SUMMARY OF SAFETY AND PROBABLE BENEFIT (SSPB)

I. GENERAL INFORMATION

Device Generic Name: Temporary Percutaneous Transluminal Cerebral Artery Dilatation Device

Device Trade Name: NeVa VS

Device Procode: QTK

Applicant's Name and Address: Vesalio
2305 Historic Decatur Road, Suite 100
San Diego, California 92106

Date(s) of Panel Recommendation: None

Humanitarian Device Exemption (HDE) Number: H210004

Humanitarian Use Device (HUD) Designation Number: HUD #17-0390

Date of HUD Designation: February 27, 2018

Date of Notice of Approval to Applicant: September 9, 2022

II. INDICATIONS FOR USE

The NeVa VS is indicated for use as an adjunct treatment for symptomatic cerebral vasospasm in the internal carotid artery (ICA), middle cerebral artery (MCA), anterior cerebral artery (ACA), posterior cerebral artery (PCA), or basilar artery caused by aneurysmal subarachnoid hemorrhage in adults 22 years of age or older who have exhausted maximal medical treatment and have had the intracranial aneurysm secured by either surgical or endovascular intervention. Symptomatic cerebral vasospasm is defined as more than 50% narrowing of the indicated cerebral vessels confirmed by angiographic imaging and a decreased level of consciousness or a focal neurological deficit.

The indication for use statement has been modified from that granted for the HUD designation. The HUD designation was for “treatment of aneurysmal subarachnoid hemorrhage patients who experience symptomatic cerebral vasospasm despite maximal medical management.” It was modified for the HDE approval because the revised indications for use (IFU) statement more clearly identifies the patient population in which the safety and probable benefit of the device is supported by the available clinical data. The patient population in the modified IFU falls within the patient population granted by the HUD designation.

III. CONTRAINDICATIONS

The NeVa VS is contraindicated for use in patients with:

- An unsecured, ruptured intracranial aneurysm.
- An allergy to the NeVa VS components (nickel).
- Suspected or known allergies to contrast media.
- Pregnancy.
- Excessive vessel tortuosity that prevents the placement of the device.
- Known hemorrhagic diathesis, coagulation factor deficiency or oral anticoagulant therapy with international normalized ratio (INR) >1.7.
- Baseline platelets < 30,000.
- Evidence of rapidly improving neurological signs of stroke.
- Large territory completed cerebral infarction, edema with mass effect and intra-parenchymal hemorrhage in vascular territory to be treated.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the NeVa VS labeling.

V. DEVICE DESCRIPTION

The NeVa VS is a temporary use, self-expanding, nitinol, stent-like, percutaneously introduced transluminal cerebral artery dilatation device (see Figures 1 and 2). It includes a nitinol push wire that is delivered through a commercially available microcatheter with a minimum internal diameter of 0.021 inches. When deployed at the target treatment area, the tip of the NeVa VS, which was compressed in the microcatheter, expands into its original shape in the artery and applies expansive radial forces to the wall of the artery to dilate the target vessel. The NeVa VS can be deployed in the M1 and M2 branches of the middle cerebral artery (MCA), intracranial internal carotid artery (ICA), basilar artery, anterior cerebral artery (ACA), and the P1 posterior cerebral artery (PCA). The sizing guidelines are summarized in Table 1. The device is provided sterile and is intended for single-use only.

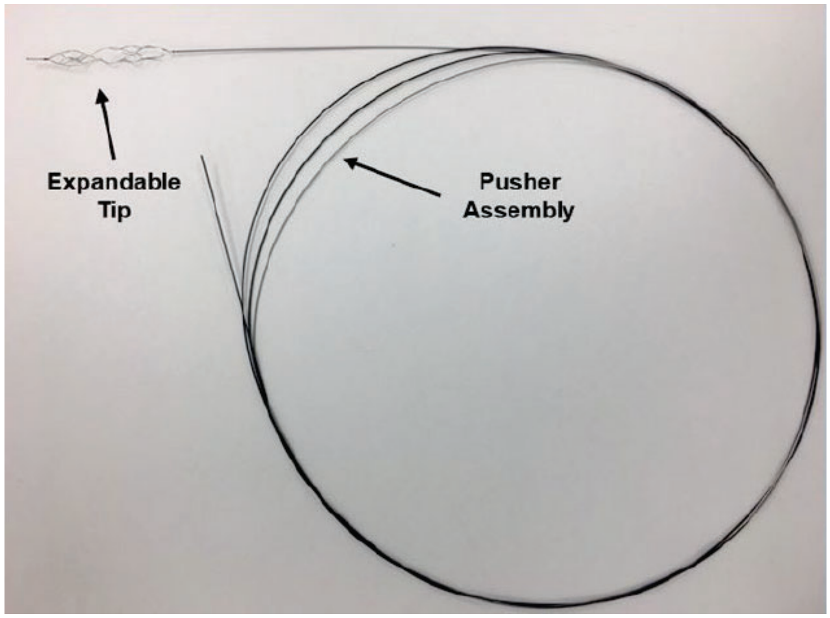

Figure 1: NeVa VS Device

Figure 2: NeVa VS Expandable Tip

Table 1: NeVa VS System Sizing Guidelines

Product Name	Labeled Device Diameter (mm)	Labeled Device Length (mm)	Self Expanded Device Diameter (mm)	Recommended Pre-vasospasm Vessel Diameter (mm)	Pusher Length
NeVa VS	4.0	22	4.0	≥ 2.0 and ≤ 4.0	180 cm

