February 15, 2018

Concentric Medical, Inc.
Rhoda M. Santos
Senior Principal Regulatory Affairs Specialist
301 East Evelyn Avenue
Mountain View, California 94041

Re: K173352
Trade/Device Name: Trevo ProVue Retriever and Trevo XP ProVue Retriever (Trevo Retriever)
Regulation Number: 21 CFR 882.5600
Regulation Name: Neurovascular Mechanical Thrombectomy Device for Acute Ischemic Stroke Treatment
Regulatory Class: Class II
Product Code: POL, NRY
Dated: January 12, 2018
Received: January 16, 2018

Dear Ms. Rhoda M. Santos:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820);

and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/) and CDRH Learn (http://www.fda.gov/Training/CDRHLearn). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (http://www.fda.gov/DICE) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,

Carlos L. Pena -S

Carlos L. Peña, PhD, MS
Director
Division of Neurological
and Physical Medicine Devices
Office of Device Evaluation
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: 06/30/2020
See PRA Statement below.

510(k) Number *(if known)*
K173352

Device Name
Trevo ProVue Retriever and Trevo XP ProVue Retriever
(Trevo Retriever)

Indications for Use *(Describe)*

1. The Trevo Retriever is 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.

2. The Trevo Retriever is intended to restore blood flow in the neurovasculature by removing thrombus in patients experiencing ischemic stroke within 8 hours of symptom onset. Patients who are ineligible for intravenous tissue plasminogen activator (IV t-PA) or who fail IV t-PA therapy are candidates for treatment.

3. The Trevo Retriever is 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 of the internal carotid artery (ICA) or middle cerebral artery (MCA)-M1 segments with smaller core infarcts (0-50 cc for age < 80 years, 0-20 cc for age ≥ 80 years). Endovascular therapy with the device should start within 6-24 hours of time last seen well in patients who are ineligible for intravenous tissue plasminogen activator (IV t-PA) or who fail IV t-PA therapy.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

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510(k) Summary

Trade Name:	Trevo ProVue Retriever and Trevo XP ProVue Retriever (Trevo Retriever)
Common Name:	Trevo Retriever
Classification Name:	Neurovascular Mechanical Thrombectomy Device for Acute Ischemic Stroke Treatment, 21 CFR 882.5600, Class II, POL - Percutaneous Catheter, 21CFR 870.1250, Class II, NRY
Product Code:	POL, NRY
Submitter:	**Concentric Medical, Inc.** 301 E. Evelyn Avenue Mountain View, CA 94041 Tel 510-413-2269 Fax 510-413-2558 Facility Registration #2954917
Contact:	**Rhoda M. Santos** Senior Principal Regulatory Affairs Specialist
Date Prepared:	**February 6, 2018**
Predicate Device:	**Trevo ProVue Retriever and Trevo XP ProVue Retriever (DEN150049)**
Reference Predicate Device:	**Trevo Retriever (K120961)**

Device Description

The Trevo Retriever family, including the Trevo ProVue and Trevo XP ProVue Retriever consists of a flexible, tapered core wire with a shaped section at the distal end. Platinum markers at the distal end allow fluoroscopic visualization. In addition, the shaped section is also radiopaque. Retriever dimensions are indicated on product label. The Retriever has a hydrophilic coating to reduce friction during use. The Retriever has a shaft marker to indicate proximity of Retriever tip relative to Microcatheter tip. A torque device is provided with the Retriever to facilitate manipulation. The torque device is used to lock the core wire to the microcatheter during the procedure. Locking of the torque device to the wire allows the microcatheter and Retriever to be retracted as a system during clot retrieval. An insertion tool is provided to introduce the Retriever into a Microcatheter. The Insertion Tool is a sheath in which the Retriever comes preloaded. Once half the retriever's length is inserted into the microcatheter, the insertion tool is removed. Retrievers have a modified proximal end that permits attachment of the Abbott Vascular DOC Guide Wire Extension (REF 22260). Joining Guide Wire Extension to Retriever facilitates removal or exchange of a catheter while maintaining Retriever position in anatomy. After exchange has been completed, the extension can be detached.

Accessories

The Retriever is provided with two accessories: a torque device facilitates manipulation of the Retriever; and an insertion tool is used to introduce the Retriever into a microcatheter.

Indications for Use

The Indications for Use for the Trevo ProVue and Trevo XP ProVue Retrievers are as follows:

1. The Trevo Retriever is 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.

2. The Trevo Retriever is intended to restore blood flow in the neurovasculature by removing thrombus in patients experiencing ischemic stroke within 8 hours of symptom onset. Patients who are ineligible for intravenous tissue plasminogen activator (IV t-PA) or who fail IV t-PA therapy are candidates for treatment.

3. The Trevo Retriever is 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 of the internal carotid artery (ICA) or middle cerebral artery (MCA)-M1 segments with smaller core infarcts (0-50 cc for age < 80 years, 0-20 cc for age ≥ 80 years). Endovascular therapy with the device should start within 6-24 hours of time last seen well in patients who are ineligible for intravenous tissue plasminogen activator (IV t-PA) or who fail IV t-PA therapy.

Technological Characteristics and Product Feature Comparison

The Trevo ProVue and Trevo XP ProVue Retriever subject devices are identical to the predicate devices and differ only by the expanded indications for use.

