SAfety and Effectiveness of the Treatment of Wide Neck, Saccular IntracraniaL Aneurysms with the Neuroform Atlas™ Stent System

Short Study Name: ATLAS

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Date/Version:	19 November, 2019 / CDM 10000880 VerAF
Revision History	Initial FDA Submission: Ver03; Date: 06 Jan, 2015 Revised FDA Submission: Ver04; Date: 04 Feb, 2015 Release of Alpha Version: VerAA; Date: 19 Mar, 2015 Internal Release of Version AB: VerAB; Date: 18 Jan, 2016 (VerAB was not released externally to sites) Release of Version AC: VerAC; Date: 02 Feb, 2016 Release of Version AD: VerAD; Date: 24 Jun, 2016 Release of Version AE: VerAE; Date: 15 Aug, 2019 (VerAE was not released externally to sites)

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Investigator's Signature Page

STUDY TITLE: Safety and Effectiveness of the Treatment of Wide Neck, Saccular Intracranial Aneurysms with the Neuroform Atlas™ Stent System

Short Study Name: **ATLAS**

STUDY CENTER: _____

(Print name of study center)

We, the undersigned, have read and understand the protocol specified above and agree on its content. We agree to perform and conduct the study as described in the protocol. In addition, when applicable, we agree to enlist sub-investigators who also agree to perform and conduct the study as described in the protocol.

_____ _____

Principal Investigator Date

Print name:

_____ _____

Co-Principal Investigator (if applicable) Date

Print name:

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SAfety and Effectiveness of the Treatment of Wide Neck, Saccular IntracraniaL Aneurysms with the Neuroform Atlas™ Stent System

Short Study Name: ATLAS

Protocol Synopsis

Study Title:	SAfety and Effectiveness of the Treatment of Wide Neck, IntracraniaL, Saccular Aneurysms with the Neuroform Atlas™ Stent System Short Study Name: ATLAS
Design:	This study is designed as a prospective, multicenter, open-label, single-arm 2-cohort (anterior and posterior circulation) study. Eligible subjects presenting with a wide neck (neck ≥4mm or a dome-to-neck ratio <2), intracranial, saccular aneurysm arising from a parent vessel with a diameter of ≥2mm and ≤4.5 mm will receive stent-assisted coiling with the Neuroform Atlas™ Stent System and any approved bare metal embolic coils currently on the market. Data collected through the 12-month follow-up visit are intended to support Premarket Approval (PMA) application to the Food and Drug Administration (FDA). Long-term follow-up data collected through 3 years postoperative are intended to support post-approval study (PAS) requirements.
Device Name and Intended Use:	For purposes of this study, "investigational device" or "test device" refers to Stryker Neurovascular's Neuroform Atlas™ Stent System. Intended Use: The Neuroform Atlas™ Stent System is intended for use with bare metal embolic coils for the treatment of wide neck, intracranial, saccular aneurysms arising from a parent vessel with a diameter ≥ 2 mm and ≤ 4.5 mm. Wide-neck aneurysms are defined as those having a neck ≥ 4 mm or a dome-to-neck ratio of < 2.
Device Regulatory Status	The Neuroform Atlas Stent System was FDA-approved for use in the anterior circulation on May 16, 2019, with the following indication: *The Neuroform Atlas Stent System is indicated for use with neurovascular embolization coils in the anterior circulation of the neurovasculature for the endovascular treatment of patients ≥ 18 years of age with saccular wide-necked (neck width ≥ 4 mm or a dome-to-neck ratio of < 2) intracranial aneurysms arising from a parent vessel with a diameter of ≥ 2.0 mm and ≤ 4.5 mm.* Use of the Neuroform Atlas Stent System for use in the posterior circulation is investigational in the United States and subject to all Investigational Device Exemption (IDE) regulations imposed by FDA as of the release date of the ATLAS study protocol Revision AF.

SAfety and Effectiveness of the Treatment of Wide Neck, Saccular IntracraniaL Aneurysms with the Neuroform Atlas™ Stent System

Short Study Name: ATLAS

Device Description:	The Neuroform Atlas™ Stent System includes: • A self-expanding, open-cell, nitinol stent with three radiopaque marker bands on each end (proximal and distal) and 4 interconnects between the central stent segments, designed to provide support of the coil mass within an aneurysm and to minimize stent deflection. • A stent delivery wire. The stent is pre-loaded on the stent delivery wire and is protected by an introducer sheath. • An accessory pouch containing an optional torque device. The physician may attach the torque device to the proximal end of the stent delivery wire in order to facilitate handling and stabilization. The stent delivery wire is not designed to be torqued. The Neuroform Atlas Stent is available in 3 diameters (3.0 mm, 4.0 mm, and 4.5 mm), 4 lengths (15, 21, 24, and 30 mm), and 2 tip configurations (with an 8.5 mm distal tip, and without a distal tip).
Primary Endpoints:	The primary effectiveness endpoint of the study is: Complete aneurysm occlusion (100% occlusion – Raymond Class 1) of the treated target lesion on 12 month angiography, in the absence of retreatment, or parent artery stenosis (> 50%) at the target location. The primary safety endpoint of the study is: Any major ipsilateral stroke or neurological death within 12 months.
Secondary Endpoints:	The secondary safety endpoint is the percent of subjects experiencing one or more serious adverse events (SAEs) through 12 months post-index procedure within the following categories: • New or worsening major ipsilateral stroke as measured by the National Institute of Health Stroke Scale (NIHSS) • Device-related SAEs • Subarachnoid hemorrhage (SAH) • Aneurysm rupture The secondary effectiveness endpoints identified below will be assessed post-index procedure through 12 months per the schedule requirements: • Procedural technical success • Incidence of retreatment • Incidence of recanalization • Incidence of parent artery stenosis at the target aneurysm location (>50% stenosis) • Incidence of stent migration based on follow-up angiogram • Proportion of aneurysms with occlusion of Raymond Class 1, 2, or 3 • Proportion of aneurysms with occlusion of Raymond Class 1 and 2 combined • Incidence of progressive occlusion at the target aneurysm location

Long-term Follow-up	The pre-specified safety endpoint is neurological death or major ipsilateral stroke at 12 months as adjudicated by the Clinical Events Committee (CEC). Long-term data on this pre-specified safety endpoint will continue to be collected. For the duration of the PAS study, all new or ongoing adverse events will be collected, reported, reviewed, and adjudicated per the CEC charter. Long-term safety events of interest will be grouped into the following combined categories for FDA reporting purposes: • Any ischemic or hemorrhagic adverse event of any severity or duration (including transient ischemic attacks [TIAs], subarachnoid hemorrhage [SAH], and aneurysm rupture) • Device-related SAEs For imaging performed per standard of care, the long-term effectiveness outcomes identified below will be assessed from 12 months through 3 years (± 6 months) post-index procedure per the long-term follow-up schedule requirements: • Retreatment • Parent artery stenosis at the target aneurysm location (>50% stenosis) • Composite effectiveness measure (complete aneurysm occlusion [Raymond Class 1] without significant parent artery stenosis at the target aneurysm location (>50% stenosis) or retreatment) • Recanalization • Stent migration based on follow-up angiogram • Aneurysm occlusion of Raymond Class 1, 2, or 3 • Aneurysm occlusion of Raymond Class 1 and 2 combined • Progressive occlusion of the target aneurysm
Planned Number of Subjects:	Up to a total of 360 subjects may be enrolled as follows: <u>Anterior Circulation Cohort:</u> A sample size of up to 180 subjects with intracranial aneurysms in the anterior circulation (excluding the petrous Internal Carotid Artery (ICA) to superior hypophyseal ICA region) has been selected for this study in order to provide 153 evaluable subjects at 12 months, with an estimated 15% attrition rate. Assuming an effectiveness primary endpoint response rate of 62%, the expected lower bound of the exact binomial two-sided 95% confidence interval around the success rate is greater than 50%. Assuming a safety primary endpoint rate of 8%, the expected upper bound of the exact binomial two-sided 95% confidence interval around the success rate is less than 20%. A sample size of 153 evaluable subjects provides 85% power to demonstrate the effectiveness endpoint, and a power of approximately 99% to successfully demonstrate the safety endpoint given the observed rates stated above. The combined probability of the two endpoints is (.85) x (.99) = .842. <u>Posterior Circulation Cohort:</u> A sample size of up to 180 subjects with intracranial aneurysms in the posterior circulation (including vertebral, basilar and posterior cerebral arteries) may be enrolled in order to provide 153 evaluable subjects at 12 months, with an estimated 15% attrition rate. Assuming an effectiveness primary endpoint response rate of 62%, the expected lower bound of the exact binomial two-sided 95% confidence interval around the success

	rate is greater than 50%. Assuming a safety primary endpoint rate in the posterior circulation of 12%, the expected upper bound of the exact binomial two-sided 95% confidence interval around the success rate is less than 25%. A sample size of 153 evaluable subjects provides 85% power to demonstrate the effectiveness endpoint, and a power of approximately 99% to successfully demonstrate the safety endpoint given the observed rates stated above. The combined probability of the two endpoints is (.85) x (.99) = .842. For the posterior circulation cohort, a Bayesian adaptive study design ("Goldilocks" approach[1]) providing for interim analyses of accumulated data will be used to select the final sample-size. The first interim data analysis will occur once 100 posterior circulation subjects have been enrolled. Based on enrollment rates and the frequency of disease in the posterior circulation, at the time this interim analysis is performed it is estimated that primary endpoint data will be available for approximately 39 – 63 posterior circulation subjects. If, at an interim analysis, there is at least a 95% predictive probability of observing a true rate of complete occlusion that is higher than 50%, enrollment in the posterior circulation cohort will be stopped early for success. The maximum sample-size for the posterior circulation cohort will be no more than 180 subjects.
Planned Number of Sites:	Up to 40 sites will participate in the clinical study.
Randomization:	This study is a non-randomized, open label, single-arm study.
Follow-Up Schedule:	All subjects enrolled in the study will be followed clinically through hospital discharge, at 2 months, 6 months, and 12 months post-procedure to collect primary study endpoint data. The following assessments and procedures will be performed through the 12-month follow-up visits: Discharge: • Subjects will be evaluated using neurologic rating/grading scales (mRS for all subjects; Hunt and Hess for subjects who previously had a ruptured aneurysm and evidence of subarachnoid hemorrhage). Any adverse events will be recorded. Clinical follow-up at 2 months and 6 months: • Subjects will have a neurological assessment (mRS). Antiplatelet regimen compliance and adverse events will be recorded. Clinical follow-up at 12 months: • Subjects will have a neurological examination and will be evaluated using neurological rating/grading scales (NIHSS, mRS; and, Hunt and Hess, as appropriate). Quality of Life assessment, compliance with antiplatelet regimen, and adverse events will be recorded.

[1] Kristine R. Broglio, Jason T. Connor & Scott M. Berry (2014) Not Too Big, Not Too Small: A Goldilocks Approach To Sample Size Selection, Journal of Biopharmaceutical Statistics, 24:3, 685-705, DOI: 10.1080/10543406.2014.888569

	Angiographic follow-up: • Digital Subtraction Angiography (DSA) will be performed at 12 months to determine the rate of complete aneurysm occlusion. For long-term follow-up, subjects will be followed through 3 years (± 6 months) post-procedure with neurological exams and safety assessments. If both the 2-year and the 3-year visit windows have elapsed at the initiation of the PAS, subjects will be asked to return for at least 1 follow-up visit. Imaging assessment of intracranial aneurysm occlusion and parent artery stenosis will be performed if imaging assessments are conducted per institutional standard of care.
Key Inclusion Criteria:	Eligible subjects must meet ALL of the following inclusion criteria: • Subject is between 18 and 80 years of age • Documented wide neck (neck ≥ 4 mm or a dome-to-neck ratio of < 2), intracranial, saccular aneurysm arising from a parent vessel with a diameter of ≥ 2mm and ≤ 4.5 mm, which will be treated with bare metal coils • Subject or legal representative is willing and able to provide informed consent • Subject is willing and able to comply with protocol follow-up requirements
Key Exclusion Criteria:	Subjects will be excluded from this study if they do not meet the specific inclusion criteria, or if any of the following exclusion criteria are present: • Known multiple untreated cerebral aneurysms, other than non-target blister aneurysm, infundibulum, or aneurysm measuring <3mm for each of three dimensions assessed (height, width, and depth) that will not require treatment during the study period • Target lesion is a blister aneurysm, infundibulum, or aneurysm measuring <3mm for each of three dimensions assessed (height, width, and depth) • Target aneurysm that will require an Investigator to intentionally leave a neck remnant in order to preserve blood flow in a bifurcation or branch • Coiling or stenting of a non-target intracranial aneurysm within 30 days prior to study treatment • Target aneurysm is in the anterior circulation proximal to the superior hypophyseal ICA • Acute target aneurysm rupture less than 14 days prior to study treatment • Hunt and Hess score ≥ 3 or a premorbid mRS score ≥4 • An admission platelet count of <50,000, any known coagulopathy, or an International Normalized Ratio (INR)>3.0 without oral anticoagulation therapy • A known absolute contraindication to angiography • Evidence of active cancer, terminal illness or any condition which, in the opinion of the treating physician, would/could prevent subject from completing the study (e.g., a high risk of embolic stroke, atrial fibrillation, co-morbidities, psychiatric disorders, substance abuse, major surgery ≤ 30 days pre-procedure, etc.) • Known absolute contraindication to the use of required study medications or agents (e.g., heparin, aspirin, clopidogrel, and radiographic contrast agents, etc.) • Female subject who is pregnant or intends to become pregnant during the study • Moya-Moya disease, arteriovenous malformation(s), arteriovenous fistula(e), intracranial tumor(s), or intracranial hematoma(s) (unrelated to target aneurysm)

	• Significant atherosclerotic stenosis, significant vessel tortuosity, vasospasm refractory to medication, unfavorable aneurysm morphology or vessel anatomy, or some other condition(s) that, in the opinion of the treating physician, would/could prevent or interfere with access to the target aneurysm and/or successful deployment of the Neuroform Atlas™ Stent • Previous treatment (e.g., surgery, stenting) in the parent artery that, in the opinion of the treating physician, would/could prevent or interfere with successful use of the Neuroform Atlas™ Stent System and/or successful adjunctive deployment of embolic coils • Previous stent-assisted coiling of the target aneurysm
Trial Success/Failure Criteria:	• For both the anterior and posterior circulation cohorts, the lower limit of the 95% confidence interval of the proportion of subjects who achieve the primary effectiveness endpoint (i.e., complete aneurysm occlusion, in the absence of retreatment, or > 50% parent artery stenosis at the target location, based on angiographic assessment at 12 months) is >50%. • For the anterior circulation cohort, the upper limit of the 95% confidence interval of the proportion of subjects who experience the primary safety endpoint (i.e., any major ipsilateral stroke or neurological death within 12 months) is <20%. • For the posterior circulation cohort, the upper limit of the 95% confidence interval of the proportion of subjects who experience the primary safety endpoint (i.e., any major ipsilateral stroke or neurological death within 12 months) is <25%.

1 Study Purpose

1.1 Introduction and Background

An aneurysm is a balloon-like enlargement of an artery resulting from a weakening of the vessel wall. Aneurysms may occur in any artery in the body. Intracranial aneurysms are a significant health problem in the United States with an estimated 0.4% to 6% of the adult population harboring cerebral aneurysms.[1-3]

Left untreated, aneurysms may continue to grow until they rupture. The annual risk of rupture of an intact intracranial aneurysm is estimated to be approximately 1.9%.[2] Aneurysms documented to be enlarging on serial neuroimaging studies have an estimated annual rupture risk of 2.4%.[4] The International Study of Unruptured Intracranial Aneurysms (ISUIA) evaluated the natural history of 1,937 unruptured aneurysms in 1,449 subjects with a mean follow-up of 8.3 years.[5] The study showed that 2.2% of these subjects had a confirmed rupture during follow-up, and 66% of these ruptures were fatal.

If an intracranial aneurysm ruptures, blood leaks into the highly sensitive subarachnoid space around the brain, resulting in a subarachnoid hemorrhage (SAH). SAH causes cerebral vasospasm (constriction of brain arteries due to noxious blood in the subarachnoid space), which in turn causes ischemic stroke in up to 15-20% of subjects.[6, 7] Aneurysmal SAH is associated with a high rate of mortality, and close to half of these ruptures result in death within six months.[2, 5, 8] Subjects who survive an initial SAH are at significant risk of subsequent re-rupture. Various reports indicate that if left untreated, there is a re-bleeding rate of more than 50% within the first six months from initial presentation of a SAH.[9, 10]

Even if an intracranial aneurysm does not rupture, it can lead to severe complications. As the aneurysm grows, it can press on nerves, put pressure on brain tissue, or interfere with other arteries or veins. Blindness, paralysis, hydrocephalus and other morbidities can result. In addition, as thrombus forms in the aneurysmal sac, a piece of thrombus can break free, travel downstream, and cause a thromboembolic ischemic stroke.

Current Treatment Options

Surgical Clipping

Prior to 1995, the traditional treatment for intracranial aneurysms was surgical clipping. In performing surgical clipping, the skull is surgically opened, and metal clips are applied across the aneurysm's neck so as to occlude it from the parent artery and prevent a rupture. Surgical clipping is generally regarded as being highly effective with durable long-term results, but it is associated with higher morbidity and mortality rates when compared with endovascular repair of aneurysms that are amenable to either form of treatment. In addition, this form of treatment is more invasive, requires longer hospital convalescence, and is technically difficult to perform in certain parts of the brain (such as the posterior circulation).[11, 12] Further, wide neck aneurysms may be difficult if not impossible to treat using surgical clipping, as often there is no true neck present, or the neck is too wide to successfully clamp it with a surgical clip.

Thus, this treatment modality is not a viable option for a significant number of subjects, particularly during the acute phase of SAH, when the presence of cerebral edema and evolving thrombus formation makes access to a ruptured aneurysm difficult, if not impossible. In fact, in current treatment guidelines for ruptured aneurysmal SAH, the American Heart Association (AHA) and the American Stroke Association (ASA) jointly recommend that surgical clipping should only be considered in subjects with large intraparenchymal hematomas and middle cerebral artery aneurysms; otherwise, endovascular coiling should be first considered when ruptured aneurysms are judged to be technically amenable to either coiling or clipping.[13] For unruptured aneurysms, surgical clipping is recommended as a treatment choice only in low-risk cases, such as young subjects with small, anterior circulation aneurysms.[14]

Embolic Coils

In the early 1990's, endovascular treatment of intracranial aneurysms was significantly advanced by Guido Guglielmi, who used electrolytically detached platinum coils to pack and embolize the aneurysm sac.[15] The rationale was to exclude the aneurysm from the circulation and thus reduce the risk of rupture and SAH. Several well-conducted, prospective, randomized, controlled trials of both ruptured and unruptured aneurysms demonstrated that angiographic and clinical outcomes from this treatment modality were equivalent to if not better than those obtained from surgical clipping.[5, 16-19] As a result, embolic coiling has become the standard of care worldwide for endovascular occlusion of both unruptured and ruptured intracranial aneurysms.

