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APOLLO™ ONYX™ DELIVERY MICRO CATHETER POST MARKET SAFETY STUDY

CLINICAL PROTOCOL

Protocol Number: NV-APL001

REVISION: A, 05-Aug-2014

Study Sponsor:
Micro Therapeutics, Inc. d/b/a
ev3 Neurovascular
9775 Toledo Way
Irvine, CA 92618

Sponsor Signatures:

Signature: _____ **Date:** _____

Senior Director, Clinical Affairs

Signature: _____ **Date:** _____

/ Sr RA Product Specialist, Regulatory Affairs

Signature: _____ **Date:** _____

) / Principal Medical Monitor, Medical Affairs

Apollo™ Onyx™ Delivery Micro Catheter Post Market Safety Study

Investigational Plan Investigator Agreement

I have read the Investigational Plan Rev A and agree to adhere to the requirements.

I agree to conduct the Study in accordance with the current protocol and will only make changes in the protocol after notifying the Sponsor, except when necessary to protect the safety, rights, or welfare of Subjects.

I agree to personally conduct or supervise the herein described investigation and ensure all appropriate participating Investigators and research staff are appropriately informed and/or trained regarding the conduct of the investigation prior to participating in any study related activities.

I will ensure that the requirements in applicable regulations/guidelines relating to obtaining informed consent (ICF) according to 21 CFR Part 50 and institutional review board (IRB) review and approval are met.

I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the Study are informed about their obligations in meeting the above commitments.

I agree to maintain adequate and accurate records in accordance with 21 CFR 812.140 and to make those records available for inspection in accordance with 21 CFR 812.145.

I will ensure that the IRB complies with the requirements of 21 CFR Part 56 and will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human Subjects or others. Additionally, I will not make any changes in research without IRB approval, except where necessary to eliminate apparent immediate hazards to human Subjects.

I agree to comply with all other requirements regarding the obligations of clinical Investigators and all other pertinent requirements in 21 CFR Part 812, Good Clinical Practices, and/or the laws and regulatory requirements of the country in which the site resides.

_____ ____/_____/_____

Principal Investigator Signature **DD MMM YYYY**

_____

Principal Investigator Printed Name

PROTOCOL SYNOPSIS	
Sponsor: **Micro Therapeutics, Inc. d/b/a** **ev3 Neurovascular** **9775 Toledo Way** **Irvine, CA 92618**	**Protocol Number:** NV-APL001
	Revision: A, 05-Aug-2014
	Product: Apollo™ Onyx™ Delivery Micro Catheter
	Regulatory Class: Class III
	Development Phase: Phase IV
Title: Apollo™ Onyx™ Delivery Micro Catheter Post Market Safety Study	
Study Design: Prospective, non-randomized, single arm, multi-center post market study	
Objective: To evaluate the safety of the Apollo™ Onyx™ Delivery Micro Catheter used for delivery of the Onyx™ Liquid Embolic System during brain arteriovenous malformation (AVM) embolization procedures.	

Background:

Brain AVMs are relatively rare but increasingly detected lesions that can lead to significant neurological morbidity or death.[1] The prevalence of AVMs varies between 10 and 18 per 100,000 adults,[2,3] with an annual incidence of 1.1-1.3 AVMs per 100,000 person-years.[4] In the United States, assuming the total population in the range of 300 million, this would lead to an estimated annual AVM incidence of 3,300 – 3,900 (avg. 3,600). Children comprise approximately only 3-20% of patients diagnosed with AVMs.[5] The natural history of AVMs involves a 2 to 4% annual hemorrhage rate.[6] Giant AVMs have been shown to have hemorrhage risk as high as 9.6% annually translating to a 64% risk of hemorrhage during a 10 year period.[7]

Current treatment strategies for brain AVMs include surgical excision, radiosurgery, and embolization therapy or may involve pretreatment of the AVMs using a multimodality strategy of surgical excision, radiosurgery, and embolization techniques.[8,9] Based on a large meta-analysis of 13,698 patients with brain AVMs, radiosurgery was the most common technique (48%), followed by microsurgery (29%), embolization (10%) and fractionated radiotherapy (5%) and multimodal therapies (8%). Presurgical embolization of brain AVMs is an effective means to help reduce the AVM size, minimize intraoperative blood loss during surgery, and decrease resection time.

Cases of catheter entrapment and difficulty in retrieval of the catheter have been observed in a number of studies using Onyx™ Liquid Embolic System (LES), particularly in cases requiring long injection and when there is a large amount of reflux.[10-17] A review of literature constrained to studies/ case reports with at least 50 patients demonstrates that catheter entrapment/abandonment occurred in 0-9.7% of Subjects treated with Onyx™ as shown in Table 1-1.[10,12,14-16,18,19] To establish a reliable estimate of catheter entrapment, a review of literature was constrained to studies/ case reports with 50 or greater patients, and revealed an average entrapment rate of 5.76%. Reported side effects related to catheter entrapment/abandonment included inguinal cellulitis, thrombophlebitis of the leg, femoral artery occlusion, and knee pain.[16] Additionally, difficulty in micro catheter withdrawal may result in vessel rupture leading to severe brain hemorrhage, causing severe sequelae and an increased patient death risk.[10]

PROTOCOL SYNOPSIS

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Background (cont.):

Given the potential side effects of catheter retainment and increased procedural risk associated with alternative methods necessary for removing entrapped catheters, a catheter technology that will not leave behind the entire length of a micro catheter is needed. This led to the development of the Apollo™ Onyx™ Delivery Micro Catheter. In the event of catheter retainment, using the Apollo™ Onyx™ Delivery Micro Catheter versus any other standard micro catheter represents leaving behind a 1.5-3.0 cm long detachable tip in the Onyx™ cast versus an average 165 cm long catheter in the vasculature.

Number of Subjects:	**Number of Study Centers:**
161 Subjects with estimated 322 catheter utilizations (~ 2 catheters per Subject)	Up to 25 sites across the United States

Duration of Study:

- Enrollment: 30 months
- Follow-up period: Up to 12 months
- Total Study Duration: Up to 42 months

Primary Composite Endpoint (30 days):

Incidence of catheter-related adverse events per Subject:

- Premature (unintentional) catheter tip detachment with clinical sequelae*
- Catheter rupture/break/fracture with clinical sequelae*, and
- Retained catheter body in the vasculature

*Clinical sequelae are defined as all focal neurologic deficits related to lesions within the vascular territory catheterized.

Acute Secondary Endpoints (30 days):

1. Rate of premature (unintentional) catheter tip detachment
2. Rate of intentional catheter tip detachment
3. Rate of migration of the retained catheter tip post embolization
4. Incidence of procedure-related adverse events
5. Rate of catheter/tip leakage from detachment zone

Long-Term Secondary Endpoints (12 months):

1. Incidence of adverse events (AEs)
2. Rate of migration of the retained catheter tip post embolization

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	Development Phase: Phase IV

Clinical Events Committee (CEC):

A CEC will be in place for the Study using a minimum of three physicians knowledgeable in the treatment and embolization of brain AVMs. This committee will be responsible for the review and assessment of all study adverse events (AEs) that occur throughout the Study. The CEC is expected to meet each quarter at the minimum.

Study Population:

Subjects with a brain AVM that are indicated for AVM embolization with Onyx™ Liquid Embolic System (LES) using the Apollo™ Onyx™ Delivery Micro Catheter.

Inclusion Criteria:

1. The Subject or Subject's legally authorized representative has signed and dated an informed consent form.
2. The Subject has a confirmed diagnosis of a brain AVM.
3. The Subject is clinically and neurologically stable for a minimum of 48 hours prior to embolization.
4. The Subject has a life expectancy of at least 1 year.
5. The Subject agrees to and is capable of completing all study-required procedures.

Exclusion Criteria:

1. Current participation in another investigational drug or device study that evaluates treatments for brain AVMs or other cerebrovascular disease.
2. The Subject has a bleeding disorder.
3. The Subject is not a candidate for the use of vasodilators.

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Treatment:

An enrollment screening log will be maintained at each study site. Subjects with brain AVMs enrolled in the study will undergo embolization(s) with Onyx™ 18 LES or Onyx™ 34 LES using the Apollo™ Onyx™ Delivery Micro Catheter. Subjects may undergo multiple procedures over a several week period from the date of the initial study procedure.

Follow-up:

All Subjects will complete a 30-day post-embolization visit to assess safety. Once a Subject has completed the study procedures, all ongoing adverse events will be followed until resolution or until event has stabilized.

If the catheter and/or tip are retained (intentionally or unintentionally) during the initial procedure or any subsequent procedures, the Subject will be followed for 30 days from the date of the initial procedure to assess any adverse events ascribed to the study procedure or the retained catheter or tip. For Subjects where surgical resection of the Onyx™ cast and retained catheter tip is not undertaken or is incomplete and the catheter and/or tip are retained (intentionally or unintentionally), the Subject will also complete a 12-month follow-up visit to assess safety. Once a Subject has completed the study procedures, all ongoing adverse events will be followed until resolution or until event has stabilized.

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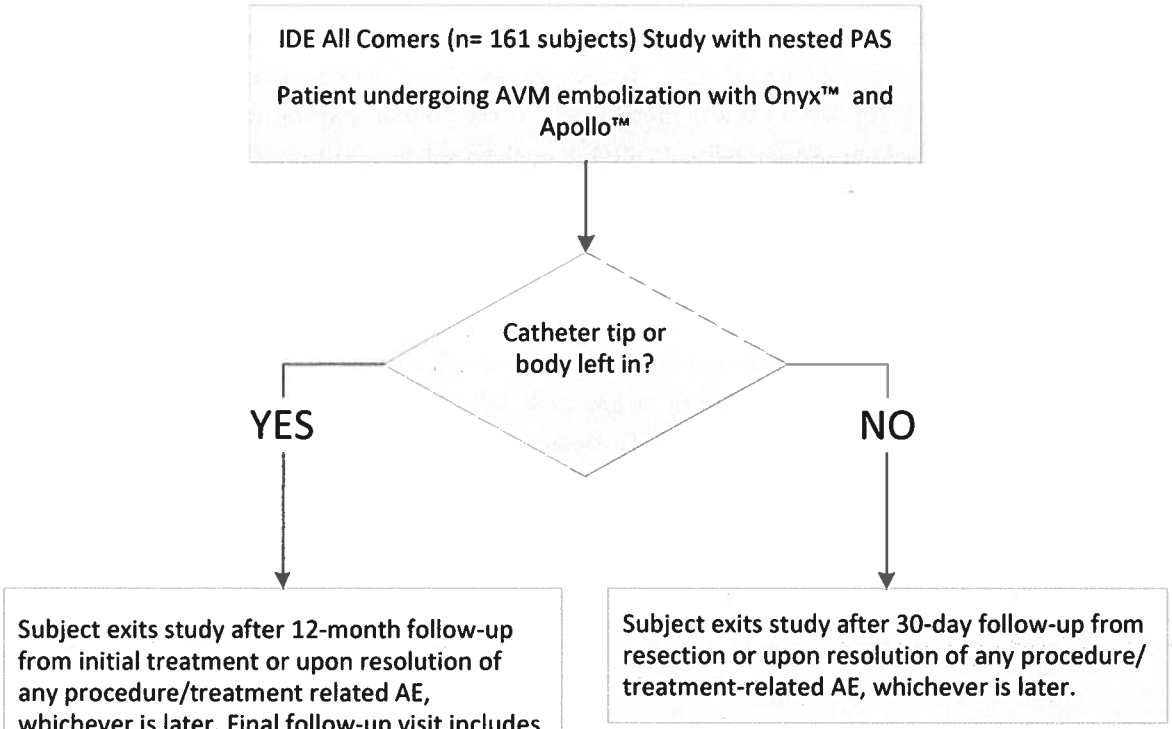
Study Flowchart:



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	Development Phase: Phase IV

Statistical Analysis:

The primary endpoint will be summarized as the event rate per Subject with a one-sided 95% upper confidence bound using the Exact method. The upper bound will be compared to the performance goal of 9.6%. If this upper bound is less than 9.6%, it is considered that the Apollo™ micro catheter meets the primary objective. Additionally, an interim analysis will be performed when 80 subjects have reached the 30-day follow-up. The interim prediction power will be calculated and the sample size may be adjusted as appropriate.

