SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Intracranial Coil-Assist Stent
Device Trade Name:	Neuroform Atlas® Stent System
Device Procode:	QCA
Applicant's Name and Address:	Stryker Neurovascular 47900 Bayside Parkway Fremont, California 94538
Date(s) of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P180031/S001
Date of FDA Notice of Approval:	July 30, 2020

The original PMA P180031 was approved on May 16, 2019, and 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. The SSED to support the indication is available on the CDRH website and is incorporated by reference here. The current supplement was submitted to expand the indication for the Neuroform Atlas Stent System to include treatment of posterior circulation intracranial aneurysms (IAs).

II. INDICATIONS FOR USE

The Neuroform Atlas Stent System is indicated for use with neurovascular embolization coils in the anterior and posterior 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.

III. CONTRAINDICATIONS

The Neuroform Atlas Stent System is contraindicated in the following patients:

- Patients in whom the parent vessel size does not fall within the indicated range.
- Patients in whom antiplatelet and/or anticoagulation therapy (e.g., aspirin and clopidogrel) is contraindicated.

- Patients who have not received anti-platelet agents prior to stent implantation.
- Patients with an active bacterial infection.
- Patients in whom a pre-existing stent is in place in the parent artery at the target intracranial aneurysm location.
- Patients in whom angiography demonstrates the anatomy is not appropriate for endovascular treatment due to conditions such as:
    - Severe intracranial vessel tortuosity or stenosis;
    - Intracranial vasospasm not responsive to medical therapy.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Neuroform Atlas Stent System labeling.

V. DEVICE DESCRIPTION

The Neuroform Atlas Stent System is an intracranial stent intended to be used with neurovascular embolization coils to treat saccular wide-necked intracranial aneurysms. The Neuroform Atlas Stent System consists of:

- An implantable self-expanding nitinol stent;
- Stent delivery wire;
- Introducer sheath; and
- Accessory pouch with a torque device.

The Neuroform Atlas Stent System is delivered through a microcatheter. The device is offered in the stent configurations shown in Table 1. The delivery system is available in two tip configurations: with an 8.5 mm distal tip and without a distal tip. All of the devices are compatible with Stryker Neurovascular Excelsior XT-17 and SL-10 Microcatheters.

Table 1. Stent Configurations

Device Diameter	Device Length			
	15 mm	21 mm	24 mm	30 mm
3.0 mm	X	X	X	X
4.0 mm	X	X	X	X
4.5 mm	X	X	X	X

Description of the Stent: The Neuroform Atlas Stent is a self-expanding, open cell, nitinol stent with flared proximal and distal ends. The stent ring is comprised of zig-zag-shaped stent struts joined by interconnects. There are six radiopaque marker bands on the stent, three on each end. The stent is pre-loaded on the stent delivery wire and is constrained by the introducer sheath until transferred into the microcatheter.

Description of the Delivery System: The Neuroform Atlas Stent Delivery System consists of the stent delivery wire and introducer sheath. The stent delivery wire is similar in

construction to a guidewire. The delivery wire is a stainless-steel wire with an overall length of 185 cm. The delivery wire has a radiopaque distal tip marker and a fluoro-saver marker on the proximal end. The delivery system is available in two configurations: with a distal tip (8.5 mm) and without a distal tip on the delivery wire. The introducer sheath consists of a clear thin-walled polymer shaft and a distal tapered tip. It has an overall length of 49 cm and inner diameter of 0.0165 inches.

Description of the Accessory Pouch: An accessory pouch containing an optional torque device is also included. The physician may attach the torque device to the proximal end of the stent delivery wire to facilitate handling and stabilization.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the treatment of wide-necked intracranial aneurysms in the posterior circulation of the neurovasculature including open surgical clipping, endovascular treatment using embolization coils supported with other Premarket Approval (PMA) and Humanitarian Device Exemption (HDE) approved neurovascular coil-assist stents, or balloon catheter assisted coiling of the intracranial aneurysm.

Neurovascular coil-assist stents have been approved via the PMA regulatory pathway from MicroVention, Inc. for the Low-Profile Visualized Intraluminal Support (LVIS) and LVIS Jr. (P170013). Other neurovascular coil-assist stents have been approved through the HDE regulatory pathway including the Stryker Neurovascular Neuroform EZ, 3, and Neuroform Atlas Stent Systems (H020002) and the Codman & Shurtleff, Inc. Enterprise Vascular Reconstruction Device and Delivery System (H060001). A similar HDE approved device that is indicated to support neurovascular embolization coils specifically for the treatment of unruptured wide-necked intracranial aneurysms originating on or near a vessel bifurcation of the basilar tip and carotid terminus is the Medos International, SARL, PulseRider Aneurysm Neck Reconstruction Device (H160002).

Another PMA approved device that can treat certain posterior circulation IAs is an intrasaccular IA flow disruption device called the MicroVention, Inc. Woven EndoBridge (WEB) Aneurysm Embolization System (P170032). This device is indicated for use at the middle cerebral artery (MCA) bifurcation, internal carotid artery (ICA) terminus, anterior communicating artery (AComm) complex, or basilar artery apex for the endovascular treatment of saccular, wide-necked, bifurcation intracranial aneurysms with certain aneurysm size dimensions. This device is implanted within the sac of the intracranial aneurysm and is intended to protect the neck of the intracranial aneurysm to disrupt flow from entering.

In addition to these alternative treatments, certain intracranial aneurysms may be managed medically or by observation only with no treatment but with regular imaging follow-up examinations to ensure there are no morphological changes in the intracranial aneurysms over time. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The Neuroform Atlas Stent System is available in the following countries: Argentina, Australia, Austria, Bahrain, Belgium, Brazil, Bulgaria, Canada, Canary Islands, Chile, China, Colombia, Costa Rica, Croatia, Cyprus, Czech Republic, Denmark, Dominican Republic, Ecuador, Egypt, Estonia, Finland, France, Georgia, Germany, Great Britain (United Kingdom (UK)), Greece, Honduras, Hong Kong, Hungary, Iceland, India, Iran, Ireland, Israel, Italy, Jamaica, Japan, Jordan, Korea, Kuwait, Latvia, Lithuania, Malaysia, Malta, Mexico, Netherlands, New Zealand, Norway, Oman, Peru, Philippines, Poland, Portugal, Qatar, Romania, Russia, Saudi Arabia, Serbia, Singapore, Slovakia, Slovenia, South Africa, Spain, Sweden, Switzerland, Taiwan, Thailand, Tunisia, Turkey, Vietnam, United Arab Emirates and United States.

The Neuroform Atlas Stent System has not been withdrawn from marketing for any reason relating to the safety and effectiveness of the device.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device.