Table 1: Product Feature Comparison of Subject Device to Predicate Device

Feature	**Reference Predicate Device** **Trevo Retriever (K120961)**	**Primary Predicate Device** **Trevo ProVue Retriever and Trevo XP ProVue Retriever (DEN150049)**	**Subject Device** **Trevo ProVue Retriever and Trevo XP ProVue Retriever with Expanded Indications**	**Rationale for Modification (if applicable)**
Intended Use	The Trevo Retriever is intended to restore blood flow in the neurovasculature by removing thrombus in patients experiencing ischemic stroke within 8 hours of symptom onset. Patients who are ineligible for intravenous tissue plasminogen activator (IV-tPA) or who fail IV t-PA therapy are candidates for treatment.	Neurovascular mechanical thrombectomy device for acute ischemic stroke treatment used in the treatment of acute ischemic stroke to improve clinical outcomes.	Same	Not applicable.

Feature	**Reference Predicate Device** **Trevo Retriever (K120961)**	**Primary Predicate Device** **Trevo ProVue Retriever and Trevo XP ProVue Retriever (DEN150049)**	**Subject Device** **Trevo ProVue Retriever and Trevo XP ProVue Retriever with Expanded Indications**	**Rationale for Modification (if applicable)**
Indications for Use	The Trevo Retriever is intended to restore blood flow in the neurovasculature by removing thrombus in patients experiencing ischemic stroke within 8 hours of symptom onset. Patients who are ineligible for intravenous tissue plasminogen activator (IV-tPA) or who fail IV t-PA therapy are candidates for treatment.	The Trevo Retriever is 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-tPA). Endovascular therapy with the device should start within 6 hours of symptom onset.	1. The Trevo Retriever is 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. 2. The Trevo Retriever is intended to restore blood flow in the neurovasculature by removing thrombus in patients experiencing ischemic stroke within 8 hours of symptom onset. Patients who are ineligible for intravenous tissue plasminogen activator (IV t-PA) or who fail IV t-PA therapy are candidates for treatment. 3. The Trevo Retriever is 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 of the internal carotid artery (ICA) or middle cerebral artery (MCA)-M1 segments with smaller core infarcts (0-50 cc for age < 80 years, 0-20 cc for age ≥ 80 years). Endovascular therapy with the device should start within 6-24 hours of time last seen well in patients who are ineligible for intravenous tissue plasminogen activator (IV t-PA) or who fail IV t-PA therapy.	The results of DAWN study (IDE G130223) demonstrate that the expanded indications do not raise any new or different questions of safety or effectiveness.
REGULATORY INFORMATION				
Regulation Number/ Name/ Class/ Product Code	21 CFR 870.1250, Percutaneous Catheter, Class II, NRY	21 CFR 882.5600, Neurovascular Mechanical Thrombectomy Device for Acute Ischemic Stroke Treatment, Class II, POL	Same	Not applicable.

Feature	Reference Predicate Device Trevo Retriever (K120961)	Primary Predicate Device Trevo ProVue Retriever and Trevo XP ProVue Retriever (DEN150049)	Subject Device Trevo ProVue Retriever and Trevo XP ProVue Retriever with Expanded Indications	Rationale for Modification (if applicable)
Target Population	Patients experiencing acute ischemic stroke		Same	Not applicable.
Anatomical Sites	Neurovasculature		Same	Not applicable.
TECHNOLOGICAL CHARACTERISTICS				
Device Description	The Retriever consists of a flexible, tapered core wire with a shaped section at the distal end. A platinum coil allows fluoroscopic visualization. The Retriever has a hydrophilic coating to reduce friction. The Retriever has a shaft marker to indicate proximity of Retriever tip relative to Microcatheter tip. A torque device and insertion tool are provided with the Retriever.	The Retriever consists of a flexible, tapered core wire with a shaped section at the distal end. Platinum markers at the distal end allow fluoroscopic visualization. In addition, the shaped section is also radiopaque. Retriever dimensions are indicated on product label. The Retriever has a hydrophilic coating to reduce friction during use. The Retriever has a shaft marker to indicate proximity of Retriever tip relative to Microcatheter tip. A torque device is provided with the Retriever to facilitate manipulation. The torque device is used to lock the core wire to the microcatheter during the procedure. Locking of the torque device to the wire allows the microcatheter and Retriever to be retracted as a system during clot retrieval. An insertion tool is provided to introduce the Retriever into a Microcatheter. The Insertion Tool is a sheath in which the Retriever comes preloaded. Once half the retriever's length is inserted into the microcatheter, the insertion tool is removed. Retrievers have a modified proximal end that permits attachment of the Abbott Vascular DOC Guide Wire Extension (REF 22260). Joining Guide Wire Extension to Retriever facilitates removal or exchange of a catheter while maintaining Retriever position in anatomy. After exchange has been completed, the extension can be detached.	Same	Not applicable.
Principle of Operation	The Trevo Retriever is delivered to the thrombus using a microcatheter. The microcatheter is then retracted to deploy the shaped section of the Retriever. The Retriever and Microcatheter are pulled back to capture the thrombus. The Retriever, thrombus and Microcatheter are then removed from the body.		Same	Not applicable.