Adverse events for all enrolled Subjects will be collected and reported. For adverse event reporting, which includes the primary and secondary endpoints, the primary analysis will be based on Subject counts (e.g., the number and percentage of Subjects with event among the total number of Subjects). The data will be presented in the format of p% (x/N) [e], with p and x being the percentage and number of Subjects with events, respectively, N being the sample size of the analysis population, and e being the total number of events occurred in the x Subjects. For example, the data of 3.1% (5/161) [8] indicates that a total of 8 events occurred in 5 Subjects out of a total of 161 Subjects (3.1%). In addition, the data based on device (e.g., the number and percentage of devices with events among the total number of deployed devices) will also be provided.

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	Development Phase: Phase IV

Sample Size Justification:

The maximum number of Subjects to be enrolled into this clinical investigation is 161 (with 13% attrition included). To establish a safety performance goal for the primary endpoint, literature research was conducted on the reported data of catheter retainment. The table below summarizes the rates from the peer-reviewed literature. The rate ranges from 1% to 9.7% with an un-weighted average rate of 5.8% and weighted average of 5.7%. The one-sided 95% upper confidence interval for the individual studies ranged from 4.6% to 16.3%.

Table 1-1. Event Rate Based on Literature Review

Citation	Purpose	Catheter*	Country	Catheter Retainment Frequency (pts)	One-Sided 95% Upper Bound **
Gao, K et a. Chinese Med J 2009; 122:1851-1856.	Onyx delivery	M, U	China	5/115= 4.4%	8.9%
Katsaridis, V et al 2008 Neuroradiology 2008; 50: 589-597.	Onyx delivery bAVM	M, U	Greece	1/101 = 1%	4.6%
Mounayer, C et al AJNR 2007; 28: 518-523.	NBCA, Onyx delivery bAVM	F, U	France	4/94 = 4.3%	9.5%
Panagiotopoulos, V et al AJNR 2009; 30: 99-106.	Onyx delivery bAVM	M, U	Germany	1/82 = 1.2%	5.7%
Saatci, I et al J Neurosurg 2011; DOI: 10 3171/2011.2 JNS 09830.	Onyx, NBCA delivery bAVM	F, U, M	Turkey	28/350 = 8.0%	10.8%
Song, D et a. Intervent Neuroradiol 2005; 11 (SUPPL. 1): 179-184.	Onyx delivery BAVM	M, U	China	3/50 = 6.0%	14.8%
Weber et al. AJNR 2007; 28: 371-377.	Onyx Delivery bAVM	U	Germany	9/93 = 9.7%	16.3%
Un-weighted Average				**51/885 = 5.8%**	
Weighted Average				**5.7%**	

Note: Table 1-1 is identical to Table 3 in clinical protocol.
*M = Marathon; U = UltraFlow; E = Echelon; F = FlowRider.
**95% one-sided upper bound is calculated using the Exact method.

The weighted average of catheter retainment event from the table above was used as an estimate of the primary endpoint event rate for this study. Based on a sample size of 161 (maximum sample size), if the event rate is 5.6%, the 95% upper bound is 9.6%. The 5.6% event rate is a conservative estimate calculated by using the weighted average of 5.7% rounded down to account for a whole patient. Based on this upper bound, it is proposed that the performance goal for the primary endpoint be 9.6%. The one-sided 95% upper confidence bound of the observed primary endpoint event rate will be compared to 9.6%. If this upper bound is less than 9.6%, then it is considered that the Apollo™ micro catheter meets the primary endpoint performance goal.

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Sample Size Justification (con't):

In order to ensure a sufficient number of cases for long-term follow-up, the expectation is that with 161 subjects enrolled there will be approximately 16 to 26 subjects with 1-year follow-up. The basis of this estimate is that approximately 50% to 80% of the subjects will have the tip retained by design and approximately 20% of these subjects will not undergo surgery and shall be followed for 1-year. Any retained catheter bodies will be followed. Relative to the precision of the estimates with 16 subjects followed for 1 year, if the incidence of composite primary endpoint events is zero or 1, the exact upper 1-sided Clopper-Pearson 95% limit would be 17.07% and 26.40%, respectively. If the incidence of composite primary endpoint events with 26 subjects was zero or 1, the exact upper 1-sided Clopper-Pearson 95% limit would be 10.88% and 16.98%, respectively.

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Appendix A: Glossary
Appendix B: Abbreviation of terms

1 INTRODUCTION

1.1 Purpose

The Apollo™ Onyx™ Delivery Micro Catheter (Apollo™ micro catheter) was added to the Onyx™ Liquid Embolic System (Onyx™ LES) Premarket Approval Application [redacted]. In compliance with FDA's Post-Approval Study requirement, the primary objective of this study is to evaluate the safety of the Apollo™ Onyx™ Delivery Micro Catheter. During the brain arteriovenous malformation embolization procedure, when catheter entrapment in the Onyx™ cast occurs, the tip of the Apollo™ micro catheter is expected to detach when the tip detachment force is less than the extraction force from an Onyx™ cast. The physician will not have to exert excessive force in an attempt to remove the catheter, risk rupturing the catheter, or be forced to purposefully sever the catheter and leave an excessively long segment in the patient vasculature.

1.2 Background and Significance

1.2.1 Clinical Background

Brain arteriovenous malformations (AVMs) are congenital vascular lesions consisting of direct connections between arteries and veins, without an intervening capillary bed. The prevalence of AVMs varies between 10 and 18 per 100,000 adults,[2,3] with an annual incidence of 1.1-1.3 AVMs per 100,000 person-years.[4] In the United States, assuming the total population in the range of 300 million, this would lead to an estimated annual AVM incidence of 3,300-3,900 (avg. 3,600). Most brain AVMs are diagnosed before the age of 40 and are potentially life-threatening with patients presenting with cerebral hemorrhage, seizures, headaches, or progressive neurological deficit.[1,20] Left untreated, brain AVMs are associated with significant morbidity and mortality due to cerebral hemorrhage occurring at a 2 to 4% annual rate.[6] The hemorrhage risk of giant brain AVMs is as high as 9.6% annually and translates to a 64% risk of hemorrhage over a 10 year period.[7] The cumulative lifetime risk of intracranial hemorrhage attributable to AVMs can be estimated by subtracting a person's age from 105 (e.g., lifetime risk (%) of a brain hemorrhage for a 35 year old with an AVM is 70%). In one study collecting information from 300 patients with brain AVMs, 151 patients (51%) presented with a brain AVM hemorrhage. The morbidity associated with these brain AVMs included mild neurological defects (37%), moderate disabilities (13%) and severe disabilities (3%).[21] For patients with prior hemorrhage, the risk of recurrent hemorrhage is 32.9% during the first year and 11.3% thereafter.[20]

1.2.2 Current Brain AVM Treatment Options

Multiple treatment options are available to patients with brain AVMs depending upon the location, size, and overall complexity of the lesion. Current treatment strategies for brain AVMs include endovascular embolization, micro-surgical resection, and stereotactic radiosurgery. Often involving a multidisciplinary approach, endovascular embolization plays an essential role in the treatment of cerebral AVMs as the first step of a multimodal treatment strategy combining embolization techniques together with surgical excision or radiosurgery.[8,9] Endovascular embolization of brain AVMs involves the use of catheters to deliver a variety of occlusive agents

to block blood flow to the intracranial lesion, and include; permanent balloons, sclerosing drugs, thrombosing coils, polyvinyl alcohol (PVA) particles, rapidly acting glues (e.g., n-Butyl cyanoacrylate (NBCA)), and ethylene vinyl alcohol (Onyx™ LES). In a published literature review comprising over 1200 patients who underwent embolization of brain AVM with various embolic agents (e.g., NBCA, PVA, coils, etc.), rates of temporary morbidity, permanent morbidity and mortality were observed after embolization in 10%, 8% and 1% of patients, respectively.[22] Additionally, the benefits of embolization include an increased safety margin for subsequent treatments (i.e. surgery, radiosurgery). When embolic treatment leads to a significant reduction in size of the AVM, the lesion may become amenable to techniques not previously possible for a larger lesion.

Embolization of brain AVMs can be performed with a high degree of technical success in the aim of reducing nidal size in advance of surgical resection or radiosurgery and towards reducing hemorrhage risk by attempting to eliminate specific areas at high risk for hemorrhage. The degree of safety and rate of treatment-related complications of embolization is also factored as a key component of understanding risks of therapy versus conservative management, especially for unruptured brain AVMs. Several historical series have reported the complication rates with AVM embolization treatment-related morbidity ranging from 3% to 11%.[23-25] In a retrospective study devoted to examine the overall neurologic complication rate in patients undergoing AVM embolization, transient neurologic deficits occurred in 11.5%, with permanent nondisabling complications and permanent disabling complications or deaths in 2.6% and 1.6% of patients, respectively.[26] Constituting part of the Japanese Registry of Neuroendovascular, 987 embolization procedures were retrospectively analyzed to report a 2.5% procedural morbidity rate of and 0.3% mortality rate per procedure.[27] Intracranial hemorrhage represents the most severe complication of brain AVM treatment. Baharvahdat et al specifically investigated hemorrhagic complications and found 11% procedure related hemorrhage rate having 48% of these complications on account of periprocedural arterial perforation.[28] Research overall has showed that increasing patient age, number of embolizations and higher injected volume of embolic agent, deposition on the venous outflow before complete occlusion of the AVM, and absence of a pretreatment neurological deficit has been associated with new neurological deficits following endovascular embolization for cerebral AVM.

Recent advances in the embolization technique during the past decade have centered on the development of softer flow-directed micro catheters and the increased use of liquid embolic agents. Presurgical embolization of brain AVMs represents an effective means to help reduce the AVM size, minimizes intraoperative blood loss during surgery and results in a decreased resection time. Both the role of endovascular embolization as a stand-alone curative treatment and its use as a presurgical and preradiosurgical procedure have been significantly expanded following introduction of the Onyx™ LES.[16,19,29,30] Onyx™ LES is a non-adhesive liquid embolic agent comprised of Ethylene Vinyl Alcohol (EVOH) copolymer dissolved in dimethyl sulfoxide (DMSO) and micronized tantalum powder.

A possible complication in performing endovascular procedures involving liquid embolic agents, such as Onyx™ LES, is the occurrence of micro catheters being entrapped in the neurovasculature.

In these instances, increased risk to the patient exists due to vessel damage resulting from attempts to remove the embedded catheter or may result from abandoning the catheter in the blood vessel due to difficulties in removing the catheter without risk of causing further damage. Typically, during neurovascular embolization, a solid mass is formed from an embolic agent, delivered *in situ* to the embolization site. The embolic agent is ejected distally from the micro catheter tip and forms a solid mass at this distal point. In certain cases, "flow back" or "reflux" of the liquid composition prior to solidification can occur and the embolic agent can engulf the micro catheter tip. In such cases, the micro catheter tip can become entrapped in the solid mass upon solidification of the embolic agent. Even in instances where reflux is avoided, the micro catheter may become trapped in the blood vessel as a result of vasospasm caused by the presence of DMSO or other spasmodic materials in the embolic composition.