Despite early successes, embolic coils nonetheless have their limitations because they cannot be used to treat all aneurysms with different morphologies. In particular, aneurysms with a wide neck are not ideal candidates for embolic coil treatment, and neither are large or giant aneurysms, as most large and giant aneurysms tend to have a wide neck.[20, 21] A wide neck can allow coils near the base of the aneurysm to prolapse into the parent artery, potentially causing thrombus formation in the parent artery and distal ischemic strokes. A wide neck thus may prevent complete packing of the aneurysm with coils, resulting in a relatively high rate of aneurysm recanalization, and often requiring subsequent re-treatment of the lesion. Guglielmi et al were the first to report achieving complete occlusion in only 15.4% of aneurysms with a wide neck as compared to 81.0% of those with a small neck.[22] This observation was later confirmed in other studies.[21, 23-25] Complete occlusion of 289 wide neck intracranial aneurysms has been reported at rates between 7.1% - 50.0% at mean angiographic follow-up times ranging from of 3- 30 months.[20-22, 26-31] Achieving complete occlusion is important since intracranial aneurysm rerupture, an infrequent but important complication of treatment of ruptured aneurysms, has been reported to be strongly associated with residual filling of the treated intracranial aneurysm.[32] Similarly, complete occlusion following endovascular treatment of unruptured aneurysms is associated with a lower likelihood of aneurysm recanalization.[33]

Adjunctive Techniques

The often unsatisfactory results associated with embolic coiling of wide neck aneurysms has led to exploration of other treatment options. These treatment options include the use of coils with complex shapes and 3-dimensional structures to better fit the aneurysm shape, the use of ultra-soft coils to more densely pack the aneurysm[34], the use of liquid polymer techniques to enhance aneurysm occlusion[35], and the use of balloon remodeling to stabilize coil conformation within the aneurysm during coil embolization.[36-42] In an extensive study of these adjunctive techniques, Murayama et al reached the conclusion that in spite of their introduction, recanalization remained problematic (particularly in large and giant aneurysms), and as a result, the development of new adjunctive therapies was necessary.[24]

Stent Assisted Coiling

During stent assisted coiling, a stent is deployed across the neck of the aneurysm in order to provide protection of the parent vessel, and to stabilize the aneurysm while allowing for insertion of embolic coils through the stent interstices into the aneurysmal sac. The stent prevents coils from herniating into the parent vessel, and allows for a higher packing density of embolic coils in the aneurysmal sac, with the latter being associated with a reduction in aneurysm recanalization, rupture, and re-rupture rates.[26, 43] Technological advances in stents have allowed for the endovascular treatment of aneurysms that in the past would have resulted in a poor outcome, or would have not been possible due to morphological characteristics of the aneurysm.[26, 44, 45] In comparison to balloon-assisted coiling, stent-assisted coiling of wide neck aneurysms may yield lower rates of retreatment and higher rates of aneurysm obliteration and progression of occlusion at follow-up, with a similar morbidity rate.[38]

Stryker Neurovascular's Neuroform Microdelivery Stent System was initially approved for humanitarian use by the FDA via a Humanitarian Device Exemption (HDE) on September 11, 2002, and subsequent product changes (Neuroform EZ and EZ3) were approved via HDE supplements. The next-generation Neuroform Atlas Stent System was initially approved under an HDE supplement in November 2017, and

subsequently received approval via Premarket Approval (PMA) application for use with embolic coils in the treatment of wide-neck saccular intracranial aneurysms in the anterior circulation (P180031; May 2019).

Since the original approval, stent assisted coiling using the Neuroform Stent System has been the subject of numerous scientific articles.[26, 44, 46-58] In a meta-analysis of the published literature on the Neuroform Stent System, King et al[59] reported that complete occlusion rates on final follow-up averaged 61.1% overall in 2,111 aneurysms treated during a 10 year period (2004 to 2014). In the treatment of wide neck aneurysms, this represents a substantial improvement in outcomes compared to embolic coiling alone.

Since the Neuroform Microdelivery System market introduction in the US, there have been a number of SAC devices approved by FDA via HDE such as the Codman Enterprise Vascular Reconstruction Device, MicroVention's LVIS device, Pulsar Vascular's PulseRider Aneurysm Neck Reconstruction Device, and Stryker Neurovascular's Neuroform Atlas Stent System. In May 2018, MicroVention's LVIS and LVIS Jr. coil assist stents received PMA approval (P170013). In May 2019, Stryker Neurovascular's Neuroform Atlas Stent System received PMA approval for use in the anterior circulation.

Flow Diverters

Flow diverters are typically used in situations where established techniques such as coiling and stent-assisted coiling are not viable options.[60] At present, the Pipeline Embolization Device (PED) and Surpass Streamline™ Flow Diverter are the only FDA-approved flow diverters available in the United States, and approved use of these products is limited to the treatment of wide neck aneurysms in the internal carotid artery (ICA) up to the terminus. A study conducted by Lanzino et al showed that flow diverters (specifically PED) performed better than the control group (coils).[61]

According to Brinjikji et al[62] subjects with posterior circulation aneurysms who are treated with flow diverters are at higher risk of ischemic stroke, particularly perforator infarction, and subjects with larger aneurysms are at increased risk of ischemic stroke and SAH. These findings should be considered when determining the best therapeutic option for intracranial aneurysms.

1.2 Rationale for Study Design and Study Population

This will be a prospective, multi-center, single arm, open label interventional study of wide neck, intracranial, saccular aneurysms in which subjects will undergo stent-assisted coiling using the Neuroform Atlas™ Stent System. Subjects invited to participate in this study will be those who have an aneurysm arising from a parent vessel with a diameter of 2.0 - 4.5 mm in either the distal anterior or posterior intracranial circulation that is accessible for endovascular treatment.

A major shift in intracranial aneurysm treatment has occurred over the past 30 years, from exclusively surgical to primarily endovascular strategies, and aneurysm morphologies once considered untreatable endovascularly are now routinely treated with coiling with or without the adjunctive use of stents.[26] Particularly for wide neck saccular aneurysms, stent-assisted coiling has become a common technique used worldwide. However, in the United States, neurovascular stents are currently FDA-approved for this indication as humanitarian use devices only. This study is being conducted to gather sufficient data for a premarket approval application (PMA) submission to the FDA to support a safety and effectiveness determination and marketing approval of the Neuroform Atlas™ Stent System.

As previously described in **Section 1.1**, wide neck aneurysms have been reported to have complete occlusion rates as low as 15.4% when treated with coils alone.[22] Due to the poor effectiveness rates associated with coiling alone, wide neck aneurysms are not routinely treated by this method. Surgical clipping of wide neck aneurysms in locations accessible for endovascular treatment occurs infrequently, and is no longer the treatment of choice due to the higher morbidity and mortality rates associated with surgery.[16] As such, there are no suitable alternative treatments that could form a reasonable concurrent control group. Therefore, a prospective, single arm interventional study design was selected.

Evaluation of effectiveness results will be undertaken by comparing 12 month complete occlusion rates to performance goals derived from a random effect meta-analysis of published data from subject cohorts with similar aneurysms who underwent coil embolization, balloon-assisted coil embolization, or stent assisted coiling, and had follow-up angiography. The outcome of this random effect meta-analysis was a weighted average rate of total occlusion of 48.8%. This outcome was found to be similar to the outcome of a second separate random effect meta-analysis that was performed using published data for aneurysms treated using coil embolization or balloon-assisted coil embolization in combination with patient-level data from a subset of subjects (N = 197) from the Matrix and Platinum Science (MAPS) Trial. The MAPS Trial was a multinational, multicenter, randomized controlled trial conducted at 43 investigational sites and into which 626 patients with either ruptured or unruptured intracranial aneurysms at any location (ranging in size from 4-20 mm) were enrolled and treated using embolic coils.[63] Key screening criteria, similar to the key study entry criteria developed for the ATLAS trial, were applied to identify the MAPS patient cohort used for this second meta-analysis. This second meta-analysis yielded a weighted average rate of total occlusion of 46.7%. (Note: In a previously conducted comprehensive literature search, Stryker Neurovascular found that there are no published data available on similar subject cohorts who underwent surgical clipping and had follow-up angiography results to which suitable comparisons could be made. As a result, surgical clipping cohorts were excluded from these two meta-analyses.)

The success criteria for effectiveness chosen for this study [i.e., for both the anterior and posterior circulation cohorts, the lower limit of the 95% confidence interval of the proportion of subjects who achieve the primary effectiveness endpoint (i.e., complete aneurysm occlusion, in the absence of retreatment, or > 50% parent artery stenosis at the target location, based on angiographic assessment at 12 months) is >50%] are based upon review and synthesis of data from these sources (see **Section 4.5.1 Justification for Effectiveness Criteria** for additional details).

Evaluation of safety results will be undertaken by comparing rates of major ipsilateral stroke and neurological death in the ATLAS study population to performance goals derived from 1) stroke and neurological death rates in the previously mentioned MAPS wide neck aneurysm patient cohort, and 2) literature-based rates of procedural and long-term morbidity and mortality during embolic coiling, balloon-assisted embolic coiling, or stent assisted coiling.

The success criteria for safety chosen for this study (i.e., upper limit of the 95% confidence interval of the proportion of subjects who achieve the primary safety endpoint is <20% in the anterior circulation cohort and <25% in the posterior circulation cohort) are based upon review and synthesis of data from these sources (see **Section 4.5.2 Justification for Safety Criteria** for additional details).

The anatomic criteria for the intracranial aneurysms targeted for inclusion in this study are based on the results of numerous studies conducted on prior generation Neuroform Stents that are FDA-approved for humanitarian use. The similarities and differences between the Neuroform Atlas™ Stent System and Neuroform Stents (Neuroform and Neuroform EZ) are summarized in **Section 8**. Changes in the design of the Neuroform Atlas™ Stent System have allowed for a stent with a thinner, lower profile and higher flexibility. This may provide increased navigability and improved outcomes in the treatment of more challenging aneurysms.

While the Neuroform Atlas™ Stent is the next generation Neuroform Stent and may have advantages over Neuroform and Neuroform EZ, all three stents were designed for the same clinical application; for use with embolic coils for the treatment of wide neck intracranial aneurysms. Additionally, the Neuroform Atlas™ Stent System is intended for use in target intracranial aneurysms that could also be considered for surgical clipping based on anatomic location, and this is consistent with current clinical practice worldwide wherein this subpopulation is routinely treated with stent-assisted coiling as the preferred treatment of choice.

1.3 Name of Device

For purposes of this study, “investigational device” or “test device” refers to Stryker Neurovascular’s (SNV) Neuroform Atlas™ Stent System.

1.4 Intended Use of the Device

The Neuroform Atlas™ Stent System is intended for use with bare metal embolic coils for the treatment of wide neck, intracranial, saccular aneurysms arising from a parent vessel with a diameter of ≥ 2 mm and ≤ 4.5 mm. Wide neck aneurysms are defined as having a neck ≥ 4 mm or a dome-to-neck ratio of < 2.

1.5 Brief Description of the Device

The Neuroform Atlas™ Stent System is comprised of a stent and delivery system and is designed for use as an adjunct to embolic coils in the treatment of wide neck, intracranial, saccular aneurysms. The Neuroform Atlas™ Stent System is comprised of three components: an implant, an introducer sheath, and a delivery wire assembly. The implant component is made of biocompatible nitinol tubular material. Three radiopaque markers are attached to the distal and proximal ends of the implant. The introducer sheath component has a clear thin-walled polymer shaft with a distal tapered tip designed to fit inside the hub of the delivery catheter. The implant is pre-loaded on the stent delivery wire and protected by a transfer sheath. (A detailed description of the device is provided in **Section 8.1**.)

1.6 Study Purpose and Objectives

The purpose of this investigational study is to evaluate safety and effectiveness of the Neuroform Atlas™ Stent System for use with bare metal embolic coils for the treatment of wide neck, intracranial, saccular aneurysms arising from a parent vessel with a diameter of ≥ 2 mm and ≤ 4.5 mm.

The primary study objectives are as follows:

- To evaluate effectiveness of the Neuroform Atlas™ Stent System as an adjunct to embolic coiling for the endovascular treatment of wide neck, intracranial saccular aneurysms by comparing complete aneurysmal occlusion rates achieved with stent-assisted coiling to performance goals established based on historical control data for occlusion rates achieved with coiling, balloon-assisted coiling, or stent assisted coiling. In the study population, complete aneurysm occlusion will be defined as 100% occlusion (Raymond Class 1) of the target aneurysm, in the absence of retreatment, or parent artery stenosis (>50%) at the target location, as measured with 12 month angiography evaluated by an independent Imaging Core Laboratory (Core Lab). Results from a meta-analysis of data from the published literature will serve as a basis for the established effectiveness performance goals.
- To evaluate safety of the Neuroform Atlas™ Stent System as measured by the rate of major ipsilateral stroke or neurological death within 12 months. Safety data from a MAPS wide-neck aneurysm patient cohort and published rates of procedural and long-term morbidity and mortality for embolic coiling, balloon assisted embolic coiling, or stent assisted coiling will serve as a basis for the established safety performance goals.

1.7 Duration of the Study

It is anticipated that the enrollment of a maximum of 360 subjects in this pivotal trial will take approximately 40 months at up to 40 centers. Evaluation of the primary safety and effectiveness endpoints will be completed on all subjects at 12 months. The time required to complete enrollment of up to 360 subjects and 12 month follow up for all study subjects is anticipated to take approximately 52 months.

Evaluation of long-term safety will continue through 3-year (± 6 months) follow-up. Inclusive of long-term follow-up it is anticipated the entire duration of the study, from the date the first subject enrolled into the IDE study through the date the last subject completed a 3-year PAS follow-up visit, will be approximately 6 years (the PAS phase of the study is anticipated to last 24 months). To allow adequate monitoring of PAS progress, PAS study milestones are summarized in **Table 1**.

Table 1 – Post-Approval Study Milestones

Study Milestone	Timeframe	Due Date
FDA Protocol Approval	60 calendar days after revised PAS protocol submission to FDA	January 31, 2020
IRB Enrollment Initiation	First IRB approval for PAS protocol	February 29, 2020
Patient Enrollment Initiation	First subject long-term follow-up after IRB approval of PAS protocol at first site	March 31, 2020
IRB Enrollment Completion	Last IRB approval of the PAS protocol	September 30, 2020
Patient Enrollment Completion	Last subject 3-year long-term follow-up in-person visit	June 30, 2021
Complete Follow-up of All Study Participants	Subjects complete 3-year assessment	August 31, 2021
Final Report	Within 3 months after study completion	October 31, 2021

2 Investigational Protocol

2.1 Study Design Overview

The purpose of this study is to evaluate safety and effectiveness of the Neuroform Atlas™ Stent System in the endovascular treatment of wide neck, intracranial, saccular aneurysms.

This is a prospective, multicenter, single arm, open-label interventional study. Subjects presenting with wide neck, intracranial, saccular aneurysms arising from a parent vessel with a diameter of 2.0 - 4.5 mm in either the distal anterior or posterior circulation will undergo stent assisted coiling using the Neuroform Atlas™ Stent System in conjunction with any approved bare metal embolic coils currently on the market. Wide neck aneurysms are defined by a neck ≥4mm or a dome-to-neck ratio of<2. Each subject will be followed and assessed for the primary study endpoints at 2, 6, and 12 months after treatment.

Long-term follow-up will continue through 3 years (± 6 months) post-procedure. Sites will schedule at least one long-term follow-up visit for each subject, including those who are beyond the 3-year visit window.

2.2 Study Scope and Participating Institutions

2.2.1 Participating Institutions and Planned Number of Sites

This pivotal trial will include a maximum of 40 clinical sites. A list of participating institutions will be updated every 6 months and provided to regulatory authorities as required.

2.2.2 Subject Population

Detailed subject enrollment criteria are provided in **Section 2.6, Study Population and Source of Subjects**. Up to a total of 360 subjects with wide neck, intracranial, saccular aneurysms will be enrolled as follows:

- Anterior Circulation (AC) Cohort:

  Up to 180 subjects with intracranial aneurysms in the anterior circulation (excluding the petrous ICA to superior hypophyseal ICA region) may be enrolled in order to provide 153 evaluable subjects at 12 months, with an estimated 15% attrition rate. These data will be used to support a safety and effectiveness analysis for an indication for use of the Neuroform Atlas™ Stent System in the anterior circulation.

- Posterior Circulation (PC) Cohort:

  Up to 180 subjects with intracranial aneurysms in the posterior circulation (including vertebral, basilar and posterior cerebral arteries) may be enrolled in order to provide 153 evaluable subjects at 12 months, with an estimated 15% attrition rate. These data will be analyzed separately from the AC Cohort data, and will be used to support an indication for use of the Neuroform Atlas™ Stent System in the posterior circulation.

  For the posterior circulation cohort, a Bayesian adaptive study design ("Goldilocks" approach) providing for interim analyses of accumulated data will be used to select the final sample-size. The first interim data analysis will occur once 100 posterior circulation subjects have been enrolled. Based on enrollment rates and the frequency of disease in the posterior circulation, at the time this interim analysis is performed it is estimated that primary endpoint data will be available for approximately 39 – 63 posterior circulation subjects. If, at an interim analysis, there is at least a 95% predictive probability of observing a true rate of complete occlusion that is higher than 50%, enrollment in the posterior circulation cohort will be stopped early for success. The maximum sample-size for the posterior circulation cohort will be no more than 180 subjects.

2.3 Study Objectives

2.3.1 Primary Objectives

The primary objectives of this study are to:

- To evaluate effectiveness of the Neuroform Atlas™ Stent System as an adjunct to embolic coiling for the endovascular treatment of wide neck, intracranial, saccular aneurysms by comparing complete aneurysm occlusion rates achieved with stent-assisted coiling to performance goals established based on historical control data for occlusion rates achieved with coiling, balloon-assisted coiling, or stent assisted coiling. In the study population, complete aneurysm occlusion will be defined as 100% occlusion (Raymond Class 1) of the target aneurysm, in the absence of retreatment, or parent artery stenosis (>50%) at the target location, as measured with 12-month angiography evaluated by an independent Core Lab. A meta-analysis of data from the published literature will serve as a basis for the established effectiveness performance goals.
- To evaluate safety of the Neuroform Atlas™ Stent as measured by the rate of any major ipsilateral stroke or neurological death within 12 months. Safety data from a MAPS wide-neck aneurysm patient cohort and published rates of procedural and long-term morbidity and mortality for embolic coiling, balloon-assisted embolic coiling, or stent assisted coiling will serve as a basis for the established safety performance goals.

2.3.2 Secondary Objectives

The secondary objectives of this study are:

- To evaluate procedural technical success (defined as the proportion of subjects in whom the stent was successfully delivered to, and deployed at, the target location) using the Neuroform Atlas™ Stent System.
- To evaluate the incidence of ipsilateral ischemic stroke post treatment.
- To evaluate safety of the device as measured by the incidence of device related serious adverse events.
- To evaluate functional outcome as defined by the modified Rankin Scale (mRS).
- To evaluate all-cause mortality.
- To evaluate the rate of target aneurysm occlusion and recanalization.
- To evaluate the rate of target aneurysm retreatment.
- To evaluate stent migration at the 12 month angiogram.
- To evaluate parent artery patency at 12 months post procedure.

2.3.3 Long-term Follow-up Objectives

The objective of long-term follow-up is to gather safety and effectiveness information on the durability and safety of treatment using the Neuroform Atlas™ Stent System up to 3 years (± 6 months) postoperative. The specific long-term objectives are:

- To evaluate safety of the device as measured by the occurrence of 1 or more SAEs from 12 months through 3 years post-index procedure within the following categories:
    - Neurological death or major ipsilateral stroke
    - Any ischemic or hemorrhagic adverse event of any severity or duration (including transient ischemic attacks [TIAs], subarachnoid hemorrhage [SAH] and aneurysm rupture)
    - Device-related SAEs

  All new and ongoing adverse events will be recorded and adjudicated as specified by the CEC charter.
- To evaluate the long-term effectiveness and durability of treatment from 12 months through 3 years post-index procedure, based on 2- and 3-year (± 6 months) clinical follow-up and imaging performed per standard of care, for the following endpoints:
    - Retreatment
    - Parent artery stenosis at the target aneurysm location (>50% stenosis)
    - Composite effectiveness measure (complete aneurysm occlusion [Raymond Class 1] without significant parent artery stenosis at the target aneurysm location (>50% stenosis) or retreatment)
    - Recanalization
    - Stent migration based on follow-up angiogram
    - Aneurysm occlusion of Raymond Class 1, 2, or 3
    - Aneurysm occlusion of Raymond Class 1 and 2 combined
    - Progressive occlusion of the target aneurysm

2.4 Study Endpoints

The study contains a single treatment arm with subjects receiving the Neuroform Atlas™ Stent. The primary endpoints will be evaluated for all subjects treated with this investigational device.

