Medtronic

INSTRUCTIONS FOR USE

Pipeline™ Vantage Embolization Device with Shield Technology™

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Pipeline™ Vantage Embolization Device with Shield Technology™

CAUTION

- Federal (USA) law restricts this device to sale, distribution, and use by or on the order of a physician.
- This device should be used only by physicians with a thorough understanding of angiography and/or percutaneous neurointerventional procedures.

DESCRIPTION

The Pipeline™ Vantage Embolization Device with Shield Technology™ consists of a permanent implant combined with a guidewire-based delivery system. The Pipeline™ Vantage Embolization Device with Shield Technology™ implant is a braided, multi-alloy, mesh cylinder woven with cobalt-chromium-nickel and platinum wires. An image of the Pipeline™ Vantage Embolization Device with Shield Technology™ implant is shown in Figure 1 and the design of the device is shown in Figure 2. The woven 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 unconstrained diameter is 0.25 mm larger than the labeled diameter. Shield Technology™ is a surface-modification that is not derived from any animal or human sources.

The Pipeline™ Vantage Embolization Device with Shield Technology™ implant is assembled on a guide-wire based delivery system that consists of a 304-stainless steel core wire and a 304L stainless steel hypotube. The implant is assembled over 304 stainless steel resheathing components. A Platinum-Iridium Restraint is distal to the resheathing components and is termed the Resheathing Marker. Refer to Figure 6 for the Resheathing Marker position.

The tip coil is made of platinum-tungsten alloy. The tip, distal, and proximal solder joints are a tin-silver. The ePTFE protective sleeves cover and protect the distal portion of the braid while the Pipeline™ Vantage Embolization Device with Shield Technology™ implant is advanced through the micro catheter.

The Resheathing components allow the user to resheath the implant back into the micro catheter. The Resheathing Marker provides the user fluoroscopic visualization for the limit of resheathing the implant. The Pipeline™ Vantage Embolization Device with Shield Technology™ implant is compressed inside an introducer sheath. The Pipeline™ Vantage Embolization Device with Shield Technology™ implant is designed to be delivered through a compatible micro catheter of 0.021 inch (0.53 mm) inner diameter and minimum 135 cm in length. Refer to Table 1 for micro catheter compatibility for each device size.

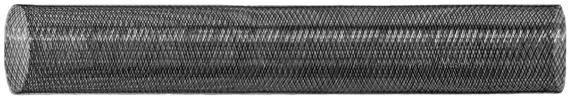


Figure 1. The Pipeline™ Vantage Embolization Device with Shield Technology™

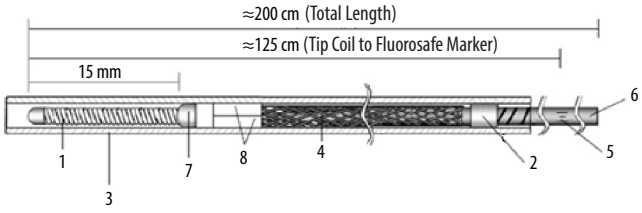


Figure 2. The Pipeline™ Vantage Embolization Device with Shield Technology™ delivery system and implant (not to scale)

1. Tip Coil
2. Proximal Bumper
3. Introducer Sheath
4. Braid
5. Fluorosafe Marker
6. Delivery Wire
7. Distal Marker
8. ePTFE Sleeves

Table 1. Size Ranges: Pipeline™ Vantage Embolization Device with Shield Technology™

Labeled Diameter (mm)	Self-Expanded Diameter (mm)	Largest Target Vessel Landing Zone Diameter		Compatible micro catheter inner diameter	Labeled Lengths (mm)
		Min (mm)	Max (mm)		
2.50	2.75	2.00	2.50	0.021 inch (0.53 mm)	10, 12, 14, 16, 18, 20
2.75	3.00	2.25	2.75		10, 12, 14, 16, 18, 20
3.00	3.25	2.50	3.00		10, 12, 14, 16, 18, 20, 25
3.25	3.50	2.75	3.25		10, 12, 14, 16, 18, 20, 25
3.50	3.75	3.00	3.50		10, 12, 14, 16, 18, 20, 25

DEVICE COMPATIBILITY

Micro catheter compatibility is defined on the product label:

The Pipeline™ Vantage 021 system is designed to be delivered through a compatible micro catheter of 0.021 inch (0.53 mm) inner diameter at least 135 cm in length. Compatibility testing has been performed with the Phenom 21 Catheter.

INTENDED USE / INDICATIONS FOR USE

The Pipeline™ Vantage Embolization Device with Shield Technology™ is indicated for the endovascular treatment of adults (22 years of age or older) with large or giant wide-necked intracranial aneurysms (IAs) in the internal carotid artery from the petrous to the superior hypophyseal segments.

The Pipeline™ Vantage Embolization Device with Shield Technology™ is also 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 aneurysm (IAs) arising from a parent vessel with a diameter ≥ 2.0 mm and ≤ 5.0 mm.

CONTRAINDICATIONS

- 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.

PREPARATIONS FOR USE

1. Choose a Pipeline™ Vantage device with a labeled diameter that is the recommended size of the largest target vessel landing zone diameter per Table 1. Ensure that the ends of the device are not deployed in a vessel that is larger than the labeled diameter of the selected size.

   An incorrectly sized Pipeline™ Vantage device may result in inadequate device placement, incomplete opening, migration, or stent braid deformation.

   - Select a Pipeline™ Vantage device that allows for distal deployment and proximal landing in a straight vessel segment and/or in a location that allows for complete wall apposition on the distal and proximal ends. Adjusting the device length selected may be necessary to ensure that the distal and proximal segments land in a straight vessel. Landing on a curve can result in poor wall apposition, increasing the risk of braid deformation, thrombosis and stroke.
2. Choose a Pipeline™ Vantage device with labeled length that is at least 6 mm longer than the aneurysm neck and ≥ 3 mm landing zone on both sides of the aneurysm neck, see Figure 3.
   - Take device foreshortening into account when deploying the Pipeline™ Vantage device.
   - The Pipeline™ Vantage device foreshortens 47 - 58% during deployment.
   - Adjusting the device length selected and landing zone length may be necessary to ensure that the segments distal and proximal to the aneurysm are positioned and anchored to avoid unanticipated post-procedure foreshortening, device movement, device deformation, and herniation, especially in curved vessels, and with large aneurysm necks.

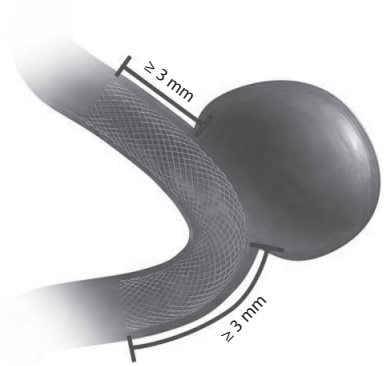


Figure 3. Illustration of landing zone and aneurysm neck

3. Remove packaging hoop from the pouch and pull the distal end of the introducer sheath from the blue clip on the packaging hoop.
4. Carefully remove device from the packaging hoop until the delivery wire is exposed.

WARNING

- Pre-deploying the distal end of the device prior to introduction into the micro catheter may cause damage to the distal end of the braid.

5. Partially insert introducer sheath into the rotating hemostatic valve (RHV) at the micro catheter hub and close the RHV. Use a minimum flush pressure of 250 mmHg and confirm back flush of the saline at the proximal end of the introducer sheath prior to advancing the Pipeline™ Vantage device into the micro catheter.
6. Advance introducer sheath into the RHV; visually confirm the tip of the sheath is seated deeply in the hub of the micro catheter.

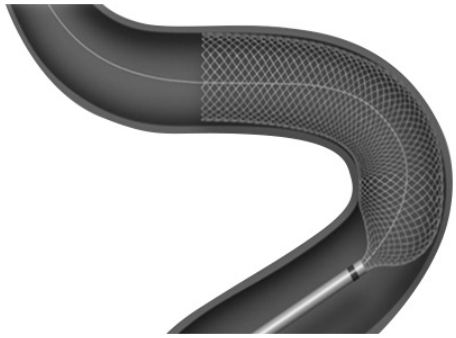
DIRECTIONS FOR USE

1. Using standard interventional radiographic technique, place the micro catheter tip at least 20 mm past the distal edge of the aneurysm. Gently retract the micro catheter to reduce slack in the micro catheter prior to inserting the Pipeline™ Vantage device.
   NOTE: It is recommended to use a heparinized saline drip to continuously flush micro catheter during Pipeline™ Vantage device use.
2. Secure introducer sheath to the hub by locking down the RHV tightly.
   CAUTION: Avoid deploying the device prior to introduction into the micro catheter.
3. Advance the proximal end of the delivery wire until it aligns with the proximal end of the introducer sheath.
4. Remove the introducer sheath.
   NOTE: The delivery wire has a fluorosafe marker no further than 125 cm from the distal end.
   CAUTION: The fluorosafe marker is only compatible with micro catheters with a minimum length of 135 cm.
5. Advance the Pipeline™ Vantage device into the micro catheter by pushing the delivery wire until the tip of the delivery wire aligns with the tip of the micro catheter.
   CAUTION: If high forces or excessive friction are encountered during delivery, discontinue delivery of the device and identify the cause of the resistance, remove device and micro catheter simultaneously. Advancement of the Pipeline™ Vantage device against resistance may result in device damage or patient injury.
   CAUTION: The presence of other indwelling endovascular stents may interfere with proper deployment and function of the Pipeline™ Vantage device.
6. Once the tip of delivery wire and micro catheter are aligned, verify that the Pipeline™ Vantage implant is in the desired location. The distal end of Pipeline™ Vantage implant should be placed at least 3 mm past the distal edge of the aneurysm neck.

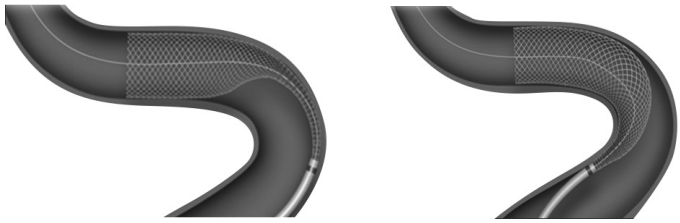
Device Deployment

7. Begin to deliver the Pipeline™ Vantage implant using a combination of unsheathing the Pipeline™ Vantage implant and pushing the delivery wire simultaneously.

- **NOTE:** When deploying within tortuous anatomy (particularly around a curve), attempt to keep the micro catheter tip centered to allow for forces to be evenly transferred to the implant, see Figure 4. Avoid uneven application of force to the implant, such as pushing it to one side, as this may lead to incomplete device opening, poor wall apposition, ribboning, and twisting. Gently push or pull on the device and catheter system to maintain alignment within the center of the vessel.

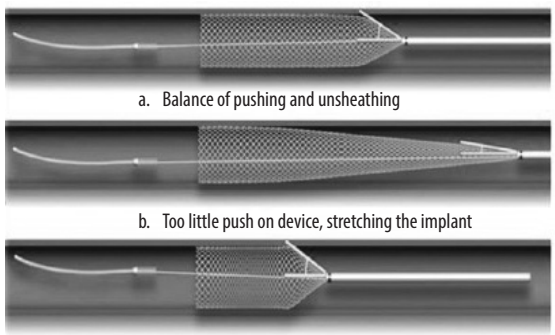


a. Micro catheter tip centered in vessel, even transfer of forces



b. Micro catheter tip not centered in vessel, uneven transfer of forces

Figure 4. Micro catheter tip centered in tortuous vessel



a. Balance of pushing and unsheathing

b. Too little push on device, stretching the implant

c. Too much push on device, compressing the implant

Figure 5. Illustration of combination of implant unsheathing and push on delivery wires

WARNINGS

- Pushing delivery wire without retracting the micro catheter at the same time will cause the open-end of the braid to move distally in the vessel. This may cause damage to the braid or vessel.
- Use in anatomy with severe tortuosity, stenosis or parent vessel narrowing may result in difficulty or inability to deploy the Pipeline™ Vantage device and can lead to damage to the Pipeline™ Vantage device and micro catheter. To mitigate potential problems as a result of increased delivery forces, reduce the load in the system by:
  - Unloading the micro catheter to the inner curves of vessel by pulling back on the system (i.e., the micro catheter and delivery wire together).
  - Continue unloading the system until advancement of the device (inside of micro catheter) is observed, while minimizing the distal tip movement to prevent loss of position.
  - Begin to re-advance the delivery wire while maintaining reduced load in the micro catheter. This process should be repeated until the device passes through tortuous area and the delivery force is decreased.
- Following distal deployment and device anchoring:
  - Avoid stretching and/or creating tension in the implant before unsheathing the proximal end.
  - Avoid deploying the implant if kinking or twisting is observed.

