SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Intracranial Aneurysm Flow Diverter

Device Trade Name: Pipeline™ Flex Embolization Device

Device Procode: OUT

Applicant's Name and Address: Micro Therapeutics, Inc. d/b/a ev3 Neurovascular
9775 Toledo Way
Irvine, CA 92618

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P100018/S015

Date of FDA Notice of Approval: December 14, 2018

The current supplement was submitted to expand the indication for the Pipeline™ Flex Embolization Device for use in the endovascular treatment of adults (22 years of age or older) with small and medium wide-necked (neck width ≥ 4 mm or dome-to-neck ratio < 2) saccular or fusiform intracranial aneurysms (IAs) in the internal carotid artery located up to the terminus. The Pipeline™ Flex Embolization Device features a modified device delivery system compared to the original Pipeline™ Embolization Device, and was approved on January 26, 2015 under a 180-Day PMA Supplement for a device design change (P100018/S011). The original PMA P100018 for the Pipeline™ Embolization Device was approved on April 6, 2011 and is indicated for the endovascular treatment of adults (age 22 and above) with large or giant wide-necked intracranial aneurysms in the internal carotid artery from the petrous to the superior hypophyseal segments. The SSED to support the indication is available on the CDRH website and is incorporated by reference here.

II. INDICATIONS FOR USE

The Pipeline™ Flex Embolization Device is indicated for use in the internal carotid artery up to the terminus for the endovascular treatment of adults (22 years of age or older) with small and medium wide-necked (neck width ≥ 4 mm or dome-to-neck ratio < 2) saccular or fusiform intracranial aneurysms (IAs) arising from a parent vessel with a diameter ≥ 2.0 mm and ≤ 5.0 mm.

III. CONTRAINDICATIONS

The Pipeline™ Flex Embolization Device is contraindicated for use in the following patients:

- Patients with active bacterial infection.
- Patients in whom dual antiplatelet and/or anticoagulation therapy (aspirin and clopidogrel) is contraindicated.
- Patients who have not received dual antiplatelet agents prior to the procedure.
- Patients in whom a pre-existing stent is in place in the parent artery at the target aneurysm location.
- Patients in whom the parent vessel size does not fall within the indicated range.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Pipeline™ Flex Embolization Device labeling.

V. DEVICE DESCRIPTION

The Pipeline™ Flex Embolization Device ("Pipeline Flex") consists of a permanent implant combined with a guidewire-based delivery system.

Implant

The Pipeline Flex implant is a multi-alloy, mesh cylinder braided from platinum/tungsten and cobalt-chromium-nickel alloy wires (Figure 1). The braided wires of the device provide approximately 30% metal coverage of the arterial wall surface area. The implant is designed for placement in a parent vessel across the neck of an intracranial aneurysm (IA). The expanded or un-constrained diameter is 0.25 mm larger than the labeled diameter.

Figure 1. Pipeline Flex Implant

Delivery System

The Pipeline Flex delivery system is a 200 cm guidewire-based system. The primary component is the 304-stainless steel wire with a spiral cut 304L stainless steel hypotube and polytetrafluoroethylene (PTFE) jacket covering the hypotube. The Pipeline Flex braided implant is mounted on the guide-wire and compressed inside an introducer sheath (see **Figure 2**). The Pipeline Flex delivery system includes a resheathing pad that allows

the clinical user to resheath the implant back into the microcatheter, up to two (2) times. The resheathing marker provides the clinical user fluoroscopic visualization for the deployment limit of resheathing the Pipeline™ Flex implant.

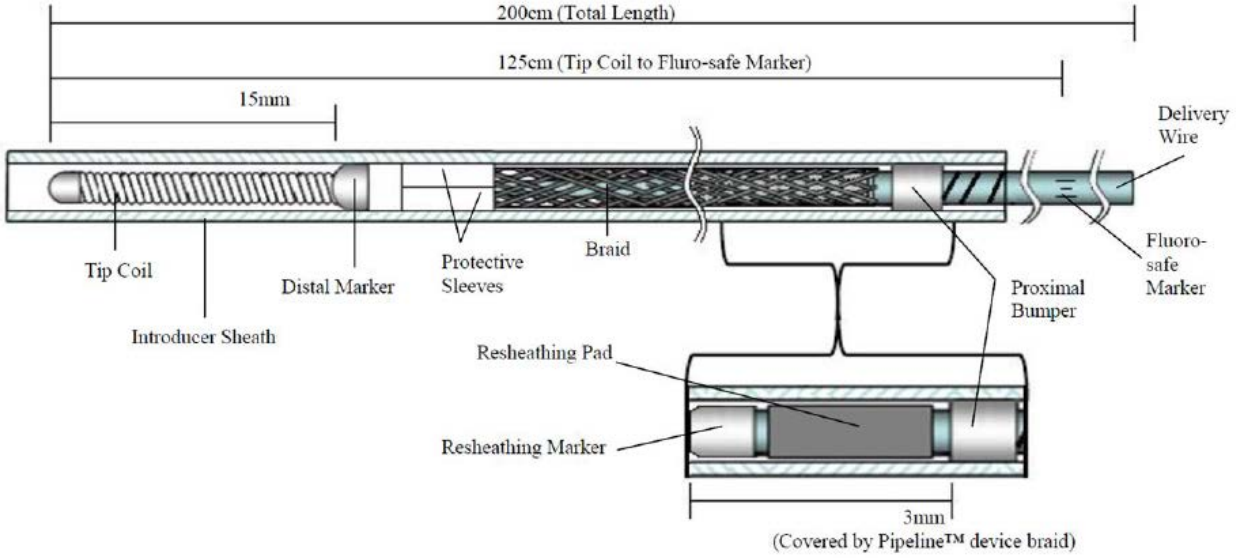


Figure 2. Pipeline™ Flex Embolization Device Delivery System

The Pipeline Flex implant is available in diameters from 2.5 to 5.0 mm and lengths from 10 to 35 mm. The maximum length available for the 2.5 and 2.75 mm diameter implants is 20 mm (Table 1). The expanded or un-constrained diameter is 0.25 mm larger than the labeled diameter. The Pipeline™ Flex is designed to be delivered only through a compatible microcatheter of 0.027 inch (0.69 mm) inside diameter (ID) and at least 135 cm in length.

Table 1. Available Sizes of the Pipeline™ Flex Embolization Device

Labeled Diameter (mm)	Self-Expanded Diameter (mm)	Labeled Lengths (mm)
2.50	2.75	10, 12, 14, 16, 18, 20
2.75	3.00	10, 12, 14, 16, 18, 20
3.00	3.25	10, 12, 14, 16, 18, 20, 25, 30, 35
3.25	3.50	10, 12, 14, 16, 18, 20, 25, 30, 35
3.50	3.75	10, 12, 14, 16, 18, 20, 25, 30, 35
3.75	4.00	10, 12, 14, 16, 18, 20, 25, 30, 35
4.00	4.25	10, 12, 14, 16, 18, 20, 25, 30, 35
4.25	4.50	10, 12, 14, 16, 18, 20, 25, 30, 35
4.50	4.75	10, 12, 14, 16, 18, 20, 25, 30, 35
4.75	5.00	10, 12, 14, 16, 18, 20, 25, 30, 35
5.00	5.25	10, 12, 14, 16, 18, 20, 25, 30, 35

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the treatment of small or medium wide-necked IAs located in the internal carotid artery (ICA) up to the terminus, including surgical clipping and endovascular treatment using neurovascular embolic coil-assist stents or balloon catheter assisted coiling of the intracranial aneurysm. The neurovascular embolic coil-assist stents available in the United States (US) for use in wide-neck IAs located in the ICA were approved through the premarket approval (PMA) regulatory pathway (i.e., MicroVention, Inc. Low-Profile Visualized Intraluminal Support (LVIS) and LVIS Jr. (P170013)) and the Humanitarian Device Exemption (HDE) regulatory pathway, which include the Stryker Neurovascular Neuroform EZ, 3, and Atlas Stent Systems (H020002) and the Codman & Shurtleff, Inc. Enterprise Vascular Reconstruction Device and Delivery System (H060001).

In addition to these alternative treatments, certain IAs 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 IAs 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 Pipeline Flex Embolization Device is approved for marketing in the following countries: Afghanistan, Argentina, Australia, Austria, Belarus, Belgium, Bosnia, Brazil, Bulgaria, Canada, China, Colombia, Croatia, Czech Republic, Denmark, Ecuador, Egypt, Estonia, Finland, France, Germany, Greece, Hong Kong, Hungary, India, Indonesia, Iraq, Ireland, Israel, Japan, Italy, Kazakhstan, Korea, Latvia, Macedonia, Malaysia, Malta, Mexico, Netherlands, New Zealand, Norway, Peru, Poland, Portugal, Russia, Saudi Arabia, Serbia, Singapore, Slovakia, South Africa, Spain, Sweden, Switzerland, Taiwan, Thailand, Turkey, Ukraine, United Arab Emirates, United Kingdom, United States, Uruguay, and Vietnam.

The Pipeline Flex Embolization Device has not been withdrawn from the market outside of the United States for safety or effectiveness reasons.

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.

- Adverse reaction to antiplatelet/anticoagulation agents, anesthesia, reactions due to radiation exposure (such as alopecia, burns ranging in severity from skin reddening to ulcers, cataracts, and delayed neoplasia) or contrast media, including organ failure.