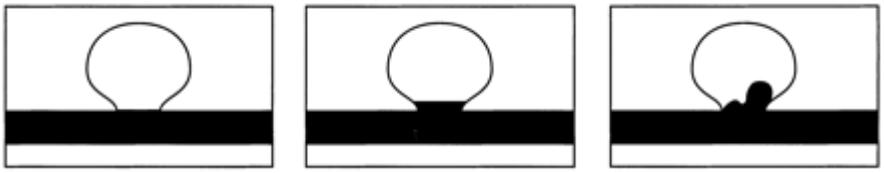
2.4.1 Primary Endpoints

2.4.1.1 Primary Effectiveness Endpoint

The primary effectiveness endpoint of the study is:

Complete aneurysm occlusion (100% occlusion – Raymond Class 1) of the treated target lesion on 12 month angiography, in the absence of retreatment, or parent artery stenosis (>50%) at the target location.

The Raymond Class 1[64] designation of complete occlusion (**Figure 1**) will be used to define occlusion success.



Class 1
Complete Obliteration

Class 2
Residual Neck

Class 3
Residual Aneurysm

Figure 1 - Raymond Classification of Angiographic Results

When assessing effectiveness, all images will be reviewed by an independent Core Lab per a Core Lab Radiographic Imaging Protocol. The Core Lab will be selected and qualified by the Sponsor prior to enrollment of the first study subject, and will develop the Core Lab Radiographic Imaging Protocol prospectively. To avoid interobserver variability, the Sponsor will use a Core Lab where all Core Lab readings will be performed by a single reviewer who will be blinded to assessments made by the clinical sites. In order to ensure reliable collection of images suitable for analysis, the Core Lab that is selected will develop guidelines for image acquisition, and will share these guidelines with clinical sites participating in the study.

2.4.1.2 Primary Safety Endpoint

The primary safety endpoint is:

Any major ipsilateral stroke or neurological death within 12 months.

An ipsilateral stroke will be defined as an acute episode of focal or global neurological dysfunction due to brain or retinal infarction, or due to an intracranial hemorrhage inclusive of subarachnoid, intraventricular or intraparenchymal hemorrhage, occurring in the same hemisphere as the target aneurysm.

A major ipsilateral stroke will be defined as an ipsilateral stroke that is associated with an increase of 4 or more points on the NIHSS at 24 hours after symptoms onset.

Note: For the purpose of consistency with the primary endpoint definition, strokes in the posterior circulation adjudicated as being strokes “within the treated vascular territory” will be called “ipsilateral” strokes.

2.4.2 Secondary Endpoints

2.4.2.1 Effectiveness

The secondary effectiveness endpoints identified below will be assessed post-index procedure through 12 months per the schedule requirements.

- Procedural technical success (defined as the proportion of subjects in whom the stent was successfully delivered to, and deployed at, the target location)
- Incidence of retreatment
- Incidence of recanalization (defined as a categorical increase in aneurysm filling over time after some degree of occlusion has been achieved initially)
- Incidence of parent artery stenosis at the target aneurysm location (>50% stenosis)
- Incidence of stent migration based on follow up angiogram
- Proportion of aneurysms with occlusion of Raymond Class 1, 2 or 3
- Proportion of aneurysms with occlusion of Raymond Class 1 and 2 combined
- Incidence of progressive occlusion at the target aneurysm location

2.4.2.2 Safety

The secondary safety endpoint is the percent of subjects experiencing one or more serious adverse events (SAE) through 12 months post-index procedure within the following categories (definitions are provided in the Appendices).

- New or worsening major ipsilateral stroke as measured by NIHSS
- Device related serious adverse events
- Subarachnoid hemorrhage (SAH)
- Aneurysm rupture

2.5 Study Success/Failure Criteria

- For both the anterior and posterior circulation cohorts, the lower limit of the 95% confidence interval of the proportion of subjects who achieve the primary effectiveness endpoint (i.e., complete aneurysm occlusion, in the absence of retreatment and > 50% parent artery stenosis at the target location, based on angiographic assessment at 12 months) is >50%.
- For the anterior circulation cohort, the upper limit of the 95% confidence interval of the proportion of subjects who experience the primary safety endpoint (i.e., any major ipsilateral stroke or neurological death within 12 months) is <20%.
- For the posterior circulation cohort, the upper limit of the 95% confidence interval of the proportion of subjects who experience the primary safety endpoint (i.e., any major ipsilateral stroke or neurological death within 12 months) is <25%.

2.6 Study Population and Source of Subjects

Subjects over 18 years of age presenting with wide neck, intracranial, saccular aneurysms requiring treatment with stent-assisted coiling may be eligible for study participation. Potential study candidates or their legal representatives will provide informed consent prior to any data collection. A screening and enrollment log will be provided to study sites to maintain a record of all screened subjects.

Subjects will be identified and recruited by Clinical Investigators and/or their designated research staff at a maximum of up to 40 investigative sites. Clinical investigators selected to participate in the study may enroll and treat a maximum of 20% of subjects enrolled in either cohort.

Subjects who sign an IRB or EC approved consent form will be considered enrolled in the study. Any subject consented, whether treated or not, will be assigned a screening number. Subjects who consent to participate but withdraw or are found to be ineligible prior to initiation of the procedure will be considered a screening failure, and the reasons for the screening failure will be documented on the site

screening log. In all cases where subjects are consented but not treated using a Neuroform Atlas™ Stent, replacement subjects will be enrolled. Subjects in whom an investigational procedure is attempted but stent delivery is unsuccessful will be followed through the two month follow-up visit; these subjects will be considered treatment failures but will not be evaluated for the primary endpoints at 12 months. All treated subjects with successful stent delivery and deployment will be evaluated for the primary endpoints at 12 months post-procedure.

For long-term follow-up, subjects will be asked to return for clinical follow-up visits at 2 years and 3 years (± 6 months) post-index procedure.

The study flow is depicted in **Figure 2**.

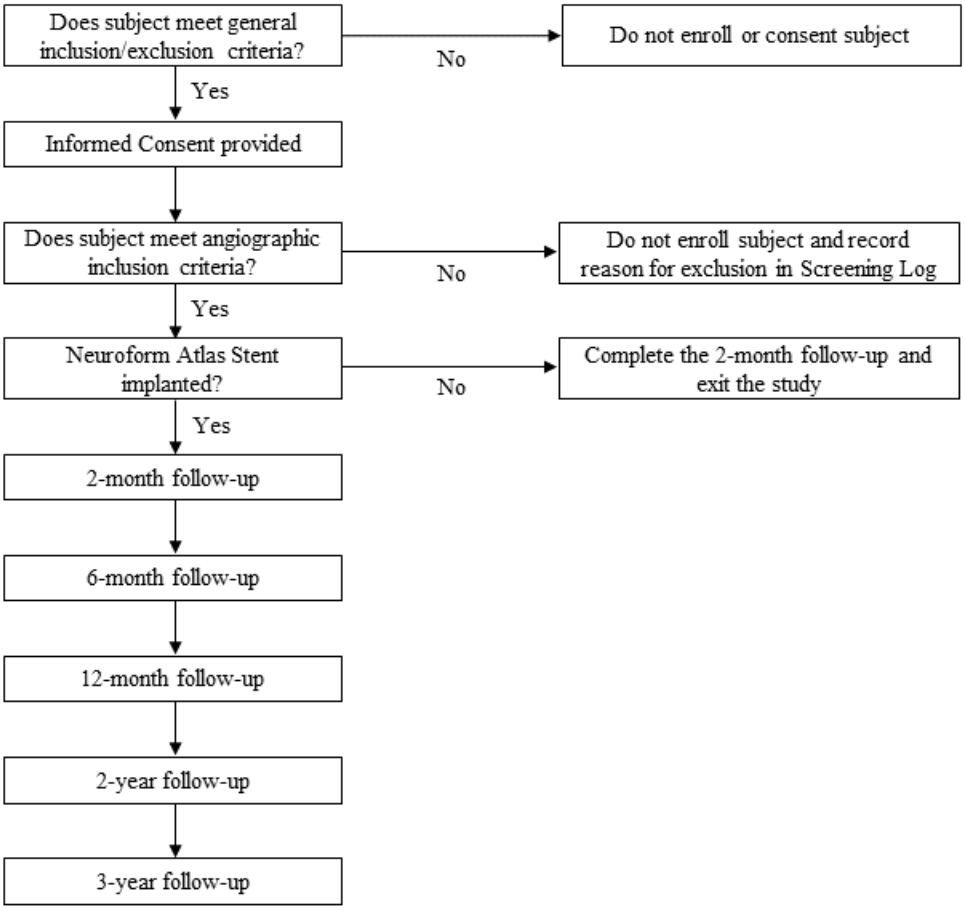


Figure 2 - Schematic of Study Flow

2.6.1 Inclusion Criteria

Candidates must meet ALL of the following inclusion criteria:

1. Subject is between 18 and 80 years of age
2. Subject has a documented, wide neck (neck ≥4mm or a dome-to-neck ratio <2), intracranial, saccular aneurysm arising from a parent vessel with a diameter of ≥ 2mm and ≤ 4.5 mm, which will be treated with bare metal coils
3. Subject or legal representative is willing and able to provide informed consent

4. Subject is willing and able to comply with protocol follow up requirements

2.6.2 Exclusion Criteria

Candidates will be excluded from this study if they do not meet the specific inclusion criteria, or if ANY of the following exclusion criteria are present:

1. Subject has known multiple untreated cerebral aneurysms, other than non-target blister aneurysm, infundibulum, or aneurysm measuring <3mm for each of three dimensions assessed (height, width, and depth) that will not require treatment during the study period
2. Subject has a target lesion that is a blister aneurysm, infundibulum, or aneurysm measuring <3mm for each of three dimensions assessed (height, width, and depth)
3. Subject has a target aneurysm that will require an Investigator to intentionally leave a neck remnant in order to preserve blood flow in a bifurcation or branch
4. Subject has undergone coiling or stenting of a non-target intracranial aneurysm within 30 days prior to study treatment
5. Subject has a target aneurysm in the anterior circulation proximal to the superior hypophyseal ICA
6. Subject has acute target aneurysm rupture less than 14 days prior to study treatment
7. Subject has a Hunt and Hess score ≥ 3 or a premorbid mRS score ≥4
8. Subject has an admission platelet count of<50,000, any known coagulopathy, or an International Normalized Ratio (INR)>3.0 without oral anticoagulation therapy
9. Subject has a known absolute contraindication to angiography
10. Subject has evidence of active cancer, terminal illness, or any condition which, in the opinion of the treating physician, would/could prevent the subject from completing the study (e.g., a high risk of embolic stroke, atrial fibrillation, co-morbidities, psychiatric disorders, substance abuse, major surgery ≤ 30 days pre-procedure, etc.)
11. Subject has a known absolute contraindication to the use of required study medications or agents (e.g., heparin, aspirin, clopidogrel, and radiographic contrast agents etc.)
12. Subject is female and is pregnant or intends to become pregnant during the study
13. Subject has Moya-Moya disease, arteriovenous malformation(s), arteriovenous fistula(e), intracranial tumor(s), or intracranial hematoma(s) (unrelated to target aneurysm)
14. Subject has significant atherosclerotic stenosis, significant vessel tortuosity, vasospasm refractory to medication, unfavorable aneurysm morphology or vessel anatomy, or some other condition(s) that, in the opinion of the treating physician, would/could prevent or interfere with access to the target aneurysm and/or successful deployment of the Neuroform Atlas™ Stent
15. Subject has had previous treatment (e.g., surgery, stenting) in the parent artery that, in the opinion of the treating physician, would/could prevent or interfere with successful use of the Neuroform Atlas™ Stent System and/or successful deployment of embolic coils
16. Subject has undergone previous stent-assisted coiling of the target aneurysm

2.6.3 Withdrawal and Replacement of Subjects

While study withdrawal is discouraged, subjects may withdraw from the study at any time, with or without reason and without prejudice to further treatment. Withdrawn subjects who received treatment will not undergo any additional follow-up, nor will they be replaced (the justified sample size considers an estimated allowance for attrition). If a subject is consented and not treated, a replacement subject will be enrolled.

2.7 Method of Assigning Subjects to Treatment

This is a prospective single arm study in which all subjects who present for stent-assisted coiling, provide informed consent, and meet inclusion/exclusion criteria may receive treatment (Neuroform Atlas™ Stent System). Eligible subjects will be consecutively enrolled at each site. Reason for screen failures will be documented.

2.8 Measures to Increase Validity and Minimize Bias

The following measures will be in place to increase validity and minimize bias.

1. Multiple clinical trial sites will be utilized to ensure generalizability of results and minimize site/operator effect.
2. The primary study effectiveness endpoint will be based on angiographic readings from an independent Core Lab blinded to operator assessment of outcomes and clinical data. Pre-determined evaluation criteria will be applied to review and analysis of the data.
3. The primary safety endpoint will be based on the incidence of established safety parameters as adjudicated by an independent CEC.
4. Study monitors will review and verify data collection forms against source documentation to ensure that there are no missing, illegible or incorrect data. Missing, illegible or incorrect data will be corrected following ICH/GCP guidelines.
5. Investigative site personnel will contact subjects prior to their scheduled study visits to increase compliance with the subject follow up protocol.

3 Study Procedures

3.1 Subject Screening

Subjects will not be recruited until the Food and Drug Administration (FDA), local regulatory authorities (as applicable), and the local Institutional Review Board (IRB) or Independent Ethics Committee (IEC) have approved the study. Site Investigators will assess potential subjects with wide neck intracranial aneurysms for enrollment in the study. The subject's suitability for treatment with the Neuroform Atlas™ Stent System will be evaluated based on medical and anatomical criteria as outlined in the inclusion/exclusion criteria. Angiograms (CTA, DSA or MRA) to determine suitable subjects may be generated up to 6 months prior to the treatment date.

NOTE: Data obtained prior to consenting as standard of care can be used for screening and completion of study CRFs.

If a subject meets the eligibility criteria for the study, this will be documented in the site's study screening log. If a subject fails to meet the eligibility criteria, the reason(s) for this will likewise be documented in the screening log. The screening log serves as a method for the Sponsor to ensure that there is no selection bias in the trial.

3.2 Informed Consent

Subjects will be informed by the Investigator or the Investigator's designee that they are free to refuse participation in this research study. If they elect to participate, it will be made clear that they may withdraw from the study at any time without prejudicing further care.

The Investigator or the Investigator's designee will inform subjects that their medical records will be subject to review by the Sponsor or appropriate regulatory bodies. This information will be used during the analysis of the results of the clinical study, but the subjects' identities will be treated as confidential. Subjects will be assigned a unique identification code. This code will be used on all data and data collection forms during the study period. It will not reveal the subject's identity.

The Investigator will explain the conditions of the study, giving the subject sufficient time to ask questions and to consider whether or not they want to participate. Subjects will be informed that active study participation is expected through their 12-month follow-up visit, but the informed consent form will allow for continued follow-up through 60 months post-treatment should longer term follow-up

become necessary. Eligible subjects who agree to participate will be asked to sign and date an IRB approved informed consent form. One copy of the signed and dated informed consent form shall be returned to the Investigator and filed in the subject's case history, and one copy shall be provided to the subject for his/her personal records.

3.3 Subject Withdrawal

A subject has the right to voluntarily withdraw from the study at any time and for any reason without prejudice to his or her future medical care by the Investigator(s) or the Institution. The Investigator(s) may elect at any time to withdraw a subject from the study for any reason unrelated to the study treatment if such a decision is in the subject's best medical interest. If a subject discontinues the study after undergoing the investigational procedure, or is withdrawn by the Investigator(s), as much follow-up data as possible will be obtained. Attempts will be made to retrieve follow-up data, prior to the time point at which voluntary consent was withdrawn, in particular regarding possible AEs at the time of study discontinuation.

An enrolled subject who is found to be ineligible to participate in the study after signing the consent form will be exited from the study at determination of ineligibility. If a subject is consented and not treated, a replacement subject will be enrolled. If a subject is withdrawn from the study after treatment for any reason, he or she will not be replaced.

All enrolled subjects are expected to continue to participate in the study through the final follow up assessment as outlined in this protocol, or until such time as the Sponsor or the Sponsor's authorized designee notifies the Investigator in writing that further follow up is no longer required, except in the event of death, or upon the subject's written request for early withdrawal from the clinical study. If a request for early withdrawal is received, a copy of the request should be forwarded directly to the Sponsor or the Sponsor's authorized designee for documentation purposes.

3.4 Lost to Follow Up

A subject will be considered "lost to follow up" and will be terminated from the study when he or she can no longer be reached by study staff and have missed study visits. The site must notify the Sponsor of subject status, and must consult with the Sponsor regarding discontinuation of any study subject prior to ceasing all attempts to contact such subjects. A subject may only be categorized as lost to follow up if the following criteria are met:

- Failure to complete 12-month or two consecutive follow up visits, and
- Documentation of three unsuccessful attempts by the Investigator or his/her designee to contact the subject and/or next of kin

For long-term follow-up, subjects will be considered lost-to-follow-up if the documentation criterion is met.

3.5 Allocation of Subjects to Competing Studies

In the event that a study center is participating in similar and competing research studies with the same or similar subject populations, the Investigator must provide documentation to the Sponsor or the Sponsor's authorized designee outlining the methods that the center is using for appropriate subject allocation in order to minimize selection bias.

3.6 Study Schedule of Events

Table 2 - Study Event Schedule through PAS Follow-up presents a schedule of the observations and assessments that have taken or will take place from subject enrollment into the IDE study through the duration of the PAS phase of the study.

Table 2 - Study Event Schedule through PAS Follow-up

	ATLAS IDE Event Schedule						ATLAS PAS Event Schedule£		
	Pre-Implant	**Implant / Procedural**	**Post-Implant†**	**2 Months (60d) ± 1 month**	**6 Months (180d) ± 1 month**	**12 Months (365d) ± 2 months**	**2 Years (730d) ± 6 months**	**3 Years (1095d) ± 6 months**	**Post 3-Years (43 – 60 months) ††**
Medical History	X								
Neurological Exam*	X					X	X∞	X∞	X∞
mRS*	X		X	X	X	X	X∞	X∞	X∞
NIHSS*/**	X			+/-**	+/-**	X	X∞	X∞	X∞
Hunt and Hess*/***	X		X			X	X∞	X∞	X∞
Angiography******	X**** (MRA, CTA or DSA)	X (DSA)		+/-**** (MRA or DSA, per institution standards)	+/-**** (MRA or DSA, per institution standards)	X (DSA)	+/-**** (MRA, CTA, or DSA, per institution standards)	+/-**** (MRA, CTA, or DSA, per institution standards)	+/-**** (MRA, CTA, or DSA, per institution standards)
Adverse Event	X	X	X	X	X	X	X∞	X∞	X∞
Antiplatelet	X		X	X	X	X	X	X	X
Quality of Life	X					X			

† Assessments must be performed within 72 hours after implant procedures, and prior to hospital discharge.

†† Post 3-year visits are required only for those subjects whose index procedure took place ≥ 43 months and ≤60 months prior to their enrollment into the PAS phase of the study.