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Conventional procedures used in the treatment of symptomatic cerebral vasospasm caused by aneurysmal subarachnoid hemorrhage (aSAH) include oral nimodipine. Based on clinical guidelines (Connoly et al. *Stroke* 2012), other procedures that physicians may employ in patients experiencing symptomatic cerebral vasospasm caused by aSAH who have exhausted maximal medical treatment may include use of intra-arterial vasodilators or angioplasty balloon catheters, although these therapies are not specifically labeled for this patient population.

The CoAxia NeuroFlo Catheter was previously approved under HDE H030005 for the treatment of cerebral ischemia resulting from symptomatic vasospasm following aSAH, secured by either surgical or endovascular intervention for patients who have failed maximal medical treatment. The NeuroFlo Catheter includes different technology than the NeVa VS. The NeuroFlo Catheter is a balloon catheter placed in the descending aorta. The NeuroFlo Catheter is designed to partially obstruct the abdominal descending aorta thereby potentially increasing blood flow to the brain.

VII. MARKETING HISTORY

The NeVa VS is approved for marketing in the following countries: Argentina, Armenia, Austria, Bahrain, Belgium, Bosnia-Herzegovenia, Bulgaria, Chile, Colombia, Croatia, Czech Republic, Denmark, Ecuador, Estonia, Finland, Germany, Greece, Hungary, Iceland, Ireland, Israel, Italy, Jordan, Kazakhstan, Latvia, Lithuania, Luxembourg, Macedonia, Moldova, Netherlands, Norway, Qatar, Panama, Paraguay, Poland, Portugal, Romania, Russia, Saudi Arabia, Serbia, Singapore, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey, United Arab Emirates, United Kingdom, and Vietnam.

The NeVa VS has not been withdrawn from marketing for any reason relating to the safety and probable benefit of the device.

VIII. PROBABLE ADVERSE EFFECTS OF THE DEVICE ON HEALTH

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

- Vessel perforation or dissection
- Air embolism
- Subarachnoid or interventricular hemorrhage due to vessel perforation
- Vascular spasm or vascular occlusion
- Neurologic deterioration
- Distal embolization including to a previously uninvolved territory
- Pseudoaneurysm formation
- Device(s) deformation, collapse, fracture or malfunction
- Displacement of coils or clips used to secure an intracranial aneurysm
- Intraprocedural thrombotic events
- Cerebral ischemia
- Coagulopathy
- Confusion
- Death
- Embolic stroke
- Hematoma, pain, infection at access site
- Intracerebral or intracranial hemorrhage
- Post-procedure bleeding
- Renal failure
- Vessel thrombosis
- Complications of radiation exposure, such as alopecia, burns ranging in severity from skin reddening to ulcers, cataracts, and delayed neoplasia

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

IX. SUMMARY OF NON-CLINICAL STUDIES

A. Laboratory Studies

The objectives of the laboratory studies were to conduct design verification and validation of the NeVa VS, evaluate the biocompatibility, and validate the shelf-life and sterilization of the final, finished device.

Design Verification and Validation Testing

The devices used for testing were assembled and packaged in a controlled environment and subjected to sterilization. Table 2 below summarizes the design verification and validation testing conducted on the NeVA VS.

Table 2: Design Verification and Validation Testing of NeVa VS

Test	Method	Results/ Conclusions
Physical and Dimensional Inspection	Verify that all physical and dimensional attributes meet design specifications.	PASS
Tensile Strength	Verify that the critical locations of the device meet tensile strength requirements.	PASS
A_f Temperature	Tha A_f temperature should be within the existing A_f temperature specification.	PASS
Radial Forces	Compare the expansive radial forces for the device to that of commercially available neurovascular stent-retrievers and verify that compressive radial forces meet design specifications.	PASS
Torque Strength	Verify that the device can withstand the pre-specified number of rotations in a tortuous anatomical model without failure.	PASS
Delivery	Demonstrate the ease of delivery and deployment in an anatomical model.	PASS
Retrieval	Demonstrate in an anatomical model that the device can be retrieved into a guiding catheter without damage and smoothly.	PASS
Multiple Re-sheathing Durability	Establish that the device is able to withstand the pre-specified number of sequential cycles of deployment and withdrawal without failure in a tortuous anatomical model.	PASS
Kink Resistance	Verify that the device is resistant to kinking around bends with radii representative of the neurovasculature.	PASS

Tip Deflection	Verify the tip deflection force of the distal marker coil of the device is equal or less than that of the comparator device.	PASS
Radiopacity	Verify that radiopaque markers are visible using standard fluoroscopic equipment.	PASS
Corrosion Resistance	Establish that metallic components of the device show no sign of corrosion after conditioning.	PASS
Particulate Testing	Evaluate the device particulate generation under simulated use in a tortuous anatomical model with comparison to a control device.	PASS
Physician Usability Testing	Demonstrate that the device scores a usability score above the minimum requirement when evaluated by physicians in a simulated use model.	PASS

Biocompatibility

The NeVa VS is an externally communicating device in direct contact with circulating blood with a limited duration of contact of ≤ 24 hours. All patient contacting components of the NeVa VS were tested to evaluate the materials for biocompatibility and toxicity in accordance with ISO 10993-1 and the FDA guidance document, "Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"." Table 3 summarizes the biocompatibility tests conducted for the NeVa VS.