<table>
<tr><th>Feature</th><th><u>Reference Predicate Device</u>
Trevo Retriever (K120961)</th><th><u>Primary Predicate Device</u>
Trevo ProVue Retriever and Trevo XP ProVue Retriever (DEN150049)</th><th><u>Subject Device</u>
Trevo ProVue Retriever and Trevo XP ProVue Retriever with Expanded Indications</th><th>Rationale for Modification (if applicable)</th></tr>
<tr><td>Sizes</td><td>4x20mm</td><td>3x20mm, 4x20mm, 4x30mm, 6x25mm</td><td>Same</td><td>Not applicable.</td></tr>
<tr><td>Accessory Devices</td><td colspan="2">Insertion tool and torque device provided within product package</td><td>Same</td><td>Not applicable.</td></tr>
<tr><td>Microcatheter (MC) Compatibility</td><td><table><tr><td>Retriever size</td><td>Trevo 18 MC</td></tr><tr><td>Trevo ProVue 4X20mm</td><td>✓</td></tr></table></td><td><table><tr><td>Retriever size</td><td>Trevo Pro14 MC</td><td>Trevo Pro18 MC</td><td>Excelsior ® XT-27® Microcatheters (150cm x 6cm straight REF 275081)</td></tr><tr><td>Trevo XP ProVue 3X20mm</td><td>✓</td><td>✓</td><td></td></tr><tr><td>Trevo XP ProVue 4X20mm</td><td></td><td>✓</td><td></td></tr><tr><td>Trevo ProVue 4X20mm</td><td></td><td>✓</td><td></td></tr><tr><td>Trevo XP ProVue 4X30mm</td><td></td><td>✓</td><td>✓</td></tr><tr><td>Trevo XP ProVue 6X25mm</td><td></td><td></td><td>✓</td></tr></table></td><td>Same</td><td>Not applicable.</td></tr>
<tr><td colspan="5">Materials</td></tr>
<tr><td>Core Wire</td><td colspan="2">Nitinol (nickel titanium alloy)</td><td>Same</td><td>Not applicable.</td></tr>
<tr><td>Shaped Section</td><td colspan="2">Nitinol</td><td>Same</td><td>Not applicable.</td></tr>
<tr><td>Distal Coil</td><td colspan="2">Platinum/Tungsten</td><td>Same</td><td>Not applicable.</td></tr>
<tr><td>Shaped Section Radiopaque Wire</td><td>Not applicable.</td><td>Platinum/Tungsten</td><td>Same</td><td>Not applicable.</td></tr>
<tr><td>Proximal Coil</td><td colspan="2">304 Stainless Steel</td><td>Same</td><td>Not applicable.</td></tr>
<tr><td>Solder</td><td colspan="2">Gold/Tin</td><td>Same</td><td>Not applicable.</td></tr>
<tr><td>Hydrophilic Coating</td><td colspan="2">Sodium hyaluronate mixture</td><td>Same</td><td>Not applicable.</td></tr>
</table>

Risk Assessment

Risk assessment of the modifications has been conducted in accordance with EN ISO 14971:2012. Concentric Medical, Inc. has determined that the expanded indications raise no new questions of safety or effectiveness. Results of clinical testing are appropriate for use in determining that the subject device is substantially equivalent to the predicate device.

The expanded indications did not result in the identification of any new failure modes nor were there any changes to existing failure modes, including no change to severity or occurrence; and, therefore, no change to overall residual risk.

Leveraged Non-Clinical Data

Performance testing for the subject device is leveraged from the predicate device cleared under reclassification order DEN150049 and the reference predicate device cleared under K120961. The subject device (Trevo ProVue and Trevo XP ProVue Retrievers with Expanded Indications) differs from the predicate devices (DEN150049, K120961) only by the indications for use. The technological characteristics and principles of operation remain unchanged. There are no changes in the device design, materials, manufacturing, packaging and sterilization methods, therefore biocompatibility data, bench-top data, sterilization and stability data from the predicate devices (DEN150049, K120961) are directly applicable and no additional testing is required or was performed.

Clinical Data

The DAWN™ study (IDE G130223) was a multi-center, Bayesian adaptive-enrichment, prospective, randomized, open, masked endpoint trial, conducted in multiple countries to evaluate the safety and effectiveness of the subject device with the expanded indications. The data from the DAWN study constitutes the premarket clinical data required to demonstrate substantial equivalence with the predicate device.

Study Design

The DAWN study was designed to evaluate the hypothesis that Trevo thrombectomy plus medical management leads to superior clinical outcomes at 90 days as compared to medical management alone in appropriately selected subjects experiencing an acute ischemic stroke when treatment is initiated within 6-24 hours after last seen well; 90-day disability assessed by modified Rankin scale (mRS) is the primary endpoint.

The first co-primary analysis, based on the utility weighted (UW)-mRS, evaluated the posterior probability the Trevo thrombectomy increases expected scores relative to medical management alone, using a statistical model that adjusts for baseline core infarct volume. The threshold for success was a posterior probability of at least 0.986, increased from 0.975 to account for the potential for enrichment and different final sample sizes. The second co-primary analysis based on the dichotomized mRS (0-2 vs. 3-6) was conducted in the same model and carried out in a hierarchical fashion. The trial had 86% power to detect a UW-mRS difference of 1.0 between the treatment arms. Study success was predicated on simultaneous success of the co-primary endpoint analyses.