* At each Clinical Trial Site, a non-treating physician (or an appropriately trained/qualified designee) will be responsible for performing neurological examinations and/or performing assessments using neurologic rating/grading scales (mRS, NIHSS, Hunt and Hess). In addition, a neurological examination and/or an assessment using a neurologic rating/grading scale may be performed at any point in time if it is appropriate to do so, or in the case of a new neurological event.

** The NIHSS is required at baseline and at 12 months of follow-up. In addition, the NIHSS is required at the 2- and 6-month follow-up visit and at any unscheduled visit if the subject's mRS score is > 0 in association with an adverse neurological event.

*** Hunt and Hess scoring will be performed only when evaluating subjects who have evidence of subarachnoid hemorrhage.

**** Pre-implant angiography (MRA, CTA, or DSA) may be performed up to 6 months prior to treatment. In addition to the post-implant and 12 month angiographic studies, it is recommended that an imaging study be performed within 24 hours of the onset of symptoms in any treated subject suspected of having a stroke. Although not required, if it is standard of care to do so at a given Clinical Trial Site, imaging (MRA or DSA) may be performed at the 2- or 6-month follow-up visit or per standard of care at each institution for the 2 and 3 years long term follow up visit.

∞ At 2-year, 3-year, and post 3-year follow-up, NIHSS, mRS and neurological exams will be collected if performed. For any suspected stroke events that occur in the PAS, NIHSS will be collected at the time of event and at 24 hours post event; mRS will be collected at discharge from event and at a minimum of 90 days post event. For any aneurysm rupture case, Hunt and Hess grade will be performed or collected if available. Any imaging performed due to suspected stroke event will be submitted to the sponsor. AEs can be collected via retrospective chart review, phone calls or in-person visits and will include all the new and ongoing adverse events.

£ At least one (1) ATLAS PAS visit will be conducted in-person.

3.7 Pre-implant

3.7.1 Baseline Evaluation

Once the Site Investigator has verified that the subject meets all of the study eligibility criteria, and once the subject has signed the informed consent, the subject will undergo a baseline evaluation. This will consist of the following assessments and/or procedures as performed on all subjects prior to implant:

- Medical history
- Neurological examination (including global neurological assessments and evaluation for cranial nerve deficits)

  NOTE: If visual field abnormalities are evident upon examination, a formal ophthalmology consult with visual field analysis should be obtained.
- Neurologic rating/grading scales including the following:
  - mRS (all subjects)
  - NIHSS (all subjects)
  - Hunt and Hess (for subjects with a ruptured aneurysm and evidence of subarachnoid hemorrhage)
- Angiography (DSA, CTA, or MRA; may be performed up to 6 months prior to treatment)
- Quality of Life (QoL) assessment

  QoL data will be collected using the EQ-5D-3L™ system, a generic, standardized, validated [65] measure of health status consisting of two parts:

  Descriptive System
  - Consists of 5 dimensions (5D) including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression
  - Subjects rate each dimension using 3 levels (3L) including no problems, some problems, and extreme problems

  Visual Analogue System (VAS)
  - Presented in a thermometer-like fashion
  - Records the self-rated health of a subject on a scale of 0-100 (worst to best imaginable health state)

3.7.2 Pre-Implant Pharmacotherapy

The following standard antiplatelet regimen is recommended for pre-implant use in enrolled subjects with unruptured aneurysms in accordance with routine clinical practice. Substitutions for these medications are allowed at the discretion of the Investigator as long as the antiplatelet efficacies are equivalent. Do not use the Neuroform Atlas™ Stent System or embolic coils in subjects in whom antiplatelet therapy is contraindicated.

Recommended Dosage:

- Aspirin (ASA) 75 or 81 mg (minimum dose) to 325 mg (maximum dose) PO q.d. for at least 5 days prior to the implant procedure
- Clopidogrel/Plavix 75 mg PO q.d. for at least 5 days prior to the implant procedure

3.8 Implant

3.8.1 Implant/Procedural Pharmacotherapy

All procedures will be performed under general anesthesia. Subjects will be anticoagulated during the implant procedure. Anticoagulation will be managed in accordance with site standard of care.

3.8.2 Implant/Procedural Steps

As previously indicated, the Neuroform Atlas™ Stent System consists of a laser cut, nitinol, self-expanding stent preloaded over a delivery wire inside an introducer sheath. The Neuroform Atlas™ Stent System is shipped with detailed written Directions for Use (DFU). Prior to enrolling and treating a subject in the study, all Investigators will review and understand the DFU, and will be trained by the Sponsor with regards to use of the Neuroform Atlas™ Stent System.

1. Select an appropriate stent diameter based on reference vessel diameter, and select a stent length that is at least 8mm longer than the width of the aneurysm neck (in order to maintain a minimum of 4mm of stent length along the parent vessel on either side of the aneurysm neck). Refer to **Section 8, Device Description**, for additional stent sizing recommendations.
2. Follow the procedure outlined in the DFU regarding preparation, positioning and deployment of the Neuroform Atlas™ Stent System. In summary, these steps are as follows:
    - The sheath and delivery wire are used to transfer the Neuroform Atlas™ stent into a 0.0165" - 0.0170" ID microcatheter
    - After transfer, the sheath is removed from the proximal end of the delivery wire
    - The delivery wire is then used to advance the stent to the distal end of the microcatheter
    - The microcatheter, stent, and delivery wire are repositioned as a unit in order to ensure that the stent is located across the aneurysm
    - The stent is deployed across the neck of the aneurysm by stabilizing the delivery wire and withdrawing the catheter
3. The beginning of the procedure will be defined as the point in time when the first puncture or incision is made. The end of the procedure will be defined as the point in time when wound closure is complete. If these start and stop times are not documented in the nursing or anesthesia records, the time stamp of the initial procedural angiogram and final procedural angiogram will be used.

The following types of information will be collected regarding the implant procedure:

- Date of admission
- Procedure date, time, clinical site, investigator performing procedure
- Duration of procedure
- Device information
    - Neuroform Atlas™ Stent
    - Coil type used – brand/model
    - Adjunctive device use (e.g., balloon)
- Technical success of stent assisted coiling procedure
- Intra-operative AEs

3.8.3 Treatment of Previously Treated Aneurysms

Target aneurysms that have previously been treated with embolic coiling can be treated under this Study Protocol, assuming that the subjects involved meet all of the study inclusion/exclusion criteria as outlined in **Section 2.6, Study Population and Source of Subjects**. Subjects who have had previous stent-assisted coiling of the target aneurysm are not eligible for inclusion in this study.

3.8.4 Implant of More than One Stent

Up to two stents may be deployed in the treatment of a given aneurysm, but both stents must be Neuroform Atlas™ Stents. The use of other intracranial stents for treatment of the target aneurysm is not allowed in this study.

3.9 Post-Implant

3.9.1 Post-Implant Pharmacotherapy

A standard antiplatelet regimen is required for post-implant use in enrolled subjects with unruptured intracranial aneurysms in accordance with routine clinical practice, unless it becomes contraindicated in an individual subject due to a medical condition. Substitutions for these medications are allowed at the discretion of the Investigator as long as the antiplatelet efficacies are equivalent.

Recommended Dosage and Required/Recommended Duration:

- ASA 75 or 81 mg (minimum dose) to 325 mg (maximum dose) PO q.d., required for at least 3 months after the implant procedure; recommended for life
- Clopidogrel/Plavix 75 mg PO q.d., required for at least 3 months after the implant procedure

3.9.2 Post-Implant Assessments

At the Investigator's discretion, a treated subject may be discharged from the hospital when he/she is clinically stable. Prior to discharge and within 72 hours of the procedure, the following assessments and/or procedures will be performed on all treated subjects:

- Neurologic rating/grading scales including the following:
  - mRS (all subjects)
  - Hunt and Hess (for subjects who previously had a ruptured aneurysm and evidence of subarachnoid hemorrhage)
- Assessment and documentation of any adverse events arising after the procedure but prior to discharge.

At the time of discharge, designated staff at the clinical site will review the study requirements with the subject in order to maximize compliance with the follow-up schedule and the post-implant medication regimen. The staff will instruct the subject to return for follow-up assessments in accordance with the study event schedule outlined in **Table 2**, and if possible, they will establish and schedule a date for the first follow-up visit and/or procedure. In addition, the staff will instruct the subject to take the recommended antiplatelet medication, and will ask the subject to check in with the clinical site prior to discontinuing any antiplatelet medication in the absence of an emergency.

3.10 Follow Up Visits

Enrolled and treated subjects will return for follow-up visits and collection of primary and/or secondary endpoint data as required at two, six, and twelve months. Long-term outcomes data will be collected at

two and three years post-implant. During these follow-up visits, assessments and/or procedures will be performed as follows:

Two Months (60 days) ± 1 Month Post-Implant:

- Neurological rating/grading scales including the following:
  - mRS (all subjects)
  - NIHSS (only if mRS score is > 0 in association with an adverse neurological event)
- Angiography (MRA or DSA) - only if required per site standard of care
- Assessment and documentation of any adverse events arising since discharge
- Assessment of compliance to the antiplatelet regimen

Six Months (180d) ± 1 Month Post-Implant:

- Neurologic rating/grading scales including the following:
  - mRS (all subjects)
  - NIHSS (only if mRS score is > 0 in association with an adverse neurological event)
- Angiography (MRA or DSA) - only if required per site standard of care
- Assessment and documentation of any adverse events arising since the previous follow-up visit
- Assessment of compliance to the antiplatelet regimen

Twelve Months (365d) ± 2 Months Post-Implant:

- Neurological examination (including global neurological assessments and evaluation for cranial nerve deficits)
- Neurologic rating/grading scales including the following:
  - mRS (all subjects)
  - NIHSS (all subjects)
  - Hunt and Hess (for subjects who previously had a ruptured aneurysm and evidence of subarachnoid hemorrhage)
- Angiography (DSA)

  NOTE: 12-month angiography (DSA) is used to assess the primary endpoint and is required for all subjects
- Assessment and documentation of any adverse events arising since the previous follow-up visit
- Assessment of compliance to the antiplatelet regimen
- Quality of Life assessment

Two Years (730d) ± 6 Months Post-Implant:

- Neurological examination (including global neurological assessments and evaluation for cranial nerve deficits, if applicable)
- mRS assessment
- Radiological imaging (MRA, DSA or CTA), if performed per institutional standard of care
- Assessment and documentation of any adverse events arising since the previous follow-up visit, including all new and ongoing adverse events

- Assessment of antiplatelet regimen
- Retreatment assessment

Three Years (1095d) ± 6 Months Post-Implant:

- Neurological examination (including global neurological assessments and evaluation for cranial nerve deficits, if applicable)
- mRS assessment
- Radiological imaging (MRA, DSA or CTA), if performed per institutional standard of care
- Assessment and documentation of any adverse events arising since the previous follow-up visit, including all new and ongoing adverse events
- Assessment of antiplatelet regimen
- Retreatment assessment

NOTE: Two- and 3-year office visits with neurological examination are required. If the 3-year visit window has elapsed at the initiation of the PAS, subjects will be asked to return for at least 1 follow-up visit. In the event a subject refuses to return for an office visit, effort should be made to conduct telephone follow-up to complete an adverse event assessment and obtain mRS scores.

3.11 Unscheduled Visits

Imaging performed in response to an adverse event will be documented in the case report forms. These images will be shared with the Imaging Core Lab, and copies of the images will be provided to the Sponsor so that CEC review and event adjudication can be facilitated. If a subject is suspected of having a stroke, it is recommended that an imaging study be performed within 24 hours of the onset of symptoms in order to confirm, and to evaluate whether the stroke is/was ischemic or hemorrhagic in nature. In addition, a neurological examination and/or an assessment using neurologic rating/grading scales (mRS, NIHSS, Hunt and Hess) should be performed as required in order to determine the severity of the stroke.

If a subject presents with an adverse event, he/she will receive appropriate treatment per site standard of care. If the subject's condition precludes him/her from undergoing angiography or any other evaluation specified in the protocol, the Investigator should document whether a stable clinical endpoint has been reached, or whether the subject's status is associated with an adverse event possibly related to the device or procedure. All efforts will be made to retain the subject for safety follow up. If the subject is withdrawn from the study, reasons for the subject's inability to continue with study evaluations will be documented.

4 Statistical Methods and Considerations

4.1 Trial Success/Failure Criteria

This is a single arm trial of the Neuroform Atlas™ Stent System in subjects with wide neck aneurysms who will receive stent-assisted coiling with any approved bare metal embolic coils. Up to 360 subjects with wide neck saccular aneurysms who meet all eligibility criteria will be enrolled. The primary effectiveness endpoint is complete occlusion of the targeted lesion at 12 months, and the related study success criterion is to demonstrate that the lower bound of the 95% exact CI observed rate of complete occlusion at 12 months is greater than 50% in both the anterior and posterior circulation cohorts. The primary safety endpoint is any major ipsilateral stroke or neurological death within 12 months, and the

related study success criteria are to demonstrate that the rate of primary safety events is less than 20% in the anterior circulation cohort, and less than 25% in the posterior circulation cohort.

4.2 Sample Size Estimate and Justification

Anterior Circulation Cohort:

A sample size of up to 180 subjects with intracranial aneurysms in the distal anterior circulation has been selected for this study in order to provide 153 evaluable subjects at 12 months, with an estimated 15% attrition rate. Assuming an effectiveness primary endpoint response rate of 62% (per the findings of a meta-analysis of Neuroform stent literature as performed by King et al[59]), the expected lower bound of the exact binomial two-sided 95% confidence interval around the success rate is greater than 50%. Assuming a safety primary endpoint rate of 8%, the expected upper bound of the exact binomial two-sided 95% confidence interval around the success rate is less than 20%. A sample size of 153 evaluable subjects provides 85% power to demonstrate the effectiveness endpoint, and a power of approximately 99% to successfully demonstrate the safety endpoint given the observed rates stated above. The combined probability of the two endpoints is (.85) x (.99) = .842.

Posterior Circulation Cohort:

Separate analyses of these cohort data will be performed to support an indication for use in the posterior circulation.

A sample size of up to 180 subjects with intracranial aneurysms in the posterior circulation (including vertebral, basilar and posterior cerebral arteries) will also be enrolled in order to provide 153 evaluable subjects at 12 months, with an estimated 15% attrition rate. While the safety endpoint rate for posterior circulation subjects may be higher than that for the anterior circulation subjects, that rate is not expected to exceed 12%. Assuming a safety primary endpoint rate of 12%, the expected upper bound of the exact binomial two-sided 95% confidence interval around the success rate is less than 25%. A sample size of 153 evaluable subjects provides a power of approximately 99% to successfully demonstrate the safety endpoint given the observed rates stated above. Based on outcomes in the MAPS study, the effectiveness rate for posterior circulation subjects is expected to be very close to that of anterior circulation subjects. Therefore, the statement of power to demonstrate effectiveness for a sample size of 153 evaluable anterior circulation subjects also holds for a sample size of 153 evaluable posterior circulation subjects.

For the posterior circulation cohort, a Bayesian adaptive study design ("Goldilocks" approach) providing for interim analyses of accumulated data will be used to select the final sample-size. The first interim data analysis will occur once 100 posterior circulation subjects have been enrolled. Based on enrollment rates and the frequency of disease in the posterior circulation, at the time this interim analysis is performed it is estimated that primary endpoint data will be available for approximately 39 – 63 posterior circulation subjects. If, at an interim analysis, there is at least a 95% predictive probability of observing a true rate of complete occlusion that is higher than 50%, enrollment in the posterior circulation cohort will be stopped early for success. The maximum sample-size for the posterior circulation cohort will be no more than 180 subjects.

4.3 Eligibility of Subjects, Exclusions and Missing Data

All efforts will be made to avoid any missing data, especially data related to the primary endpoints. Subjects who suffer neurological death prior to one year follow up will be imputed as Raymond 3 (the worst case) in the analysis of the primary effectiveness endpoint. Regression methods will be used to impute missing endpoint data. For either the safety endpoint or the effectiveness endpoint, five separate imputed data sets will be constructed in this manner. Inferences will then be completed using pooled estimates across the five data sets. In the event that no predictor variables can be found for the regression models, missing data will be imputed by a random draw from observed data for patients with similar baseline characteristics (e.g., gender, aneurysm location, race, etc.) as those with the missing data.

4.4 Analysis Populations

ITT (Intent to Treat): All subjects who have signed the Informed Consent Form for this trial, and in whom the Neuroform Atlas™ Stent implantation procedure has been attempted (i.e., a component of the stent system was introduced into the body).

mITT (Modified Intent to Treat): All subjects who have signed the Informed Consent Form for this trial, and in whom the Neuroform Atlas™ Stent has been successfully implanted.

PP (Per Protocol): All subjects who have signed the Informed Consent Form for this trial, who have had the Neuroform Atlas™ Stent successfully implanted, and who have not been the subject of any major protocol deviations.

Enrolled Not Treated: All subjects who have signed the Informed Consent Form for this trial, but in whom no component of the Neuroform Atlas™ Stent System has ever been introduced into the body as part of an implantation procedure.

PAS ITT (ITT for the PAS): All subjects who have signed the Informed Consent Form for this trial, and in whom the Neuroform™ Atlas Stent has been successfully implanted. This cohort is identical to the mITT cohort.

PAS mITT (**Modified Intent to Treat in PAS**): All mITT subjects who have not withdrawn, died, or refused follow-up.

The primary safety and effectiveness analyses will be performed on the mITT population. The 95% Confidence Interval (CI) for each endpoint will be calculated using the exact binomial distribution. In addition, safety data will include any adverse events reported to occur among ITT subjects in whom a Neuroform Atlas™ Stent implantation procedure was attempted but did not successfully occur. For long-term follow-up, all analyses completed for the PAS mITT cohort will also be completed for the PAS ITT cohort for comparison

4.5 Primary Endpoints Justification

4.5.1 Justification for Effectiveness Criteria

As is evident from the literature, the treatment of wide neck aneurysms with embolic coiling is generally associated with low complete occlusion rates and a high incidence of recanalization. Surgical clipping is widely perceived to be associated with high occlusion rates but greater risk of major morbidity and mortality events. However, the reliability of published data on occlusion rates following surgical clipping has recently been called into question. In a meta-analysis of surgical treatment of unruptured intracranial aneurysms conducted by Kotowksi et al—which included 60 studies published between 1990 and 2011 that described outcomes among 9,845 subjects with 10,845 aneurysms—the authors reported that occlusion outcomes were not reported for 82.2% of the aneurysms and recommended against using the results of these studies to formulate treatment plans.[66] Quality published data on surgical clipping of wide neck aneurysms are not available.

Certain aneurysms are unable to achieve treatment success by surgery or by coiling alone. Treatment efficacy increases (increased occlusion, decreased recanalization) with the use of adjunctive devices such as stent assisted coiling as well as with more favorable aneurysm morphologies. Effectiveness outcomes based on occlusion rates, as reported in the literature, can vary widely depending on the degree of heterogeneity in the study population (which is often very high) and the methods of reporting outcomes (e.g., immediate vs. follow-up angiography results).

