May 23, 2022
Medical Device Evaluation Division
Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Report on the Deliberation Results

Classification	Instrument & Apparatus 51, Suckers, tubes and catheters for infusion or drainage
Term Name	Catheter for embolic capture in the central circulatory system
Brand Name	ENROUTE Transcarotid Neuroprotection System
Applicant	Silk Road Medical, Inc.
Designated Marketing Authorization Holder	Vorpal Technologies K. K.
Date of Application	May 14, 2021 (Application for marketing approval of medical devices manufactured in foreign countries)

Results of Deliberation

In its meeting held on May 23, 2022, the Committee on Medical Devices and In-vitro Diagnostics reached the following conclusion, and decided that this conclusion should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

This product should be designated and approved as a medical device subject to a use-results survey. The product is not classified as a biological product or a specified biological product.

The use-results survey period should be 3 years with the following conditions.

Approval Conditions

1. The applicant is required to take necessary measures to ensure that the product is used in compliance with the indication, only by surgeons with sufficient knowledge and experience in the procedure and in handling complications associated with the treatment. The surgeons also must have gained full understanding of the product's efficacy and safety through training on the surgical procedures and endovascular treatment for carotid artery stenosis using the product.
2. The applicant is required to take necessary measures to ensure that the product is used at medical institutions having surgeons experienced in the treatment of carotid artery stenosis and a system responsive to various cases including complications associated with treatment involving the product.

Review Report

April 25, 2022
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following medical device submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Classification	Instrument & Apparatus 51, Suckers, tubes and catheters for infusion or drainage
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Reviewing Office	Office of Medical Devices II

Review Results

April 25, 2022

Classification	Instrument & Apparatus 51, Suckers, tubes and catheters for infusion or drainage
Term Name	Catheter for embolic capture in the central circulation system (44841004)
Brand Name	ENROUTE Transcarotid Neuroprotection System
Applicant	Silk Road Medical, Inc.
Designated Marketing Authorization Holder	Vorpal Technologies K. K.
Date of Application	May 14, 2021 (Application for marketing approval of medical devices manufactured in foreign countries)

Results of Review

The ENROUTE Transcarotid Neuroprotection System (ENROUTE Transcarotid NPS or "the product") gains transcarotid vascular access in patients with carotid artery stenosis and provides embolic protection during carotid artery angioplasty and carotid artery stenting (CAS). The product consists of Transcarotid Arterial Sheath, Venous Return Sheath, Flow Controller, Arterial Dilator, Venous Dilator, and Guidewire.

The applicant submitted non-clinical data supporting biological safety, stability, durability, performance, and directions for use. The data indicated no particular problems.

The applicant submitted clinical data from the ROADSTER Plus study. This single-arm, prospective, multi-center study was conducted in the US and Europe to evaluate efficacy and safety of the product as a cerebral embolic protection device during carotid artery angioplasty and CAS in patients at a high risk of complications from carotid endarterectomy (CEA).

The primary endpoint "a composite of any stroke, myocardial infarction, and death during 30-day post-procedural period" occurred in 3.5% of subjects (5 of 141 subjects; 95% confidence interval, 1.16-8.08), indicating that the result met the prespecified threshold (11.0%). The "acute device success" and "technical success" were both 99.3% (140 of 141 subjects), indicating favorable results. Clinically important adverse events involving the ENROUTE Transcarotid NPS include artery dissection that is classified as serious or leading to discontinuation of the procedure (2.8%, 4 of 141 subjects), access site complications (10.6%, 15 of 141 subjects), and serious hypotension (2.8%, 4 of 141 subjects). Albeit some cases requiring additional treatment such as surgical procedure, all events had favorable outcomes.

Subsequently, a foreign post-marketing clinical study demonstrated that artery dissection can be minimized by product modification. These findings, together with other events, showed no particular problems as compared with conventional CAS data. The efficacy and safety of transcarotid CAS using the ENROUTE Transcarotid NPS are generally equivalent to those of conventional transfemoral CAS. Therefore, the product is considered a valuable option as embolization protection device used in stenting procedures in patients with carotid artery stenosis.