Table 3: Biocompatibility Testing of NeVa VS

Test	Method	Results / Conclusions
Cytotoxicity	Minimum Essential Medium (MEM) Elution Assay with L-929 Cells (ISO 10993-5)	Non-cytotoxic
Sensitization	Guinea Pig Maximization Test (ISO 10993-10)	Non-sensitizing
Intracutaneous Reactivity	Intracutaneous Reactivity Test (ISO10993-10)	Non-irritating
Acute Systemic Toxicity	Acute Systemic Injection Test (ISO 10993-11)	Non-toxic
Material-mediated Pyrogenicity	Rabbit Pyrogen Test (Material Mediated) (ISO 10993-11)	Non-pyrogenic
Hemocompatibility	ASTM Hemolysis Assay - Direct Contact and Extract Method (ASTM F756/ISO 10993-4)	Non-hemolytic
	SC5b-9 Complement Activation Assay (ISO 10993-4)	Not an activator of the complement system
	Partial Thromboplastin Time (PTT) – Direct Contact (ISO 10993-4/ASTM F2382)	Does not have effect on coagulation compared to controls

	Beta Thromboglobulin Activation – Direct Contact (ISO 10993-4)	Does not induce platelet activation
	In Vitro Hemocompatibility Assay for Coagulation and Hematology (ISO 10993-4)	Does not have an effect on tested hematological parameters

Shelf-Life Testing

NeVa VS test samples were subjected to real-time aging for 2 years in addition to sterilization and distribution conditioning. The devices were tested for compliance to the device specifications including package integrity, product visual inspection, product dimensional testing, simulated use, tensile testing, torque strength, and particulate testing. All test samples met the acceptance criteria supporting a 2-year shelf-life for the NeVa VS.

Sterilization

The NeVa VS is sterilized using gamma radiation. The sterilization cycle was validated to a sterility assurance level (SAL) of 10^{-6} per ISO 11137-1:2006/(R)2010, "Sterilization of Healthcare Products - Radiation – Part 1: Requirements for Development, Validation, and Routine Control of a Sterilization Process for Medical Devices," and ISO 11137-2:2013, "Sterilization of Healthcare Products - Radiation - Part 2: Establishing the Sterilization Dose." The NeVa VS was tested for bacterial endotoxins and met the specified endotoxin specification of < 2.15 endotoxin units per device for devices with potential contact with cerebrospinal fluid (CSF).

B. Animal Studies

The objectives of the animal studies were to evaluate the safety and usability of the NeVa VS in an *in vivo* porcine model. Two Good Laboratory Practice (GLP) animal studies were completed.

NeVa GLP-1:
The first GLP animal study (referred to as NeVa GLP-1) was performed to evaluate the acute safety and usability of the device. In NeVa GLP-1, no complications were noted during insertion, deployment, or retraction of the device. During gross necroscopy, no vessel perforation or dissection was observed, none of the abdominal or thoracic organs were negatively affected by the procedure, and no obvious signs of hemorrhage were noted. All attributes evaluated for usability were scored similarly or better than existing neurovascular devices. No downstream tissue effects were observed via histology. In addition, minor and superficial vascular injury was similar to what is commonly seen in intra-arterial procedures and in previously published work for similar neurovascular devices.

NeVa GLP-2:

The second GLP animal study (referred to as NeVa GLP-2) was performed to specifically evaluate the safety and performance of the NeVa VS. The NeVa VS was compared to two (2) control devices used for vasodilation procedures. Both acute and chronic (30 day) assessments were performed to compare the safety and performance of the NeVa VS to the control devices.

There were no complications noted during insertion, deployment, or retraction of any of the test or control articles deployed. A total of 54 deployments with the NeVa VS test article were performed evenly over 9 arteries (across 3 animals). All attributes evaluated for usability were ranked for the NeVa VS to be similar or better than the control devices. No observations related to the device use (test or control) were made during gross necropsy.

No risk to animal health was observed during the in-life portion of the study. Histological findings did not reveal any significant downstream tissue effects. Observations from the pathological evaluation demonstrated the NeVa VS had similar scores to control devices that consisted of minor and superficial injuries to treated vessels. Based on the results of the study, the deployment of the NeVa VS appears to be safe with no evidence of downstream effects and successfully met the *in vivo* safety and usability criteria for the device.

X. SUMMARY OF CLINICAL INFORMATION

Study Design

Vesalio performed a 30-subject single-arm observational clinical study, "The Vesalio NeVa VS for the Treatment of Symptomatic Cerebral Vasospasm Following Aneurysmal Subarachnoid Hemorrhage (aSAH) Study (VITAL)," to determine the safety and probable benefit of the NeVa VS as an adjunct treatment for symptomatic cerebral vasospasm caused by aSAH in adults 22 years of age or older who have exhausted maximal medical treatment and have had the intracranial aneurysm secured by either surgical or endovascular intervention. The VITAL study was conducted in the United States (U.S.) under Investigational Device Exemption (IDE) G180094. The VITAL study was an open-label, single-arm, multi-center, observational study with 30-day follow-up conducted at 10 sites in the U.S.