  Fully deploying the device under the conditions above may lead to poor wall apposition, unanticipated device foreshortening, device migration, thromboembolic risk, and impaired aneurysm occlusion. Device kinking, twisting, or stretching may be resolved with appropriate positioning of the micro catheter or by resheathing the entire implant and repeating distal deployment, adjusting the technique combination of unsheathing the implant and pushing the delivery wire. If it cannot be resolved, consider replacing the device.

8. **Resheathing Instructions:**
   During deployment of the Pipeline™ Vantage device resheathing can be performed by either:
   - Advancing the micro catheter while pinning the delivery wire
   - Advancing the micro catheter while applying tension on the delivery wire
   - Advancing the micro catheter while gently pulling the delivery wire proximally
   - During deployment, the point of no return/Resheathing limit is reached when the Resheathing marker aligns with the Distal marker of the micro catheter (see Figure 6). The Resheathing limit is the maximum length of the implant that can be deployed while maintaining the ability to fully resheath the device.
   - The Pipeline™ Vantage device implant is fully resheathed when the distal marker is retracted completely inside the micro catheter. The system is designed to allow for a 2 full cycles of resheathing of the Pipeline™ Vantage device.

WARNING

- Avoid deploying the implant if kinking or twisting is observed.

9. After the distal end of the implant has successfully expanded, deploy the middle segments of the implant using a balanced combination of unsheathing the implant by pulling the micro catheter back and pushing the delivery wire simultaneously. Manipulation of the micro catheter by locking down the delivery wire and moving both as a system may facilitate expansion of the implant, see Figure 5. Adjust tension on the device by pushing more or less on the device wire or system.
   Deploy the proximal segment of the device by simultaneously unsheathing the implant by pulling the micro catheter back with minimal forward pressure or tension on the delivery wire to achieve optimal opening.
   Prior to releasing the proximal end of the device, ensure that the proximal end of the device, will land ≥3 mm proximal to the edge of the aneurysm neck without stretching the implant. If this cannot be achieved, consider fully resheathing and repositioning or replacing with a longer device.
   NOTE: Ensure complete wall apposition along the full Pipeline™ Vantage device during the course of device deployment before final release of the device. If adequate apposition cannot be achieved, consider resheathing the implant up to the resheathing marker or removing and replacing the device.
   CAUTION: Avoid using excessive push to the implant. Using excessive push may result in braid deformation (such as braid narrowing, braid collapse) and/or insufficient opening at the time of deployment. Avoid repositioning the distal end of device under tension after device distal end is open and fully apposed to the vessel wall.
   CAUTION: Under fluoroscopy, carefully monitor the tip coil position during deployment of the Pipeline™ Vantage device.
   CAUTION: Avoid applying excessive tension to the implant during final deployment. Excessive tension may result in delayed device migration, herniation into the aneurysm neck, thromboembolic risk, and stroke.
   CAUTION: For lack of adequate wall apposition in the medial section after device deployment, attempt addressing the lack of apposition in the medial section of the implant with a guidewire. If unsuccessful, adjunctive balloon angioplasty may be used to address the apposition issue, however, once both ends of the device are anchored, adjunctive device use may be temporary or ineffective. Placement of another flow diverter is not recommended to attempt opening of a narrowed medial section of the device. Be careful to maintain access while attempting adjunctive device use.

WARNINGS

- Avoid deploying the implant if kinking or twisting is observed.
- Incomplete wall apposition can result in unanticipated device foreshortening, device migration, and/or device deformation which can lead to thromboembolic risks, elevated neointimal hyperplasia formation and/or reduced intracranial aneurysm occlusion.
- Resheathing the Pipeline™ Vantage device more than 2 full cycles may cause damage to the distal or proximal ends of the braid.
- Resheathing the Pipeline™ Vantage device past the distal marker of the delivery system may cause damage to the distal end of the braid.

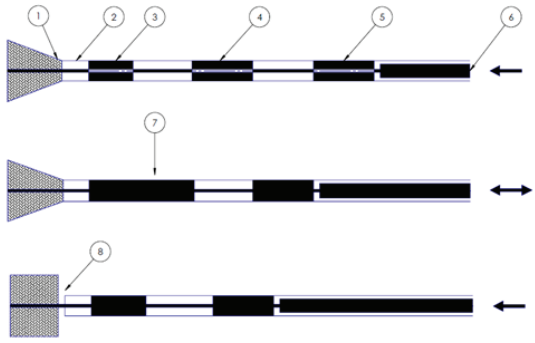


Figure 6. Pipeline™ Vantage Embolization Device with Shield Technology™ (Resheathing schematic as seen under fluoroscopy, image not to scale).

1. Proximal End of device
2. Micro Catheter
3. Micro Catheter Distal Marker
4. Resheathing Marker
5. Proximal Bumper
6. Delivery Wire
7. Resheathing Limit
8. Device Detached

10. After the entire implant is deployed, advance the micro catheter through the implant making sure not to dislodge the braid. When the micro catheter tip is distal to the implant, retract the delivery wire into the micro catheter tip.
    CAUTION: Avoid advancing or retracting the Resheathing Marker within the implant without coverage of the micro catheter.
    CAUTION: If the catheter cannot be advanced through the Pipeline™ Vantage implant, carefully withdraw the delivery wire through the implant.
    CAUTION: If the delivery wire cannot be retracted into the micro catheter, carefully remove the delivery wire and micro catheter simultaneously as a system.
11. Carefully inspect the deployed implant under fluoroscopy to confirm it is completely apposed to the vessel wall and the braid is not deformed (e.g., kinking, twisting, or fishmouthing).
    If poor wall apposition or significant braid deformation are observed, in the distal or proximal ends of the implant, attempt to resolve the malapposition utilizing an adjunctive device such as a guidewire, an angioplasty balloon, or another stent.
    Verify that the distal and proximal landing zones are both ≥3 mm and not under tension, see Figure 3. If less than 3 mm or under tension such that the device may foreshorten in a way that the landing zone is less than 3 mm, consider deployment of an additional device in a telescoping manner, such as an overlapping Pipeline™ or other neurovascular flow-diverting stent to ensure adequate securement of the ends of the implant.
    CAUTION: In order to place another stent, the existing Pipeline™ Vantage device must be traversed, this may lead to foreshortening and prolapse of the original stent into the intracranial aneurysm. Consider adjusting the access system to ensure maximum stability while attempting to cross the Pipeline™ Vantage and deploy another device.
    CAUTION: It is not recommended to use the Pipeline™ Vantage delivery wire to influence apposition of the implant. Additional interaction between components on delivery wire and braid may lead to braid damage.
    CAUTION: Avoid using the micro catheter or intermediate/support catheter to modify the position or wall apposition of the proximal end of the implant as this may lead to implant deformation, thromboembolic risk, and elevated neointimal hyperplasia.
    CAUTION: Excessive manipulation of the device using adjunctive devices such as balloons and secondary stents may lead to adverse events such as device herniation, stroke and death. Modification of the device with excessive manipulation may not be maintained post procedure.

WARNING

- Malapposition to the vessel wall at the proximal end of the implant may lead to stenosis, stroke or death.

POTENTIAL COMPLICATIONS

Potential complications of the device and the endovascular procedure include or are synonymous with, but may not be limited to the following:

- Access site complications such as hematoma, pain, retroperitoneal hemorrhage, skin discoloration, nerve damage, abscess, edema
- Adverse reactions to antiplatelet/anticoagulation agents, contrast media, or anesthesia such as pain, hemorrhage, organ failure, aspiration, nausea
- Cardiac complications such as arrhythmia, myocardial infarction
- Compartmental complications such as brain edema, intracranial hypertension, mass effect, hydrocephalus
- Complications of radiation exposure such as alopecia, burns ranging in severity from skin reddening to ulcers, cataracts, and delayed neoplasia
- Device complications such as kink, stretching, device fracture, device migration, device misplacement, friction, foreign body in patient, premature deployment, inadequate deployment, premature detachment, non-detachment, braid deformation. Braid deformation is a potential complication with all flow diverters and may occur during or following the index procedure and has been observed to occur months after implantation.
- Hematologic complications such as coagulopathy, thrombosis, hemolysis, intracranial hemorrhage
- Neurological deficits or dysfunctions such as headache, seizures, coma, emotional changes, paresis, transient ischemic attack, stroke
- Systemic complications such as fever, infection, inflammation, edema, shock, toxicity, hypersensitivity, allergic reaction, organ failure, hypotension, hypertension, pain
- Decreased therapeutic response including need for target aneurysm treatment
- Vascular complications such as dissection, perforation, rupture, ischemia, vasospasm, hyperplasia, stenosis, necrosis, granuloma, fistula, pseudoaneurysm, occlusion, thromboembolism, embolism including to unintended territory
- Visual complications such as transient blindness, blindness, diplopia, reduced visual acuity/field, retinal artery occlusion, retinal ischemia, retinal infarction, scintillations, blurred vision, eye floaters
- Death

*Consult *Instructions for Use* for other therapy devices and medications for additional potential complication information. If a serious incident related to the device occurs, contact your Medtronic representative and the competent authority in your respective country/region.

WARNINGS

- Persons with known allergy to platinum or cobalt/chromium alloy (including the major elements platinum, cobalt, chromium, nickel, molybdenum or tungsten) may suffer an allergic reaction to the Pipeline™ Vantage Embolization Device with Shield Technology™ implant.
- Person with known allergy to platinum alloy (including major elements platinum, tungsten, iridium), tin, silver, stainless steel or silicone elastomer may suffer an allergic reaction to the Pipeline™ Vantage Embolization Device with Shield Technology™ delivery system.
- Do not reprocess or resterilize. Reprocessing and resterilization increase the risk of patient infection and compromised device performance.
- Post-procedural movement (migration and/or foreshortening) of the Pipeline™ Vantage Embolization Device with Shield Technology™ implant may occur following implantation and can result in serious adverse events and/or death.
- Factors which may contribute to post procedural device movement include (but are not limited to) the following:
  - Failure to adequately size the implant (i.e., under sizing)
  - Failure to obtain adequate wall apposition during the implant deployment
  - Implant stretching
  - Vasospasm
  - Severe vessel tapering
  - Tortuous anatomy
- Delayed rupture may occur with large and giant aneurysms.
- Placement of multiple Pipeline™ Vantage Embolization Device with Shield Technology™ may increase the risk of ischemic complications.

