DE NOVO CLASSIFICATION REQUEST FOR TREVO PROVUE AND XP PROVUE RETRIEVERS

REGULATORY INFORMATION

FDA identifies this generic type of device as:

> **Neurovascular Mechanical Thrombectomy Device for Acute Ischemic Stroke Treatment.** A neurovascular mechanical thrombectomy device for acute ischemic stroke treatment is a prescription device used in the treatment of acute ischemic stroke to improve clinical outcomes. The device is delivered into the neurovasculature with an endovascular approach, mechanically removes thrombus from the body, and restores blood flow in the neurovasculature.

NEW REGULATION NUMBER: 21 CFR 882.5600

CLASSIFICATION: CLASS II

PRODUCT CODE: POL

BACKGROUND

DEVICE NAME: TREVO PROVUE AND XP PROVUE RETRIEVERS ("TREVO RETRIEVERS")

SUBMISSION NUMBER: DEN150049

DATE OF *DE NOVO*: OCTOBER 26, 2015

CONTACT: CONCENTRIC MEDICAL, INC. (A BUSINESS UNIT OF STRYKER NEUROVASCULAR)
301 EAST EVELYN AVENUE
MOUNTAIN VIEW, CALIFORNIA 94041

REQUESTER'S RECOMMENDED CLASSIFICATION: CLASS II

INDICATIONS FOR USE

The Trevo Retrievers are indicated for use to restore blood flow in the neurovasculature by removing thrombus for the treatment of acute ischemic stroke to reduce disability in patients with a persistent, proximal anterior circulation, large vessel occlusion, and smaller core infarcts who have first received intravenous tissue plasminogen activator (IV t-PA). Endovascular therapy with the device should start within 6 hours of symptom onset.

LIMITATIONS

The sale, distribution, and use of the device are restricted to prescription use in accordance with 21 CFR 801.109.

The safety and effectiveness of the Trevo Retrievers in reducing disability has not been established in patients with large core infarcts (i.e., Alberta Stroke Program Early Computed Tomography (CT) score (ASPECTS) ≤ 7). There may be increased risks, such as intracerebral hemorrhage, in these patients.

The safety and effectiveness of the Trevo Retrievers in reducing disability has not been established or evaluated in patients with occlusions in the posterior circulation (e.g., basilar or vertebral arteries) or for more distal occlusions in the anterior circulation.

Administration of IV t-PA should be within the FDA-approved window (within 3 hours of stroke symptom onset).

The safety and effectiveness data supporting the granting of the Neurovascular Mechanical Thrombectomy Device for Acute Ischemic Stroke Treatment is based on use of this device type in conjunction with IV t-PA. At the time of this granting, IV t-PA is approved for treatment of acute ischemic stroke within 3 hours after symptom onset. FDA-approved changes to the drug labeling may have an impact on the safety and effectiveness of the device type.

PLEASE REFER TO THE LABELING FOR A MORE COMPLETE LIST OF WARNINGS AND PRECAUTIONS.

DEVICE DESCRIPTION

The Trevo ProVue and XP ProVue Retrievers consist of a flexible, tapered core wire with a shaped self-expanding section at the distal end for clot capture and removal. Radiopaque platinum wires in the shaped section and radiopaque markers on the distal end allow fluoroscopic visualization. The Trevo Retrievers have a hydrophilic coating to reduce friction during use. A torque device and an insertion tool are provided with the Retrievers. The Trevo Retrievers are delivered to the site of occlusion in the neurovasculature through a microcatheter. The torque device may be used to lock the core wire of the Trevo Retriever to the microcatheter during the procedure, allowing the Trevo Retriever and microcatheter to be retracted as a system through the guide catheter and removed from the body with captured clot.

Figure 1 below includes images of the distal shaped sections of the Trevo ProVue and XP ProVue Retrievers. **Table 1** below includes a summary of the Trevo ProVue and XP ProVue Retriever configurations.