A total of 30 subjects were treated from nine institutions in the U.S. Twenty-seven (27) subjects were treated once, two (2) subjects were treated twice, and a single subject was treated on three (3) separate occasions, for a total of 34 procedures in 30 study subjects. Twenty (20) of the 30 subjects presented with symptomatic cerebral vasospasm (66.7%) and the remaining 10 subjects' cerebral vasospasm was identified initially on transcranial Doppler (33.3%) and no clinical exam were conducted on these 10 subjects because Vesalio noted that most of these subjects had clinical presentations where assessment of symptomatic cerebral vasospasm may have been challenging, such as modified Rankin Scale (mRS) scores greater than 4.

On Day 0, eligible patients with confirmed symptomatic cerebral vasospasm (> 50% stenosis in the target vessel demonstrated by digital subtraction angiography (DSA) or computed tomograpy angiography (CTA)) were treated with the NeVa VS. The National Institutes of Health Stroke Scale (NIHSS) scores were obtained at 24-hours and 21 days post-intervention, and mRS scores were obtained at 21 days and 30 days post-intervention. If symptomatic cerebral vasospasm recurred in a previously treated or in a different vessel, re-treatment with the NeVa VS was allowed if the subject still met all study eligibility criteria.

The primary study outcomes were safety and procedural success defined as the proportion of vessels with ≥ 50% vessel caliber on DSA compared to the baseline vessel diameter prior to the symptomatic cerebral vasospasm. The imaging data were assessed by an independent Core Laboratory ("Core Lab"). The performance goal for the primary probable benefit outcome was specified by Vesalio as at least 25% for the lower limit of the 95% confidence interval (CI).

There were 76 patients consented for the VITAL study between January 31, 2019, and February 12, 2021, and 46 of these patients (60.5%) were screen failures primarily because these patients were not considered to have symptomatic cerebral vasospasm that warranted intervention with the NeVa VS. The remaining 30 patients were treated with the NeVa VS and all of these patients were included in the analysis population used to analyze the outcomes of the VITAL study.

Study Selection Criteria

Enrollment in the VITAL study was limited to patients who met all of the following inclusion criteria:

- Age ≥ 18 years.
- Subarachnoid hemorrhage secondary to ruptured intracranial aneurysm.
- Ruptured intracranial aneurysm secured with surgical clipping or endovascular intervention.
- DSA or CT angiography at the time of aSAH clinical presentation or aSAH intervention with well-visualized intra-cerebral vessels available for review.
- Vasospasm in one or more of the following: the internal carotid artery (ICA), basilar, middle cerebral artery (MCA), anterior cerebral artery (ACA), or posterior cerebral artery (PCA) territory on transcranial Doppler (TCD), and/or CT angiography, and/or clinical signs of symptomatic cerebral vasospasm (change in level of consciousness, focal neurological deficit) confirmed by > 50% narrowing in these territories on DSA.
- Vasospasm despite maximized medical management defined as oral nimodipine (unless contraindicated), systemic hypertension with systolic blood pressure greater than 130 mmHg and euvolemia.
- Target vessel pre-vasospasm diameter ≥ 2.0 mm and ≤ 4.0 mm.
- Patient or legal representative able and willing to give informed consent.

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

- The presence of an unsecured ruptured intracranial aneurysm. *Note unsecured unruptured intracranial aneurysms remote to the site of treated aSAH were not exclusionary.*
- Symptoms attributable to other causes (e.g., hydrocephalus, metabolic, infection).
- Hunt and Hess Grade of 5.
- Large infarct on CT scan defined as Alberta Stroke Program Early Computed Tomography Score (ASPECTS) 0-5.
- Intracranial hemorrhage not caused by intracranial aneurysm rupture.
- History of bleeding disorders.
- Baseline platelets < 30,000.
- International normalized ratio (INR) > 1.7.
- Any known contraindications to mechanical dilation of vasospastic vessels including but not limited to:
    - Excessive vessel tortuosity preventing the placement of the device,
    - Evidence of rapidly improving neurological signs of stroke,
    - Large territory completed cerebral infarction, edema with mass effect and intra-parenchymal hemorrhage in vascular territory to be treated, or
    - Any other vascular anatomic variants or anomalies.
- Pre-existing neurological or psychiatric disease that would confound the neurological or functional evaluations, e.g., dementia with prescribed anticholinesterase inhibitor.
- History of severe allergy to contrast medium.
- Known allergy to NeVa VS materials (nitinol, stainless steel).
- Suspected or confirmed septic embolus, or bacterial endocarditis.
- Septic shock or central nervous system infection confirmed via CSF sampling.
- Known current or recent use of illicit drugs or alcohol abuse.
- Females who were pregnant or breastfeeding.
- Any other condition that, in the opinion of the investigator, precluded an endovascular procedure or posed a significant hazard to the patient if an endovascular procedure was performed.

