision deterioration, and DVS thrombosis. Mahasin et al. 1998 also reported a case of transverse sinus thrombosis and cerebral venous infarction after venous ligation.

Reports on venous sinus stenting to treat pulsatile tinnitus in 100 patients (Table 1, attached document)

Little has been published regarding endovascular treatment of pulsatile tinnitus due to venous stenosis in particular. We conducted a search of the literature available on PubMed detailing the outcomes of endovascular treatment of venous stenosis leading to pulsatile tinnitus and found that all were retrospective case reports or case series reports (Mathis et al. 1997, Donnet et al. 2008, Arac et al. 2009, Ahmed et al. 2011, Fields et al. 2013, Signorelli et al. 2011, Radvany et al. 2013, Baomin et al. 2014). From the search, 100 patients (Table 1) were found to have had endovascular treatment (stenting alone and stenting with angioplasty). Of those 100 patients, all but 3 patients reported resolved or improved tinnitus following the procedure. At follow-up of at least 2 months (ranging up to maximum 9 years), all treatments were considered successful with complete resolution of tinnitus except for 1 case which reported the return of tinnitus at a low level around 8 months (Mathis et al. 1997). All cases also reported long-term stent patency at follow-up. 8 patients experienced re-stenosis adjacent to the stent, 7 of which required re-stenting and 1 shunt placement. Only two cases experienced serious adverse events. One patient experienced vein perforation which eventually lead to a subdural hematoma. Another patient experienced subdural, subarachnoid and intracranial bleeding.

Baomin et al.'s (2014) paper was the most extensive report of endovascular treatment of pulsatile tinnitus due to venous stenosis. Forty-six cases were examined of patients who had failed medical treatment and masking therapies. Angioplasty and stenting were performed and all 46 patients reported immediate relief of tinnitus upon recovery from anesthesia. At 3-month follow-up, 2 patients reported recurrence of nonpulsatile tinnitus but this disappeared in both patients at the 6-month follow-up.

Our experience treating patients with Idiopathic Intracranial Hypertension and pulsatile tinnitus using venous sinus stenting

Our institution has had success treating patients (N=20) who have idiopathic intracranial hypertension (IIH) concomitant with pulsatile tinnitus (N=18). In addition to pulsatile tinnitus, IIH patients have symptoms of headache, diplopia, visual field deficits, hearing loss, and vertigo. These patients typically undergo a regimen of medication as the first line of treatment. If the IIH becomes refractory to maximal medication, surgery (shunt placement) or stenting are options for treatment. Stenting of the dural venous sinus has been shown to eliminate tinnitus among pseudotumor cerebri patients (Mathis et al. 1997), and we were able to replicate this effect in our study. We enrolled patients in the FDA approved trial "Venous sinus stenting in patients with idiopathic intracranial hypertension refractory to medical therapy" over a three-year period from January 2012-December 2014. Patients eligible for venous stenting outside the trial were enrolled in a prospective database. Out of the 20 patients, 18 experienced pulsatile tinnitus. Nine patients presented with grade-4, 5 patients had grade-3, and 2 patients each had grade-2 and grade-1 tinnitus. Out of eighteen patients with IIH and pulsatile tinnitus treated with venous sinus stenting, there was immediate resolution of tinnitus in seventeen patients. All patients had unilateral distal transverse-sigmoid sinus stenting. There was no recurrence of tinnitus for the duration of follow-up period. The 1 patient who had persistent tinnitus after the procedure had grade-1 tinnitus and did not report any change in severity. No serious neurological adverse events occurred after the procedure. All non-serious adverse events were treated without the need for invasive treatment. Of these, seven patients experienced headaches afterwards and were treated with steroids, one patient developed a small retroperitoneal hematoma, and another patient developed free intra-abdominal hemorrhagic fluid collection a few days after the procedure that was attributed to a ruptured hemorrhagic ovarian cyst. There were no neurological adverse events or device related complications.

From these results, we conclude that stenting is a safe and effective treatment for pulsatile tinnitus in the pseudotumor cerebri population. We believe that these successful results can be replicated in our proposed study for all patients who experience venous

pulsatile tinnitus and who have venous stenosis as the etiology. The presence of stenosis causes turbulent venous flow that is transmitted to the ear via the temporal bone. The immediate resolution of tinnitus supports this argument, as the alternative explanation (normalization of CSF pressure) is not immediate post-stenting but rather than a more delayed effect.

