COVIDIEN

PREMIER

PROSPECTIVE STUDY ON EMBOLIZATION OF INTRACRANIAL ANEURYSMS WITH PIPELINE™ EMBOLIZATION DEVICE

CLINICAL PROTOCOL

Protocol Number: NV-PED-07

IDE Number: G140084

REVISION: B, 24-Mar-2015

Sponsor:
Covidien – Neurovascular
9775 Toledo Way
Irvine, California, USA 92618

Sponsor Signatures:

Signature: _____ **Date:** _____

/ Senior Director, Medical Affairs

Signature: _____ **Date:** _____

/ Manager, Regulatory Affairs

Signature: _____ **Date:** _____

/ Medical Monitor

PREMIER

PROSPECTIVE STUDY ON EMBOLIZATION OF INTRACRANIAL ANEURYSMS WITH PIPELINE™ EMBOLIZATION DEVICE

Clinical Protocol Investigator Agreement

I have read the Clinical Protocol Rev (B) 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 relating to obtaining informed consent in 21 CFR Part 50, ICH E6 and institutional review board/Ethics Committee (IRB/EC) review and approval in 21 CFR Part 56 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 and ICH E6.

I will ensure that the IRB/EC complies with the requirements of ICH E6 and 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/EC 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/EC 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 ICH E6 and 21 CFR Part 812, 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

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Sponsor: Covidien - Neurovascular **9775 Toledo Way** **Irvine, California, USA 92618** **Telephone:**	**Protocol Number:** NV-PED-07
	Product: Pipeline™ Embolization Device[1]
	Regulatory Class: III
	Development Phase: IV
Title: Prospective study on embolization of intracranial aneurysms with Pipeline™ Embolization Device (PREMIER)	
Study Design: The study is a global, prospective, single-arm, multi-center clinical study evaluating outcomes in subjects with intracranial aneurysms measuring ≤ 12 mm who are treated with Pipeline™ device.	
Objective: To assess the safety and effectiveness of the Pipeline™ device in the treatment of unruptured, wide-necked, intracranial aneurysms measuring ≤ 12 mm, located in the internal carotid artery (up to the terminus) or the vertebral artery segment up to and including the posterior inferior cerebellar artery.	
Background: Intracranial aneurysms (IAs) measuring ≤ 12 mm in size comprise approximately 80% of all intracranial aneurysms.[1,2] IAs can rupture suddenly and without warning, leading to cerebral bleeding or subarachnoid hemorrhage (SAH). SAH is a devastating complication with a case-fatality rate of 45%.[3] The average size of ruptured IAs is approximately 6.6 to 6.8 mm.[1,2,4] In order to prevent aneurysmal rupture, small and medium wide-necked IAs are commonly treated endovascularly with stent-assisted coiling. Although initial occlusion rates are good, the primary limitation of stent-assisted coiling is the inability to provide sustained long-term aneurysm occlusion. Aneurysm recurrence rates of up to 16% have been reported in the literature after stent-assisted coil treatment of small and medium IAs.[5-15] The presence of major aneurysm recurrence requires retreatment up to 10% for small and medium IAs.[6,8,10,11,16] indicating current treatment outcomes are sub-optimal. Therefore, an alternative approach for obtaining sustained aneurysm occlusion is needed for small and medium wide-necked IAs. Recently, flow-diverting devices represent a paradigm shift in the endovascular treatment philosophy for IAs. At present, the only FDA-approved flow diverter is the Pipeline™ device, which is indicated for the endovascular treatment of adults (22 years of age or older) with large or giant wide-necked IAs in the ICA from the petrous to the superior hypophyseal segments. Clinical trial data from the PUFs study have shown that 87.4% of the target IAs were completely occluded at one year. There were no cases of aneurysm recurrence. The rate of ipsilateral major stroke or neurologic death at 1-year follow-up was 5.6%. In addition, published data on the Pipeline™ device used to treat complex large/giant aneurysms show rates of 68-94.4% complete occlusion that remains persistent 2-3 years after the index procedure and 0-13.9% associated morbidity and 0%-6.4% mortality.[17-23] These rates are similar to or better than those for conventional IA treatments of surgery or coiling.[24,25]	

[1] And future devices upon approval by FDA

PROTOCOL SYNOPSIS

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	Product: Pipeline™ Embolization Device[1]
	Regulatory Class: III
	Development Phase: IV

Currently, treatment with the Pipeline™ device is indicated for IAs in the ICA from the petrous to the superior hypophyseal segments and the present study aims to include IAs in the ICA up to the terminus. Data from 277 patients with IAs ≤ 12 mm located in the ICA up to the terminus were collected in the IntrePED retrospective study, which demonstrate neurological morbidity and mortality rates of 2.9% and 1.1%, respectively. These rates demonstrate that the Pipeline™ device can serve as a potentially safe treatment option for IAs of the ICA (up to the terminus). The treatment of IAs in the posterior circulation is typically associated with a higher rate of complications. However when limited to only the vertebral and posterior inferior cerebellar arteries, published literature indicates that the morbidity and mortality rates are similar to the rates reported for stent-assisted coil treatment of small-wide-necked IAs. Studies evaluating the treatment of aneurysms located in the VA or PICA demonstrate morbidity rates ranging 0%-13% and mortality rates ranging 0%-7%.[26-33] These rates are comparable to the stent-assisted coiling morbidity rates of 3.9%-9.2% and mortality rates of 0%-6.8%.[5,7,9,34-38] Within this current study, the safety and effectiveness of the Pipeline™ device for the treatment of unruptured wide-necked IAs measuring ≤ 12 mm in the vertebral artery segment up to and including the PICA will be investigated.

Number of Subjects: Up to 200 subjects enrolled to ensure 141 treated subjects	**Number of Study Centers:** Up to 28 study centers

Duration of Study Participation:

- Enrollment Duration: Approximately 18 months
- Follow-up: 3 years
- Total Study Duration: Approximately 54 months

Primary Endpoints:

- Safety: Occurrence of major stroke in the territory supplied by the treated artery or neurological death at 1 year post-procedure
- Effectiveness: Complete aneurysm occlusion (defined by scale of Roy) without significant parent artery stenosis (≤ 50%) at 1 year post-procedure

Secondary Endpoints:

- Safety:
  - Occurrence of major stroke in the territory supplied by the treated artery or neurological death at 30 days post-procedure due to procedural complications
  - Delayed intracerebral hemorrhage >30 days post-procedure
- Effectiveness: Device deployment success rate at the target site

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Additional Data:

- Device-related neurologic adverse event rate by 1 year post-procedure
- Modified Rankin Scale (mRS) score at 1 year
- Aneurysm occlusion at 3 years post-procedure
- Recurrence and retreatment rates at 1, 2 and 3 years post-procedure
- Procedure time
- Radiation exposure (dosage and time)
- Number of Pipeline™ devices utilized

Inclusion Criteria:

1. Subject has provided written informed consent using the IRB/EC-approved consent form and agrees to comply with protocol requirements.
2. Age 22-80 years.
3. Subject has a target intracranial aneurysm (IA) located in the:
    a) Internal carotid artery (up to the carotid terminus) OR
    b) Vertebral artery segment up to and including the posterior inferior cerebellar artery
4. Subject has a target IA that is ≤ 12 mm.
5. Subject has a target IA that has a parent vessel with diameter 1.5–5.0 mm distal/proximal to the target IA.
6. Subject has a target IA with an aneurysm neck ≥ 4mm or a dome to neck ratio ≤ 1.5.
7. Subject has a pre-procedure PRU value between 60–200.

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	Development Phase: IV

Exclusion Criteria:

1. Subject has received an intracranial implant (e.g. coils) in the area of the target IA within the past 12 weeks.
2. Subarachnoid hemorrhage in the past 30 days.
3. Subject with anatomy not appropriate for endovascular treatment due to severe intracranial vessel tortuosity or stenosis determined from baseline or pre-procedure imaging, or a history of intracranial vasospasm not responsive to medical therapy.
4. Major surgery in the last 30 days.
5. History of irreversible bleeding disorder and/or subject presents with signs of active bleeding.
6. Any known contraindication to treatment with the Pipeline™ device, including:
    a. Stent is in place in the parent artery at the target IA location
    b. Contraindication to dual antiplatelet therapy
    c. Relative contraindication to angiography (e.g., serum creatinine >2.5 mg/dL, allergy to contrast that cannot be medically controlled).
    d. Known severe allergy to platinum or cobalt/chromium alloys.
    e. Evidence of active infection at the time of treatment (e.g., fever with temperature >38°C and/or WBC >1.5 10^9/L).
7. The Investigator determines that the health of the subject or the validity of the study outcomes (e.g., high risk of neurologic events, worsening of clinical condition in the last 30 days) may be compromised by the subject's enrollment.
8. Pregnant or breast-feeding women or women who wish to become pregnant during the length of study participation.
9. Participating in another clinical trial during the follow-up period that could confound the treatment or outcomes of this investigation.

PROTOCOL SYNOPSIS

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Telephone:

Protocol Number: NV-PED-07

Product: Pipeline™ Embolization Device[1]

Regulatory Class: III

Development Phase: IV

Treatment/Follow-up:

Eligible subjects will be treated with the Pipeline™ device.

The study will consist of the following study visits:

- Baseline
- Procedure
- Discharge exam
- Follow-up at 30-day, 180-day, 1-year, 2-year, and 3-year post-procedure

A schedule of assessments to be performed at each study visit is listed in the table below.

Visit and Assessment Schedule

Visits		Screening and Baseline	Device placement		Follow-up					
			Procedure	Discharge exam	30-day	180-day	1-year	2-year	3-year	Unscheduled
Assessments	Time (Windows)	Pre-procedure (-60 days)	Day 0	Day 0-7	Day 30 (± 7 days)	Day 180 (±30 days)	Day 365 (± 42 days)	Day 730 (± 42 days)	Day 1095 (± 42 days)	--
Assess Inclusion / Exclusion		◆								
Demographics and Medical History		◆								
Blood Labs		◆[1]	◆[2]	○[3]						
Medications		◆	◆	◆	◆	◆	◆	◆	◆	◆
Modified Rankin Scale score		◆		◆	◆	◆	◆	◆	◆	
Imaging[4]		◆ (180 days)	◆[5]			○[6]	◆	◆[7]	◆[7]	◆[7]
NIH Stroke Scale		◆	◆	◆	◆	◆	◆	◆	◆	◆
Pipeline™ Placement			◆							
Assess Adverse Events		◆	◆	◆	◆	◆	◆	◆	◆	◆

1 Includes CBC, HCT, platelet count, platelet function testing as per standard patient care, serum creatinine, and pregnancy test, if applicable
2 Includes platelet count and platelet function testing
3 If platelet function testing is performed as standard patient care the results should be recorded.
4 Angiograms in the anterioposterior, lateral and working positions for analysis by a core laboratory.
5 Includes a pre-treatment and post-treatment angiogram
6 If an angiogram is performed as standard patient care it should be sent to the core laboratory for analysis.
7 If aneurysm is completely occluded at 1 year, angiography is optional at subsequent follow-up visits. Otherwise if aneurysm is not occluded at 1 year, angiography must be performed thereafter until the aneurysm is completely occluded or the subject has completed the study. Any angiograms performed at other time points should be sent to the core laboratory for analysis.

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Statistical Analysis:

With the general exception of the tests comparing the response to an *a priori* threshold, all statistical tests will be 2-sided, performed at the 5% significance level. *Baseline* is defined as the last observation recorded prior to the study procedure.

The primary safety endpoint is the incidence of major stroke in the territory supplied by the treated artery or neurological death recorded within 1 year of the study procedure. The incidence will be summarized using counts and percentages; the 1-sided upper bound of the 97.5% confidence limit for the incidence will be evaluated relative to the *a priori* threshold of 15%. The primary effectiveness endpoint is the incidence of complete aneurysm occlusion at 1 year post-procedure. Results will be summarized using counts and percentages; the 1-sided lower bound of the 97.5% confidence limit for the incidence will be evaluated relative to the *a priori* threshold of 50%.

To ensure the study is not under-powered, the primary endpoint will be monitored by the DSMB. After 50 subjects have been treated and followed for a minimum of 6 months post-procedure, an interim assessment will be performed. It is understood that monitoring off an earlier time point does not correspond with the primary endpoint. However, to derive an initial signal to ensure that the observed incidence is commensurate with the planning estimates, this time point should conservatively represent approximately 80% of events at 1 year. Details of the procedure will be described in the DSMB Charter.