- Vascular complications like vasospasm, stenosis, dissection, perforation, rupture, fistula formation, pseudo aneurysm, occlusion, thromboembolic complications including ischemia (to unintended territory).
- Device complications like fracture, breakage, misplacement, migration/delayed forshortening or reaction to device materials.
- Systemic complications like: infection, pain, fever, allergic reactions, organ failure, nerve damage.
- Bleeding/hemorrhagic complication including retroperitoneal hemorrhage.
- Neurological deficits or dysfunctions including stroke, infarction, loss of vision, seizures, transient ischemic attack (TIA), headache, cranial nerve palsies, confusion, coma.
- Decreased therapeutic response including need for target aneurysm retreatment.
- Risks associated with visual symptoms include amaurosisfugax/transient blindness, blindness, diplopia, reduced visual acuity/field, retinal artery occlusion, retinal ischemia, retinal infarction, vision impairment including scintillations, blurred vision, eye floaters.
- Intracranial hemorrhage (including from aneurysm rupture), brain edema, hydrocephalus, mass effect.
- Death

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

IX. SUMMARY OF NONCLINICAL STUDIES

The Pipeline™ Flex Embolization Device was approved under P100018/S011. The Pipeline™ Embolization Device (PED) is the previous generation of the Pipeline Flex that was approved under P100018. Both devices utilize the same braided implant; therefore, non-clinical studies conducted on the implant applies to both configurations of the device. However, since the Pipeline Flex features a different delivery system compared to the PED, non-clinical bench and animal testing was conducted on the Pipeline Flex to support device approval in P100018/S011. No additional non-clinical bench or animal studies were required for this application. A summary of the non-clinical studies conducted on the PED implant component can be found in the Summary of Safety and Effectiveness Data (SSED) for P100018 at the following location: https://www.accessdata.fda.gov/cdrh_docs/pdf10/P100018B.pdf.

A summary of the non-clinical studies conducted on the Pipeline Flex submitted to support approval of the device under P100018/S011 is described in Tables 2-5 below.

A. Laboratory Studies

Table 2. Pipeline Flex Embolization Device Design Verification and Validation Studies

Bench Verification Test	Acceptance Criteria	Results
Dimensional Verification	Dimensional requirements within specification	Pass
Delivery Deployment and Retraction - Flushability	Delivery system must allow for flushing through the entire length of the introducer sheath from a pressure source at 250 mmHg.	Pass
Delivery Deployment and Retraction - Hub Loading	Must be able to be successfully loaded from the introducer sheath into the catheter hub.	Pass
Delivery Deployment and Retraction - Deliverability	Peak delivery force within specification.	Pass
Delivery, Deployment, Retraction – Distal Deployment	Braid must release from the distal protective system (DPS) after a maximum of two deployment attempts.	Pass
Delivery, Deployment, Retraction – Proximal Deployment	Braid must release from the resheathing pad upon full deployment.	Pass
Delivery, Deployment, Retraction – Resheathability	Device must be resheathable until the distal pad restraint aligns with the microcatheter distal marker band.	Pass
Delivery, Deployment, Retraction - Delivery System Durability	The delivery system must be durable enough to withstand simulated use without sustaining clinically relevant damage.	Pass
Delivery, Deployment, Retraction - DPS Durability	The distal protective subassembly must remain attached to the delivery system throughout simulated use.	Pass
Delivery, Deployment, Retraction - Braid Durability	The braid must be durable enough to withstand simulated use without sustaining clinically relevant damage.	Pass
Delivery, Deployment, Retraction – Braid Opening	The braid must open following deployment in a clinically relevant vessel after simulated use.	Pass
Delivery, Deployment, Retraction - Delivery System Retraction	The delivery system must be retrievable through a 0.027” microcatheter following final deployment and detachment of the braid.	Pass
Delivery, Deployment, Retraction – Particulate Evaluation	Particulate generated during simulated use (including multiple deployment cycling): 10 micrometer particles ≤ 6000 per container per USP <788> 25 micrometer particles ≤ 600 per container per USP <788>	Pass
Durability - Delivery System Bond Strength – Distal Tip	Distal tip joint strength within specification.	Pass

Bench Verification Test	Acceptance Criteria	Results
Joint		
Durability - Delivery System Bond Strength – DPS Restraint Joint	DPS restraint joint strength within specification.	Pass
Durability - Delivery System Bond Strength – Distal Pad Restraint	Distal pad restraint joint strength within specification.	Pass
Durability - Delivery System Bond Strength – Distal Hypotube Joint	Distal hypotube joint strength within specification.	Pass
Durability - Delivery System Bond Strength – Proximal Hypotube Joint	Proximal hypotube joint strength within specification.	Pass
Durability - Delivery System Bond Strength – Torque Resistance	The delivery system post deployment will withstand rotation on the proximal prior to failure.	Pass
Distal Tip Joint Test - Tip Shape Test	Tip must maintain an appropriate angle during use.	Pass
Distal Tip Joint Test - Tip Stiffness Test	Tip stiffness within specification.	Pass
Braid Securement	Device must be resheathable until the distal pad restraint aligns with the microcatheter distal marker band.	Pass
Radiopacity	Verify that all markers have sufficient material and dimensional properties to provide visibility.	Pass
Cosmetic Condition	Delivery system must be constructed of corrosion resistant materials.	Pass
Delivery System Device Handle	Device handle inner diameter (ID) within specification.	Pass
Sheath Visibility	Sheath color must be different from microcatheter hub and delivery system wire.	Pass
Ancillary Products: Microcatheter	Maximum delivery system within specification.	Pass
Ancillary Products: Rotating Hemostasis Valve (RHV)	RHV tightening on the introducer sheath to a clinically relevant level must not interfere with the ability to flush through the sheath or deliver Pipeline device through the sheath.	Pass
Sheath Retention Inspection	Device must not be damaged following industry standard packaging conditioning testing.	Pass

Bench Verification Test	Acceptance Criteria	Results
Cadaver Study	The purpose of this study was to determine if the delivery system met the specific needs of the physician relative to delivery, deployment, detachment and resheathing.	Pass

Table 3. Biocompatibilty Studies (Finished Device with Delivery System)

Test Description		Results
Cytotoxicity Minimum Essential Medium (MEM) Elution Using L-929 Mouse Fibroblast Cells		Pass
Sensitization Guinea Pig Maximization Sensitization (Extract)		Pass
Irritation Intracutaneous Irritation Test (Extract)		Pass
Acute Systemic Toxicity	Acute Systemic Injection Test (Extract)	Pass
	Materials Mediated Rabbit Pyrogen (Extract)	Pass
Hemocompatibility	Hemolysis (ASTM F756 Direct Contact and Extract)	Pass
	Partial Thromboplastin Time Test (PTT)	Pass
	Platelet and Leukocyte Count	Pass
	Complement Activation C3a and SC5b-9 Assay	Pass
	Thrombosis (In Vivo) – Dog (4 hr)	Pass
Genotoxicity	Bacterial Mutagenicity Test (Ames Assay) using Four Salmonella Strains and One E. Coli Strain	Pass
	In Vitro Mouse Lymphoma Assay – 2 Extracts	Pass
	In Vivo Mouse Micronucleus Assay – 2 Extracts	Pass

B. <u>Animal Studies</u>

Table 4. Animal Studies

Test	Purpose	Results
Animal Study	The purpose of this study was to determine if the delivery system met specific user needs including delivery, deployment, detachment, and resheathing.	Pass
Animal Safety Study	To evaluate the device interaction with vessel wall and corresponding tissue response of the Pipeline Flex Embolization Device as compared to PED during a 30-day Good Laboratory Practice (GLP) animal study.	Pass

C. Additional Studies

Table 5. Additional Studies

Test	Acceptance Criteria	Results
Shelf Life Testing		
Device Performance	Device meets performance specifications following 3 year accelerated and real-time aging.	Pass
Packaging Integrity	Packaging integrity is maintained following 3 year accelerated and real-time aging.	Pass
Sterilization		
Sterilization	100% ethylene oxide (EO) sterilization process with a sterility assurance level (SAL) of at least 10^{-6}.	Pass

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of the Pipeline Flex for use in the ICA up to the terminus for the endovascular treatment of adults (22 years of age or older) with small and medium wide-necked (neck width ≥ 4 mm or dome-to-neck ratio < 2) saccular or fusiform IAs arising from a parent vessel with a diameter ≥ 2.0 mm and ≤ 5.0 mm in the United States (US) and Canada under Investigational Device Exemption (IDE) # G140084. 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 enrolled between July 24, 2014 and November 16, 2015. The database for this Panel Track Supplement reflected data collected through the 1 year follow-up completed on December 6, 2016 and included 197 patients. There were 22 investigational sites in the US and 1 site in Canada.

The study was a multi-center, prospective, non-randomized (single arm) clinical study titled "Prospective Study on Embolization of Intracranial Aneurysms with the Pipeline™ Device (PREMIER)." The pivotal study included follow-up at discharge, 30 days, 6 months and 1 year post-procedure. The pre-specified primary endpoints in the clinical study protocol were:

- Safety: Occurrence of major stroke in the territory supplied by the treated artery or neurological death one year post-procedure, as adjudicated by an independent Clinical Events Committee (CEC).

- Effectiveness: Complete intracranial aneurysm occlusion (defined by the Raymond-Roy I classification) without significant parent artery stenosis (≤

50%), as adjudicated by an independent Core Laboratory ("Core Lab"), or retreatment of the target IA one year post-procedure.