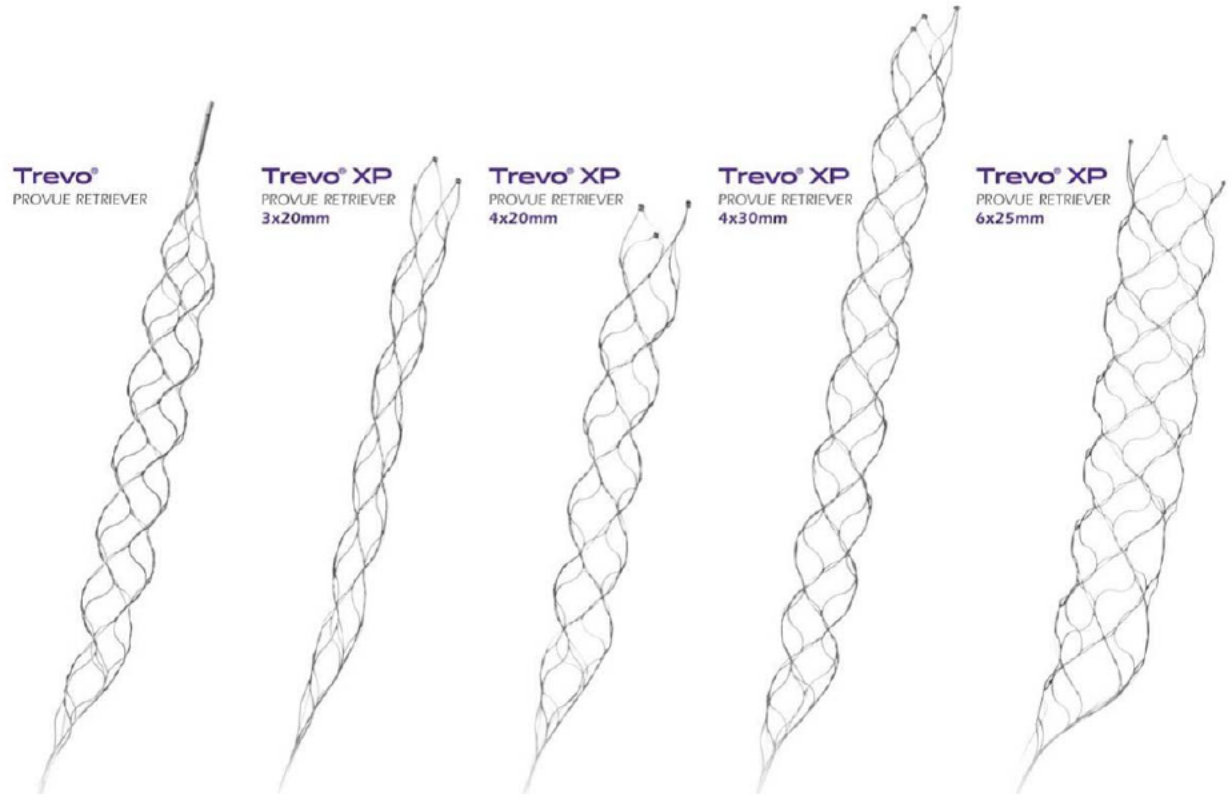

Figure 1: Trevo Retrievers Distal Shaped Section (Trevo ProVue and Trevo XP ProVue)

Table 1: Summary of the Trevo ProVue and XP ProVue Retriever Configurations

Trevo Retriever Size (mm)	Shaped Section Diameter (mm)	Clot Capture Area (mm) (Active Shaped Section Length)	Total Shaped Section Length (mm)	Overall Length (cm)
Trevo ProVue				
4x20	4	20	37	180
Trevo XP ProVue				
3x20	3	20	36	190
4x20	4	20	32	180
4x30	4	30	44	180
6x25	6	25	40	180

SUMMARY OF NONCLINICAL/BENCH STUDIES

Non-clinical bench studies considered in the review of the subject *de novo* submission that were leveraged from information previously evaluated for the Trevo Retrievers in prior submissions for different intended uses (K150616, K143077, K133464, K132641, K122478 and K120961) are summarized in the sections below. The technological characteristics and device design of the Trevo Retrievers for the subject *de novo* are the same as the devices previously cleared in K150616, K143077, K133464, K132641 and K122478.

BIOCOMPATIBILITY/MATERIALS

The Trevo Retrievers come in contact with the patient's circulating blood and are classified as external communicating devices of limited contact duration (< 24 hours). Biocompatibility information was leveraged from information previously provided for the Trevo Retrievers cleared under K120961 because there were no new materials introduced into the finished device and no changes to the manufacturing process. Therefore, per International Standard Organization (ISO) 10993-1:2009/AC:2010 (Biological Evaluation of Medical Devices – Part 1: Evaluation and Testing), biocompatibility tests leveraged for the Trevo Retrievers in the subject *de novo* included hemocompatibility/coagulation, hemocompatibility/hemolysis, cytotoxicity – ISO elution (minimum essential medium (MEM) extract), maximization test for delayed hypersensitivity, intracutaneous (intradermal) reactivity, acute systemic toxicity, and material mediated rabbit pyrogenicity testing.