WARNINGS

- Use in anatomy with severe tortuosity, stenosis or parent vessel narrowing may result in difficulty or inability to deploy the Pipeline™ Vantage Embolization Device with Shield Technology™ and can lead to damage to the Pipeline™ Vantage Embolization Device with Shield Technology™ and micro catheter. Advancement or retraction of the Pipeline™ Vantage Embolization Device with Shield Technology™ against resistance may result in damage, including unintended device or component separation, fracture, or breakage of the delivery system due to inherent flexibility limits of device design. Device damage may result in patient injury or death. Refer to page 4 in the *Instructions for Use* for additional information.
- Do not attempt to reposition the device after full deployment.
- The benefits may not outweigh the risks of treatment of small and medium asymptomatic extradural intracranial aneurysms, including those located in the cavernous internal carotid artery. The risk of rupture for small and medium asymptomatic extradural intracranial aneurysms is very low if not negligible.
- A decrease in the proportion of patients who achieve complete aneurysm occlusion without significant parent artery stenosis has been observed with the use of the device in the communicating segment (C7) of the internal carotid artery (47.4% (9/19 subjects in the PREMIER study at 1 year)), including those IAs fed by the posterior circulation or have retrograde filling. Ensure appropriate patient selection and weigh the benefits and risks of alternative treatments prior to use of this device for the treatment of intracranial aneurysms located in this region of the ICA. The following anatomical characteristics, associated with retrograde filling, should be carefully considered during procedural planning of C7 intracranial aneurysms:
  1. PComm of fetal origin (A PCA of fetal origin is defined as a small, hypoplastic, or absent P1 segment of the PCA with the PComm artery supplying a majority of blood flow to the ICA);
  2. PComm overlapping with the aneurysm neck; and/or
  3. PComm branch arising from the dome of the aneurysm.
- Pipeline™ Vantage Embolization Device with Shield Technology™ has not been tested for radial artery access. Radial artery access should only be used when femoral artery access is not feasible.
- For additional Materials of Concerns information such as CA Prop 65 or other product stewardship programs, go to www.medtronic.com/productstewardship

PRECAUTIONS

- The Pipeline™ Vantage Embolization Device with Shield Technology™ should be used only by physicians trained in percutaneous, intravascular techniques and procedures at medical facilities with the appropriate fluoroscopic equipment.
- Physicians should undergo appropriate training prior to using the Pipeline™ Vantage Embolization Device with Shield Technology™ in patients.
- The Pipeline™ Vantage Embolization Device with Shield Technology™ is intended for single use only.
  - Carefully inspect the sterile package and device components prior to use to verify that they have not been damaged during shipping.
  - Do not use kinked or damaged components.
  - Do not use product if the sterile package is damaged.
- Use the Pipeline™ Vantage Embolization Device with Shield Technology™ system prior to the "Use-by date" printed on the package.
- The appropriate anti-platelet and anti-coagulation therapy should be administered in accordance with standard medical practice.
- A thrombosing aneurysm may aggravate pre-existing, or cause new, symptoms of mass effect and may require medical therapy.
- Use of implants with labeled diameter larger than the parent vessel diameter may result in decreased effectiveness and additional safety risk due to incomplete foreshortening resulting in an implant longer than anticipated.
- The Pipeline™ Vantage Embolization Device with Shield Technology™ may create local field inhomogeneity and susceptibility artifacts during magnetic resonance angiography (MRA), which may degrade the diagnostic quality to assess effective intracranial aneurysm treatment.
- Take all necessary precautions to limit X-ray radiation doses to patients and themselves by using sufficient shielding, reducing fluoroscopy times, and modifying X-ray technical factors where possible.
- Carefully weigh the benefits of treatment vs. the risks associated with treatment using the device for each individual patient based on their medical health status and risks factors for intracranial aneurysm rupture during their expected life time such as age, medical comorbidities, history of smoking, intracranial aneurysm size, location, and morphology, family history, history of prior asymptomatic subarachnoid hemorrhage (aSAH), documented growth of intracranial aneurysm on serial imaging, presence of multiple intracranial aneurysms, and presence of concurrent pathology. The benefits of device use may not outweigh the risks associated with the device in certain patients; therefore, judicious patient selection is recommended.
  - In the INSPIRE-A registry, there was an observation of increased braid deformity in female patients, especially in female patients less than 45 years of age.

- The safety and effectiveness of the device has not been established for treatment of fusiform IAs.
- There may be a decrease in effectiveness and increase in safety events when the device is used in patients ≥ 60 years old.
- The safety and effectiveness of the device has not been evaluated or demonstrated for ruptured aneurysms.

HOW SUPPLIED

This device is supplied STERILE using ethylene oxide. This device is non-pyrogenic.

STORAGE AND DISPOSAL

- This device should be stored in a dry place, away from sunlight.
- Dispose of device in accordance with hospital, administrative, and/or local government policy.

MAGNETIC RESONANCE IMAGING (MRI) SAFETY INFORMATION

Non-clinical testing has demonstrated that the Pipeline™ Vantage device is MR Conditional for single and overlapping stents up to 70 mm in length. A patient with the Medtronic Pipeline™ Vantage Device can be scanned safely in an MR system immediately after placement under the following conditions. Failure to follow these conditions may result in injury.

Parameter	Condition of Use / Information
Static Magnetic Field Strength (B_0) [T]	1.5T, 3T
Type of Nuclei	Hydrogen Proton
Static Magnetic Field (B_0) Orientation	Horizontal, Cylindrical bore
Maximum Spatial Field Gradient (SFG) [T/m] and [gauss/cm]	30 T/m (3000 gauss/cm)
RF Polarization	Circularly Polarized (CP) (i.e., quadrature drive)
RF Transmit Coil	Integrated Whole Body Transmit RF Coil Detachable Extremity Transmit / Receive RF coil
RF Receive Coil	Any receive-only RF coil may be used
MR System (RF) Operating Modes or Constraints	Normal Operating Mode
Whole Body Averaged SAR [W/kg]	≤ 2 W/kg
Head SAR [W/kg]	≤ 3.2 W/kg
Scan Duration	60 minutes of continuous radiofrequency (RF) (a sequence or back to back series/scan without breaks) followed by a wait time of 5 minutes if this limit is reached.
Anatomy at Isocenter	Any anatomic location at isocenter is acceptable
Patient position in scanner	Any patient position is acceptable
Item Configuration	Multilayer implant configuration of the Pipeline™ Vantage device does not affect its MRI compatibility, including temperature rise, torque, displacement, and artifact.
MR Image Artifact	In non-clinical testing, the image artifact caused by the Pipeline™ Vantage device extends approximately 20.2 mm from this implant when imaged using a T1-weighted spin echo pulse sequence and a 3 Tesla MR system.

CAUTION: The MRI safety when using a detachable head transmit/receive RF coil to image a patient with the Pipeline™ Vantage device has not been evaluated. Use of the integrated whole body transmit coil with a receive-only head coil is acceptable.

OBSERVED ADVERSE EVENTS

There were two prospective investigational trials conducted on the Pipeline™ device, the PUFS and PREMIER studies.

PUFS was a prospective, multicenter international study of patients with large and giant wide-necked unruptured aneurysms of the internal carotid artery treated with the Pipeline™ Embolization device (PED). 108 subjects were enrolled and treated in the PUFS study. The PUFS-CA study was also a prospective, multicenter study of patients with large and giant unruptured aneurysms of the internal carotid artery treated with the Pipeline™ Embolization device (PED). 27 subjects were enrolled and treated in the PUFS-CA study. The PUFS-PAS study was a single arm-prospective, multicenter cohort study of patients implanted with PED, the study population consisted of patients with large and giant unruptured aneurysms that were enrolled in the PUFS-PUFS-CA studies. 135 subjects were enrolled and 134 subjects were treated in the PUFS-PAS study. Serious adverse events reported to five year follow-up are shown in Table 2 and non-serious adverse events are shown in Table 3. In the PUFS-PAS study, cerebral haemorrhage was reported in 4.5% (6/134) subjects, cerebral ischaemia was reported in 2.2% (3/134) subjects, and ischaemic stroke was reported in 1.5% (2/134) subjects at 5 years (Table 2). Five occurred in the peri-procedural period (prior to discharge) and 6 in the post-procedural period. Two of the events were fatal, both intracerebral hemorrhages. One peri-procedural ischemic stroke and 2 post-procedural ischemic strokes were associated with parent artery occlusion. A history of hypertension is associated with increased risk of ipsilateral stroke or neurovascular death following PED treatment.

NOTE: *With the exception of the surface modification, the Pipeline™ Flex Embolization device with Shield Technology™ implant is identical to the Pipeline™ embolization device implant used in the PUFS-PAS trial.*

The Pipeline™ Vantage Embolization Device with Shield Technology™ has been studied in a prospective, post-market study, the "Innovative Neurovascular Product Surveillance Registry (INSPIRE)" outside of the United States (U.S.). The safety and effectiveness of Pipeline™ Vantage Embolization Device with Shield Technology™ will be monitored in a post-approval study in the U.S. and labeling will be updated as data becomes available.

Table 2. Serious adverse events in PUFS-PAS by MedDRA®* category and term – cumulative incidence at 180 days, one year, three years and five years (N= 134 subjects).

MedDRA®* Category	MedDRA®* Term	180 days	1 year	3 year	5 year
Nervous system disorders	Total	18 (13.4%)	18 (13.4%)	24 (17.9%)	27 (20.1%)
	Cerebral haemorrhage	6 (4.5%)	6 (4.5%)	6 (4.5%)	6 (4.5%)
	Headache	5 (3.7%)	6 (4.5%)	6 (4.5%)	6 (4.5%)
	Cerebral ischaemia	3 (2.2%)	3 (2.2%)	3 (2.2%)	3 (2.2%)
	Convulsion	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.5%)
	IIIrd nerve disorder	2 (1.5%)	2 (1.5%)	2 (1.5%)	2 (1.5%)
	Ischaemic stroke	2 (1.5%)	2 (1.5%)	2 (1.5%)	2 (1.5%)
	Syncope	0 (0.0%)	1 (0.7%)	2 (1.5%)	2 (1.5%)
	Carotid artery aneurysm	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
	Carotid artery occlusion	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
	Carpal tunnel syndrome	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.7%)
	Cerebral artery embolism	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.7%)
	Cerebral artery stenosis	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.7%)
	Cerebrovascular accident	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
	Dementia alzheimer's type	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.7%)
	Dizziness	0 (0.0%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
	Hemiparesis	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
	Nervous system disorder	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
	Transient ischaemic attack	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.7%)
	VIth nerve disorder	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)

MedDRA®* Category	MedDRA®* Term	180 days	1 year	3 year	5 year
Gastrointestinal disorders	Total	7 (5.2%)	8 (6.0%)	9 (6.7%)	10 (7.5%)
	Gastrointestinal haemorrhage	0 (0.0%)	1 (0.7%)	3 (2.2%)	3 (2.2%)
	Colitis	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
	Diverticulitis intestinal haemorrhagic	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.7%)
	Intra-abdominal haemorrhage	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
	Nausea	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
	Oesophageal spasm	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
	Peptic ulcer	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
	Rectal haemorrhage	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
	Retroperitoneal haematoma	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
	Vomiting	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
Injury, poisoning and procedural complications	Total	5 (3.7%)	5 (3.7%)	7 (5.2%)	10 (7.5%)
	Hip fracture	0 (0.0%)	0 (0.0%)	1 (0.7%)	2 (1.5%)
	Joint injury	1 (0.7%)	1 (0.7%)	2 (1.5%)	2 (1.5%)
	Ankle fracture	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
	Arterial injury	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
	Corneal abrasion	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
	Procedural haemorrhage	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
	Road traffic accident	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
	Vascular pseudoaneurysm	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
Surgical and medical procedures	Total	0 (0.0%)	2 (1.5%)	9 (6.7%)	10 (7.5%)
	Aneurysm repair	0 (0.0%)	2 (1.5%)	6 (4.5%)	6 (4.5%)
	Arterial aneurysm repair	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.7%)
	Atrial septal defect repair	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.7%)
	Intra-cerebral aneurysm operation	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.7%)
	Knee arthroplasty	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
Eye disorders	Total	5 (3.7%)	6 (4.5%)	9 (6.7%)	9 (6.7%)
	Amaurosis fugax	1 (0.7%)	2 (1.5%)	3 (2.2%)	3 (2.2%)
	Ophthalmoplegia	1 (0.7%)	1 (0.7%)	2 (1.5%)	2 (1.5%)
	Eye pain	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
	Retinal artery embolism	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
	Vision blurred	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
	Visual impairment	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.7%)
Cardiac disorders	Total	4 (3.0%)	4 (3.0%)	5 (3.7%)	8 (6.0%)
	Atrial fibrillation	1 (0.7%)	1 (0.7%)	1 (0.7%)	2 (1.5%)
	Bradycardia	1 (0.7%)	1 (0.7%)	1 (0.7%)	2 (1.5%)
	Arrhythmia	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
	Myocardial infarction	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.7%)
	Ventricular fibrillation	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
	Wolff-parkinson-white syndrome	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)