Data from the MAPS Trial

The MAPS Trial was a multinational, multicenter, randomized controlled trial conducted at 43 investigational sites and into which 626 patients with either ruptured or unruptured intracranial

aneurysms at any location (ranging in size from 4-20 mm) were enrolled and treated using embolic coils.[63] The original purpose of the MAPS non-inferiority trial was to compare effectiveness of Matrix-2 biopolymer–modified coils with effectiveness of bare metal coils when using a composite clinical outcome measure (i.e., Target Aneurysm Recurrence [TAR]) as the primary study endpoint. Secondary effectiveness endpoints included angiographic occlusion (as assessed by an independent Core Laboratory using the modified Raymond Scale) and clinical outcomes (as assessed using the modified Rankin Scale) (mRS). At 12-month follow-up (± 3months), it was shown that there was no significant difference in angiographic occlusion rates or other effectiveness outcomes between the two groups. Similar findings have been reported elsewhere. In another large-scale randomized controlled trial of endovascular coiling, Molyneux et al. reported no significant difference in angiographic occlusion rates between patients randomized to treatment with polymer-loaded coils versus those randomized to treatment with bare metal coils.[67] In a recent systematic review/meta-analysis designed to assess differences in reported unfavorable angiographic outcomes for coiled cerebral aneurysms as a function of coil type, it was similarly demonstrated that across 82 studies, there were no significant differences based on coil type.[68]

A large proportion of patients enrolled in the MAPS trial were similar to the study population for which use of the Neuroform Atlas Stent System is intended. When key screening criteria that will be used to enroll patients into the ATLAS IDE trial were applied to the MAPS database, a total of 247 patients who underwent coiling alone were available for comparative analysis. These key criteria included: a) inclusion of wide-neck aneurysms (defined as being aneurysms having a neck width ≥ 4 mm or a dome-to-neck ratio < 2) located in the posterior or anterior "non-petrous" circulation (i.e., excluding the petrous Internal Carotid Artery [ICA] to superior hypophyseal ICA region); b) exclusion of patients with a baseline Hunt and Hess score ≥ 3; and c) exclusion of patients with a baseline mRS score ≥ 4. In the MAPS study, of the 247 wide-neck aneurysms that met these criteria, 205 (83%) were located in the anterior non-petrous circulation and 42 (17%) were located in the posterior circulation. Within this subgroup, twelve-month (± 3 months) angiographic data were available for 197/247 patients (80%) and were reviewed by the independent Core Laboratory that was used for the MAPS study (i.e. the University of California at San Francisco).

As the patient population comprising this subgroup closely matches the patient population to be enrolled in the ATLAS IDE trial, and the prospectively defined secondary endpoints used in the MAPS trial are similar to the effectiveness endpoints to be used in the ATLAS IDE trial, this data set of 247 patients represents a valid, reasonable and homogenous historical control group upon which performance goals can be based. Further, the major findings from the MAPS trial and other studies that examined the effect of coil type on angiographic outcome justify and support the inclusion of MAPS patients treated with either polymer-coated or bare metal coils in the comparative dataset.

Table 3 provides a summary of angiographic outcomes in the above-described MAPS patient cohort, comparing immediate and 12 (± 3) month occlusion outcomes by aneurysm location. At 12 (± 3) month follow-up, total occlusion rates were slightly less than 40% and there was no significant difference in outcomes between groups of patients with anterior non-petrous and posterior circulation aneurysms.

Table 3 - MAPS Cohort - Angiographic Outcomes as Assessed by an Independent Core Lab

Modified Raymond Scale – Class I	Wide Neck Aneurysms [1,2] (N =247)		P-value
	Anterior Non-petrous (n =205)	Posterior (n =42)	
12 (± 3) month FU or Re-intervention	37.2% (61/164)	36.4% (12/33)	0.93

[1] Neck width ≥ 4mm or dome-to-neck ratio < 2
[2] Excludes subjects with a pre-procedure Hunt and Hess score ≥ 3; excludes subjects with a pre-procedure mRS score ≥ 4

Data from the Scientific Literature

A comprehensive search of current scientific literature was conducted in order to identify published articles suitable for inclusion in a meta-analysis of wide neck aneurysm treatment outcomes. To be included, each published article had to meet the following key criteria: (1) English language; (2) published in 2000 or later; (3) contained data regarding safety, performance, and/or effectiveness involving the treatment of wide neck intracranial aneurysms in a clinical setting, or analyses of data maintained in registries and/or institutional databases; (4) contained data derived from a minimum sample size of n = 5; (5) could not be superseded by a publication with the same sample group, or contribute to a later publication including data from the same study (unless the article addressed a different objective); (6) contained data for complete occlusion (Raymond Score 1) rate as assessed by angiography at follow-up; (7) included literature containing data for balloon-assisted coiling; (8) included literature containing data for coiling alone; and (9) contained data from clinical and angiographic follow-up ranging from 6 to 18 months post-treatment. An important exclusion criterion was the absence of appropriate clinical or angiographic follow-up data (e.g., no long-term follow-up, or no Raymond scores reported).

The literature search yielded 339 articles using the search terms “wide neck aneurysms and occlusion”. Of these 339 articles, 329 were excluded for failing to meet the pre-determined criteria for inclusion. An additional relevant article by Hetts et al[26] was included as it contained a subset of wide neck aneurysms treated in the Stryker sponsored MAPS Trial. This yielded 11 published articles whose data could be assessed via a meta-analysis in order to derive effectiveness performance goals for both the anterior and posterior cohorts.[26, 30, 31, 37-42, 69, 70] Stent assisted coiling data from two of these articles (Hetts et al.[26] and Chalouhi et al.[38]) were included in this meta-analysis. A summary of effectiveness data contained in these 11 articles is presented in **Table 4.**

Table 4 - Summary of Effectiveness Data Derived from Literature Search

Reference	*N*	*Neck <4mm*	*Neck ≥4mm*	*Dome-to-Neck Ratio*	*Ruptured*	*Location*	*Coiling BAC SAC*	*Anz Coiled (Anz at FUP)*	*Immediate Complete Occlusion ALL*	*Immediate Complete Occlusion WNA*	*Complete Occlusion at Follow-Up ALL*	*Complete Occlusion at Follow-Up WNA*	*Recanaliz"/ Retreatment ALL*	*Recanaliz"/ Retreatment WNA*	*Time to Follow-Up Angio Mean (Range)*
2000 Aletich JNS [37]	*75 anz 72 pts*	*52/75 (69%)*	*23/75 (31%)*	*53/75 (71%) = <2 22/75 (29%) = ≥2*	*20/75 (27%)*	*75% Ant 25% Post*	*100% BAC*	*66 anz (64 anz)*	*N/A*	*17/66 (26%)*	*N/A*	*24/64 (38%)*	*N/A*	*N/A*	*11.2 mo (6 - 29 mo)*
2001 Cottier AJNR [39]	*45 anz 44 pts*	*100% Wide-neck anz*			*27/44 (61%)*	*95% Ant 5% Post*	*100% BAC*	*45 anz (45 anz)*	*N/A*	*31/45 (69%)*	*N/A*	*30/45 (67%)*	*N/A*	*N/A*	*16 mo (3 mo - 5 yr)*
2001 Nelson AJNR [41]	*22 anz 22 pts*	*100% Wide-neck anz*			*9/22 (41%)*	*100% Ant*	*100% BAC*	*22 anz (20 anz)*	*N/A*	*15/22 (68%)*	*N/A*	*17/20 (85%)*	*N/A*	*0/20 (0%)*	*19 mo (12 - 30 mo)*
2002 Lozier Stroke [30]	*495 anz 489 pts (meta-analysis of 12 studies)*	*40%*	*60% Wide-neck anz*		*19%*	*100% Post*	*100% Coiling*	*483 anz (All = 208 anz; WNA = 112 anz)*	*217/456 (48%)*	*N/A*	*93/208 (45%)*	*26/112 (23%)*	*46/208 22%*	*32/112 (29%)*	*16.8 mo (mean for 6/12 studies) and 26.1 mo (mean for 6/12 studies)*
2006 Niimi Stroke [31]	*74 anz 70 pts*	*43/74 58%*	*10/74 (14%) = Small wide-neck 20/74 (27%) = Large (assumed to be wide-neck) 1/74 (1%) = Giant (assumed to be wide-neck)*		*31/74 (42%)*	*80% Ant 20% Post*	*79% Coiling 16% BAC 5% SAC*	*All = 74 anz; WNA = 31 anz (All = 47 anz; WNA = 25 anz)*	*13/74 (18%)*	*4/31 (13%)*	*10/47 (21%)*	*5/25 (20%)*	*27/47 (57%)*	*18/25 (72%)*	*12 mo (4d - 34 mo)*
2013 Chalouhi AJNR [38]	*101 pts total; 32 BAC*	*100% Wide-neck*			*21/32 (66%)*	*81% Ant 19% Post*	*32/101 (32%) BAC*	*32 anz (32 anz)*	*N/A*	*11/32 (34%)*	*N/A*	*16/32 (50%)*	*N/A*	*5/32 (16%)*	*6.5 mo (3 - 36 mo)*
2013 Chalouhi AJNR [38]	*101 pts total; 69 SAC*	*100% Wide-neck*			*8/69 (12%)*	*84% Ant 16% Post*	*69/101 (68%) SAC*	*69 anz (69 anz)*	*N/A*	*22/69 (32%)*	*N/A*	*52/69 (75%)*	*N/A*	*3/69 (4%)*	*8.0 mo (5 - 48 mo)*

Reference	*N*	*Neck <4mm*	*Neck ≥4mm*	*Dome-to-Neck Ratio*	*Ruptured*	*Location*	*Coiling BAC SAC*	*Anz Coiled (Anz at FUP)*	*Immediate Complete Occlusion ALL*	*Immediate Complete Occlusion WNA*	*Complete Occlusion at Follow-Up ALL*	*Complete Occlusion at Follow-Up WNA*	*Recanaliz^{n} / Retreatment ALL*	*Recanaliz^{n} / Retreatment WNA*	*Time to Follow-Up Angio Mean (Range)*
2014 Hetts AJNR [26]	*361 pts total; 224 pts coiled*	*73/224 (33%) were wide-neck anz*			*None*	*N/A*	*224/361 (62%) coiling*	*All = 224 anz; WNA = 73 anz (All = 180 anz; WNA = 59 anz)*	*76/224 (34%)*	*20/73 (27%)*	*80/180 (44%)*	*16/59 (27%)*	*19/224 (8%)*	*10/73 (14%)*	*Clinical = 1yr, 2yr Angio = 12 ± 3mo*
2014 Hetts AJNR [26]	*361 pts total; 137 pts SAC*	*85/137 (62%) were wide-neck anz*			*None*	*N/A*	*137/361 (38%) SAC*	*All = 137 anz SAC; WNA = 85 anz SAC (All = 114 anz; WNA = 70 anz)*	*29/137 (21%)*	*16/85 (19%)*	*59/114 (52%)*	*32/70 (46%)*	*12/137 (9%)*	*12/85 (14%)*	*Clinical = 1yr, 2yr Angio = 12 ± 3mo*
2014 Liu J Clin Neurosci [69]	*235 anz 235 pts with coiling (& 56 anz 56 pts SAC)*	*Mostly Wide-neck (Mean neck width for coiled anz = 4.08 ± 2.85mm)*			*165/235 (70%)*	*100% PComA*	*81% Coiling 19% SAC*	*235 anz (203 anz)*	*N/A*	*83/235 (35%)*	*N/A*	*103/203 (51%)*	*N/A*	*57/203 (28%)*	*13.2 ± 9.5 mo = mean angio FUP*
2014 Peterson Neurosurg [42]	*35 anz 35 pts with BAC; (& 71 anz 71 pts with SAC)*	*100% Wide-neck*			*None*	*89% Ant 11% Post*	*35/106 (33%) = BAC; 71/106 (67%) = SAC*	*35 anz (35 anz)*	*N/A*	*18/35 (51%)*	*N/A*	*19/35 (54%)*	*N/A*	*2/35 (6%)*	*Angio FUP at 6mo and 12 mo*
2015 Song J Korean Neurosurg Soc [70]	*53 anz 53 pts*	*100% Wide-neck*			*28/53 (53%)*	*17% AComA 9% MCA Bifurc^{n} 8% Cavernous 26% Paraclinoid 19% PComA 8% Basilar Tip 13% Unk*	*85% Coiling 15% SAC*	*45 anz coiling alone; 8 anz SAC (45 anz coiling alone; 8 anz SAC)*	*N/A*	*25/45 (56%)*	*N/A*	*20/45 (44%)*	*N/A*	*15/45 (42%) = major recurrence; 7/45 (16%) = minor recurrence; 8/53 (15%) = retreatment*	*Angio FUP 37.9 mo (12 - 120 mo)*
2011 Modi Interv Neuroradiol [40]	*11 anz 11 pts*	*100% Wide-neck*			*6/11 (55%)*	*64% Ant 36% Post*	*100% BAC*	*11 anz (11 anz)*	*N/A*	*8/11 (73%)*	*N/A*	*8/11 (73%)*	*N/A*	*1/11 (9%)*	*11 mo (6-20 mo)*

N = sample size; BAC = balloon-assisted coiling; SAC = stent assisted coiling; Anz= aneurysm; FUP = follow-up; ALL = all aneurysms studied; WNA = wide neck aneurysm; Angio = angiography/angiogram; pts = patients; ant = anterior circulation; post = posterior circulation; N/A = not available; mo = months; yr = years; PComA = posterior communicating artery; AcomA = anterior communicating artery; MCA = middle cerebral artery; Bifurc^{n} = bifurcation; Unk = unknown

Random Effect Model Meta-Analyses

Two random effect model meta-analyses were performed in order to determine overall complete occlusion rates of treated aneurysms at final follow-up. One meta-analysis was performed using complete occlusion data from published literature only, with data from the article by Hetts et al[26] being used as data from the MAPS study. This meta-analysis included data for coiling alone, balloon-assisted coiling, and stent assisted coiling, with the latter coming from articles by Hetts et al[26] and Chalouhi et al[38]. For this meta-analysis, data specific to wide neck aneurysms yielded an average weighted complete occlusion rate of 49% (**Figure 3**). The second meta-analysis was performed using complete occlusion data from published literature for coiling and balloon assisted coiling in combination with complete occlusion data for coiling only subjects from the previously described MAPS wide neck aneurysm patient cohort (N = 247). For this meta-analysis, data specific to wide neck aneurysms yielded an average weighted compete occlusion rate of 47% (**Figure 4**). Given the findings of these two meta-analyses, a historical control rate of 50% for complete occlusion is conservative and is justified.

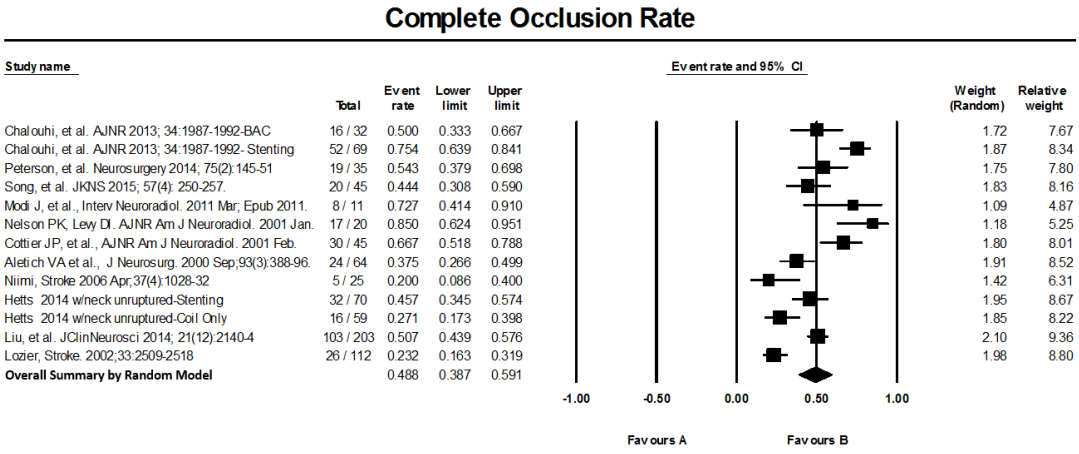


Figure 3 - Complete Occlusion Rates, Wide Neck Intracranial Aneurysms Only, MAPS Data from Hetts et al., Includes Stent Assisted Coiling Data from Hetts et al. and Chalouhi et al.

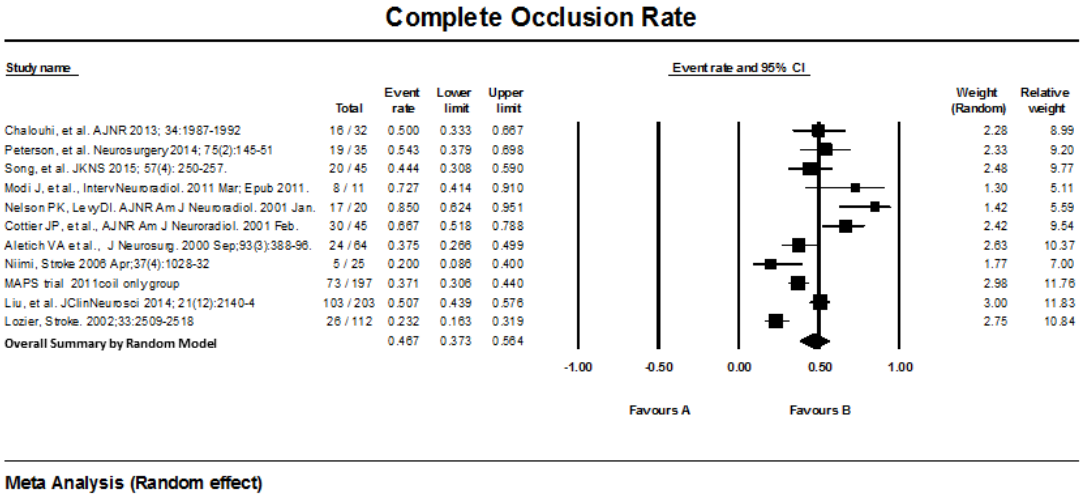


Figure 4 - Complete Occlusion Rates, Wide Neck Intracranial Aneurysms Only, MAPS Data from MAPS Dataset, Includes Coiling or Balloon Assisted Coiling Data Only

4.5.2 Justification of Safety Criteria

Data from the MAPS Trial

As presented in **Table 5**, analysis of the 12-month (± 3 months) safety data from the previously described MAPS wide-neck aneurysm patient cohort (N = 247) showed that the overall stroke rate was 6.9% (17/247), and in the anterior and posterior subgroups, the stroke rates were 5.9% (12/205) and 11.9% (5/42), respectively (P = 0.18). There was one neurological death, which occurred in the anterior circulation subgroup (0.5%). When stroke and neurological death rates were combined, the overall incidence rate was 7.3% (18/247).

Table 5 - MAPS Cohort - Primary Safety Outcomes

Primary Safety Outcomes	Wide Neck Aneurysms [1,2] (N =247)		P-value
	Anterior Non-petrous (n =205)	Posterior (n =42)	
Stroke [3]	5.85% (12/205)	11.90% (5/42)	0.1787
Neurological Death	0.49% (1/205)	0.00% (0/42)	1.0000
Composite of Stroke and Neurological Death	5.85% (12/205)	11.90% (5/42)	0.1787

[1] Neck width ≥ 4mm or dome-to-neck ratio < 2
[2] Excludes subjects with a pre-procedure Hunt and Hess score ≥ 3; excludes subjects with a pre-procedure mRS score ≥ 4
[3] Includes strokes of any type or severity

Safety data from the MAPS wide neck aneurysm patient cohort are consistent with the primary safety endpoints that have been chosen for each cohort in this study. Assuming a primary safety endpoint of 8% in the anterior circulation cohort and 12% in the posterior circulation cohort, the upper limit of the 95% confidence interval of the proportion of subjects who achieve the primary safety endpoint is <20.0% and <25.0% in each cohort, respectively.

Data from the Scientific Literature

The 11 articles located via the comprehensive literature search that was performed to locate relevant historical effectiveness data were likewise used to develop objective performance benchmarks against which the safety results of this study could be measured.[26, 30, 31, 37-42, 69, 70] A summary of safety data derived from these articles is presented in **Table 6**.