Revision History

Revision	Effective Date
A	10 Jun 2014
B	24 Mar 2015

Summary of Changes

Revision A to Revision B		
Section	**Change**	**Rationale**
Synopsis	Updated subarachnoid hemorrhage fatality rate in the background, sample size, number of centers, visit and assessment schedule, and statistical analysis.	To reflect the changes throughout the protocol.
Clinical Background	Subarachnoid hemorrhage fatality rate updated and annual aneurysm rupture rate updated.	Corrections noted during literature review.
Clinical Study Experience with the Pipeline™ Device	IntrePED outcomes updated.	Updated based on additional data analysis.
Device labeling	The IDE IFU will be provided separately to investigators	The commercial status of the study device.
Device Tracking	Only usage of devices in treated subjects will be tracked.	The commercial status of the study device.
Number of Sites and Subjects	Updated the enrolled sample size to 200 to ensure 141 treated subjects and the number of sites to 28.	In response to conditions noted in FDA letter dated 5 June 2014.
Expected Duration of the Study and Subject Participation	Clarified subjects who meet the eligibility criteria and treated with the study device are followed for 3 years.	In response to conditions noted in FDA letter dated 5 June 2014.
Study population	Updated 'enrolled' to 'treated' throughout.	In response to conditions noted in FDA letter dated 5 June 2014.
Study procedures	Updated the section to reflect new enrollment definition, enrolled ineligible definition, and impacted subject procedures.	In response to conditions noted in FDA letter dated 5 June 2014.
Study procedures	Update medication collection to include current medications throughout the section.	Relevant medical history information for safety assessment
Study procedures	Updated the platelet function testing at screening and discharge.	To reflect current standard patient care.
Imaging	Updated screening imaging to require that must be taken within 180 days of the planned procedure.	Patient safety. To reduce the number of invasive procedures a subject may need to undergo.
Antiplatelet agents	Updated the minimum aspirin dose to 81 mg	To reflect current standard patient care.
Discharge exam	Updated the platelet function testing.	To reflect current standard patient care.
Visit and Assessment Schedule	Update the table to reflect changes to Study Procedures section (medication and platelet function testing) and removed the line item from neurologic exam.	To reflect the changes throughout the protocol. Neuroloigc exam was duplicative of Modified Rankin Scale score and NIH Stroke Scale.
Adverse Events	Removed SAE Hotline information	Administrative update.
Adverse Events	Updated terms for follow-up for subjects who do not received the Pipeline™ device	In response to conditions noted in FDA letter dated 5 June 2014.
Adverse Events	Updated the event definitions to include the full ISO 14155:2011 definition notes	Omitted in error.
Adverse Events	Updated the categories and definitions for relatedness	CEC recommendation.
Adverse Events	Provided more detail on method to report adverse events.	Administrative update.
Device Specific Event	Simplified the definition of device-specific event	Minor correction for readability.
Statistical Methods And Data Analysis	Updated the section to reflect new enrollment definition and address impact on analysis populations.	In response to conditions noted in FDA letter dated 5 June 2014.
Definitions	Updated definition for enrolled ineligible, intention to treat population, point of enrollment, screen failure	To reflect the changes throughout the protocol.

1 INTRODUCTION

1.1 Purpose

The primary study objective is to assess the safety (occurrence of major stroke in the territory supplied by the treated artery or neurological death at 1 year post-procedure) and effectiveness (complete aneurysm occlusion without significant parent artery stenosis at 1 year post-procedure) of the Pipeline™ device in the treatment of unruptured, wide-neck intracranial aneurysms , measuring ≤ 12 mm, located in the internal carotid artery (up to the terminus) or the vertebral artery segment up to and including the posterior inferior cerebellar artery.

1.2 Background and Significance

1.2.1 Clinical Background

Intracranial aneurysms (IAs) are common cerebrovascular abnormalities with a prevalence of 0.4-3.6% based on conventional angiography, computed tomography, and autopsy studies.[39-42] IAs occur in either the anterior or posterior circulation and may occur anywhere within a major cerebral artery (e.g., sidewall, bifurcation).[40] The predominant location for IAs is the anterior circulation (90%), with 30% arising from the internal carotid artery (ICA).[43] In the posterior circulation, common locations for IAs are the basilar apex (5%), posterior inferior cerebellar artery (3%), superior cerebellar artery (3%), and the vertebrobasilar junction (2%).[43] In addition to anatomical location, IAs are classified according to size: small (< 7 mm), medium (7–12 mm), large (13–25 mm), and giant (≥ 25 mm).[1] The majority (approximately 80%) of IAs are ≤ 12 mm in size.[1,2] Approximately one third are wide-necked IAs (defined as having a neck ≥ 4 mm in diameter and/or a dome-to-neck ratio ≤1.5).[44-47]

Most IAs are asymptomatic until they rupture, which can occur suddenly and without warning, leading to cerebral bleeding or subarachnoid hemorrhage (SAH). SAH is a devastating complication with a case-fatality rate of up to 45%, leaving nearly half of its survivors functionally incapacitated with less than 5% good outcomes.[3,48,49] Given the high mortality rate and poor prognosis associated with ruptured IAs, the goal of aneurysm therapy is to reduce the incidence of spontaneous rupture or to alleviate symptoms of mass effect related to aneurysm growth. The anatomic goals of IA treatment are 1) to completely isolate the aneurysm sac from the circulation (i.e., complete occlusion) and, 2) to restore the morphologic integrity of the parent artery.

Risk of aneurysm rupture is attributed to various factors, including size, morphology, location, previous SAH, and subject characteristics, which are taken into consideration when deciding on treatment approach.[50] Aneurysm size has been found to be a significant predictor of aneurysm rupture.[51,52] Previous natural history studies have reported annual rupture rates ranging 0.05%-1.1% for IAs less than 10 mm IAs and the rate increases with aneurysm size.[1,2,51,53,54] Although the rupture rates reported in these studies are low, small IAs warrant critical consideration since the majority of ruptured aneurysms appear to be small in size.[4,55-57] In the International Subarachnoid Aneurysm Trial (ISAT), a landmark trial on the treatment of 2143 ruptured IAs, 92% of the ruptured aneurysms were ≤ 10 mm.[55] Similarly, in the CLARITY study of ruptured IAs, 90%

(700/782) of the subjects had an IA ≤ 10 mm.[58] In another large study of 534 subjects with ruptured aneurysms, 86% were < 10mm.[59] In the recently published Barrow Ruptured Aneurysm Trial (BRAT) of 471 IAs, the average size was 6.6 to 6.8 mm.[4]

In addition to aneurysm size, location is a significant predictor for rupture.[52,60] IAs located in the posterior circulation carry a higher risk of rupture than anterior circulation IAs.[52,60] Prospective data from the ISUIA study reported a 2.9% risk of rupture for aneurysms 7-12 mm in the posterior circulation.[1] Likewise, a study performed by Ishibashi et al. found that posterior circulation location aneurysms had a hazard ratio of 2.9.[52] Due to the risk of rupture, posterior circulation aneurysms warrant higher consideration for treatment.

1.2.2 Current IA Treatment Options

Current approaches to treat small and medium, wide-necked IAs include observation (no treatment), open neurosurgical (surgical clipping), and closed endovascular techniques (coiling, stent-assisted coiling, flow diverters).

Surgical clipping of IAs is generally associated with reasonable occlusion but high procedure-related mortality and morbidity rates. Data from a 61-study meta-analysis that included 2460 subjects with various IA sizes reported 2.6% overall mortality and 10.9% permanent morbidity.[61] When surgical clipping is decided on for wide-necked IAs < 10 mm in size, it can be technically challenging due to their small size and wide neck.[54,62] IAs < 10 mm in size are often difficult to treat surgically because of their fragile walls. Surgical treatment of wide-necked aneurysms remains challenging because the wide necks of these aneurysms include the wall of the parent artery and are often deeply embedded in brain parenchyma, which makes the procedure considerably risky. In many cases, these subjects cannot undergo neurosurgery for treatment of their IAs because of difficulty accessing the target IA or other surgical limitations. The high rates of morbidity and mortality, along with technical procedural difficulty, advocate that alternative (endovascular) methods likely provide a safer, more effective treatment option for wide-necked IAs measuring < 10 mm.

Endovascular treatment of IAs by coiling has become an acceptable alternative to surgical clipping, with lower morbidity and mortality rates in select cases. However, despite technological advances there remain a substantial number of IAs (particularly wide-necked) that cannot be successfully treated with coiling methods. Many patients with wide-necked saccular IAs cannot be treated with coil embolization because the geometry of the sac does not allow acute retention of placed coils. Coil embolization of non-saccular IAs is typically not attempted because the IA does not have a neck that can hold coils in place. Complete occlusion rates with coiling alone post-procedure range from 10%-51% for wide-necked IAs measuring < 10 mm.[63,64] The most commonly used endovascular approach for wide-necked IAs < 10 mm in size is stent-assisted coil embolization in which a self-expandable porous stent is first placed across the aneurysm neck, and small coils are then placed within the IA sac using a microcatheter.[65] In theory, this technique keeps the coils within the aneurysm sac and facilitates endothelization around the stent. A thrombus or clot forms on the coils retained in the IA sac, resulting in isolation of the aneurysm from the parent artery. In the US, neurovascular stents used in stent-assisted coiling procedures

(e.g. Neuroform stent commercialized by Stryker and the Enterprise Vascular Reconstruction device commercialized by Codman) are not approved by the FDA for IA treatment; however, these devices are covered under Humanitarian Device Exemption (HDE) approval to treat wide-necked IAs.

A survey from literature comprising 39 articles and 1517 subjects treated with stent-assisted coiling has reported an overall procedure complication rate of 19%, with a periprocedural mortality rate of 2.1%.[65] Recent publications have reported neurological morbidity rates ranging 3.9%-9.2% and procedure/device-related mortality rates ranging 0%-6.8% for studies in which the majority of subjects have small and medium wide-necked IAs (**Table 1**).[5,7,9,34-38] With regards to effectiveness, aneurysm occlusion generally occurs over time. The literature survey reported that approximately 45% of IAs were completely occluded at first treatment session, which increased to 61% on follow-up.[65] Other studies have reported that complete occlusion has been achieved in 46%-75% of small and medium wide-necked IAs at one year post-procedure.[36,66] Even when complete occlusion has been achieved, coil compaction may lead to a recurrence of the initially occluded aneurysm, necessitating retreatment. Aneurysm recurrence rates up to 16% have been reported for small and medium IAs, often requiring the subject to be retreated after the initial procedure (**Table 2**).[5-15] Up to 10% of small and medium IAs treated with stent-assisted coiling have required retreatment.[8,10] These data highlight a need for a more effective, long-term treatment option for small and medium wide-necked IAs.

Table 1. Morbidity and Mortality of Small and Medium Wide-Necked IAs Treated with Stent-Assisted Coiling

Article	Morbidity[1]	Mortality[2]
Sedat 2009	1/14 (7.1%)	0 (0%)
Mocco 2009	13/141 (9.2%)	3/141 (2.12%)
Liang 2010	6/107 (5.6%)	1/107 (0.9%)
Gao 2011	10/232 (4.3%)	3/232 (1.3%)
Fargen 2012	14/223 (6.3%)	8/223 (3.5%)
Galal 2013	2/43 (4.6%)	--
Clajus 2013	4/102 (3.9%)	3/102 (2.9%)
Kulcsar 2013	--	8/113 (6.8%)

1 Procedure and/or Device Related/ Neurologic Deficit
2 Procedure and/or Device Related
*All percentages noted are per subject
**All subject cohorts consist of IAs in which the majority is small and medium with wide neck.

Table 2. Aneurysm Recurrence and Retreatment Rates for Small and Medium IAs Treated with Stent-Assisted Coiling

ARTICLE	RATE
RECURRENCE	
Vendrell 2011	16%
Clajus 2013	15%
Lee 2012	13%
Yuan 2013	11%
Fiorella 2010	9%
Biondi 2007	9%
Gao 2011	9%
Sedat 2009	4%
Jia 2012	4%
Yao 2013	4%
Piotin 2010	3%

ARTICLE	RATE
RETREATMENT	
Vendrell 2011	10%
Biondi 2007	9%
Jia 2012	4%
Lopes 2014	6%
Fiorella 2012	3%

*Most subject cohorts consist of IAs in which the majority is small and medium. Some subject cohorts include IAs in which the majority is also wide-necked

Recently, flow-diverting devices represent a paradigm shift in the endovascular treatment philosophy for IAs and act in a two-fold manner:

(1) They divert flow away from the aneurysm sac, thereby inducing thrombosis within the sac and obviating the need for coil embolization; and

(2) They facilitate reconstruction of the parent vessel by providing a scaffold for endothelization.