- Aphasia
- Allergic reaction to nitinol metal and medications
- Aneurysm perforation or rupture, leak or contrast extravasation
- Blindness
- Cardiac arrhythmia
- Coil herniation through stent into parent vessel
- Cranial neuropathy
- Death
- Embolus
- Headache
- Hemiplegia
- Hemorrhage (i.e., intracerebral, subarachnoid, retroperitoneal, or in other locations)
- Hydrocephalus
- In-stent stenosis
- Infection
- Ischemia
- Mass effect
- Myocardial infarction
- Neurological deficit or intracranial sequelae
- Pseudoaneurysm
- Reaction to radiation exposure (i.e., alopecia, burns ranging in severity from skin reddening to ulcers, cataracts, delayed neoplasia)

- Reactions to anti-platelet or anti-coagulant agents
- Renal failure
- Seizure
- Stent fracture, migration, embolization, or misplacement
- Stent thrombosis
- Stroke
- Transient ischemic attack
- Vasospasm
- Vessel occlusion or closure including parent vessel or non-target side branches
- Vessel perforation, dissection, trauma or damage
- Vessel thrombosis
- Visual impairment
- Other procedural complications including, but not limited to, anesthetic and contrast media risks, hypotension, hypertension, access site complications including pain, hematoma, local bleeding, local infection, and injury to the artery (i.e., dissection), vein, or adjacent nerves
- Unplanned intervention

For the specific adverse events that occurred in the clinical study, please see Section X below.

IX. SUMMARY OF NONCLINICAL STUDIES

The Neuroform Atlas Stent System was approved under P180031. No additional non-clinical bench or animal studies were required for this application because there were no changes to the device design from the version approved under P180031. A summary of the non-clinical studies conducted on the Neuroform Atlas Stent System can be found in the Summary of Safety and Effectiveness Data (SSED) for P180031 at the following location: https://www.accessdata.fda.gov/cdrh_docs/pdf18/P180031B.pdf.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of the Neuroform Atlas Stent System for the expanded indication for use with neurovascular embolization coils in the posterior 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. The clinical study was performed in the US under IDE #G150006. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

Patients were treated between June 30, 2015, and December 15, 2017. The database for this Panel Track Supplement reflected data collected through December 14, 2018, and included 124 patients. There were 25 investigational sites.

The study was a prospective, multi-center, non-randomized, one-arm, unmasked clinical study titled "*Safety and Effectiveness of the Treatment of Wide Neck, Saccular Intracranial Aneurysms with the Neuroform Atlas™ Stent System (ATLAS).*" The pivotal ATLAS study included follow-up at post-implant, 2 months, 6 months, and 12-months post-procedure to support the current PMA Panel Track Supplement. The pre-specified primary endpoints in the clinical study protocol were:

- Safety: Any major ipsilateral stroke or neurological death within 12 months. A major ipsilateral stroke was defined as an ipsilateral stroke that is associated with an increase of 4 or more points on the National Institutes of Health Stroke Scale (NIHSS) at 24 hours after symptoms onset. An ipsilateral stroke was 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 intracranial aneurysm.

- Effectiveness: Complete intracranial aneurysm occlusion (100% occlusion – Raymond-Roy Class 1) of the treated target lesion on 12-month angiography, in the absence of retreatment or significant parent artery stenosis (> 50%) at the target location as evaluated by an independent Core Laboratory.

The trial design does not address whether there is decreased disability or decreased incidence of cerebral aneurysm rupture in the long term in patients treated with the device compared to patients treated with a more conservative approach. There was no active concurrent control group in the ATLAS study. The primary endpoint results were compared to performance goals developed using published clinical data from endovascular treatments of wide-necked intracranial aneurysms using neurovascular stents for stent-assisted coiling (SAC), balloon-assisted coiling (BAC), and coiling alone.

A sample size of up to 180 subjects with intracranial aneurysms in the posterior circulation of the neurovasculature, including vertebral, basilar and posterior cerebral arteries, was planned to be enrolled into the ATLAS 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.*), 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 12%, the expected upper bound of the exact binomial two-sided 95% confidence interval around the success rate is less than 25%. The primary safety and effectiveness endpoint analyses were performed on

the modified Intent-to-Treat (mITT) population defined as all subjects who signed the informed consent form and in whom the Neuroform Atlas Stent System procedure was attempted.

The ATLAS study included an independent Clinical Events Committee (CEC), Data Safety and Monitoring Board (DSMB), angiographic imaging Core Laboratory ("Core Lab") with a single reader, and study monitors who confirmed neurological assessments, adverse events, and study data with source documentation.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the ATLAS study was limited to patients who met the following inclusion criteria:

   - Subject is between 18 and 80 years of age.
   - Subject has a documented, wide neck (neck ≥ 4 mm or a dome-to-neck ratio < 2), intracranial, saccular aneurysm arising from a parent vessel with a diameter of ≥ 2 mm 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.

   Patients were not permitted to enroll in the ATLAS study if they met any of the following exclusion criteria:

   - Subject has known multiple untreated cerebral aneurysms, other than non-target blister aneurysm, infundibulum, or aneurysm measuring < 3 mm for each of three dimensions assessed (height, width, and depth) that will not require treatment during the study period.
   - Subject has a target lesion that is a blister aneurysm, infundibulum, or aneurysm measuring < 3 mm for each of three dimensions assessed (height, width, and depth).
   - 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.
   - Subject has undergone coiling or stenting of a non-target intracranial aneurysm within 30 days prior to study treatment.
   - Subject has a target aneurysm in the anterior circulation proximal to the superior hypophyseal ICA.
   - Subject has acute target aneurysm rupture less than 14 days prior to study treatment.
   - Subject has a Hunt and Hess score ≥ 3 or a pre-morbid modified Rankin Scale (mRS) score ≥ 4.
   - Subject has an admission platelet count of < 50,000, any known coagulopathy, or an International Normalized Ratio (INR) > 3.0 without oral anticoagulation

therapy.

- Subject has a known absolute contraindication to angiography.
- Subject has 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).
- Subject has a known absolute contraindication to the use of required study medications or agents (e.g., heparin, aspirin, clopidogrel, and radiographic contrast agents).
- Subject is female and is pregnant or intends to become pregnant during the study.
- Subject has Moya-Moya disease, arteriovenous malformation(s), arteriovenous fistula(e), intracranial tumor(s), or intracranial hematoma(s) (unrelated to target aneurysm).
- 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.
- 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.
- Subject has undergone previous stent-assisted coiling of the target aneurysm.

2. Follow-up Schedule

All patients were scheduled to return for follow-up examinations at 2-months, 6 months, and 12-months postoperatively. Preoperatively, the patients underwent a review of their concomitant medications and medical history, neurological examination, completion of neurological rating and grading scales (mRS, NIHSS), laboratory, and angiographic evaluations. Postoperatively, the objective parameters measured during the study included a review of the concomitant medications, neurological, and angiographic evaluations (see Table 2). Adverse events and complications were recorded at all visits.

The key timepoints are shown below in the tables summarizing safety and effectiveness.

Table 2. ATLAS Study Required Evaluations from Baseline through 12-Month Follow-Up Visit

	Pre-Implant	Implant /Procedural	Post-Implant†	2 ± 1 Month	6 ± 1 Month	12 ± 2 Months
Medical History	✓					
Neurological Exam*	✓					✓
mRS*	✓		✓	✓	✓	✓
NIHSS*/**	✓			+/-**	+/-**	✓
Hunt and Hess*/***	✓		✓			✓
Angiography******	✓**** (MRA, CTA or DSA)	✓ (DSA)		+/-**** (MRA or DSA, per institution standards)	+/-**** (MRA or DSA, per institution standards)	✓ (DSA)
Adverse Event Assessment	✓	✓	✓	✓	✓	✓
Antiplatelet Medication	✓		✓	✓	✓	✓
Quality of Life Assessment	✓					✓

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

* At each 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 to the assessment schedule outlined in tabular form above, 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 as outlined in tabular form above only when evaluating subjects who have evidence of subarachnoid hemorrhage.