Significance of the Proposed Project

There have been few published studies that examine the efficacy and safety of endovascular treatments on patients with pulsatile tinnitus with venous stenosis. Despite the limited experience with venous sinus stenting to treat pulsatile tinnitus, preliminary results show that venous sinus stenting could represent a viable alternative for refractory pulsatile tinnitus patients with venous sinus stenosis. The purpose of our study is to evaluate the safety and efficacy of this procedure in a controlled fashion, using strict inclusion and exclusion criteria, and long-term clinical and imaging follow-up. We hope to provide robust data regarding the safety and efficacy of venous sinus stenting for patients with pulsatile tinnitus.

DEVICE DESCRIPTION

We selected the **Cordis PRECISE PRO Nitinol Stent System** because it is a relatively flexible stent that can be successfully navigated in the target area. It has been used extensively for the treatment of carotid stenosis and has enough radial force to maintain the stenosis open. Another advantage of this stent is that it can be delivered via a 5F or 6F guide catheter system, as opposed to other systems that require 6F guide catheters or more). The Cordis PRECISE PRO Rx Nitinol Stent System consists of a nitinol self-expanding stent preloaded on a .065" (1.65 mm) or .078" (1.98 mm) sheathed delivery system. The delivery system consists mainly of an inner shaft and an outer sheath with radiopaque markers. The inner shaft consists of a support member and wire lumen. The proximal portion of the support member is comprised of a hub connected to a stainless steel wire and hypotube, and distally of a stainless steel coil. The wire lumen originates distally in a catheter tip and terminates proximally at a guidewire exit port designed to accept a .014" (0.36 mm) guidewire. The outer sheath has a proximal shaft and distal

outer sheath with a nominal working length of 135 cm. The self-expanding stent is constrained within the space between the inner shaft and the distal outer sheath, located between distal and proximal stent markers on the inner shaft. The stent expands to its unconstrained diameter when released from the deployment catheter. Upon deployment, the stent forms an open lattice and pushes outward on the luminal surface, helping to maintain the patency of the artery. Due to the self-expanding behavior of nitinol, the stents are indicated for placement into vessels that are 1-2 mm smaller in diameter than the unconstrained diameter of the stent.

We are currently using the same device for the same procedure in another study with different indications (IDE# G090050). Device-related information was provided by the manufacturer to the FDA during that application. Since the device and site of implantation (venous sinuses; transverse and sigmoid sinuses) is the same we will be obliged if the FDA would refer to the same information provided by the manufacturer. We are happy to provide additional information as needed.

METHODOLOGY

The proposed research is a prospective single-arm clinical trial. The aim of the study is to evaluate the effectiveness of dural sinus stenting in patients with severe intractable venous pulsatile tinnitus.

Inclusion and Exclusion Criteria

Inclusion criteria:

- Severe or catastrophic venous pulsatile tinnitus defined as Grades 4 or 5 on Tinnitus Handicap Inventory
- 50% or more stenosis of the lateral venous sinus on MRV or CTV, ipsilateral to the side of more severe tinnitus
- Length of stenosis ≤ 70mm
- Transstenotic gradient ≥ 4mm Hg evidenced by venous manometry
- Failure of conservative or non-surgical therapies (including sound therapy, sound masking, hearing aids, tinnitus retraining (desensitization) therapy. Failure is

defined as Grades 4 or 5 on the Tinnitus Handicap Inventory despite prior treatments that have lasted for at least 3 months.

- Adults, age > 18 years
- Informed consent signed by the patient

Exclusion criteria

- Tinnitus contralateral to dominant narrowed side for patients with bilateral transverse sinus stenosis
- Arterial Pulsatile Tinnitus
- Dural Arteriovenous Fistula of other vascular malformation of the brain, head or neck
- Paragangliomas
- Non-pulsatile tinnitus
- Otologic disorders
- Disorders involving vestibular system and balance
- Visual Field Defects or Papilledema consistent with increased intracranial pressure
- Lateral venous sinus thrombosis
- Contra-indication to iodinated contrast
- Contra-indication to antiplatelet therapy
- Contra-indication to general anesthesia
- Pregnancy or plans for immediate pregnancy