Cases of catheter entrapment and difficulty in retrieval of the catheter have been observed in a number of studies using Onyx™ LES, particularly in cases requiring long injection and when there is a large amount of reflux.[10-17] A review of literature constrained to studies/ case reports with at least 50 patients demonstrates that catheter entrapment/abandonment occurred in 0-9.7% of Subjects treated with Onyx™ LES.[10,12,14-16,18,19,31] Reported side effects related to catheter entrapment/abandonment included inguinal cellulitis, thrombophlebitis of the leg, femoral artery occlusion, and knee pain.[16] Additionally, difficulty in micro catheter withdrawal may result in vessel rupture leading to severe brain hemorrhage, causing severe sequelae and an increased patient death risk.[10] As a consequence, various alternative techniques to remove an entrapped catheter or prevent catheter entrapment have been published.[32-38] One technique uses a 'monorail snare technique' in which a Amplatz Goose Neck microsnare was loaded into another micro catheter and inserted in the far distal end of the embedded catheter.[32] The embedded catheter was then ensnared and both catheters were pulled free. Another technique uses a coaxial 'push-pull' method in which an Outreach distal access catheter (DAC) was advanced over the micro catheter and through the guide catheters in a coaxial fashion. Using the DAC for counter traction, the embedded micro catheter was released from the Onyx casts.[36]

The Apollo™ micro catheter is a micro catheter designed for superselective infusion of Onyx™ LES. The Apollo™ micro catheter is specifically designed to allow for catheter retrieval in the event the catheter becomes entrapped within the vasculature. The distal section of the catheter incorporates a detachment zone that allows detachment of the distal tip when the force required to extract the catheter exceeds the force required to detach the tip, making the Apollo™ micro catheter an invaluable tool for procedures where catheter entrapment is a concern. Furthermore, in the event of catheter entrapment, use of the Apollo™ micro catheter versus any other standard micro catheter results in leaving behind a 1.5-3.0 cm long detachable tip in the Onyx™ cast versus an average 165 cm long catheter in the vasculature.

1.3 Clinical Study Experience

This study represents the first clinical trial on the Apollo™ micro catheter. The device was approved for commercialization in the European Union in 2009.

Two key clinical studies have reported on the use of Onyx™ LES: 1) a prospective randomized controlled trial comparing Onyx™ LES with NBCA and 2) an international prospective, multicenter registry. These studies are summarized below.

1.3.1 Randomized Controlled Trial of Onyx™ LES vs. NBCA

In 2001 a prospective, equivalence, multicenter, randomized controlled trial was initiated to verify the safety and efficacy of Onyx™ LES compared with NBCA for the pre-surgical treatment of brain AVMs. Loh et al. reported on the pivotal trial for Onyx™ LES on behalf of the trial Investigators.[39]

The analysis included 117 Subjects with brain AVMs who were randomized and treated with either Onyx™ LES (54 Subjects) or NBCA (63 Subjects) for pre-surgical endovascular embolization between May 2001 and April 2003. Technical success in achieving a ≥50% reduction in AVM volume was the primary endpoint. Secondary endpoints were operative blood loss and resection time. All adverse events (AEs) were collected and assessed for relationship to the Onyx™ LES or NBCA system, treatment, disease, surgery or other/unknown. The Data Safety Monitoring Board adjudicated AEs, and a blinded, independent core lab assessed volume measurements. Study Subjects were followed through discharge after the final surgery or, if resection was not performed or was incomplete, Subjects were followed through 3- and/or 12-month follow-up.

Technical success in achieving a ≥50% AVM volume reduction with Onyx™ LES was achieved in 96% of cases versus 85% of cases with NBCA (p=NS). The secondary endpoints of resection time and blood loss as well as serious AEs were similar between treatment groups. System-related serious AEs during treatment with Onyx™ LES included 3 cases of neurological decline, including cranial neuropathy with permanent deficit and transient paresis post-embolization following difficult catheter removal; worsening seizures and neurological decline related to contrast extravasation from ruptured catheter shaft, bilateral retinal hemorrhages caused by increased intracranial pressure, and transient hemiparesis and hemianopia; and difficult catheter removal and vasospasm with prolonged hospitalization for significant but transient deficits. One stroke with permanent deficit occurred following embolization of unintended vessel and subsequent infarction. One intracranial hemorrhage caused by catheter rupture and resulting in permanent deficit occurred. One vessel dissection was noted at the time of second embolization which was presumably from the first embolization procedure; the vessel was stented for moderate stenosis. Technical and procedural events included: difficulty removing catheter (n=6), rupture of delivery catheter (n=2), failed access (n=9), fragmentation of Onyx™ (n=1), poor penetration/visualization (n=6), small amount of Onyx™ in vein (n=1), vasospasm (n=1), vessel dissection (n=1), and laboratory/imaging abnormalities (n=6). The Investigators concluded that Onyx™ LES is equivalent to NBCA in safety and efficacy as a preoperative embolic agent in reducing brain AVM volume by at least 50%.

1.3.2 BRAVO Registry

An international, prospective, multicenter registry (BRAVO) was conducted to evaluate the safety and performance of Onyx™ LES in the treatment of brain AVMs until treatment completion. The primary efficacy endpoint was the AVM occlusion rate at the end of all Onyx™ treatment sessions

measured by angiography and evaluated by an independent core laboratory. The primary safety endpoint was rate of Subject morbidity and mortality. Pierot *et al.* reported on the results of the BRAVO registry.[40]

A total of 123 Subjects were enrolled in the registry. Six Subjects were excluded due to not meeting the inclusion/exclusion criteria (2 were <18 years old, 3 had dural fistula, and 1 had been previously treated for AVM). One hundred seventeen (117) Subjects were included in the analyses. The average age was 42.6 ± 13.6 years with 61.5% male. Clinical presentation was primarily hemorrhage (34.2%) and seizures (28.2%). The size of the AVMs was <3 cm for 52.1% of Subjects and ≥3 cm for 47.9% of Subjects. Following all Onyx™ LES treatments, the degree of occlusion was 100% for 23.5% of Subjects, 75-99% for 33.9%, 50-75% for 27.8% and <50% occlusion for 14.8% of Subjects. For Subjects with smaller AVMs <3 cm, the 100% occlusion rate was 37.7%. The treatment-related mortality rate was 4.3%, including 4 deaths due to bleeding and 1 death due to an extensive venous thrombosis. The treatment-related morbidity rate was 7.1% with morbidity due to bleeding for 4 cases and due to other causes for 4 cases. Treatment-related hemorrhage occurred in 12.8% of Subjects. Other treatment-related serious adverse events included left hemiplegia with residual deficit, pneumopathy, dysmetry right deficit with residual deficit, venous thrombosis resulting in death, and two access site complications. The Investigators concluded that Onyx™ LES "proved to be suitable for brain AVM embolization, with acceptable morbidity and mortality and good efficacy."

1.4 Rationale of Clinical Study

Although endovascular embolization of brain AVMs with Onyx™ LES is performed regularly, catheter entrapment/abandonment is a complication that has been reported in up to 10% of Subjects treated with Onyx™ LES.[10,12,15,16,18,19] In order to help prevent catheter entrapment/abandonment, the Apollo™ micro catheter was designed with a detachable distal tip that allows for catheter retrieval. This device was approved for commercialization by the Food and Drug Administration on May 27th 2014 for the controlled selective infusion of Onyx™ LES. The present study aims to evaluate the safety of the Apollo™ micro catheter through the assessment of catheter-related AEs and long-term follow-up of Subjects in whom the catheter tip/body is retained.

1.4.1 Study Population

A total of 161 Subjects will be enrolled into this study and are expected to contribute data on an estimated 322 Apollo™ micro catheter utilizations (e.g., approximately 2 catheters used per Subject). Males or females with a confirmed diagnosis of a brain AVM will be eligible for participation in the study if they satisfy the inclusion and exclusion criteria. The Apollo™ micro catheter will be used to deliver Onyx™ LES to eligible Subjects for either presurgical embolization of brain AVMs or for the embolization of brain AVMs without subsequent surgery. This patient population has been selected in order to collect post-approval data on the safety of the Apollo™ micro catheter when used by a broad group of physicians under commercial use conditions.

1.4.2 Single-Arm Study Design

The proposed study design is a prospective single-arm multicenter trial to evaluate the use of the Apollo™ micro catheter to deliver Onyx™ LES during AVM embolization procedures. A single-arm design was selected since the incidence rates associated with catheter retainment are published in the literature and can be used to define objective performance criteria. Furthermore, there are no alternative micro catheters that could form a reasonable concurrent control group. There is only one other micro catheter with a detachable tip (Sonic Micro Catheter, Balt Extrusion), however, it is not approved for use in the United States.

1.4.3 Conclusion

In summary, left untreated, brain AVMs are potentially life-threatening and are associated with significant morbidity and mortality. Treatment of AVMs with liquid embolics such as Onyx™ LES can result in avoidance of AVM rupture and minimizes intraoperative blood loss during surgical resection of the AVM, thereby reducing morbidity and mortality. Although these rates are reduced compared to those for AVMs left untreated, treatment with liquid embolics could lead to catheter entrapment. Use of the Apollo™ micro catheter has the potential to decrease the incidence of this complication.

Thus, the aim of the present study is to assess the safety of the Apollo™ micro catheter used for delivery of the Onyx™ LES during brain AVM embolization procedures.

2 DEVICE DESCRIPTION

2.1 Intended Use

The Apollo™ micro catheter is intended to access the neuro vasculature for the controlled selective infusion of the Onyx™ LES.

2.2 Device Name

Apollo™ micro catheter is used to deliver the Onyx™ LES, which received PMA approval in the US in 2005. Onyx™ LES is available in the United States in two formulations: Onyx™ 18 LES and Onyx™ 34 LES. Onyx™ 18 LES contains 6% EVOH and Onyx™ 34 LES contains 8% EVOH. Onyx™ 18 LES will travel more distally and penetrate deeper into the nidus due to its lower viscosity compared to Onyx™ 34 LES.

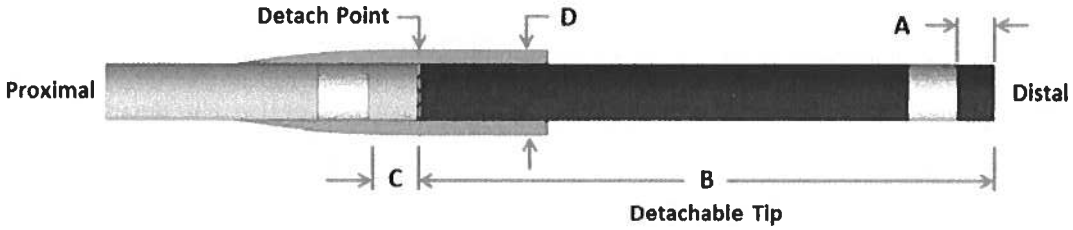
2.3 Device Description

The Apollo™ micro catheter is a single-lumen, endhole catheter intended to access the neurovasculature for the controlled selective infusion of Onyx™ LES. The catheter has a semi-rigid proximal shaft and a highly flexible distal shaft to facilitate the advancement of the catheter in the anatomy. The proximal end of the catheter incorporates a standard luer adapter to facilitate the attachment of accessories. The outer surfaces of the catheter are coated to increase lubricity.