SHELF LIFE/STERILITY

Sterilization and shelf-life information was leveraged from data in prior submissions of the Trevo Retrievers (K120961, K143077, and K150616). The Trevo Retrievers are provided sterile for single use. The devices are sterilized by ethylene oxide (EO) to achieve a sterility assurance level (SAL) of 10^{-6}. The devices are packaged in a high density polyethylene hoop, placed on a polycarbonate mounting card along with a torque device and insertion tool, and inserted into a Tyvek®/polymylar pouch. The sterilization validation was conducted in accordance with ISO 11135-1:2007 (Sterilization of Health-Care Products - Ethylene Oxide - Requirements for the Development, Validation and Routine Control of a Sterilization Process for Medical Devices). Sterilant residuals were tested per ISO 10993-7:2008 (Biological Evaluation of Medical Devices - Part 7: Ethylene Oxide Sterilization Residuals). In addition, endotoxin testing using the limulus amebocyte lysate (LAL) method was conducted to meet the endotoxin limit of 2.15 Endotoxin Units (EU)/device per United States Pharmacopeia (USP) <161>.

The devices are labeled with a 24 month shelf-life, which is supported by accelerated shelf-life testing (Trevo XP ProVue 3x20, 4x20, 4x30, 6x25) and real-time shelf-life testing (Trevo ProVue 4x20), which includes packaging integrity and component functional performance testing (i.e., dimensional verification, tensile strength, radial force, tip flexibility, torque/tensile durability, retriever platinum wire and joint durability, radiopacity, deliverability, simulated use, coating integrity and particulate testing). Packaging integrity testing included testing to the following standards:

- ASTM D4169:2009 - Standard Practice for Performance Testing of Shipping Containers and Systems
- ASTM F1980:2011 - Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices
- ASTM F1929:2004 - Standard Test Method for Detecting Seal Leaks in Porous Medical Packaging by Dye Penetration
- ASTM F2906:2011 - Standard Test Method for Detecting Gross Leaks in

Packaging by Internal Pressurization (Bubble Test)

- ASTM F88/ F88M:2009 - Standard Test Method for Seal Strength of Flexible Barrier Materials

PERFORMANCE TESTING – BENCH

The Trevo Retrievers were tested and passed the following performance (bench) tests summarized in Table 2 below. This information was leveraged from testing provided in prior submissions for the Trevo Retrievers (K150616, K143077, K133464, K132641, K122478 and K120961).

Table 2: Bench Testing and Test Method Summary

Test	Test Method Summary
Dimensional Verification	Verified dimensions using specified measurement tool.
Retriever Mid Joint Tensile Strength	Identified joint and cut sample for test. Recorded peak tensile force results.
Retriever Tip Tensile Strength	Loaded sample. Recorded peak tensile force results.
Retriever Shaped Section Radial Force	Constrained and released shaped section of retriever to specified diameter. Recorded radial force results.
Retriever/Vessel Interaction (Tip Flexibility)	Loaded sample so that the distal tip was flexed. Recorded peak compression/flex force results.
Retriever Torque Tensile Durability	Gripped device and applied rotations to torque device. Pulled tensile cycles to a max load then last cycle to failure. Recorded results.
Retriever Platinum Wire Joint Strength	Identified joint and cut sample for test. Recorded peak tensile force results for each individual platinum wire.
Retriever Platinum Wire and Joint Durability	Wrapped and unwrapped the entire length of the shaped section of the retriever (sheathed in insertion tool) around a pin and repeat. Performed visual inspection and recorded results. Performed deploy/reload cycles into insertion tool. Performed visual inspection and recorded results.
Radiopacity	Radiopacity was assessed based on visual assessment of the device being used under fluoroscopy.
Retriever/Microcatheter Deliverability	Measured the force to push the device through a tortuous model.
Particulate Evaluation	Measured total number of particulate and size of particulate generated during the simulated delivery, deployment and resheathing of the device. Particulate counting was assessed for ≥ 10µm, ≥ 25µm, and ≥ 50µm size ranges.

Test	Test Method Summary
Coating Integrity Evaluation	A visual assessment of the coating integrity of the subject device was performed before (baseline) and after tracking through a tortuous path fixture representative of clinical conditions (simulated use). The visual assessment evaluation utilized high magnification and a dye to assess the adhesion of the coating. Proximal and distal coating edges were evaluated to determine if the coating was intact. The entire coating length of the device was evaluated for defects (visible voids or scratches).
Simulated Use	Simulated use testing used a silicone neurovascular model cast from actual human neurovascular arteries. This bench testing model replicates the tortuosity, diameter and location of the arteries in the neurovasculature including the internal carotid artery (ICA) siphon. The model ends at the mid carotid arteries and proximal support is provided by a guide catheter. The model incorporates a re-circulating water bath at 37 ºC pressurized between 2 – 2.5 psi (100 – 126 mm Hg) to simulate the human arterial circulation. All testing follows the procedural instructions outlined in the Instructions for Use. Simulated thrombus is used to assess the device's ability to retrieve clot.