MedDRA®* Category	MedDRA®* Term	180 days	1 year	3 year	5 year
Vascular disorders	Total	5 (3.7%)	5 (3.7%)	6 (4.5%)	8 (6.0%)
	Haematoma	2 (1.5%)	2 (1.5%)	2 (1.5%)	2 (1.5%)
	Aneurysm	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.7%)
	Deep vein thrombosis	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
	Embolism	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
	Hypotension	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
	Intermittent claudication	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
	Peripheral vascular disorder	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	Total	0 (0.0%)	2 (1.5%)	4 (3.0%)	7 (5.2%)
	Adenocarcinoma	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.7%)
	Breast cancer	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.7%)
	Breast cancer recurrent	0 (0.0%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
	Colon cancer	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
	Lung neoplasm malignant	0 (0.0%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
	Metastatic neoplasm	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.7%)
	Non-small cell lung cancer stage IIIB	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
	Prostate cancer	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
Infections and infestations	Total	2 (1.5%)	3 (2.2%)	5 (3.7%)	6 (4.5%)
	Cholecystitis infective	1 (0.7%)	2 (1.5%)	2 (1.5%)	2 (1.5%)
	Abdominal abscess	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.7%)
	Herpes zoster	0 (0.0%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
	Meningitis viral	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.7%)
	Pneumonia	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
	Upper respiratory tract infection	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
Respiratory, thoracic and mediastinal disorders	Total	2 (1.5%)	2 (1.5%)	5 (3.7%)	6 (4.5%)
	Epistaxis	2 (1.5%)	2 (1.5%)	2 (1.5%)	2 (1.5%)
	Haemoptysis	0 (0.0%)	0 (0.0%)	1 (0.7%)	2 (1.5%)
	Emphysema	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.7%)
	Pulmonary embolism	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.7%)
General disorders and administration site conditions	Total	2 (1.5%)	3 (2.2%)	4 (3.0%)	4 (3.0%)
	Catheter site discharge	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
	Death	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
	Multi-organ failure	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.7%)
	Oedema peripheral	0 (0.0%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
Endocrine disorders	Total	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.2%)
	Hypothyroidism	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.2%)
Musculoskeletal and connective tissue disorders	Total	0 (0.0%)	1 (0.7%)	2 (1.5%)	2 (1.5%)
	Arthritis	0 (0.0%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
	Intervertebral disc degeneration	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.7%)
Blood and lymphatic system disorders	Total	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
	Bone marrow failure	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)

MedDRA®* Category	MedDRA®* Term	180 days	1 year	3 year	5 year
Ear and labyrinth disorders	Total	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
	Tinnitus	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
Psychiatric disorders	Total	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
	Depression	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
Renal and urinary disorders	Total	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
	Haematuria	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
Total		**37 (27.6%)**	**43 (32.1%)**	**62 (46.3%)**	**70 (52.2%)**

*MedDRA® Medical Dictionary for Regulatory Activities

Table 3. Non-serious adverse events in PUFS-PAS by Five years – by decreasing incidence (N= 134 subjects).

MedDRA®* Category	MedDRA®* Term	180 days	1 year	3 year	5 year
Nervous system disorders	Total	47 (35.1%)	48 (35.8%)	56 (41.8%)	62 (46.3%)
	Headache	39 (29.1%)	39 (29.1%)	44 (32.8%)	46 (34.3%)
	Dizziness	2 (1.5%)	4 (3.0%)	5 (3.7%)	6 (4.5%)
	Hypoaesthesia	3 (2.2%)	3 (2.2%)	4 (3.0%)	5 (3.7%)
	Paraesthesia	1 (0.7%)	2 (1.5%)	3 (2.2%)	4 (3.0%)
	Migraine	1 (0.7%)	1 (0.7%)	1 (0.7%)	3 (2.2%)
	Visual field defect	1 (0.7%)	2 (1.5%)	2 (1.5%)	2 (1.5%)
	Carotid artery occlusion	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
	Cerebral artery stenosis	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.7%)
	Convulsion	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
	Coordination abnormal	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.7%)
	Dementia	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
	Facial paresis	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.7%)
	Facial spasm	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
	Formication	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.7%)
	Hyperaesthesia	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
	Hypotonia	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
	IIIrd nerve disorder	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
	IIIrd nerve paralysis	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
	Intracranial aneurysm	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
	IVth nerve paralysis	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
	Migraine with aura	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
	Sciatica	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.7%)
	Transient ischaemic attack	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.7%)
	Tremor	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.7%)
	Upper motor neurone lesion	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
	VIth nerve paralysis	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
	VIth nerve paresis	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
Eye disorders	Total	28 (20.9%)	28 (20.9%)	32 (23.9%)	35 (26.1%)
	Visual impairment	14 (10.4%)	14 (10.4%)	14 (10.4%)	14 (10.4%)
	Eyelid ptosis	4 (3.0%)	4 (3.0%)	4 (3.0%)	4 (3.0%)
	Diplopia	3 (2.2%)	3 (2.2%)	3 (2.2%)	3 (2.2%)
	Eye pain	1 (0.7%)	1 (0.7%)	2 (1.5%)	2 (1.5%)
	Glaucoma	2 (1.5%)	2 (1.5%)	2 (1.5%)	2 (1.5%)
	Photopsia	0 (0.0%)	0 (0.0%)	1 (0.7%)	2 (1.5%)
	Vision blurred	1 (0.7%)	1 (0.7%)	2 (1.5%)	2 (1.5%)
	Visual acuity reduced	1 (0.7%)	1 (0.7%)	1 (0.7%)	2 (1.5%)
	Abnormal sensation in eye	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
	Amaurosis	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.7%)
	Amblyopia	0 (0.0%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
	Conjunctivitis	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.7%)
	Eye haemorrhage	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
	Eye pruritus	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
	Ophthalmoplegia	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.7%)
	Optic nerve disorder	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
	Vitreous floaters	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
Vascular disorders	Total	11 (8.2%)	12 (9.0%)	13 (9.7%)	20 (14.9%)
	Vasospasm	4 (3.0%)	4 (3.0%)	4 (3.0%)	5 (3.7%)
	Haematoma	4 (3.0%)	4 (3.0%)	4 (3.0%)	4 (3.0%)
	Hypertension	1 (0.7%)	1 (0.7%)	1 (0.7%)	3 (2.2%)
	Aneurysm	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.5%)
	Aortic aneurysm	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
	Arterial occlusive disease	0 (0.0%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
	Arterial stenosis	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
	Blood pressure inadequately controlled	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
	Orthostatic hypotension	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.7%)
	Thrombophlebitis superficial	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
	Thrombosis	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
Gastrointestinal disorders	Total	14 (10.4%)	14 (10.4%)	15 (11.2%)	17 (12.7%)
	Nausea	11 (8.2%)	11 (8.2%)	11 (8.2%)	12 (9.0%)
	Constipation	2 (1.5%)	2 (1.5%)	2 (1.5%)	2 (1.5%)
	Vomiting	2 (1.5%)	2 (1.5%)	2 (1.5%)	2 (1.5%)
	Abdominal distension	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
	Abdominal pain upper	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.7%)
	Haematochezia	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
	Paraesthesia oral	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
	Rectal haemorrhage	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)

MedDRA®* Category	MedDRA®* Term	180 days	1 year	3 year	5 year
Injury, poisoning and procedural complications	Total	10 (7.5%)	10 (7.5%)	13 (9.7%)	14 (10.4%)
	Contusion	4 (3.0%)	4 (3.0%)	5 (3.7%)	5 (3.7%)
	Head injury	2 (1.5%)	2 (1.5%)	3 (2.2%)	3 (2.2%)
	Ankle fracture	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
	Contrast media reaction	0 (0.0%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
	Corneal abrasion	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
	Foot fracture	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.7%)
	Muscle strain	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
	Radiation exposure	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
	Radiation injury	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
	Spinal compression fracture	0 (0.0%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
General disorders and administration site conditions	Total	9 (6.7%)	10 (7.5%)	10 (7.5%)	11 (8.2%)
	Pain	2 (1.5%)	2 (1.5%)	2 (1.5%)	2 (1.5%)
	Pyrexia	2 (1.5%)	2 (1.5%)	2 (1.5%)	2 (1.5%)
	Adverse drug reaction	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
	Catheter site discharge	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
	Catheter site swelling	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
	Chest pain	0 (0.0%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
	Facial pain	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
	Fatigue	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.7%)
	Feeling cold	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
	Oedema peripheral	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
	Vessel puncture site haemorrhage	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
Musculoskeletal and connective tissue disorders	Total	4 (3.0%)	5 (3.7%)	8 (6.0%)	11 (8.2%)
	Neck pain	1 (0.7%)	1 (0.7%)	2 (1.5%)	3 (2.2%)
	Arthralgia	0 (0.0%)	0 (0.0%)	1 (0.7%)	2 (1.5%)
	Arthritis	0 (0.0%)	0 (0.0%)	1 (0.7%)	2 (1.5%)
	Muscular weakness	0 (0.0%)	1 (0.7%)	2 (1.5%)	2 (1.5%)
	Back pain	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
	Groin pain	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
	Pain in extremity	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
Infections and infestations	Total	6 (4.5%)	6 (4.5%)	7 (5.2%)	9 (6.7%)
	Infection	6 (4.5%)	6 (4.5%)	6 (4.5%)	6 (4.5%)
	Cellulitis	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.7%)
	Chronic sinusitis	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.7%)
	Sinusitis	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.7%)
	Tooth abscess	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
	Urinary tract infection	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
Psychiatric disorders	Total	0 (0.0%)	1 (0.7%)	5 (3.7%)	7 (5.2%)
	Depression	0 (0.0%)	0 (0.0%)	2 (1.5%)	2 (1.5%)
	Alcoholism	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.7%)
	Anxiety	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
	Behavioural and psychiatric symptoms of dementia	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.7%)
	Mental status changes	0 (0.0%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
	Panic attack	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
Respiratory, thoracic and mediastinal disorders	Total	5 (3.7%)	5 (3.7%)	7 (5.2%)	7 (5.2%)
	Epistaxis	3 (2.2%)	3 (2.2%)	4 (3.0%)	4 (3.0%)
	Oropharyngeal pain	2 (1.5%)	2 (1.5%)	2 (1.5%)	2 (1.5%)
	Cough	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.7%)
Blood and lymphatic system disorders	Total	5 (3.7%)	5 (3.7%)	5 (3.7%)	5 (3.7%)
	Haemorrhagic disorder	3 (2.2%)	3 (2.2%)	3 (2.2%)	3 (2.2%)
	Anaemia	2 (1.5%)	2 (1.5%)	2 (1.5%)	2 (1.5%)
	Thrombocytopenia	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
Investigations	Total	2 (1.5%)	3 (2.2%)	4 (3.0%)	4 (3.0%)
	Corneal reflex decreased	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
	Electrocardiogram qt prolonged	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.7%)
	Ophthalmological examination abnormal	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
	Weber tuning fork test abnormal	0 (0.0%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
Metabolism and nutrition disorders	Total	0 (0.0%)	0 (0.0%)	3 (2.2%)	4 (3.0%)
	Hypercholesterolaemia	0 (0.0%)	0 (0.0%)	2 (1.5%)	2 (1.5%)
	Diabetes mellitus	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
	Iron deficiency	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.7%)
Renal and urinary disorders	Total	2 (1.5%)	2 (1.5%)	2 (1.5%)	3 (2.2%)
	Haematuria	2 (1.5%)	2 (1.5%)	2 (1.5%)	2 (1.5%)
	Pollakiuria	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
Reproductive system and breast disorders	Total	3 (2.2%)	3 (2.2%)	3 (2.2%)	3 (2.2%)
	Breast cyst	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
	Female genital tract fistula	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
	Ovarian cyst	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
	Vaginal haemorrhage	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
Ear and labyrinth disorders	Total	1 (0.7%)	2 (1.5%)	2 (1.5%)	2 (1.5%)
	Tinnitus	1 (0.7%)	2 (1.5%)	2 (1.5%)	2 (1.5%)