In order to introduce the ENROUTE Transcarotid NPS into Japan effectively and safely, involved surgeons or medical teams must be well experienced in the conventional treatments of carotid artery stenosis and gain full understanding of the product's efficacy, safety, and procedure through a training program or workshop so that they become competent to determine the eligibility of patients after due consideration of the use of conventional options as well. Furthermore, the ENROUTE Transcarotid NPS should be used by surgeons and at medical facilities capable of providing both medical and surgical cares including CEA against complications associated with the treatment involving the product.

The ENROUTE Transcarotid NPS is the first embolic protection device for CAS to be launched in Japan. Information on patient characteristics, devices used with the product, adverse events, and other data associated with the use of the product need to be collected through a use-results survey to take additional risk minimization measures, as necessary.

Based on the results of review, PMDA has concluded that the ENROUTE Transcarotid NPS may be approved for the following intended use with approval conditions below, and that the results should be presented to the Committee on Medical Devices and *In-vitro* Diagnostics for further deliberation.

Intended Use

The ENROUTE Transcarotid Neuroprotection System provides transcarotid vascular access and embolic protection during carotid artery angioplasty and stenting procedures for patients with carotid artery stenosis.

Eligible patients are those who have

- a common carotid artery greater than 6 mm in reference diameter
- a carotid bifurcation located at least 5 cm above the clavicle

Approval Conditions

1. The applicant is required to take necessary measures to ensure that the product is used in compliance with the indication, only by surgeons with sufficient knowledge and experience in the procedure and in handling complications associated with the treatment. The surgeons also must have gained full understanding of the product's efficacy and safety through training on the surgical procedures and endovascular treatment for carotid artery stenosis using the product.

2. The applicant is required to take necessary measures to ensure that the product is used at medical institutions having surgeons experienced in the treatment of carotid artery stenosis and a system responsive to various cases including complications associated with treatment involving the product.

Review Report

April 25, 2022

Product for Review

Classification	Instrument & Apparatus 51, Suckers, tubes and catheters for infusion or drainage
Term Name	Catheter for embolic capture in the central circulation system
Brand Name	ENROUTE Transcarotid Neuroprotection System
Applicant	Silk Road Medical, Inc.
Designated Marketing Authorization Holder	Vorpal Technologies K. K.
Date of Application	May 14, 2021 (Application for marketing approval of medical devices manufactured in foreign countries)
Proposed Intended Use	The ENROUTE Transcarotid Neuroprotection System provides transcarotid vascular access and embolic protection during carotid artery angioplasty and stenting procedures for patients with carotid artery stenosis. Intended patients are those who have • adequate femoral venous access • a common carotid artery greater than 6 mm in reference diameter • a confirmed carotid bifurcation located at least 5 cm above the clavicle as measured by doppler ultrasound scanning (DUS), computed tomography scan (CT) angiography, or magnetic resonance (MR) angiography.

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List of Abbreviations

AV	Arteriovenous
Bi-PAP	Bilevel Positive Airway Pressure
CAS	Carotid Artery Stenting
CEA	Carotid Endarterectomy
COPD	Chronic Obstructive Pulmonary Disease
CT	Computed Tomography Scan
DUS	Doppler Ultrasound Scanning
ITT	Intention-To-Treat
LVEF	Left Ventricular Ejection Fraction
MAE	Major Adverse Event
MI	Myocardial Infarction
MR	Magnetic Resonance
NYHA	New York Heart Association
PTFE	Polytetrafluoroethylene
TIA	Transient Ischemic Attack

I. Product Overview

The ENROUTE Transcarotid Neuroprotection System (ENROUTE Transcarotid NPS or "the product") is a device to create an arteriovenous shunt (AV Shunt) from the carotid artery to the femoral vein for the prevention of cerebral embolism associated with carotid artery angioplasty and stenting in patients with carotid artery stenosis. The product consists of (1) the Transcarotid Arterial Sheath, (2) the Venous Return Sheath, (3) the Flow Controller, the Arterial Dilator, the Venous Dilator, and the Guidewire (Figure 1).

Using a standard surgical technique, the Transcarotid Arterial Sheath is placed in the carotid artery central to the targeted narrowed area, and the Venous Return Sheath is placed into the femoral vein. Both sheaths are connected by the Flow Controller having an integrated filter with 200 μm-pores, thereby an AV Shunt is established. The carotid artery is then occluded near the insertion site of the Transcarotid Arterial Sheath using a clamp, etc., which creates an arterial/venous pressure difference, reversing blood flow from the internal and external carotid arteries into the venous circulation, thereby preventing cerebral embolism during carotid artery angioplasty and stenting (Figure 2). The reverse blood flow during the use of the ENROUTE Transcarotid NPS is determined by arterial/venous pressure difference, cerebral circulation, and the sum of flow resistance of sheaths and shunt. The flow can be controlled at 2 levels, high or low flow by Flow Controller (Figure 1).