Demographic Data

Demographics of the VITAL study patients are summarized in Table 4 below.

Table 4. Demographics

Parameter		**N = 30**
Age (Years)	N	30
	Mean	51.8
	Minimum	31
	Maximum	74
	< 60	22/30 (73.3%)
	≥ 60	8/30 (26.7%)

Gender	Male	4/30 (13.3%)
	Female	26/30 (86.7%)
Race	White	24/30 (80.0%)
	Black	2/30 (6.7%)
	Asian	1/30 (3.3%)
	Native Hawaiian or Pacific Islander	0/30 (0.0%)
	Other*	3/30 (10.0)
Ethnicity	Hispanic or Latino	9/30 (30.0%)
	Not Hispanic or Latino	20/30 (66.7%)
	Missing	1/30 (3.3%)

* 1 Multiracial and 2 Unknown

Baseline characteristics for the 30 patients treated with the NeVa VS are summarized in Table 5 below.

Table 5. Baseline Characteristics

Parameter		N=30
Treatment of aSAH	Surgical clipping	2/30 (6.7%)
	Endovascular intervention	28/30 (93.3%)
Presentation of Cerebral Vasospasm	TCD	10/30 (33.3%)
	Symptomatic	20/30 (66.67%)
Modified Fisher Scale Score (at aSAH)	Mean	3.2
	Standard Deviation	1.0
	Median	3.5
	Minimum	1
	Maximum	4
Modified Hunt-Hess Grading System Score (at aSAH)	Mean	3.1
	Standard Deviation	0.9
	Median	3.0
	Minimum	1
	Maximum	4
NIHSS at Screening	Mean	12.7
	Standard Deviation	12.8
	Median	7.5
	Minimum	0
	Maximum	40
mRS at Screening	Mean	3.5
	Standard Deviation	1.5
	Median	4.0
	Minimum	0
	Maximum	5
Pre-hospitilization mRS	Mean	0.0
	Standard Deviation	0.2
	Median	0.0

	Minimum	0
	Maximum	1
ASPECTS	Mean	8.5
	Standard Deviation	1.5
	Median	9.0
	Minimum	6
	Maximum	10

Clinical Data Analysis and Results

The VITAL study data was analyzed using descriptive statistics due to the small sample size (N=30). All of the observed adverse events (AEs) recorded in the VITAL study are shown in Table 6. All serious adverse events (SAEs) are shown in Table 7.

Table 6: Adverse Events

Adverse Events	**34 Procedures in 30 Subjects**	
	Number of Reports	**Number (Percent) of Subjects with Event**
Adverse Events ≤ 24 Hours Post NeVa VS Intervention	**17**	**12 (40.0%)**
Intraprocedural thrombotic event	3	3 (10.0%)
Anemia	2	2 (6.7%)
Cerebral infarct	1	1 (3.3%)
Cerebral infarct secondary to vasospasm	1	1 (3.3%)
Desaturation	1	1 (3.3%)
Diarrhea	1	1 (3.3%)
Hypernatremia	1	1 (3.3%)
Hypotension	1	1 (3.3%)
Pseudoaneurysm of the contralateral femoral artery	1	1 (3.3%)
Retrocardiac atelectasis	1	1 (3.3%)
Ruptured vessel due to balloon angioplasty	1	1 (3.3%)
Syndrome of inappropriate ADH production	1	1 (3.3%)
Ventricular tachycardia	1	1 (3.3%)
Worsening cardiomyopathy	1	1 (3.3%)
Adverse Events > 24 Hours Post NeVa VS Intervention	**77**	**22 (73.3%)**
Urinary tract infection	8	8 (26.7%)
Anemia	6	6 (20.0%)
Deep vein thrombosis	6	5 (16.7%)
Cerebral salt wasting syndrome	5	5 (16.7%)
Pneumonia	5	5 (16.7%)
Diarrhea	4	4 (13.3%)
Cerebral infarct secondary to vasospasm	3	3 (10.0%)
Tachycardia	3	3 (10.0%)

Anxiety	2	2 (6.7%)
Hyponatremia	2	2 (6.7%)
Thrush	2	2 (6.7%)
Tooth abscess	2	2 (6.7%)
Amnesia	1	1 (3.3%)
Aspiration pneumonia	1	1 (3.3%)
Atrial fibrillation	1	1 (3.3%)
Bacteremia	1	1 (3.3%)
Cellulitis	1	1 (3.3%)
Cerebral hemorrhage secondary to right ventriculostomy catheter removal	1	1 (3.3%)
Cerebral infarct	1	1 (3.3%)
Cervical, thoracic, and lumbar pain	1	1 (3.3%)
Cranial tissue flap infection	1	1 (3.3%)
Decubitus ulcer	1	1 (3.3%)
Epistaxis	1	1 (3.3%)
Fall	1	1 (3.3%)
Glossitis	1	1 (3.3%)
Hepatitis	1	1 (3.3%)
Hypernatremia	1	1 (3.3%)
Hypokalemia	1	1 (3.3%)
Pneumoperitoneum	1	1 (3.3%)
Pseudoaneurysm of the brachial artery	1	1 (3.3%)
Recurrent SAH	1	1 (3.3%)
Renal failure	1	1 (3.3%)
Ruptured vessel due to balloon angioplasty	1	1 (3.3%)
Seizure	1	1 (3.3%)
Sepsis	1	1 (3.3%)
Thrombocytopenia	1	1 (3.3%)
Transient ischemia of finger tip	1	1 (3.3%)
Ventricular tachycardia	1	1 (3.3%)
Worsening ascites	1	1 (3.3%)
Worsening cerebral edema	1	1 (3.3%)
Worsening hydrocephalus	1	1 (3.3%)
Total	**94**	**25 (83.3%)**