The Apollo™ micro catheter is designed to facilitate catheter retrieval in the event the catheter becomes entrapped within the Onyx™ LES cast. The distal section of the catheter incorporates a detachment

zone that allows detachment of the distal tip when the force required to extract the catheter exceeds the force required to detach the tip (Figure 1). The catheter has two radiopaque marker bands to visualize the position of the catheter and the detach zone area (Figure 2):

- Proximal to the detach zone
- At the distal end of the detachable tip (distal end of catheter)



REF*	A	B-Tip Length	C	D
105-5095-000	0.5 mm	1.5 cm / 15 mm	1.25 mm	1.9 F / 0.63 mm
105-5096-000	0.5 mm	3 cm / 30 mm	1.25 mm	1.9 F / 0.63 mm

**Table indicates micro catheter dimensions. Letters A, B, C, and D listed in the table correspond to the sections/points labeled on the figure.*

Figure 1. Apollo™ Onyx™ Delivery Micro Catheter Dimensions

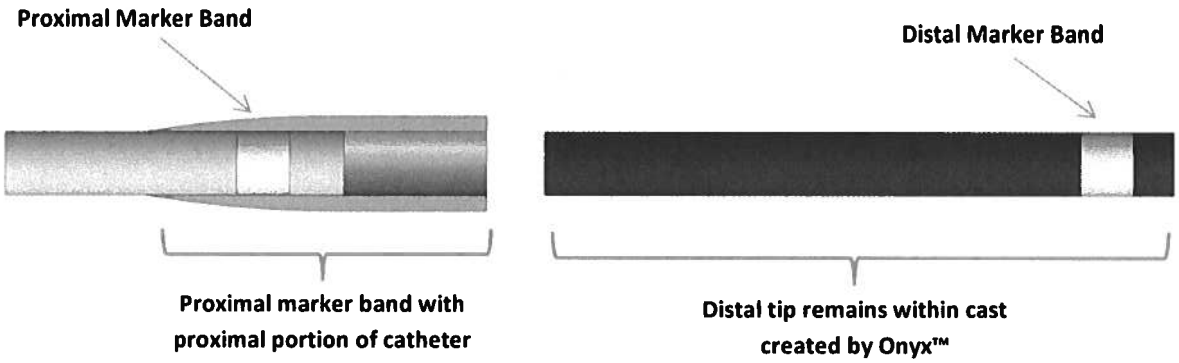


Figure 2. Marker bands of Apollo™ Onyx™ Delivery Micro Catheter

2.4 Device Labeling

The Apollo™ micro catheter is an approved, commercially available device. However, this device is being investigated for the potential safety effects of retaining the catheter tip in the neurovasculature.

2.5 Device Tracking

The lot number of each Apollo™ micro catheter will be captured on the case report forms. Due to commercial availability, all shipments will not be tracked for the study.

2.6 Devices and Equipment

In addition to Onyx™ LES and the Apollo™ micro catheter, devices that may be required for the study procedure include (but are not limited to) those listed below. All devices required to perform the procedure will be provided by the site.

- Access devices: Guiding catheter and sheath
- Non-ionic contrast
- Guidewires
- Any other adjunctive, approved/cleared device for AVMs

The Onyx™ delivery procedure is described in detail in the Instructions For Use (IFU) document.

Note: The Investigator will undergo training on the use of the Apollo™ micro catheter and on the IFU prior to performing any Onyx™ delivery procedures with the Apollo™ micro catheter in this clinical study.

3 STUDY OBJECTIVES

3.1 Primary Composite Endpoint (30 days)

- Incidence of catheter-related AEs per Subject:
  - Premature (unintentional) catheter tip detachment with clinical sequelae*
  - Catheter rupture/break/fracture with clinical sequelae*, and
  - Retained catheter body in the vasculature.

*Clinical sequelae are defined as all focal neurologic deficits related to lesions within the vascular territory catheterized. Vascular territory catheterized is defined as the brain tissue supplied by the vascular tree selectively catheterized using the Apollo™ micro catheter.

3.2 Acute Secondary Endpoints (30 days)

- Rate of premature (unintentional) catheter tip detachment
  - Unintentional tip detachment is defined as detachment of the catheter tip within the vasculature at an unintended location.
- Rate of intentional catheter tip detachment
  - Intentional catheter tip detachment is defined as deliberately applying the necessary force on the catheter to detach catheter tip.
- Rate of migration of the retained catheter tip post embolization
- Incidence of procedure-related AEs
- Rate of catheter/tip leakage from detachment zone

3.3 Long-Term Secondary Endpoints (12 months)

- Incidence of AEs
- Rate of migration of the detached catheter tip post embolization

Incidence is defined as the cumulative number of endpoint events divided by the total number of embolizations completed in the study.

Migration is defined by an observed change in position of the detached tip during imaging or by discovering the detached tip at some location other than the one identified at the last imaging.

4 STUDY DESIGN

4.1 Study Design and Projected Timeline

This study is a prospective, single-arm, multi-center, post market safety evaluation of Subjects indicated for embolization of brain AVMs with Onyx™ LES, delivered with the Apollo™ micro catheter.

The projected timeline for this study is as follows:
Expected date of study initiation:
Expected monthly number of study sites with IRB approvals:
Expected number of subjects enrolled per month:
Expected date of enrollment completion:
Expected date of study follow-up completion:
Expected date for Final Report submission:

4.2 Number of Sites and Subjects

Up to 161 Subjects with an estimated 322 catheter utilizations (~2 catheters per Subject) will be enrolled in this study from up to 25 US sites.

4.3 Study Population

Subjects with a brain AVM indicated for embolization with Onyx™ LES using the Apollo™ micro catheter will be enrolled in this study.

4.4 Subject Selection Criteria

Waivers will not be granted by the Sponsor regarding Subject inclusion/exclusion criteria.

4.4.1 Inclusion Criteria

1. The Subject or Subject's legally authorized representative has signed and dated an informed consent form.
2. The Subject has a confirmed diagnosis of a brain AVM.
3. The Subject is clinically and neurologically stable for a minimum of 48 hours prior to embolization.
4. The Subject has a life expectancy of at least 1 year.
5. The Subject agrees to and is capable of completing all study-required procedures.

4.4.2 Exclusion Criteria

1. Current participation in another investigational drug or device study that evaluates treatments for brain AVMs or other cerebrovascular disease.
2. The Subject has a bleeding disorder.
3. The Subject is not a candidate for the use of vasodilators.

5 STUDY PROCEDURES

5.1 Overview of Study Flow

A representative overview of the study flow is shown below.

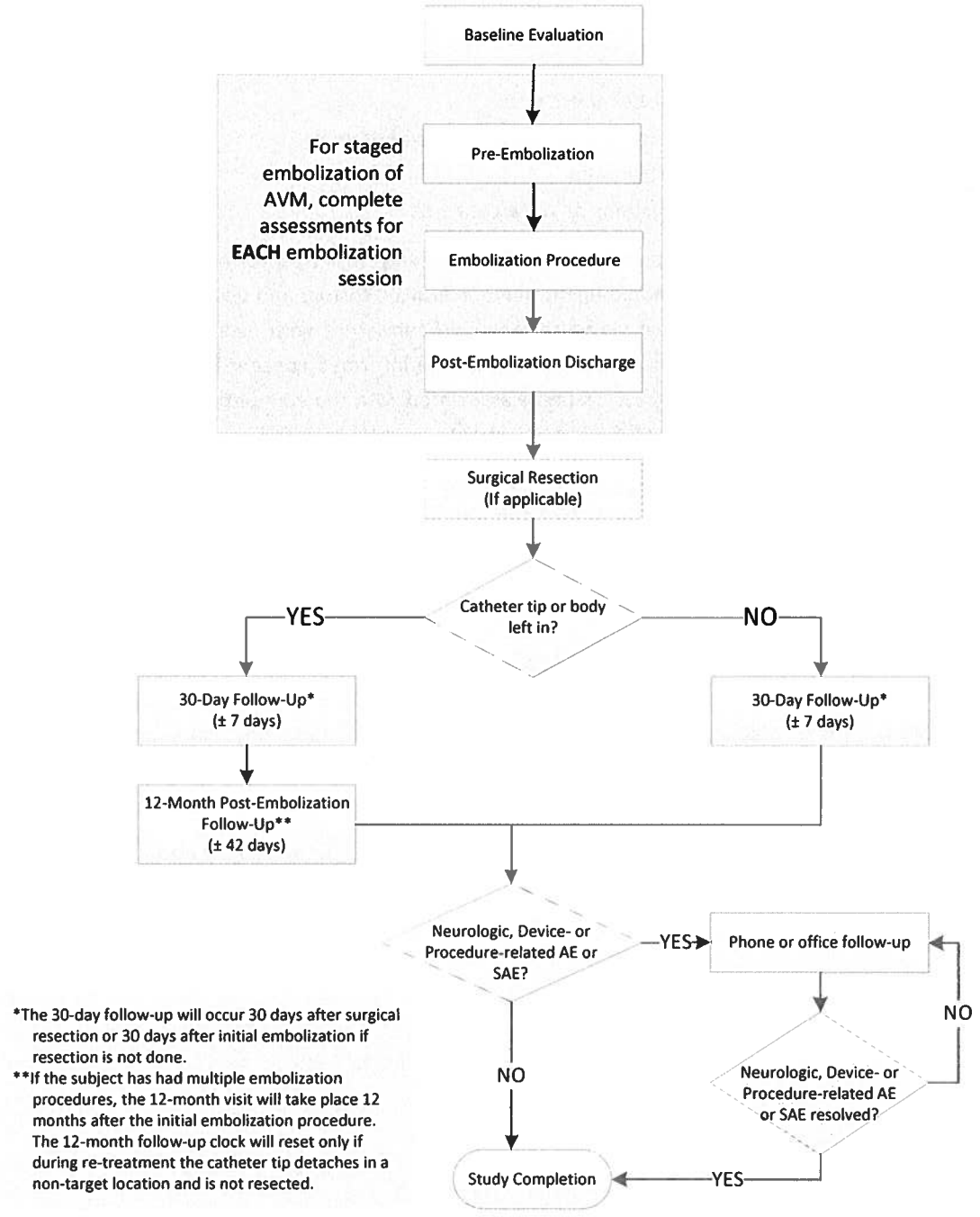


Figure 3. Study Flow

5.2 Informed Consent and Privacy

A thorough explanation will be provided to the Subject (or legally authorized representative) as to the nature and objectives of this study. Details of the study should include (but are not limited to) the following terms:

- Purpose of the study
- Alternative treatments
- Need to return for 30-day, and 12-month visits
- Participation is voluntary, and there is no penalty for withdrawal
- Potential risks/benefits for participation
- Contact information to ask questions or voice concerns

The study Investigator and/or staff are responsible for obtaining written informed consent from each potential Subject. Informed consent should be obtained in written format and using a form approved by the local IRB. The form should contain standard language consistent with local policies for ensuring privacy of confidential information. All Subjects must sign the informed consent form (ICF) prior to any procedures/tests that go beyond initial assessments associated with the standard care for Subjects with AVMs and before any study-related treatments assessments are administered.

It is the responsibility of the Investigator to give each Subject (or Subject's legally authorized representative) prior to inclusion in the study, full and adequate verbal and written information regarding the objective of this study and the confidentiality of the data collected.

5.3 Screening

Subject eligibility assessment is to be performed based on data available to the Investigator at the time of screening. This initial screening phase may include review of existing Subject information (previously performed angiography, radiographs, laboratory studies, medical history, physical examination, etc.) and referral to the treating physician. Subjects must comply with all inclusion and exclusion criteria. Waivers will not be granted by the Sponsor regarding Subject inclusion/exclusion criteria.

All Subjects screened should be included on the study screening log. The reason of non-eligibility for all Subjects who are deemed ineligible by the Investigator should also be recorded on the study screening log. The screening log serves as a method for Covidien to ensure that there is no selection bias in the trial.

5.3.1 Schedule of Assessments

An overview of the assessments to be performed is provided in Table 1.