**** Pre-implant angiography (magnetic resonance angiography (MRA), computed tomography angiography (CTA), or digital subtraction angiography (DSA)) may be performed up to 6 months prior to treatment. In addition to the post-implant and 12-month angiographic studies outlined in tabular form above, 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 site, imaging (MRA or DSA) may be performed at the 2- or 6-month follow-up visit.

3. Clinical Endpoints

With regards to safety, the percentage of patients who had a major ipsilateral stroke or neurological death within 12-months post-procedure was used to analyze the clinical study results.

With regards to effectiveness, the percentage of patients who had complete (100%) occlusion (equivalent to Raymond-Roy Class I) of the target intracranial aneurysm without clinically significant parent artery stenosis (> 50%) or target intracranial aneurysm re-treatment within 12-months post-procedure was used to analyze the clinical study results.

With regard to success/failure criteria, the primary endpoints were compared to performance goals developed from the published literature based on a similar patient population as those treated in the ATLAS trial using alternative treatment modalities such as neurovascular stents used for SAC, BAC, or coiling embolization alone. The primary endpoints were analyzed using the modified intent-to-treat (mITT) population and Fisher's Exact Binomial test. For the posterior circulation cohort that is the subject of the current PMA Panel Track Supplement, for safety, a one-sided p-value < 0.025 results in rejecting the null hypothesis that the primary safety endpoint is 25% or higher when treated with the Neuroform Atlas Stent System. For effectiveness, a one-sided p-value < 0.025 results in rejecting the null hypothesis that the primary effectiveness endpoint is $\leq$ 50% in favor of the alternative hypothesis that the treatment is effective in more than 50% of the subjects.

B. Accountability of PMA Cohort

At the time of database lock, of 124 patients enrolled in the PMA study for the posterior circulation cohort, 93.5% (116/124) patients are available for analysis at the completion of the study, the 12-month post-operative visit (see Figure 1).

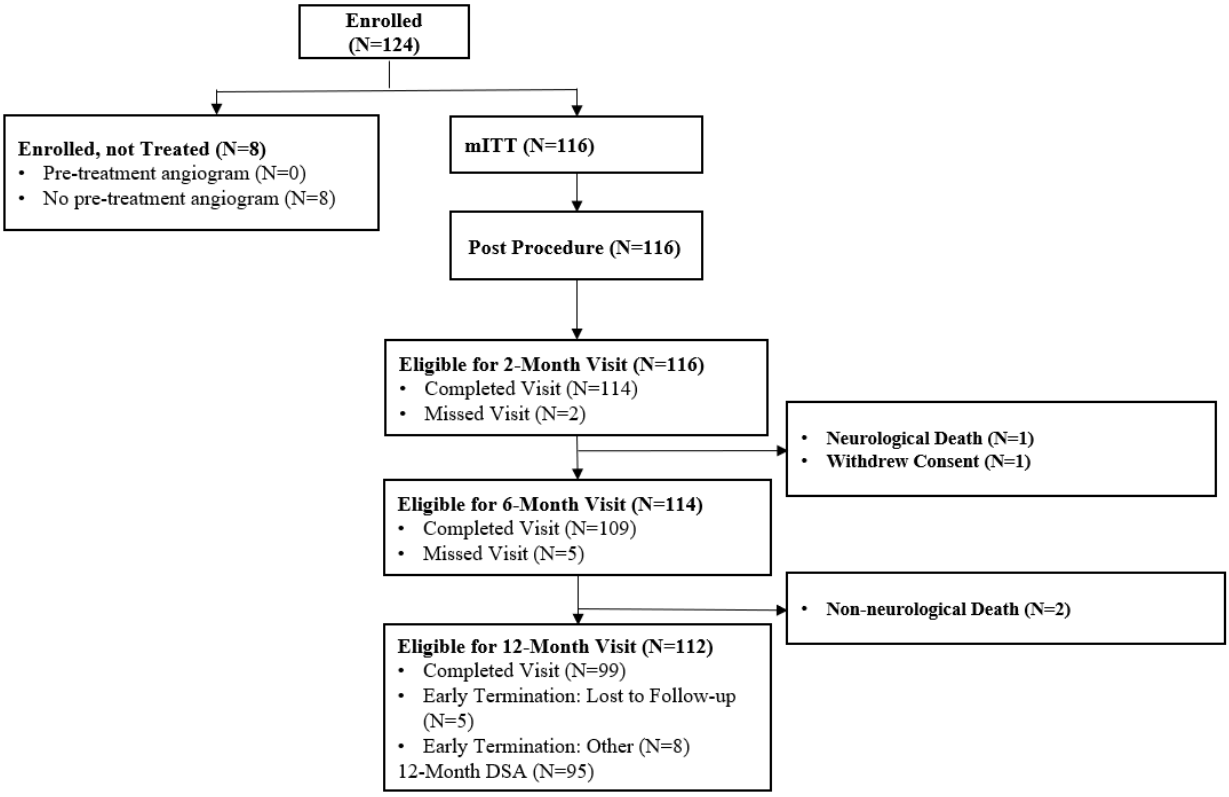

Figure 1. Subject Accountability Flowchart – Posterior Cohort

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for an intracranial treatment study performed in the US. This disease predominantly affects more women than men, and most patients are Caucasian, similar to the demographic and baseline characteristics of the posterior circulation patient population in the ATLAS trial (Table 3). Table 4, Table 5, and Table 6 present the location, measurement characteristics, and rupture status of the intracranial aneurysms treated in the ATLAS trial based on the baseline (pre-procedure) site-reported results of digital subtraction angiography (DSA) exams.

Table 3. Demographic and Baseline Characteristics – mITT Population (Posterior Cohort)

Characteristic	mITT Subjects (N=116)
Age (years)	
Mean ± Standard Deviation (SD) (N)	60.2 ± 10.5 (116)
Median (Q1 - Q3)	61.0 (53.5 - 67.5)
Minimum (Min) – Maximum (Max)	37.0 - 80.0
Height (cm)	
Mean ± SD (N)	165.6 ± 8.8 (116)
Median (Q1 - Q3)	165.0 (160.0 - 170.1)
Min – Max	149.9 - 193.0

Characteristic	mITT Subjects (N=116)
Weight (kg)	
Mean ± SD (N)	77.2 ± 17.4 (116)
Median (Q1 - Q3)	74.9 (63.9 - 88.5)
Min – Max	47.0 - 131.2
Body Mass Index (BMI) (kg/m²)	
Mean ± SD (N)	28.1 ± 5.8 (116)
Median (Q1 - Q3)	27.8 (23.6 - 31.5)
Min – Max	17.8 - 45.2
Gender	
Female	81.0% (94/116)
Male	19.0% (22/116)
Race	
White	91.4% (106/116)
Black or African American	7.8% (9/116)
Asian	0.0% (0/116)
Native Hawaiian or other Pacific Islander	0.0% (0/116)
American Indian or Alaskan Native	0.9% (1/116)
Other [1]	0.0% (0/116)
Ethnicity	
Not Hispanic or Latino	97.4% (113/116)
Hispanic or Latino	2.6% (3/116)
[1] Specified as Arabic (n=1), Portuguese (n=1), Hispanic (n=1), and mixed race (n=1).	