Screening Process

The study will be announced to physicians via mail, email, presentations and talks. The information about the study will be available to the public on the Internet. All patients with complaints of tinnitus and who have failed previous non-invasive treatments will undergo comprehensive evaluation by an ENT physician, which will include comprehensive medical history and full head and neck exam. Otologic evaluation will consist of binocular microscopy, tuning fork exam, pneumatic otoscopy, audiogram, tympanometry, and auscultation for audible bruit. If indicated, imaging studies will be obtained as part of the standard tinnitus evaluation. For patients with pulsatile tinnitus,

vascular imaging studies of the brain, MRA, MRV, CTA, CTV, will be ordered. Imaging protocols for tinnitus vary depending on the patient's history and exam. All patients with venous pulsatile tinnitus considered for the trial will have at least MRA and MRV studies done as part of the work-up of venous pulsatile tinnitus. Patients with contraindication to MRI scans will be evaluated with CTA and CTV instead. This imaging work-up is important for screening and selection of patient but is not experimental and is not part of the trial. It should be done however within 6 months from enrollment. In addition to the previously mentioned imaging studies, every patient will be evaluated with an MRI of the Head and Temporal Bone (Internal Auditory Canal protocol) in order to rule out the presence of other causes of venous pulsatile tinnitus. Patients with contraindication to MRI will be evaluated with CT of the Head and Temporal Bone. The patients who are diagnosed with venous pulsatile tinnitus and in whom presence of venous sinus stenosis is confirmed by imaging studies, will be informed about the trial and provided with the contact information for enrollment. As there is variability in the normal diameter of the transverse venous sinuses in terms of the entire length of the sinus (Ayanzen 2014), a pathologic stenosis will be defined as a >50% decrease in caliber in a focal area or segment of the sinus when compared to the normal diameter before and after.

All patients will be required to have a comprehensive work-up of tinnitus and ENT evaluation within 6 months of enrollment in the trial.

Eligible patients will meet with the investigators to discuss inclusion and exclusion criteria, procedural details, risks and alternatives and sign the IRB consent form.

Venous sinus stenting procedure

Pre-procedure anti-thrombotic regimen

Patients will receive daily aspirin 325mg and clopidogrel (Plavix®) 75 mg for 7 days prior to the intervention.

Direct Retrograde Cerebral Venography (DRCV) and Manometry

The first part of the procedure is to perform a venography and manometry study, using standard angiographic techniques under local anesthesia. Vascular access is obtained from the femoral vein with placement of a 6 French sheath. Then the right or left jugular vein (per MRV or CTV findings) is catheterized with a 6 French guide catheter. A microcatheter is advanced distal to the stenosis and venography is performed. If at least 50% venous sinus stenosis is confirmed, venous sinus manometry is performed proximally and distally to the stenosis with a microcatheter. It is important to perform this part of the procedure without general anesthesia because general anesthesia may cause artificially elevated venous sinus pressures. Sinus catheterization with the soft microcatheters used for DRCV is painless and generally well tolerated. If the venous pressure gradient across the stenosis is ≥ 4 mmHg, we will proceed with stenting.

Venous sinus stenting

The procedure requires general anesthesia because stent navigation into the venous sinuses can be painful. Vascular access is obtained from the femoral vein and a 6 French sheath catheter is positioned in the jugular vein. Subsequently, a microcatheter is navigated using standard neurointerventional techniques into the superior sagittal sinus. A venogram will be performed with contrast injection via the microcatheter to confirm the location and degree of stenosis. After the venogram, the microcatheter will be exchanged for an intravascular ultrasound catheter, and intravascular ultrasound will be performed to confirm degree of stenosis. Following this step, the intravascular ultrasound catheter will be withdrawn and balloon angioplasty will be performed across the stenosis, followed by deployment of a self-expandable stent (Cordis Precise-Pro Stent). An embolic protection device is not required and will not be used because there is no risk of cerebral embolism. After the catheters are removed, hemostasis at the puncture site is achieved with manual compression. In patients with stenosis on the dominant transverse sinus, the stent is placed in the dominant side. In patients with co-dominant transverse sinuses and bilateral stenosis, the stent is placed across the stenosis on the side of worse tinnitus.