A review of these articles yielded ranges for procedural complication rates (1% - 36%), procedural morbidity (mRS ≥3) rates (0% - 17%), procedural neurologic mortality rates (0% - 9%), stroke rates through follow-up (0% - 12%), long-term morbidity (mRS ≥3) rates (2% - 13%), and long-term neurologic mortality rates (2% - 10%) for all aneurysms that were treated using embolic coiling, balloon-assisted embolic coiling, or stent assisted coiling. For the sub-set of wide neck aneurysms that were treated using embolic coiling, balloon-assisted embolic coiling, or stent assisted coiling, long-term morbidity and mortality rates ranged from 0% - 25%.

Again, given these findings, the success criteria for safety that have been chosen for this study (i.e., upper limit of the 95% confidence interval of the proportion of subjects with anterior or posterior circulation aneurysms who achieve the primary safety endpoint is < 20 % and <25%, respectively) are within range and appropriate.

Table 6 - Summary of Safety Data Derived from Literature Search

Reference	*N*	*Neck <4mm*	*Neck ≥4mm*	*Dome-to-Neck Ratio*	*Ruptured*	*Location*	*Coiling BAC SAC*	*Procedural Complications*	*Procedural Morbidity (mRS ≥3)*	*Procedural Neurologic Mortality*	*Stroke (Procedure Thru Follow-up)*	*Long-Term Morbidity (mRS ≥3)*	*Long-Term Neurologic Mortality*	*Long-Term Morbidity & Mortality for WNA Subset*	*Follow-Up Period Mean (Range)*
2000 Aletich JNS [37]	*75 anz 72 pts*	*52/75 (69%)*	*23/75 (31%)*	*53/75 (71%) = <2 22/75 (29%) = ≥2*	*20/75 (27%)*	*75% Ant 25% Post*	*100% BAC*	*7/72 (10%); 2 = anz rupture 1 = TE stroke*	*4/72 (6%)*	*3/72 (4%)*	*2/72 (3%)*	*N/A*	*N/A*	*7/72 (10%)*	*11.2 mo (6-29 mo)*
2001 Cottier AJNR [39]	*45 anz 44 pts*	*100% Wide-neck anz*			*27/44 (61%)*	*95% Ant 5% Post*	*100% BAC*	*2/44 (5%); 2 = TE*	*0/44 (0%)*	*0/44 (0%)*	*0/44 (0%)*	*N/A*	*N/A*	*N/A*	*16 mo (3 mo - 5 yr)*
2001 Nelson AJNR [41]	*22 anz 22 pts*	*100% Wide-neck anz*			*9/22 (41%)*	*100% Ant*	*100% BAC*	*7/22 (32%); 1 = minor stroke 2 = groin hematomas 1 = groin pseudoanz 1 = TE 2 = TIA (1 in pt who also had a groin hematoma)*	*1/22 (5%)*	*2 /22 (9%)*	*1/22 (5%)*	*N/A*	*N/A*	*2/22 (5%)*	*angio 19 mo clinical 29 mo*
2002 Lozier Stroke [30]	*495 anz 489 pts (meta-analysis of 12 studies)*	*40%*	*60% Wide-neck anz*		*19%*	*100% Post*	*100% Coiling*	*62/489 (13%); 13 = rupture 14 = coil protrusion 27 = thrombosis 5 = embolism 3 = dissection*	*25/489 (5%)*	*7/489 (1% procedural); 33/489 (7% at 30 days)*	*N/A*	*24/450 (5%)*	*44/450 (10%)*	*N/A*	*16.8 mo (mean for 6/12 studies) and 26.1 mo (mean for 6/12 studies)*
2006 Niimi Stroke [31]	*74 anz 70 pts*	*43/74 58%*	*10/74 (14%) = Small wide-neck 20/74 (27%) = Large (assumed to be wide-neck) 1/74 (1%) = Giant (assumed to be wide-neck)*		*31/74 (42%)*	*80% Ant 20% Post*	*79% Coiling 16% BAC 5% SAC*	*12/70 (17%); 4 = TE events 4 = coil protrusion 1 = thrombus, extravasation (death) 3 = asymptomatic*	*1/70 (1%)*	*1/70 (1%)*	*2/70 (3%); 1 = TE 1 = delayed rupture*	*8/62 (13%)*	*3/62 (5%)*	*N/A*	*15 mo (1-37 mo)*
2013 Chalouhi AJNR [38]	*101 pts total; 32 BAC*	*100% Wide-neck*			*21/32 (66%)*	*81% Ant 19% Post*	*32/101 (32%) BAC*	*3/32 (9%) 1 = rupture 1 = thrombus 1 = infarct*	*1/32 (3%)*	*N/A*	*1/32 (3%)*	*N/A*	*N/A*	*1/32 (3%); permanent morbidity*	*Angio FUP 6.5 mo (3 - 36 mo)*
2013 Chalouhi AJNR [38]	*101 pts total; 69 SAC*	*100% Wide-neck*			*8/69 (12%)*	*84% Ant 16% Post*	*69/101 (68%) SAC*	*4/69 (6%) 1 = rupture 2 = clinical infarct 1 = silent infarct*	*2/69 (3%)*	*N/A*	*3/69 (4%)*	*N/A*	*N/A*	*2/69 (3%); permanent morbidity*	*Angio FUP 8.0 mo (5 - 48 mo)*

Reference	N	Neck <4mm	Neck ≥4mm	Dome-to-Neck Ratio	Ruptured	Location	Coiling BAC SAC	Procedural Complications	Procedural Morbidity (mRS ≥3)	Procedural Neurologic Mortality	Stroke (Procedure Thru Follow-up)	Long-Term Morbidity (mRS ≥3)	Long-Term Neurologic Mortality	Long-Term Morbidity & Mortality for WNA Subset	Follow-Up Period Mean (Range)
2014 Hetts AJNR [26]	361 pts total; 224 pts coiled	73/224 (33%) were wide-neck anz			None	N/A	224/361 (62%) coiling	**All coiled anz** 10/224 (5%) **Coiled WNA** 1/73 (1%)	N/A	N/A	**All coiled anz** 5/224 (2%) = ischemic stroke; 1/224 (<1%) = delayed rupture **Coiled WNA** 3/73 (4%) = ischemic stroke; 0/73 (0%) = delayed rupture	5/202 (3%)	4/202 (2%)	1/66 (2%) morbidity; 0/66 (0%) mortality	Clinical = 1yr, 2yr Angio = 12 ± 3mo
2014 Hetts AJNR [26]	361 pts total; 137 pts SAC	85/137 (62%) were wide-neck anz			None	N/A	137/361 (38%) SAC	**All SAC anz** 9/137 (7%) **SAC WNA** 3/85 (4%)	N/A	N/A	**All SAC anz** 12/137 (9%) = ischemic stroke; 4/137 (3%) = delayed rupture **SAC WNA** 10/85 (12%) = ischemic stroke; 2/85 (2%) = delayed rupture	2/128 (2%)	3/128 (2%)	0/73 (0%) morbidity; 0/73 (0%) mortality	Clinical = 1yr, 2yr Angio = 12 ± 3mo
2014 Liu J Clin Neurosci [69]	235 anz 235 pts with coiling (& 56 anz 56 pts SAC)	Mostly Wide-neck (Mean neck width for coiled anz = 4.08 ± 2.85mm)			165/235 (70%)	100% PComA	81% Coiling 19% SAC	27/235 (11%); 9 = TE 5 = rupture 13 = coil protrusion	39/235 (17%); oculomotor nerve paresis	N/A	N/A	N/A	N/A	N/A	53/211 (25%)	13.3 ± 9.3 mo for 211/235
2014 Peterson Neurosurg [42]	35 anz 35 pts with BAC; (& 71 anz 71 pts with SAC)	100% Wide-neck			None	89% Ant 11% Post	35/106 (33%) = BAC; 71/106 (67%) = SAC	3/35 (9%) = minor complications (groin complications, asymptomatic vessel dissection)	0/35 (0%)	0/35 (0%)	0/35 (0%)	N/A	N/A	0/35 (0%)	Mean 24.5 mo; 6 and 12 mo angios
2015 Song J Korean Neurosurg Soc [70]	53 anz 53 pts	100% Wide-neck			28/53 (53%)	17% AComA 9% MCA Bifurc^{n} 8% Cavernous 26% Paraclinoid 19% PComA 8% Basilar Tip 13% Unk	85% Coiling 15% SAC	6/53 (11%); 2 = TE (1 resolved, 1 infarction) 2 = aneurysm rupture 1 = occluded ophthalmic (flow restored at FU) 1 = coil migration	1/53 (2%)	0/53 (0%)	1/53 (2%); cerebral infarction	N/A	N/A	0/53 (0%)	Angio 37.9 mo (12 - 120 mo)
2011 Modi Interv Neuroradiol [40]	11 anz 11 pts	100% Wide-neck			6/11 (55%)	64% Ant 36% Post	100% BAC	4/11 (36%); 3 = local thrombus 1 = dissection 1 = groin hematoma	0/11 0%	0/11 0%	0/11 (0%)	N/A	N/A	0/11 (0%)	11 mo (6-20 mo)

N = sample size; BAC = balloon-assisted coiling; SAC = stent-assisted coiling; WNA = wide neck aneurysms; anz = aneurysms; pts = patients; Ant = anterior circulation; Post = posterior circulation; TE = thromboembolic; N/A = not available; mo = months; yr = years; TIA = transient ischemic attack; Angio = angiography/angiogram; FUP = follow-up; mm = millimeters; PComA = posterior communicating artery; AcomA = anterior communicating artery; MCA = middle cerebral artery; Bifurc^{n} = bifurcation; Unk = unknown; FU = follow-up

4.6 Statistical Analysis

All analyses will be performed using SAS, version 9.4 or higher. Some interim analyses and figures may require the use of R 3.2.3 or above.

Primary analysis will initially be carried out when data from 153 evaluable subjects from the mITT group of anterior circulation subjects are available.

Due to the substantially lower incidence of aneurysms in the posterior circulation (approximately 15-20% of diagnosed cases), the subject enrollment period for the posterior circulation cohort will be much longer in duration versus that of the anterior circulation cohort. As a result, analysis of data from the posterior circulation cohort will be completed after results for the anterior circulation subjects have already been submitted for review by the FDA, and data from that analysis will be used to support an expanded indication for use of the Neuroform Atlas™ Stent System, i.e. an indication for use in the posterior circulation. For the posterior circulation cohort, a Bayesian adaptive study design ("Goldilocks" approach) providing for interim analyses of accumulated data will be used to select the final sample-size. The first interim data analysis will occur once 100 posterior circulation subjects have been enrolled. Based on enrollment rates and the frequency of disease in the posterior circulation, at the time this interim analysis is performed it is estimated that primary endpoint data will be available for approximately 39 – 63 posterior circulation subjects. If, at an interim analysis, there is at least a 95% predictive probability of observing a true rate of complete occlusion that is higher than 50%, enrollment in the posterior circulation cohort will be stopped early for success. The maximum sample-size for the posterior circulation cohort will be no more than 180 subjects.

Analyses for both cohorts will be performed by constructing two-sided 95% confidence intervals about the estimates of the percentage of subjects with complete aneurysm occlusion and the percentage of subjects experiencing a major ipsilateral stroke or neurological death using the exact binomial (Clopper-Pearson) method. For the effectiveness endpoint of total occlusion, the lower bound of this confidence interval will be compared to 50% for both the anterior and posterior circulation cohorts. For the safety endpoint of major ipsilateral stroke and neurological death, the upper bound of the confidence interval will be compared to 20% for the anterior circulation cohort, and 25% for the posterior circulation cohort.

Success requires safety and effectiveness endpoints to be met in each cohort separately. Success in the anterior cohort occurs when the lower bound of the effectiveness endpoint is above 50% and the upper bound of the safety endpoint is below 20%. Success in the posterior cohort occurs when the lower bound of the effectiveness endpoint is above 50% and the upper bound of the safety endpoint is below 25%.

The analysis of long-term safety and effectiveness data will be descriptive only, as no formal hypotheses will be tested based on data collected during this phase of the study. Survival analysis will be used to estimate the incidence of specified safety endpoint events, as well as retreatment of the target aneurysm. Details regarding the survival analyses are summarized in **Table 7**.

Table 7 – Endpoint Measure Definitions in the Post-approval Study

	Survival Analysis		Incidence Rate		% Subjects who Experienced the Outcome [2]	
	Competing Risk [1]	Event	Numerator	Denominator	Numerator	Denominator
Primary Safety Outcome	Non-neurologic death	The first event	Number of events (N1)	Person-time based on follow-up date (D1)	Number of subjects who experienced new outcome in the interval (N2)	Number of subjects present for one or more visits during or after the interval or experienced outcomes during the interval (D2)
Neurological death						
New or worsening major ipsilateral stroke	Death					
Any ischemic or hemorrhagic AE(s)						
Hemorrhagic Stroke						
Ischemic Stroke						
SAH						
Aneurysm Rupture						
TIA						
Device-related SAE(s)						
Grade 1 Raymond class in the absence of retreatment, or parent artery stenosis (>50%) at the target location	N/A	N/A	N/A	N/A	Number of subjects who are not retreated and whose current DSA met the outcome definition	Number of subjects with valid DSA or underwent retreatment
Retreatment	Death	The first event	N1	D1	N2	D2
Raymond Class	N/A	N/A	N/A	N/A	Number of subjects whose current DSA met the outcome definition	Number of subjects with valid DSA
Parent Artery Stenosis > 50%	N/A	N/A	N/A	N/A		
Recanalization	Death	The first event	N1	Person-time based on DSA date		
Stent Migration						
Progressive Occlusion of the Target Aneurysm	N/A	N/A	N/A	N/A		

[1] Subjects are censored on the date of the event; other censoring events include lost-to-follow-up, consent withdrawal, and study early discontinuations due to other reasons.

[2] Repeated for each visit interval, i.e. 2-year, 3-year, post-3-year intervals.

[3] The observational period for the survival analysis and incidence rate starts on the day after a subject's 12-month follow-up visit.

4.6.1 Baseline Variables

Baseline variables will be collected including but not limited to: gender, race, age, BMI, hypertension, heart disease, diabetes, smoking status, previous stroke history, baseline rupture/un-rupture status,

aneurysm size, dome size, neck size, dome to neck ratio, aneurysm location, use of antiplatelet agents, and other factors. For baseline ruptured aneurysms, the days/time from the most recent rupture to the index procedure will be summarized and reported. For unruptured aneurysms measuring <7mm for each of three dimensions assessed (height, width, and depth), a baseline variable of "reason for treatment" will also be collected.

The baseline variables will be summarized using descriptive statistics. Continuous variables such as age and BMI will be summarized using mean, standard deviation and N. Categorical variables such as hypertension and diabetes will be summarized using a percentage of subjects exhibiting the characteristic along with the numerator and denominator of that percentage.

4.6.2 Post-procedure Variables

Stryker Neurovascular will analyze the success rate of the Neuroform Atlas™ Stent post-procedure with 95% CI. Stryker Neurovascular will also report any device malfunctions, and all available post procedure clinical outcomes as well as the immediate post procedure image score (Raymond score by Core Lab reading).

4.6.3 Long Term Follow-up Variables

Long-term safety data will be collected from 12 months through 3 years (± 6 months) post-index procedure within the following categories:

- Neurological death or major ipsilateral stroke
- Any ischemic or hemorrhagic event of any severity or duration (including TIAs, SAH, and aneurysm rupture)
- Device-related SAEs

In addition, neurological assessments will be conducted in person at each follow-up visit, and all new and ongoing adverse events will be recorded and adjudicated as specified by the CEC charter.

For imaging performed per standard of care, the long-term effectiveness endpoints identified below will be assessed from 12 months through 3 years (± 6 months) post-index procedure per the long-term follow-up schedule requirements:

- Retreatment
- Parent artery stenosis at the target aneurysm location (>50% stenosis)
- Composite effectiveness measure (complete aneurysm occlusion [Raymond 1] without significant parent artery stenosis at the target aneurysm location [>50% stenosis] or retreatment)
- Recanalization
- Stent migration based on follow-up angiogram
- Aneurysm occlusion of Raymond Class 1, 2, or 3
- Aneurysm occlusion of Raymond Class 1 and 2 combined
- Progressive occlusion of the target aneurysm

4.6.4 Pooling across Institutions

Subgroup analysis will be done to assess if there is heterogeneity among the sites, and to determine if pooling of the data is reasonable. The percentage of patients with total occlusion within each site will be determined and a Pearson chi-square statistic will be used to determine if there are differences between sites. If the p-value of the Pearson chi-square statistic is greater than 0.10 then the sites will be considered poolable. If there are one or two outlier sites, a sensitivity analysis will be done by including them in the analysis as well as excluding those sites in the repeat comparable analysis.

4.6.5 Additional Comparisons

There is no plan for any additional comparisons at this time.

4.6.6 Other Analysis Methods

Stryker Neurovascular may carry out additional analyses for exploratory purposes, such as using the following variables as the stratified variable for additional subgroup analysis: gender, race and other baseline characteristics.

4.6.7 Covariates

Baseline variables are mentioned in **Section 4.6.1** above. Additional procedural variables will be the length of the procedure, the number of coils successfully implanted, packing density, etc. Post procedure variables have been described in **Section 4.6.2**.

These additional covariates will be summarized using descriptive statistics as described for the baseline variables.

4.7 Subject Accountability

All subjects will be included in a summary of subject accountability for this study. The frequency and percentages of subjects enrolled, present at each visit, discontinuing before study completion (including reason for discontinuation) and completing the study will be presented in the final report. For subjects lost to follow-up, the date of last contact will be used to define the censor date.

4.8 Follow-up and Reporting

All subjects enrolled and devices used in the clinical investigation will be accounted for in the final report. All reasons for exclusion from analysis will be documented. Similarly, for all subjects and devices included in an analysis population, the measurements of all important variables will be accounted for at all relevant time points.

Subjects lost to follow-up or withdrawn from the study will be identified, and a descriptive analysis of them will be provided, including the reasons for their loss to follow-up and known treatment outcomes.

All PAS mITT subjects will be asked to return for a 2-year visit and a 3-year visit. If the 3-year visit window has elapsed at the initiation of the PAS follow-up, subjects will be asked to return for at least one long-term follow-up visit.

The analysis of long-term safety and effectiveness data will be descriptive only, as no formal hypotheses will be tested based on data collected during this phase of the study. Survival analysis will be used to estimate the incidence of specified safety endpoint events, as well as retreatment of the target aneurysm.

4.9 Assessment of Attrition Bias

Differential attrition rates among subgroups of the ATLAS subjects could potentially bias the observed safety and durability status in both directions. Adverse events may prevent patients from adequately participating in the study, i.e., informative censorings are created. On the other hand, certain tests may be biased due to the under-participation of the healthier subgroup. Adverse events may result in more frequent hospital visits and therefore a better chance to report mRS and NIHSS. Difficult-to-treat aneurysms with suboptimal occlusion status may be more likely to undergo additional angiograms and to be evaluated with the Raymond-Roy scale.

Analyses will be performed at various stages of the PAS to evaluate the potential effects of attrition bias. Since subjects who died, withdrew, or are lost to follow-up can no longer be followed in the PAS, statistics reported for the PAS mITT cohort should be interpreted as conditional on a given subject's

survival of the first 12 months after the procedure. At the initiation of the PAS, summary statistics on demographics and key clinical characteristics at 12-month follow-up visits will be compared between cohorts with and without deaths, withdrawals, and loss to follow-up. Once patient enrollment for the PAS begins, we will update the PAS mITT cohort with the actual enrollment and present the updated comparison in the interim progress reports and final report.. Sensitivity analyses will be carried out based on different assumptions of the pattern of loss to follow-up. Raymond-Roy scale and mRS will be reported within the context of previous test results. All analyses performed on the PAS mITT cohort will be compared to the PAS ITT population.