Table 4. Target Intracranial Aneurysm Location – mITT Population (Posterior Cohort)

Target Aneurysm Location	mITT Population (N=116)
Internal Carotid Artery-Posterior Communicating Artery	0.9% (1/116)
Basilar Apex	75.9% (88/116)
Basilar Trunk	6.0% (7/116)
Superior Cerebellar Artery	4.3% (5/116)
Posterior Inferior Cerebellar Artery	4.3% (5/116)
Vertebral Artery	4.3% (5/116)
Vertebrobasilar Junction	1.7% (2/116)
Other [1]	2.6% (3/116)
[1] Persistent Trigeminal Artery Origin (n=1), Fetal Posterior Cerebral Artery (n=1), and Posterior Cerebral (n=1)	

Table 5. Site-reported Pre-implant Target Intracranial Aneurysm Characteristics – mITT Population (Posterior Cohort)

	mITT Subjects (N=116)
Subjects with Number of Target IAs	
1	100.0% (116/116)
Type of imaging used	

	mITT Subjects (N=116)
1. DSA	87.1% (101/116)
2. CTA/MRA/Other [1]	12.9% (15/116)
Aneurysm height (mm) (superior inferior on anteroposterior (AP) or lateral)	
Mean ± SD (N)	6.1 ± 2.9 (116)
Median (Q1 - Q3)	5.5 (4.0 - 7.5)
Min - Max	1.7 - 20.2
Aneurysm width (mm) (horizontal on AP)	
Mean ± SD (N)	6.1 ± 2.8 (116)
Median (Q1 - Q3)	5.5 (4.0 - 7.1)
Min - Max	1.7 - 18.2
Aneurysm depth (mm) (AP or lateral)	
Mean ± SD (N)	6.1 ± 2.5 (116)
Median (Q1 - Q3)	5.8 (4.2 - 7.4)
Min - Max	1.4 - 17.0
Aneurysm neck width (mm)	
Mean ± SD (N)	4.7 ± 1.7 (116)
Median (Q1 - Q3)	4.3 (3.6 - 5.5)
Min - Max	1.9 - 12.2
Aneurysm Size (mm) [2]	
Mean ± SD (N)	7.1 ± 3.0 (116)
Median (Q1 - Q3)	6.5 (5.0 - 8.2)
Min - Max	2.6 - 20.2
Dome-to-Neck Ratio [3]	
Mean ± SD (N)	1.2 ± 0.3 (116)
Median (Q1 - Q3)	1.1 (1.0 - 1.4)
Min - Max	0.3 - 3.2
Parent vessel diameter proximal to the aneurysm neck (mm)	
Mean ± SD (N)	2.9 ± 0.6 (116)
Median (Q1 - Q3)	3.0 (2.5 - 3.3)
Min - Max	1.9 - 4.5
Parent vessel diameter distal to the aneurysm neck (mm)	
Mean ± SD (N)	2.4 ± 0.5 (116)
Median (Q1 - Q3)	2.3 (2.0 - 2.7)
Min - Max	1.6 - 4.5
Parent vessel stenosis pre-implant	
No	97.4% (113/116)
Yes	2.6% (3/116)
% stenosis:	
25% or less	33.3% (1/3)
26% - 50%	66.7% (2/3)

	mITT Subjects (N=116)
[1] This includes computed tomography angiography (CTA) (n=8), magnetic resonance angiography (MRA) (n=7), and no other imaging. [2] The IA size is defined as the maximum of three dimensions (anteroposterior (AP) plane, lateral plane, height). [3] The dome size is defined as the minimum of two widths (AP plane, lateral plane).	

Table 6. Target Intracranial Aneurysm Rupture Status at Baseline and Prior Target Intracranial Aneurysm Treatment - mITT Population (Posterior Cohort)

	mITT Population (N=116)		
Measure	**Ruptured**	**Unruptured**	**Total**
Previous target intracranial aneurysm status	11.2% (13/116)	88.8% (103/116)	100.0% (116/116)
Days from last rupture to index procedure			
Mean ± SD (N) [1]	800.4 ± 1171.5 (12)		
Median (Q1 - Q3)	189.0 (120.5 - 1257.0)		
Min - Max	5.0 - 3927.0		
Prior Treatment/Intervention			
Coiling only	76.9% (10/13)	3.9% (4/103)	12.1% (14/116)
Balloon assisted coiling	15.4% (2/13)	0.0% (0/103)	1.7% (2/116)
Other [2]	0.0% (0/13)	1.0% (1/103)	0.9% (1/116)
None	7.7% (1/13)	95.1% (98/103)	85.3% (99/116)
[1] Data on the days from last rupture to index procedure was missing for one subject. [2] One subject with an unruptured target intracranial aneurysm underwent clipping prior to the index procedure.			

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the mITT cohort of 116 patients available for the 12-month evaluation. The key safety outcomes for this study are presented below in Tables 9 and 10. Adverse effects are reported in Tables 7 and 8.

Adverse effects that occurred in the PMA clinical study:

Table 7 reports the serious adverse events (SAEs) and non-SAEs that occurred in the posterior circulation cohort in the ATLAS trial with an overall frequency greater than 1% through one-year follow-up.

Table 7: Adverse Events (AEs) with > 1% Overall Frequency through 12-Months Post-Procedure by Medical Dictionary for Regulatory Activities (MedDRA) Codes – mITT Population (Posterior Cohort)

	mITT Population (N=116)					
	Serious AE		Non-serious AE		All AE	
MedDRA System Organ Class/Preferred Term	**Events**	**Subjects with Events (%)**	**Events**	**Subjects with Events (%)**	**Events**	**Subjects with Events (%)**
Any Adverse Event (AE)	71	39 (33.6%)	254	84 (72.4%)	325	88 (75.9%)
Blood and lymphatic system disorders						
Increased tendency to bruise	0	0	5	5 (4.3%)	5	5 (4.3%)
Ear and labyrinth disorders						
Ear pain	0	0	3	3 (2.6%)	3	3 (2.6%)
Tinnitus	0	0	2	2 (1.7%)	2	2 (1.7%)
Eye disorders						
Diplopia	0	0	2	2 (1.7%)	2	2 (1.7%)
Photophobia	0	0	2	2 (1.7%)	2	2 (1.7%)
Vision blurred	1	1 (0.9%)	1	1 (0.9%)	2	2 (1.7%)
Visual impairment	0	0	4	4 (3.4%)	4	4 (3.4%)
Gastrointestinal disorders						
Abdominal pain upper	0	0	2	2 (1.7%)	2	2 (1.7%)
Constipation	0	0	3	3 (2.6%)	3	3 (2.6%)
Dysphagia	1	1 (0.9%)	3	3 (2.6%)	4	4 (3.4%)
Nausea	0	0	3	3 (2.6%)	3	3 (2.6%)
Vomiting	0	0	3	3 (2.6%)	3	3 (2.6%)
General disorders and administration site conditions						
Application site haematoma	2	2 (1.7%)	2	2 (1.7%)	4	4 (3.4%)
Chest pain	3	3 (2.6%)	0	0	3	3 (2.6%)
Fatigue	0	0	2	2 (1.7%)	2	2 (1.7%)
Wound secretion	0	0	3	3 (2.6%)	3	3 (2.6%)
Infections and infestations						
Upper respiratory tract infection	0	0	4	3 (2.6%)	4	3 (2.6%)
Urinary tract infection	0	0	9	9 (7.8%)	9	9 (7.8%)
Injury, poisoning and procedural complications						
Catheter site hemorrhage	0	0	2	2 (1.7%)	2	2 (1.7%)
Fall	2	1 (0.9%)	5	5 (4.3%)	7	5 (4.3%)
Vascular pseudoaneurysm	2	2 (1.7%)	0	0	2	2 (1.7%)
Metabolism and nutrition disorders						
Hypokalemia	0	0	4	3 (2.6%)	4	3 (2.6%)
Musculoskeletal and connective tissue disorders						
Back pain	0	0	2	2 (1.7%)	2	2 (1.7%)
Muscle spasms	0	0	4	4 (3.4%)	4	4 (3.4%)
Neck pain	1	1 (0.9%)	4	4 (3.4%)	5	5 (4.3%)
Pain in extremity	0	0	3	3 (2.6%)	3	3 (2.6%)
Nervous system disorders						
Cerebral infarction	1	1 (0.9%)	3	3 (2.6%)	4	4 (3.4%)
Cerebral vasoconstriction	0	0	13	12 (10.3%)	13	12 (10.3%)
Convulsion	1	1 (0.9%)	2	2 (1.7%)	3	2 (1.7%)
Dizziness	0	0	8	8 (6.9%)	8	8 (6.9%)