Immediate post-procedure care

Each patient will be admitted to ICU for overnight monitoring. Patients will be discharged home 24 hours after the procedure and will continue aspirin 325mg daily and clopidogrel (Plavix®) 75mg daily for 1 month, after which time they will return for a follow-up office visit. Plavix will be discontinued one month after the procedure and the patients will continue on aspirin (325mg daily) alone for 11 more months (total time on aspirin = 12 months). Typically, patients with coronary or carotid atherosclerosis treated with stent placement are prescribed aspirin and clopidogrel for 1-3 months, followed by aspirin alone indefinitely. This regimen is essential to prevent in-stent thrombosis and distal thromboembolism. Since there is no atherosclerotic disease in the venous sinuses and the risk of late in-stent thrombosis and distal thromboembolism is low, the risks of long-term anti-thrombotic treatment outweigh the possible benefits.

Follow-up (Patient Flow Chart, page 28)

Office visits

Office visits with neurologic evaluation will be performed at one, six, twelve, and twenty-four months after treatment. At this time the patients will also fill the Tinnitus Handicap Inventory Questionnaire. The visits will last about 45 minutes.

Audiometric assessment

Audiometric assessment will be performed at the three-month mark after stenting to assess inner ear function.

Imaging studies

Magnetic Resonance Venogram (MRV) will be done at 12 months after the stent. If MRV is contraindicated, Computed Tomographic Venogram (CTV) will be performed instead.

Other treatments

Patients will be expected to discontinue all prior treatments so as to effectively measure the sole effect of stenting.

Endpoints

Primary Endpoints:

- Safety Endpoint: absence of procedure related and device related complications.
- Efficacy Endpoint:
    - Improvement of more than one grade in the Tinnitus Handicap Inventory Questionnaire at 1, 6, 12, and 24 months after stent placement.

Secondary Endpoints:

- No recurrence of tinnitus within 24 months after treatment
- Stent patency at 12 months after treatment
- Adverse events probably or possibly related to the treatment within a 24-month period after treatment

Number of Patients

We wish for permission to enroll 20 patients in this study, all at New York Presbyterian/Weill Cornell Medical Center.

Data Analysis

Data from all patients enrolled in the study will be reported.
We will calculate and report the proportion of patients for each endpoint.

ADVERSE EVENTS AND ASSESSMENT OF RISKS

Risk assessment and prevention:

- Risks related to antithrombotic therapy: intracranial or systemic hematoma. Antithrombotic therapy is important to prevent stent thrombosis. According to the literature and our experience in patients with carotid and intracranial stenting, the risks related to anticoagulation are minimal. The benefit of administering two

medications (aspirin and clopidogrel) for 1 month and then continuing with aspirin alone has been demonstrated in large studies in patients with cardiac, carotid and intracranial stents. We will ask all female patients of childbearing age to avoid becoming pregnant during the time-course of anticoagulation. We will also instruct all patients to avoid contact sports and trauma.

- Risks related to general anesthesia: nausea, vomiting, fever, dizziness, headache, drowsiness, hoarseness, and sore throat.
  Experienced anesthesiologists will administer general anesthesia using standard techniques. Pre-procedure evaluation and standard protocol for patient preparation (i.e. empty stomach) will be used to minimize the risks.
- Risks related to femoral vein puncture: hematoma at puncture site, pain at puncture site, infection, and thrombophlebitis.
  To minimize the risks of femoral vein puncture we will use standard angiographic techniques in a sterile environment. In patients with difficulty in accessing the femoral vein (obesity), ultrasound can be used to guide the puncture.
- Risks related to venous sinus stent placement: venous rupture, venous thrombosis or occlusion, intracranial hematoma, progressive visual loss, stroke, death.
  Although venous sinus stenting is a new procedure, review of the literature shows that complications are rare. In only two cases, retrograde venous angiography demonstrated thrombosed stent in the immediate postoperative course, necessitating thrombolysis. In these two cases, it was not mentioned whether the procedure was performed under anticoagulation only or if antiplatelet therapy was also administered. In addition to the cases reporting venous sinus stenting for IIH, there is an additional recent report of treatment of 10 dural arteriovenous fistulas of the transverse sigmoid sinus using similar techniques of self-expanding stent placement and balloon angioplasty (Levrier O et al. 2006). In this series, one patient experienced a brain parenchyma hematoma secondary to the occlusion of a superficial cortical draining vein. That patient was not pre-medicated with anticoagulation prior to the procedure and since then the authors started using clopidogrel for 3 days prior to the procedure without further complications. All subjects of this protocol will be pretreated with

antiplatelet agents before the procedure (aspirin and clopidogrel). Pretreatment with these medications before the stent placement is routinely performed for patients undergoing coronary, carotid and intracranial stents. In addition, the procedure will be done under systemic administration of heparin, also routinely used for endovascular procedures. Therefore, the risk of stent or cortical vein thrombosis will be minimal.