Key Inclusion Criteria

Acute ischemic stroke with confirmed occlusion of intracranial ICA and/or M1, that failed or were contraindicated for IV t-PA, treatment within 6-24 hours after time last known well, baseline NIHSS $\geq$ 10, informed consent given and age 18 or over; In patients younger than 80, a stroke score equal to or greater than 10 must be associated with a core volume less than 51 ml. In patients 80 or older, the stroke score must be greater than 10 and volume less than 21 ml. Clinical-core mismatch which is defined as the mismatch between baseline infarct volume (or core) on CT or MRI imaging and the extent of total brain tissue at risk.

Key Exclusion criteria

Rapid improvement in neurological status to an NIHSS < 10 or evidence of vessel recanalization prior to randomization; Arterial blood pressure > 185/110 mmHg; laboratory evidence of electrolyte imbalance (i.e., sodium < 130 mmol/L, potassium < 3 mEq/L or > 6 mEq/L); laboratory evidence of renal failure (i.e., serum creatinine > 3.0 mg/dL (264 µmol/L); laboratory evidence of coagulation abnormalities (i.e., platelet count < 50,000/uL, APTT > 3 times normal or INR > 3.0, if given factor Xa inhibitor 24-48 hours ago must have normal PTT); laboratory evidence of bleeding (i.e., hemoglobin < 7 mmol/L).

Primary Effectiveness Analysis

Study success was based on simultaneous success criteria of both the 90 day UW-mRS as well as the dichotomized 90 day mRS (0-2 vs. 3-6) of the ITT population. **Table 2** shows the overall distribution and descriptive statistics of the 90 day mRS. In all analyses, outcomes for the Treatment arm were significantly better than the Control arm.

Table 2: 90 Day Imputed Modified Rankin Scale ITT Population

Modified Rankin Scale (mRS)	Treatment Arm N=107	Control Arm N= 99
0 - No symptoms / UW = 10	9.3% (10/107)	4.0% (4/99)
1 - No significant disability / UW = 9.1	22.4% (24/107)	5.1% (5/99)
2 - Slight disability / UW = 7.6	16.8% (18/107)	4.0% (4/99)
3 - Moderate disability / UW = 6.5	13.1% (14/107)	16.2% (16/99)
4 - Moderately severe disability / UW = 3.3	13.1% (14/107)	34.3% (34/99)
5 - Severe disability / UW = 0	6.5% (7/107)	18.2% (18/99)
6 - Dead / UW = 0	18.7% (20/107)	18.2% (18/99)
90 Day mRS [0-2]	48.6% (52/107)	13.1% (13/99)
90 Day Weighted mRS**		
Mean ± SD (N) Median (Q1, Q3) Range(min, max) [95% Conf. Interval][1]	5.5 ± 3.8 (107) 6.5 (0.0, 9.1) (0.0, 10.0) [4.8, 6.3]	3.4 ± 3.2 (99) 3.3 (0.0, 6.5) (0.0, 10.0) [2.7, 4.0]

[1] By normal approximation
*** mRS =(0,1,2,3,4,5,6) was assigned a corresponding numerical value =(10,9.1,7.6,6.5,3.3,0,0), which represents its clinical utility*

Table 3 summarizes the co-primary outcomes. The mean value of UW-mRS was 5.5 in the Treatment group and 3.4 in the Control group. The core infarct adjusted posterior mean treatment benefit of the ITT analysis population was 2.04 with 95% Credible Interval 1.1 to 2.98. The Treatment arm had superior rates of functional independence at 90 days (48.6 % vs. 13.1%); core adjusted posterior treatment benefit of 32.8%, 95% Credible Interval 21.1% to 44.1%. The posterior probability of superiority for both co-primary endpoints was highly significant at > 0.9999.

Table 3: Co-Primary outcomes ITT population

Outcome	Trevo Arm (N=107)	Control Arm (N=99)	Mean Absolute Difference (95% CI)	Posterior mean benefit, core-adjusted (95% credible interval) *	Probability of superiority
Utility-Weighted mRS-mean (SD)	5.5 (3.8)	3.4 (3.1)	2.1 (1.2, 3.1)	2.0 (1.1, 3.0)	>0.9999[1]
Functional Independence (mRS 0-2)	48.6%	13.1%	35.5% (23.9%, 47.0%)	32.8% (21.1%, 44.1%)	>0.9999

*Estimated by Bayesian general linear model adjusting for Core Infarct

[1]The overall probability of a device benefit is then the average of the benefit probabilities for the imputed data sets, weighted by the imputation probabilities of those data sets. This probability is 0.999986.

To provide additional context, the UW-mRS expected benefit of 2.04 represents 20.4% of the total value of preventing a single death and, instead, achieving a normal neurologic

outcome for that individual patient. Accordingly, the number needed to treat to save one life is 10/2.04 = 4.9 (95% credible interval 3.4-9.1). This value indicates that 4.9 patients need to be treated with Trevo thrombectomy rather than medical care alone for the accrued benefit to equal saving one life with return to normal function. Additionally, the number needed to treat to achieve functional independence (90-day mRS 0-2) is 2.8.

Primary Endpoint by Time

The randomization stratification of the DAWN Trial included a stratification variable of 6-12 hours and 12-24 hours to ensure balance of randomization across time. The minimum and maximum TLSW were 6.1 to 23.9 hours demonstrating subjects across the entire intended time spectrum were enrolled.

Figure 1 below plots the unadjusted probability of 90 day functional independence (mRS 0-2) by TLSW, demonstrating durability of treatment benefit across the 12-24 hour time spectrum.