Table 1. Schedule of Assessments

Assessment	Baseline (-30 days)	Pre-Embolization	Embolization Procedure	Post-Embolization Discharge or +24 hours post-embolization	Surgical Resection	30 Day Follow-up[1] (+/-7 days)	12 Month Follow-up[2] (+/-42 days)
Informed Consent	◆						
Inclusion/Exclusion	◆						
Demographic Characteristics	◆						
Medical History	◆						
Brain AVM characteristics	◆						
Physical Exam	◆						
Neurologic Exam	◆						
Barthel Index		◆		◆		◆	◆
Modified Rankin Scale (mRS)		◆		◆		◆	◆
National Institutes of Health Stroke Scale (NIHSS)		◆		◆		◆	◆
Imaging	◆	◆	◆	◆	◆	◆[3]	◆
Embolization Procedure Information and Device Usage or Surgical Resection			◆	◆	◆		
Technical Events			◆				
Concomitant Medications	◆	◆	◆	◆	◆	◆	◆
Adverse Events			◆	◆	◆	◆	◆

1. 30 day follow-up will occur 30 days after surgical resection, or 30 days after initial embolization if resection is not done.
2. Only for Subjects with catheter and/or catheter tip retainment. If the Subject has had multiple embolization procedures, the 12-month visit will take place 12 months after the initial embolization procedure.
3. Subjects with catheter and/or catheter tip retainment, or based on physician assessment.

5.4 Baseline Evaluation

Baseline information will be collected for each Subject to assess the presence of neurological symptoms potentially related to the AVM. The presence and history of any significant medical illnesses and any symptoms related to the AVM will also be collected. For additional assessments that will be performed at baseline, please refer to Table 1.

5.4.1 Imaging

A review of images of the AVM at baseline will be completed to confirm the diagnosis of a brain AVM. Baseline imaging will be conducted no earlier than 1 month prior to the embolization procedure.

5.4.2 Concomitant Medications

All medications that a patient is taking starting 30 days prior to screening will be collected and followed for the duration of the study. In addition, the following medications will be collected throughout the study: antithrombotic, antiplatelet, anticoagulant, all medications administered during the study procedure, and medications associated with adverse events.

5.5 Screen Failure

Subject will be considered a screen failure if:

- The Subject signs the ICF but fails to meet study inclusion/exclusion criteria during the screening and baseline phase.
- The Subject signs the ICF, meets the study inclusion/exclusion criteria but an attempt to use the Apollo™ micro catheter is not performed.

5.6 Enrollment

A Subject will be considered enrolled once the Apollo™ micro catheter is advanced inside the blood stream of the Subject.

5.7 Pre-Embolization

Neurological functioning will be assessed using the mRS, NIHSS, and Barthel Index. Pre-embolization imaging will also be collected.

5.8 Embolization Procedure

Embolization with Onyx™ 18 LES or Onyx™ 34 LES will be performed in a neuroangiography suite using customary endovascular techniques. Intravenous sedation or general anesthesia will be used to assure Subject comfort and safety. Additional safety measures such as neurophysiological monitoring, or similar practice standards are permitted. Subjects will be heparinized, per the institutional protocol, after placement of an arterial sheath. The anticoagulation regimen and all medications used will be recorded.

The intended use of the study device and components are outlined in the IFU. Any additional pre-operative imaging and neurologic exams performed will be collected to assess changes since baseline. Table 1 describes a list of assessments that will be performed at this visit. For Subjects undergoing staged embolization procedures, data from each embolization procedure will be captured in the study electronic case report forms (eCRFs).

5.8.1 Device Use

Detailed information on devices used during the procedure will be collected for the following:

- Ancillary devices
- DMSO
- Onyx™ LES
- Apollo™ micro catheter

5.9 Post-Embolization Discharge

All Subjects will undergo a discharge assessment to evaluate neurological functioning after the embolization procedure. Table 1 describes a list of assessments that will be performed at this time point.

5.10 Surgical Resection

Some Subjects may undergo complete or partial surgical resection of their AVM. Information about the surgical resection procedure, imaging, concomitant medications, and AEs as defined in Section 6.1 will be collected (see Table 1). Data regarding the degree of resection and catheter retainment will be captured.

5.11 Follow-up Evaluations

5.11.1 30-Day

Subject who underwent surgical resection will complete a 30-day visit 30 days after surgical resection. For Subjects not undergoing surgical resection, the 30 day visit will be performed 30 days after the initial study embolization. Table 1 describes a list of assessments that will be performed at this visit. Subjects with a retained catheter/tip will undergo imaging at this time point. Subjects experiencing AEs may undergo imaging per physician discretion. Subjects not experiencing an AE and in whom no part of the catheter was retained will complete the study. Subjects experiencing an AE and in whom no part of the catheter was retained will continue to be followed up until AE resolution.

5.11.2 12-Month

Subjects in whom a catheter and/or tip were retained will have a 12-month study visit. If the Subject has had multiple embolization procedures, the 12-month visit will take place 12 months after the initial embolization procedure. If the Subject is experiencing ongoing AEs at 12 months, the Subject will be followed until resolution of the AE. The clock will only reset, if during re-treatment the catheter tip detaches in a non-target location and is not resected. Final imaging will be required at this visit. Table 1 describes a list of assessments that will be performed at this visit.

5.12 New Information

Study Subjects will be informed of new information as it becomes available during the course of this study. Subjects will be notified, at a minimum, in accordance with the IRB's procedure for providing updated information to clinical study Subjects.

5.13 Termination of Subject Participation

Subjects may withdraw from the study at any time without penalty or loss of medical care, or they may be withdrawn at any time at the discretion of the PI or Sponsor for safety or administrative reasons (such as early termination of the study by the Sponsor).

5.13.1 Subject Withdrawal

All enrolled Subjects have the right to withdraw their consent at any time during the study. Data collected until the time of withdrawal will remain in the study database and may be used during analysis. Whenever possible, the site staff should obtain written documentation from the Subject that wishes to withdraw his/her consent for future follow-up visits and contact. If the site staff is

unable to obtain written documentation, all information regarding the Subject's withdrawal must be recorded in the Subject's medical record. In addition, the appropriate eCRFs must be completed for the Subject and clear documentation of the Subject's withdrawal be provided to the Sponsor.

5.13.2 Subject Discontinuation by Investigator

An Investigator may discontinue a Subject from the study, with or without the Subject's consent, for any reason that may, in the Investigator's opinion, negatively affect the well-being of the Subject. If a Subject is withdrawn from the study, the Investigator will promptly inform the Subject and Sponsor.

5.13.3 Lost to Follow-Up

A Subject will be considered lost to follow-up if the Subject cannot be reached after three attempts; attempts can include telephone, email and registered letter. These failed contact attempts will be documented on the eCRF. Every effort should be made to maintain contact with the Subject during the study.

5.14 Deviations to the Investigation

A protocol deviation is defined as an event where the Investigator or study personnel did not conduct the study according to the clinical protocol. Deviations shall be reported to the Sponsor regardless of whether medically justifiable or taken to protect the Subject in an emergency.

Except a change that is intended to eliminate an immediate hazard to a Subject, the protocol will be followed as described. Subject specific deviations and non-Subject specific deviations will be reported. Investigators will also adhere to procedures for reporting study deviations to their IRB in accordance with their specific IRB reporting policies and procedures.

Sites with a high rate of protocol deviations will be closely evaluated and are expected to implement corrective action to prevent further deviations. If a site demonstrates persistent deviations, as described above, the site may be terminated.

Some information collected in this study is not essential to the study endpoint and will not be considered a deviation if absent.

5.14.1 Discontinuation by IRB

The IRB may choose to discontinue the Study at any center(s) for which they granted approval if:

- The research study is not conducted in accordance with the IRB's requirements.
- The research study indicates unexpected serious harm to Subjects.

The Investigator needs to report to the Sponsor within 5 working days a withdrawal of approval by the reviewing IRB (21 CFR 812.150).

5.14.2 Study Discontinuation by Sponsor

The Sponsor may choose to discontinue the study should the Sponsor discover additional information during the study that may cause harm to Subject safety.

If the study is terminated prematurely or suspended, the Sponsor will promptly inform all clinical Investigators of the termination or suspension and the reason(s) for this. The IRB will also be informed, either by the Sponsor or Investigator if a local IRB is utilized, promptly and provided with the reasons(s) for the termination. If applicable, regulatory authorities will be informed. Enrolled Subjects will be asked to complete all remaining study visits and the Subjects will then be seen by the treating physician according to standard patient care following AVM treatment.

6 ADVERSE EVENTS

The following AEs will be collected during the course of the study on the eCRFs:

- All Serious Adverse Events (SAEs)
- All Device-related Adverse Events
- All Procedure-related Adverse Events
- All AEs with an underlying neurological cause (Neurological Adverse Event)

See Section 6.1 for event definitions and categorizations. The status of the AEs will be evaluated throughout the study. AEs will be collected from the point of enrollment in the study until a Subject exits the study. Investigators must obtain all information available to determine the causality, location with respect to the vascular territory catheterized, and outcome of the AE and to assess whether it meets the criteria for classification as a serious and/or unanticipated device event requiring expedited notification to the Sponsor, regulatory agency, and IRB (if applicable) within the specified reporting timeframe.

All study AEs, as well as the treatment and follow-up required, should be documented in the Subject's medical records and in the eCRF. All study AEs will be followed by the Investigator until resolution. A list of potential anticipated AEs is provided in Section 10.2.

6.1 Event Definitions

An *Adverse Event (AE)* is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in Subjects, users or other persons, whether or not related to the investigational medical device. (ISO 14155:2011)

Note 1: This includes events related to the investigational device or the comparator.
Note 2: This includes events related to the procedures involved (any procedure in the clinical investigational plan).
Note 3: For users or other persons this is restricted to events related to the investigational medical device.

An *Adverse Device Effect (ADE)* is defined as an adverse event related to the use of an investigational medical device. (ISO 14155:2011) The investigational medical device for this study is the Apollo™ micro catheter.

Note 1: This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational device.
Note 2: This includes any event that is a result of a use error or intentional misuse.

A *Serious Adverse Event (SAE)* is defined as an AE that:

a) Led to death,
b) Led to serious deterioration in the health of the Subject, that either resulted in
    a. A life-threatening illness or injury, or
    b. A permanent impairment of a body structure or a body function, or
    c. In-patient or prolonged hospitalization, or
    d. Medical or surgical intervention to prevent permanent life-threatening illness or injury or permanent impairment to a body structure or a body function,
c) Led to fetal distress, fetal death or a congenital abnormality or birth defect (ISO 14155:2011)

Note 1: This includes device deficiencies that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate. These are handled under the SAE reporting system.
Note 2: A planned hospitalization for pre-existing condition, or a procedure required by the Clinical Investigational Plan, without a serious deterioration in health, is not considered to be a serious adverse event.

A *Serious Adverse Device Effect (SADE)* is defined as an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. (ISO 14155:2011)

An *Unanticipated Serious Adverse Device Effect (USADE)* is defined as a serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report. (ISO 14155:2011)

Note: Anticipated: an effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report.

An *Unanticipated Adverse Device Effect (UADE)* is defined as 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. (21 CFR 812.3)

Severity:

- Mild: No limitation of usual activities, no therapy or only symptomatic therapy required to treat the injury or illness.
- Moderate: Some limitation of usual activities or specific therapy is required.
- Severe: Inability to carry out usual activities, hospitalization, emergency treatment, life threatening events, or death.