MedDRA®* Category	MedDRA®* Term	180 days	1 year	3 year	5 year
Neoplasms benign, malignant and unspecified (incl. cysts and polyps) Congenital, familial and genetic disorders	Total	0 (0.0%)	0 (0.0%)	1 (0.7%)	2 (1.5%)
	Cervix carcinoma recurrent	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
	Neoplasm malignant	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.7%)
	Total	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.7%)
	Arnold-chiari malformation	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.7%)
Immune system disorders	Total	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
	Hypersensitivity	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
Skin and subcutaneous tissue disorders	Total	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
	Pruritus	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
Surgical and medical procedures	Total	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
	Rotator cuff repair	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
Total		**84 (62.7%)**	**84 (62.7%)**	**91 (67.9%)**	**98 (73.1%)**
MedDRA®: Medical Dictionary for Regulatory Activities					

*NEC; Not Elsewhere Classified

PREMIER was a prospective, multi-center, single-arm study of patients with small and medium unruptured wide-neck intracranial aneurysms of the internal carotid artery and vertebral artery segments treated with the Pipeline™ device. A total of 141 subjects were enrolled and treated with the Pipeline™ device. All CEC adjudicated adverse events through 1-years by system organ class and preferred term are presented in Table 4. Eight strokes occurred in 7 subjects (5.0%) at 1-year, of which 3 were major (a stroke, which is present for 24 hrs or more and increases the NIH Stroke Scale of the subject by ≥ 4) and 5 were minor (A stroke, which is present for 24 hrs or more and increases the NIH Stroke Scale of the subject by ≤ 3). All strokes were ischemic in nature, with 3 of the 8 strokes having a hemorrhagic transformation of the core ischemic infarct. No stroke events were observed peri-procedurally (Day 0), two of the 3 major stroke events occurred in the Acute period (Day 1-Day 30), and 1 event occurred in the delayed period (Day 31-Day 365). Of the 3 major stroke events that occurred through 1-year, one resulted in death, one was disabling (modified Rankin Scale (mRS) score of ≥ 3 at a minimum of 90-days post-stroke event) at 1-year and one was non-disabling at 1-year. Of the 5 minor strokes that occurred through 1-year, no events were observed peri-procedurally. Four of the 5 events occurred in the acute period and 1 event was delayed.

NOTE: The Pipeline™ embolization device and Pipeline™ Flex Embolization Device utilize the same implant and were both used in the PREMIER trial. With the exception of the surface modification, the Pipeline™ Flex Embolization Device with Shield Technology™ implant is identical to the Pipeline™/Pipeline™ Flex embolization device implant used in the PREMIER trial.

Table 4. 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]
	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

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]
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]
Metabolism and nutrition disorders	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
	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 (incl. 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
	Total	61/141 (43.3%) [95]	14/141 (9.9%) [19]	52/141 (36.9%) [76]

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]
Nervous system disorders	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]
	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]
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]
Vascular disorders	Flushing	1/141 (0.7%) [1]	0	1/141 (0.7%) [1]
	Haematoma	2/141 (1.4%) [2]	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®* 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]

NOTE1: Events numbers are total episodes of each type of event among all subjects.

NOTE2: In CEC form, if CEC adjudicated the site reported event is Not an Adverse Event, the event was excluded in CEC adjudicated event analysis.

Rate of Subjects with Event numbers are percent of subjects who experienced one or more episodes of the event.

Events numbers for TOTAL are the sum of the individual event category totals.

Rate of Subjects with Event numbers for TOTAL is the percent of subjects who experienced an adverse event.

CLINICAL TRIAL RESULTS – PUFS, PUFS-CA, AND PUFS-PAS (PIPELINE™ FOR UNCOILABLE OR FAILED ANEURYSMS) STUDIES

Purpose

The purpose of the PUFS study was to evaluate the short-term safety and effectiveness of PED for the endovascular treatment of patients with unruptured large and giant intracranial aneurysms of the internal carotid artery from the petrous to superior hypophyseal segments. The purpose of the PUFS-CA study was to provide investigators with continued access to Pipeline™ (PED) during the PMA approval process. The purpose of the PUFS-PAS study was to combine the PUFS and PUFS-CA study cohorts to evaluate the long-term safety and effectiveness of PED for endovascular treatment of patients with unruptured large and giant intra-cranial aneurysms of the internal carotid artery from the petrous to superior hypophyseal segments.

Design

PUFS and PUFS-CA were prospective, multi-center, single-arm, open label clinical studies. PUFS was conducted at 8 sites in the US and 2 sites outside of the US. PUFS-CA was conducted at 2 sites in the US. PUFS-PAS combines PUFS and PUFS-CA cohorts; the PUFS-PAS study was conducted at 10 sites in the US and 2 sites outside of the US. PUFS-PAS subjects were adults with a single target aneurysm on the internal carotid artery with size ≥10 mm and neck ≥4 mm. Patients were excluded if they had recent surgery or subarachnoid hemorrhage, if they had a bleeding disorder and if a stent was already in place. All patients received perioperative aspirin (325 mg daily for 2 days prior to PED and 325 mg daily for 6 months after PED) and clopidogrel (75 mg daily for 7 days [or a 650 mg oral bolus the day prior to the procedure] and 75 mg daily for 3 months after PED).*

The primary effectiveness endpoint of the PUFS study was complete occlusion of the target aneurysm on 180-day cerebral angiography in the absence of use of other treatments and in the absence of major (>50%) stenosis of the parent artery. The primary effectiveness endpoint was judged by a core radiologic laboratory. The primary safety endpoint of the PUFS study was the occurrence of major ipsilateral stroke or neurologic death by 180 days. The primary safety endpoint of the PUFS-PAS study was occurrence of ipsilateral stroke or neurologic death at 5 years. The primary safety endpoints were judged by a clinical events committee. Based on a literature review, PUFS was designed to be considered a success if the primary effectiveness endpoint rate was statistically greater than 50% and the primary safety endpoint rate was statistically <20%. A Bayesian statistical approach with non-informative prior distributions was used for the primary endpoint analysis. The long-term primary safety endpoint for PUFS-PAS includes all ipsilateral stroke events while the short-term primary safety endpoint for PUFS only includes major ipsilateral stroke events. The PUFS-PAS study did not have a primary effectiveness endpoint. Therefore, all data analyses are combined and reported under PUFS-PAS except for the analyses of the short-term primary safety and effectiveness endpoints which are reported separately under the PUFS study.

Demographics

Demographic characteristics of the study population were typical for patients with large and giant wide-necked intracranial aneurysms (Table 5). Subjects were predominantly female and hypertension was common. There was a history of subarachnoid hemorrhage in 11 subjects (11/135, 8.1%), one of which had occurred within 60 days of treatment. Target IAs (Table 6) were predominantly in the cavernous and paraophthalmic portions of the internal carotid artery.

Table 5. Baseline characteristics – PUFS-PAS (n=135).

Characteristic	Value
Age, mean (SD, range)	56.2 (12.0, 23.7-75.5)
Female gender, n (%)	115 (85.2%)
Race	
White	124 (91.9%)
Black	8 (5.9%)
Not reported	3 (2.2%)
Ethnicity, % Hispanic or Latino	7 (5.2%)
Medical history	
Subarachnoid hemorrhage	11 (8.1%)
Stroke	9 (6.7%)
Coronary artery disease	70 (51.9%)
Smoking	
Never smoker	56 (41.5%)
Current smoker	38 (28.1%)
Previous smoker	41 (30.4%)
Prior treatments for target IA	14 (10.4%)
Coil embolization	11 (8.1%)
Surgery	2 (1.5%)
Other	1 (0.7%)

Table 6. Target IA characteristics in PUFS-PAS (n=135).

Characteristic	N (%) or Mean (Range)
Side	
Left	68 (50.4%)
Right	67 (49.6%)
Location	
Petrous	6 (4.4%)
Cavernous	54 (40.0%)
Carotid cave	2 (1.5%)
Ophthalmic	5 (3.7%)
Paraclinoid	8 (5.9%)
Superior hypophyseal	11 (8.1%)
Lateral clinoidal	2 (1.5%)
Paraophthalmic	37 (27.4%)
Supraclinoid	9 (6.7%)
Posterior communicating	1 (0.7%)
Maximum fundus diameter (mm), mean (SD, range)	18.0 (6.3, 6.2-36.1)
"Small" (<10 mm), N (%)	3 (2.2%)
"Large" (>10 mm), N (%)	106 (78.5%)
"Giant" (>25 mm), N (%)	26 (19.3%)
Neck (mm), mean (SD, range)	9.5 (7.1, 4.0-60.0)
Target IA partially thrombosed, N (%)	22 (16.3%)

Technical Results

PED was placed successfully in 134 of 135 attempted subjects. In one subject, the parent artery distal to the IA could not be catheterized and the PED procedure was aborted. A mean of 3.1 PEDs was placed per subject (Table 7). PEDs of most diameters and lengths were used (Table 8).

* Mean procedure time was 124 minutes and mean fluoroscopy time was 48.4 minutes.

Table 7. Number of PEDs placed per subject in PUFS-PAS (n = 134 subjects)

# of PEDs placed	N (%)
1	9 (6.7%)
2	43 (32.1%)
3	57 (42.5%)

# of PEDs placed	N (%)
4	13 (9.7%)
5 or more	12 (9.0%)
Mean (range)	3.1 (1-15)

Table 8. Length and diameter of PEDs used in PUFS -PAS (n=134 subjects)

Length, mm	N	Diameter, mm	N
10	15	3.25	7
12	61	3.50	38
14	76	3.75	97
16	78	4.00	105
18	84	4.25	75
20	95	4.50	57
25	4	4.75	21
30	3	5.00	19
35	3		
		Total	**419**

PUFS Short-Term Patient Follow-Up

Of the 104 subjects with 106 IAs in the IAs treated population, 97 subjects with 99 treated IAs had angiography 180 days after treatment and 89 subjects with 91 treated IAs had angiography 1 year after treatment. Clinical and angiographic follow-up was obtained in 96% of available subjects at 180 days.

PUFS Short-Term Results

The analysis of effectiveness was evaluated in three populations (Table 9). The posterior probability that the study met its primary effectiveness endpoint was >0.9999 in all three analyses. Complete IA occlusion was seen in 81.8% (81/99) of treated IAs at 180 days and 85.7% (78/91) at 1 year for only those subjects that had available angiographic data at these follow-up visits (Table 10).
*Lengths greater than 20 mm were not available during the study.

Table 9. Analyses of proportion of PUFS subjects who met the primary effectiveness endpoint.

Population	180 day	Posterior Probability***	1 year
Intracranial aneurysms treated (N=106)	78/106 73.6% (64.4, 81.0)*	>0.9999	75/106 70.8% (61.1, 79.2)**
Subjects treated (N=104)	76/104 73.1% (63.8, 80.7)*	>0.9999	73/104 70.2% (60.4, 78.7)**
Intracranial aneurysms attempted (N=110)	80/110 72.7% (63.7, 80.2)*	>0.9999	77/110 70.7% (58.6, 76.7)**

*95% posterior credible interval (Confidence/credible intervals are calculated without multiplicity adjustment. As such, the confidence/credible intervals are provided to show variability only and should not be used to draw any statistical conclusions)

**95% exact confidence interval (Confidence/credible intervals are calculated without multiplicity adjustment. As such, the confidence/credible intervals are provided to show variability only and should not be used to draw any statistical conclusions)

***Probability that observed effectiveness rate was >50%

Table 10. IA occlusion status at 180 days and 1 year for PUFS subjects with angiographic data.

Occlusion Ranking	180 days (N=99 IAs)	1 year (N=91 IAs)
Complete occlusion	81 (81.8%)	78 (85.7%)
Residual neck	8 (8.1%)	5 (5.5%)
Residual aneurysm	6 (6.1%)	5 (5.5%)
Other	4* (4.0%)	3** (3.3%)
Total	99 (100%)	91 (100%)

*1 subject with carotid-cavernous fistula and 3 subjects with carotid occlusion in whom IA not visualized

**2 subjects with carotid occlusion, 1 transvenous coil embolization in whom IA not visualized

The analysis of the PUFS primary safety endpoint was based on the safety cohort of 107 subjects treated with PED. The study's primary safety endpoint, ipsilateral major stroke or neurologic death by 180 days after treatment, occurred in 6 subjects (5.6%, 95% posterior credible interval CI 2.6 - 11.7%). The posterior probability that the major safety endpoint rate was less than 20%, the predetermined safety success threshold, was 0.999979.