Currently, the only FDA-approved flow diverter is the Pipeline™ device, which is indicated for the endovascular treatment of adults (22 years of age or older) with large or giant wide-necked IAs in the ICA from the petrous to the superior hypophyseal segments. Published data on the Pipeline™ device used to treat complex large/giant aneurysms show rates of 68-94.4% complete occlusion that remains persistent 2-3 years after the index procedure and 0-13.9% associated morbidity and 0%-6.4% mortality.[17-23] These rates are similar to or better than those for conventional IA treatments of surgery or coiling.[24,25]

1.2.3 Clinical Study Experience with the Pipeline™ Device

At least three clinical studies have reported on the use of the Pipeline™ device: Pipeline for Intracranial treatment of Aneurysms (PITA), Pipeline™ Embolization device for Uncoilable or Failed Aneurysms (PUFs), and International Retrospective Study of the Pipeline Embolization Device (IntrePED). The PITA and PUFs studies included subjects with only complex large and giant aneurysms. IntrePED was a global retrospective study evaluating the post-market use of the Pipeline™ device per standard of practice. These key studies are summarized below.

PITA Study

The PITA study was the first prospective multicenter trial of a flow-diverting construct for the treatment of intracranial aneurysms.[22] Thirty-one subjects with wide-necked (>4 mm) and unfavorable dome/neck ratios (<1.5 mm) were included. Of the 31 aneurysms, 65% were small (<10 mm) and the remaining 35% were large and giant in size. In total, 46 of 47 Pipeline™ device braids were placed successfully (97.9%). In 30 out of 31 subjects, the entire neck of the targeted intracranial aneurysm was covered by the Pipeline™ device braid. Complete aneurysm occlusion was observed in 93.3% (28/30) subjects at 180 days. Two subjects experienced a major periprocedural stroke and no deaths occurred.

PUFs Study

The PUFs study was a multicenter, prospective, single-arm trial to evaluate the safety and effectiveness of the Pipeline™ device in complex IAs.[67] One hundred seven subjects with large and giant unruptured wide-necked aneurysms in the petrous to the superior hypophyseal segment of the ICA were treated with the Pipeline™ device. The aneurysms measured ≥ 10 mm in diameter and had a neck ≥ 4 mm. A total of 104 subjects with 106 aneurysms were included in the primary effectiveness cohort. Of the 106 aneurysms, 78 demonstrated complete occlusion without major stenosis at 180 days (73.6%; 95% posterior probability interval: 64.4%–81.0%). At one year, 87.4% (83/95) of the target aneurysms were completely occluded. There were no cases of aneurysm recurrence. The primary safety endpoint was the occurrence of ipsilateral major stroke or neurologic death at 180 days, which occurred in six of the 107 subjects (5.6%; 95% posterior probability interval: 2.6%–11.7%). At one year follow-up, the rate of ipsilateral major stroke or neurologic death was 5.6%.

IntrePED

The IntrePED study was a retrospective global post market study of subjects treated with the Pipeline™ device at 17 centers worldwide. A total of 793 subjects with 906 aneurysms of various sizes and locations were included. The median follow-up period was 19.3 months with 89% subjects with greater than 1 year follow-up. The overall neurological morbidity rate was 7.4% (59/793) and the neurological mortality rate was 3.8% (30/793). The combined neurological morbidity and mortality rate was 8.4% (67/793). Data from the IntrePED study report the safety of the Pipeline™ device in the treatment of various IAs in a real-world clinical setting.

Further exploration of IntrePED data was conducted in cases of small and medium wide-necked IAs in the anterior ICA and posterior circulation. Data from 239 subjects harboring small or medium wide-necked IAs (including fusiform IAs) located in the ICA up to the terminus were evaluated (**Table 3**). Neurological morbidity and mortality rates of 4.2% and 1.7%, respectively were shown in cases involving the anterior ICA. In the posterior circulation, data from 28 subjects with small and medium wide-necked IAs (including fusiform IAs) demonstrated neurological morbidity of 3.6% and mortality rates of 0% for both measures. Excluding ruptured and dissecting IAs, which will be excluded in the present study, the combined neurological morbidity and mortality rates for the small and medium IAs in the anterior ICA and posterior circulation are 4.1% and 5.3%, respectively.

Table 3. IntrePED Study: Morbidity and Mortality of Small and Medium Wide-Necked IAs Treated with the Pipeline™ Device

OUTCOME	Small + Medium Aneurysms (≤12mm) (n=267 subjects; 287 aneurysms)	
	Anterior ICA (n= 239)	Posterior (n=28)
Mean ± SD aneurysm size (mm)	7.8 ± 2.8	8.6 ± 3.0
Neurological morbidity	10 (4.2%)	1 (3.6%)
Neurological mortality	4 (1.7%)	0(0%)
Neurological morbidity and mortality	10 (4.2%)	1 (3.6%)
Neurological morbidity & mortality *(excluding ruptured or dissecting)*	9/221 (4.1%)	1/19 (5.3%)

Overall, data from the IntrePED retrospective study has documented the physician utilization of the Pipeline™ device in small and medium (≤ 12 mm) wide-necked IAs in both the anterior and posterior circulations. The relative rates of complications appear to be similar or better than published literature on stent-assisted coiling. Furthermore, the IntrePED data included fusiform IAs, which are otherwise not treatable by coiling or stent-assisted coiling methods.

1.2.4 Study Rationale

The Pipeline™ device has been commercialized in the US since 2011 for the endovascular treatment of adults with large (≥ 10 – 24 mm) or giant (≥ 25 mm) wide-necked IAs in the ICA from the petrous to the superior hypophyseal segments. Over this period of time, additional long-term data has been generated which further confirms the safety and effectiveness of the Pipeline™ device for this indication. Of particular note, long-term data from the PUFs study demonstrate a 0% recurrence rate of occluded aneurysms up to 3-years post-procedure.[68] Additionally, in much geography outside the US, the Pipeline™ device has been approved and commercialized since 2008 for endovascular embolization of cerebral aneurysms.

Although alternative treatment options (surgical clipping or stent-assisted coiling) exist for some small and medium, wide-necked IAs, there remains a need for more effective and durable long-term IA treatments. To that end, the present study aims to evaluate the safety and effectiveness of the Pipeline™ device in unruptured, wide-necked IAs measuring ≤ 12 mm (small and medium sized) located in the ICA up to the terminus and the vertebral artery (VA) segment up to and including the posterior inferior cerebellar artery (PICA). The justification for the aneurysm sizes and locations to be included in this study is provided below.

Small/Medium (≤ 12 mm) Wide-Necked IAs

IAs measuring ≤ 12 mm in size comprise approximately 80% of all intracranial aneurysms.[1,2] The risk of rupture for IAs less than < 10 mm in size is approximately 1.0% per year and the risk of rupture increases with aneurysm size.[1,2,51,53,54] As ruptures can lead to SAH, a devastating complication with a case-fatality rate of over 50%, these small and medium wide-necked aneurysms are commonly treated endovascularly with stent-assisted coiling. Although initial occlusion rates are good, the primary limitation of stent-assisted coiling is the inability to provide sustained long-term aneurysm occlusion. Aneurysm recurrence rates of up to 16% have been reported in the literature after stent-assisted coil treatment of small and medium IAs (**Table 2**).[5-9,37,66] The presence of major aneurysm recurrence requires retreatment, which is evidenced by aneurysm retreatment rates of up to 10% for small and medium IAs.[6,8-10,13,34,36,69] Therefore, an alternative approach for obtaining sustained aneurysm occlusion is needed for small and medium wide-necked IAs. Within this current study, the safety and effectiveness of the Pipeline™ device for the treatment of unruptured, wide-necked IAs measuring ≤ 12 mm will be investigated.

IAs in the ICA (Up to the Terminus) and Vertebral Artery Segment (Up to and including the PICA)

Currently, treatment with the Pipeline™ device is indicated in US for IAs in the ICA from the petrous to the superior hypophyseal segments and the present study aims to include IAs in the ICA up to the terminus. Data from 239 patients with IAs ≤ 12 mm located in the ICA up to the terminus were collected in the IntrePED retrospective study which demonstrate neurological

morbidity and mortality rates of 4.2% and 1.7%, respectively (**Table 3**). These rates demonstrate that the Pipeline™ device can serve as a potentially safe treatment option for IAs of the ICA (up to the terminus).

The treatment of IAs in the posterior circulation is typically associated with a higher rate of complications. However when limited to only the vertebral and posterior inferior cerebellar arteries, published literature indicates that the morbidity and mortality rates are similar to the rates reported for stent-assisted coil treatment of small-wide-necked IAs. Studies evaluating the treatment of aneurysms located in the VA or PICA demonstrate morbidity rates ranging 0%-13% and mortality rates ranging 0%-7%.[26-33] (**Table 4**) These rates are comparable to the stent-assisted coiling morbidity rates of 3.9%-9.2% and mortality rates of 0%-6.8% presented in **Table 1**. Within this current study, the safety and effectiveness of the Pipeline™ device for the treatment of unruptured, wide-necked IAs measuring ≤ 12 mm in the vertebral artery segment up to and including the PICA will be investigated.

Table 4. Morbidity and Mortality Rates of PICA and VA IAs Treated Surgically and Endovascularly

Article	PICA or VA	Ruptured Prior to Treatment	Morbidity	Mortality
Mukonoweshuro 2003	All PICA	23/23 (100%)	3/23 (13%)	0/23 (0%)
Bradac 2004	All PICA	17/18 (94%)	1/18 (5.6%)	1/18 (5.6%)
Mericle 2006	All PICA	26/31 (84%)	--	2/31 (6.5%)
Pandey 2007	VA and PICA	23/41 (56%)	4/41 (9.8%)	1/41 (2.4%)
Peluso 2008	All PICA	10/47an. (21%)	2/46 (4.3%)	2/46 (4.3%)
Deng 2011	All VA	17/38 (45%)	0/38 (0%)	0/38 (0%)
Crowley 2012	All PICA	13/20 (65%)	2/20 (10%)	0/20 (0%)
Chalouhi 2013	All PICA	61/76 (80%)	2/71 (2.8%)	2/57 (3.5%)

*All percentages noted are per subject, except where noted.

Study Design

The proposed study design is a single-arm study of unruptured, wide-necked IAs, measuring ≤ 12 mm in which subjects will be treated with the Pipeline™ device. Alternative minimally invasive treatments that could form a reasonable concurrent control group are not available. Currently, the most common treatment method for these IAs is stent-assisted coiling. Although stent-assisted coiling is commonly performed, it is also important to note that not all IAs (e.g. fusiform IAs), which can be treated with the Pipeline™ device can be treated with stent-assisted coiling. As a result, if stent-assisted coiling were considered as a control treatment in the proposed study, it would limit the types of aneurysms that could be evaluated in the trial.

As discussed above, the aneurysm retreatment and recurrence rates associated with stent-assisted coiling demonstrate the need for a more durable treatment. In the scenario of a randomized controlled trial, if a subject is randomized to stent-assisted coiling and the IA recurs or enlarges to the extent of requiring retreatment, potential retreatment options will be limited. In particular, retreatment with flow diversion therapy is not possible in cases where a stent is already placed in the target IA. The labeling of the Pipeline™ device specifically states that it is contraindicated in patients who have a pre-existing stent in place in the parent artery at the target IA location.

Furthermore, stents are not approved by the FDA for use in the treatment of IAs and may only be used under the conditions of HDE approval. To date, no endovascular technology with FDA-accepted evidence of effectiveness is commercially available to address small and medium wide-necked IAs.

However, the safety and effectiveness rates associated with stent-assisted coiling for these IAs are published in the literature and can be used to define objective performance criteria. Clinical trial data and published studies have shown that the Pipeline™ device is safe and effective at treating larger sized IAs and it is expected that the Pipeline™ device will perform similarly in smaller IAs. To put the study results into perspective, results will be compared with historical information derived from earlier studies in which subjects with similar IAs underwent stent-assisted coil embolization.