PERFORMANCE TESTING – ANIMAL

The Trevo Retrievers were previously evaluated in animal studies to support device safety. These animal studies were previously provided in K120961, K143077 and K150616. Animal studies consisting of an acute animal (swine) study and a chronic animal (swine) study were performed using devices with up to 6 passes in the treated vessels. Safety (vessel response) was assessed based on the presence or absence of arterial transmural dissection or perforation due to device use in the treated vessels based on results of intra-procedural angiography and histopathology. The acute study angiography results revealed no evidence of vessel dissection, perforation, or thrombosis at Day 0. The chronic study angiography results revealed no evidence of dissection, perforation, or thrombosis at Day 0 and no evidence of stenosis, vessel irregularity, intimal flap or pseudoaneurysm at treatment sites at Day 30. Histopathology for treated vessels in both acute (Day 0) and chronic studies (Day 30), including semi-quantitative scoring of pathologic changes in treated vessels (e.g., endothelial loss, thrombus, hemorrhage, and medial injury), was found to be consistent with arterial healing after routine catheterization commonly seen with guidewires / catheters.

SUMMARY OF CLINICAL INFORMATION

Clinical data from the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) trial was used to support the expanded indication for the Trevo Retrievers in the subject *de novo*. The clinical study design and results are further

summarized below. While the MR CLEAN study allowed use of a variety of intra-arterial therapies, the data used to support the subject *de novo* request for the Trevo Retrievers was limited to data from MR CLEAN that only used the Trevo Retrievers as the thrombectomy device. Further, while these data were generated outside of the United States (US), FDA determined that these data represent valid scientific evidence and are applicable to the intended use population in the US.

Design:

MR CLEAN was a prospective, randomized, open label, controlled, multicenter trial in which every endovascular hospital center in the Netherlands participated. Intra-arterial treatment ("IAT"), which could include mechanical thrombectomy, plus best medical management (MM), which included intravenous administration of IV t-PA in eligible subjects, was compared with best MM alone (control group) in patients with acute ischemic stroke with a proximal intracranial arterial occlusion of the anterior circulation that was confirmed on vessel imaging. MR CLEAN randomized 500 patients (233 treatment ["IAT"], 267 control) at 16 medical centers. Retrievable stents (including the Trevo Retriever product family) were used in 190 of the 233 patients (81.5%) assigned to the IAT arm, of which 120/190 patients received first line intra-arterial treatment with a Trevo Retriever and if eligible for IV t-PA, received IV t-PA within 3 hours from symptoms onset (TREVO FDA cohort). The TREVO FDA cohort group was compared to the entire MR CLEAN MM control group, excluding the MM patients who received IV t-PA greater than the FDA approved window of 3 hours from stroke symptom onset (249/267 patients in the MM control group). The 18 patients who were excluded from the MM control group received IV t-PA within 3-4.5 hours from symptom onset, which is in accordance with the European Union (EU) approved administration for IV t-PA where the study was conducted. Most of the patients received IV t-PA within the FDA approved window of 3 hours from stroke symptom onset, including 104/120 patients in the IAT Trevo FDA group and 224/249 in the MM group.

Key inclusion criteria for MR CLEAN were: clinical diagnosis of acute ischemic stroke with a National Institutes of Health Stroke Scale (NIHSS) score > 2; computed tomography (CT) or magnetic resonance imaging (MRI) scan ruling out intracranial hemorrhage; intracranial arterial occlusion of the distal ICA or proximal regions in the middle (M1/M2) or anterior (A1/A2) cerebral arteries, demonstrated with CT angiography (CTA), MR angiography (MRA) or digital subtraction angiography (DSA); treatment within 6 hours of symptom onset, age 18 or older and informed consent given.

Additional key inclusion criteria for Trevo Retriever subset analysis from MR CLEAN: first line treatment with Trevo Retriever and IV t-PA treatment within 3 hours of symptom onset.

Key exclusion criteria for MR CLEAN were: arterial blood pressure >185/110 mmHg; blood glucose < 2.7 or >22.2 mmol/L; intravenous treatment with thrombolytic therapy in a dose exceeding 0.9 mg/kg alteplase or 90 mg; intravenous treatment with thrombolytic therapy despite contraindications (i.e., major surgery, gastrointestinal bleeding or urinary tract bleeding within the previous 2 weeks, or arterial puncture at a non-compressible site within the previous 7 days); cerebral infarction in the distribution of the relevant occluded artery in the previous 6 weeks; and

laboratory evidence of coagulation abnormalities (i.e., platelet count <$40x10^9$/L, activated partial thromboplastin time (APTT) > 50 sec or international normalized ratio (INR) >3.0).