Both the effectiveness and safety endpoint posterior probability values exceeded the pre-study probability threshold of 0.975, indicating that both results were statistically significant.

Adverse events are listed in "Observed Adverse Events" Section.

PUFS-PAS Long-term Patient Follow-up

Of the 134 subjects treated in the PUFS-PAS study, clinical follow-up was obtained for (107/130) 82.3% of subjects at 3 years and (100/128) 78.1% of subjects at 5 years. Angiographic follow-up was obtained for 100 subjects at 3 years after treatment and 80 subjects at 5 years after treatment.

Table 11. Subject Disposition (Number of Patients) in the PUFS-PAS (PUFS + PUFS-CA) Trial

	30-Day	180-Day	1-Year	2-Year	3-Year	4-Year	5-Year
All Subjects	135	135	135	135	135	135	135
Deaths	3	3	3	4	5	6	7
Discontinued	1	3	6	7	13	13	19
Not yet due for Follow-up	0	0	0	0	0	0	0
Expected Due[1]	132	132	132	131	130	129	128
Actually Included	130	124	114	122	107	106	100
Missed Visit	1	5	12	2	10	10	9
Follow-up rate[2]	98.5%	93.9%	86.4%	93.1%	82.3%	82.2%	78.1%

[1] Expected Due is all subjects minus any deaths

[2] Based on the number of subjects 'Actually Included' and 'Expected Due'

Table 12. Occlusion status at 180 days, 1 year, 3 years, and 5 years for PUFS-PAS subjects with angiographic data.

Occlusion Ranking	180 days (N=124 IAs)	1 year (N=117 IAs)	3 years (N=100 IAs)	5 years (N=80 IAs)
Complete Occlusion	95 (76.6%)	98 (83.8%)	90 (90.0%)	75 (93.8%)
Residual Neck	12 (9.7%)	7 (6.0%)	4 (4.0%)	3 (3.8%)
Residual Aneurysm	14 (11.3%)	11 (9.4%)	2 (2.0%)	2 (2.5%)
Indeterminate	3 (2.4%)	1 (0.9%)	4 (4.0%)	0 (0.0%)
Total	124 (100%)	117 (100%)	100 (100%)	80 (100%)

Table 13. Ipsilateral stroke or neurological death at 5 years for PUFS-PAS.

Primary Endpoint	Safety Success Threshold	Result	5-Year Kaplan-Meier Estimate
PUFS-PAS	<25%	8.2% (11/134)	8.3% (4.7%, 14.4%)

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.

NOTE: The intervals noted in the table for the 5 year Kaplan-Meier Estimate are the 95% posterior credible intervals CI.

PUFS-PAS Long-Term Results

Complete aneurysm occlusion was measured according to the total number of intracranial aneurysms with available imaging. Aneurysm occlusion status at 180 days, 1 year, 3 years, and 5 years are shown in Table 12. Complete IA occlusion was seen in 76.6% (95/124) of subjects at 180 days, 83.8% (98/117) of subjects at 1 year, 90% (90/100) of subjects at 3 years and 93.8% (75/80) of subjects at 5 years (Table 12).

The analysis of the PUFS-PAS primary safety endpoint was based on the safety cohort of 134 subjects treated with PED. The study's primary safety endpoint, ipsilateral stroke or neurologic death at 5 years occurred in 11 subjects (8.3%, 95% posterior credible interval CI 4.7% - 14.4%) (Table 13).

Final Conclusions

The PUFS study met the pre-specified primary effectiveness and safety endpoints at 180 days which remained statistically significant at one year. The primary safety endpoint was also met at 5 years in the combined PUFS-PAS study.

CLINICAL TRIAL RESULTS - PREMIER (PROSPECTIVE STUDY ON EMBOLIZATION OF INTRACRANIAL ANEURYSMS WITH THE PIPELINE™ DEVICE)

Purpose

The purpose of the PREMIER study was to evaluate the safety and effectiveness of the Pipeline™ device for the endovascular treatment of patients with unruptured wide-neck intracranial aneurysms, measuring ≤ 12 mm, located in the internal carotid artery (up to the terminus) or the vertebral artery segment up to and including the posterior inferior cerebellar artery.

Design

PREMIER was a prospective, multi-center, single-arm clinical study conducted at 22 sites in the US and 1 site outside of the US. PREMIER subjects were adults with a target aneurysm on the internal carotid artery or vertebral artery with size ≤ 12 mm, neck ≥ 4 mm or dome to neck ratio ≤ 1.5 mm. Patients were excluded if they had major surgery or subarachnoid hemorrhage within 30 days, if they had an irreversible bleeding disorder, signs of active bleeding, and if a stent was already in place at the target aneurysm. All patients were required to receive aspirin (minimum of 81 mg daily for a minimum of 7 days prior to PED and 81 mg daily for a minimum of 6 months after PED) and clopidogrel (minimum of 75 mg daily for a minimum of 7 days prior to PED and 75 mg daily for a minimum of 3 months after PED). The primary effectiveness endpoint of the study complete aneurysm occlusion (defined by the Scale of Roy[1]) without significant parent artery stenosis (≤ 50%) or retreatment of the target aneurysm 1-year postprocedure. The primary effectiveness endpoint was judged by a core radiologic laboratory and was graded using the Raymond-Roy occlusion scale[1]. The primary safety endpoint was the occurrence of major stroke in the territory supplied by the treated artery or neurological death by 1-year post-procedure. The primary safety endpoint was judged by an independent clinical events committee. Based on a literature review, PREMIER was designed to be considered a success if the primary effectiveness endpoint rate was statistically greater than 50% and the primary safety endpoint rate was statistically less than 15%. Primary endpoints analyses were based on 1-sided 97.5% Clopper- Pearson exact binomial confidence interval.

[1]Roy D, Milot G, Raymond J.Endovascular treatment of unruptured aneurysms. Stroke. 2001;32 (9): 1998-2004

Demographics

Demographic characteristics of the study population were typical for patients with small and medium wide-necked IAs (Table 14); Subjects were predominately female and hypertension was co on. There was a history of subarachnoid hemorrhage in 13 (9.2%) subjects. Target IAs (Table 14) were predominately in the ophthalmic, communicating and clinoid segments of the ICA.

Table 14. Baseline characteristics – PREMIER (n=141).

Variable	Overall (N=141 Subjects)
Age	54.6±11.3 (141) [53.0] (30 - 77)
≥ 22 to <50	34.8% (49)
50 to <60	31.2% (44)
60 to <70	22.7% (32)
70 to 80	11.3% (16)
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)
Native Hawaiian or Other Pacific Islander	0.0% (0)
White	80.9% (114)
Unknown	0.0% (0)
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)
Medical History	
Hypertension	72 (51.1%)
History of SAH	14 (9.9%)
Current cigarette smoking	41 (29.1%)
Former smoker within past 10 years	21 (14.9%)
Drug use	1 (0.7%)
Alcohol abuse	3 (2.1%)
Epilepsy	13 (9.2%)
Psychiatric disorder	71 (50.4%)
Atrial fibrillation	7 (5.0%)
Cardiac arrhythmias	20 (14.2%)
Congestive heart failure	2 (1.4%)
Myocardial infarction	2 (1.4%)
Smoking	
Never smoked or has not smoked within the last 10 years	56.0% (79/141)
Current or Past Smoker (within the past 10 years)	44.0% (62/141)
Not a current smoker, but has smoked within the past 10 years	14.9% (21/141)
Current smoker, less than one pack per day	19.1% (27/141)
Current smoker, greater than or equal to one pack per day	9.9% (14/141)

Table 15. Target IA characteristics in PREMIER (n=141).

Aneurysm Characteristics	Target aneurysm % (n/N) (N=141 Aneurysms)
Imaging Type	
CT	0
CTA	0
MR	0
MRA	0
Angiogram	100.0% (141/141)
Other	0
Aneurysm Side	Aneurysm Side
Right	48.9% (69/141)
Left	51.1% (72/141)
Parent Artery Location	
Internal Carotid Artery	95.0% (134/141)
C1 (Cervical Segment)	0

Aneurysm Characteristics	Target aneurysm % (n/N) (N=141 Aneurysms)
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)
Aneurysm Morphology	
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	-
Partially Thrombosed	Partially Thrombosed
Yes	3.5% (5/141)
Aneurysm Measurement	
Aneurysm Maximal Diameter (mm)	5.0±1.92 (141)[4.6] (1.7 - 11.1)
Dome Width (mm)	4.5±1.83 (141)[4.2] (1.3 - 11)
Dome Height (mm)	4.0±1.60 (141)[3.8] (1 - 9.2)
Aneurysm Neck Length (mm)	4.0±1.42 (141)[3.7] (1.3 - 9.5)
Dome/Neck Ratio	1.1±0.28 (141)[1.1] (0.6 - 1.9)
Parent Artery Diameter Proximal to Target Aneurysm (mm)	3.9±0.60 (141)[3.9] (2.1 - 5)
Parent Artery Diameter Distal to Target Aneurysm (mm)	3.5±0.59 (141)[3.5] (2.2 - 5.1)
Aneurysm Size	5.0±1.92 (141)[4.6] (1.7 - 11.1)
Small (<7 mm)	84.4% (119/141)
Aneurysm Size (<3 mm)	9.9% (14/141)
Aneurysm Size (3-<7 mm)	74.5% (105/141)
Medium (7-<13 mm)	15.6% (22/141)
Large (13-<25 mm)	0
Giant (>= 25 mm)	0
Aneurysm Measurement	
1Aneurysm Size Ratio >3	4.3% (6/141)
2Aneurysm Size Ratio>3	2.1% (3/141)
3Aneurysm Aspect Ratio>1.6	6.4% (9/141)
Number of Subject with 1Aneurysm Size Ratio >3 and Aneurysm Aspect Ratio>1.6	1
Number of Subject with 2Aneurysm Size Ratio >3 and Aneurysm Aspect Ratio>1.6	1

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.

Inclusion Criteria

Subjects met all the of the following general inclusion criteria:

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

Exclusion Criteria

Subjects did not meet any of the following general exclusion criteria:

1. Subject had received an intracranial implant (e.g., coils) in the area of the target intracranial aneurysm within the past 12 weeks
2. Subarachnoid hemorrhage in the past 30 days
3. Subject with anatomy not appropriate for endovascular treatment due to severe intracranial vessel tortuosity or stenosis determined from baseline or pre-procedure imaging, or a history of intracranial vasospasm not responsive to medical therapy
4. Major surgery in the last 30 days
5. History of irreversible bleeding disorder and/or subject presented with signs of active bleeding
6. Any known contraindication to treatment with the Pipeline™ device, including:
   a. Stent in place in the parent artery at the target intracranial aneurysm location
   b. Contraindication to dual antiplatelet therapy (DAPT)
   c. Relative contraindication to angiography (e.g., serum creatinine >2.5 mg/dL, allergy to contrast that cannot be medically controlled)
   d. Known severe allergy to platinum or cobalt/chromium alloys
   e. Evidence of active infection at the time of treatment (e.g., fever with temperature > 38°C and/or WBC > 1.5 109/L)
7. 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
8. Pregnant or breast-feeding women or women who wish to become pregnant during the length of study participation
9. Participated in another clinical trial during the follow-up period that could confound the treatment or outcomes of this investigation

Technical Results:

The Pipeline™ device was placed successfully in 140 of 141 attempted subjects (99.3%) at the Index procedure. A mean of 1.1 ± 0.3 Pipeline™ devices was placed per subject with the majority of subjects (92.9%) receiving a single Pipeline™ device. PEDs of most diameters and lengths were used (Table 14). Mean time from skin incision to skin closure was 78.4 ± 40.3 minutes, mean time from first Pipeline™ device introduction to last Pipeline™ device delivery system removal was 14.3 ± 15.1 minutes and mean fluoroscopy time was 27.9 ± 14.8 minutes.