Table 7. Serious Adverse Events

Adverse Events	**34 Procedures in 30 Subjects**	
	Number of Reports	**Number (Percent) of Subjects with Event**
Adverse Events ≤ 24 Hours Post NeVa VS Intervention	**7**	**7 (23.3%)**
Intraprocedural thrombotic event	2	2 (6.7%)
Cerebral infarct	1	1 (3.3%)

Cerebral infarct secondary to vasospasm	1	1 (3.3%)
Pseudoaneurysm of the contralateral femoral artery	1	1 (3.3%)
Ruptured vessel due to balloon angioplasty	1	1 (3.3%)
Worsening cardiomyopathy	1	1 (3.3%)
Adverse Events > 24 Hours Post NeVa VS Intervention	**20**	**11 (36.7%)**
Anemia	3	3 (10.0%)
Cerebral infarct secondary to vasospasm	3	3 (10.0%)
Aspiration pneumonia	1	1 (3.3%)
Atrial fibrillation	1	1 (3.3%)
Bacteremia	1	1 (3.3%)
Cerebral hemorrhage secondary to right ventriculostomy catheter removal	1	1 (3.3%)
Cerebral infarct	1	1 (3.3%)
Fall	1	1 (3.3%)
Pneumonia	1	1 (3.3%)
Pseudoaneurysm of the brachial artery	1	1 (3.3%)
Recurrent SAH	1	1 (3.3%)
Ruptured vessel due to balloon angioplasty	1	1 (3.3%)
Sepsis	1	1 (3.3%)
Ventricular tachycardia	1	1 (3.3%)
Worsening ascites	1	1 (3.3%)
Worsening hydrocephalus	1	1 (3.3%)
Total	**27**	**17 (56.7%)**

Overall, 94 AEs were reported for 25 patients [83.3% (25/30)], 17 of these AEs presented within 24 hours of the NeVa VS procedure and 77 AEs presented after 24 hours post-procedure. A total of three (3) NeVa VS device-related AEs were reported in three subjects in the trial [10% (3/30)], all of which were intraprocedural thrombotic events. All three (3) of these events were treated during the procedure and were considered resolved at the conclusion of the procedure.

Seven subjects [23.3% (7/30)] died prior to Day 30. All remaining subjects completed the study, with a 76.7% survival rate at Day 30 (n/N = 23/30). One additional subject died after the Day 30 visit, due to cerebral infarct. Of the seven subjects who died prior to Day 30, three subjects presented with cerebral infarct secondary to cerebral vasospasm, one subject presented with a ruptured vessel related to balloon angioplasty, one subject presented with cerebral infarct, one subject presented with cerebral hemorrhage secondary to right ventriculostomy catheter removal, and one subject presented with worsening cardiomyopathy.

The probable benefit outcome assessed the procedural success with the NeVa VS defined as the proportion of treated vessels with ≥ 50% vessel caliber on DSA compared to the baseline vessel diameter prior to the symptomatic cerebral vasospasm. The performance goal specified by Vesalio for this outcome was at least 25% for the lower limit of the

95% CI. According to the Core Lab, procedural success was achieved in 86.5% or 64/74 treated vessels. These data are further summarized in Table 8.

Table 8. Procedural Success of the Proportion of Treated Vessels with ≥ 50% Vessel Caliber on DSA Compared to Baseline as Determined by the Core Lab

Method	Estimation (95% CI)
Vessel-based Procedural Success (N = 74 vessels treated)	
Procedure Success Rate Based on All Vessels Treated	64/74 (86.5%)
95% CI per Binomial Distribution Assuming Treatment Independent	(76.5%, 93.3%)
Subject-based Procedural Success Rate* (N = 30 subjects)	
N	30
Mean	92.2%
95% CI	(85.5%, 99.0%)
Median	100.0%
Min, Max	40.0%, 100.0%

* For each subject, the percentage of treated vessels with increase ≥ 50% vessel caliber on DSA compared to baseline was calculated. This resulted in 30 percentages (n=30 subjects). Then, these 30 percentages were used to generate descriptive statistics. The 95% CIs were calculated based on normal distribution.

The probable benefit outcome was also stratified by presentation of cerebral vasospasm, either by a symptomatic presentation or by TCD. These data are presented in Table 9.