	mITT Population (N=116)					
	Serious AE		Non-serious AE		All AE	
MedDRA System Organ Class/Preferred Term	Events	Subjects with Events (%)	Events	Subjects with Events (%)	Events	Subjects with Events (%)
Gait disturbance	0	0	2	2 (1.7%)	2	2 (1.7%)
Headache	1	1 (0.9%)	28	24 (20.7%)	29	25 (21.6%)
Hemiparesis	0	0	3	3 (2.6%)	3	3 (2.6%)
Hypoesthesia	0	0	6	3 (2.6%)	6	3 (2.6%)
Ischemic stroke	3	3 (2.6%)	1	1 (0.9%)	4	4 (3.4%)
Paraesthesia	1	1 (0.9%)	1	1 (0.9%)	2	2 (1.7%)
Subarachnoid hemorrhage	2	2 (1.7%)	0	0	2	2 (1.7%)
Transient ischemic attack	6	5 (4.3%)	0	0	6	5 (4.3%)
Vertebral artery dissection	1	1 (0.9%)	3	3 (2.6%)	4	4 (3.4%)
Respiratory, thoracic and mediastinal disorders						
Epistaxis	0	0	3	3 (2.6%)	3	3 (2.6%)
Oropharyngeal pain	0	0	2	2 (1.7%)	2	2 (1.7%)
Skin and subcutaneous tissue disorders						
Alopecia	0	0	2	2 (1.7%)	2	2 (1.7%)
Rash	0	0	2	2 (1.7%)	2	2 (1.7%)
Surgical and medical procedures						
Intra-cerebral aneurysm operation	11	11 (9.5%)	0	0	11	11 (9.5%)
Vascular disorders						
Hypertension	0	0	2	2 (1.7%)	2	2 (1.7%)
Retroperitoneal hemorrhage	1	1 (0.9%)	1	1 (0.9%)	2	2 (1.7%)
Thrombosis in device	2	2 (1.7%)	1	1 (0.9%)	3	3 (2.6%)

The incidence of death, stroke (ischemic or hemorrhagic), or transient ischemic attack (TIA) events that occurred in the study was 19.4% (20/103) and 7.7% (1/13) in the posterior circulation cohort subjects with unruptured and ruptured intracranial aneurysms, respectively (Table 8). For all subjects in the posterior circulation cohort of the ATLAS trial, the overall event rate was 18.1% (21/116; unadjusted 95% confidence interval (CI): 12.2%, 26.1%).

Table 8. Post-hoc FDA-requested Safety Assessment of Death, Stroke and TIA Events through 12-month Follow-up – mITT Population (Posterior Cohort)

	% Subject (# Subjects/N) [# Events]		
Adverse Event[a]	Ruptured	Unruptured	Overall
Death	0.0% (0/13) [0]	2.9% (3/103) [3]	2.6% (3/116) [3]
Neurological Death	0.0% (0/13) [0]	1. 0 % (1/103) [l]	0.9 % (1/116) [l]
Non-neurological Death	0.0% (0/13) [0]	1.9% (2/103) [2]	1.7% (2/116) [2]
Stroke[b]	7.7% (1/13) [1]	13.6 % (14/103) [15]	12.9 % (15 /116) [16]
Major Stroke	0.0% (0/13) [0]	3.9% (4/103) [5]	3.4% (4/116) [5]
Minor Stroke	7.7% (1/13) [l]	9.7% (10/103) [l0]	9.5% (11/116) [11]
TIA[c]	0.0% (0/13) [0]	3.9% (4/103) [4]	3.4% (4/116) [4]

Overall[d]	7.7% (1/13) [1]	19.4 % (20/103) [22]	18.1% (21/116) [23]

[a] All events were assessed by the CEC. Death and stroke were adjudicated by the CEC.
[b] All stroke events were ipsilateral.
[c] Per site reported.
[d] Two subjects experienced multiple events.

Based on the pre-specified primary safety endpoint definition, the primary safety endpoint was met in the mITT population (Posterior Cohort) and the null hypothesis was rejected ($p < 0.001$). The incidence of primary safety endpoint failure of major ipsilateral stroke defined as an increase in the NIHSS score from baseline by ≥ 4 points or neurological death in the mITT population was 4.3% (5/116) (see Table 9).

Table 9. Pre-specified Primary Safety Endpoint at 12-month Follow-up – mITT Population (Posterior Cohort)

Endpoint	**mITT Population (N=116)**		
	% of Subjects with Events (n/N)	**95% CI [3]**	**p-value [4]**
Any Major Ipsilateral Stroke or Neurologic Death	4.3% (5/116)	[1.4%, 9.8%]	< 0.001
Major Ipsilateral Stroke	3.4% (4/116)	[0.9%, 8.6%]	
Neurologic Death	0.9% (1/116)	[0.0%, 4.7%]	
Worst Case Analysis [1]	8.6% (10/116)	[4.2%, 15.3%]	< 0.001
Multiple Imputation [2]	4.5%	[0.1%, 8.9%]	< 0.001

[1] Missing endpoint data (n=5) was imputed as failure.
[2] Missing endpoint data was imputed using logistic regression models per the ATLAS study protocol.
[3] Clopper-Pearson exact confidence interval.
[4] One-sided Fisher's Exact test of success against the performance goal of < 0.25 at 12 months (α=0.025). P-values are unadjusted for multiplicity.