5 Data Management

5.1 Data Collection and Processing

Subject data will be collected in a secure electronic data capture (EDC) system via the Internet. The Principal Investigator or Sub-investigator must ensure the accuracy and completeness of the recorded data and then provide his/her electronic signature on the appropriate electronic Case Report Forms (eCRFs). Changes to data previously submitted to the Sponsor will require a new electronic signature by the investigator to acknowledge/approve the changes.

Visual and/or computer data review will be performed to identify possible data discrepancies. Manual and/or automatic queries will be created in the EDC system and will be issued to the site or angiographic Core Lab for appropriate response. The site staff will be responsible for resolving all queries in the database.

Results from the angiographic Core Lab will also be entered or uploaded into the EDC system. Audits may be performed for quality assurance of data handling against Core Lab procedures.

6 Adverse Events

An Adverse Event (AE) is any undesired clinical response or complication experienced by a subject. All AEs (within the study duration), whether device-related or not, will be recorded on the AE case report forms. Data to be collected will include the description of the AE event term, onset and resolution dates (or whether the AE is ongoing), severity, management/treatment, outcome, and determination of the relationship to the device and/or procedure.

6.1 Adverse Event Definitions and Classification

Table 8 – Adverse Event Definitions and Classifications

Term	Definition	Reference
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. **NOTE 1**: This definition includes events related to the investigational medical device or procedures involved.	ISO 14155

Term	Definition	Reference
Adverse Device Effect (ADE)	Adverse event related to the use of an investigational medical device. **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 device.	ISO 14155
Serious Adverse Event (SAE)	Adverse event that: A. led to death, B. led to serious deterioration in the health of the subject, that resulted in either: 1. a life-threatening illness or injury, 2. a permanent impairment of a body structure or a body function, 3. in-subject or prolonged hospitalization, 4. 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. **NOTE:** Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without serious deterioration in health, is not considered a SAE.	ISO 14155
Serious Adverse Device Effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.	ISO 14155
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 Part 812

Underlying diseases are not reported as Adverse Events (AEs) unless there is an increase in severity or frequency during the course of the investigation. Death should not be recorded as an adverse event, but should only be reflected as an outcome to another specific SAE. Any AE experienced by the study

subject after informed consent whether during or subsequent to the procedure must be recorded in the (e)CRF.

All AEs and SAEs will be monitored and collected from the time of enrollment through 3 years (± 6 months) post-index procedure.

Relationship to the Device:

The Investigator must assess the relationship of the adverse event to the study device using the following criteria categories and definitions:

- **Unrelated** - The adverse event is determined to be due to a concurrent illness or effect of another device/drug and is not related to the investigational product.
- **Possible** - The adverse event is determined to be potentially related to the investigational product, and an alternative etiology is equally or less likely compared to the potential relationship to the investigational product.
- **Probable** - There is a strong relationship to the investigational product, or recurs on re-challenge, and another etiology is unlikely.
- **Related** - There is no other reasonable medical explanation for the event.

Relationship to the Procedure:

The Investigator must assess the relationship of the adverse event to the index procedure using the following categories and definitions:

- **Unrelated** - The adverse event is determined to be due to a concurrent illness or effect of a device/drug and is not related to the index procedure.
- **Possible** - The adverse event is determined to be potentially related to the index procedure, and an alternative etiology is equally or less likely compared to the potential relationship to the index procedure.
- **Probable** - There is a strong relationship to the index procedure, or recurs on re-challenge, and another etiology is unlikely.
- **Related** - There is no other reasonable medical explanation for the event.

6.2 Reporting Requirements

The Sponsor will ensure that event reporting is as mandated by the FDA and/or local Regulatory Authorities. The communication requirements for Adverse Event reporting to the Sponsor are as follows:

Table 9 – Communication Requirements for Reporting Adverse Events to the Sponsor

Adverse Event Classification	Communication Method	Communication Timeline	Primary Sponsor Contact
UADE	Complete AE (e)CRF page including UADE question with all available new and updated information	Within 24 hours of first becoming aware of the event.	Clinical Research Associate and/or Clinical Affairs Safety Representative

Adverse Event Classification	Communication Method	Communication Timeline	Primary Sponsor Contact
SAE and/or SADE (EU only)	Complete AE (e)CRF page with all available new and updated information	Within 24 hours of first becoming aware of the event.	Clinical Affairs Safety Representative
AE	Complete AE (e)CRF page	As soon as possible	Clinical Research Associate
Device Failures, Malfunctions, and Product Nonconformities	Complete CRF pages with all available new and updated information	Within 24 hours of first becoming aware of the event	Clinical Research Associate, Clinical Affairs Safety Representative

6.3 Device Failures, Malfunctions, and Product Nonconformities

All device failures, malfunctions, and product nonconformities will be documented on the appropriate eCRF and the device should be returned to the Sponsor for analysis. Instructions for returning the investigational device will be provided in the study Manual of Operations. Device failures and malfunctions should also be documented in the subject's medical record.

Note: Device failures, malfunctions, and product nonconformities are not to be reported as adverse events. However, if there is an adverse event that results from a device failure or malfunction, that specific event would be recorded on the appropriate eCRF.

6.4 Reporting to Regulatory Authorities/IRBs / ECs /Investigators

The Sponsor is responsible for reporting adverse event information to all participating investigators and regulatory authorities, as applicable.

The Site Principal Investigator is responsible for informing the IRB/EC of UADEs, SAEs, and/or events as required by local procedure. A copy of this report should be sent to the Sponsor Clinical Research Associate.

Refer to **Section 10.2** for information pertaining to the Clinical Events Committee (CEC).

7 Risk Analysis

7.1 Known and Anticipated Risks

Subjects treated in this study will be exposed to risks associated with intravascular catheterization, stent placement, neurovascular embolization coil placement, and general anesthesia. These risks include but are not limited to:

1. Allergic reaction to Nitinol metal and medications
2. Aneurysm perforation/rupture
3. Coil herniation through stent into parent vessel

4. Death
5. Embolus
6. Hemorrhage
7. In-stent stenosis
8. Infection
9. Ischemia
10. Neurological deficit/intracranial sequelae
11. Pseudoaneurysm
12. Recanalization requiring retreatment
13. Stent fracture
14. Stent migration/embolization
15. Stent misplacement
16. Stent thrombosis
17. Stroke
18. Transient ischemic attack
19. Vasospasm
20. Vessel occlusion or closure
21. Vessel perforation/rupture, dissection, trauma or damage
22. Vessel thrombosis
23. Other procedural complications including but not limited to anesthetic and contrast media risks, hypotension, hypertension, access site complications.

Refer to the appropriate embolic coil DFU for other complications that may occur due to coil embolization.

Subjects treated with Aspirin and Clopidogrel will be exposed to certain risks. These risks include but are not limited to:

1. Bleeding, including access site, cerebral and gastrointestinal bleeding
2. Abdominal pain, nausea, vomiting, dyspepsia
3. Gastric ulcer, gastritis
4. Rash
5. Retroperitoneal hematoma
6. Anemia

7.2 Reported Benefits

Endovascular aneurysm treatment with the Neuroform Atlas™ Stent System may offer certain advantages as compared to no treatment or alternative treatment of an intracranial aneurysm. Potential benefits that may be associated with use of Neuroform Atlas™ Stent System for the intended subject population include:

- Reduced occurrence of rupture
- Reduced occurrence of recanalization

- Ability to treat wide neck aneurysms; these aneurysms are considered at the highest risk of rupture and some aneurysms are not treatable with current standard of care techniques (coiling, balloon supported coiling and surgery)
- Increased navigability and the treatment of more challenging aneurysms due to thinner, lower profile and higher flexibility of the stent
- Acceptable safety profile compared to existing technologies for treatment of wide neck aneurysms[71]

A history of successful commercialization of the previous generations of the Neuroform Atlas™ Stent System confirmed that clinical benefits associated with the use of these products outweigh clinical risks.

7.3 Risk Minimization

Subjects will be carefully evaluated before entering the study to ensure that the location, diameter, and length of the aneurysm are appropriate for treatment with the Neuroform Atlas™ Stent and embolic coiling.

Only trained surgeons with expertise in the endovascular treatment of intracranial aneurysms will participate in this study. Prior to enrolling and treating a subject in the study, all Investigators will review and understand the DFU, and will be trained by the Sponsor with regards to use of the Neuroform Atlas™ Stent System.

Subjects will be heparinized during the endovascular procedure to reduce the risk of thrombosis.

Antibiotics will be administered in subjects with increased risk of post-operative infection.

Subjects will be carefully monitored during the study and the follow-up period. The Site Principal Investigator (or designee) will examine and perform various diagnostic tests immediately after the procedure, at hospital discharge, at the 2, 6 and 12-month follow up, and at the 2- and 3-year follow-up visits.

In addition to monitoring data directly related to the Neuroform Atlas™ Stent and embolization coil placement, blood data will be obtained preoperatively and postoperatively. These data will be used to determine the subject's coagulation status, to assess for infection as indicated by white blood cell count, and to detect significant internal bleeding with hemoglobin and hematocrit levels.

Data from all clinical sites will be monitored as it is submitted to the Sponsor, or the Sponsor's representatives will conduct monitoring visits at each investigational site before the study begins and at least every six months during the study to determine if the protocol is being followed. The Sponsor will routinely review the data and any other issues that may affect the safety and welfare of the subjects.

Based on the risks identified and the procedural and monitoring methods employed to minimize these risks, the Sponsor believes that the potential benefits of treatment with the Neuroform Atlas™ Stent System outweigh the associated risks of the procedure.

7.4 Risk Benefit Analysis

7.4.1 Subject Population

Potential risks to study subjects have been minimized by establishing strict inclusion/exclusion criteria to assure only appropriate candidates participate in the study. Only those subjects presenting with a wide neck (neck ≥4mm or a dome-to-neck ratio <2), intracranial, saccular aneurysm arising from a parent vessel with a diameter of ≥2mm and ≤4.5 mm, who are deemed eligible to participate in the study, will receive stent-assisted coiling with the Neuroform Atlas™ Stent System. Selection of embolic coils will be restricted to commercially available bare metal coils only.

7.4.2 Justification for Investigation

Although there are risks associated with use of the Neuroform Atlas™ Stent System, these risks are the same as those associated with the use of prior generations of the Neuroform Stent (Neuroform EZ and Neuroform EZ3), all of which have received Humanitarian Device Exemption (HDE) approval from the FDA. HDE approval is based upon, among other criteria, a determination by the FDA that the humanitarian use device will not expose subjects to an unreasonable or significant risk of illness or injury, and the probable benefit to health from use of the device outweighs the risk of injury or illness from its use, while taking into account the probable risks and benefits of currently available devices or alternative forms of treatment.[3]

From a procedural standpoint, prior generation devices have shown a satisfactory history of clinical use. Appropriate steps have been taken to minimize the risks associated with the device design and materials. In addition, protocol-specified procedural and monitoring methods (as specified in **Section 7.3** above) will be employed to minimize risks to study subjects.

There are substantial potential benefits associated with treatment using the Neuroform Atlas™ Stent System, and the risks associated with the procedure have been identified and minimized where possible. Thus, the balance of potential risks and benefits associated with use of the Neuroform Atlas™ Stent System warrants further clinical research and justifies this investigation.

8 Device Description

8.1 Detailed Device Description

The proposed Neuroform Atlas™ Stent System is similar to the Neuroform EZ Stent System and consists of the following three components:

- Self-expanding Stent
- Stent Delivery Wire
- The stent delivery wire comes in two configurations: 1. With an 8.5 mm distal tip. 2. Without a distal tip. Select a configuration based upon physician preference
- An accessory pouch containing an optional torque device. The physician my attach the torque device to the proximal end of the stent delivery wire to facilitate handling and stabilization

The system provides a laser cut, nitinol, self-expanding stent preloaded over a delivery wire inside an introducer sheath. The sheath and delivery wire are used to transfer the stent into a 0.0165”- 0.0170” ID microcatheter. After transfer, the sheath is removed from the system via the proximal end of the delivery wire. The delivery wire is then used to advance the stent to the distal end of the catheter. The catheter, stent, and delivery wire are repositioned appropriately to ensure the stent is located across the neck of the aneurysm. The stent is deployed by stabilizing the delivery wire and withdrawing the catheter.

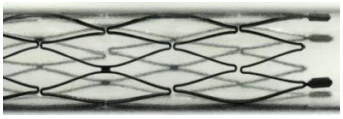
The operating principles, materials and device features of the Neuroform Atlas™ Stent System are similar to those of the Neuroform EZ Stent System with the exception of microcatheter size compatibility. To improve stent delivery and ease of use, and to reduce procedure time, the Neuroform Atlas™ Stent System has been scaled down to fit inside a 0.0165” - 0.0170” ID microcatheter. The Neuroform EZ Stent is compatible with a 0.027” ID microcatheter.

Self-expanding Stent:

Both the Neuroform EZ Stent and Neuroform Atlas™ Stent share a self-expanding, open-cell, nitinol design with radiopaque marker bands on each end (proximal and distal). Zig-zag shaped elements make up the pattern of both designs. The zig-zag elements are connected by interconnects (3/2 mix for Neuroform EZ and 4 connectors symmetrically patterned for the Neuroform Atlas™ Stent). Both stents are laser cut from a Nitinol tube. The Neuroform EZ and Neuroform Atlas™ Stents include 4 and 3 markers per end, respectively.

Although the Neuroform EZ Stent and Neuroform Atlas™ Stent cut patterns are different, the devices' ability to support embolization coils in the aneurysm and their clinical performance are expected to be similar. **Table 10** is a summary of the Neuroform EZ Stent and Neuroform Atlas Stent features.

Table 10 – Neuroform EZ Stent and Neuroform Atlas™ Stent Summary

	Neuroform EZ Stent	Neuroform Atlas™ Stent
Stent Design		
Material	Nitinol, ASTM F2063-12	Nitinol, ASTM F2063-12
Design	Open cell	Open cell
Deployment	Self-Expanding	Self-Expanding
Vessel Diameter	2.0-4.5 mm	2.0-4.5 mm
Expanded Diameters (mm)	3.0, 3.5, 4.0, 4.5, 5.0	3.5, 4.5, 5.0
Lengths (mm)	10, 15, 20, 30	15, 21, 24, 30
Cells & Interconnects	8 cells, 2-3 interconnects	8/12 cells, 4 interconnects
End ring Design	Unflared	Flared
Radiopaque Markers	4 per end, crimped sleeve, Pt/Ir alloy	3 per end, crimped sleeve, Pt/Ir alloy

Delivery System:

Stent Delivery Wire

The function and operating principles of the Neuroform Atlas™ Stent Delivery Wire are the same as those for the Neuroform EZ Stent Delivery Wire. The stent delivery wire is a component similar in construction to a guidewire, and is composed of 304V stainless steel. The stent delivery wire is designed to be used with 150cm microcatheters. The stent comes preloaded on the stent delivery wire inside the introducer sheath and is used to advance the stent into the microcatheter.

Introducer Sheath

The introducer sheath for the Neuroform Atlas™ Stent System and the Neuroform EZ Stent System is a polymer-based material which covers both the stent and the stent delivery wire. The purpose of the introducer sheath is to constrain the stent prior to use and to assist in transferring the stent into the microcatheter. The introducer sheath is also used to protect the stent during sterilization, storage, shipping, and handling.

Microcatheter

Please note: Similar to the 0.027" ID microcatheter that is used in conjunction with the Neuroform EZ Stent System, the 0.0165" - 0.0170" ID microcatheters used in conjunction with the Neuroform Atlas™ Stent System are sold separately and will not be part of the Neuroform Atlas™ Stent System.

8.2 Procedural Technique

The Neuroform Atlas™ Stent System will be used as an adjunct to coil embolization in accordance with the instructions provided in **Section 3.8.2 Implant/Procedural Steps**, and the Directions for Use (DFU) included in each device package

8.3 Device Labeling

A copy of the Directions for Use (DFU) will be included in each device package which includes a description of all relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions.

The study devices will be labeled on the Package Carton and Sterile Barrier (pouch). The labels will contain the following information:

- Name and place of business of the manufacturer, packer, or distributor
- Quantity of contents
- "CAUTION--Investigational device. Limited by Federal (or United States) law to investigational use."
- Device Dimensions
- Lot Number
- Expiration Date

9 Monitoring Plan

Monitoring for this study will be conducted by the Sponsor or designee in accordance with the study monitoring plan. The study will be monitored to ensure that the protocol, applicable regulations, and Good Clinical Practice (GCP) Guidelines are followed. The Monitor will ensure that the rights and well-being of subjects are protected in compliance with Title 21 of the Code of Federal Regulations (21 CFR), parts 50, 56 and 812, and Title 45 (45 CFR), part 46, and that the clinical trial data are accurate, complete, and verifiable.

9.1 Monitoring Procedures

9.1.1 Qualification and Initiation

All sites will undergo a qualification process to confirm acceptability for participation into the study. Study initiation training visits or webcasts will be performed at the start of the clinical study to ensure that the study personnel have a complete understanding of the protocol, procedures, responsibilities, and regulations involved with the conduct of a clinical trial. Study personnel will be trained on all essential aspects of the trial prior to the first subject being enrolled in the study. This training will include an in-depth review of the protocol and case report forms, regulatory requirements, serious adverse experience reporting, and other activities as documented in the monitoring plan.

9.1.2 Periodic Monitoring

Periodic monitoring activities will be conducted at all active investigational sites throughout the clinical study in order to assure that the Investigator obligations are fulfilled and all applicable regulations and guidelines are being followed. During monitoring activities (on-site or remote), the monitor will verify the following data:

- Verification that informed consent was obtained appropriately
- Adherence to protocol eligibility criteria
- Procedures for documenting appropriate accountability and administration of the investigational product
- Conduct and documentation of procedures and assessments related to:
  - study endpoints
  - protocol-required safety assessments
  - evaluating, documenting, and reporting serious adverse events and unanticipated adverse device effects, subject deaths, and withdrawals, especially when a withdrawal may be related to an adverse event
  - conduct and documentation of procedures essential to trial integrity

9.1.3 Documentation

Documentation of monitoring activities will include the following to provide sufficient detail to verify that the monitoring plan was followed:

- The date of the activity and the individual(s) conducting and participating in it
- A summary of the data or activities reviewed
- A description of any noncompliance, potential noncompliance, data irregularities, or other deficiencies identified
- A description of any actions taken, to be taken, or recommended, including the person responsible for completing actions and the anticipated date of completion

9.2 Name and Address of Monitor

The Sponsor of the study, SNV, or designated Contract Research Organization (CRO), is responsible for the monitoring of the study. The Sponsor will ensure that the study is monitored by personnel qualified by training and experience to monitor the progress of the investigation.

The Clinical Affairs department has overall responsibility for monitoring this study and is located at:

Stryker Neurovascular
47900 Bayside Parkway
Fremont, CA 94538-6515
Tel. 510 413-2500

NOTE: A complete list of study monitors and their qualifications will be maintained and will be available upon request.

9.3 Auditing

The study may be subject to a quality assurance audit by the Sponsor or its designees, as well as inspection by appropriate regulatory authorities.

It is important that the Investigator and relevant study personnel are available during any audits, and that sufficient time is devoted to the process.

9.4 Device Accountability

Device accountability records must be maintained at the study site. The quantity of devices received by the study site, those returned to the supplier, and those devices used at the study site will be recorded in the device accountability record. The Site Investigator must explain in writing the reasons for any discrepancy noted in device accountability.