Conclusion

In summary, IAs can potentially rupture and lead to serious complications with significantly poor outcomes. SAH resulting from aneurysmal rupture is associated with a high mortality rate of 51%.[48,49] The majority of IAs identified in routine practice are ≤ 12 mm in size and the average size of ruptured IAs is approximately 6.6-6.8 mm.[4] Small and medium wide-necked IAs are most commonly treated endovascularly with stent-assisted coiling, however, treatment outcomes are sub-optimal. Given the high recanalization and retreatment rates reported with stent-assisted coiling, alternative options with sustained curative effects are necessary. Treatment with the Pipeline™ device has demonstrated high rates of long term complete occlusion, low rates of re-treatment and low rates of adverse transient and persistent neurologic events in large and giant wide-necked IAs. Data collected in the IntrePED retrospective study and published literature suggests that the Pipeline™ device could be a possible treatment option for small and medium wide-necked IAs.

Thus, the aim of the present study is to assess the safety and effectiveness of the Pipeline™ device beyond the present indication to include IAs measuring ≤ 12 mm in the ICA (up to the terminus) and vertebral artery segment up to and including the PICA.

2 DEVICE DESCRIPTION

2.1 Intended Use of Device

The Pipeline™ device is intended for endovascular treatment of unruptured, wide-necked IAs, measuring ≤ 12 mm, located in the internal carotid artery (up to the terminus) or the vertebral artery segment up to and including the PICA.

The Pipeline™ device (manufactured by Covidien) is a braided, platinum and nickel-cobalt chromium alloy, wire mesh cylindrical implanted device that is intended to treat IAs.

The Pipeline™ device is designed to be placed across the opening (or 'neck') of a brain aneurysm and redirect blood flow away from the aneurysm, causing the blood within the aneurysm to clot. The device is designed for use in the neurovasculature.

2.1.1 Device Name

The Pipeline™ device will be used in this clinical study. The implanted braid, shown in **Figure 1**, is mounted on a guidewire-based delivery system.

Figure 1. Pipeline™ Device Braid

Continued development on the delivery system is ongoing and Pipeline™ devices with modified delivery systems with no changes to the braid implant may be used in this study upon agreement and approval by FDA.

2.2 Device Labeling

The Pipeline™ device is an approved, commercially available device. However due to the modification in indication, the device is considered investigational in this study and is required to be used per the protocol and as specified in the IDE Instructions for Use (IFU) document. The IDE IFU is provided separately to each investigator.

2.3 Device Tracking

The Pipeline™ device is tracked by lot number. Usage of all Pipeline™ devices in enrolled subjects who undergo the procedure will be tracked. Due to commercially availability, all shipments will not be tracked for the study.

2.4 Devices and Equipment

In addition to the Pipeline™ device, devices that may be required for the study procedure include (but are not limited to) those listed below. All ancillary devices required to perform the procedure will be provided by the site.

- Access devices: Guiding catheter and sheath
- Delivery catheters: Microcatheters (Covidien Marksman is recommended for use with the Pipeline™ device)
- Non-ionic contrast
- Guidewires
- Any other adjunctive, approved/cleared device for intracranial aneurysm treatment

The placement procedure is described in detail in the Instructions For Use (IFU) document.

Note: The Investigator should review and understand the complete IDE IFU prior to performing any Pipeline™ device placement in this clinical study.

3 STUDY OBJECTIVES

3.1 Primary Endpoints

- Safety: Occurrence of major stroke in the territory supplied by the treated artery or neurological death at 1 year post-procedure
- Effectiveness: Complete aneurysm occlusion (defined by scale of Roy) without significant parent artery stenosis (≤ 50%) at 1 year post-procedure

For the purposes of this study protocol, stroke is defined as a focal neurological deficit of presumed vascular origin persisting more than 24 hours from symptom onset AND a neuro-imaging study or other quantitative study that does not indicate a different etiology. The 24-hour criterion is excluded if the subject undergoes cerebrovascular surgery or dies during the first 24 hours of symptom onset.

The definition includes:

- Subjects presenting with clinical signs and symptoms suggestive of subarachnoid hemorrhage, intracerebral hemorrhage, or cerebral infarction.
- Sudden loss or worsening of visual acuity due to retinal artery occlusion or retinal emboli.

The definition excludes:

- Slowly progressive cranial nerve palsies or progressive visual field deficits due to continued aneurysm growth.
- Stroke events in cases of blood disorders such as leukemia or external events such as trauma.

Stroke severity will be graded by the Investigator as major or minor:

- Major Stroke: A stroke, which is present after seven days and increases the National Institutes of Health Stroke Scale (NIHSS) of the subject by ≥ 4.
- Minor Stroke: A stroke, which resolves completely within seven days OR increases the NIHSS of the subject by ≤ 3.

Neurological death is any subject death due to neurologic reasons.

The safety endpoint events will be adjudicated by an independent clinical events committee (CEC) (**Section 8.1**). The effectiveness endpoint will be assessed by an imaging core lab according to the scale of Roy (**Section 8.2.2**).

3.2 Secondary Endpoints

- Safety
  - Occurrence of major stroke in the territory supplied by the treated artery or neurological death at 30 days post-procedure due to procedural complications
  - Delayed intracerebral hemorrhage >30 days post-procedure
- Effectiveness: Device deployment success rate at the target site

3.3 Additional Data

- Device-related neurologic adverse event rate by 1 year post-procedure
- Modified Rankin Scale (mRS) score at 1 year.
- Aneurysm occlusion at 3 years post-procedure
- Recurrence and retreatment rates at 1, 2 and 3 years post-procedure
- Procedure time
- Radiation exposure (dosage and time)
- Number of Pipeline™ devices utilized

Event-relatedness will be adjudicated by an independent CEC (**Section 8.1**).

The mRS, a validated scoring system for neurologic status after stroke, will be judged by the Investigator and/or staff.

Aneurysm occlusion status will be assessed by an imaging core lab according to the scale of Roy.

4 STUDY DESIGN

The study is a global, prospective, single-arm, multi-center clinical study evaluating outcomes in subjects with intracranial aneurysms measuring ≤ 12 mm who are treated with Pipeline™ device.

4.1 Number of Sites and Subjects

Up to 200 subjects will be enrolled at up to 28 sites worldwide over a period of approximately 18 months to ensure the study has an adequate number of treated subjects; up to 141 (see **Section 9.2**). The enrollment number takes into account an approximate 30% screen failure rate observed in the initial roll-out of the PREMIER study. Each participating investigational site will be allowed to enroll a maximum of 25 subjects who meet all study eligibility criteria (see **Section 4.3**) and are treated with the Pipeline™ device.

4.2 Expected Duration of the Study and Subject Participation

Up to 141 subjects who meet the eligibility criteria (see **Section 4.3**) and are treated with the Pipeline™ device will actively participate for up to 3 years. Study participation includes consent, initial screening and baseline, treatment using the Pipeline™ device, discharge exam and follow-up visits at 30 days, 180 days, 1 year, 2 years, and 3 years.

The total study duration is expected to be approximately 54 months.

4.3 Study Population

The study population will consist of subjects who have an intracranial aneurysm. Treatment of more than one aneurysm may be permitted, but will require Sponsor approval before the subject can be treated in the study.

4.3.1 Inclusion Criteria

Subjects must meet all of the following general inclusion criteria:

1. Subject has provided written informed consent using the IRB/EC-approved consent form and agrees to comply with protocol requirements.
2. Age 22-80 years.
3. Subject has a target intracranial aneurysm (IA) located in the:
    a. Internal carotid artery (up to the carotid terminus) OR
    b. Vertebral artery segment up to and including the posterior inferior cerebellar artery
4. Subject has a target IA that is ≤ 12 mm.
5. Subject has a target IA that has a parent vessel with diameter 1.5–5.0 mm distal/proximal to the target IA.
6. Subject has a target IA with an aneurysm neck ≥ 4mm or a dome to neck ratio ≤ 1.5.
7. Subject has a pre-procedure PRU value between 60–200.

4.3.2 Exclusion Criteria

The subject must not meet any of the following general exclusion criteria:

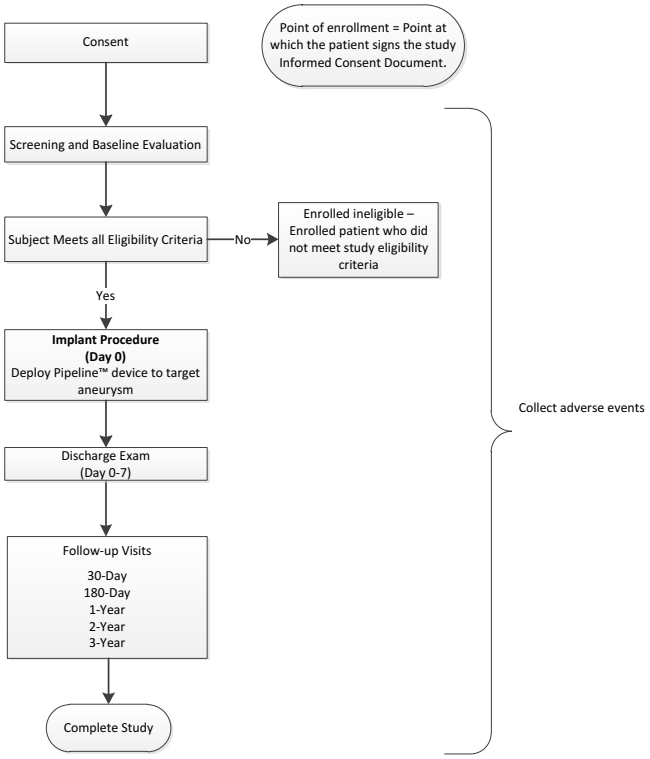
1. Subject has received an intracranial implant (e.g. coils) in the area of the target IA within the past 12 weeks.
2. Subarachnoid hemorrhage in the past 30 days.
3. Subject with anatomy not appropriate for endovascular treatment due to severe intracranial vessel tortuosity or stenosis determined from baseline or pre-procedure imaging, or a history of intracranial vasospasm not responsive to medical therapy.
4. Major surgery in the last 30 days.
5. History of irreversible bleeding disorder and/or subject presents with signs of active bleeding.
6. Any known contraindication to treatment with the Pipeline™ device, including:
    a. Stent is in place in the parent artery at the target IA location
    b. Contraindication to dual antiplatelet therapy
    c. Relative contraindication to angiography (e.g., serum creatinine >2.5 mg/dL, allergy to contrast that cannot be medically controlled).
    d. Known severe allergy to platinum or cobalt/chromium alloys.
    e. Evidence of active infection at the time of treatment (e.g., fever with temperature >38°C and/or WBC >1.5 10^9/L).
7. The Investigator determines that the health of the subject or the validity of the study outcomes (e.g., high risk of neurologic events, worsening of clinical condition in the last 30 days) may be compromised by the subject's enrollment.
8. Pregnant or breast-feeding women or women who wish to become pregnant during the length of study participation.
9. Participating in another clinical trial during the follow-up period that could confound the treatment or outcomes of this investigation.

Before any subject is treated in the study, the baseline angiogram will be reviewed by a Pipeline™ device expert to ensure that the target IA is amenable to treatment with the Pipeline™ device.

5 STUDY PROCEDURES

5.1 Overview of Study Flow

A representative overview of the study flow is shown below.



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, 180-day, 1-year, 2-year, and 3-year follow-up 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 before any study specific procedures required by the protocol are performed. Informed consent should be obtained in written format and using a form approved by the local IRB/EC. The form should contain standard language consistent with local policies for ensuring privacy of confidential information. All subjects must sign the informed consent prior to any procedures/tests that go beyond initial assessments associated with the standard care for subjects with intracranial aneurysms and before any study related treatment assessments are administered and subject-related health information can be entered into the study database.

Subjects are considered enrolled in the study once the subject signs the study Informed Consent Form.

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 and Baseline Evaluations

Each subject will undergo a neurologic examination and assessment using the mRS and NIHSS, blood draw for hematocrit, platelet count, platelet function testing as per standard patient care (e.g. using VerifyNow (Accumetrics)), serum creatinine, and a pregnancy test (if applicable) within 60 days from the planned procedure. In female subjects, pregnancy may be ruled out by urine or blood pregnancy test, or medical history (menopause or surgical sterility). Each subject's relevant medical history and pre-existing conditions will be assessed and documented for all enrolled subjects. Current medication use within the last 30 days will be assessed and documented at baseline.

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.

If the subject meets the dimensional criteria outlined in the inclusion criteria, they 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 Imaging

Screening imaging must be taken within 180 calendar days from the planned procedure date. Screening imaging to characterize the IA will consist of angiography.