- Risks related to administration of iodinated contrast: contrast allergy, contrast induced nephropathy.

  To minimize the risk of contrast allergy and nephropathy, a standard screening questionnaire for iodinated contrast will be reviewed before the procedure. Patients at risk for allergy (i.e. prior severe allergic reaction) or at risk for contrast nephropathy (i.e. history or evidence of renal function impairment) will be excluded from the study (see exclusion criteria).
- Risks related to MRI scan: minimal risks.

  We will use standard equipment and protocols. We will screen all patients for contraindications to MRI using standard questionnaire and interview.

  Risks related to gadolinium (MRI contrast): contrast allergy, nephrogenic systemic fibrosis

  Patients with compromised renal function are excluded from the study (see exclusion criteria) and thus the risk of nephrogenic systemic fibrosis from the use of MRI contrast is minimal.
- Risks related to invasion of privacy: minimal risks.

  All personal data and medical records will be kept confidential according to hospital regulations and legal requirements. No participant in this study will be identified personally in any reports or publications.

Definition of Adverse Events

The investigators will determine the seriousness, intensity, and causality of an adverse experience associated with the use of the test procedure (*i.e.*, experiences where there is a reasonable possibility that the experience may have been caused by the test procedure) based on the following definitions:

1. Serious Adverse Experiences

   The definition of a serious adverse event (SAE) is any of the following:

   - Any death that occurs while the patient is enrolled in the study including the follow-up period or within 30 days of completing the study.
   - Immediately life-threatening adverse event.
   - Requires inpatient hospitalization.
   - Prolongation of an existing hospitalization.
   - Congenital anomaly/birth defect.
   - Medically important event*
   - Disability/incapacity (persistent or significant)

   *Medically important events that may not result in death, be life-threatening or require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, the experience may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.

2. Unexpected Adverse Experience

   An **unexpected adverse experience** is any adverse device experience, the specificity or severity of which is not consistent with those noted in the current research protocol. This refers to any adverse device experience that has not been previously observed, rather than from the perspective of such an experience not being anticipated from the pharmacologic properties of the product.

3. Non-serious Adverse Experiences

   All other adverse experiences, not fulfilling the previous definitions, are classified as non-serious.

Documenting Adverse Experiences:

All adverse experiences are to be accurately recorded on the Adverse Events & Description of AE columns of the patient's CRF. Each experience will be categorized as either: serious AE, non-serious AE, or unexpected AE (see CRF). The date of onset as well as the duration of the experience will be recorded. In addition, the method used to treat the adverse experience and the outcome of the adverse experience will also be

noted. The investigator will attempt to assess the relationship of the experience (unrelated, remote, possible, probable, related) to the test procedure.

Reporting SAEs, Unexpected Adverse Experiences, and Patient Deaths

1. Time-frame for Reporting:

Any harm experienced by a participant related to the research procedure, intervention, and/or device when ALL of the following three (3) conditions are met will be reported within 7 calendar days:

1. The harm is "unexpected" when its specificity and severity are not accurately reflected in the WCMC consent document and protocol **AND**
2. The harm is "related or possibly related", where there is a reasonable possibility that the harm may have been caused by the research procedure or intervention **AND**
3. The harm suggests that the research places subjects at greater risk of harm (including physical, psychological, economic or social harm) than was previously known or recognized

In addition to the above, any unanticipated adverse effect (any serious adverse effect on health or safety or any life threatening problem or death) will be reported within 7 calendar days that is EITHER:

1. 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 IDE application (including a supplementary plan or application); **OR**
2. Any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of participants.