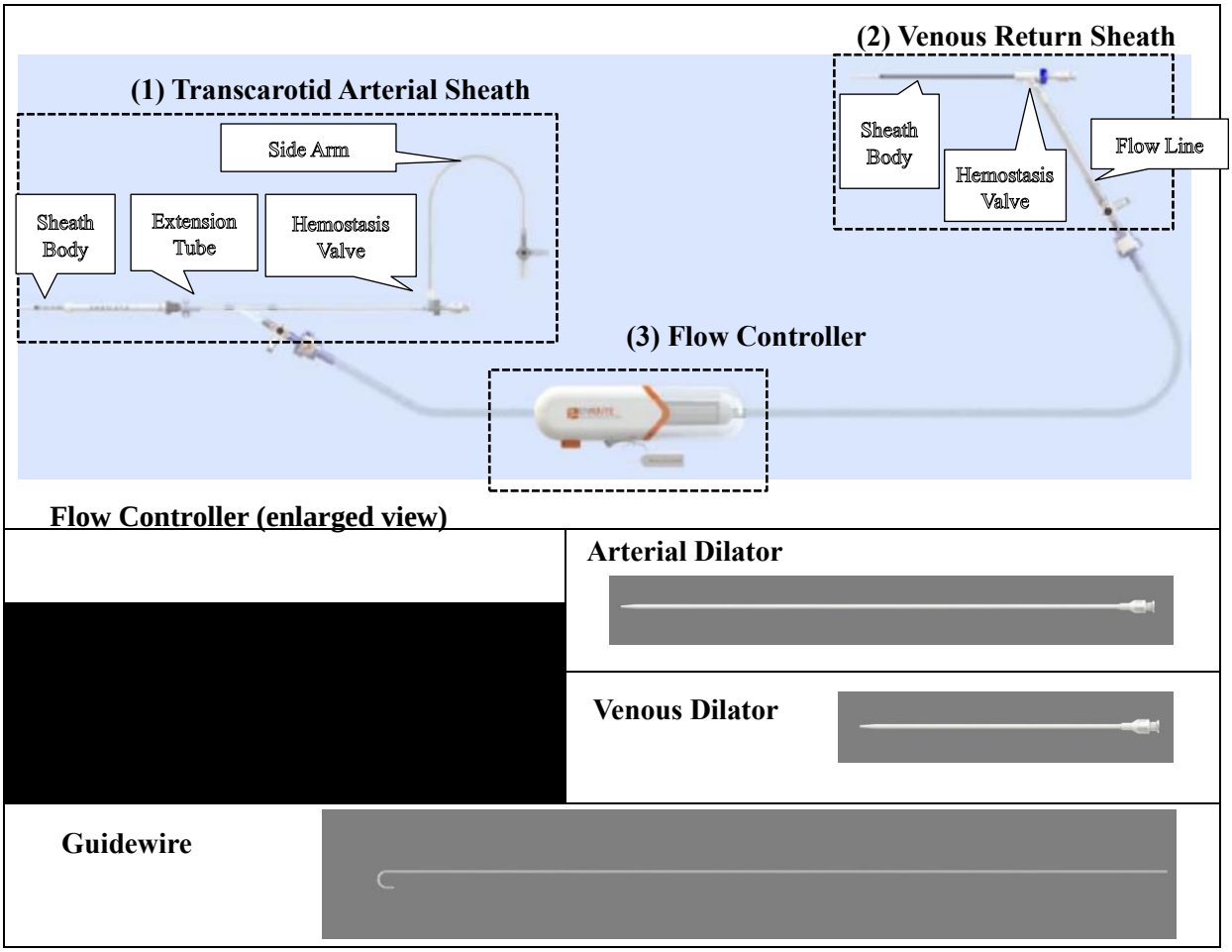

Figure 1. Components of the ENROUTE Transcarotid NPS

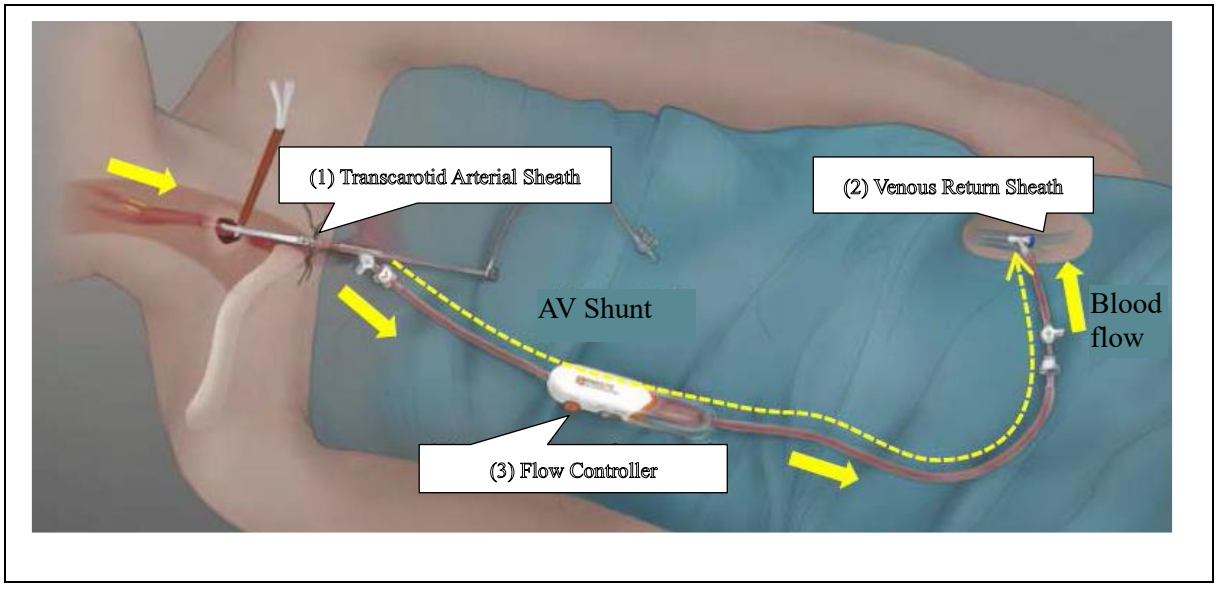

Figure 2. Schematic diagram of the ENROUTE Transcarotid NPS used in procedure

II. Summary of the Data Submitted and Outline of the Review Conducted by the Pharmaceuticals and Medical Devices Agency

The data submitted for the current application and the applicant's responses to the inquiries from the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined below.

The expert advisors present during the Expert Discussion on the ENROUTE Transcarotid NPS declared that they did not fall under Item 5 of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1. History of Development, Use in Foreign Countries, and Other Information

1.A Summary of the data submitted

1.A.(1) History of development

Carotid artery stenosis is a narrowing of the carotid arteries resulting from the deposition of cholesterol inside the wall at the bifurcation separating the internal and external carotid arteries which increased with the progression of atherosclerosis. Vascular stenosis may cause the formation of blood clots in the narrowed area, which can break off from the blood vessel wall and cause cerebral infarction. If symptomatic, patients may present with disturbance of consciousness, dyslalia, hemiplegia, disturbance of perception, and aphasia.

Treatments for carotid artery stenosis include medications (pharmacotherapies), carotid endarterectomy (CEA), and carotid artery stenting (CAS). According to the treatment guidelines published in and outside Japan,[1,2] the selection of intervention is based on the degree of stenosis, systemic condition, etc. of the patient.

CEA is a surgical procedure, in which an approximately 10-cm incision was made in the narrowed carotid artery under general anesthesia, and the lesion is resected with the surrounding intima to improve blood flow to the brain. CAS is a technique with a catheter inserted in the femoral artery, through which a carotid artery stent is placed in the internal carotid artery to dilate the narrowed carotid artery. Unlike CEA, transfemoral CAS does not require neck incision or general anesthesia, and is thus considered less invasive than CEA and advantageous in terms of less burden in older patients and patients with various comorbidities. However, due to problems with CAS, including cerebral embolism risk caused by debris produced during the procedure or possible recurrent stenosis, etc., CEA remains as the recommended first-line therapy in Japan. To reduce associated cerebral embolism risk, CAS is always performed with an embolic protection device that captures debris produced in the series of procedures.