Figure 1: Functional Independence (mRS 0-2) by TLSW

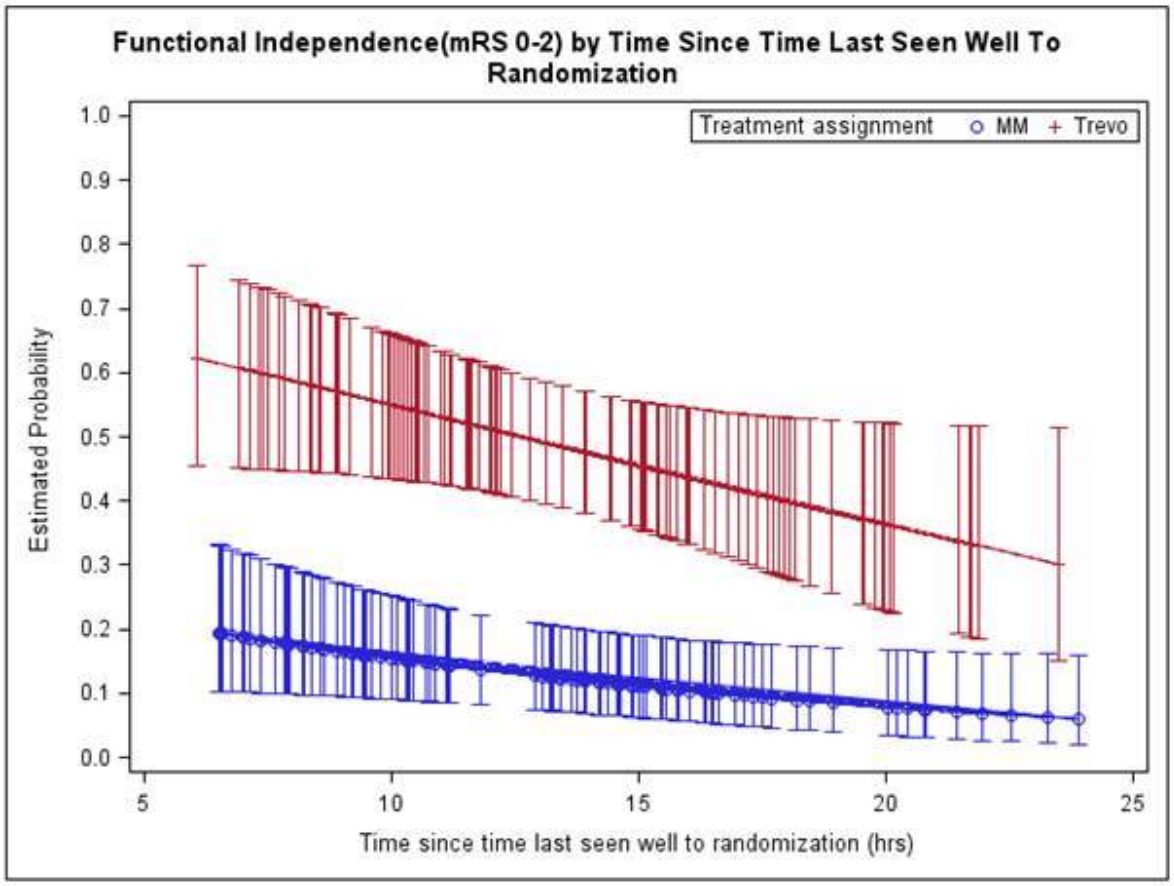

Table 4 further sub-groups 90 day functional independence (mRS 0-2) by 3 hour intervals. Although some intervals (i.e. 18-21 and 21-24 hours) had small numbers, the benefit of thrombectomy as measured by absolute difference was observed in each subgroup.

Table 4: Functional independence (90 Day mRS 0-2) Sub-grouped by Time

TLSW Intervals	Treatment	Control	Difference	P-value
6-9 hrs	50.0% (9/18)	14.3% (3/21)	35.7% [8.2%, 63.2%]	0.0346[a]
9-12 hrs	58.1 % (18/31)	26.1%(6/24)	33.1% [8.5%, 57.6%]	0.0273 [a]
6-12 hrs Total	**55.1% (27/49)**	**20.0% (9/45)**	**35.1% [16.9%, 53.3%]**	**0.0006[a]**
12-15 hrs	37.5% (6/16)	9.1% (2/22)	28.4% [1.8%, 55.0%]	0.0498[a]
15-18 hrs	50.0% (13/26)	5.3% (1/19)	44.7% [23.1%, 66.4%]	0.0025[a]
18-21 hrs	36.4% (4/11)	0.0% (0/8)	36.4% [7.9%, 64.8%]	0.1032[a]
21-24 hrs	40.0% (2/5)	20.0% (1/5)	20.0% [-35.4%, 75.4%]	1.0000[a]
12-24 Total*	**43.1% (25/58)**	**7.4% (4/54)**	**35.7% [21.2%, 50.2%]**	**< 0.0001[a]**

a.. Fisher's exact test
***** Greater level of uncertainty in the results shown for subjects in the 18-24 hour time from last seen well.
The p-value was not adjusted for multiplicity.