Results:

The primary effectiveness endpoint of the MR CLEAN trial was functional independence (modified Rankin Scale (mRS) ≤ 2) at 90 days. The 90 day mRS assessment was performed by an assessor who was blinded to the subject's treatment allocation. For the analyses of the Trevo Retriever, the primary effectiveness endpoint was to demonstrate that Trevo Retriever thrombectomy plus MM leads to clinically meaningful functional independence (mRS ≤ 2) at 90 days as compared to MM alone in eligible subjects experiencing an acute ischemic stroke.

There were 24 subjects who also underwent carotid stenting during the procedure. Since such procedures could confound the results as it may not be possible to separate out any beneficial or adverse effects from the effect of the Trevo Retriever, these subjects were excluded from the effectiveness endpoint analyses. Additionally, there was 1 subject in the Trevo arm with an additional arterial therapy (intra-arterial lytic), which was counted as a failure (mRS > 2) in the analysis. After these adjustments, the proportion of subjects with mRS at day 90 that met the primary effectiveness endpoint in the MM control arm was 48/249 (19.3%) with 95% exact confidence interval (14.6%, 24.7%); and was 28/96 (29.2%) with 95% exact confidence interval (20.3%, 39.3%) in the Trevo Retriever treatment group (Table 3). The associated odds ratio [95% confidence interval (CI)] was 1.88 [1.07, 3.29], with a p-value of 0.014.

Table 3: Distribution of 90-day mRS

90 DAY mRS	**TREVO excluding concomitant carotid stenting (N=96)**	**MM (N=249)**
0	4.2% (4/96)	0.4% (1/249)
1	8.3% (8/96)	5.2% (13/249)
2	17.7% (17/96)	13.7% (34/249)
3	15.6% (15/96)	16.5% (41/249)
4	32.3% (31/96)	31.3% (78/249)
5	7.3% (7/96)	10.4% (26/249)
6	14.6% (14/96)	22.5% (56/249)
mRS [0, <3] with Any IA Lytic Use Considered Treatment Failure*	29.2% (28/96)*	19.3% (48/249)

*1 subject with IA lytic use was counted as a failure

Note: Most subjects in both arms received IV tPA (81 out of 96 subjects in the Trevo cohort and 224 out of 249 subjects in the medical management arm). Only 15 subjects in the Trevo group summarized above and 25 subjects in the medical management group did not receive IV tPA.

The first secondary effectiveness endpoint analysis of the Trevo Retrievers was the percentage of patients with no intra-cranial occlusion assessed by a consensus review by up to three readers after 24 hours (Table 4). The endpoint was assessed by CTA or MRA using the Arterial Occlusive Lesion (AOL) scale.

Table 4: Percentage of Subjects with No Intra-Cranial Occlusion after 24 Hours

Occlusion Free (24 Hours)	TREVO excluding concomitant carotid stenting % (x/N[1]) (LCL, UCL)[2]	MM % (x/N[1]) (LCL, UCL)[2]
Percentage (%) of patients with no intra-cranial occlusion after 24 hours	77.5% (62/80) (66.8%, 86.1%)	33.51% (65/194) (26.90%, 40.62%)

[1] Subjects without 24 hour CTA or MRA were excluded from the analysis.
[2] Two-sided 95% Exact Clopper Pearson confidence intervals (lower confidence limit (LCL) and upper confidence limit (UCL)).

The second secondary effectiveness endpoint analysis of the Trevo Retrievers was the percentage of Trevo patients that achieved recanalization including a Thrombolysis in Cerebral Infarction (TICI) score of 2a or better (Table 5). This endpoint was also assessed by a consensus review by at least three readers.

Table 5: Recanalization Rates of Subjects Treated with Trevo

	TREVO excluding concomitant carotid stenting % (x/N) (LCL, UCL)[1]
Percentage of patients with TICI ≥ 2a	81.3% (78/96) (72.0%, 88.5%)

[1] Two-sided 95% Exact Clopper Pearson confidence intervals (lower confidence limit (LCL) and upper confidence limit (UCL)).

The third secondary effectiveness endpoint was defined as the difference in neurological outcomes assessed by NIHSS at 24 hours and at 5-7 days post-randomization between Trevo Retriever plus MM in comparison to the MM alone control group (Table 6).