2. Information to be provided by the Investigator

At the time of the report, the investigator must transmit information regarding the following:

- Underlying diagnosis and extent of disease
- Dates of procedure
- Description of event, including date of onset and duration
- Date of death (if applicable)
- Intervention(s) required
- Concomitant therapy (including regimen(s) and indication)
- Pertinent laboratory data/diagnostic test (including dates)
- Pertinent medical history
- Severity of the adverse experience
- Relationship of the adverse experience to research study treatment
- Outcome of the adverse experience

Follow-up Information on an SAE:

Appropriate diagnostic tests should be performed and therapeutic measures, if indicated, should be instituted. Appropriate consultation and follow-up evaluations should be carried out until the event has resolved or is otherwise explained. Follow-up data concerning the SAE (*e.g.*, diagnostic test reports, physician's summaries, etc.) will also be submitted.

Review of an SAE:

After an SAE, enrollment will be halted until the DSMB reviews the SAE and determines that the study can be continued. Additionally, the PI will notify the FDA and will review each serious and unexpected adverse experience report and further evaluate the relationship of this adverse experience to the test device and to the patient's underlying disease. Based on this assessment, a decision will be made concerning the need for further action. The primary consideration governing further action is whether new findings affect the safety of other patients participating in the clinical research study. If the discovery of a new adverse experience related to the test device raises concern over the safety of its continued administration to patients, the PI will take immediate steps to

notify the IRB and all investigators participating in clinical studies of the test drugs used in this research protocol.

Further action required may include any of the following:

· Modification of the research protocol.

· Discontinuation or suspension of the research study.

· Alteration of the informed consent process by modification of the existing consent form and informing current research study participants of new findings.

· Modification of previously identified expected adverse experiences lists to include adverse experiences newly identified as test procedure-related.

CONDITIONS FOR TERMINATION

1. Discontinuing patients from the study

Every effort will be made to keep the patient on the research study. However, in the event that a patient is withdrawn from the research study, the investigator should document the reasons for withdrawal as thoroughly as possible and notify the PI. This evaluation should include final observations, as required by the research protocol at the time of the patient's withdrawal. The reason(s) for early termination must be clearly documented on the appropriate page of the patient's case report form (CRF). A CRF must be completed for any patient who receives ANY amount of treatment on this research study.

<u>Criteria for Early Termination of Treatment under this Research Protocol</u>

1) Significant deviation from the research protocol or eligibility criteria. Such patients will be considered protocol violations and will be removed from research study.
2) Patients who develop a concurrent illness, which, in the opinion of the investigator, would prevent their safe completion of treatment or required research study-related evaluations.
3) Patients who are non-compliant with the research study or follow-up procedures.
4) Patients who withdraw consent and elect to terminate their participation in the research study.

5) The occurrence of a grade 3 or greater hematologic toxicity, persisting 7 days or longer according to NCI CTCAE VERSION 4.03.
6) Termination of the research study by the Sponsor.

2. Study termination

The study will be discontinued if a serious adverse event (SAE) that is unexpected and protocol-related occurs in more than two of the first five or more than three of the first ten procedures.

STUDY MONITORING

The study will be monitored by the Weill Cornell Medical College Data Safety Monitoring Board (WCMC DSMB).

Data Safety Monitoring Board
1300 York Avenue, Box #89
Telephone: 646-962-8192
Fax: 646-962-0533
E-mail: **dsmb@med.cornell.edu**

Adverse events will be reported to the WCMC DSMB according to the same policies as they will be reported to the FDA and WCMC IRB:

Reporting SAEs, Unexpected Adverse Experiences, and Patient Deaths

1. Time-frame for Reporting:

Any harm experienced by a participant related to the research procedure, intervention, and/or device when ALL of the following three (3) conditions are met will be reported within 7 calendar days:

1. The harm is "unexpected" when its specificity and severity are not accurately reflected in the WCMC consent document and protocol **AND**

2. The harm is "related or possibly related", where there is a reasonable possibility that the harm may have been caused by the research procedure or intervention **AND**

3. The harm suggests that the research places subjects at greater risk of harm (including physical, psychological, economic or social harm) than was previously known or recognized

In addition to the above, any unanticipated adverse effect (any serious adverse effect on health or safety or any life threatening problem or death) will be reported within 7 calendar days that is EITHER:

1. 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 IDE application (including a supplementary plan or application); **OR**
2. Any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of participants.