Secondary Effectiveness Outcome: Vessel Perfusion Rates

The proportion of subjects with early Neurological response at Day 5-7/Discharge (whichever was earlier), was also assessed. This endpoint was defined as a NIHSS drop of ≥ 10 points from baseline or an NIHSS score of 0 or 1. **Table 5** exhibits this acute improvement in the NIHSS scores among Treatment Arm subjects when compared with Control Arm subjects.

Table 5: Early Neurological Response at Day 5-7/Discharge

Outcome	Intervention N=107	Control N=99	Mean Absolute Difference (95% CI)	Risk Ratio (95% CI)	P-Value
Early Response†	47.7%	19.2%	28.5% (16.2%, 40.7%)	2.5 (1.6, 3.9)	<0.001

† Defined as NIHSS drop of ≥ 10 points from baseline or NIHSS 0 or 1 at day 5-7 or discharge (whichever was earlier)
The p-value was not adjusted for multiplicity.

Secondary Effectiveness Outcome: Revascularization Rates at 24 Hours

Recanalization of the qualifying occlusive lesion on the 24-hour follow-up CTA or MRA scans was also analyzed. Vessel occlusion status on CTA or MRA at 24 hours was characterized by the imaging core laboratory according to a scale ranging from 0 (no recanalization) to 1 (partial recanalization) to 2 (complete recanalization). Revascularization at 24 hours was defined as the presence of partial or complete recanalization. If the initially occluded MCA-M1 segment was found to be completely or partially recanalized on follow-up CTA or MRA but both MCA-M2 divisions remained occluded, recanalization was considered as unsuccessful. For reference, the Post

procedure mTICI ≥ 2b was 84.8% in the Treatment arm. Revascularization rates are shown in **Table 6**. The absolute difference in revascularization at 24 hours was 40.2% demonstrating superiority of Trevo thrombectomy compared to standard of care medical management (p<0.0001).

Table 6: Revascularization rates at 24 hours

	Total N=206	Treatment Arm N=107	Control Arm N= 99	Difference [95% CI]	p-value
Difference in revascularization rates at 24 (-6/+24) hours from randomization	58.7% (121/206)	76.6% (82/107)	38.4% (38/99)	40.2% [27.1%, 51.5%]	< 0.0001[a]

Revascularization at 24 hours was defined as the presence of partial or complete recanalization.
a. Fisher's exact test. ***The p-value was not adjusted for multiplicity.***

Primary and Secondary Safety Outcomes

The primary safety endpoint was the incidence of stroke-related mortality at 90 days. The secondary safety outcomes for both Treatment and Control Arms are incidence of sICH, by ECASS III definition, within 24 (-6/+24) hours post randomization, and incidence of neurological deterioration from baseline NIHSS score through Day 5- 7/discharge (whichever is earlier) post randomization. Neurological deterioration was defined as ≥ 4 point increase in the NIHSS score from the baseline score.

Primary Safety Outcome: Incidence of Stroke-Related Mortality at 90 days

The primary safety endpoint is incidence of stroke-related mortality at 90 days. In total, 17.0% (35/206) of the study subjects had stroke-related mortality within 90 days of enrollment into study: 15.9% (17/107) in the Treatment Arm and 18.2% (18/99) in the Control Arm. Stroke-related mortality rates at 90 days did not differ significantly (p= 0.7126) between study arms, as shown in **Table 7.**

Table 7: Stroke-Related Mortality at 90 Days

	Total N=206	Treatment Arm N=107	Control Arm N= 99	Difference [95% CI][1]	p-value
Incidence of all stroke-related mortality at 90 days	17.0% (35/206)	15.9% (17/107)	18.2% (18/99)	-2.3% [-12.6%, 8.0%]	0.7126[a]

[1] By normal approximation
a. Fisher's exact test. The p-value was not adjusted for multiplicity.

Secondary Safety Outcome: Incidence of sICH

Incidence of sICH, by ECASS III definition, within 24 (-6/+24) hours post randomization (time zero) was assessed in both study arms. These results are shown in **Table 8**.

Table 8: Incidence of sICH by CEC Adjudication

	Total N=206	Treatment Arm N=107	Control Arm N= 99	Difference [95% CI][1]	p-value
sICH at 24 (-6/+24) hrs post randomization	4.4% (9/206)	5.6% (6/107)	3.0% (3/99)	2.6% [-2.9%, 8.1%]	0.5011[a]

[1] By normal approximation
a. Fisher's exact test. The p-value was not adjusted for multiplicity.

The CEC adjudicated sICH in 4.4% (9/206) of subject cases: 5.6% (6/107) in the Treatment Arm and 3.0% (3/99) in the Control Arm. There was no statistical difference in sICH rates between arms. There was also no difference in the occurrence of sICH relative to TLSW between the Treatment arm and Control arm. The average TLSW for Treatment arm subjects with sICH was 13.4 $\pm$ 4.6 hours and 8.1 $\pm$ 2.3 hours in the control arm (p=0.11). For reference, the published rates from a large meta-analysis of over 1200 patients, sICH rates within 6 hours of TLSW are 4.4% for thrombectomy and 4.3% for medical management.

Secondary Safety Outcome: Incidence of Neurological Deterioration

Incidence of neurological deterioration was defined as a $\geq$ 4 point increase in the NIHSS score from baseline through Day 5-7/Discharge post randomization.

As presented in **Table 9**, neurological deterioration was reported in 19.9% (41/206) of subject cases with 14.0% (15/107) of the cases in the Treatment Arm and 26.3% (26/99) in the Control Arm per CEC adjudication, with a p-value of 0.0358.