Table 6: NIHSS at 24 Hours and 5-7 Days Post-Randomization

NIHSS	TREVO excluding concomitant carotid stenting Mean± SD (N[1]) Median (Min, Max) (LCL, UCL)[2]	MM Mean± SD (N[1]) Median (Min, Max) (LCL, UCL)[2]
NIHSS (24 Hours)	14.23 ± 9.23 (96) 14 (1, 42) (12.36, 16.10)	16.19 ± 7.77 (240) 16 (0, 42) (15.20, 17.18)
NIHSS (5-7 Days)	13.02 ± 12.16 (94) 12 (0, 42) (10.53, 15.51)	15.76 ± 11.49 (237) 15 (0, 42) (14.29, 17.23)

[1] Subjects with missing NIHSS were excluded from the analysis. Subjects who expired prior to discharge were assigned a NIHSS value of 42.
[2] Two-sided 95% confidence limits by normal approximation (lower confidence limit (LCL) and upper confidence limit (UCL)).

Adverse Events:

For all safety analyses, subjects exposed to the Trevo Retriever with or without concomitant carotid stenting are included. In analyses of the Trevo Retriever cohort, the primary safety

objective analysis was defined as the all-cause mortality rate between Trevo Retriever plus MM in comparison to the all-cause mortality rate in the MM alone control group (Table 7).

Table 7: Mortality at 90 Days

Mortality by 90 Days	TREVO FDA Cohort % (x/N) (LCL, UCL)[1]	MM % (x/N) (LCL, UCL)[1]
Rate of Mortality (%)	13.3% (16/120) (7.8%, 20.7%)	22.89% (57/249) (17.82%, 28.62%)

[1]Two-sided 95% Exact Clopper Pearson confidence intervals (lower confidence limit (LCL) and upper confidence limit (UCL)).

The first secondary safety analysis was the proportion of patients by treatment group who had a symptomatic intracranial hemorrhage (sICH) reported as an adverse event within 24 hours of the patient's index stroke (Table 8).

Table 8: Symptomatic ICH within 24 Hours

Symptomatic ICH in 24 hours	TREVO FDA Cohort % (x/n) (LCL, UCL)[1]	MM % (x/n) (LCL, UCL)[1]
Rate of Symptomatic ICH (%)	6.67% (8/120) (2.92%, 12.71%)	4.42% (11/249) (2.23%, 7.77%)

[1]Two-sided exact 95% confidence limits (lower confidence limit (LCL) and upper confidence limit (UCL)).

The second secondary safety endpoint was the proportion of patients that had neurological deterioration within 5-7 days or discharge, whichever is earlier (Table 9). Deterioration was defined as an increase of 4 or more points in the NIHSS from baseline stroke score. The proportions were reported descriptively for all patients for which NIHSS at 5 to 7 days were available for this endpoint in the table below.

Table 9. Neurological Deterioration

Neurological Deterioration	TREVO FDA Cohort % (x/N[1]) (LCL, UCL)[2]	MM % (x/N[1]) (LCL, UCL)[2]
Yes	9.17% (10/109) (4.49%, 16.23%)	9.57% (22/230) (6.09%, 14.12%)

[1] Subjects with missing NIHSS were excluded from this analysis. Subjects who expired prior to discharge were assigned a NIHSS value of 42.

[2] Two-sided exact 95% confidence limits (lower confidence limit (LCL) and upper confidence limit (UCL)).

The third secondary safety endpoint was a descriptive presentation of other important safety endpoints through 90 days of follow-up including serious adverse events (SAE) (Table 10). The MR CLEAN study defined classes of events using the following categories: new ischemic stroke in a different vascular territory, progressive ischemic stroke, pneumonia, other infection, cardiac ischemia, extra-cranial hemorrhage, allergic reaction, and other complications are presented in the table below. The MR CLEAN study did not define events classified as "other complications"; however, a more detailed description of adverse events coded by the Medical Dictionary for Regulatory Activities (MedDRA) classification that is included in Table 11.

Table 10: Adverse Event Summary with MR CLEAN Study Categorization

MR CLEAN Class	TREVO FDA Cohort 120 Subjects w/189 Events % (x/N) [LCL, UCL][1] Number of Events	MM 249 Subjects w/331 Events % (x/N) [LCL, UCL][1] Number of Events
Ischemic stroke	2.5% (3/120) [0.5%, 7.1%] 3	0.8% (2/249) [0.1%, 2.9%] 2
Symptomatic intracranial hemorrhage	7.5% (9/120) [3.5%, 13.8%] 9	6.8% (17/249) [4.0%, 10.7%] 17
Extracranial hemorrhage	2.5% (3/120) [0.5%, 7.1%] 3	4.4% (11/249) [2.2%, 7.8%] 11
Cardiac Ischemia	0	2.0% (5/249) [0.7%, 4.6%] 5
Allergic reaction	1.7% (2/120) [0.2%, 5.9%] 2	0.4% (1/249) [0.0%, 2.2%] 1
Pneumonia	18.3% (22/120) [11.9%, 26.4%] 24	19.3% (48/249) [14.6%, 24.7%] 52
Other infection	23.3% (28/120) [16.1%, 31.9%] 34	13.7% (34/249) [9.6%, 18.6%] 41
Other complication	47.5% (57/120) [38.3%, 56.8%] 89	38.6% (96/249) [32.5%, 44.9%] 154
Progression of stroke	20.8% (25/120) [14.0%, 29.2%] 25	18.9% (47/249) [14.2%, 24.3%] 48