2. Information to be provided by the Investigator

At the time of the report, the investigator must transmit information regarding the following:

- Underlying diagnosis and extent of disease
- Dates of procedure
- Description of event, including date of onset and duration
- Date of death (if applicable)
- Intervention(s) required
- Concomitant therapy (including regimen(s) and indication)
- Pertinent laboratory data/diagnostic test (including dates)
- Pertinent medical history
- Severity of the adverse experience
- Relationship of the adverse experience to research study treatment

· Outcome of the adverse experience

In addition, a cumulative list of unexpected AEs and serious AEs will be reported after every 5 patients, as determined by the WCMC DSMB. Detailed, narrative descriptions of each AE from the last report will accompany the cumulative list.

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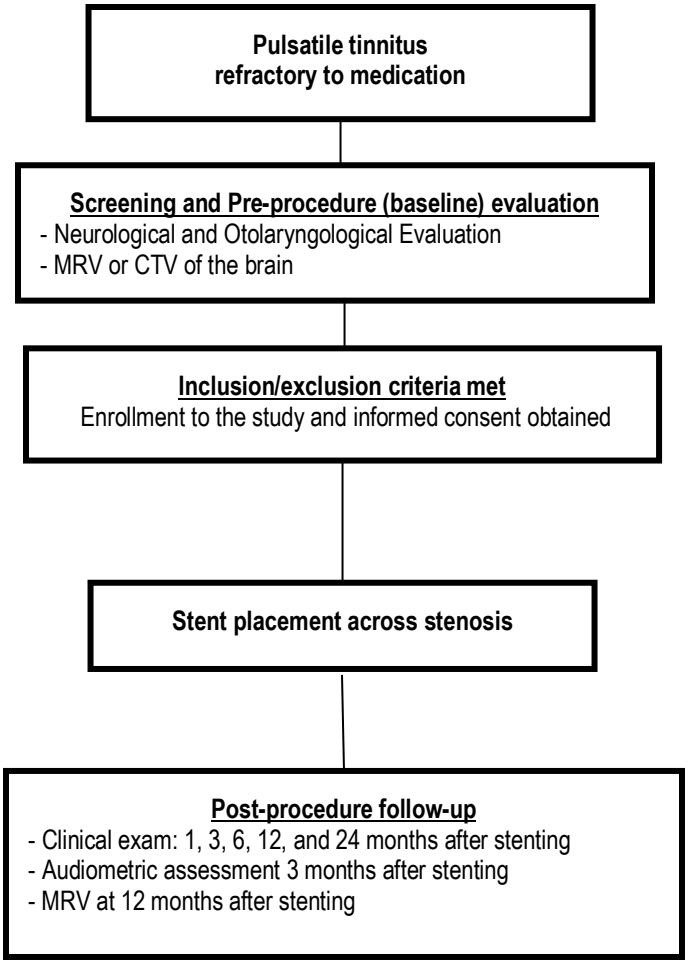
Patient Flow Chart



PRINT OUT OF ELECTRONIC CASE REPORT FORM

Name: _____

Age: _____

DOB: _____

MRN: _____

Tinnitus Grade:
- ○ 0
- ○ 1
- ○ 2
- ○ 3
- ○ 4
- ○ 5

Tinnitus Location:
- ○ Right
- ○ Left
- ○ Bilateral

Venous Dominance:
- ○ Right
- ○ Left
- ○ Codominant

Stenosis Location:
- ○ Right
- ○ Left
- ○ Bilateral

Stenting Date: _____

Stenting Result:
- ○ no residual stenosis
- ○ residual stenosis <50%
- ○ residual stenosis >50%
- ○ technical failure

Adverse Events:
- ○ Serious
- ○ Non-serious
- ○ Unexpected

Description of Adverse Event _____
_____
_____
_____

Tinnitus Grade: Post-Stent (1 month)
- ○ 0
- ○ 1
- ○ 2
- ○ 3
- ○ 4
- ○ 5

Tinnitus Grade: Post-Stent (6 mos)
- ○ 0
- ○ 1
- ○ 2
- ○ 3
- ○ 4
- ○ 5

Tinnitus Grade: Post-Stent (12 mos)
- ○ 0
- ○ 1
- ○ 2
- ○ 3
- ○ 4
- ○ 5

Tinnitus Grade: Post-Stent (24 mos)
- ○ 0
- ○ 1
- ○ 2
- ○ 3
- ○ 4
- ○ 5

MRV (12 mos)

- ○ no residual stenosis or thrombosis
- ○ in-stent stenosis <50%
- ○ in-stent stenosis >50%
- ○ new stenosis
- ○ stent thrombosis

Any procedure-related adverse event after 24 months

_____
_____
_____
_____
_____

MANUFACTURING INFORMATION

We (the sponsors) do not have access to the manufacturing information of the device. In a letter attached to this application, the manufacturer (Cordis Corporation) grants FDA the permission to reference the files used for the PMA#030047 in its review for the application for IDE# G090050.