Relatedness:

- Study Disease-related: Event is clearly attributable to the underlying study disease state with no temporal relationship to the device, treatment, or medication.
- Concomitant disease-related: Event is clearly attributable to the underlying concomitant disease state with no temporal relationship to the device, treatment, or medication.
- Procedure-related: Event has a strong temporal relationship to the study procedure.
- Device-related: Event has a strong temporal relationship to the study device, and alternative etiology is less likely.
    - Study device: Apollo™ micro catheter

  All events considered "device-related" will be further characterized as either:
    - Anticipated: When the event was previously identified in nature, severity or degree of incidence in the investigational plan. Or
    - Unanticipated: When the event was not previously identified in nature, severity or degree of incidence in the investigational plan.
- Ancillary device-related: Any device(s) other than the Apollo™ micro catheter used at embolization, such as access devices, delivery micro catheters, non-ionic contrast, guidewires, or any other adjunctive, approved/cleared device for treatment of AVMs.
- Unknown: Event relationship cannot be attributed to any of the above categoriesand remains undetermined.

6.2 Expedited Event Reporting

The Investigator is required to report to the Sponsor any UADEs/USADEs within 24 hours and all SAEs within 72 hours after first learning of the event (see Table 2). All expedited events will be reported to the Sponsor primarily via site entry of the event into the eCRFs. If unable to access database to meet reporting timelines, then the expedited event information can be provided via fax at
Site reported entry of the event into the eCRFs should promptly follow. Subsequent to reporting the event via site entry of the eCRFs or fax, the Investigator will fax and/or email all available supporting documentation (de-identified as to the Subjects' identity) to the Sponsor.

As additional information becomes available, copies of that source documentation which contain significant information related to the event such as progress notes, consultations, nurse's notes, operative reports, imaging studies and Subject summaries etc. are requested for a complete evaluation of the event.

Table 2. Expedited Adverse Event Reporting Requirements

UADEs/USADEs	Investigator will notify Sponsor of all UADEs and USADEs within 24 hours of being aware of the event.
SAEs	Investigator will notify Sponsor of all SAEs within 72 hours of being aware of the event.
Sponsor contact information:	**Fax:** **Email:**

In regard to Subject deaths, it is requested that a copy of the death certificate and a copy of the autopsy report, if applicable, be sent to the Sponsor when available. Any other source documents related to the death should also be provided to the Sponsor. In the event that no source documents are available, the Principle Investigator (PI) is requested to describe the circumstances of the Subject's death in a letter, e-mail or other written communication.

UADEs/USADEs have expedited reporting requirements. Any event that meets the definition of UADE (Section 6.1) must be reported to FDA, all Investigators and reviewing IRBs within 10 working days after becoming aware of information that an UADE has occurred. The investigator must also follow their local IRB requirements for SAE/UADE/USADE reporting.

The site will notify the reviewing IRB within 10 working days after becoming of aware of the effect. The Sponsor will notify the all Investigators, IRBs and the FDA within 10 working days after first receiving notification of the event. In addition, the Sponsor will comply with Medical Device Reporting / MDR regulations where applicable.

6.3 Adverse Event Reporting

All adverse events (not meeting expedited reporting criteria) will be reported by site entry of the eCRFs in a timely manner.

7 DEVICE-SPECIFIC EVENT

A device-specific event is any malfunction or deficiency of the device.

Device deficiency is defined as inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance (ISO 14155:2011 3.15)

Malfunction is defined as a failure of an investigational device to perform in accordance with the Instructions For Use or Clinical Investigational Plan (ISO 14155:2011 3.27)

All device-specific events, malfunctions or deficiencies must be reported to both the Sponsor and local authorities as required by governing law. If a device malfunction results in an adverse event, this adverse event will be considered reportable to the Sponsor.

8 STUDY COMMITTEE / CORE LABORATORY

To avoid and minimize bias, an independent Clinical Events Committee (CEC) and Imaging Core Laboratory will be in place to assess AE relationship and device migration, respectively.

8.1 Clinical Events Committee

A CEC will be in place for the study using a minimum of three (3) physicians knowledgeable in the treatment and embolization of brain AVMs. This committee will be responsible for the review and adjudication of all study AEs.

The CEC will adjudicate to specified event definitions (where available), event relatedness, event severity, and event outcome.

The CEC can request additional source documentation and any potential imaging obtained in support of the AE to assist with adjudication. The CEC is expected to meet, at a minimum, each quarter.

8.2 Imaging Core Laboratory

For Subjects in whom the catheter or catheter tip is retained, 30-day, and 12-month imaging will be obtained to assess potential catheter tip migration. Thirty-day imaging will also be collected if it is performed as a result of physician discretion.

Any subsequent imaging obtained as standard of care during participation in the study will be documented on the eCRFs and may be collected.

9 STATISTICAL METHODS

9.1 Sample Size and Safety Performance Goal

The maximum number of Subjects to be enrolled into this clinical investigation is 161 (with 13% attrition included). To establish safety performance goal for the primary endpoint, literature research was conducted on the reported data of catheter retention. Table 3 summarizes the rates from the peer-reviewed literature. The rate ranges from 1% to 9.7% with an un-weighted average rate of 5.8% and weighted average of 5.7%. The one-sided 95% upper confidence interval for the individual studies ranged from 4.6% to 16.3%.

Table 3. Event Rate Based on Literature Review

Citation	Purpose	Catheter*	Country	Catheter Retainment Frequency (pts)	One-Sided 95% Upper Bound**
Gao, K et a. Chinese Med J 2009; 122:1851-1856.	Onyx delivery	M, U	China	5/115= 4.4%	8.9%
Katsaridis, V et al 2008 Neuroradiology 2008; 50: 589-597.	Onyx delivery bAVM	M, U	Greece	1/101 = 1%	4.6%
Mounayer, C et al AJNR 2007; 28: 518-523.	NBCA, Onyx delivery bAVM	F, U	France	4/94 = 4.3%	9.5%
Panagiotopoulos, V et al AJNR 2009; 30: 99-106.	Onyx delivery bAVM	M, U	Germany	1/82 = 1.2%	5.7%
Saatci, I et al J Neurosurg 2011; DOI: 10 3171/2011.2 JNS 09830.	Onyx, NBCA delivery bAVM	F, U, M	Turkey	28/350 = 8.0%	10.8%
Song, D et a. Intervent Neuroradiol 2005; 11 (SUPPL. 1): 179-184.	Onyx delivery BAVM	M, U	China	3/50 = 6.0%	14.8%
Weber et al. AJNR 2007; 28: 371-377.	Onyx Delivery bAVM	U	Germany	9/93 = 9.7%	16.3%
Un-weighted Average				**51/885 = 5.8%**	
Weighted Average				**5.7%**	

*M = Marathon; U = UltraFlow; E = Echelon; F = FlowRider.
**95% one-sided upper bound is calculated using the Exact method.

The weighted average of catheter retainment event from the table above was used as an estimate of the primary endpoint event rate for this study. Based on a sample size of 161 (maximum sample size), if

the event rate is 5.6%, the 95% upper bound is 9.6%. The 5.6% event rate is a conservative estimate calculated by using the weighted average of 5.7% rounded down to account for a whole patient.

Based on the one-sided 95% upper-bound it is proposed that the performance goal for the primary endpoint be 9.6%. The one-sided 95% upper confidence bound of the observed primary endpoint event rate will be compared to 9.6%. If this upper bound is less than 9.6%, then it is considered that the Apollo™ micro catheter device meets the primary endpoint performance goal.

9.2 Data Analysis Plan

9.2.1 General Principles

All statistical analyses will be performed using Statistical Analysis System (SAS) for Windows (version 9.2 or higher, SAS Institute Inc. Cary, NC) or other widely accepted statistical or graphical software. In general, data for all study Subjects combined will be presented. Individual data will be presented in Subject listings.

Descriptive statistics will be used to present the data and to summarize the results. Discrete variables will be presented using frequency distributions and cross tabulations. Continuous variables will be summarized by presenting the number of observations (N), mean, standard deviation, median, minimum, and maximum values.

For adverse event reporting, which includes the primary and secondary endpoints, the primary analysis will be based on Subject counts (e.g., the number and percentage of Subjects with event among the total number of Subjects). The data will be presented in the format of p% (x/N) [e], with p and x being the percentage and number of Subjects with events, respectively, N being the sample size of the analysis population, and e being the total number of events occurred in the x Subjects. For example, the data of 3.1% (5/161) [8] indicates that a total of 8 events occurred in 5 Subjects out of a total of 161 Subjects (3.1%). In addition, the data based on device (e.g., the number and percentage of devices with events among the total number of deployed devices) will also be provided.

9.2.2 Analysis Samples

Results will be presented based on two populations:

- Intention to Treat (ITT), defined as all Subjects consented and enrolled, independent of the study device being deployed
- Full Analysis Set (FAS), defined as all Subjects consented and enrolled where the study device was deployed, independent of the success of the procedure

All reported adverse events will be presented based on the ITT population and the success of the study will be based on the FAS.

9.2.3 Analysis Baseline Demographics and Procedural Characteristics

Descriptive statistics will be generated for pre-intervention demographics, procedural characteristics, and follow-up data collected. Categorical variables will be analyzed using

frequency, incidence, and event rate. For continuous variables collected in the study, analysis will include mean, median, standard deviation, and range.

9.2.4 Analysis of Primary Endpoint

The primary endpoint is the composite of any of the following catheter related adverse events:

- Premature (unintentional) catheter tip detachment with clinical sequelae
- Catheter rupture/break/fracture with clinical sequelae
- Retained catheter body in the vasculature

The primary analysis for the primary endpoint is based on Subject counts, not event counts. A Subject with more than one event will be counted only once toward the event rate based on the total number of Subjects with adverse events. An event rate based on event counts will also be presented. For example, if a Subject experiences one "Premature (unintentional) catheter tip detachment with clinical sequelae" and one "Retained catheter body in the vasculature", the Subject will be counted once in the rate of total Subjects with primary endpoint; the same Subject will be counted once in the individual event category of "Premature (unintentional) catheter tip detachment with clinical sequelae" and once in the "Retained catheter body in the vasculature" category.

The primary endpoint will be summarized as the event rate per Subject with a one-sided 95% upper confidence bound using the Exact method. The upper bound will be compared to the performance goal of 9.6%. If this upper bound is less than 9.6%, it is considered that the Apollo™ micro catheter meets the primary objective.

One interim analysis is planned for this study. An interim assessment will be performed when 80 subjects have reached the 30-day follow-up. If the one-sided 96% upper confidence bound is below the pre-specified threshold of 9.6%, the primary safety objective is considered to be met and early trial stop for success will be claimed. On those subjects already enrolled, follow-up will continue according to the protocol. Otherwise, the trial will continue and the final analysis will be performed at the end of study. The 96% confidence level is used for the interim analysis to ensure the overall type I error is controlled at the 0.05 level. In addition, the conditional power will be calculated at the interim analysis to determine if a sample size adjustment is necessary. It will not be necessary to adjust the alpha level if the conditional power is greater than 50% (Chen et al., 2004). However, in case that the conditional power is below 50%, the procedure of Cui et al. (1999) will be followed to ensure the study-wise type I error rate is well controlled.

The event rates based on device counts will also be provided.

9.2.5 Pre-planned Subgroup Analysis

It has been planned to evaluate the primary endpoint in the FAS population using the following subgroups:

- Respective Spetzler-Martin Grades (I-V)
- Subjects where Apollo™ micro catheter tip was surgically resected

- Subjects where the Apollo™ micro catheter tip was not resected
- Centers enrolling small/medium/ large volume of patients

The subgroup analyses are exploratory in nature. No formal statistical hypotheses are proposed. Descriptive statistics will be provided for the subgroup analysis. Event rates based on Subject count and device count will be provided for the subgroups.