The primary endpoint results were compared to performance goals (PGs) developed using prior published clinical data from endovascular treatments of small and medium wide-neck IAs using neurovascular embolic coil-assist stents. Sample size estimates were prepared separately for the primary safety and effectiveness endpoints and were based on generating a 1-sided 97.5% Clopper-Pearson exact binomial confidence interval (CI). The upper bound of the CI for safety and the lower bound of the CI for effectiveness were examined relative to the respective *a priori* PG thresholds. The primary safety and effectiveness endpoints were analyzed per the statistical analysis plan to test the null hypothesis that the primary safety event rate is ≥ 15% and the primary effectiveness rate is ≤ 50%.

Per the study protocol, a maximum enrollment of 200 subjects (any subject who signed the informed consent form (ICF)) was allowed in order to ensure 141 subjects were treated. The total enrollment limit took into account an estimated 30% screen failure rate observed in the initial roll-out of the PREMIER study. Each participating investigational site was allowed to enroll a maximum of 25 subjects.

To avoid and minimize bias in interpreting and analyzing the pivotal study results and oversee the safety of the study subjects, an independent CEC, imaging Core Lab, and Data Safety Monitoring Board (DSMB) were established to assess adverse event relationship, IA occlusion status, and percentage of vessel stenosis.

1. Clinical Inclusion and Exclusion Criteria

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

   - Subject provided written informed consent using the Institutional Review Board (IRB)/Ethics Committee (EC)-approved consent form and agreed to comply with protocol requirements.
   - Age 22-80 years.
   - Subject had a target intracranial aneurysm located in the:
     - Internal carotid artery (up to the carotid terminus), or
     - Vertebral artery segment up to and including the posterior inferior cerebellar artery.
   - Subject had a target intracranial aneurysm that was ≤ 12 mm.
   - Subject had a target intracranial aneurysm that had a parent vessel with diameter 1.5-5.0 mm distal/proximal to the target intracranial aneurysm.
   - Subject had a target intracranial aneurysm with an aneurysm neck ≥ 4 mm or a dome to neck ratio ≤ 1.5.
   - Subject had a pre-procedure platelet reactivity unit (PRU) value between 60–200.

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

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

2. Follow-up Schedule

All patients were scheduled to return for follow-up examinations at 30 days, 180 days, and 1 year postoperatively. Preoperatively, the patients underwent a review of their concomitant medications, medical history, physical, clinical, neurological, laboratory, and angiographic evaluations. Postoperatively, the objective parameters measured during the study included a review of the concomitant medications, medical, physical, clinical, neurological, and angiographic evaluations (see Table 6). Adverse events and complications were recorded at all visits. The key timepoints are shown below in the tables summarizing safety and effectiveness.

Table 6. Visits and Assessment Schedule

Visits		Screening and Baseline	Device Placement		Follow-up			
			Procedure	Discharge Exam	30-Day	180-Day	1-Year	Unscheduled
Assessments	**Time (Windows)**	**Pre-procedure (-60 days)**	**Day 0**	**Day 0-7**	**Day 30 (± 7 days)**	**Day 180 (± 30 days)**	**Day 365 (± 42 days)**	**--**
Assess Inclusion/Exclusion Criteria		◆						
Demographics and Medical History		◆						
Blood Labs		◆[1]	◆[2]	◆[3]				
Medications		◆	◆	◆	◆	◆	◆	◆
Modified Rankin Scale (mRS) Score		◆		◆	◆	◆	◆	
Imaging[4]		◆ (within 180 days pre-procedure)	◆[5]			◆[6]	◆	◆[7]
National Institutes of Health Stroke Scale (NIHSS)		◆	◆	◆	◆	◆	◆	◆
Pipeline Flex Placement			◆					
Assess Adverse Events		◆	◆	◆	◆	◆	◆	◆

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

3. Clinical Endpoints

With regards to safety, the percentage of patients who had a disabling stroke (defined as mRS score ≥ 3 assessed at a minimum of 90 days post-stroke event), major stroke (increase of 4 or more points on the NIHSS at 24 hours after symptom onset), or neurological death within 12-months post-procedure was used to analyze the clinical study results. A stroke is defined as any "rapidly developing clinical signs of focal (or global) disturbance of cerebral function lasting more than 24 hours with no apparent cause other than of vascular origin, including ischemic stroke and/or hemorrhagic stroke (i.e., intraparenchymal

hemorrhage (IPH), subarachnoid hemorrhage (SAH), subdural hemorrhage (SDH), epidural hemorrhage (EDH)) accompanied with radiological evidence."

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 significant parent artery stenosis (≤ 50%) or retreatment one year post-procedure was used to analyze the clinical study results.

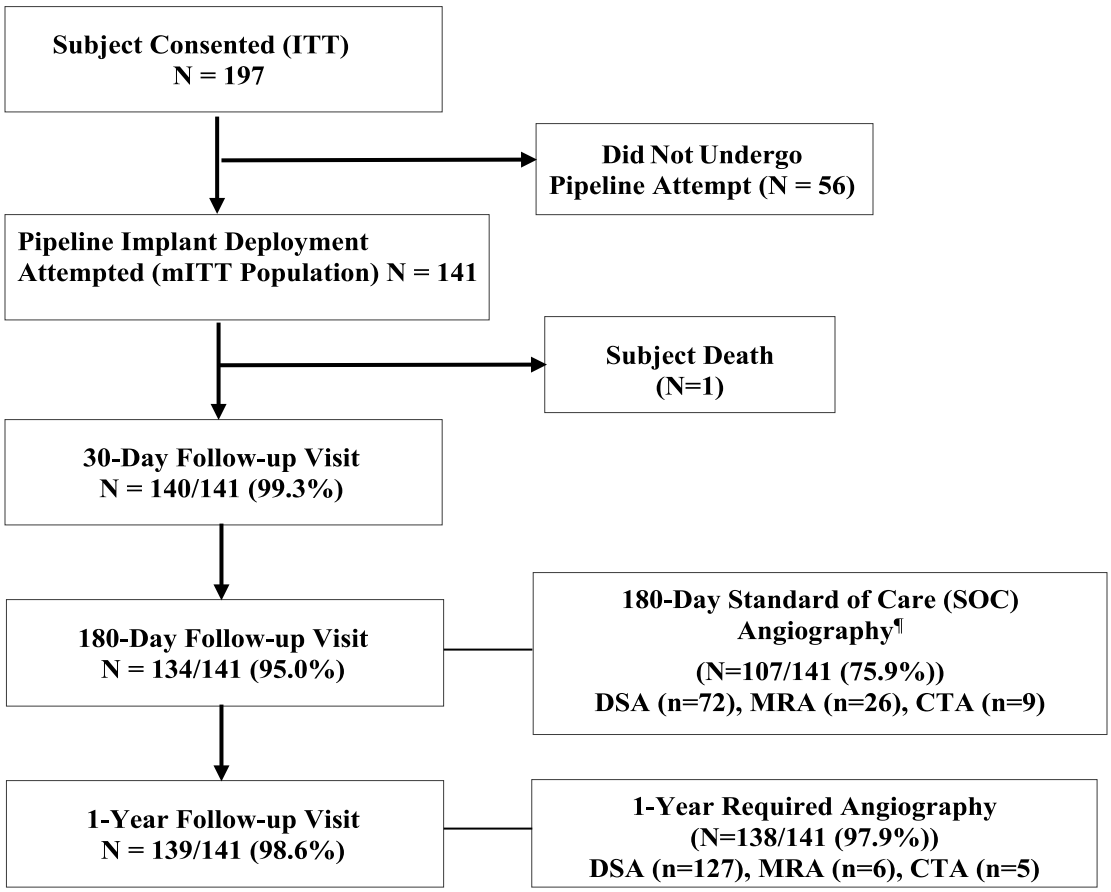
These primary safety and effectiveness endpoints were determined to be most clinically meaningful for evaluating the safety and performance of the Pipeline Flex, and are consistent with the recommendations from the March 1, 2018 and April 17, 2015 general issues meetings of the Neurological Devices Panel of the Medical Devices Advisory Committee to discuss the evaluation of benefits vs. risks of new endovascular medical devices intended to treat IAs. The pre-specified primary endpoints for the PREMIER trial are described earlier in Section X (A. Study Design).

With regard to success/failure criteria, the primary endpoints were compared to PGs. The clinical study would be considered a success for effectiveness if the primary effectiveness endpoint rate was greater than 50%, with a one-sided lower bound of 97.5% CI calculated using the Clopper-Pearson method. The clinical study would be considered a success for safety if the primary safety endpoint rate was less than 15%, with a one-sided upper bound of 97.5% CI using the exact Clopper-Pearson method.

B. Accountability of PMA Cohort

At the time of database lock, of 197 patients (intent-to-treat (ITT) population) enrolled in the PMA study, 71.6% (141) patients (modified ITT (mITT) population) are available for primary analysis at the completion of the study, the 1 year post-operative visit. Figure 3 shows the disposition of patients in the PREMIER trial. The mITT population was used for the analysis of the primary endpoints in the PREMIER study.

Figure 3. Subject Disposition in PREMIER Trial



¶Angiography at 180-day follow-up was not required per the clinical protocol and was performed per site standard of care. However, if performed, imaging was sent to Core Lab.
DSA = Digital Subtraction Angiography
MRA = Magnetic Resonance Angiography
CTA = Computed Tomography Angiography

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for an intracranial aneurysm 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 patient population in the PREMIER trial (see Table 7).