[1] Exact Clopper Pearson confidence intervals on individual proportions (lower confidence limit (LCL) and upper confidence limit (UCL)).

Adverse events were also reported for the Trevo and MM groups based on Medical Dictionary for Regulatory Activities (MedDRA) v18.0 coded adverse events, with a frequency over 1% (Table 11).

Table 11: MedDRA Adverse Event Summary, over 1% Frequency

MedDRA Preferred Term	Trevo FDA Cohort (N=120) Patients with Events (%)	Control (N=249) Patients with Events (%)
Stroke in evolution	19 (15.8%)	41 (16.5%)
Haemorrhage intracranial	13 (10.8%)	20 (8.0%)
Urinary tract infection	11 (9.2%)	17 (6.8%)
Atrial fibrillation	10 (8.3%)	10 (4.0%)
Pyrexia	6 (5.0%)	6 (2.4%)
Neurological decompensation	6 (5.0%)	6 (2.4%)
Pneumonia aspiration	5 (4.2%)	8 (3.2%)
Delirium	4 (3.3%)	6 (2.4%)
Bone graft	4 (3.3%)	1 (0.4%)
Cardiac failure	3 (2.5%)	7 (2.8%)
Diarrhoea	3 (2.5%)	4 (1.6%)
Urosepsis	3 (2.5%)	4 (1.6%)
Fall	3 (2.5%)	4 (1.6%)
Headache	3 (2.5%)	1 (0.4%)

MedDRA Preferred Term	Trevo FDA Cohort (N=120) Patients with Events (%)	Control (N=249) Patients with Events (%)
Ischaemic stroke	3 (2.5%)	1 (0.4%)
Cardiac arrest	2 (1.7%)	0
Hypersensitivity	2 (1.7%)	1 (0.4%)
Clostridium difficile infection	2 (1.7%)	0
Gout	2 (1.7%)	3 (1.2%)
Carotid artery dissection	2 (1.7%)	0
Epilepsy	2 (1.7%)	3 (1.2%)
Depression	2 (1.7%)	4 (1.6%)
Urinary retention	2 (1.7%)	2 (0.8%)
Pulmonary embolism	2 (1.7%)	6 (2.4%)
Haematoma	2 (1.7%)	2 (0.8%)
Anaemia	1 (0.8%)	3 (1.2%)
Bradycardia	1 (0.8%)	3 (1.2%)
Seizure	1 (0.8%)	3 (1.2%)
Respiratory failure	1 (0.8%)	3 (1.2%)
Gastrointestinal tube insertion	1 (0.8%)	5 (2.0%)
Hypotension	1 (0.8%)	3 (1.2%)
Phlebitis	1 (0.8%)	3 (1.2%)
Vasospasm	1 (0.8%)	0
Arrhythmia	0	3 (1.2%)
Myocardial ischaemia	0	3 (1.2%)
Renal failure	0	3 (1.2%)
Deep vein thrombosis	0	3 (1.2%)

LABELING

The labeling includes instructions for use for the physician and satisfies the requirements of 21 CFR § 801.109 for prescription devices. The labeling includes:

- Directions for recommended device preparation and thrombus retrieval procedure.
- Information on the specific patient population for which the device is intended for use in the treatment of acute ischemic stroke, including specifying starting the endovascular procedure with the device within 6 hours of stroke symptom onset and specifying the presence of smaller core infarcts affected by occlusions in the proximal anterior circulation of the neurovasculature.
- A summary of the clinical testing results, including a detailed summary of the device- and procedure-related complications and adverse events.
- A shelf life.

Please see the Limitations section above for important warnings and precautions presented in the device labeling.

RISKS TO HEALTH

Table 12 below identifies the risks to health associated with use of a Neurovascular Mechanical Thrombectomy Device for Acute Ischemic Stroke Treatment and the measures necessary to mitigate these risks.