5.3.2 Antiplatelet agents

The subject will be tested for antiplatelet response (using VerifyNow (Accumetrics) and the appropriate dose of antiplatelet agents will be given before Pipeline™ device treatment as defined below.

- **Aspirin:** At least 81 mg daily for a minimum of 7 days
- **Clopidogrel:** At least 75 mg daily for a minimum of 7 days

A loading dose option will not be permitted in the study. Subjects resistant to Clopidogrel will not be included in the study.

5.4 Procedure

Subjects must undergo the device placement procedure within 60 calendar days of completion of all baseline assessment tests and procedures. The status of the target IA may change between the screening evaluation and the procedure that may change the risk profile of the study procedure.

Therefore, a pre-treatment (baseline) angiogram will be required before the procedure to confirm that the study procedure can be safely carried out and to collect precise images for the core laboratory. If in the unlikely event that the subject is deemed to be ineligible, the subject will not require any study follow-up.

Each subject will undergo a neurologic examination and assessment using NIHSS. The subject will be tested for antiplatelet response (e.g. using VerifyNow (Accumetrics)). Periprocedural heparin per institutional protocol is required. Prior to inserting the study device, the activated clotting time (ACT) should be checked and adjusted as clinically appropriate. Further ACTs will be checked per standard practice.

The physician will place and deploy the appropriate number of Pipeline™ device braids at the target site to treat the IA.

Post-treatment, the investigator will assess device occlusion, placement and overall status of the aneurysm. Angiograms in the anterioposterior (AP), lateral, and working positions will be obtained. The Investigator will take necessary steps to ensure that pre- and post-placement angiograms are performed using similar views, magnifications, and contrast amount to ensure valid “before/after” comparisons. However, these angiographic details will not be collected in case report forms (CRFs). The Investigator will submit procedural angiograms to the imaging core laboratory. The Investigator will ensure that subject identifiers are removed from all submitted images. Image files/CDs should be labeled with the subject’s study ID number.

Medications appropriate for general anesthesia will be administered using standard hospital practice. Platelet inhibition and aggregations status pre- and post-surgical intervention, including antiplatelet antibodies will be evaluated. All medication use during surgery and immediately post-procedure will be documented. Radiation exposure will be recorded as absorbed radiation dose and cumulative fluoroscopy time will be recorded.

At the investigator’s discretion, the target IA may be retreated at any time during the study. In the event that the target IA is not treated with the Pipeline™ device at the initial scheduled procedure, the subject may be brought in later to undergo the Pipeline™ device placement procedure. In such situations, the date that the subject receives the Pipeline™ device implant will be considered Day 0. Data will be collected for all initial and retreatment procedures.

5.5 Post-placement Antiplatelet Agents

The subject should be tested for antiplatelet response per standard of care, and the appropriate dose of antiplatelet agents will be given after the Pipeline™ device placement procedure as defined below.

- **Aspirin:** At least 81 mg daily for a minimum of 6 months
- **Clopidogrel:** At least 75 mg daily for a minimum of 3 months

Medications could be continued beyond above regimen if medically indicated.

5.6 Discharge Exam

Each subject will undergo a neurologic examination and assessment using the mRS and NIHSS. The Investigator will also document all medications currently being taken and adverse events. The subject may undergo platelet function testing as per standard patient care.

5.7 Follow-up Evaluations

Subjects will undergo follow-up at a location designated by the research staff at 30 days, 180 days, 1 year, 2 years, and 3 years post-procedure.

5.7.1 30-Day

At this visit, the subject will undergo a neurologic examination and assessment using the mRS and NIHSS. The Investigator will also document all medications currently being taken and assess adverse events.

5.7.2 180-Day

At this visit, the subject will undergo a neurologic examination and assessment using the mRS and NIHSS. The Investigator will also document all medications currently being taken and adverse events. If the subject undergoes angiography of the target IA as standard care, the angiogram will be sent to the Core Laboratory for analysis. In addition, any axial imaging done in place of angiography may be collected and sent to the Core Laboratory for analysis.

5.7.3 1-Year

At this visit, the subject will undergo a neurologic examination and assessment using the mRS and NIHSS. The Investigator will also document all medications currently being taken and adverse events. The subject will undergo angiography of the target IA. If available, imaging should include rotational angiography with 3D reconstruction. Imaging will be sent to the Core Laboratory for analysis.

5.7.4 2-Year

At this visit, the subject will undergo a neurologic examination and assessment using the mRS and NIHSS. The Investigator will also document all medications currently being taken and adverse events. The subject may undergo angiography of the target IA if the aneurysm was not occluded at 1 year. If applicable, imaging will be sent to the Core Laboratory for analysis. In addition, any axial imaging done in place of angiography may be collected and sent to the Core Laboratory for analysis.

5.7.5 3-Year

At this visit, the subject will undergo a neurologic examination and assessment using the mRS and NIHSS. The Investigator will also document all medications currently being taken and adverse events. The subject may undergo angiography of the target IA if the aneurysm was not occluded at 2 years. If applicable, imaging will be sent to the Core Laboratory for analysis. In addition, any

axial imaging done in place of angiography may be collected and sent to the Core Laboratory for analysis. This visit is the final study visit.

5.7.6 Unscheduled Visits

Any visit by the subject to the Investigator related to the target IA treated or a potentially associated adverse event should include a neurologic examination using NIHSS. The Investigator should document the review of the adverse event status and all medications taken by the subject.

5.8 Schedule of Assessments

An overview of the assessments to be performed at each follow-up interval along with the required timing is provided in **Table 5.** Visits occurring outside of the specified date range will be considered protocol deviations.

Table 5. Visit and Assessment Schedule

Visits		Screening and Baseline	Device placement		Follow-up					
			Procedure	Discharge exam	30-day	180-day	1-year	2-year	3-year	Unscheduled
Assessments	Time (Windows)	Pre-procedure (-60days)	Day 0	Day 0-7	Day 30 (± 7 days)	Day 180 (±30 days)	Day 365 (± 42 days)	Day 730 (± 42 days)	Day 1095 (± 42 days)	--
Assess Inclusion / Exclusion		◆								
Demographics and Medical History		◆								
Blood Labs		◆[1]	◆[2]	○[3]						
Medications		◆	◆	◆	◆	◆	◆	◆	◆	◆
Modified Rankin Scale score		◆		◆	◆	◆	◆	◆	◆	
Imaging[4]		◆ (180 days)	◆[5]			○[6]	◆	◆[7]	◆[7]	◆[7]
NIH Stroke Scale		◆	◆	◆	◆	◆	◆	◆	◆	◆
Pipeline™ Placement			◆							
Assess Adverse Events		◆	◆	◆	◆	◆	◆	◆	◆	◆

1 Includes CBC, HCT, platelet count, platelet function testing as per standard patient care, serum creatinine, and pregnancy test, if applicable
2 Includes platelet count and platelet function testing
3 If platelet function testing is performed as standard patient care the results should be recorded.
4 Includes angiograms in the anterioposterior, lateral and working positions for analysis by a core laboratory.
5 Includes a pre-treatment and post-treatment angiogram
6 If an angiogram is performed as standard patient care it should be sent to the core laboratory for analysis.
7 If aneurysm is completely occluded at 1 year, angiography is optional at subsequent follow-up visits. Otherwise if aneurysm is not occluded at 1 year, angiography must be performed thereafter until the aneurysm is completely occluded or the subject has completed the study. Any angiograms performed at other time points should be sent to the core laboratory for analysis.

5.9 New Information

Study subjects will be informed of new information that becomes available during the course of this study by their treating physician. Subjects will be notified, at a minimum, in accordance with the IRB/EC's procedure for providing updated information to clinical study subjects.

5.10 Study Exit

Upon completion of the specified study follow-up the subject will be exempt from further data collection. The subject will be seen by the treating physician according to standard care following intracranial aneurysm treatment.

5.11 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.

5.11.1 Subject Withdrawal

All enrolled subjects have the right to withdraw their consent at any time during this study. All data collected until the time of subject withdrawal will remain in the study database and will be used for analysis. Whenever possible, the site staff should obtain written documentation from the subject who wishes to withdraw his/her consent for future follow-up visits. 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 should be provided to the Sponsor.

5.11.2 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.

5.11.3 Lost to Follow-up

A subject will be considered lost to follow-up if the subject cannot be reached after three (3) attempts to contact the subject for a follow-up visit. The site must document a minimum of three (3) attempts, and the final documented attempt should be made via registered letter.

5.12 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 for 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, (e.g. unauthorized use of a study device outside the study, unauthorized use of a study device by a physician, etc.) will be reported. Investigators will also adhere to procedures for reporting study deviations to their IRB/EC in accordance with their specific IRB/EC's reporting policies and procedures.

Sites with a high rate of protocol deviations will be closely evaluated and are expected to implement corrective actions 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 endpoints and will not be considered a deviation if absent.

5.12.1 Discontinuation by IRB/EC

The IRB/EC 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/EC's requirements.
- The research study indicates unexpected serious harm to subjects.

5.12.2 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/EC will also be informed, either by the Sponsor or Investigator if a local IRB/EC 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 subject will then be seen by the treating physician according to standard care following intracranial aneurysm treatment.

Any investigator who is discovered during monitoring to have not reported neurologic adverse events may be terminated from the study at the discretion of the Sponsor

6 ADVERSE EVENTS

The following adverse events will be collected during the course of the study on the eCRFs.

- All Adverse Events (AE) with an underlying neurological cause (Neurological Adverse Events)
- All Device Related Adverse Events
- All Procedure Related Adverse Events
- All Serious Adverse Events (SAE's)

Adverse event status will be evaluated throughout the study. These will include new events occurring after the point of consent in the study until a subject exits the study. Subjects who are enrolled, underwent surgery to implant to study device but did not have the Pipeline™ device implanted for any reason will be followed for 30 days and relevant safety events will be collected. Investigators must obtain all information available to determine the causality and outcome of the AE and to assess whether it meets the criteria for classification as a serious and/or unexpected event requiring notification to the Sponsor, regulatory agency, and as applicable, IRB/EC, within the specified reporting timeframe. AEs will be categorized using the definitions in **Section 6.1**.

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 or until the end of the 3-year follow-up. A list of potential anticipated adverse events is provided in **Section 10.2**.

6.1 Adverse 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 3.2)

NOTE 1: This definition includes events related to the investigational medical device or the comparator.

NOTE 2: This definition includes events related to the procedures involved.

NOTE 3: For users or other persons, this definition is restricted to events related to investigational medical devices.

An *Adverse Device Effect* (ADE) is defined as an adverse event related to the use of an investigational medical device. (ISO 14155:2011 3.1) The investigational medical device for this study is the Pipeline™ device used during the procedure (Day 0).

NOTE 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.
NOTE 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

A *Serious Adverse Event* (SAE) is defined as an 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-subject or prolonged hospitalization, or
    d. Medical or surgical intervention to prevent 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 3.37

NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered 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 3.36)

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 3.42)

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 (s))

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 procedure (Day 0). This includes AEs attributable to any device(s) other than the Pipeline™ device used at procedure (day 0), such as access devices, delivery microcatheters, non-ionic contrast, guidewires, or any other adjunctive, approved/cleared device for treatment of intracranial aneurysms.
- Device-related: Event has a strong temporal relationship to the study device, and alternative etiology is less likely.
    - Pipeline™ device used at the procedure (Day 0) including the braid and the delivery system.
    - If the event is related to the Pipeline™ device used at a procedure other than the procedure (Day 0), it should be characterized with an event relationship of “Non-index procedure related”.

  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.
- Non-index procedure related: This includes AEs attributable to any device(s) used at procedures other than day 0, such as access devices, delivery microcatheters, non-ionic contrast, guidewires, or any other adjunctive, approved/cleared device for treatment of intracranial aneurysms. This may include commercially available Pipeline™ devices used in procedures other than at Day 0 or those used on non-target lesions.
- DAPT-related: Event is clearly attributable to dual antiplatelet therapy (DAPT) with no temporal relationship to the device, treatment, or medical history.
- Unknown: Event relationship cannot be attributed to any of the above categories and remains undetermined.

6.2 Event Reporting

The investigator is required to report all SAEs within 72 hours and any UADEs/USADE's within 24 hours after first learning of the event to the Sponsor. The primary method of reporting SAEs will be through the eCRFs. If the database is unavailable the investigator may send the information to the SAE Hotline. As soon as the database becomes available, the investigator must complete data entry. The investigator will send all available supporting documentation (blinded/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.