Table 7. Subject Baseline Characteristics – PREMIER Trial (N=141)

Characteristic	Overall (N=141 Subjects)
Mean Age (standard deviation (SD), range)	54.6 (11.3, 30 – 77)
Gender	
Male	12.1% (17)
Female	87.9% (124)
Race	
American Indian or Alaska Native	0.7% (1)
Asian	2.8% (4)
Black or African American	11.3% (16)
White	80.9% (114)
Not Reported	4.3% (6)
Ethnicity	
Hispanic or Latino	8.5% (12)
Not Hispanic or Latino	81.6% (115)
Not Reported	5.0% (7)
Unknown	5.0% (7)
Smoking	
Never smoked or has not smoked within the last 10 years	56% (79)
Not a current smoker but has smoked in the past 10 years	14.9% (21)
Current smoker, less than one pack per day	19.1% (27)
Current smoker, greater than or equal to one pack per day	9.9% (14)
Target Intracranial Aneurysm Previously Ruptured	
Yes	3.5% (5)
Target Intracranial Aneurysm Previously	
Coiled	4.3% (6)
Clipped	1.4% (2)
De Novo	94.3% (133)

Table 8 below presents the characteristics of the intracranial aneurysms treated in the PREMIER trial.

Table 8. Summary of Baseline Intracranial Aneurysm Characteristics per Core Lab (mITT Population with Observed Data)

IA Characteristics	Target Intracranial Aneurysm (N=141)
Aneurysm Side	
Right	48.9% (69/141)
Left	51.1% (72/141)
Internal Carotid Artery	95.0% (134/141)

IA Characteristics	Target Intracranial Aneurysm (N=141)
C1 (Cervical Segment)	0
C2 (Petrous Segment)	0.7% (1/134)
C3 (Lacerum Segment)	0
C4 (Cavernous Segment)	2.2% (3/134)
C5 (Clinoid Segment)	8.2% (11/134)
C6 (Ophthalmic Segment)	74.6% (100/134)
C7 (Communicating Segment)	14.2% (19/134)
Vertebral Artery	5.0% (7/141)
V1 (Pre-Foraminal)	0
V2 (Foraminal)	0
V3 (C2 to Dura)	0
V4 (Intradural)	100.0% (7/7)
Saccular	96.5% (136/141)
Sidewall	-
Terminus	-
Involved Side Branch	-
Bifurcation Branch	-
No Side Branch	65.4% (89/136)
Side Branch	34.6% (47/136)
Branch arising from neck of aneurysm	17.6% (24/136)
Branch arising from dome of aneurysm	8.8% (12/136)
Branch adjacent to aneurysm neck	8.1% (11/136)
Fusiform	3.5% (5/141)
Pseudoaneurysm	0
Partially Thrombosed	
Yes	3.5% (5/141)
Aneurysm Measurement	
Aneurysm Maximal Diameter (mm)	5.0 ± 1.92 [4.6] (1.7 - 11.1)
Dome Width (mm)	4.5 ± 1.83 [4.2] (1.3 - 11)
Dome Height (mm)	4.0 ± 1.60 [3.8] (1 - 9.2)
Aneurysm Neck Length (mm)	4.0 ± 1.42 [3.7] (1.3 - 9.5)
Dome/Neck Ratio	1.1 ± 0.28 [1.1] (0.6 - 1.9)
Parent Artery Diameter Proximal to Target Aneurysm (mm)	3.9 ± 0.60 [3.9] (2.1 - 5)
Parent Artery Diameter Distal to Target Aneurysm (mm)	3.5 ± 0.59 [3.5] (2.2 - 5.1)
Aneurysm Size	5.0 ± 1.92 [4.6] (1.7 - 11.1)

IA Characteristics	Target Intracranial Aneurysm (N=141)
Small (< 7 mm)	84.4% (119/141)
Aneurysm Size (< 3 mm)	9.9% (14/141)
Aneurysm Size (≥ 3 and < 7 mm)	74.5% (105/141)
Medium (≥ 7 and < 13 mm)	15.6% (22/141)
Large (≥ 13 and < 25 mm)	0
Giant (≥ 25 mm)	0
Note 1: Numbers are presented as % (Count/Sample Size) or Mean ± SD [Median] (Mininum, Maximum). Note 2: Results were based on the pre-procedure imaging assessed by the independent Core Lab with the exception of previous aneurysm rupture information which was based on site reported data.	

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the mITT cohort of 141 patients available for the 12-month evaluation. The mITT cohort included all enrolled subjects in whom deployment of the Pipeline Flex device was attempted. The key safety outcomes for this study are presented below in Tables 9 to 12. Adverse effects are reported in Table 13.

Table 9. Primary Safety Endpoint (mITT Population)

Primary Safety Endpoint	Rate (%) (N = 141 Subjects)	1-Sided 97.5% Exact Upper Binomial CI	Threshold	1-Sided P-Value from Binomial Distribution
Major stroke in the territory supplied by the treated artery or neurological death within 1 year follow-up.	2.17%*	6.51%	15%	0.0002
Analyzed with PROC MIANALYZE *Note:* Missing data for subjects who failed to complete the 1-year post-procedure evaluation without any evidence of a major stroke in the territory supplied by the treated artery or neurological death were imputed in the analysis using the multiple imputation procedure from SAS (Proc MI). Subjects who withdraw from the study prior to the 1-year evaluation visit and have experienced a major stroke in the territory supplied by the treated artery or neurological death at any time prior to the 1-year evaluation will be counted as having experienced the event of interest. *Note:* Three subjects experienced a major stroke during the 1 year follow-up period (N=141 subjects). One (1) of the 3 subjects who had a major stroke resulted in neurological death within 1 year follow-up.				

An additional post-hoc analysis was performed where the mITT population was analyzed using a composite primary safety endpoint definition of disabling stroke (mRS score of ≥ 3 at a minimum of 90 days post-stroke event) or neurological death at 1-year post-procedure based on the recommendations of the Medical Devices Advisory Committee of the Neurological Devices Panel at the March 1, 2018 general issues meeting (see Table 10).

Table 10. *Post-Hoc* Modified Primary Safety Endpoint – mITT Population with Observed Data

	Rate	**1-Sided 97.5% Exact Upper Binomial CI**
Primary Safety Composite Rate (Disabling Stroke or Neurological Death within 1-Year Post-Procedure)	1.4% (2/141)	5.0%
Disabling Stroke within 1 Year Post-Procedure	0.7% (1/141)	3.9%
Neurological Death within 1-Year Post-Procedure	0.7% (1/141)	3.9%
Note: The CI was calculated without multiplicity adjustment. As such, the CI is provided to show the variability only and should not be used to draw any statistical conclusions.		

In summary, there were a total of 3 subjects in the mITT population who experienced a major stroke, disabling stroke, or neurological death within 1 year post-procedure. All 3 subjects had a major stroke (increase of 4 points or more on the NIHSS) within the 1 year follow-up period, with 1 major stroke also being a disabling stroke and 1 subject with a major stroke that resulted in neurological death. There were also 2 subjects with missing data at the 1 year follow-up visit and 1 of the 2 subjects with missing data was the subject who died as a result of a major stroke. Therefore, accounting for a worst-case analysis of the primary safety endpoint based on the incidence of subjects in the mITT population who experienced a major stroke, disabling stroke, or neurological death within 1 year post-procedure and counting subjects with missing data as failures, there were a total of 4 subjects who experienced a primary safety endpoint event (4/141 = 2.8%). This primary safety endpoint event rate is still much lower than the pre-specified PG and the device is considered to have met its safety success criteria for the expanded indications for use.

The incidence of all ischemic and hemorrhagic events (includes major stroke, minor stroke, symptomatic cerebral infarction, asymptomatic cerebral infarction, intracranial hemorrhage (ICH), transient ischemic attack (TIA), and IA rupture) in the mITT population is presented in Table 11. Table 11 does not account for a worst-case analysis with missing subjects at the 1 year follow-up visit assessed as failures of having one of these adverse events.

Table 11. Cerebrovascular Events (Ischemic and Hemorrhagic) in the mITT Population up to 1-Year Post-Procedure

Variable	mITT Population % (n/N) [E]
Analysis of Cerebrovascular Events (Ischemic and Hemorrhagic)	7.8% (11/141) [18]
n = Number of subjects with events. N = Total number of subjects. E = Total number of events.	

The change in modified Rankin Scale (mRS) scores compared to the pre-procedure mRS measurements in the mITT population with evaluable data (mITT Evaluable Population) is presented in Table 12. Table 12 only contains data and mRS analyses for the subjects in the mITT population that had evaluable mRS data at 1 year post-procedure (N=136). One of the limitations in the PREMIER study was that the mRS assessments at all applicable study visits may not have been performed by an independent assessor such as a vascular neurologist. Therefore, the mRS analyses in Table 11 should be interpreted with caution and there may be bias in the results presented.

Table 12. Change in mRS Compared to Pre-Procedure in the mITT Evaluable Population at 1-Year Post-Procedure

mRS Change	mITT Evaluable Population[a] % (n/N) [Confidence Interval]
Decrease in mRS	10.3% (14/136) [5.74%, 16.67%]
No Change	80.1% (109/136) [72.45%, 86.49%]
Increase in mRS	9.6% (13/136) [5.19%, 15.79%]
[a]The mITT population had 5 subjects that did not have paired mRS readings and thus, not included in this analysis. Therefore, N = 136 subjects. *Note:* The CI is based on an exact binomial distribution. The confidence intervals are calculated without multiplicity adjustment. As such, the confidence intervals are provided to show the variability only and should not be used to draw any statistical conclusions.	

Adverse effects that occurred in the PMA clinical study:

Table 13 presents all adverse events (AEs), serious adverse events (SAEs), and non-serious adverse events through one year follow-up in the PREMIER trial.