There were 11 subjects in the mITT population who experienced a minor stroke, defined as a stroke associated with an increase in NIHSS score ≤ 3 as adjudicated by the CEC (9.5%; 11/116). Six of these 11 minor stroke events were site-reported as serious and were MedDRA-coded as TIA (n = 2), ischemic stroke (n = 2), cerebral infarction (n = 1), and embolic stroke (n = 1). Five events were site-reported as non-serious and were MedDRA-coded as visual impairment (n = 1), ischemic stroke (n = 1), dizziness (n = 1), hyperesthesia (n = 1), and cerebral infarction (n = 1). For 10 of the 11 subjects with minor stroke, events resolved with no residual effects. For 1 of the 11 subjects with minor stroke, the event resolved with residual effects (mRS 1 at 2 months later and mRS 0 at 9 months post-event).

Baseline and 12-month mRS scores were obtained by study personnel to evaluate long-term clinical outcome. The shifts in numerical mRS scores from baseline to the 12-month follow-up visit were analyzed on a per subject basis. The results for subjects in the mITT population with posterior circulation IAs are shown in Table 10. Among those subjects who had 12-month mRS data available, the majority

(90.2%; 92/102) had unchanged or improved functional outcomes compared to baseline. A total of 73 subjects (71.6%) had unchanged mRS scores and 19 subjects (18.6%) had improved mRS scores at 12 months compared to their baseline mRS. There were 10 subjects with worsened mRS scores (10/102; 9.8%). For 14 subjects, the mRS assessment was not performed due to loss-to-follow-up (n = 5), study discontinuation (n = 8), and subject withdrawal of consent (n = 1).

One of the 10 subjects with worsened 12-month mRS scores experienced a major ipsilateral stroke on the day of the index procedure and had a mRS score of 2 at the 12-month follow-up. One subject experienced a fall and subsequently developed pneumonia aspiration that led to neurological death; 1 subject experienced a myocardial infarction and 1 subject experienced a congestive heart failure that both led to non-neurological deaths. Six subjects had a mRS score change from 0 at baseline to 1 at 12 months; 2 of these 6 subjects experienced minor strokes at 18 and 40 days post-procedure while the remainder experienced no neurological SAEs.

Table 10. Change in mRS Score through 12-month Follow-up Compared to Baseline – mITT Population, Posterior Cohort

	Score at 12 Month Follow-up Visit								
Score at Baseline	**ND[+]**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**Total**
0	12	63	6	1	0	0	0	2	84
1	2	14	8	0	0	0	0	0	24
2	0	3	1	1	0	0	0	0	5
3	0	0	0	1	1	0	0	1	3
Total	14	80	15	3	1	0	0	3	116

*Grey = no change
[+]ND = No Data

2. Effectiveness Results

The analysis of effectiveness was based on the 116 evaluable patients in the mITT population at the 12-month time point. Key effectiveness outcomes are presented in Table 11.

The primary effectiveness endpoint in the ATLAS trial was defined as a composite of the percent of subjects with 100% occlusion (Raymond-Roy Class 1) of the treated target lesion in the absence of retreatment or significant parent artery stenosis (> 50%) at the target vessel location at 12 months as adjudicated by an independent Core Laboratory. The pre-specified primary effectiveness endpoint analysis was performed on the mITT population using regression methods to impute missing data. Subjects who suffered neurological death prior to 1-year follow-up were imputed as Raymond-Roy Class 3 (the worst-case) and regression methods were used to impute other missing data. Five separate imputed data sets were constructed and inferences were completed using pooled estimates

across the five data sets. In the event that no predictor variables were found for the regression models, missing data were imputed by a random draw from observed data for patients with similar baseline characteristics (e.g., gender, intracranial aneurysm location, race) as those with the missing data. As summarized in Table 11, the primary effectiveness endpoint composite success rate in the mITT population with regression imputation was 76.7% (95% CI: 67.0, 86.5).

Table 11: Primary Effectiveness Endpoint at 12-month Follow-up – mITT Population (Posterior Cohort)

Primary Effectiveness Composite Success	% (n/N) (95% CI) [4]	p-value [5]
Primary Effectiveness Analysis		
mITT Population with Regression Imputation [1]	76.7% [67.0%, 86.5%]	< 0.001
Additional Analyses of Primary Effectiveness Endpoint		
Complete-Case Analysis [2]	77.0% (77/100) [67.5%, 84.8%]	< 0.001
Worst-Case Analysis [3]	66.4% (77/116) [57.0%, 74.9%]	< 0.001

[1] Missing endpoint data was imputed using regression methods. The five separate imputed data sets were constructed. One subject who suffered neurological death was imputed as a failure.
[2] Subgroup of mITT subjects who had DSA results available at 12 months (n = 95), had a known retreatment at 12 months without DSA data (n = 4), or experienced neurological death (n = 1) imputed as a failure.
[3] Missing endpoint data (n = 16) was imputed as failure.
[4] Clopper-Pearson exact confidence interval.
[5] One-sided Fisher's Exact test of success against the performance goal of > 0.50 at 12 months (α=0.025).

Per pre-established protocol requirement, one Core Lab reader adjudicated the intracranial aneurysm occlusion results. Therefore, these results may be subject to assessment variability and greater uncertainty for intracranial aneurysm occlusion scores presented in Table 11. An independent, blinded review of a selected sample of the DSA data from 20/116 evaluable subjects was conducted as part of this PMA Panel Track Supplement review and showed assessment variability around the estimate of the primary effectiveness endpoint.

The subject device is a neurovascular coil-assist stent and the primary function of the device is to hold embolization coils within the sac of the wide-necked IA. The ATLAS study protocol did not pre-specify or guide site investigators on the packing of the IA sac with neurovascular embolization coils. Coil packing is dependent on clinical practice with utilization of currently marketed neurovascular embolization coils, and can vary based on intracranial aneurysm size, location, morphology and shape. Therefore, how many embolization coils were held within the sac of the wide-necked IA and packing coil density was not directly evaluated.

3. Subgroup Analyses

No subgroup analyses were pre-specified based on any preoperative characteristics.

4. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 71 investigators of which none were full-time or part-time employees of the sponsor and 18 investigators had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0
- Significant payment of other sorts: 18 investigators
- Proprietary interest in the product tested held by the investigator: 0
- Significant equity interest held by investigator in sponsor of covered study: 0

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

Not applicable.

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Neurological Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

FDA did convene a general issues, non-voting, meeting on March 1, 2018, of the Neurological Devices Panel of the Medical Devices Advisory Committee regarding factors to consider in the evaluation of benefits and risks when reviewing clinical evidence of new endovascular medical devices intended to treat intracranial aneurysms. Recommendations from the Neurological Devices Panel at the March 1, 2018, meeting was considered during the review of this PMA Panel Track Supplement, primarily to assess safety and effectiveness of the subject device as described within the SSED in Section X. The background and meeting materials for the March 1, 2018, general issues meeting can be accessed at the following link: https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/NeurologicalDevicesPanel/ucm598450.htm.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The primary effectiveness endpoint in the ATLAS trial was defined as a composite of the percent of subjects with 100% occlusion (Raymond-Roy Class 1) of the treated target lesion on 12-month angiography in the absence of re-treatment or significant parent artery stenosis (> 50%) at the target vessel location. The results of the primary effectiveness endpoint analysis showed the composite success rate in the mITT population with regression imputation was 76.7% (95% CI: 67.0, 86.5) in patients with posterior circulation IAs. A worst-case analysis accounting for missing data subjects as failures of the primary effectiveness endpoint identified a success rate of 66.4% (77/116) with 95% CI between 57% and 74.9%. In addition, the procedural technical success demonstrated that 100% (116/116) of patients with posterior circulations IAs had successful delivery, deployment, and placement of the Neuroform Atlas Stent at the target location. All subjects were implanted with either one (1) Neuroform Atlas Stent (65.5%; 76/116) or two (2) Neuroform Atlas Stents (34.5%; 40/116). On a per device basis, 94.5% (156/165) of attempted device implantations were successful. The re-treatment rate within 1-year post-operative in the mITT population was 7.8% (9/116) in patients with posterior circulation IAs.