In the SAPPHIRE study,[3] which was conducted in patients at high risk for CEA, and the CREST study,[4] which was conducted in patients with normal risk for CEA, the difference in the composite incidence of serious adverse events associated with CEA and transfemoral CAS (stroke, myocardial infarction [MI], and death) was not statistically significant. However, when point estimates of the incidence were

compared, mild stroke tended to occur at a higher incidence in transfemoral CAS while myocardial infarction tended to occur at a higher incidence in CEA. The higher incidence of mild stroke in patients undergoing transfemoral CAS is suggested to be attributable to debris coming in contact with the aortic arch, lesion, or other areas during the delivery of the distal embolic protection device, or debris that cannot be captured by a filter-type embolic protection device.

To address the above-mentioned problem pertaining to transfemoral CAS, a distal embolic protection technique (Parodi's technique)[5] was devised. With this technique, flow reversal is established in the lesion area by balloon occlusion in the vessel proximal to the lesion. The ENROUTE Transcarotid NPS developed for the prevention of embolism by the applicant, Silk Road Medical, Inc., employs the transcarotid approach for flow reversal in combination with the Parodi's technique in CEA to reduce the risk of debris produced during device delivery.

The ROADSTER Plus study was conducted in 2012 in patients at high risk for CEA using the previous-generation of the ENROUTE Transcarotid NPS. Later, some modifications were made as listed in Table 1 for the integration of the Flow Controller components, etc., which improved device operability, leading to the development of the ENROUTE Transcarotid NPS, the upgraded model.

Table 1. Main improvements in the ENROUTE Transcarotid NPS from the previous-generation device

Improvements	Previous-generation device	ENROUTE Transcarotid NPS
Flow characteristics (specifications)	Resistance of the Criado's flow reversal circuit at the "low flow rate" setting: [redacted]	Resistance of the Criado's flow reversal circuit at the "low flow rate" setting: [redacted]%, [redacted]%
Flow Controller configuration	Low flow line, filter, and check valve are separately structured from the Flow Controller	Low flow line, filter, and check valve are integrated in the Flow Controller
Transcarotid Arterial Sheath tip shape	Straight	Angled (15° ± [redacted]°)
Guidewire diameter	[redacted]	0.89 mm (0.035″) diameter
Guidewire main raw materials		Nitinol, stainless steel
Raw materials		New raw materials are used in the Side Arm of Transcarotid Arterial Sheath

1.A.(2) Use in foreign countries

Table 2 shows the statuses of authorization/licensing and marketing of the ENROUTE Transcarotid NPS in foreign countries.

Table 2. Authorization/licensing and marketing in foreign countries (as of June 2021)

Countries	Intended use	Date approved	Quantity sold
US	The ENROUTE Transcarotid NPS provides transcarotid vascular access, introduction of diagnostic agents and therapeutic devices, and embolic protection during carotid artery angioplasty and stenting procedures for patients diagnosed with carotid artery stenosis who have • adequate femoral venous access • a common carotid artery >6 mm in reference diameter • a confirmed carotid bifurcation located ≥5 cm above the clavicle as measured by dual doppler ultrasound scanning (DUS), computed tomography scan (CT) angiography, or magnetic resonance (MR) angiography.	March 2016	[redacted]
Europe		January 2016	

1.A.(3) 1AMalfunctions and adverse events reported outside Japan

Table 3 shows the incidence of malfunctions of the ENROUTE Transcarotid NPS reported in foreign countries.

Table 3. Malfunctions reported in foreign countries (January 2016 to February 2021)

Type of malfunction	Number of cases	Incidence* (%)
Carotid artery dissection	[redacted]	0.41%
Seizure (stroke)		0.26%
Thrombosis		0.01%
(Transient ischaemic attack) debility		0.007%
Extravasation		0.004%
Procedural complications (dizziness)		0.004%
Problem of device (sheath breakage)		0.004%

* Incidence = (number of cases / total number of procedures [redacted] × 100

1.B Outline of the review conducted by PMDA

All reported events are known and their incidences were within the acceptable range. These events are evaluated in Section 6.