INVESTIGATOR INFORMATION

All participating investigators and the monitor are listed below. All investigators have signed the agreement and no other investigator will be added until the agreement is signed.

List of investigators

Athos Patsalides MD MPH
Assistant Professor of Radiology in Neurosurgery
Division of Interventional Neuroradiology
Weill Cornell Medical College
525 East 68th Street, Box 99
New York, NY 10065
Tel: 212-746-2821
Fax: 212-746-8111
atp9002@med.cornell.edu

Maria Suurna MD
Assistant Professor
Department of Otolaryngology – Head & Neck Surgery
Weill Cornell Medical College
1305 York Avenue, 5th Floor
New York, NY 10065
Tel: 646-962-9135
Fax: 646-962-0162
mas9390@med.cornell.edu

Kelly Hannsgen MSN NP
Nurse Practitioner
Department of Neurological Surgery
Weill Cornell Medical College
525 East 68th Street, Box 99
New York, NY 10065
Tel: 212-746-2821
Fax: 212-746-8111
kec9053@med.cornell.edu

Xem Bui
Research Coordinator
Department of Neurological Surgery
Weill Cornell Medical College
525 East 68th Street, Box 99
New York, NY 10065
Tel: 212-746-1788
Fax: 212-746-8111
xeb2001@med.cornell.edu

Relevant Experience

Athos Patsalides, MD, MPH

Dr. Patsalides has previously worked with the Cordis Precise Pro Rx Nitinol Stent System on another IDE protocol (IDE# G090050) at Weill Cornell Medical College and is thus experienced with the device and its use to treat venous sinus stenosis.

Maria Suurna, MD, FACS

Dr. Suurna has five years of experience as a board-certified otolaryngologist and extensive experience working with patients with pulsatile tinnitus during her time at the University of Cincinnati, NYU Langone Medical Center, and Weill Cornell Medical College.

Kelly Hannsgen, MSN, FNP-C

Mrs. Hannsgen has eight years of experience as a nurse at Good Samaritan Hospital and New York Presbyterian-Weill Cornell Medical College. She has assisted Dr. Patsalides with patients who have received stenting to treat venous sinus stenosis both during the procedure and for follow-up.

Xem Bui

Ms. Bui will be responsible for overseeing the coordination of the study and handling data collection, analysis, and all IRB-related matters. She has experience as a research coordinator for the Department of Neurological Surgery at Weill Cornell Medical College and various research assistant experience.

Sample investigator's agreement

This is to certify that I agree to participate in the investigation titled "Venous sinus stenting to treat intractable pulsatile tinnitus caused by venous sinus stenosis". I will conduct the investigation in accordance with the agreement, the investigational plan, Part 812 and other applicable FDA regulations and conditions of approval imposed by the reviewing IRB and FDA. I will supervise all testing of the device involving human subjects and ensure that the requirements for obtaining informed consent are met. I have no financial interest to disclose regarding this study, and I will provide sufficient, accurate financial disclosure information, and update information if any relevant changes occur during the investigation and for one year following the completion of the study.

IRB INFORMATION

All parts of the study will be conducted at New York Presbyterian Hospital/ Weill Cornell Medical College and there will be no other institution involved in this study. Thus, only the IRB at Weill Cornell Medical College will review the investigation, pending IDE approval by the FDA. The investigation has not been reviewed by the IRB yet.

Chairperson at Weill Cornell Medical College IRB:

Mary Simmerling, Ph.D.
Assistant Dean, Research Integrity
Office of Research Integrity
Location: 1300 York Avenue, Box #89
New York, NY 10065
P: (646) 962-8200
E: mcs2006@med.cornell.edu

SALES INFORMATION

The device will not be sold or commercialized.

LABELING

We will use the standard device labeling as approved by the FDA for carotid stenting.