Because the Neuroform Atlas Stent System is a permanent implant and the pivotal study with 1-year follow-up data was used to support the PMA Panel Track Supplement, the long-term durability of treatment after 1-year post-procedure is currently unknown. Also, because most of the subjects in the mITT population in the ATLAS trial had unruptured posterior circulation IAs [88.8% (103/116)], the effectiveness of treatment to reduce the natural risk of IA rupture is unknown. Additional sources of uncertainty in the primary effectiveness endpoint results is the use of a single Core Lab reader, which can cause greater assessment variabilityin the adjudication of the DSA imaging results. Also, the subject device is a neurovascular coil-assist stent, and the primary function of the device is to hold embolization coils within the sac of the wide-necked IA. The ATLAS study protocol did not pre-specify or guide site investigators on the packing of the IA sac with neurovascular embolization coils. Therefore, there may be some uncertainty on the primary

effectiveness endpoint due to potential variability in how IAs were packed with adjunctive neurovascular embolization coils. The primary effectiveness endpoint may not solely be attributed to the Neuroform Atlas Stent System and there is confounding treatment due to the packing density of the neurovascular embolization coils used. The lack of a concurrent control group of neurovascular embolization coils alone in the target patient population makes it difficult to assess whether the addition of the Neuroform Atlas Stent System improved the IA occlusion and the comparison of effectiveness is made to a performance goal developed from a meta-analysis of the literature from endovascular treatments of wide-necked intracranial aneurysms using neurovascular stents for SAC, BAC, and coiling alone.

B. Safety Conclusions

The risks of the device are based on non-clinical laboratory and animal studies as well as data collected in a clinical study conducted to support PMA approval as described above. The primary safety endpoint comprised of the rate of major ipsilateral stroke defined as an increase in the NIHSS score from baseline by ≥ 4 points or neurological death in the mITT population and was analyzed to be 4.3% (5/116) in patients with posterior circulation IAs in the ATLAS study. The incidence of major ipsilateral stroke was 3.4% (4/116) and the incidence of neurological death was 0.9% (1/116) that resulted from a major ipsilateral stroke.

In the mITT population, there were 5 subjects that did not have a 12-month primary safety endpoint assessment. In a worst-case analysis, if these 5 missing data subjects were imputed as failures for the primary safety endpoint as having the adverse events of interest, the primary safety endpoint is 8.6% (10/116) with a 95% unadjusted confidence interval of 4.2% to 15.3%.

For all CEC adjudicated ischemic or hemorrhagic adverse events (i.e., ischemic and hemorrhagic, ipsilateral and contralateral, of all severities, at all times after enrollment, and of any duration, including TIAs) or deaths, the incidence occurred in the study was 19.4% (20/103) and 7.7% (1/13) for unruptured and ruptured intracranial aneurysms in the posterior circultion, respectively. For all mITT subjects, the overall ischemic or hemorrhagic adverse event rate or death was 18.1% (21/116).

Among those subjects who had 12-month mRS data available, the majority (90.2%; 92/102) had unchanged or improved functional outcomes compared to baseline (Table 23). A total of 73 subjects (71.6%) had unchanged mRS scores and 19 subjects (18.6%) had improved mRS scores at 12 months compared to their baseline mRS. There were 10 subjects with worsened mRS scores (10/102; 9.8%). For 14 subjects, the mRS assessment was not performed due to loss-to-follow-up (n = 5), study discontinuation (n = 8), and subject withdrawal of consent (n = 1).

The primary safety endpoint rate for the patients with posterior circulation IAs observed in the ATLAS trial with the Neuroform Atlas Stent System is within the safety rates published in the scientific literature for stent-assisted coiling of wide-

necked intracranial aneurysms and the study met the a priori study success criteria with statistical significance.

C. Benefit-Risk Determination

The probable benefits of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. The results of the primary effectiveness endpoint analysis showed the composite success rate in the mITT population with regression imputation was 76.7% (95% CI: 67.0, 86.5) in patients with posterior circulation IAs. A worst-case analysis accounting for missing data subjects as failures of the primary effectiveness endpoint identified a success rate of 66.4% (77/116) with 95% CI between 57% and 74.9%. In addition, the procedural technical success demonstrated that 100% (116/116) of patients with posterior circulations IAs had successful delivery, deployment, and placement of the Neuroform Atlas Stent at the target location. The re-treatment rate within 1-year post-operative in the mITT population was 7.8% (9/116) in patients with posterior circulation IAs.

Because the Neuroform Atlas Stent System is a permanent implant and the pivotal study with 1-year follow-up data was used to support the PMA Panel Track Supplement, the long-term durability of treatment after 1-year post-procedure is currently unknown. Also, because most of the subjects in the mITT population in the ATLAS trial had unruptured posterior circulation IAs [88.8% (103/116)], the effectiveness of treatment to reduce the natural risk of IA rupture is unknown. Additional sources of uncertainty in the primary effectiveness endpoint results is the use of a single Core Lab reader, which can cause concerns of assessment variability in the adjudication of the DSA imaging results. Even with these uncertainties, the rate of the Raymond-Roy I occlusion combined with the number of patients who had stable Raymond-Roy II occlusions with the low re-treatment rate within 1-year post-operative demonstrate the stability of treatment within 1 year.

The probable risks of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. The primary safety endpoint comprised of the rate of major ipsilateral stroke defined as an increase in the NIHSS score from baseline by ≥ 4 points or neurological death in the mITT population and was analyzed to be 4.3% (5/116) in patients with posterior circulation IAs in the ATLAS study. The incidence of major ipsilateral stroke was 3.4% (4/116) and the incidence of neurological death was 0.9% (1/116) that resulted from a major ipsilateral stroke.

For all CEC adjudicated ischemic or hemorrhagic adverse events (i.e., ischemic and hemorrhagic, ipsilateral and contralateral, of all severities, at all times after enrollment, and of any duration, including TIAs) or deaths, the incidence occurred in the study was 19.4% (20/103) and 7.7% (1/13) for unruptured and ruptured intracranial aneurysms in the posterior circultion, respectively. For all mITT subjects, the overall ischemic or hemorrhagic adverse event rate or death was 18.1% (21/116).