Table 9. Procedural Success of the Proportion of Treated Vessels with ≥ 50% Vessel Caliber Compared to Baseline by Presentation of Cerebral Vasospasm as Determined by the Core Lab

Method	Estimation (95% CI)	
	TCD	Symptomatic Presentation
Vessel-based Procedural Success (N = 74 vessels treated)		
Procedure Success Rate Based on All Vessels Treated	16/18 (88.9%)	48/56 (85.7%)
95% CI per Binomial Distribution Assuming Treatment Independent	(65.3%, 98.6%)	(73.8%, 93.6%)
Subject-based Procedural Success Rate* (N = 30 subjects)		
N	10	20
Mean	90.0%	93.3%
95% CI	(74.9%, 100.0%)	(85.4%, 100.0%)
Median	100.0%	100.0%
Min, Max	50.0%, 100.0%	40.0%, 100.0%

* For each subject, the percentage of treated vessels with increase ≥ 50% vessel caliber on DSA compared to baseline was calculated. This resulted in 30 percentages (n=30 subjects). Then, these 30 percentages were used to generate descriptive statistics. The 95% CIs were calculated based on normal distribution.

A summary of the procedural parameters for subjects treated in the VITAL study is described in Table 10 below.

Table 10. Procedural Parameters

		N = 30 Subjects	
		Number	**Percent**
# of NeVa VS Interventions per subject (N = 30)	1	27/30	90.0%
	2	2/30	6.7%
	3	1/30	3.3%
# Vessels Treated per procedure (N = 34 interventions)	Mean	2.3	
	Standard Deviation	1.5	
	Median	2.0	
	Minimum	1	
	Maximum	7	
Vessels Treated (N = 74)	Basilar	4/74	5.4%
	Left ACA	5/74	6.8%
	Left ICA	6/74	8.1%
	Left MCA	17/74	23.0%
	Left Vertebral*	1/74	1.4%
	Right ACA	3/74	4.1%
	Right ICA	10/74	13.5%
	Right MCA	26/74	35.1%
	Right PCA	2/74	2.7%
Percent Stenosis at Baseline per Investigator's Assessment per vessel treated (N = 74)	Mean	65.59	
	Standard Deviation	9.77	
	Median	64.00	
	Minimum	51.0	
	Maximum	95.0	
# of Deployments per Vessel per vessel treated (N = 74) (Total # of deployments = 95)	Mean	1.28	
	Standard Deviation	0.61	
	Median	1.00	
	Minimum	1.0	
	Maximum	3.0	
Duration of Total Deployment Time (min) per vessel treated (N = 74)	Mean	5.45	
	Standard Deviation	2.24	
	Median	5.00	
	Minimum	0.25	
	Maximum	11.00	
Concomitant Procedures and Treatments Performed per procedure (N = 34)	Yes	34/34	100%
	No	0/34	0%
Device Performance – Performed as Intended per procedure (N = 34)	Yes	27/34	79.4%
	No	7/34	20.6%
Procedure Had Complications	Yes	5/34	14.7%

per procedure (N = 34)	No	29/34	85.3%

*There was only one (1) vertebral artery treated that was a protocol violation because this was not a location specified in the inclusion criteria. Also, with a sample size of one, no statistical or clinical conclusions can be made. Therefore, this vessel was excluded from final indications for use of the NeVa VS.

Seven procedures in six subjects included events where the device did not perform as intended. Two events in two subjects included thrombus formation; two events in one subject included difficulty to deploy and retrieve the NeVa VS and poor angiography vessel caliber improvement; two events in two subjects included failure to expand the vessel; and one event in one subject included difficulty to recapture the NeVa VS.

Five subjects experienced complications during the procedure, which included intraprocedural thrombotic event in three subjects; pseudoaneurysm of the contralateral femoral artery in one subject; worsening cardiomyopathy in one subject; and ruptured vessel due to balloon angioplasty in one subject. One of the five subjects experienced multiple complications (intraprocedural thrombotic event and vessel rupture due to balloon angioplasty).

Pediatric Extrapolation

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

XI. FINANCIAL DISCLOSURE

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 11 investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XII. SAFETY AND PROBABLE BENEFIT ANALYSIS

A. Probable Benefit Conclusions

The 30-subject observational single-arm VITAL study demonstrated that 64 of 74 treated vessels in 30 subjects achieved procedural success defined by the proportion of treated vessels with increase of ≥ 50% vessel diameter from baseline prior to the cerebral vasospasm as determined by the Core Lab. The subject based procedural success rate (N=30 subjects) was a mean of 92.2% with a 95% confidence interval of 85.5% to 99.0%. Of the 20 subjects enrolled based on symptomatic cerebral vasospasm presentation, sixteen were alive at Day 30 (80%, 16/20). There is uncertainty in the results because there was no concurrent control or blinding of evaluators, subjects, or investigators. The effects of concomitant treatment are possible significant confounders. Because of the study design, the clinical significance of the change in vessel diameter is not accompanied by evidence of improvement in patient survival or function.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and animal studies as well as data collected in the VITAL clinical study conducted to support HDE approval as described above. In Table 6, which reports all adverse events from the VITAL study, the most common adverse events within 24 hours of the procedure were intraprocedural thrombotic event [10.0% (3/30)] and anemia [6.7% (2/30)]. The most common adverse events > 24 hours post-procedure were urinary tract infection [26.7% (8/30)], anemia [20.0% (6/30)], deep vein thrombosis [16.7% (5/30)], cerebral salt washing syndrome [16.7% (5/30)], pneumonia [16.7% (5/30)], diarrhea [13.3% (4/30)], cerebral infarct secondary to vasospasm [10.0% (3/30)], and tachycardia [10.0% (3/30)]. A total of three (3) NeVa VS device-related adverse events were reported in the trial, all of which were intraprocedural thrombotic events. All three (3) of these events were treated during the procedure and were considered resolved at the conclusion of the procedure. Seven subjects died prior to Day 30 and one subject died after the Day 30 visit, resulting in a total known mortality rate of 26.7% (n/N = 8/30).