9.2.6 Analysis of Secondary Endpoints

For acute and long-term secondary endpoints, descriptive statistics will be provided. Event rates based on Subject count and device count will be provided.

The incidence of catheter and / or tip retention following any deployment of the study device will be summarized using counts, percentages, and 2-sided 95% exact binomial confidence intervals.

Separately, the incidence of catheter and tip retention by the number of deployments of the study device will be summarized using counts, percentages, and 2-sided 95% exact binomial confidence intervals. This tabulation assumes that each procedure / deployment is a separate trial. The intra-subject rate of catheter and tip entrapment will be summarized using descriptive statistics and tabulated by the number of events and the number of deployments.

In order to ensure a sufficient number of cases for long-term follow-up, the expectation is that with 161 subjects enrolled there will be approximately 16 to 26 subjects with 1-year follow-up. The basis of this estimate is that approximately 50% to 80% of the subjects will have the tip retained by design and approximately 20% of these subjects will not undergo surgery and shall be followed for 1-year. Any retained catheter bodies will be followed. Relative to the precision of the estimates with 16 subjects followed for 1 year, if the incidence of composite primary endpoint events is zero or 1, the exact upper 1-sided Clopper-Pearson 95% limit would be 17.07% and 26.40%, respectively. If the incidence of composite primary endpoint events with 26 subjects was zero or 1, the exact upper 1-sided Clopper-Pearson 95% limit would be 10.88% and 16.98%, respectively.

9.2.7 Adverse Events

Specified adverse events for all enrolled subjects will be collected and reported. All reported adverse events will be presented based on the ITT population and tabulated by system organ class and preferred term. The incidence of peri-procedural and post-procedural events related to the actual procedure or the study device will be summarized and reported using counts, and percentages.

9.2.8 Analysis of Ability to Pool Data Across Investigational Sites

This is a multi-center clinical study, with standardization of Subject enrollment, data entry and adverse event reporting. All investigational sites will follow the requirements of a common protocol, data collection procedures and forms. To present the data from this clinical study in a summary form, a comparison of the following variables will be completed to assess the appropriateness of pooling data from across all sites:

- Baseline demographics such as age, gender and race
- Procedural characteristics

The distributions of the above variables across the sites will be tabulated. To detect site differences, the Kruskal-Wallis test will be used for continuous variables and the Chi-Square test or the Fisher's exact test will be used for categorical variables, depending on variable distribution.

9.2.9 Handling of Missing Data

For the primary endpoint, the assessment is done peri-procedurally and it is projected that there will be minimal reduction in the eligible population based on the time of the measurement. Therefore, no imputations are planned for the primary endpoint. The above-mentioned potential sample size attrition is likely due to enrolled Subjects not treated with study device or subject withdrawals and not due to missing data on primary endpoint.

10 RISK / BENEFIT

10.1 Potential Benefits

The use of embolization to treat brain AVMs is an effective treatment for this condition and is associated with less morbidity and mortality than if an AVM was left untreated. The design of the Apollo™ micro catheter enables access through small, torturous vessels for embolization of brain AVMs with a variety of angioarchitectures. The Apollo™ micro catheter also allows the release of the detachable tip in case of catheter tip entrapment. The Apollo™ micro catheter provides benefit to Subjects undergoing embolization of an AVM with Onyx™ LES by reducing the risk of catheter entrapment/abandonment and its associated complications.

10.2 Potential Risks

Potential risks associated with the Apollo™ micro catheter, imaging, neuroendovascular intervention, and clinical research are outlined below:

Risks associated with the use of the Apollo™ micro catheter

- Arrhythmia
- Pain and tenderness
- Air Embolism
- Brain Edema
- Intracranial Hemorrhage
- Infection (local or systemic)
- Inflammatory response (local or systemic)
- Structural vascular damage including but not limited to vessel dissection, vessel perforation, vessel rupture, vessel stenosis.
- Thromboembolism/Thrombotic episodes
- Neurological Deficit permanent or transient (including stroke and death)

- Shock
- Vasospasm

Risks identified for imaging/angiography:

- Vascular access site complications including hematoma, hemorrhage, pseudoaneurysms
- Neurological deficit (permanent or transient) including stroke and death
- Organ impairment/ damage/failure
- Inflammatory response (local or systemic)
- Infections (local or systemic)
- Radiation effects including increased risk of cancer

Risks identified with Neuro endovascular intervention:

- Hemorrhage, Hematoma and Pseudoaneurysms
- Vessel damage (perforation, aneurysms, dissections, stenosis, thrombosis)
- Neurological deficit (permanent or transient) including stroke and death
- Organ impairment/ damage/failure
- Thromboembolism, thrombotic episodes
- Arrhythmias
- Shock
- Skin discoloration
- Microembolism including air embolism
- Infections (local or systemic)
- Inflammatory response (local or systemic)

Risks associated with clinical research:

As in all clinical studies, confidentiality of protected health information may be breached due to study-related activities beyond those of clinical care.

10.3 Risk Mitigation

Several safeguards are incorporated into the study to minimize Subject risk. Multiple preclinical studies performed in swine have shown Apollo™ micro catheter to perform equivalently or superior to competitor products based on retrieval characteristics, softness, navigation, pushability, and detachment force.[41-46] All preclinical device testing were performed in accordance with regulations and recognized standards.

At each investigational site, the study will be conducted under the direction of a qualified physician experienced in the neurovascular embolization of AVMs, and will have been trained and certified by the Sponsor in the use of Onyx™ LES. All participating Investigators will have adequate personnel to assure compliance to the study protocol.

Subjects will be monitored closely as part of the study to allow for detection of adverse events, should they be present. This will allow for early treatment, if necessary. Personally identifying Subject

information will not be collected on eCRFs or other study-related documentation to be provided to the Sponsor.

All study data will be monitored by individual site and combined sites. Clinical outcomes of all study Subjects will be routinely monitored by the Sponsor during the course of the study. All AEs collected will be reviewed and adjudicated by an independent CEC. In the event of unforeseen or increased risks to Subjects encountered during the course of the study, the study may be suspended or terminated.

10.4 Justification

Given the absence of an approved detachable tip catheter in the U.S., and an average catheter entrapment rate of approximately 6% and associated sequelae with conventional catheters, the Sponsor considers the benefits of using the Apollo™ micro catheter to outweigh the risks in the defined Subject population.

11 MONITORING PROCEDURES

The Sponsor will be responsible for ensuring that monitoring will be done in accordance to applicable regulations and will be outlined in the study's Clinical Monitoring Plan. All monitoring personnel for this study will be qualified by training, education and/or experience to perform their respective tasks.

The primary contact for the study is:

Clinical Affairs
9775 Toledo Way
Irvine, CA 92618
Tel:

Study monitors will conduct site visits to ensure accuracy of data, timeliness of data submissions, compliance with applicable laws and regulations, compliance with the protocol, compliance with the signed Investigator agreement, and compliance with IRB conditions and guidelines. Any non-compliance with these items that is not adequately addressed by the PI/site staff is cause for the Sponsor to put the Investigator/site staff on probation or withdraw the Investigator/site staff from the study. Frequency of monitoring will be based upon enrollment, study duration, compliance, and any suspected inconsistency in data that requires investigation.

All Subject treatment, follow-up visits and phone conversations/interviews are to be fully documented either on the source document worksheets or in the Subject's medical records. All information entered onto the eCRFs will be verified against the source documents and Subject's medical records. Additional Subject medical record review may be required for AE adjudication. De-identified source documents may be photocopied, if required. The study monitor will also check the Investigator Site File (ISF) to ensure that all study-related documents are current.

11.1 Study Monitoring

After each monitoring visit, the monitor will send the PI a letter summarizing the monitoring visit. The applicable monitoring report will be prepared for the Sponsor (initiation, interim monitoring, and closing

visit). The PI will be responsible for ensuring that follow-up actions at the site are completed in an accurate and timely manner.

11.1.1 Close-out Visit

Final close out visits at the sites will be conducted at the end of the study. The purpose of the final visit is to collect all outstanding study data documents, ensure that the PI's files are accurate and complete, review record retention requirements with the principal Investigator, make a final accounting of all study supplies shipped to the PI/site, provide for appropriate disposition of any remaining supplies, and ensure that all applicable requirements are met for this study.

12 ELECTRONIC CASE REPORT FORMS

Study data will be collected using eCRFs and a 21 CFR Part 11-complaint electronic data capture system. The application provides the capability of data collection remotely through the internet so the participating site personnel may log on the system securely and enter the data. All Subjects' data collected in the system will be extensively verified through data validation programs, database integrity rules, and investigation-specific data entry conventions for data accuracy and logical meaningfulness. Periodic analysis of all Subjects' collected data will be performed in order to examine the expected distributions of data and to identify outliers for possible data entry errors.

The Investigator is responsible for reviewing all eCRF entries for completion and correctness. Changes in case report forms will be made electronically and the system used will keep an audit trail of changes. If necessary, an explanation for the change(s) may be provided. All study staff that will enter data into eCRFs will undergo appropriate training for use of eCRFs.

Further information regarding eCRF navigation and use may be found in the eCRF completion guidelines.

13 RESEARCH COMPLIANCE

13.1 Sponsor Compliance

The Sponsor is responsible for implementing and maintaining quality assurance and a quality control system to ensure that the data generated are recorded and reported in accordance with established procedures. The study will be organized, performed, and reported in compliance with this research study protocol, standard operating procedures, applicable regulations and recognized standards and any additional requirements imposed by the IRB or regulatory authority.

The Sponsor is responsible for obtaining and maintaining appropriate insurance policies for the clinical study.

The Sponsor will secure an agreement with all parties to allow direct access to all study-related sites, source documents, and reports for the purpose of monitoring and auditing by the Sponsor and/or its designee(s) and inspection by regulatory agencies.

The Sponsor will apply quality control measures to all stages of data collection and handling to ensure reliability and accuracy. In addition, the Sponsor will confirm that the data are processed correctly.

Data from eCRFs and other external data (i.e., core laboratory data) will be entered into a clinical database as specified in the data management plan. Quality control and data validation procedures will be applied to ensure the validity and accuracy of the clinical database.

The clinical database will be reviewed and checked for omissions, apparent errors, and values requiring further clarification in accordance with the data management plan. Data queries requiring clarification will be documented and returned to the study site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections will be documented in an audit trail. An internal quality control audit by data management will be performed and documented prior to database lock.

During the course of the study, an amendment to the protocol may be necessary. Only the Sponsor is allowed to amend this protocol. Any amendments or modifications must be approved by the research site's IRB prior to research-study staff implementation, unless the modifications increase Subject safety. The research sites will receive the following for their regulatory file, and if applicable, IRB submission:

- A memorandum outlining the changes and justification for modifications
- An updated protocol
- Changes to ICF template (if necessary)

13.2 Investigator Compliance

The site PI assumes full responsibility for performance of the research study in accordance with the Clinical Study Agreement, this protocol, Good Clinical Practice (GCP), all regulatory requirements applicable to the jurisdictions in which the study is being conducted, and any additional requirements imposed by the IRB.

Any physician participant who is discovered during monitoring to have not reported appropriate AEs may be terminated from the study at the discretion of the Sponsor.

13.3 Onsite Audits

Representatives of the Sponsor may visit the study site(s) to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection and comparison with the eCRFs. Subject privacy will be respected.

Similar auditing procedures may also be conducted by agents of any regulatory body reviewing the results of the study in support of a regulatory submission. The Investigator should immediately notify the Sponsor if he/she has been contacted by a regulatory agency concerning an upcoming inspection.