Table 13. Summary of CEC Adjudicated Adverse Events through 1-Year by System Organ Class and Preferred Term (mITT Population with Observed Data)

MedDRA* System Organ Class	MedDRA Preferred Term	All AEs Incidence of AE (n/N) (%) [# of events]	All SAEs Incidence of AE (n/N) (%) [# of events]	All Non-SAEs Incidence of AE (n/N) (%) [# of events]
Total	Total	116/141 (82.3%) [313]	39/141 (27.7%) [64]	104/141 (73.8%) [249]
Blood and Lymphatic System Disorders	Total	4/141 (2.8%) [4]	1/141 (0.7%) [1]	3/141 (2.1%) [3]
	Anaemia	1/141 (0.7%) [1]	1/141(0.7%) [1]	0
	Haemorrhagic Diathesis	2/141 (1.4%) [2]	0	2/141(1.4%) [2]
	Lymphoid Tissue Hyperplasia	1/141 (0.7%) [1]	0	1/141 (0.7%) [1]
Cardiac Disorders	Total	3/141 (2.1%) [3]	3/141 (2.1%) [3]	0
	Atrial Flutter	1/141 (0.7%) [1]	1/141 (0.7%) [1]	0
	Cardiac Failure Congestive	1/141 (0.7%) [1]	1/141 (0.7%) [1]	0
	Ventricular Tachycardia	1/141 (0.7%) [1]	1/141 (0.7%) [1]	0
Ear and Labyrinth Disorders	Total	3/141 (2.1%) [3]	0	3/141 (2.1%) [3]
	Vertigo	2/141 (1.4%) [2]	0	2/141 (1.4%) [2]
	Vertigo Positional	1/141 (0.7%) [1]	0	1/141 (0.7%) [1]
Eye Disorders	Total	33/141 (23.4%) [40]	1/141 (0.7%) [1]	32/141 (22.7%) [39]
	Blepharospasm	1/141 (0.7%) [1]	0	1/141 (0.7%) [1]
	Conjunctival Haemorrhage	1/141 (0.7%) [1]	0	1/141 (0.7%) [1]
	Diplopia	3/141 (2.1%) [3]	0	3/141 (2.1%) [3]
	Eye Pain	2/141 (1.4%) [2]	0	2/141 (1.4%) [2]
	Photophobia	1/141 (0.7%) [2]	0	1/141 (0.7%) [2]
	Photopsia	2/141 (1.4%) [2]	0	2/141 (1.4%) [2]
	Vision Blurred	8/141 (5.7%) [8]	1/141 (0.7%) [1]	7/141 (5.0%) [7]
	Visual Impairment	15/141 (10.6%) [15]	0	15/141 (10.6%) [15]
	Vitreous Detachment	1/141 (0.7%) [1]	0	1/141 (0.7%) [1]
	Vitreous floaters	5/141 (3.5%) [5]	0	5/141 (3.5%) [5]
Gastrointestinal Disorders	Total	10/141 (7.1%) [14]	6/141 (4.3%) [9]	5/141 (3.5%) [5]
	Abdominal Pain	1/141 (0.7%) [1]	1/141 (0.7%) [1]	0
	Gastrointestinal Haemorrhage	3/141 (2.1%) [5]	3/141 (2.1%) [5]	0
	Gastrointestinal Inflammation	1/141 (0.7%) [1]	0	1/141 (0.7%) [1]
	Hiatus Hernia	1/141 (0.7%) [1]	0	1/141 (0.7%) [1]

MedDRA* System Organ Class	MedDRA Preferred Term	All AEs Incidence of AE (n/N) (%) [# of events]	All SAEs Incidence of AE (n/N) (%) [# of events]	All Non-SAEs Incidence of AE (n/N) (%) [# of events]
	Nausea	4/141 (2.8%) [4]	1/141 (0.7%) [1]	3/141 (2.1%) [3]
	Pancreatitis	1/141 (0.7%) [1]	1/141 (0.7%) [1]	0
	Peritoneal Haemorrhage	1/141 (0.7%) [1]	1/141 (0.7%) [1]	0
General Disorders and Administration Site Conditions	Total	34/141 (24.1%) [35]	4/141 (2.8%) [4]	30/141 (21.3%) [31]
	Adverse Drug Reaction	3/141 (2.1%) [3]	2/141 (1.4%) [2]	1/141 (0.7%) [1]
	Catheter Site Haematoma	13/141 (9.2%) [13]	0	13/141 (9.2%) [13]
	Catheter Site Haemorrhage	9/141 (6.4%) [9]	0	9/141 (6.4%) [9]
	Catheter Site Pain	6/141 (4.3%) [6]	0	6/141 (4.3%) [6]
	Chest Pain	1/141 (0.7%) [1]	1/141 (0.7%) [1]	0
	Fatigue	1/141 (0.7%) [1]	0	1/141 (0.7%) [1]
	Local Swelling	1/141 (0.7%) [1]	0	1/141 (0.7%) [1]
	Thrombosis in Device	1/141 (0.7%) [1]	1/141 (0.7%) [1]	0
Hepatobiliary Disorders	Total	1/141 (0.7%) [1]	1/141 (0.7%) [1]	0
	Portal Vein Thrombosis	1/141 (0.7%) [1]	1/141 (0.7%) [1]	0
Immune System Disorders	Total	1/141 (0.7%) [1]	1/141 (0.7%) [1]	0
	Anaphylactic Reaction	1/141 (0.7%) [1]	1/141 (0.7%) [1]	0
Infections and Infestations	Total	5/141 (3.5%) [5]	4/141 (2.8%) [4]	1/141 (0.7%) [1]
	Catheter Site Infection	1/141 (0.7%) [1]	0	1/141 (0.7%) [1]
	Diverticulitis	1/141 (0.7%) [1]	1/141 (0.7%) [1]	0
	Gastroenteritis	1/141 (0.7%) [1]	1/141 (0.7%) [1]	0
	Influenza	1/141 (0.7%) [1]	1/141 (0.7%) [1]	0
	Wound Infection	1/141 (0.7%) [1]	1/141 (0.7%) [1]	0
Injury, Poisoning and Procedural Complications	Total	7/141 (5.0%) [7]	2/141 (1.4%) [2]	5/141 (3.5%) [5]
	Concussion	1/141 (0.7%) [1]	0	1/141 (0.7%) [1]
	Fall	1/141 (0.7%) [1]	0	1/141 (0.7%) [1]
	Head Injury	1/141 (0.7%) [1]	0	1/141 (0.7%) [1]
	Periorbital Haemorrhage	1/141 (0.7%) [1]	0	1/141 (0.7%) [1]
	Procedural Hypertension	1/141 (0.7%) [1]	1/141 (0.7%) [1]	0
	Vascular Pseudoaneurysm	2/141 (1.4%) [2]	1/141 (0.7%) [1]	1/141 (0.7%) [1]
	Total	3/141 (2.1%) [4]	1/141 (0.7%) [2]	2/141 (1.4%) [2]
	Dehydration	1/141 (0.7%) [2]	1/141 (0.7%) [2]	0

MedDRA* System Organ Class	MedDRA Preferred Term	All AEs Incidence of AE (n/N) (%) [# of events]	All SAEs Incidence of AE (n/N) (%) [# of events]	All Non-SAEs Incidence of AE (n/N) (%) [# of events]
Metabolism and Nutrition disorders	Hypervolaemia	1/141 (0.7%) [1]	0	1/141 (0.7%) [1]
	Hypovolaemia	1/141 (0.7%) [1]	0	1/141 (0.7%) [1]
Musculoskeletal and Connective Tissue Disorders	Total	6/141 (4.3%) [6]	1/141 (0.7%) [1]	5/141 (3.5%) [5]
	Compartment Syndrome	1/141 (0.7%) [1]	1/141 (0.7%) [1]	0
	Muscular Weakness	1/141 (0.7%) [1]	0	1/141 (0.7%) [1]
	Musculoskeletal Pain	1/141 (0.7%) [1]	0	1/141 (0.7%) [1]
	Neck Pain	1/141 (0.7%) [1]	0	1/141 (0.7%) [1]
	Pain in Extremity	1/141 (0.7%) [1]	0	1/141 (0.7%) [1]
	Spinal Osteoarthritis	1/141 (0.7%) [1]	0	1/141 (0.7%) [1]
Neoplasms Benign, Malignant and Unspecified (Including Cysts and Polyps)	Total	2/141 (1.4%) [2]	2/141 (1.4%) [2]	0
	Adenocarcinoma of Colon	1/141 (0.7%) [1]	1/141 (0.7%) [1]	0
	Basal Cell Carcinoma	1/141 (0.7%) [1]	1/141 (0.7%) [1]	0
Nervous System Disorders	Total	61/141 (43.3%) [95]	14/141 (9.9%) [19]	52/141 (36.9%) [76]
	Aphasia	3/141 (2.1%) [3]	0	3/141 (2.1%) [3]
	Balance Disorder	3/141 (2.1%) [3]	0	3/141 (2.1%) [3]
	Carotid Artery Dissection	1/141 (0.7%) [1]	1/141 (0.7%) [1]	0
	Carotid Artery Stenosis	1/141 (0.7%) [1]	1/141 (0.7%) [1]	0
	Cerebral Haemorrhage	3/141 (2.1%) [3]	3/141 (2.1%) [3]	0
	Cerebral Infarction	3/141 (2.1%) [3]	1/141 (0.7%) [1]	2/141 (1.4%) [2]
	Cerebral Vasoconstriction	1/141 (0.7%) [1]	0	1/141 (0.7%) [1]
	Disturbance in Attention	1/141 (0.7%) [1]	0	1/141 (0.7%) [1]
	Dizziness	5/141 (3.5%) [6]	0	5/141 (3.5%) [6]
	Haemorrhage Intracranial	1/141 (0.7%) [1]	0	1/141 (0.7%) [1]
	Headache	36/141 (25.5%) [40]	4/141 (2.8%) [5]	33/141 (23.4%) [35]
	Hemiparesis	1/141 (0.7%) [1]	0	1/141 (0.7%) [1]
	Hypoaesthesia	2/141 (1.4%) [2]	0	2/141 (1.4%) [2]