Table 16. Summary of the Number of Pipeline™ Devices Attempted During the Study Index Procedure by Dimension -mITT Population with Observed Data

	Study Device Length (mm)								
Study Device Diameter (mm)	10	12	14	16	18	20	25	30	Total
2.50	0	0	1	0	0	0	0	0	1
3.00	0	1	1	1	0	1	0	0	4

Study Device Length (mm)									
3.25	0	1	1	1	0	0	1	0	4
3.50	2	2	7	2	4	2	1	0	20
3.75	1	4	6	5	2	2	2	0	22
4.00	1	6	10	9	4	3	2	0	35
4.25	1	5	6	6	1	2	1	1	23
4.50	0	2	8	8	3	3	1	0	25
4.75	0	3	0	1	4	1	0	0	9
5.00	1	0	1	4	1	2	1	2	12
Total	**6**	**24**	**41**	**37**	**19**	**16**	**9**	**3**	**155**

Patient Follow-Up: Of the 141 treated subjects, the rate of one-year follow-up was high with clinical follow-up obtained in 98.6% (139/141) of subjects and imaging follow-up obtained in 97.9% (138/141) of subjects. One subject died prior to one-year follow-up, one subject missed the 1-year follow-up visit and one subject returned for the 1-year visit but did not have imaging performed.

Patient Analysis Population:

Modified Intention to Treat (mITT): defined as all enrolled subjects in whom deployment of the Pipeline™ device was attempted. The mITT population consisted of 141 subjects.

Internal Carotid Artery Population (ICA Population): defined as a subset of the mITT population that included subjects with small or medium wide-neck aneurysms of the internal carotid artery (up to the terminus); subjects with aneurysms of the posterior circulation (aneurysms of vertebral artery) were not included in the ICA population. The ICA population consisted of 134 subjects (excludes 7 subjects with aneurysm in the vertebral artery). An additional effectiveness endpoint analysis was performed excluding the 5 subjects from the ICA population as they underwent adjunctive coiling (N = 129).

Results: The primary effectiveness endpoint were higher than the a priori threshold of 50% for both the ICA Population (N=134) and for ICA Population excluding subjects with adjunctive coiling (N = 129); thus, the primary effectiveness endpoint was met (Table17).

Table 17. Summary of Incidence of Primary Effectiveness Endpoint 1-Year Post-Procedure ICA Population

Primary Effectiveness Endpoint Parameter	Rate (%)	1-sided 97.5% Exact Lower Binomial Confidence Interval
Complete Aneurysm Occlusion without significant parent artery stenosis (≤ 50%) or retreatment of the target aneurysm (N=134) - Multiple Imputations	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%
Complete Aneurysm Occlusion without significant parent artery stenosis (≤ 50%) or retreatment of the target aneurysm (excluding 5 subjects with use of coils as adjunctive devices at procedure) (N=129) - Multiple Imputations	78.91%	71.84%
Complete Aneurysm Occlusion without significant parent artery stenosis (≤ 50%) or retreatment of the target aneurysm (excluding 5 subjects with use of coils as adjunctive devices at procedure) (N=129); Subjects with missing data (n=2) considered failures*	77.52% (100/129)	69.34%

NOTE1: ICA population-Indication Population

NOTE2: 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 failure

Table 18. Reasons for Primary Effectiveness Endpoint Non-Success (ICA Population)

Reason	Rate % (n/N) (N = 134 Subjects)*	Rate % (n/N) (N = 129 Subjects)**
Residual neck	1.5% (2/132)	1.6% (2/129)
Residual aneurysm	14.4% (19/132)	14.0% (18/129)
Stenosis greater than 50%	3.0% (4/132)	3.1% (4/129)
Target aneurysm retreatment	3.0% (4/132)	3.1% (4/129)
Total	21.2% (28/132)	20.9% (27/129)

*ICA Population; 1-year imaging follow-up for 2 subjects was missing from the ICA Population

** ICA Population excluding the 5 subjects with adjunctive coiling

The primary safety endpoint, occurrence of major stroke in the territory supplied by the treated artery or neurological death 1-year post-procedure occurred in 2.17% and 2.2% (3/134) of subjects in the mITT and ICA populations respectively. The 1-sided 97.5% exact upper binomial confidence interval was 4.61% and 6.40% in the mITT and ICA populations respectively, which was below the threshold of 15%; therefore, the primary safety endpoint of the study was met.

Table 19. Primary Safety Endpoint (Major stroke in the territory supplied by the treated artery or Neurological death)-mITT Population and ICA Population

Primary Safety Endpoint	Rate (%)	1-Sided 97.5% Exact Upper Binomial Confidence Interval	Threshold	1-Sided p-value from Binomial Distribution
mITT Population (N=141)*	2.17%	6.51%	15%	0.0002
ICA population (N=134)	2.20% (3/134)	6.40%	15%	<0.0001

*Missing data for subjects who fail 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 were counted as having experienced the event of interest.

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.

Adverse events are listed in "Observed Adverse Events" Section

The safety endpoints and events by age ≥60 years and <60 years are presented in table 20.

Table 20. Subgroup Analysis of Safety Endpoints and Events by Age≥60 Yrs* vs. <60 Yrs (mITT Population)

Analysis Parameter	Age < 60 yrs (N=93)	Age ≥ 60 yrs (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 Stroke** (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 Parameter	Age < 60 yrs (N=93)	Age ≥ 60 yrs (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%]

*Use of PFED in patients >60 years of age may result in decreased effectiveness and additional safety risks.

** A total of 8 stroke events (major and minor) were reported in 7 subjects; 1 subject (≥60 years age) had a major and minor stroke.

NOTE1: mITT: modified Intent-to-Treat population

NOTE2: Numbers are % (Count/Sample Size) [Confidence Interval]. Confidence Interval is based on exact Binomial Distribution

NOTE3: 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 post-hoc analysis showing the composite occurrence of neurological death and disabling stroke (defined as mRS ≥3 at a minimum of 90 days after stroke event)) for the mITT population is presented in Table 21 and ICA population is presented in Table 22.

Table 21. Post-hoc Safety Analysis of Neurological Death or Disabling Stroke at 1-Year Post-Procedure – mITT Population

Variable	Rate (N=141)	1-sided 97.5% exact upper binomial confidence interval
Composite Safety Rate (disabling stroke with mRS score ≥ 3 or neurological death at 1-year post procedure)	1.4% (2/141)	5.0%
Disabling stroke with mRS score ≥ 3 at 1-year post procedure[1]	0.7% (1/141)	3.9%
Neurological death at 1-year post procedure	0.7% (1/141)	3.9%

[1]Disabling stroke defined as mRS of 3 or higher measured at least 90 days after stroke event

Table 22. Post-hoc Safety Analysis of Neurological Death or Disabling Stroke at 1-Year Post- Procedure – ICA Population

Variable	Rate (N=134)	1-sided 97.5% exact upper binomial confidence interval
Primary Safety Composite Rate (disabling stroke with mRS score >= 3 or neurological death at 1-Year post procedure)	1.5% (2/134)	5.3%
Disabling stroke with mRS score >= 3 at 1 Year post procedure	0.7% (1/134)	4.1%
Neurological death at 1-Year post procedure	0.7% (1/134)	4.1%

The incidence of all ischemic and hemorrhagic events (includes Major Stroke, Minor Stroke, Symptomatic Cerebral Infarction, Asymptomatic Cerebral Infarction, ICH, TIA, and Aneurysm Rupture) in the mITT and ICA population is presented in Table. 23.

Table 23. Additional Safety Analysis; Cerebrovascular Events (Ischemic and Hemorrhagic) in the mITT and ICA Population up to 1-Year Post-Procedure

Variable	mITT Population % (n/N)[E]	ICA Population % (n/N)[E]
Analysis of Cerebrovascular Events (Ischemic and Hemorrhagic) *	7.8% (11/141)[18]	8.2% (11/134)[18]

n = number of subjects with events, N = total number of subjects, E = total number of events

*Includes incidence of Stroke (Major or Minor, Ipsilateral or Contralateral), Cerebral Infarction (Symptomatic or Asymptomatic), Intracranial Hemorrhage, Transient Ischemic Attack, and Target Aneurysm Rupture

The change in mRS (same, worse, or better) compared to the pre-procedure mRS measurements in the mITT and ICA population is presented in Table 24.

Table 24. Change in mRS (same, worse, or better) compared to pre-procedure in the mITT and ICA population at 1-Year Post-Procedure

mRS Change	mITT Population[a] % (n/N) [Confidence Interval]	ICA Population[b] % (n/N) [Confidence Interval]
Decrease in mRS	10.3% (14/136), [5.74%,16.67%]	9.2% (12/131), [4.82%,15.4
No change	80.1% (109/136), [72.45%,86.49%]	80.9% (106/131), [73.13%,87.25%]
Increase in mRS	9.6% (13/136), [5.19%,15.79%]	9.9% (13/131), [5.39%,16.37%]

NOTE1: mITT: modified Intent-to-Treat population.

NOTE2: Numbers are % (Count/Sample Size) [Confidence Interval]. Confidence Interval is based on exact Binomial Distribution

[a] The mITT Population had 5 subjects that did not have paired mRS readings and thus, not included in this analysis

[b] The ICA Population had 3 subjects that did not have paired mRS readings and thus, not included in this analysis

NOTE3: 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.

The summary of Primary Effectiveness and Safety Endpoints at 1-Year Post-Procedure, by Aneurysm Size (mITT Population)*is presented in Table 25

Table 25. Summary of Primary Effectiveness and Safety Endpoints at 1-Year Post-Procedure, by Aneurysm Size (mITT Population)*

Primary Endpoint Analysis Parameter	1 mm-<2 mm (N=1)	2 mm-<3 mm (N=13)	3 mm-<4 mm (N=36)	4 mm-<5 mm (N=29)	5 mm-<6 mm (N=26)	6 mm-<7 mm (N=14)	7 mm-<8 mm (N=10)	8 mm-<9 mm (N=5)	9 mm-<10 mm (N=4)	10 mm-<11 mm (N=1)	11 mm-<12 mm (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: No 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

NOTE1: mITT: modified Intent-to-Treat population.

NOTE2: Numbers are % (Count/Sample Size).

Final Conclusions

The PREMIER study met the primary effectiveness and safety endpoints at one year in the ICA population.

Table 26. Follow-up Compliance Visit - mITT and ICA Population with Observed Data

Variable	mITT Subjects (N=141)	ICA Subjects (N=134)
Underwent the study procedure	100.0% (141)	100.0% (134)
Evaluated at the 30-day follow-up visit	99.3% (140)	99.3% (133)
Evaluated at the 180-day follow-up visit	95.0% (134)	94.8% (127)
Imaging completed at the 180-day follow-up visit (not a mandatory follow-up visit)	76.6% (108)	76.9% (103)
Evaluated at the 1-year follow-up visit	98.6% (139)	99.3% (133)
Imaging completed at the 1-year follow-up visit	97.9% (138)	98.5% (132)
Evaluated at the 2-year follow-up visit	95.0% (134)	96.3% (129)
Imaging completed at the 2-year follow-up visit (mandatory only for those with incomplete occlusion at 1 year)	39.7% (56)	39.6% (53)
Mandatory Imaging at 2-year follow up visit	76.0% (19/25)*	76.2% (16/21)
Evaluated at the 3-year follow-up visit	90.8% (128)	91.0% (122)
Imaging completed at the 3-year follow-up visit (mandatory only for those with incomplete occlusion at 1 and/or 2- year)	39.0% (55)	38.1% (51)
Mandatory Imaging at 3-year follow up visit	64.0% (16/25)**	66.7% (14/21)

*Reasons for 6 subjects missing the 2-year imaging follow up visits: Subject refusal/unable to undergo follow-up DSA (3 subjects) and Imaging not expected as initial single reader core lab assessment was complete occlusion (later adjudicated as incomplete occlusion by multi-reader core lab) (3 subjects)

**Reasons for 9 mITT subjects missing the 3-year imaging: Subject refusal/unable to undergo follow-up DSA – (4 subjects), Imaging not expected as initial single reader core lab assessment was complete occlusion (later adjudicated as incomplete occlusion by multi-reader core lab) (3 subjects), and lost to follow-up (2 subjects)

NOTE1: mITT- Modified Intent to treat population.