14 RESPONSIBILITIES, RECORDS, AND REPORTS

14.1 Investigator Responsibilities

The PI shall be responsible for the day-to-day conduct of the clinical investigation, as well as for the safety and well-being of the human Subjects involved in the clinical investigation. The PI also assumes overall responsibility and accountability for the clinical team and for data obtained from each Subject participating in the study.

14.1.1 Investigator Record Retention

The Investigator shall maintain all study documentation in his/her possession and/or control and institute measures to prevent accidental or premature destruction any data and/or documents related to the study.

The Investigator shall retain study documentation during the study and for a period of two (2) years after the latter of the following two dates: The date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol.

14.2 Sponsor Record Retention

The Sponsor will maintain all study documentation in its possession and/or contact and institute measures to prevent accidental or premature destruction of any data and/or documents related to the research study.

The Sponsor shall retain the study documentation during the study and for a period of 2 years after the latter of the following two dates: The date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol.

14.3 Records Custody

An Investigator may withdraw from the study. If the PI withdraws from the study, the responsibility of conducting follow-up and maintaining records must be transferred to another responsible party within institution (i.e. Sub-Investigator). Notice of transfer must be provided in writing by the PI to the Sponsor, FDA and the IRB no later than 10 working days after transfer occurs.

15 INSTITUTIONAL REVIEW BOARD

The Sponsor and/or Investigator must submit this protocol to the appropriate IRB, and is required to forward to the Sponsor a copy of the written and dated approval.

The study (study number, protocol title, and version), documents reviewed (e.g. protocol, ICF, etc.) and the date of the review should be clearly stated on the written IRB approval/favorable opinion.

The study will not start at a site and Subjects will not be enrolled until a copy of written and dated approval/favorable opinion by the IRB has been received by the Sponsor.

Any amendment or modification to the protocol should be sent to the IRB. The IRB should also be informed of any event likely to affect the safety of Subjects or the conduct of the study. The ICF used by the Investigator for obtaining the Subjects informed consent must be reviewed and approved by the Sponsor prior to submission to the appropriate IRB for review.

16 QUALITY CONTROL AND QUALITY ASSURANCE

16.1 Data Control

Every effort will be taken to ensure the accuracy and reliability of data including the selection of qualified Investigators and appropriate study centers, review of protocol procedures with the Investigator and associated personnel before the study commences, and periodic onsite monitoring visits by the Sponsor as deemed appropriate by the Sponsor. Guidance for eCRF completion will be provided and reviewed with the study personnel prior to the start of the study. The Sponsor will review eCRFs for accuracy and completeness and any discrepancies will be resolved with the Investigator or designee, as appropriate.

16.2 Site Selection

The Sponsor or representative of the Sponsor will assess each potential site to ensure the PI and his/her staff has the facilities and expertise required for the study. Sites will be selected based upon a site assessment, appropriate facilities, and the qualifications of the Investigator(s). Individual Investigators will be evaluated by the Sponsor based on experience with the intended procedure(s) and ability to conduct the study according to the study protocol.

To participate, a site must have the following components:

- Previous experience with clinical research and embolization of brain AVMs
- An Investigator trained and certified by the Sponsor in the use of Onyx™ LES
- Commitment from the participating physician to pursue details of any safety outcomes
- Commitment from the participating physician to enroll only patients meeting inclusion and exclusion criteria
- Ability to perform required clinical testing and study procedures
- Ability and willingness to provide the Sponsor's representatives access to the hospital records, study files, and Subject files as they pertain to the study

16.3 Site Training

Each investigational site will be trained to the investigational plan. Investigator/Site Personnel will undergo training prior to performing any study-related procedures. All training must be documented. Training to the investigational plan will include the following topics:

- Study objectives

- Protocol review
- Delegation of authority for study-related tasks
- Informed Consent process, including any relevant IRB requirements; Confidentiality/HIPAA (Health Insurance Portability and Accountability Act of 1996)
- eCRFs and completion instructions
- Documentation of protocol deviations
- AE reporting
- Device-specific events reporting
- IFU of the Apollo™ micro catheter
- Responsibilities and obligations of the Investigator/staff
- General guidelines for good clinical practices
- Study documentation required (essential documents)

Existing study site personnel who have been delegated new tasks and new study site personnel will undergo training to the investigational plan, as appropriate.

16.4 Site Initiation

The Sponsor or a designated representative will conduct a training session with study Investigators and respective staff to review the protocol, eCRFs, the informed consent process, IRB involvement and guidelines, responsibilities and obligations, reporting requirements, and general guidelines for good clinical practices.

Prior to enrolling Subjects at an investigational site, the following documentation must be provided to the Sponsor:

- IRB approval for the Investigational Plan
- IRB- and Sponsor-approved ICF for the study
- Signed Clinical Study Agreement (CSA)
- Documentation that verifies the appropriate study staff has been trained on the protocol, eCRFs and study conduct.
- Financial Disclosure(s) for the PI and Sub-I(s)
- PI and Sub-I(s) curriculum vitae (CV)

16.5 Data Quality Assurance

ORACLE Clinical Remote Data Capture (OC/RDC) is the electronic data capture (EDC) system that will be used to support data collection for this study. Documentation pertinent to the use of the EDC system will be made available for use by appropriate site personnel. All individuals who will be expected to use the EDC system will be given adequate training necessary to perform their assigned tasks as described in (21 CFR 11.10). Training will be conducted by qualified individuals initially and on a continuing basis, as needed.

16.6 Data Handling

The Sponsor is responsible for compilation and verification of the study data, retention of the clinical study database, performance of statistical analysis, and preparation of the study reports. The Sponsor will ensure that the performance of data management activities occur in accordance with the study data management plan.

17 DATA OWNERSHIP

Rights, duties, and obligations regarding ownership of any ideas, concepts, inventions, or results, whether patentable or not, shall be in accordance with the terms and conditions set forth in the Clinical Study Agreement by and between the Institution and Sponsor unless otherwise expressly set forth in the Clinical Study Agreement, the Sponsor retains exclusive ownership of all data, results, reports, findings, discoveries and any other information collected during this study. The Sponsor reserves the right to use the data from the database in the present study.

18 CONFIDENTIALITY

The Investigator shall consider all information, results, discoveries, records accumulated, acquired, or deduced in the course of the study, other than that information to be disclosed by law, as confidential and shall not disclose any such results, discoveries, records to any third party without the Sponsor's prior written consent.

IRB members have the same obligation of confidentiality.

19 PUBLICATIONS

The Sponsor intends to publish the results of this multicenter study. Individual Investigators are therefore asked to refrain from reporting results from their study participants prior to publication of the main multi-center report. The Sponsor will establish authorship criteria for such publications for the study group, based on the Apollo study conduct and compliance, contribution to the Apollo study, management or enrollment, and willingness to accept the rights and responsibilities of an author. The Sponsor will enter the study into a public clinical trials repository such as *http://clinicaltrials.gov/*.

20 REFERENCES

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APPENDIX A: GLOSSARY

Adverse Device Effect (ADE): An adverse event related to the use of an investigational medical device (ISO 14155:2011). *Note 1*: This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational device. *Note 2*: This includes any event that is a result of a use error or intentional misuse.
Adverse Event (AE): Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in Subjects, users, or other persons, whether or not related to the investigational medical device (ISO 14155:2011). *Note 1*: This includes events related to the investigational device or the comparator. *Note 2*: This includes events related to the procedures involved (any procedure in the clinical investigational plan). *Note 3*: For users or other persons this is restricted to events related to the investigational medical device.
Anticipated Adverse Event: An adverse event previously identified in nature, severity or degree of incidence in the investigational plan.
Arteriovenous malformation (AVM): A cerebral arteriovenous malformation is an abnormal connection between the arteries and veins in the brain that usually forms before birth.
Concomitant Medication: Medication use related to the study.
Device Malfunction: A failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the Instructions For Use or Clinical Investigational Plan. (ISO 14155:2011).
Documentation: All records, in any form (including, but not limited to, written, electronic, magnetic, and optical records, and scans, x-rays and electrocardiograms) that describe or record the methods, conduct, and/or results of the trial, the factors affecting the trial and the actions taken.
Electronic Case Report Form (eCRF): An electronic document designed to record all of the protocol-required information to be reported to the Sponsor on each trial Subject.
Informed Consent: A process by which a Subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the Subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
Intent-to-Treat: All Subjects consented and enrolled, independent of the study device being deployed.
Investigator: An individual who actually conducts a clinical Investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a Subject, or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team.

Monitoring: An individual who oversees the progress of an investigation.

Screen Failure: Subjects who sign the ICF and subsequently fail to meet all of the inclusion/exclusion criteria, and do not receive the study device will be considered screen failures. Upon determination that the patient does not qualify for this study, the reason for termination will be documented and Subjects will not be followed per the investigational plan requirements.

Serious Adverse Event (SAE): Adverse Event that

A. Led to death,
B. Led to serious deterioration in the health of the Subject, that either resulted in
    a. A life-threatening illness or injury, or
    b. A permanent impairment of a body structure or a body function, or
    c. In-patient or prolonged hospitalization, or
    d. Medical or surgical intervention to prevent permanent life-threatening illness or injury or permanent impairment to a body structure or a body function,
C. Led to fetal distress, fetal death or a congenital abnormality or birth defect (ISO 14155:2011)

Note 1: This includes device deficiencies that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate. These are handled under the SAE reporting system.

Note 2: A planned hospitalization for pre-existing condition, or a procedure required by the Clinical Investigational Plan, without a serious deterioration in health, is not considered to be a serious adverse event.

Source Data: All information in original records and certified copies of original records of clinical findings, observations, or other activities in the clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

Serious Adverse Device Effect: An adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event (ISO 14155:2011).

Source Documents: Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, Subjects` diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, Subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).

Sponsor: A person who initiates, but who does not actually conduct, the investigation, that is, the investigational device is administered, dispensed, or used under the immediate direction of another individual. A person other than an individual that uses one or more of its own employees to conduct an investigation that it has initiated is a Sponsor, not a Sponsor-Investigator, and the employees are Investigators.

Study AEs: Any SAE, and any device- or procedure-related adverse events.

Sub-Investigator: Any individual member of the clinical trial team designated and supervised by the

Investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions (e.g., associates, residents, research fellows).
Unanticipated Adverse Device Effects (UADE): Any serious adverse effect on health or safety 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.
Unanticipated Serious Adverse Device Effect (USADE): A serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report (ISO 14155:2011). *Note:* Anticipated: an effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report.

APPENDIX B: ABBREVIATION OF TERMS

Abbreviation	Term
ADE	Adverse Device Effect
AE	Adverse Event
AVM	Arteriovenous malformation
CDA	Confidentiality Agreement
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CRA	Clinical Research Associate (a.k.a. Monitor)
CRF	Case Report Form
eCRF	Electronic Case Report Form
CSA	Clinical Study Agreement
CT	Computed Tomography
CV	Curriculum Vitae
DAC	Distal-Access Catheter
DMSO	Dimethyl Sulfoxide
EDC	Electronic Data Capture
EVOH	Ethylene Vinyl Alcohol
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDE	Investigational Device Exemption
IFU	Instructions For Use
IRB	Institutional Review Board
ISF	Investigator Site File
ITT	Intent-To-Treat
LAR	Legally Authorized Representative

Abbreviation	Term
MDR	Medical Device Reporting
MRI	Magnetic Resonance Imaging
NBCA	N-butyl cyanoacrylate
OC/RDC	ORACLE Clinical Remote Data Capture
Onyx™ LES	Onyx™ Liquid Embolic System
PI	Principal Investigator
PMA	Pre-Market Approval
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
Sub-I	Sub-Investigator
UADE	Unanticipated Adverse Device Effect
US	United States
USADE	Unanticipated Serious Adverse Device Effect