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 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 Unanticipated Adverse Device Effect (**Section 6.1**) must be reported to FDA, all investigators and reviewing IRBs within 10 working days after becoming aware of information that an unanticipated adverse device effect has occurred.

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.

7 DEVICE SPECIFIC EVENT

A device-specific event (DSE) 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 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 3.27).

All device specific events must be reported to both the Sponsor and local authorities as required by governing law. If a device malfunction results in an adverse event for the subject, this adverse event will be considered a reportable adverse event and must be reported as an Adverse Event (AE).

8 STUDY COMMITTEES / CORE LABORATORY

To avoid and minimize bias, an independent Clinical Events Committee, Imaging Core Laboratory, and Data Safety Monitoring Board will be in place to assess event relationship, aneurysm occlusion, and vessel stenosis.

8.1 Clinical Events Committee (CEC)

A CEC will be in place for the study using a minimum of three (3) physicians knowledgeable in the appropriate disciplines and medical specialties pertinent to the disease state being evaluated in this clinical study. This committee will be responsible for the review and adjudication to the study endpoints of the following events reported by the site:

1. Events leading to sudden neurological worsening/deterioration ≥ 3 point NIHSS score
2. All Device related adverse events
3. All Procedure related adverse events

The CEC will independently adjudicate to specified endpoint event definitions, event relatedness, event severity, and event outcomes.

The CEC can request additional source documentation and any potential imaging obtained in support of the adverse event to assist with adjudication.

8.2 Imaging Core Laboratory

An imaging protocol will be provided to the site. The imaging core laboratory will be responsible for the qualitative image analysis to determine aneurysm occlusion, parent artery stenosis, and device migration.

8.2.1 Baseline anatomy

Baseline imaging will be reviewed to assess baseline aneurysm and parent artery characteristics.

8.2.2 Aneurysm Occlusion

Post-procedure angiograms will be reviewed to assess aneurysm occlusion according to the scale of Roy[48] (**Figure 2**).

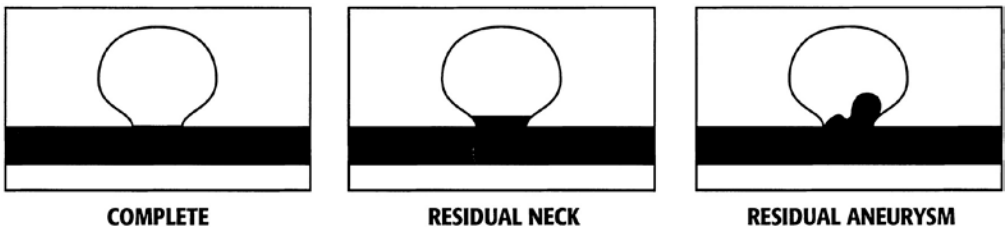


Figure 2. Scale of Roy for Judging IA Endosaccular Embolization Success

- **Complete** = Complete occlusion, no flow of contrast seen in the aneurysm sac
- **Residual Neck** = Partial occlusion, some flow or eddying flow in the aneurysm sac
- **Residual Aneurysm** = Incomplete occlusion, apparent flow in the aneurysm sac

Several published studies showed that the reliability of individual radiologist raters in judging complete vs. incomplete post-treatment occlusion was very high (kappa=0.96 and 0.99 for each rater).[70] Moreover, inter-rater reliability of the complete vs. incomplete judgment was also reported to be very high (kappa=0.87; intra-class correlation coefficient (ICC)=0.76, 95% CI 0.69-0.82; P<0.0001).[70,71]

8.2.3 Parent Artery Stenosis

Post-procedure angiograms will be reviewed to assess stenosis in the parent artery across the entire Pipeline™ device. Vessel stenosis will be measured and judged according to the scale in **Table 6**.

Table 6. Scoring System for Stenosis

Category	Degree of Stenosis
0	0 – 25%
1	>25 – 50%
2	>50 – 75%
3	>75 – 100%

8.3 Data Safety Monitoring Board (DSMB)

The DSMB will be an independent group that will serve as a data monitoring committee to the Sponsor of this Study. The DSMB will be comprised of individuals who are independent of the investigational sites and of representatives from multiple disciplines including but not limited to neurology, biostatistics/epidemiology, neurosurgery and interventional neuroradiology.

In the safety monitoring role, this board shall provide recommendations to the Sponsor regarding stopping /continuing enrollment in the Study. In so doing, this board will propose interim analysis methodology with stopping rules related to Study safety. The DSMB will establish proposed monitoring criteria for the Study and will establish and document any required interim analysis time points for assessing safety. The group will also establish a mission statement and operating procedures.

The DSMB will also advise the Sponsor concerning the content of interim reports and the analyses that are required for data interpretation.

9 STATISTICAL METHODS AND DATA ANALYSIS

9.1 General Principles

Tabulations of summary statistics, graphical presentations, and statistical analyses will be performed using SAS software version 9.2 or higher. The statistical analyses will be based on data pooled across sites in aggregate, retaining s*ite* in the statistical models that allow for the inclusion of fixed effects. All subset summary tables and data listings will be sorted by subject and site. The pre-procedure observations will be used as the baseline value for calculating post-procedural changes from baseline.

Continuous demographic parameters, such as the age of the subject at the time of enrollment, will be summarized for the ITT population using descriptive statistics (N, mean, median, standard deviation, minimum and maximum value, and 95% 2-sided confidence limits). Categorical demographic parameters, such as gender, will be summarized as a proportion of the ITT population using Clopper-Pearson 95% 2-sided confidence limits. Clinical and high risk factors will also be summarized as a proportion of the ITT population with Clopper-Pearson 95% 2-sided confidence limits.

Data obtained during the neurological examination using the Modified Rankin will be summarized at each time point using descriptive statistics.

Adverse events will be coded according to the MedDRA system dictionary. The percentage of subjects experiencing adverse events will be summarized by body system and preferred term. Subject counts will be tabulated for all adverse events for the ITT population. Adverse events will also be tabulated for events that occurred within the first 30 days of the procedure. Tabulated subject counts will be presented as a proportion of the ITT population with 95% binomial confidence intervals.

Summarizations predicated on continuous variables will be based on a generalized linear model, predicated on maximum likelihood, specifying the dependent variable as a variable with a continuous distribution. The single factor included in the model will be site. The baseline scores for specific parameters may be added to the analysis to increase the precision of the model. Probability values <0.05 will be considered significant.

Summarizations predicated on proportions will be based on a generalized linear model, predicated on maximum likelihood, specifying the dependent variable as a dichotomous variable with a binomial distribution. The single factor included in the model will be site.

The analyses predicated on ordinal categorical parameters will be based on a generalized linear model, predicated on maximum likelihood, specifying the dependent variable as a categorical variable with a multinomial distribution. The single factor included in the model will be site.

Specific algorithms for imputing missing or partially missing dates will be discussed in the Statistical Analysis Plan. Derived data will be identified in the individual subject data listings. Imputed data for dates will not be incorporated into the case report form datasets. Imputed data for dates will be used in the preparation of the derived datasets.

Small sites (i.e., sites that have less than 4 subjects) will be identified and the following method will be used for combining the data. Data from all small sites (<4 subjects) will be combined to form a single site in order to obviate non-estimable situations in the evaluation of site and site interaction effects. Once combined, the pooled site will remain as such for all analyses for which a site effect is determined. If the pooled smaller sites represent a single site that has more than twice as many subjects as the largest single site, however less than 3 times as many subjects, the small sites will be ranked by size and divided into 2 pooled assignments using an alternating sequence (ABABAB). If the pooled smaller sites represent a site that has more than three times as many subjects as the largest single site, however less than 4 times as many subjects, the small sites will be ranked by size and divided into 3 pooled assignments using an alternating sequence (ABCABCABC).

To understand the potential effect of a site effect, *site* will be included as a covariate in a logistic regression model, designating the occurrence of major stroke in the territory supplied by the treated artery or neurological death at 1 year as the dependent variable and calculating the Breslow-Day test of homogeneity of the odds ratios. A probability value less than 0.05 will be considered evidence of a significant difference among the sites. Under this scenario, *site* would be retained in the model for calculating the adjusted confidence intervals. The intra-site event rate will also be displayed graphically using exact 95% binomial confidence limits.

To understand the potential effect of a Site effect on the primary performance endpoint, *Site* will be included as a covariate in a logistic regression model, designating the 1 year post-procedure aneurysm occlusion as the dependent variable and calculating the Breslow-Day test of homogeneity of the odds ratios. A probability value less than 0.05 will be considered evidence of a significant difference among the sites. Under this scenario, *Site* would be retained in the model for calculating the adjusted confidence intervals. The intra-site event rate will also be displayed graphically using exact 95% binomial confidence limits.

In the absence of data to suggest otherwise, a subject who does not attend the 1 year post-treatment visit in the allotted time window will not be considered a primary safety endpoint failure unless it is known that the subject experienced stroke or death.

All recorded data will be presented in the individual data listings.

9.2 Sample Size Calculation

Estimates were prepared separately for the primary safety and performance endpoints and based on generating a 1-sided 97.5% Clopper-Pearson exact binomial confidence interval. The upper bound of the confidence interval for safety and the lower bound for performance will be examined relative to the respective *a priori* thresholds. For the primary safety endpoint, the null and alternative hypotheses are as follows:

Ho: Incidence at 1 year post-procedure of major stroke in the territory supplied by the treated artery or neurological death ≥ 0.15

Ha: Incidence at 1 year post-procedure of major stroke in the territory supplied by the treated artery or neurological death < 0.15

Reasonable estimates of the observed rate were considered to range between 5% and 9%; the sample size estimates under these scenarios are presented in **Table 7** below:

Table 7. Observed Incidence at 1 Year Post-Procedure of Major Stroke in the territory supplied by the treated artery or Neurological Death

Observed Incidence at 1 Year	Minimum Sample Size
5%	52
6%	63
7%	80
8%	104
9%	141

For the primary effectiveness endpoint, the null and alternative hypotheses are as follows:

Ho: Incidence at 1 year post-procedure of aneurysm occlusion without significant parent artery stenosis ≤ 0.50

Ha: Incidence at 1 year post-procedure of aneurysm occlusion without significant parent artery stenosis > 0.50

Reasonable estimates of the observed rate were estimates at 61% to 65%; the sample size estimates under these scenarios are presented in **Table 8** below:

Table 8. Observed Incidence at 1 Year Post-Procedure of Aneurysm Occlusion Without Significant Parent Artery Stenosis

Observed Incidence at 1 Year	Minimum Sample Size
61%	100
62%	83
63%	71
64%	61
65%	53

The maximum number of subjects to be enrolled in this clinical investigation will be 141 subjects, based on an incidence at 1 year of major stroke in the territory supplied by the treated artery or neurological death of 9%. Based on the expected incidence of the primary endpoints, a minimum of 80 subjects will be enrolled.

9.3 Analysis Population

The analysis population will be comprised of the results from 141 treated subjects. Results will be presented based on two populations:

Intention to Treat (ITT): defined as all enrolled subjects in whom deployment of the Pipeline™ device was attempted. It is possible that the Pipeline™ device may not reach the target site and the operator would not attempt to deploy it, in the rare event that happens, that subject will not be considered part of the ITT population.

Full Analysis Set (FAS): defined as a subset of ITT including only those in whom the Pipeline™ device was implanted.

Per protocol (PP): defined as all enrolled subjects, had the Pipeline™ device implanted, and were followed without any major protocol deviations.

9.4 Analysis of the Primary Safety Endpoint and Objective

The primary safety endpoint is the incidence of major stroke or neurological death at 1-year post-procedure in the ITT population. The primary safety objective is to determine if the incidence of major stroke in the territory supplied by the treated artery or neurological death at 1-year of the study procedure is below a pre-specified threshold of 15% with 97.5% confidence.

In the previous Pipeline™ device IDE trial (PUFs), the safety endpoint of occurrence of ipsilateral major stroke or neurological death was evaluated. The most commonly used endovascular approach for small and medium, wide-necked IAs is stent-assisted coil embolization. Published literature on stent-assisted coiling for mainly small and medium wide-necked IAs (**Table 1**)[5,7,9,34-38] demonstrates rates of procedure/device-related neurologic deficit ranging from 3.9% to 9.2% and rates of procedure/device-related mortality rates ranging from 0% to 6.8%, yielding combined procedure-/device-related morbidity and mortality rates up to 16%. Although technological advancements have been made, subjects eligible for PREMIER have few reasonable alternatives for sustained occlusion. They face a risk of often-fatal spontaneous bleeding without treatment. They also face a high rate of stroke or death with currently available treatments such as neurosurgery or stent-assisted coiling. A procedure with a high effectiveness rate and perioperative stroke/death rate whose upper confidence limit is <15% represents a significant advance for this patient population. The lack of reasonable alternatives justifies the proposed safety study success parameters.