NOTE2: Imaging completed denotes that a subject had core lab reviewed data for analysis.

NOTE3: Evaluated denotes that a subject had assessment per NIHS, mRS and Site Imaging form.

NOTE4: N=number of subjects with observed data

Table 27. Summary Of Post-Procedure Target Aneurysm Occlusion Results at 1-, 2-, and 3-year Follow-up Visits Post-Procedure (mITT and ICA Population with Observed Data) (LOCF for 2- and 3-year Data)

Population	Variable	1-Year	2-Year (LOCF)*¥	3-Year (LOCF)* ¥
mITT (N=141 Subjects)	Complete Occlusion	81.9% (113/138)	81.9% (113/138)	83.3% (115/138)
	Residual Neck	2.2% (3/138)	3.6% (5/138)	5.1% (7/138)
	Residual Aneurysm	15.9% (22/138)	14.5% (20/138)	11.6% (16/138)
ICA (N=134 Subjects)	Complete Occlusion	84.1% (111/132)	84.1% (111/132)	85.6% (113/132)
	Residual Neck	1.5% (2/132)	3.0% (4/132)	4.5% (6/132)
	Residual Aneurysm	14.4% (19/132)	12.9% (17/132)	9.8% (13/132)

Population	Variable	1-Year	2-Year (LOCF)*¥	3-Year (LOCF)* ¥

*Using this LOCF approach, for subjects with 2-year/3-year evaluable imaging, the results from the 2-year/3-year core lab consensus reading were utilized, whereas, for the remaining subjects, the core lab consensus reading from 1-year/2-year follow-up images were used

¥**NOTE:** Imaging was only mandatory at 2- and 3 -year if the aneurysm was not completely occluded at the 1- and/or 2-year imaging; additionally, for subjects with complete aneurysm occlusion, imaging was collected and assessed by core lab only if performed per standard of care. At 2-year follow-up, of the 138 mITT subjects, 56 subjects completed imaging, 34 subjects had complete occlusion, 4 subjects had residual neck, 15 subjects had residual aneurysm and 3 images could not be read. For 3-year follow-up, 55 mITT subjects completed imaging, 40 subjects had complete occlusion, 6 subjects had residual neck, 8 subjects had residual aneurysm and 1 image could not be read.

For the ICA population at 2-year follow-up, of the 132 subjects, 53 subjects completed imaging, 34 subjects had complete occlusion, 4 subjects had residual neck, 12 subjects had residual aneurysm and 3 images could not be read. For 3-year follow-up, 51 ICA subjects completed imaging, 38 subjects had complete occlusion, 5 subjects had residual neck, 7 subjects had residual aneurysm and 1 image could not be read.

NOTE1: mITT- Modified Intent to treat population.

NOTE2: Numbers are % (Count/Sample Size).

NOTE3: N=number of subjects with observed data

Table 28. Recurrence and Retreatment Rates Through 3-years Post-Procedure (mITT and ICA Population with Observed Data) (LOCF for 2- and 3-year Data)

		1-Year		2-Year (LOCF)*		3-Year (LOCF)*	
Population	Variable	Overall	2-sided 95% Exact Binomial CI	Overall	2-sided 95% Exact Binomial CI	Overall	2-sided 95% Exact Binomial CI
mITT (N=141)	Target Aneurysm Recurrence *	0.0% (0/138)	[0.00%,2.64%]	0.0% (0/138)	[0.00%,2.64%]	0.7% (1/138)	[0.02%,3.97%]
	Target Aneurysm Retreatment	2.8% (4/141)	[0.78%,7.10%]	5.0% (7/141)	[2.02%,9.96%]	5.0% (7/141)	[2.02%,9.96%]
ICA (N=134)	Target Aneurysm Recurrence *	0.0% (0/132)	[0.00%,2.76%]	0.0% (0/132)	[0.00%,2.76%]	0.8% (1/132)	[0.02%,4.15%]
	Target Aneurysm Retreatment	3.0% (4/134)	[0.82%,7.47%]	3.7% (5/134)	[1.22%,8.49%]	3.7% (5/134)	[1.22%,8.49%]

*Imaging was only mandatory at 2- and 3 -year if the aneurysm was not completely occluded at the 1- and/or 2-year imaging; additionally, for subjects with complete aneurysm occlusion, imaging was collected and assessed by core lab only if performed per standard of care. For subjects with 2-year and 3-year imaging, the results from the core lab consensus reading were utilized for recurrence analysis, whereas, for the remaining subjects, the core lab consensus reading from 1-year/2-year follow-up images were used for recurrence analysis (LOCF method).

NOTE1: mITT: modified Intent-to-Treat population; ICA: ICA population.

NOTE2: Numbers are % (Count/Sample Size)

NOTE3: CI: Confidence Interval.

Table 29. Summary of CEC adjudicated Adverse Events through 3-year Follow-Up by Seriousness (mITT and ICA Population with Observed Data)

0-3-Year			
Numbers of Subject with CEC adjudicated Adverse Events [# events]	All AE's n (%) [# of Events]	All SAE's n (%) [# of Events]	All Non-Serious AE's n (%) [# of Events]
mITT Population	124/141 (87.9%) [429]	60/141 (42.6%) [134]	112/141 (79.4%) [295]
ICA Population	118/134 (88.1%) [409]	55/134 (41.0%) [128]	108/134 (80.6%) [281]

NOTE1: Event numbers are total episodes of each type of event among all subjects.

Rate of Subjects with Event numbers are percent of subjects who experienced one or more episodes of the event.

Event numbers for TOTAL are the sum of the individual event category totals.

Rate of Subjects with Event numbers for TOTAL is the percent of subjects who experienced an adverse event.

Table 30. Summary of Parent Artery Stenosis per Multiple Reader Core Laboratory Analysis for Primary Effectiveness Endpoint at 1-, 2-, and 3-year Follow Up (mITT and ICA Population with Observed Data)

	Parent Artery Stenosis (Significant stenosis (> 50%))	1-Year	2-Year	3-Year
mITT Population (N=141 Subjects)	No	97.1% (134/138)	96.2% (51/53)	100.0% (54/54)
	Yes	2.9% (4/138)	3.8% (2/53)	0
	Cannot Determine	0	3	1
ICA Population (N=134 Subjects)	No	97.0% (128/132)	96.0% (48/50)	100.0% (50/50)
	Yes	3.0% (4/132)	4.0% (2/50)	0
	Cannot Determine	0	3	1

*Imaging was only mandatory at 2- and 3 -year if the aneurysm was not completely occluded at the 1- and/or 2-year imaging; additionally, for subjects with complete aneurysm occlusion, imaging was collected and assessed by core lab only if performed per standard of care.

NOTE1: Numbers are % (Count/Sample Size) or Mean±SD (N) [Median] (Min, Max).

NOTE2: Data presented based on Core Lab.

NOTE3: Target Aneurysms only.

NOTE4: N=number of subjects with observed data

Strengths:

The PREMIER Study was the first prospective, multicenter trial to evaluate the use of the Pipeline™ device for the treatment of small and medium, unruptured aneurysms of the intracranial carotid and proximal vertebral artery. The PREMIER Study had predefined hypotheses, study objectives/endpoints, study population selections, statistical analyses, subgroup analyses, and follow-up evaluations.

To avoid and minimize bias in the PREMIER Study, an independent Clinical Events Committee (CEC), Imaging Core Laboratory, and Data Monitoring Committee (DMC) were established to assess the primary safety and effectiveness endpoints, as well as to oversee the safety of the study. All study AEs were reviewed and adjudicated by CEC, which consisted of three independent physicians knowledgeable and Board Certified in the appropriate disciplines and medical specialties pertinent to the disease state. In addition, the CEC adjudicated specified event definitions (where available), event relatedness, event severity, and event outcome. Therefore, the CEC adjudication provided an unbiased assessment for safety outcomes in the PREMIER Study. The Imaging Core Laboratory provided an independent angiography examination to assess baseline aneurysm and procedural aneurysm characteristics, aneurysm occlusion status, parent artery stenosis, and occurrence of device migration.

The PREMIER Study included a long-term 3-year follow-up with high subject retention; 90.8% (128/141) of subjects completed 3-year clinical follow up visit. The 3-year follow-up results showed durability of aneurysm occlusion with modest rise of new primary safety events, and low new overall complications, supporting the longer-term safety and efficacy of the Pipeline™ Device in the populations in treating small and medium wide-necked, intracranial aneurysms.

Weaknesses:

The PREMIER Study was a single-arm clinical study without the use of a control group. Note that a single-arm trial was necessary, as alternative, minimally invasive treatments that could form a reasonable concurrent control group were not approved at the onset of this study. The study only included a limited number of subjects with vertebral artery aneurysms (7/141). Of the subjects requiring mandatory imaging follow-ups at 2-year and 3-year visits, only 76% (19/25) and 64.0% (16/25), respectively completed the required imaging. The key reasons for missing imaging were changes in multi-reader core lab assessments (implemented post-hoc per FDA feedback), subject refusal/unable to undergo follow-up imaging, and lost-to-follow-up (details in Table 26).

QUESTIONS AND ANSWERS

Q If excessive friction is experienced during the insertion of delivery system at any time during the delivery of Pipeline™ Vantage Embolization Device with Shield Technology™, what should I do?
A Carefully remove the entire system simultaneously (micro catheter and delivery system).

Q Can I retrieve the Pipeline™ Vantage Embolization Device with Shield Technology™ if the distal end of the Pipeline™ Vantage Embolization Device with Shield Technology™ has expanded at an undesirable location?
A Yes. A partially deployed Pipeline™ Vantage Embolization Device with Shield Technology™ can be resheathed per resheathing instructions, step 8 in the Directions for Use.

Q Can I retrieve a fully deployed Pipeline™ Vantage Embolization Device with Shield Technology™?
A Once fully deployed, the Pipeline™ Vantage Embolization Device with Shield Technology™ cannot be removed. A second Pipeline™ Vantage Embolization Device with Shield Technology™ can be deployed if needed.

Q Can I place a second Pipeline™ Vantage Embolization Device with Shield Technology™ inside another Pipeline™ Vantage Embolization Device with Shield Technology™?
A Yes. A second Pipeline™ Vantage Embolization Device with Shield Technology™ can be placed inside another Pipeline™ Vantage Embolization Device with Shield Technology™. After placing the first Pipeline™ Vantage Embolization Device with Shield Technology™, advance the micro catheter over the delivery wire while keeping the delivery core wire across the Pipeline™ Vantage Embolization Device with Shield Technology™. Position the micro catheter at the desired location and retrieve the delivery wire. Select a new appropriate Pipeline™ Vantage Embolization Device with Shield Technology™ and deploy it as normal.
Caution: Placement of multiple Pipeline™ Vantage Embolization Device with Shield Technology™ may increase the risk of ischemic complications.

Q If there is a difference between the proximal and distal diameter, which Pipeline™ Vantage Embolization Device with Shield Technology™ diameter do I choose?
A Choose a Pipeline™ Vantage Embolization Device with Shield Technology™ that matches larger (typically proximal) vessel diameter to ensure proper anchoring.

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Symbol Glossary

STERILE EO	Sterilized using ethylene oxide		Non-pyrogenic
	Single sterile barrier system		Keep away from sunlight
	Do not re-use		Keep dry
Rx ONLY	Caution: Federal (USA) law restricts this device to sale by or on the order of a physician	REF	Catalogue number
	Do not resterilize		Manufacturer
 www.medtronic.com/manuals	Consult electronic instructions for use		Use-by date
	Caution	LOT	Batch code
	Do not use if package is damaged and consult instructions for use	CONTENTS	Contents of Package
MR	MR Conditional	MD	Medical device

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