MedDRA* System Organ Class	MedDRA Preferred Term	All AEs Incidence of AE (n/N) (%) [# of events]	All SAEs Incidence of AE (n/N) (%) [# of events]	All Non-SAEs Incidence of AE (n/N) (%) [# of events]
	Intracranial Artery Dissection	1/141 (0.7%) [1]	0	1/141 (0.7%) [1]
	Ischaemic Stroke	4/141 (2.8%) [5]	3/141 (2.1%) [4]	1/141 (0.7%) [1]
	Migraine	4/141 (2.8%) [4]	2/141 (1.4%) [2]	2/141 (1.4%) [2]
	Multiple Sclerosis Relapse	1/141 (0.7%) [1]	1/141 (0.7%) [1]	0
	Muscle Spasticity	1/141 (0.7%) [1]	0	1/141 (0.7%) [1]
	Neuropathy Peripheral	2/141 (1.4%) [2]	0	2/141 (1.4%) [2]
	Paraesthesia	5/141 (3.5%) [5]	0	5/141 (3.5%) [5]
	Presyncope	2/141 (1.4%) [2]	1/141 (0.7%) [1]	1/141 (0.7%) [1]
	Sensory Disturbance	1/141 (0.7%) [1]	0	1/141 (0.7%) [1]
	Subarachnoid Haemorrhage	1/141 (0.7%) [1]	0	1/141 (0.7%) [1]
	Syncope	3/141 (2.1%) [3]	0	3/141 (2.1%) [3]
	Transient Ischaemic Attack	1/141 (0.7%) [1]	0	1/141 (0.7%) [1]
	Tremor	1/141 (0.7%) [1]	0	1/141 (0.7%) [1]
	Visual Field Defect	1/141 (0.7%) [1]	0	1/141 (0.7%) [1]
Psychiatric Disorders	Total	4/141 (2.8%) [6]	2/141 (1.4%) [3]	3/141 (2.1%) [3]
	Confusional State	1/141 (0.7%) [1]	0	1/141 (0.7%) [1]
	Delirium	1/141 (0.7%) [1]	1/141 (0.7%) [1]	0
	Dysphemia	1/141 (0.7%) [1]	0	1/141 (0.7%) [1]
	Major Depression	1/141 (0.7%) [1]	1/141 (0.7%) [1]	0
	Mental Status Changes	1/141 (0.7%) [1]	0	1/141 (0.7%) [1]
	Suicide Attempt	1/141 (0.7%) [1]	1/141 (0.7%) [1]	0
Renal and Urinary Disorders	Total	1/141 (0.7%) [1]	1/141 (0.7%) [1]	0
	Renal Failure Chronic	1/141 (0.7%) [1]	1/141 (0.7%) [1]	0
Reproductive System and Breast Disorders	Total	3/141 (2.1%) [3]	2/141 (1.4%) [2]	1/141 (0.7%) [1]
	Benign Prostatic Hyperplasia	1/141 (0.7%) [1]	1/141 (0.7%) [1]	0
	Menorrhagia	1/141 (0.7%) [1]	0	1/141 (0.7%) [1]
	Ovarian Cyst Ruptured	1/141 (0.7%) [1]	1/141 (0.7%) [1]	0
Respiratory, Thoracic and Mediastinal Disorders	Total	4/141 (2.8%) [4]	0	4/141 (2.8%) [4]
	Epistaxis	4/141 (2.8%) [4]	0	4/141 (2.8%) [4]

MedDRA* System Organ Class	MedDRA Preferred Term	All AEs Incidence of AE (n/N) (%) [# of events]	All SAEs Incidence of AE (n/N) (%) [# of events]	All Non-SAEs Incidence of AE (n/N) (%) [# of events]
Skin and Subcutaneous Tissue Disorders	Total	30/141 (21.3%) [32]	0	30/141 (21.3%) [32]
	Alopecia	2/141 (1.4%) [2]	0	2/141 (1.4%) [2]
	Ecchymosis	28/141 (19.9%) [28]	0	28/141 (19.9%) [28]
	Petechiae	1/141 (0.7%) [1]	0	1/141 (0.7%) [1]
	Swelling Face	1/141 (0.7%) [1]	0	1/141 (0.7%) [1]
Surgical and Medical Procedures	Total	5/141 (3.5%) [5]	5/141 (3.5%) [5]	0
	Aneurysm Repair	5/141 (3.5%) [5]	5/141 (3.5%) [5]	0
Vascular Disorders	Total	38/141 (27.0%) [42]	3/141 (2.1%) [3]	35/141 (24.8%) [39]
	Arterial Stenosis	4/141 (2.8%) [4]	0	4/141 (2.8%) [4]
	Arteriovenous Fistula	1/141 (0.7%) [1]	0	1/141 (0.7%) [1]
	Deep Vein Thrombosis	1/141 (0.7%) [1]	0	1/141 (0.7%) [1]
	Flushing	1/141 (0.7%) [1]	0	1/141 (0.7%) [1]
	Haematoma	2/141 (1.4%) [2]	1/141 (0.7%) [1]	1/141 (0.7%) [1]
	Haemorrhage	1/141 (0.7%) [1]	0	1/141 (0.7%) [1]
	Hypertensive Crisis	1/141 (0.7%) [1]	1/141 (0.7%) [1]	0
	Hypotension	1/141 (0.7%) [1]	0	1/141 (0.7%) [1]
	Vascular Occlusion	1/141 (0.7%) [1]	1/141 (0.7%) [1]	0
	Vasospasm	28/141 (19.9%) [29]	0	28/141 (19.9%) [29]
*MedDRA = Medical Dictionary for Regulatory Activities				

2. Effectiveness Results

The analysis of effectiveness was based on the 141 evaluable patients at the 12-month time point (mITT population). Key effectiveness outcomes are presented in Table 14. Of the 141 patients in the mITT population, only 7 patients were treated with the Pipeline Flex implant in the vertebral artery. For the 7 patients with vertebral artery IAs treated with the Pipeline Flex implant, the primary effectiveness endpoint was 30.0% (with 1 subject with missing 1 year DSA data imputed in the analysis as a failure). Because there was not sufficient clinical data to support the effectiveness of the Pipeline Flex used in the vertebral artery of the posterior circulation, the indications for use were limited to use of the device in the internal carotid artery (ICA). Therefore, the primary effectiveness endpoint in Table 14 shows the results of the "ICA-mITT Population" of 134 subjects with IAs in the ICA in which treatment was attempted with the Pipeline Flex device.

The primary effectiveness endpoint was analyzed by the statistical analysis software (SAS) multiple imputation analysis and defined using the following three composite endpoints that all had to be met for the primary effectiveness endpoint to be considered a success:

1. Complete IA occlusion defined by Raymond-Roy I classification (Roy et al., 2001) and based on Core Lab review of one-year DSA images.
2. No significant parent artery stenosis (≤ 50%) based on Core Lab review of one-year DSA images.
3. No retreatment of the target IA occurring between the index procedure and 365 days post-procedure.

The primary effectiveness endpoint was met in 78.98% of subjects in the ICA-mITT population (N=134). The primary effectiveness endpoint was higher than the *a priori* PG threshold of 50%; thus, the primary effectiveness endpoint was met. The reasons for patients in the PREMIER study that failed to meet the primary effectiveness endpoint in the ICA -mITT population are summarized in Table 15.

Table 14. Primary Effectiveness Endpoint at 1-Year Post-Procedure for ICA-mITT Population

Primary Effectiveness Endpoint	Rate (%)	1-Sided 97.5% Exact Lower Binomial CI
Complete IA occlusion without significant parent artery stenosis (≤ 50%) or retreatment of the target IA (N=134)	78.98%	72.05%
Complete aneurysm occlusion without significant parent artery stenosis (≤ 50%) or retreatment of the target aneurysm (N=134); Subjects with missing data (n=2) considered failures.*	77.61% (104/134)	69.61%
Note: The confidence intervals are calculated without multiplicity adjustment. As such, the confidence intervals are provided to show the variability only and should not be used to draw any statistical conclusions. *1-year imaging follow-up for 2 subjects was missing and imputed as a primary effectiveness endpoint failure.		

Table 15. Reasons for Primary Effectiveness Endpoint Failures (ICA-mITT Population)

Reason	Rate % (n/N) (N = 134)*
Residual neck	1.5% (2/132)
Residual aneurysm	14.4% (19/132)
Stenosis greater than 50%	3.0% (4/132)
Target aneurysm retreatment	3.0% (4/132)
Total	21.2% (28/132)**

*One subject had more than one failure mode; this subject was not completely occluded and also retreated.
**1-year imaging follow-up for 2 subjects was missing from the ICA-mITT population.

3. Subgroup Analyses

The following preoperative characteristics were evaluated for potential association with outcomes: age, intracranial aneurysm size, and intracranial aneurysm location.

The subgroup analysis of the primary safety endpoint and SAEs by age (≥ 60 years vs. < 60 years) is presented in Table 16. The subgroup analysis of the primary effectiveness endpoint by age (< 50, 50 to < 60, 60 to < 70, and 70 to 80 years old) is presented in Table 17. Based on the results of this subgroup analysis in which a decrease in effectiveness and an increase in device-related SAEs were observed in patients ≥ 60 years old in comparison to patients < 60 years old, there is a precaution added to the Pipeline Flex labeling that advises the clinical user of these results.