C. Probable Benefit-Risk Conclusions

The probable benefits of the device are also based on data collected in the VITAL clinical study conducted to support HDE approval as described above. The VITAL study demonstrated that 64 of 74 treated vessels in 30 treated subjects achieved procedural success defined by the proportion of treated vessels with increase of ≥ 50% vessel diameter from baseline prior to the symptomatic cerebral vasospasm as determined by the Core Lab. The subject based procedural success rate (N=30 subjects) was a mean of 92.2% with a 95% confidence interval of 85.5% to 99.0%.

The probable risks of the device are also based on data collected in the VITAL clinical study conducted to support HDE approval as described above. A total of three (3) NeVa VS device-related adverse events were reported in the trial, all of which were intraprocedural thrombotic events. All three (3) of these events were treated during the procedure and were considered resolved at the conclusion of the procedure. Seven subjects died prior to Day 30 and one subject died after the Day 30 visit, resulting in a total known mortality rate of 26.7% (n/N = 8/30).

Additional factors to be considered in determining probable risks and benefits for the NeVa VS device included weighing the uncertainty in the clinical study data in that it was a single arm study which limits the ability to draw direct comparisons to alternative therapies, the study was not statistically powered for hypothesis testing of the safety and probable benefit outcomes, the mRS was not conducted by a blinded assessor which may introduce bias in the assessment. In addition, out of the 30 patients, 10 patients were selected based on TCD, which is not the usual care for determining whether a patient may be suspected of having symptomatic cerebral vasospasm. In the VITAL study, 20 of the 30 patients were confirmed to have symptomatic cerebral vasospasm based on both clinical signs of deterioration, such as changes in level of consciousness or focal neurological deficit, and angiographic imaging. As long as patients are appropriately confirmed to have symptomatic cerebral vasospasm determined by both a clinical exam and angiographic imaging, the uncertainty introduced by these limitations is considered to be acceptable given the severity of the underlying condition and the ability of the device to address an unmet need in which alternative therapeutic devices are not currently legally marketed for the indicated patient population or the patient has exhausted all maximal medical treatment. Delayed cerebral ischemia associated with symptomatic cerebral vasospasm remains a major cause of death and disability in patients with aSAH (Connolly et al. *Stroke* 2012).

1. Patient Perspective

   This submission either did not include specific information on patient perspectives or the information did not serve as part of the basis of the decision to approve or deny the HDE for this device.

In conclusion, given the available information above and the orphan patient population limited for use with this device, the data support that for the indication for use as an adjunct treatment for symptomatic cerebral vasospasm in the internal carotid artery (ICA), middle cerebral artery (MCA), anterior cerebral artery (ACA), posterior cerebral artery (PCA), or basilar artery caused by aneurysmal subarachnoid hemorrhage in adults 22 years of age or older who have exhausted maximal medical treatment and have had the intracranial aneurysm secured by either surgical or endovascular intervention, and with symptomatic cerebral vasospasm defined as more than 50% narrowing of the indicated cerebral vessels confirmed by angiographic imaging and a decreased level of consciousness or a focal neurological deficit, the probable benefits outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and probable benefit of this device when used in accordance with the indications for use and the orphan patient population designated by the HUD. The NeVa VS device demonstrated dilation of the cerebral artery in aSAH patients exhibiting symptomatic cerebral vasospasm who have exhausted maximal medical treatment and have had the intracranial aneurysm secured by either surgical or endovascular intervention. After exhausting maximal medical treatment, there are limited therapeutic options to treat persistent symptomatic cerebral vasospasm in this patient population.

Therefore, it is reasonable to conclude that the probable benefit to health from using the device in the target orphan patient population outweighs the risk of illness or injury, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment when used as indicated in accordance with the directions for use.

XIII. PANEL RECOMMENDATION

This HDE was not taken to a meeting of the Neurological Devices Panel of the Medical Devices Advisory Committee because this HDE does not raise unanticipated safety issues. Therefore, it was determined that this application does not need to be submitted to the advisory panel.

XIV. CDRH DECISION

CDRH has determined that, based on the data submitted in the HDE, the NeVa VS will not expose patients to an unreasonable or significant risk of illness or injury and the probable benefit to health from using the device outweighs the risks of illness or injury. CDRH issued an approval order on September 9, 2022.

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

XV. APPROVAL SPECIFICATIONS

Directions for use: See the device labeling.

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

Post-approval Requirements and Restrictions: See approval order.

XVI. REFERENCES

Connolly Jr., E. et al. "Guidelines for the Management of Aneurysmal Subarachnoid Hemorrhage." Stroke 2012; 43:1711–1737.