Table 12. Risks to Health and Mitigation Measures

Identified Risk	Mitigation Measure
Adverse Tissue Reaction	Biocompatibility Evaluation
Infection	Sterility Testing Shelf-Life Testing Labeling
Tissue or Vessel Damage: • Dissection • Perforation • Hemorrhage	Non-clinical Performance Testing Clinical Performance Testing Labeling
Stroke Progression	Non-clinical Performance Testing Clinical Performance Testing Labeling
Emboli	Non-clinical Performance Testing Clinical Performance Testing Labeling

SPECIAL CONTROLS:

In combination with the general controls of the FD&C Act, the Neurovascular Mechanical Thrombectomy Device for Acute Ischemic Stroke Treatment is subject to the following special controls:

1. The patient contacting components of the device must be demonstrated to be biocompatible.
2. Non-clinical performance testing must demonstrate that the device performs as intended under anticipated conditions of use, including:
   a. Mechanical testing to demonstrate the device can withstand anticipated tensile, torsional, and compressive forces.
   b. Mechanical testing to evaluate the radial forces exerted by the device.
   c. Non-clinical testing to verify the dimensions of the device.
   d. Non-clinical testing must demonstrate the device can be delivered to the target location in the neurovasculature and retrieve simulated thrombus under simulated use conditions.
   e. Non-clinical testing must demonstrate the device is radiopaque and can be visualized.
   f. Non-clinical testing must evaluate the coating integrity and particulates under simulated use conditions.
   g. Animal testing must evaluate the safety of the device, including damage to the vessels or tissue under anticipated use conditions.

3. Performance data must support the sterility and pyrogenicity of the patient contacting components of the device.
4. Performance data must support the shelf-life of the device by demonstrating continued sterility, package integrity, and device functionality over the specified shelf-life.
5. Clinical performance testing of the device must demonstrate the device performs as intended for use in the treatment of acute ischemic stroke and must capture any adverse events associated with the device and procedure.
6. The labeling must include:
    a. Information on the specific patient population for which the device is intended for use in the treatment of acute ischemic stroke, including but not limited to, specifying time from symptom onset, vessels or location of the neurovasculature that can be accessed for treatment, and limitations on core infarct size.
    b. Detailed instructions on proper device preparation and use for thrombus retrieval from the neurovasculature.
    c. A summary of the clinical testing results, including a detailed summary of the device- and procedure-related complications and adverse events.
    d. A shelf life.

BENEFIT/RISK DETERMINATION

The risks of the device are based on data collected in the clinical study described above, and nonclinical laboratory and animal studies. Device-related adverse events could include emboli, progression of stroke, intracranial hemorrhage, and arterial injury including perforation or dissection. Procedural risks and complications could include puncture site hemorrhage, including retroperitoneal hematoma that may require transfusion, contrast allergy, renal failure, and radiation exposure.

The probable benefits of the device for use in the treatment of acute ischemic stroke to reduce disability are based on data collected in the clinical study as described above. The benefit of the device is a reduction in disability in patients with acute ischemic stroke, with large vessel occlusion in the proximal anterior circulation and smaller core infarcts, who have first been treated with IV t-PA and are treated with the device within 6 hours of stroke symptom onset. The reduction in disability was measured at 90 days after the acute ischemic stroke and mechanical thrombectomy procedure with the Trevo Retrievers compared to MM. A decrease in disability with the Trevo Retrievers would be highly valuable and clinically meaningful to acute ischemic stroke patients since the current approved treatment option is only limited to drug therapy.

Patient Perspectives

Patient perspectives considered for the Trevo Retrievers included:

- The primary effectiveness endpoint analyzed mRS scores at 90 days, with scores of mRS 0-2 considered a favorable outcome as they are associated with functional independence. The mRS is evaluated using a set questionnaire administered to patients to measure their disability and functional independence. Given the potentially devastating outcomes with acute ischemic stroke, which may include severe disability or death, achieving greater

functional independence, 90 days post-stroke is a clinically meaningful benefit for acute ischemic stroke patients.

Benefit/Risk Conclusion

In conclusion, given the available information above, the data support that for use in the treatment of acute ischemic stroke to reduce disability in patients with persistent, proximal anterior circulation, large vessel occlusion and smaller core infarcts, who have first received IV t-PA within 3 hours and the device is used within 6 hours of stroke symptom onset, the probable benefits outweigh the probable risks for the Trevo ProVue and XP ProVue Retrievers. The device provides substantial benefits and the risks can be mitigated by the use of general and the identified special controls.

CONCLUSION

The *de novo* request for the Trevo ProVue and XP ProVue Retrievers is granted and the devices are classified under the following:

Product Code: POL
Device Type: Neurovascular Mechanical Thrombectomy Device for Acute Ischemic Stroke Treatment
Class: II
Regulation: 21 CFR 882.5600