Table 16: Subgroup Analysis of Primary Safety Endpoint and SAEs by Age (mITT Population)

Analysis	Age < 60 Years (N=93)	Age ≥ 60 Years (N=48)	mITT (N=141)
Primary Safety Endpoint: (Neurological Death + Major Stroke)	1.1% (1/93) [0.0%, 5.9%]	4.2% (2/48) [0.5%, 14.3%]	2.1% (3/141) [0.4%, 6.1%]
All Strokes** (Subject Level)	2.2% (2/93) [0.3%, 7.6%]	10.4% (5/48) [3.5%, 22.7%]	5.0% (7/141) [2.0%, 10.0%]
Major Strokes	1.1% (1/93) [0.0%, 5.9%]	4.2% (2/48) [0.5%, 14.3%]	2.1% (3/141) [0.4%, 6.1%]
Minor Strokes	1.1% (1/93) [0.0%, 5.9%]	8.3% (4/48) [2.3%, 20.0%]	3.5% (5/141) [1.2%, 8.1%]
Device Related SAEs	4.3% (4/93) [1.2%, 10.7%]	12.5% (6/48) [4.7%, 25.3%]	7.1% (10/141) [3.5%, 12.7%]

Analysis	Age < 60 Years (N=93)	Age ≥ 60 Years (N=48)	mITT (N=141)
Procedure Related SAEs	6.5% (6/93) [2.4%, 13.5%]	6.3% (3/48) [1.3%, 17.2%]	6.4% (9/141) [3.0%, 11.8%]

Note: Numbers are % (Count/Sample Size) [Confidence Interval]. Confidence Interval is based on exact binomial distribution. The confidence intervals are calculated without multiplicity adjustment. As such, the confidence intervals are provided to show the variability only and should not be used to draw any statistical conclusions.
**A total of 8 stroke events (major and minor) were reported in 7 subjects; 1 subject (≥ 60 years of age) had a major and minor stroke.

Table 17: Subgroup Analysis of Primary Effectiveness Endpoint at 1-Year Post-Procedure by Age (ICA-mITT Population)

Analysis	Age at Enrollment (Years)	Rate (N=134 subjects)*
Complete IA occlusion without significant parent artery stenosis (≤ 50%) or retreatment of the target aneurysm	22 to < 50	87.0% (40/46)
	50 to < 60	83.7% (36/43)
	60 to < 70	66.7% (20/30)
	70 to 80	61.5% (8/13)

Note: Numbers are % (Count/Sample Size).
*The 1-year imaging follow-up for 2 subjects were missing from the ICA-mITT population.

Table 18 shows the subgroup analysis of the primary effectiveness endpoint by location in the ICA. The primary effectiveness endpoint success rate for the C7 segment of the ICA was observed to be significantly lower than other segments of the ICA treated with the Pipeline Flex. Therefore, a warning is added to the device labeling to inform clinical users of the decreased effectiveness rates observed in patients with C7 segment IAs treated with the Pipeline Flex in the PREMIER study. Clinical users are also warned to carefully consider the following anatomical characteristics associated with retrograde filling when considering treatment of C7 IAs with the Pipeline Flex:

- Observed posterior communicating artery (PComm) of fetal origin (A PCA of fetal origin is defined as a small, hypoplastic, or absent P1 segment of the posterior cerebral artery (PCA) with the PComm artery supplying a majority of blood flow to the ICA);
- PComm overlapping with the aneurysm neck; and/or
- PComm branch arising from the dome of the aneurysm.

Table 18: Subgroup Analysis of Primary Effectiveness Endpoint at 1-Year Post-Procedure by Artery Segments (ICA-mITT Population (N=134 Subjects))

Analysis	C2 to C4 (N=4 Subjects)	C5 (N=11 Subjects)	C6 (N=100 Subjects)	C7 (N=19 Subjects)
Complete aneurysm occlusion without significant parent artery stenosis (≤ 50%) or retreatment of the target aneurysm	100.0% (4/4) [39.76%, 100.00%]	90.9% (10/11) [58.72%, 99.77%]	82.7% (81/98) [73.69%, 89.56%]	47.4% (9/19) [24.45%, 71.14%]
Missing Data†	0	0	2	0

† Missing data includes two subjects who did not undergo imaging at 1-year follow-up. One subject died prior to the 1-year follow-up and one subject returned for the 1-year visit but did not have DSA imaging performed.
Note: Numbers are % (Count/Sample Size) [95% CI]. The confidence intervals are calculated without multiplicity adjustment. As such, the confidence intervals are provided to show the variability only and should not be used to draw any statistical conclusions.

Table 19 shows the subgroup analysis of the primary safety endpoint by location in the ICA. The primary safety endpoint events were observed in the C6 and C7 regions, which were the regions with highest subject enrollment in the PREMIER trial. Therefore, it is difficult to draw conclusions of potential differences in the safety events by anatomical region treated with the Pipeline Flex.

Table 19: Subgroup Analysis of Primary Safety Endpoint at 1-Year Post-Procedure by Artery Segments (ICA-mITT Population (N=134 Subjects))

Analysis	C2 to C4 (N=4 Subjects)	C5 (N=11 Subjects)	C6 (N=100 Subjects)	C7 (N=19 Subjects)
Major Stroke or Neurological Death	0.0% (0/4)	0.0% (0/11)	2.0% (2/100)	5.3% (1/19)

Note: Numbers are % (Count/Sample Size)

The primary endpoints were also analyzed based on subgroups of IA size (see Table 20). The 7 mm to < 8 mm IA size range had more C7 segment aneurysms. Otherwise, IA size did not show a noticeable relationship or differences in the primary effectiveness or safety endpoints. The primary safety endpoint event rate for the 8 mm to < 9 mm IA size range was 20% (1/5), which was above the pre-specified safety PG. However, there is a limited sample size for this IA size subgroup (n=5); therefore, it is difficult to draw any conclusions from this data.

Table 20. Summary of Primary Effectiveness and Safety Endpoints at 1-Year Post-Procedure by Aneurysm Size (mITT Population (N=141))*

Primary Endpoint Analysis Parameter	1mm-<2mm (N=1)	2mm-<3mm (N=13)	3mm-<4mm (N=36)	4mm-<5mm (N=29)	5mm-<6mm (N=26)	6mm-<7mm (N=14)	7mm-<8mm (N=10)	8mm-<9mm (N=5)	9mm-<10mm (N=4)	10mm-<11mm (N=1)	11mm-<12mm (N=2)
Primary Effectiveness Endpoint: Complete aneurysm occlusion without significant parent artery stenosis (≤ 50%) or retreatment of the target aneurysm.	0.0% (0/1)	76.9% (10/13)	86.1% (31/36)	75.9% (22/29)	73.1% (19/26)	78.6% (11/14)	40.0% (4/10)	80.0% (4/5)	75.0% (3/4)	100.0% (1/1)	50.0% (1/2)
Primary Safety Endpoint: Major stroke or neurological death.	0.0% (0/1)	7.7% (1/13)	0.0% (0/36)	3.4% (1/29)	0.0% (0/26)	0.0% (0/14)	0.0% (0/10)	20.0% (1/5)	0.0% (0/4)	0.0% (0/1)	0.0% (0/2)

*Subjects who have failed to complete the 1-year evaluation visit are counted as not having met the primary effectiveness endpoint.

Note: Numbers are % (Count/Sample Size).

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 53 investigators of which none were full-time or part-time employees of the sponsor and 19 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: 19
- Proprietary interest in the product tested held by the investigator: 1
- Significant equity interest held by investigator in sponsor of covered study: 3

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

During the review of this PMA, the FDA convened a general issues meeting on March 1, 2018 of the Neurological Devices Panel (the "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. Feedback from the Panel at the March 1, 2018 meeting was considered during the review of this PMA (see clinical study results described in Section X of the SSED). 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.

The FDA also considered the recommendations from an April 17, 2015 general issues Panel meeting of the Medical Devices Advisory Committee to discuss the conduct and design of clinical studies to evaluate the benefits and risks of endovascular devices used to treat IAs including neurovascular flow diverting stents. The Panel from the April 17, 2015 meeting discussed the importance of subgroup analyses in the clinical trial design based on patient factors such as IA location, size, and morphology and the importance of well controlled studies in the evaluation of reasonable safety and effectiveness of these devices. The background and meeting materials for the April 17, 2015 general issues meeting can be accessed at the following link: https://wayback.archive-it.org/7993/20170114022911/http:/www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/NeurologicalDevicesPanel/ucm440392.htm.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The primary effectiveness endpoint was analyzed individually for the number of patients in the ICA-mITT population (N=134 subjects with exclusion of 7 subjects with vertebral artery IAs) who had complete (100%) occlusion (equivalent to Raymond-Roy I classification) of the target intracranial aneurysm without clinically significant parent artery stenosis (≤ 50%) or retreatment of the target IA within 12 months post-procedure. The primary effectiveness endpoint results showed that 78.98% (104/134, missing data imputed for 2/134 subjects as failures) of subjects in the PREMIER trial met the primary effectiveness endpoint. Therefore, the pivotal study met the primary effectiveness

endpoint success criteria at one year, and the majority of the patients in the trial exhibited a good effectiveness outcome.