Table 9: Incidence of Neurological Deterioration by CEC Adjudication

	Total N=206	Treatment Arm N=107	Control Arm N= 99	Difference [95% CI][1]	p-value
Incidence of neurological deterioration between baseline and Day 5 to 7/Discharge	19.9% (41/206)	14.0% (15/107)	26.3% (26/99)	-12.2% [-23.1%, -1.4%]	0.0358[a]

[1] By normal approximation
a. Fisher's exact test. The p-value was not adjusted for multiplicity.

Secondary Safety Outcome: Difference of All-Cause Mortality by CEC Adjudication

The difference between the two study arms in all-cause mortality rates up to and including 90 day follow-up was also assessed based upon CEC adjudication. Overall, in the study 18.4% (38/206) of subjects expired within 90 days of enrollment; 18.7% (20/107) in the Treatment Arm and 18.2% (18/99) in the Control Arm (p=1.0). These data are presented in **Table 10**.

Table 10: Incidence of All-Cause Mortality by CEC Adjudication

	Total N=206	Treatment Arm N=107	Control Arm N= 99	Difference [95% CI][1]	p-value
Incidence of all-cause mortality at 90 days	18.4% (38/206)	18.7% (20/107)	18.2% (18/99)	0.5% [-10.1%, 11.1%]	1.0000[a]

[1] By normal approximation

a. Fisher's exact test. The p-value was not adjusted for multiplicity.

Secondary Safety Outcome: Serious Adverse Events

Additional secondary safety outcome were defined as the incidence of procedure-related and device-related serious adverse events (PRSAEs and DRSAEs) through 24 (-6/+24) hours post randomization (time zero). All events were adjudicated by the Clinical Events Committee (CEC). This Safety Outcome, in the Treatment Arm, is provided in **Table 11**.

Table 11: Safety Outcome in Treatment Arm by CEC adjudication

	Device Related %(n/N)[95% Conf. Interval][2]	Procedure Related %(n/N)[95% Conf. Interval][2]	Total N=107 %(n/N)[95% Conf. Interval][2]
Vascular perforation	0.0% (0/107) [0.0%, 3.4%]	0.9% (1/107) [0.0%, 5.1%]	0.9% (1/107) [0.0%, 5.1%]
Intramural arterial dissection	0.0% (0/107) [0.0%, 3.4%]	1.9% (2/107) [0.2%, 6.6%]	1.9% (2/107) [0.2%, 6.6%]
Access site complication requiring surgical repair or blood transfusion	0.0% (0/107) [0.0%, 3.4%]	0.9% (1/107) [0.0%, 5.1%]	0.9% (1/107) [0.0%, 5.1%]
Intra-procedural mortality	0.0% (0/107) [0.0%, 3.4%]	0.0% (0/107) [0.0%, 3.4%]	0.0% (0/107) [0.0%, 3.4%]
Device failure (in vivo breakage)	0.0% (0/107) [0.0%, 3.4%]	0.0% (0/107) [0.0%, 3.4%]	0.0% (0/107) [0.0%, 3.4%]
Embolization to a new territory	3.7% (4/107) [1.0%, 9.3%]	3.7% (4/107) [1.0%, 9.3%]	3.7% (4/107) [1.0%, 9.3%]
Any other complications adjudicated by the CEC to be related to the procedure[1]	0.0% (0/107) [0.0%, 3.4%]	0.9% (1/107) [0.0%, 5.1%]	0.9% (1/107) [0.0%, 5.1%]

[1] One event of pulmonary edema in one subject (19900226) occurred during the procedure and was unrelated to the device but the relatedness to procedure could not be determined by CEC. The event is counted as procedure related.

[2] Exact Clopper Pearson confidence intervals

Table 12 presents a summary of all serious and non-serious adverse events for all Control Arm and Treatment Arm subjects by MedDRA Dictionary System Organ Classes (SOC).

Table 12: MedDRA SOC Categorization of all Adverse Events in Both Study Arms (Site Reported)