The 1-sided 97.5% confidence interval will be calculated using the exact Clopper-Pearson method. Results will be based on the Full Analysis Set. Subjects who fail to complete the 1-year post-procedure evaluation period and do not experience the events of interest will be counted as not having experienced the event.

A sensitivity analysis will be prepared using an adjusted analysis model, censoring subjects who withdraw prior to 1-year and did not experience the events of interest.

9.5 Analysis of the Primary Effectiveness Endpoint and Objective

The primary effectiveness endpoint is the incidence of aneurysm occlusion without significant parent artery stenosis at 1 year post-procedure without re-intervention in the FAS population. The primary performance objective is to determine if the incidence is above a pre-specified threshold of 50% with 97.5% confidence.

Previously, in the PUFs IDE study, the same effectiveness endpoint of complete occlusion without major stenosis was evaluated. For subject with small and medium wide-necked IAs, treatment options for sustained occlusion are fairly limited. Currently, these IAs are commonly treated with stent-assisted coiling. Published literature on stent-assisted coil embolization has reported an occlusion rate at 1 year post-procedure ranging 46% to 75%. Aneurysm recanalization rates up to 28% have been reported; often requiring the subject to be retreated.[5-9,37,66] Given that these rates represent the effectiveness of the current treatment alternative, a threshold of 50% will be established for the primary effectiveness endpoint.

Primary effectiveness evaluations of occlusion will be assessed by an independent core laboratory. The 1-sided 97.5% confidence interval will be calculated using the exact Clopper-Pearson method. Results will be based on the Full Analysis Set. Subjects who fail to complete the 1-year post-procedure evaluation will be counted as having met the primary performance endpoint.

A tipping point analysis will be performed as a sensitivity analysis for the primary effectiveness endpoint. An additional worst-case sensitivity analysis will be prepared, assuming subjects who withdraw prior to

the 1-year evaluation visit experienced significant stenosis, therefore not meeting the primary effectiveness endpoint.

9.6 Planned Interim Assessment

To ensure the study is not under-powered, the primary endpoint will be monitored by the DSMB. The DSMB will be responsible for examining the interim results to ensure the observed incidence of outcome events is consistent with the planning estimates. Monitoring will specifically focus on the incidence of major stroke in the territory supplied by the treated artery or neurological death and aneurysm occlusion without significant parent artery stenosis.

After 50 subjects have been enrolled and followed for a minimum of 6 months post-procedure, an interim assessment will be performed. It is understood that monitoring off an earlier time point does not correspond with the primary endpoint. However, to derive an initial signal to ensure that the observed incidence is commensurate with the planning estimates, this time point should conservatively represent approximately 80% of events at 1 year. The conditional power will be examined to determine if an adjustment in the sample size is required to meet the primary objective of the study. An alpha level adjustment will not be necessary if the conditional power for the primary endpoint is >50%, based on the procedure proposed by Chen, DeMets and Lan (2004).[72-76] Details of the procedure will be described in the DSMB Charter.

9.7 Analysis of the Secondary Safety Endpoints

The rate of occurrence of major stroke in the territory supplied by the treated artery or neurological death at 30 days post-procedure due to procedural complications will be tabulated for the FAS population and presented using counts, percentages, and 2-sided 95% exact binomial confidence intervals. The rate of delayed intracerebral hemorrhage >30 days post procedure will be tabulated for the FAS population and presented using counts, percentages, and 2-sided 95% exact binomial confidence intervals.

9.8 Secondary Effectiveness Endpoint

The proportion of successful device deployments will be summarized using counts, percentages, and 2-sided 95% exact binomial confidence intervals.

9.9 Analysis of the Additional Data

The device-related neurologic adverse event rate at 1 year post-procedure will be tabulated for the ITT population and presented using counts, percentages, and 2-sided 95% exact binomial confidence intervals. The mRS score at 1 year will be dichotomized (≥2 vs. <2) and summarized using counts, percentages, and 2-sided 95% exact binomial confidence intervals. Aneurysm occlusion will be tabulated for the Full Analysis Set and presented using counts, percentages, and 2-sided 95% exact binomial confidence intervals. The proportion of subjects who experience recurrence and require retreatment will be summarized using counts, percentages, and 2-sided 95% exact binomial confidence intervals. Procedure time, radiation exposure (dosage and time) and number of Pipeline™ devices utilized will be summarized using descriptive statistics (N, mean, median, standard deviation, minimum and maximum value, and 95% 2-sided confidence limits).

9.10 Handling of Missing Data and Deviations

The number and proportion of subjects eligible will be presented. Subjects who withdraw from the study will be tabulated with the reasons for the withdrawal. For the primary endpoint analyses, the last observed values or conditions will be used for the calculations. Any departure or deviation from these planned statistical methodologies will be documented and discussed in the Statistical Analysis Plan that will include the statistical rationale for divergence.

9.11 Safety Analysis

All analyses regarding subject safety will be predicated on the ITT population. The number and proportion of subjects experiencing each type of event will be summarized overall and by site. Only treatment emergent events will be included in the analysis, i.e., events that began or worsened after enrollment.

The safety of the procedure will be measured by the incidence of adverse events. The following sections describe how the safety endpoints will be analyzed.

9.11.1 Adverse Events

Adverse events will be tabulated on both an event basis (total number of events), and on a subject-basis reporting treatment-emergent events.

9.11.2 Missing and Partial Adverse Event Dates

The start dates for AEs are important for the:

1. Treatment emergent algorithm.
2. The designation of unique AE occurrences.

Completely missing or partially missing adverse event onset dates will be imputed as follows after due diligence to obtain accurate adverse event information has failed.

If the adverse event start date is completely missing then the adverse event will be considered treatment emergent unless it can be determined that the adverse event end date occurred prior to the study procedure. If this is the case, the adverse event will not be considered treatment emergent.

If the adverse event start date is partially missing and the partial date is not sufficient to determine if the event occurred after the study procedure, then the adverse event will be considered treatment emergent unless it can be determined that the adverse event end date occurred prior to the study procedure.

9.11.3 Summaries of Adverse Events

All summaries of AEs will be based on treatment-emergent AEs. Adverse events will be mapped to preferred terms and body systems using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. The number and percentage of subjects experiencing AEs will be summarized by system organ class and preferred term. Summaries by maximum severity and

relationship to study treatment will also be provided. Serious AEs and AEs leading to discontinuation from the study will be presented by system organ class and preferred term.

9.11.4 Overall Summary of Adverse Events

The Overall Summary of Treatment Emergent Adverse Events contains the number and percentage of subjects who:

- have any treatment emergent adverse events
- have any treatment emergent adverse events at least possibly related to the study device
- have any treatment emergent adverse events at least possibly related to the study procedure
- have any treatment emergent adverse events presented by maximum severity
- have any treatment emergent serious adverse events
- have any treatment emergent serious adverse events at least possibly related to the study device
- have any treatment emergent serious adverse events at least possibly related to the study procedure
- have any treatment emergent adverse events leading to discontinuation of the study
- have any treatment emergent adverse events leading to death
- have any treatment emergent adverse events leading to death that are at least possibly related to the study device
- have any treatment emergent adverse events leading to death that are at least possibly related to the study procedure.

9.11.5 Summary of Adverse Events by System Organ Class and Preferred Term

The Summary of Treatment Emergent Adverse Events by System Organ Class and Preferred Term will contain the primary presentation of the adverse event data. This table is prepared without regard to causality or relationship to the study procedure. Subjects will be counted only once at the system organ class level and will be counted once for each applicable preferred term; multiple occurrences of the same preferred term for a subject will be counted only once. System organ classes, and preferred terms within system organ class, will be displayed alphabetically. In addition, an exact 95% confidence interval for the overall adverse event rate will be displayed.

9.11.6 Assessment of Severity

All adverse events, both serious and non-serious, will be assessed for severity or intensity. The intensity of all AEs will be graded as mild, moderate, or severe.

The Summary of Treatment Emergent Adverse Events by System Organ Class and Preferred Term with Respect to Event Severity provides the presentation of adverse events with respect to the severity or intensity of the event. Subjects with multiple occurrences of the same system organ class or preferred term will be summarized at the maximum severity reported for that adverse event. The number and percentage of subjects experiencing AEs for each body system and preferred term will be displayed.

9.11.7 Assessment of Relationship to the Device

The CEC will adjudicate each AE and make the determination of relationship to study device using the definitions in Section 6.1.

The Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Relationship to the Study device provides the presentation of adverse events by relationship to the study device. Subjects with multiple occurrences of the same system organ class or preferred term will be summarized using the event with the strongest relationship to the study device. The number and percentage of subjects experiencing each system organ class and preferred term will be displayed.

9.11.8 Assessment of Relationship to the Procedure

The CEC will adjudicate each AE and make the determination of relationship to study procedure using the definitions in Section 6.1.

The Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Relationship to the Study Procedure provides the presentation of adverse events by relationship to the study procedure. Subjects with multiple occurrences of the same system organ class or preferred term will be summarized using the event with the strongest relationship to the study procedure. The number and percentage of subjects experiencing each system organ class and preferred term will be displayed.

9.11.9 Summary of Adverse Events Leading to Discontinuation

The Summary of Treatment Emergent Adverse Events Leading to Study Discontinuation by System Organ Class and Preferred Term displays all treatment-emergent adverse events resulting in an action taken of 'Discontinued'. Subjects will be counted only once at the system organ class level and will be counted once for each applicable preferred term; multiple occurrences of the same preferred term for a subject will be counted only once. The number and percentage of subjects experiencing each body system and preferred term leading to discontinuation will be displayed.

9.11.10 Summary of Serious Adverse Events

Adverse event incidence rates by system organ class and preferred term will be summarized for subjects who report a serious adverse event. Subjects with multiple SAEs will be counted only once at the system organ class level and will be counted once for each applicable preferred term; multiple occurrences of the same preferred term for a subject will be counted only once. The number and percentage of subjects experiencing each system organ class and preferred term will be displayed. In addition, an exact 95% confidence interval for the overall serious adverse event rate will be displayed.

9.12 Imaging

The presentation of imaging results will focus on the descriptive summaries at pre-procedure and post-procedure, and during the follow-up procedure. All subjects in the ITT population who have a pre-procedure, post-procedure and a follow-up assessment will be included in the presentation of the imaging data.

For each quantitative imaging parameter, the results at each time point and the change from pre-procedure results will be summarized using descriptive statistics: N, mean, standard deviation, median, and range. In addition to the change from pre-procedure results, the shift from baseline to the post-baseline visits will be summarized in tabular form for each parameter. Subjects will be classified at baseline and the post-baseline visit in one of the following categories based on a comparison of the imaging result. A shift table will be constructed in which each subject is cross-classified based upon the reference range categories. The number and percentage of subjects in each shift table cell will be displayed.

10 RISK/BENEFIT

10.1 Potential Benefits

Embolization with the Pipeline™ device can be life-saving, partially or totally curative, and can reduce symptoms. Effectiveness can be measured by angiographic evidence of aneurysm occlusion and the amount of occlusion can be classified by the 3-point Scale of Roy. The greatest Pipeline™ device clinical benefit includes a completely occluded aneurysm which does not re-form and completely eliminates all associated symptoms. Intermediate benefits include stabilizing the aneurysm and providing symptomatic relief. Studies on endovascular treatments options like stent coiling have reported that complete occlusion has been achieved in 46%-75% of small and medium wide-necked aneurysms at one year post procedure,[36,66] so flow diverters such as Pipeline™ device would increase the likelihood that the procedure will provide full benefits to the subjects, without leaving behind coil mass which may cause significant symptoms following treatment.

10.2 Potential Risks

Potential risks associated with Pipeline™ device use, general anesthesia, catheterization and diagnostic imaging for subjects with intracranial aneurysms are outlined below.