10 Study Committees

10.1 Steering Committee

A Steering Committee will be responsible for overall oversight of the science and execution of the study. It will provide key input regarding study planning, execution, and presentation.

10.2 Clinical Events Committee/Data Safety Monitoring Board (CEC/DSMB)

The Clinical Events Committee/Data and Safety Monitoring Board (CEC/DSMB) is an independent group of experts that advises the study sponsor, Stryker, and the study investigators. The members of the CEC/DSMB serve in an individual capacity and provide their expertise and recommendations. The primary responsibilities of the CEC/DSMB are to:

1) periodically review and evaluate the accumulated study data for participant safety, study conduct and progress;

2) adjudicate pre-specified clinical events as they occur through the 12 month primary endpoint of the IDE study, and through the end of the PAS study;

3) make recommendations to the study sponsor concerning the continuation, modification, or termination of the trial. The CEC/DSMB considers study-specific data as well as relevant background knowledge about the disease, or patient population under study.

The CEC/DSMB shall be composed of at least three members (physicians from the fields of stroke neurology, interventional neurology, neuroradiology or vascular neurosurgery). In order to minimize any potential bias, the members of the CEC/DSMB will be independent and will not be directly involved with the conduct of the study or have any financial conflict.

The CEC/DSMB will review the study on a regular basis as described in the charter established prior to the commencement of the trial. A mission statement and procedures for the committee will be formalized in the charter. The CEC/DSMB will be responsible for reviewing aggregate safety data in order to ensure overall safety of study subjects during the execution of the trial. Guidelines for stopping rules for pre-specified safety endpoints will be established in the charter.

The Committee will be responsible for monitoring patient safety for the duration of patient enrollment and through the end of the PAS study follow up for all subjects. The study endpoints will be reviewed, and safety event causality will be adjudicated as related to the study device, procedure, both, other (specify). Data adjudicated by the independent CEC/DSMB will be used for final analysis.

11 Ethical and Regulatory Considerations

11.1 Compliance with Good Clinical Practices (GCP)

As the Sponsor of this clinical study, SNV has overall responsibility for the conduct of the study, including assurance that the study meets US federal and local regulatory requirements appropriate to the conduct of the study. In this study, the Sponsor will have certain direct responsibilities, and will delegate other responsibilities to a Contract Research Organization (CRO). The Sponsor will adhere to Sponsor

general duties as described in ISO 14155:2011, Clinical investigation of medical devices for human subjects – Good clinical practice, and CFR Part 812, 50, 56, 54 and the World Medical Association Declaration of Helsinki.

The Site Clinical Investigators will ensure that this study is conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and that are consistent with GCP and applicable regulatory (local) requirements; whichever affords the greater protection to the subject.

11.2 Institutional Review Board/Independent Ethics Committee

A copy of the protocol, proposed Informed Consent form, other written subject information, and any proposed advertising material must be submitted to the IRB/IEC for written approval. A copy of the written IRB/IEC approval of the protocol and Informed Consent form must be received by the Sponsor before recruitment of subjects into the study and shipment of investigational product.

The Investigator must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the Informed Consent form. The Investigator must notify the IRB/IEC and Sponsor of any deviations from the protocol or any SAEs/UADEs occurring at the site and other SAE/UADE reports received from the Sponsor in accordance with local procedures.

The Investigator is responsible for obtaining annual IRB/IEC approval and renewal throughout the duration of the study. Copies of the Investigator's reports and the IRB/IEC continuance of approval must be sent to the Sponsor.

11.3 Written Informed Consent Form

The Sponsor will provide a sample Informed Consent Form to the Investigator to prepare for use at his/her site. The written Informed Consent documents should be prepared in the language(s) of the potential subject population.

The Sponsor and the reviewing IRB/IEC must first approve the Informed Consent Form(s) before use at that site/center. The Informed Consent form(s) must be in agreement with the current guidelines as outlined by the Good Clinical Practices (GCP) guidelines, Declaration of Helsinki, and the International Conference on Harmonization (ICH).

Before participating in the clinical trial, each subject must give written Informed Consent after the context of the study has been fully explained to the subject in a language that is easily understood by the subject. The subject also must be given the opportunity to ask questions and have those questions answered to his/her satisfaction. Subjects will be informed by the Investigator or Investigator's designee that they are free to refuse participation in this research study. If they elect to participate, it will be made clear that they may withdraw from the study at any time without prejudicing further care.

Written Informed Consent must be recorded appropriately by means of the subject's, or his/her legal representative's dated signature. The consent process must be documented in the subject's medical chart.

11.4 Amending the Protocol

This protocol must be followed exactly, and can be altered only by written amendments. Following appropriate approval, the revised protocol will be distributed to all protocol recipients.

11.5 Emergency Actions

The Sponsor accepts the right of the Investigator to deviate from the protocol in an emergency when necessary in order to safeguard the life or the physical wellbeing of a study subject. The Investigator must give notice of any emergency deviation, and justification for the deviation must be provided to the Sponsor and the IRB/IEC as quickly as possible after the episode, and in any event, no later than 24 hours after the emergency.

11.6 Protocol Adherence

Prior to beginning the study, the Investigator must sign the Investigator Agreement and Signature page documenting his/her agreement to conduct the study in accordance with the protocol. An Investigator must not make any changes or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency. Each deviation from the protocol must be documented with the date and reason for the deviation, and must be reported to the Sponsor and to the IRB/IEC, per local guidelines and government regulations.

11.7 Protocol Deviations

A protocol deviation is defined as an event where the clinical Investigator or site personnel did not conduct the study according to the Investigational Plan or the Investigator Agreement. GCP regulations require that Investigators maintain accurate, complete and current records, including documents showing the dates and reasons for each deviation from the protocol.

Investigators must obtain prior approval from Stryker NV clinical study management before initiating major deviations from the investigational plan, except where necessary to protect the life or physical well-being of a subject in an emergency. Such approval shall be documented in writing and maintained in clinical study management and Investigator files. Prior approval is generally not expected in situations where unforeseen circumstances are beyond the Investigator's control (e.g. subject was not available for scheduled follow-up office visit, blood sample lost by laboratory, etc.); however, the event is still considered a deviation and will be reported on the appropriate CRF.

Deviations shall be reported to the Sponsor regardless of whether medically justifiable, pre-approved, or taken to protect the subject in an emergency. Subject specific deviations will be reported on the Protocol Deviation Form. Non-subject specific deviations (e.g. unauthorized use of an investigational device outside the study, unauthorized use of an investigational device by a physician who has not signed an Investigator agreement or not been trained in the use of the device, etc.) will be reported to the Sponsor in writing. Investigators will also adhere to procedures for reporting study deviations to their IRB or IEC in accordance with their specific IRB reporting policies and procedures.

For reporting purposes, the Sponsor classifies study deviations as being major or minor, as follows:

- Major Deviation: Any deviation from subject inclusion and exclusion criteria, subject informed consent procedures or unauthorized device use.
- Minor Deviation: Deviation from a protocol requirement such as incomplete/inadequate subject testing procedures, follow-ups performed outside specified time windows, etc.

Minor Deviations that continue to occur at an investigational site may be classified as Major Deviations if corrective action is not taken to secure future compliance to the protocol.

All protocol deviations will be tabulated and summarized in the final study report.

12 Study Administration

The Sponsor will make necessary efforts to ensure that this study is conducted in compliance with GCPs and all applicable regulatory requirements.

12.1 Pre-Study Documentation Requirements

Prior to subject enrollment, the Sponsor (or designee) will obtain the essential regulatory documents required to initiate the study. The Sponsor will be responsible for the review and approval of the following essential documents:

- Protocol Signature Page

- Current Protocol Revision
- Investigator Agreement
- Financial disclosure or certification
- IRB approval letter for the protocol and consent form
- IRB approved consent form
- IRB membership roster or assurance number
- Copies of file documents will be maintained by the Sponsor

12.2 Record Retention

The Investigator will maintain all essential trial documents and source documentation, in original format, that support the data collected on the study subjects in compliance with the ICH/GCP guidelines. Documents must be retained for at least 2 years after the last approval of marketing application or until at least 2 years have elapsed since the formal discontinuation of the clinical investigation of the product. These documents will be retained for a longer period of time by agreement with the Sponsor, or in compliance with other regulatory requirements. When these documents no longer need to be maintained, it is the Sponsor's responsibility to inform the Investigator. The Investigator will take measures to ensure that these essential documents are not accidentally damaged or destroyed. If for any reason the Investigator withdraws responsibility for maintaining these essential documents, custody must be transferred to an individual who will assume responsibility. The Sponsor must receive written notification of this custodial change.

12.3 Criteria for Terminating Study

The Sponsor reserves the right to terminate the study, but intends only to exercise this right for valid scientific or administrative reasons and reasons related to the protection of subjects. Investigators and their associated IRB/IEC will be notified in writing in the event of termination.

12.4 Criteria for Suspending/Terminating a Study Center

The Sponsor reserves the right to stop the enrollment of subjects at a study center at any time after the study initiation visit. Enrollment may be discontinued by the Sponsor for reasons including, but not limited to, the following:

- Insufficient recruitment of subjects
- Persistent non-compliance with the protocol
- Persistent non-compliance with IRB/IEC or regulatory requirements

In the event the Sponsor ceases enrollment at one or more sites, the Site Investigator(s) will remain responsible for the complete follow-up of all subjects already entered into the study, in accordance with the Investigational Plan.

12.5 Clinical Trial Registration

The study will be registered with the National Institutes of Health National Library of Medicine's ClinicalTrials.gov.

12.6 Release of Study Results

A final report will be completed describing the results of all pre-specified outcomes, including negative results. The Sponsor will ensure that investigators and regulatory authorities will receive the information

contained in the final report, and will do so in a timely manner.

At the conclusion of the trial, a multi-center abstract reporting the results will be prepared and may be presented at a major meeting(s). A multi-center publication may also be prepared for publication in a reputable scientific journal. The publication of results from any single center experience within the trial is not allowed until the aggregate study results have been published, unless there is written consent from the study sponsor.

12.7 Medicare Beneficiaries

In this study, subjects up to 80 years of age are eligible for study enrollment if all other study-entry criteria are satisfied. Based on literature review and current medical practice, a large proportion of the subjects enrolled into this study are expected to be Medicare eligible. For example, in a large scale study of a similar subject population of 818 subjects harboring 916 aneurysms, who were treated with coil embolization, it was reported that 59% of the study population was over 50 years of age (and 15.5% of the total population was at least 70 years of age).[24] The results of this study are therefore expected to be generalizable to the Medicare beneficiary population on the basis of age.

13 References

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14 Appendices

A. Abbreviations

AE	Adverse Event
AGCL	Angiographic Core Laboratory
CBC	Complete Blood Count
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CRA	Clinical Research Associate
CRF	Case Report Form
CT	Computed Tomography
CV	Curriculum Vitae
CVA	Cerebrovascular Accident
DSA	Digital Subtraction Angiography
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
HDE	Humanitarian Device Exemption
IC	Informed Consent
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISO	International Organization for Standardization
ITT	Intent-to-Treat
MDR	Medical Device Report

MDV	Medical Device Vigilance Report
MEC	Medical Ethics Committee
MI	Myocardial Infarction
MR	Magnetic Resonance
MRA	Magnetic Resonance Angiography
MRI	Magnetic Resonance Imaging
PP	Per Protocol
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
SAH	Subarachnoid Hemorrhage
SNV	Stryker Neurovascular
TBD	To Be Determined
TIA	Transient Ischemic Attack

B. Definitions

ADJUNCTIVE THEARPY (ADJUNCTIVE DEVICE)

Adjunctive therapy (or an adjunctive device) is a treatment (device) that is used in addition to, or together with, the primary treatment. Its purpose is to assist the primary treatment.

ANEURISMAL

Relating to an aneurysm

ANEURYSM MORPHOLOGY

Referring to the shape of an aneurysm

ANEURYSM OCCLUSION

The degree of target aneurysm occlusion by coils and/or thrombus as measured by the modified Raymond Scale[64, 72]

- Raymond 1: complete occlusion/obliteration--no opacification of the aneurysmal sac or neck
- Raymond 2: Residual neck/dog ear – persistence of the original defect in the arterial wall but without opacification of the aneurysmal sac
- Raymond 3: Residual aneurysm – any opacification of the aneurysmal sac

ANGIOGRAPHIC

The radiographic visualization of the blood vessels after injection of a radiopaque substance

ARTERIAL DISSECTION

A tear in an artery

ATHEROSCLEROTIC STENOSIS

A narrowing of an artery due to an atherosclerotic process

CBC

Complete blood count (to include at a minimum: red cell count, white cell count, white cell differential, hemoglobin, and hematocrit)

CEREBROVASCULATURE

Blood vessels in the brain

COMPLICATION

Any undesirable clinical event that results in death, injury, or invasive intervention. Complications may include, but are not limited to aneurysmal perforation, occlusion of parent artery or side branches, distal embolization, hematoma, etc. Complications may or may not be related to the product that is the subject of this protocol.

ELECTRONIC CASE REPORT FORM (eCRF)

A record of the data and other information collected on each subject in the study as defined by the clinical protocol

EMBOLIZATION

The process by which or state in which a blood vessel or organ is obstructed by the lodgment of a material mass (as an embolus) <pulmonary embolization><embolization of a thrombus>; also: an operation in which pellets or embolic coils are introduced into the circulatory system in order to induce embolization in specific abnormal blood vessels

HEMATOMA

A localized mass of extravasated blood that is relatively or completely confined within an organ or tissue, a space, or a potential space; the blood is usually clotted (or partly clotted), and, depending on how long it has been there, may manifest various degrees of organization and decolorization

HUNT & HESS SCORE

A neurological grading system used to classify the severity of a subarachnoid hemorrhage based on a subject's clinical condition

INTRACRANIAL ANEURYSM

An abnormal blood-filled dilatation of a blood vessel and especially an artery resulting from disease of the vessel wall inside the brain

INTERVENTION

The act or fact or a method of interfering with the outcome or course especially of a condition or process (as to prevent harm or improve functioning)

INTRACRANIAL HEMORRHAGE

Bleeding within the skull

INTRACRANIAL SACCULAR ANEURYSMS

Round or lobulated focal out-pouchings of intracranial vessels that usually arise from arterial bifurcations

ISCHEMIA

Deficient supply of blood to a body part (as the heart or brain) that is due to obstruction of the inflow of arterial blood (as by the narrowing of arteries by spasm or disease)

ISCHEMIC STROKE

The most common kind of stroke; caused by an interruption in the flow of blood to the brain (as from a clot blocking a blood vessel)

IPSILATERAL STROKE

An acute episode of focal or global neurological dysfunction due to brain or retinal infarction, or from an intracranial hemorrhage (inclusive of subarachnoid, intraventricular or intraparenchymal hemorrhages) in the same hemisphere of the target aneurysm. A major ipsilateral stroke is an ipsilateral stroke which is associated with an increase of 4 or more points on the NIHSS at 24 hours after stroke onset.

Note: For the purpose of consistency with the primary endpoint definition, strokes in the posterior circulation adjudicated as being strokes "within the treated vascular territory" will be called "ipsilateral" strokes.

LEUKOCYTE

White blood cell

MODIFIED RAYMOND SCALE

Anatomical results assigned to 1 of 3 categories according to the Jean Raymond Grading Scale[64, 72]: complete obliteration of the aneurysm including the neck (class 1 or complete occlusion), persistence of any portion of the original defect of the arterial wall as seen on any single projection but without opacification of the aneurysmal sac (class 2 or residual neck), and opacification of the aneurysmal sac (class 3 or residual aneurysm)

MORBIDITY

A diseased state, or the incidence of disease

MORTALITY

The number of deaths in a given time or place or the proportion of deaths to population

MODIFIED RANKIN SCALE (mRS)

A commonly used scale that measures disability or dependence in activities of daily living in stroke victims

NEUROLOGICAL DEATH

Death from any neurological source including ischemic or hemorrhagic stroke

NEUROLOGICAL DETERIORATION

A decline in neurological status based on changes in neurological assessment

NIHSS SCORE

An assessment used to objectively quantify the impairment caused by a stroke. It is composed of 11 items, each of which scores a specific ability between 0 and 4. For each item, a score of 0 typically indicates normal function in that specific ability, while a higher score is indicative of some level of impairment. The individual scores from each item are summed in order to calculate a total NIHSS score. The maximum possible score is 42, with the minimum score being 0.

OCCLUSION

Blockage of a vessel

PARENT ARTERY

The parent artery is defined as any cerebral vessel containing a target aneurysm

PARENT ARTERY PATENCY

An assessment of the flow of blood through the parent artery

PROCEDURAL TECHNICAL SUCCESS

Defined as successful delivery and deployment of the Neuroform Atlas™ Stent at the target lesion

PRODUCT NONCONFORMITY

A departure of a quality characteristic from its intended level or state that occurs with a severity sufficient to cause an associated product or service not to meet a specification requirement

PSEUDOANEURYSM

An encapsulated hematoma in communication with an artery. It is often difficult to distinguish from an expanding hematoma at the site of arterial puncture. Usually requires surgical repair.

RECANALIZATION

A categorical increase in aneurysm filling over time after some degree of occlusion has been achieved initially.

RETREATMENT (OF TARGET ANEURYSM)

Required reintervention of the treated target lesion due to aneurysm recanalization or in-stent stenosis

STROKE

A neurological deficit lasting 24 hours or longer. The stroke shall be based on clinical presentation and imaging studies shall be utilized to discern between ischemic versus hemorrhagic origin. The 24-hour criterion is excluded if the subject undergoes cerebrovascular surgery or dies during the first 24 hours. 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.

Strokes will be categorized as ipsilateral or contralateral and periprocedural (less than or equal to 30 days) or late (greater than 30-days from the procedure). A stroke with clinical symptoms that resolves within 24 hours but with a brain imaging study showing infarction of vascular origin will be considered a minor stroke. Stroke severity will be graded by the Investigator as major or minor based on the definitions below:

- ***Permanent*:** A new neurological deficit which does not resolve completely during the period of observation
- ***Transient*:** A new neurological deficit which resolves completely during the period of observation
- ***Major Stroke:*** A stroke which is associated with an increase in the NIH Stroke Scale by ≥4
- ***Minor Stroke:*** A stroke which is associated with an increase in the NIH Stroke Scale by <4

SUSPECTED STROKE EVENT

Any event associated with sudden focal neurological worsening of patient status or stroke neuroimaging (e.g., MR or CT)

SUBARACHNOID HEMORRHAGE (SAH)

A ruptured cerebral aneurysm causes bleeding into the compartment surrounding the brain

TARGET ANEURYSM

A target aneurysm is a qualifying aneurysm treated or attempted to be treated during a stent-assisted coiling procedure

THROMBOEMBOLISM/THROMBOEMBOLIC EVENT

The blocking of a blood vessel by a particle that has broken away from a blood clot at its site of formation

THROMBOGENESIS

The formation of a thrombus

THROMBUS

A fibrous clot in the lumen of a blood vessel or inside an aneurysm; it may be occlusive or attached to the vessel wall or aneurysmal sac

TORTUOUSITY

Marked by repeated twists, bends, or turns

TRANSIENT ISCHEMIC ATTACK (TIA)

A brief episode (≤24 hours) of cerebral ischemia that is usually characterized by temporary blurring of vision, slurring of speech, numbness, paralysis, or syncope, and that is often predictive of a serious stroke

VASOSPASM

Contraction or hypertonia of the muscular coats of a blood vessel

WIDE NECK ANEURYSM

Aneurysm having a neck ≥ 4 mm or a dome-to-neck ratio of < 2