	Treatment arm N= 107						Control Arm N= 99					
MedDRA*|System Organ Class	**SAEs**	**Subjects with SAEs**	**Non SAEs**	**Subjects with Non SAEs**	**Total AEs**	**Subjects with Total AEs**	**SAEs**	**Subjects with SAEs**	**Non SAEs**	**Subjects with Non SAEs**	**Total AEs**	**Subjects with Total AEs**
Any Adverse Event(AE)	65	41 (38.3%)	476	102 (95.3%)	541	103 (96.3%)	83	47 (47.5%)	473	91 (91.9%)	556	91 (91.9%)
Blood and lymphatic system disorders	0	0	11	10 (9.3%)	11	10 (9.3%)	1	1 (1.0%)	8	8 (8.1%)	9	8 (8.1%)
Cardiac disorders	8	7 (6.5%)	37	29 (27.1%)	45	33 (30.8%)	6	5 (5.1%)	29	24 (24.2%)	35	28 (28.3%)
Endocrine disorders	0	0	1	1 (0.9%)	1	1 (0.9%)	0	0	0	0	0	0
Eye disorders	1	1 (0.9%)	0	0	1	1 (0.9%)	0	0	2	2 (2.0%)	2	2 (2.0%)
Gastrointestinal disorders	7	6 (5.6%)	42	30 (28.0%)	49	34 (31.8%)	12	11 (11.1%)	38	28 (28.3%)	50	34 (34.3%)
General disorders and administration site conditions	0	0	22	18 (16.8%)	22	18 (16.8%)	0	0	17	15 (15.2%)	17	15 (15.2%)
Hepatobiliary disorders	0	0	0	0	0	0	0	0	1	1 (1.0%)	1	1 (1.0%)
Immune system disorders	0	0	0	0	0	0	0	0	1	1 (1.0%)	1	1 (1.0%)
Infections and infestations	6	6 (5.6%)	46	34 (31.8%)	52	38 (35.5%)	7	7 (7.1%)	54	41 (41.4%)	61	43 (43.4%)
Injury, poisoning and procedural complications	2	2 (1.9%)	8	7 (6.5%)	10	9 (8.4%)	2	2 (2.0%)	8	6 (6.1%)	10	7 (7.1%)
Investigations	0	0	5	5 (4.7%)	5	5 (4.7%)	0	0	10	10 (10.1%)	10	10 (10.1%)
Metabolism and nutrition disorders	0	0	76	47 (43.9%)	76	47 (43.9%)	0	0	62	34 (34.3%)	62	34 (34.3%)
Musculoskeletal and connective tissue disorders	0	0	11	10 (9.3%)	11	10 (9.3%)	2	2 (2.0%)	22	15 (15.2%)	24	16 (16.2%)
Neoplasms benign, malignant and unspecified	0	0	1	1 (0.9%)	1	1 (0.9%)	0	0	0	0	0	0
Nervous system disorders	21	21 (19.6%)	95	63 (58.9%)	116	71 (66.4%)	34	30 (30.3%)	88	53 (53.5%)	122	66 (66.7%)
Psychiatric disorders	1	1 (0.9%)	26	24 (22.4%)	27	24 (22.4%)	2	2 (2.0%)	30	27 (27.3%)	32	28 (28.3%)
Renal and urinary disorders	0	0	18	15	18	15	1	1 (1.0%)	19	14	20	15 (15.2%)

MedDRA*|System Organ Class	Treatment arm N= 107						Control Arm N= 99					
	SAEs	**Subjects with SAEs**	**Non SAEs**	**Subjects with Non SAEs**	**Total AEs**	**Subjects with Total AEs**	**SAEs**	**Subjects with SAEs**	**Non SAEs**	**Subjects with Non SAEs**	**Total AEs**	**Subjects with Total AEs**
				(14.0%)		(14.0%)				(14.1%)		
Reproductive system and breast disorders	0	0	1	1 (0.9%)	1	1 (0.9%)	0	0	2	2 (2.0%)	2	2 (2.0%)
Respiratory, thoracic and mediastinal disorders	14	11 (10.3%)	33	28 (26.2%)	47	33 (30.8%)	11	9 (9.1%)	42	34 (34.3%)	53	37 (37.4%)
Skin and subcutaneous tissue disorders	0	0	3	3 (2.8%)	3	3 (2.8%)	0	0	10	7 (7.1%)	10	7 (7.1%)
Surgical and medical procedures	1	1 (0.9%)	1	1 (0.9%)	2	2 (1.9%)	1	1 (1.0%)	2	2 (2.0%)	3	3 (3.0%)
Vascular disorders	4	3 (2.8%)	39	33 (30.8%)	43	34 (31.8%)	4	4 (4.0%)	28	21 (21.2%)	32	23 (23.2%)

**MedDRA v17.0 was used.*

Safety Summary

No differences were observed in 90-day stroke-related mortality, 90-day all-cause mortality, or sICH, while neurologic deterioration occurred less frequently in the thrombectomy than in the control group. All serious adverse events, were comparable across the treatment groups. The SOC of Nervous System Disorders had the highest rate of SAEs with 19.6% of subjects in the Treatment arm and was 30.3% of the subjects in the Control arm.

No new safety risks were identified in the DAWN Trial expanded indication population. The risks to health associated with the use of the Trevo Retrievers for this additional indication are similar to those associated with the use of the Trevo Retrievers for the currently cleared indications.

Conclusion

The results of the co-primary analysis and supporting data from this RCT demonstrate use of Trevo Retrievers to treat ischemic stroke by restoring blood flow and reducing the incidence of disability is safe and effective in patients treated 6-24 hours since TLSW. Furthermore, the UW-mRS expected benefit of 2.04 represents 20.4% of the total value of preventing a single death and, instead, achieving a normal neurologic outcome for that individual patient. Accordingly, the number needed to treat to save one life is 10/2.04 = 4.9 (95% credible interval 3.4-9.1). This value indicates that 4.9 patients need to be treated with Trevo thrombectomy rather than medical care alone for the accrued benefit to equal saving one life with return to normal function. The number needed to treat to achieve functional independence is 2.8, demonstrating a superior therapy for a patient population with very poor prognosis.

Summary of Substantial Equivalence

As supported by the DAWN study (IDE G130223), the data demonstrated that the expanded indications for use for the subject device do not raise any new or different questions of safety or effectiveness nor do they have the potential to significantly increase a safety or effectiveness concern raised by the predicate device. The subject and predicate device have identical principles of operations and technological characteristics. The Trevo ProVue and Trevo XP ProVue Retriever with expanded indications (subject device) is therefore substantially equivalent to the cleared predicate device.