Additional factors to be considered in determining probable risks and benefits for the Neuroform Atlas Stent System included weighing the benefits and risks of device treatment with the patient's risk of intracranial aneurysm rupture during their expected lifetime. The risk of rupture of an untreated unruptured intracranial aneurysm is dependent on multiple factors including, but not limited to, intracranial aneurysm size, shape, morphology, and location; patient history of smoking; age; family history; and the patient co-morbidities such as hypertension, presence of multiple intracranial aneurysms, or diabetes. Based on natural history, it has been suggested that intracranial aneurysms have an average rupture rate of around 1% per year in patients with a diagnosed intracranial aneurysm, although that number can vary based on the study (Ishibashi et al. 2009; Juvela et al. 2013). The annual risk of rupture of an intact intracranial aneurysm is estimated to be approximately 1.9% (Rinkel et al. 1998). In the article by Wiebers (2003), intracranial aneurysms in the ICA, anterior communicating, anterior cerebral artery, or middle cerebral artery that were < 7 mm, 7-12 mm, 13-24 mm, and > 25 mm had rupture rates of 0%, 2.6%, 14.5%, and 40%, respectively, at 5 years. In addition, from this same study, rupture rates of 2.5%, 14.5%, 18.4%, and 50% were seen, for the same distribution of sizes, for aneurysms located in the posterior circulation and posterior communicating artery. Therefore, the presence of an IA in the posterior circulation may result in a higher risk of rupture.

The effect of intracranial aneurysm rupture is extremely severe, resulting in subarachnoid hemorrhage, which is associated with a high level of neurological disability and mortality. Therefore, if the patient may have a high risk of intracranial aneurysm rupture within their expected lifetime, then the probable benefit of treatment with the subject device may outweigh the risks of device use with consideration of the seriousness of the adverse effects if the intracranial aneurysm ruptures. Also, based on the complexity of the disease, the physician-patient relationship in deciding which intracranial aneurysms should be treated with the device is particularly important based on the patient's individual risk of intracranial aneurysm rupture within their lifetime.

One additional factor to be considered in determining probable risks and benefits for the Neuroform Atlas Stent System is the assessment of uncertainty in the ATLAS study, which was a non-randomized, open-label clinical study. Although the ATLAS trial was conducted in accordance with all applicable US federal regulations (including 21 CFR Parts 11, 50, 54, 56 and 812), the Declaration of Helsinki, Good Clinical Practices, ISO 14155, all conditions of approval from participating Institutional Review Boards (IRBs), the requirements of all other governing regulatory authorities, there is always bias in subject selection in a single arm study design, regardless of whether the study results were 100% monitored with safety oversight delegated to an independent CEC and DSMB. There may also be additional uncertainty in the primary effectiveness endpoint estimate due to the use of only a single Core Lab reader. Also, although it was stated the neurological examinations (NIHSS and mRS) were performed by an independent certified assessor, it is unclear

if the assessor was truly independent and free from any contact or relationships with the site investigators. Therefore, based on these uncertainties in the conduct of the ATLAS study, the results obtained should be viewed on a best-case scenario and results may vary in clinical practice. Furthermore, the lack of a concurrent control group and no blinding in the ATLAS trial results in uncertainties in whether treatment with the Neuroform Atlas Stent System may be better than or comparable to other types of treatments or no treatment at all for patients with wide-necked IAs located in the posterior circulation of the neurovasculature.

1. Patient Perspectives

   Patient perspectives considered during the review included a quality of life assessment that was performed at baseline and the 12-month follow-up visits using the EQ-5D-3L to measure general health status (King et al. 2009). The mean EQ-5D index score was 0.85 ± 0.17 at baseline and 0.87 ± 0.16 at 12 months. The mean EQ-5D visual analog scale (VAS) score was 77.7 ± 16.9 at baseline and 76.0 ± 17.5 at 12 months. No changes to the quality of life were observed by this assessment.

In conclusion, given the available information above, the data support that for the indicated use with neurovascular embolization coils in the anterior and posterior 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, the probable benefits outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. As previously specified, the primary effectiveness endpoint analysis resulted in 76.7% (95% CI: 67.0, 86.5) of patients with IAs in the posterior circulation obtaining complete (100%) intracranial aneurysm occlusion (Raymond-Roy Class 1) at 12-months post-operative without any re-treatment or significant parent artery stenosis (> 50%) at the target vessel location. Accounting for subjects with missing DSA data at 12-months follow-up as failures of the primary effectiveness endpoint, the rate was 66.4% (77/116) with a 95% CI of 57% to 74.9%. Safety results through 12-month follow-up demonstrated a 4.3% (5/116) rate with a 95% CI of 1.4% to 9.8% of primary safety endpoint events of neurological death or major ipsilateral stroke in patients with posterior circulation IAs in the ATLAS study. Accounting for 5 subjects with missing safety data at the 12-month follow-up visit as failures of the primary safety endpoint, the rate is 8.6% (10/116) with a 95% CI of 4.2% to 15.3%.

XIV. CDRH DECISION

CDRH issued an approval order on July 30, 2020.

The final clinical conditions of approval cited in the approval order are described below.

PMA Post-Approval Study - "Safety and Effectiveness of the Treatment of Wide Neck, Saccular Intracranial Aneurysms with the Neuroform Atlas Stent System (ATLAS)": The Office of Neurological and Physical Medicine Devices [Office of Health Technology (OHT) 5] will have the lead for this study initiated prior to device approval. The ATLAS study was conducted under investigational device exemption (IDE) G150006 and patients were consented to be followed for up to three (3) years post-operative. The 1-year follow-up data from the ATLAS study for patients with posterior circulation intracranial aneurysms was used to support the approval of the subject PMA Panel Track Supplement, P180031/S001. As part of the post-approval study, the long-term follow-up from the ATLAS study can provide safety and effectiveness information on the durability and safety of treatment using the Neuroform Atlas Stent System up to 3 years post-operative in patients with posterior circulation intracranial aneurysms. The pre-specified safety endpoint is the incidence of patients who experienced a major ipsilateral stroke or neurological death. The pre-specified effectiveness endpoint is the incidence of patients who had complete (100%) intracranial aneurysm occlusion (Raymond-Roy Class 1) without significant in-stent stenosis (> 50%) or re-treatment of the target intracranial aneurysm. The incidence of all ischemic or hemorrhagic adverse events (i.e., ischemic and hemorrhagic, ipsilateral and contralateral, of all severities, at all times after enrollment, and of any duration, including transient ischemic attacks) should also be reported as part of the long-term safety analysis.

Per the approved IDE G150006 study protocol, patients will be contacted and in person office visits will be scheduled to perform safety and neurological examinations at 2-year and 3-year follow-up visits (within ± 6 months). All 99 patients who completed the 12-month follow-up visit will continue to be followed annually to the 3-year follow-up visit. In addition, all new and ongoing adverse events will be recorded and adjudicated by the Clinical Events Committee per the approved G150006 study protocol. Imaging assessment of intracranial aneurysm occlusion and in-stent stenosis will be performed during year 2 and 3 if imaging assessments will be performed as part of usual care. To ensure independent assessment of all imaging outcomes data, all intracranial aneurysm occlusion results in the ATLAS study collected in the post-approval study will be evaluated by a minimum of two Core Lab readers with a third reader used to resolve any disagreements in the intracranial aneurysm occlusion scoring. The inter- and intra-reader reliability should be assessed and presented to determine the accuracy of the Core Lab reader results. All Core Lab readers should be trained neuroradiologists with experience reading intracranial aneurysm angiograms and should be independent from any affiliation with the study sponsor. Independence is defined as having no financial interests or any personal gain associated with the subject device or study sponsor and no knowledge or involvement in the care of the patients that were treated.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

XVI. REFERENCES

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