Subgroup analyses of the primary effectiveness endpoint showed that effectiveness may be impacted by age with subjects over the age of 60 years old performing with less effectiveness than subjects younger than 60 years old. Lower effectiveness rates (47.4% (9/19)) were also observed in C7 segment aneursyms based on a subgroup analysis of the primary effectiveness endpoint with respect to IA location. IAs in the C7 segment may have other branching arteries that can fill the IA after device placement. If this occurs, re-treatment options may be limited to occlude the IA if a neurovascular flow diverting stent such as the Pipeline Flex is placed because the device does not allow adjunctive neurovascular embolic coils to be placed inside the IA sac through the mesh struts of the Pipeline Flex implant. Therefore, a warning is added to the device labeling to inform clinical users of the decreased device effectiveness rates observed in patients with C7 segment IAs in the PREMIER study. Clinical users are also warned to carefully consider the IA anatomical characteristics that may be associated with retrograde filling when considering treatment of C7 segment IAs with the Pipeline Flex.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory, animal studies, as well as data collected in a clinical study conducted to support PMA approval as described above. The primary safety endpoint was analyzed based on the mITT population for the rate of patients who exhibited a major or disabling stroke (ischemic or hemorrhagic) or neurological death within 12-months post-procedure. These two (2) primary safety events are the most significant adverse events to assess the device safety for the treatment of wide-neck intracranial aneurysms because these events are the most debilitating, can result in permanent disability, or expiration of the patient. The primary safety endpoint rate observed in the PREMIER trial was 2.17% (3/141, with multiple imputation used for missing data). All three (3) primary safety endpoint events were subjects who experienced a major stroke within the 1 year follow-up period with one major stroke that was also a disabling stroke without resulting in neurological death (0.7% (1/141)), one major stroke that led to neurological death (0.7% (1/141)), and one major stroke that was non-disabling (0.7% (1/141)). There were a total of 7 patients with 8 stroke events (5.0% (7/141)) that occurred in the PREMIER trial through 12-months post-procedure of which one (1) resulted in death, one (1) resulted in a disabling stroke, and the remaining five (5) patients had non-disabling strokes. The mRS scores (measurement of patient disability) was also assessed to determine the rate of patients who had a worsening mRS score 12-months post-procedure compared to their baseline mRS prior to device treatment. Of the 141 patients in the PREMIER trial (mITT population), 10.3% (14/136, 5 subjects did not have paired mRS readings) had a worsening of the mRS at 12-months post-procedure compared to their baseline mRS.

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 primary effectiveness endpoint results showed that 78.98% (104/134, missing data imputed for 2/134 subjects as failures) of subjects in the ICA-mITT cohort in the PREMIER trial had complete (100%) intracranial aneurysm occlusion (Raymond-Roy Class I) without clinically significant parent artery stenosis or retreatment of the target intracranial aneurysm within 12-months post-procedure.

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 rate observed in the PREMIER trial (mITT population) based on the rate of major or disabling strokes (ischemic or hemorrhagic) or neurological death within 1 year post-procedure was 2.17% (3/141, with multiple imputation used for 1 subject with missing data). Eight strokes occurred in 7 subjects (5.0%, 7/141) at 1-year, of which 3 were major (a stroke which is present for 24 hours or more and increases the NIHSS score of the subject by ≥ 4 points) and 5 were minor (a stroke which is present for 24 hours or more and increases the NIHSS score of the subject by ≤ 3 points). All strokes were ischemic in nature, with 3 of the 8 strokes having a hemorrhagic transformation of the core ischemic infarct. The incidence of all ischemic and hemorrhagic events (includes major stroke, minor stroke, symptomatic cerebral infarction, asymptomatic cerebral infarction, intracranial hemorrhage (ICH), transient ischemic attack (TIA), and IA rupture) in the mITT population was 7.8% (11/141) with a total of 18 AEs experienced in 11 subjects.

Additional factors to be considered in determining probable risks and benefits for the Pipeline Flex Embolization Device included: weighing the benefits and risks of device treatment with the patient's risk of intracranial aneurysm rupture. The risk of rupture of an untreated unruptured intracranial aneurysm is dependent on multiple factors including aneurysm size, shape, and morphology, patient age, and the patient co-morbidities (e.g., high blood pressure, family history, multiple aneurysms, 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). Size and location of the intracranial aneurysm can also affect the risk of rupture. In the article by Wiebers (2003), intracranial aneurysms in the ICA, anterior communicating artery (AComm), anterior cerebral artery (ACA), or middle cerebral artery (MCA) 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. Several additional studies have suggested that smaller aneurysms (< 7 mm) rarely rupture, with a rupture rate reported at 0.7%, and therefore, may inform an opinion that these aneurysms be best treated conservatively by observation only ("The Natural Course of Unruptured Cerebral Aneurysms in a Japanese Cohort" 2012; Rinkel et al. 1998; Komotar, Mocco, and Solomon 2008). For patients with an unruptured aneurysm

without a history of SAH (Type 1), the risk of rupture rate drops to 0.1% for aneurysms < 7 mm in diameter (Ishibashi et al. 2009; Wiebers 2003). Conversely, larger aneurysms are at a greater risk for rupture (i.e., the rupture rate for aneurysms > 25 mm have a reported 6% rupture rate in the first year (Wiebers 1998) with other studies reporting an annual rupture rate as high as 43.1% (Ishibashi et al. 2009)).

Based on the natural history of patients who are at high risk for intracranial aneurysm rupture from these prior published studies, it appears that patients who will benefit the most from device treatment are those with significant co-morbidities, and/or those with longer life-expectancies. Therefore, 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. If the patient's risk of intracranial aneurysm rupture is high within their lifetime, then the use of the subject device would provide a safe and effective treatment for the indicated use in the ICA up to the terminus for the endovascular treatment of adults (≥ 22 years of age) with small and medium wide-necked (neck width ≥ 4 mm or dome-to-neck ratio < 2) saccular or fusiform intracranial aneurysms arising from a parent vessel with a diameter ≥ 2.0 mm and ≤ 5.0 mm.

Additional factors to be considered in determining probable risks and benefits for the Pipeline Flex device includes some uncertainty based on the single arm pivotal trial design that may introduce some bias in patient selection for treatment because there was no blinding or randomized concurrent control group. Since there was no active control arm in the pivotal study, there are uncertainties of whether the subject device treatment may be more or less beneficial or more or less safe than alternative treatment modalities for the proposed indicated patient population. In addition, it is unclear whether there may have been some bias in subject selection for treatment with the Pipeline Flex device to result in better clinical outcomes. Furthermore, the PREMIER trial did not utilize an independent vascular neurologist to perform the mRS assessments; therefore, there may be some bias introduced in the mRS scores presented. Lastly, the PREMIER trial only enrolled 5 patients with fusiform IAs. Although there was a small sample size of patients with fusiform IAs, there are limited alternative treatment options for these patients because it is difficult to treat these subjects with endovascular treatment using neurovascular embolic coils and patients may not be eligible or the risks may be too great for open surgical clipping dependent on the location of the fusiform IA. Therefore, treatment with a neurovascular flow diverting stent such as the Pipeline Flex is a reasonable option for patients with fusiform IAs considering the benefits and risks of alternative treatment options for these patients. The IFU statement for the Pipeline Flex includes the use of the device for fusiform IAs and a precaution was added to the labeling that advises the clinical user that the safety and effectiveness of the subject device has not been established in patients with fusiform IAs based on the PREMIER trial.

1. Patient Perspectives

   This submission did not include specific information on patient perspectives for this device.

In conclusion, given the available information above, the data support that for the indications for use of the Pipeline Flex Embolization Device in the internal carotid artery up to the terminus for the endovascular treatment of adults (22 years of age or older) with small and medium wide-necked (neck width ≥ 4 mm or dome-to-neck ratio < 2) saccular or fusiform intracranial aneurysms arising from a parent vessel with a diameter ≥ 2.0 mm and ≤ 5.0 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. The overall risk to benefit ratio is favorable for the intended patient population. While there are still risks involved with the use of the device, including major or disabling strokes and death (i.e., 2.17% (3/141, 1 subject with missing data imputed using multiple imputation)), the benefits include that 78.98% (1 subject with missing data imputed with multiple imputation) of patients in the ICA-mITT population in the pivotal clinical study achieved a good effectiveness outcome of Raymond-Roy I occlusions of their treated intracranial aneurysm without clinically significant parent artery stenosis or retreatment within one year post-procedure.

XIV. CDRH DECISION

CDRH issued an approval order on December 14, 2018. The final conditions of approval cited in the approval order are described below.

PMA Post-Approval Study – "Prospective Study on Embolization of Intracranial Aneurysms with the Pipeline™ Device (PREMIER)": The PREMIER study is a prospective, multi-center non-randomized pivotal study that was conducted under IDE G140084 and was initiated prior to device approval. The study subjects were consented to be followed for up to three (3) years post-procedure. The 1-year follow-up data from the PREMIER study was used to support the approval of the subject PMA supplement. As part of the PMA post-approval study, the long-term follow-up from the PREMIER study can provide safety and effectiveness information on the durability and safety of treatment using the Pipeline Flex™ Embolization Device up to 3 years post-procedure. The primary safety and effectiveness endpoints are the rate of major or disabling strokes or neurological deaths and the rate of patients who had complete (100%) Raymond-Roy Class I intracranial aneurysm occlusion without clinically significant parent artery stenosis or retreatment of the target aneurysm, respectively. Patients will be followed at 2 years and 3 years post-procedure with imaging assessment of intracranial aneurysm

occlusion and parent artery stenosis performed at 2 and 3 years using the approved IDE G140084 clinical study protocol. In addition, all new and ongoing adverse events will be recorded and adjudicated by the Clinical Events Committee (CEC) per the approved G140084 clinical study protocol.

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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