Risks associated with placement of the Pipeline™ device:

Possible	• Embolism • Headache • Hematoma • Hemorrhage, intracranial • Hemorrhage, non-intracranial • In-stent stenosis • Pain • Parent artery stenosis • Thromboembolic events • Vision impairment
Infrequent	• Amaurosis fugax (temporary loss of vision in one eye) • Aneurysm rupture • Arrhythmia

	• AV fistula • Blindness • Blood vessel perforation / rupture / occlusion • Carotid cavernous fistula • Cranial neuropathy • Death • Dizziness / tinnitus • Groin injury (including bleeding, bruising, infection, pain) • In-stent occlusion • Infection • Ischemia • Mass effect • Nausea / vomiting • Neurological deficits • Palsy / muscle weakness • Pseudoaneurysm • Ptosis • Stroke, hemorrhagic • Stroke, ischemic • Transient ischemic attack • Thrombosis / occlusion of the parent artery • Vasospasm (acute narrowing of the blood vessel due to irritation from the tubes being placed in the blood vessel)
Rare	• Allergic reaction to medications and/or dye • Coma • Device fracture • Device migration or misplacement. • Hydrocephalus • Seizure

Risks associated with DAPT required for flow diverter treatment:

- Abnormal bleeding
- Abnormal blood clotting
- Adverse reaction to the anesthesia
- Allergic reaction to medications (can range from a mild reaction such as rash or facial flushing to a more severe reaction such as difficulty breathing)
- Abdominal pain, nausea, vomiting and dyspepsia
- Gastritis and gastric ulcer
- Tinnitus
- Syncope
- Death

Risks associated with imaging required for flow diverter treatment:

- Reddening of the skin, blistering and even ulceration
- Developing a radiation-induced cancer later in life
- Renal injury associated with contrast

Risks associated with Clinical Research

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

10.3 Risk Mitigation

Several safeguards are incorporated into the study to minimize subject risk. All preclinical device testing for the implantable braid and the single use delivery system are performed in accordance with regulations and recognized standards. All test results have passed the required specifications supporting reasonable safety for this clinical product.

At each investigational site, the study will be conducted under the direction of a qualified physician experienced with endovascular procedures including intracranial aneurysm repair and will have completed at least 20 cases with the Pipeline™ device. All participating investigators have experience conducting clinical research and 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. Thus, in turn, should allow for early treatment, if necessary. Personally identifying subject information will not be collected on electronic Case Report Forms (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. Safety endpoint related events 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

Existing clinical studies and numerous independent publications with the Pipeline™ device provide clinical data to support the reasonable safety of the device. Therefore, the Sponsor considers the benefits of using the Pipeline™ device to outweigh the risks in the defined subject population.

11 STUDY MONITORING

Covidien, as the Sponsor, will be responsible for ensuring that adequate monitoring at each site is completed to ensure protection of the rights of subjects, the safety of subjects, and the quality and integrity of the data collected and submitted in compliance with applicable regulations. Appropriately qualified and trained personnel appointed by Sponsor will conduct monitoring at each site per the Clinical Monitoring Plan. Monitors for the clinical study will consist of Sponsor Clinical staff and/or

qualified contract services (e.g., CRO) appointed by the Sponsor. The primary contact for the clinical study will be the Clinical Project Leader.

Clinical Affairs Department
9775 Toledo Way
Irvine, CA 92618

Study Monitors will conduct site visits to ensure accuracy of data, timeliness of data submissions, adequate subject enrollment, investigational device accountability, compliance with applicable laws and regulations, compliance with the protocol, compliance with the signed investigator agreement, and compliance with IRB/EC conditions and guidelines. Any non-compliance with these items that is not adequately addressed by the principal investigator/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 will be fully documented either on the source document or in the subject's medical records. All information entered into 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. 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.

Covidien representatives or their agents may be present during the endovascular procedure.

11.1 Direct Access to Source Documents

By participating in this research study, the Investigator agrees to permit monitoring and auditing by the Sponsor and/or its designee(s) and inspection by applicable regulatory authorities. The Investigator also agrees to allow the Sponsors CRAs/monitors/auditors/FDA investigators to have direct access to his/her research-related study records (e.g. medical records, source documentation, and billing information) for review. If an Investigator is notified of a pending investigation by a regulatory agency, IRB/EC, or other similar organization, he/she will inform the Sponsor promptly.

11.2 Monitoring Reports

After each monitoring visit, the monitor will send to the principal investigator an e-mail or letter summarizing the monitoring visit. A monitoring report will be sent to the Sponsor. The report will include the date of the monitoring visit, the site name, the name of the monitor, the name of the investigator, the names of other individuals present for the monitoring visit, items reviewed during the visit, findings, and any required follow-up. The principal investigator will be responsible for ensuring that follow-up action items requiring resolution at the site are completed in an accurate and timely manner.

11.3 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 collect all outstanding study data documents, ensure that the principal investigator'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 principal investigator/site, provide for appropriate disposition of any remaining supplies, and ensure that all applicable requirements are met for the study.

12 ELECTRONIC CASE REPORT FORMS (eCRFs)

Study data will be collected using electronic case report forms and a 21 CFR Part 11-compliant 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 electronic CRFs.

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/EC 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/EC 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/EC 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 Principal Investigator assumes full responsibility for performance of the research study in accordance with the Clinical Study Agreement, this protocol, GCP, all regulatory requirements applicable to the jurisdictions in which the study is being conducted, and any additional requirements imposed by the IRB/EC.

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 AND RECORDS

14.1 Investigator Responsibilities

The Principal Investigator (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.

14.2 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 of 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.

14.3 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.

15 ETHICAL CONDUCT OF THE STUDY

This study is to be conducted in accordance with ethical principles based on the Declaration of Helsinki concerning medical research in humans and applicable regulations.

The Investigator agrees by participating in the conduct of this protocol to adhere to the instructions and procedures described and to adhere to the principals of GCP.

16 INSTITUTIONAL REVIEW BOARDS / ETHICS COMMITTEE

The Sponsor and/or Investigator must submit this protocol to the appropriate IRB/EC, 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/EC 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 has been received by the Sponsor.

Any amendment or modification to the protocol should be sent to the IRB/EC. The IRB/EC 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/EC for approval/favorable opinion.

Although not indicated in the Patient Information Sheet, in certain countries the IRB/EC requires that all subjects included in the study be affiliated with their respective national social security system. It is up to the investigator to find out if the subject has this required affiliation.

17 QUALITY CONTROL AND QUALITY ASSURANCE

17.1 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.

17.2 Site Selection

The Sponsor or representative of the Sponsor will assess each potential site to ensure the principal investigator 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:

- A physician trained and approved by Sponsor staff in the use of the Pipeline™ device with a history of completing at least 20 Pipeline™ device cases.
- Commitment from the participating physician to pursue details of any safety outcomes.
- Commitment from the participating physician to enroll only subjects meeting the study criteria.
- A dedicated study coordinator who can enter data and respond to queries.
- Internet access (for electronic data capture) in the hospital or clinic setting.
- Be willing to adhere to all relevant Core Laboratory requirements.
- Be willing to perform necessary documentation (e.g., eCRF).
- Agree to sign and adhere to the Investigator Agreement
- Agree to participate in Investigator meetings as scheduled by Covidien.

17.3 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/EC requirements; Confidentiality/HIPAA
- Electronic Case Report Forms and completion instructions

- Documentation of protocol deviations
- Adverse Event Reporting
- Device specific events reporting
- *Instructions for Use* of the Pipeline™ device
- Device tracking and accountability
- 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.

17.4 Site Initiation

The Sponsor or a representative of the Sponsor will conduct a training session with site staff to review the protocol, eCRFs, the informed consent process, IRB/EC 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/EC approval for the Investigational Plan
- IRB/EC and Sponsor approved Informed Consent Form for the study
- Signed Confidentiality Agreement (CDA)
- Signed Clinical Study Agreement (CSA) and if applicable, Sub-I Agreement(s)
- Training log documentation to verify the appropriate study staff has been trained on the protocol, eCRFs, and study conduct.
- Financial disclosure(s) for the PI and Sub-I(s)
- Investigator(s') *curriculum vitae* (CV)

17.5 Data Quality Assurance

ORACLE Clinical Remote Data Capture (OC/RDC) is the EDC system that will be deployed 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(i)). Training will be conducted by qualified individuals initially and on a continuing basis, as needed.

17.6 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.

18 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.

19 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/EC members have the same obligation of confidentiality.

20 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 multicenter report. The Sponsor will establish authorship criteria for such publications for the study group, based on the study conduct and compliance, contribution to the study design, 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 ClinicalTrials.gov.

21 DEFINITIONS

TERM	DEFINITION
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 3.2)
Adverse Device Effect (ADE)	An adverse event related to the use of an investigational medical device. (ISO 14155:2011 3.1)
Aneurysm Occlusion	According to the scale of Roy: Complete = Complete occlusion, no flow of contrast seen in the aneurysm sac Residual Neck = Partial occlusion, some flow or eddying flow in the aneurysm sac Residual Aneurysm = Incomplete occlusion, apparent flow in the aneurysm sac
Device Migration	Movement of one or more Pipeline™ devices of more than 5 mm in its parent artery location in comparison to the post-placement angiogram
Device-related Adverse Event	Event has a strong temporal relationship to the study device, and alternative etiology is less likely.
Enrolled Ineligible	Enrolled subject who did not meet study eligibility criteria.
Full Analysis Set Population (FAS)	All enrolled subjects including only those in whom the Pipeline™ device was implanted.

TERM	DEFINITION
NIH Stroke Scale (NIHSS)	Tool to quantify neurological impairment caused by stroke 0 No Stroke Symptoms 1-4 Minor Stroke 5-15 Moderate Stroke 16-20 Moderate to Severe Stroke 21-42 Severe Stroke
Procedure	The primary study procedure involving the placement of the Pipeline™ device at Day 0.
Intention to Treat Population (ITT)	All enrolled subjects in whom deployment of the Pipeline™ device was attempted. It is possible that the Pipeline™ device may not reach the target site and the operator would not attempt to deploy it, in the rare event that happens, that subject will not be considered part of the ITT population.
Medium Intracranial Aneurysm	7-12 mm
Modified Rankin Scale (mRS)	Scale for measuring general neurologic function. 0 No symptoms at all 1 No significant disability despite symptoms; able to carry out all usual duties and activities 2 Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance 3 Moderate disability; requiring some help, but able to walk without assistance 4 Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance 5 Severe disability; bedridden, incontinent and requiring constant nursing care and attention 6 Dead
Neck	Width of the opening of the aneurysm where it meets the parent vessel.
Neurological Adverse Event	An adverse event with an underlying neurological cause.
Neurological Death	Subject death due to neurologic reasons.
Per protocol (PP) population	All enrolled subjects, had the Pipeline™ device successfully implanted, and completed the study without any major protocol deviations.
Point of Enrollment	Point at which the subject signs the study Informed Consent Document.
Procedure-related Adverse Event	Event has a strong temporal relationship to the procedure (Day 0).
Procedure time	Start: Time of first Pipeline™ device introduction (i.e., once the Pipeline™ device is advanced into the microcatheter inside the blood stream of the subject.) End: Time of last Pipeline™ device delivery system removal
Retreatment	Any subsequent intervention (post procedure) performed to treat the target IA.
Screen Failure	Screened patient not enrolled in the study.
Serious Adverse Event (SAE)	An 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-subject or prolonged hospitalization, or d. Medical or surgical intervention to prevent 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 3.37)
Serious Adverse Device Effect (SADE)	An adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. (ISO 14155:2011 3.36)
Small Intracranial Aneurysm	< 7 mm

TERM	DEFINITION
Stroke	A focal neurological deficit of presumed vascular origin persisting more than 24 hours from symptom onset AND a neuro-imaging study or other quantitative study that does not indicate a different etiology. The 24-hour criterion is excluded if the subject undergoes cerebrovascular surgery or dies during the first 24 hours of symptom onset. The definition includes subjects presenting with clinical signs and symptoms suggestive of subarachnoid hemorrhage, intracerebral hemorrhage, or cerebral infarction. The definition also includes sudden loss or worsening of visual acuity due to retinal artery occlusion or retinal emboli. The definition excludes slowly progressive cranial nerve palsies or progressive visual field deficits due to continued aneurysm growth. The definition also excludes stroke events in cases of blood disorders such as leukemia or external events such as trauma. Stroke severity will be graded by the Investigator as major or minor: Major Stroke: A stroke, which is present after seven days and increases the NIHSS of the subject by ≥ 4. Minor Stroke: A stroke, which resolves completely within seven days OR increases the NIHSS of the subject by ≤ 3.
Unanticipated Adverse Device Effect (UADE)	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 (s))
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 3.42)
Wide-necked Intracranial Aneurysm	Aneurysm neck measuring ≥ 4mm or a dome to neck ratio ≤ 1.5

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