2. Design and Development

2.(1) Performance and safety specifications

2.(1).A Summary of the data submitted

The proposed performance and safety specifications for the ENROUTE Transcarotid NPS include the following: for the Transcarotid Arterial Sheath and Venous Return Sheath, flexural durability (kink resistance), leak-tightness (air leakage), leak-tightness (liquid leakage under pressure), tensile strength, and corrosion; for the Flow Controller, leak-tightness (liquid leakage under pressure), leak-tightness (venous pressure spike), and tensile strength; for the overall system, flow characterization, air emboli/clinical emboli simulation and filter performance (particle capture), biological safety, bacterial

endotoxins, and ethylene oxide sterilization residuals; for the Arterial Dilator and Venous Dilator, hub separation force, dilator withdrawal force, leak-tightness (air leakage, liquid leakage under pressure), hub stress crack resistance, and tensile strength; for the Guidewire, flexural durability, break/rupture strength, coating separation strength, tensile strength, and corrosion.

The proposed specifications for flow characterization would allow the blood flow rate to be greater than the flow resistance of the flow reversal circuit (Criado's standard flow reversal technique[6]) that can simulate the pressure gradient of AV Shunt necessary to perform transcarotid CAS under the flow reversal condition, and were shown to have sufficient embolic protection effect during CAS procedure. The specifications for air emboli/clinical emboli simulation and filter performance (particle capture) were established based on the simulation study results.

2.(1).B Outline of the review conducted by PMDA

The delamination of polytetrafluoroethylene (PTFE) coating, which can cause distal embolism, is considered critical to assure the quality and safety of the ENROUTE Transcarotid NPS. PMDA therefore requested the applicant to include particulate testing with the Guidewire in the specifications as well as radiopacity of the Guidewire.

The applicant agreed with PMDA's request, and specified values based on the data from these tests.

The applicant changed the specifications for flow characterization, specifically, the range of resistance values of the flow reversal circuit based on the Criado's standard flow reversal technique at the low flow rate setting, from [redacted] for the previous-generation device to [redacted] for the ENROUTE Transcarotid NPS. PMDA asked the applicant to explain the rationale for the change.

The applicant's response:

The flow rate of blood passing through the ENROUTE Transcarotid NPS can be increased by up to [redacted]% by lowering the minimum permissible limit of flow resistance by [redacted]%. This change is acceptable for the following reasons:

- The lower the flow resistance is, the higher the flow rate becomes. Embolic protection characteristics will not be lost.
- Of 74 patients who underwent procedures under local or general anesthesia in the ROADSTER Plus study, 1 patient was intolerant of the high flow rate setting for flow reversal but had no sequelae, indicating that the flow rate is within the clinically acceptable range.
- Given that the high flow rate setting is [redacted]% of the flow of the low flow rate, a potential increase in flow rate by [redacted]% in either the high or low flow rate setting would have only a minor impact on the acceptable range in clinical practice.
- Cautionary advice will be given against the use of the product in patients with intolerance to flow reversal.

After reviewing the validity of the proposed performance and safety specifications including those added, tests, and specification limits, PMDA concluded that there were no particular problems.

2.(2) Physicochemical properties

Data on physicochemical properties were not submitted. The physicochemical properties are evaluated collectively later in Section "2.(5) Performance."

2.(3) Biological safety

2.(3).A Summary of the data submitted

To support the product's biological safety, the applicant submitted the data from cytotoxicity, sensitization, intracutaneous reactivity, systemic toxicity, pyrogenicity, blood compatibility, and genotoxicity studies, which were conducted using the ENROUTE Transcarotid NPS. The applicant also submitted the data from the following studies conducted using newly added raw materials: cytotoxicity, sensitization, intracutaneous reactivity, systemic toxicity, pyrogenicity, and blood compatibility studies.

The results of these studies provided no problematic findings.

2.(3).B Outline of the review conducted by PMDA

PMDA reviewed the biological safety of the ENROUTE Transcarotid NPS and concluded that there were no particular problems.

2.(4) Stability and durability

2.(4).A Summary of the data submitted

The stability data of the ENROUTE Transcarotid NPS were not submitted in light of the notification of "Handling of stability studies related to the determination of the shelf life in the Application for Approvals (Certifications) for Marketing Medical Devices" (PFSB/ELD/OMDE Notification No. 1227-5, dated December 27, 2012, issued by the Office of Medical Devices Evaluation, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare). The applicant submitted a self-declaration stating that a shelf life of 3 years was specified for the product after necessary stability evaluation.

2.(4).B Outline of the review conducted by PMDA

PMDA reviewed the data on the stability and durability of the ENROUTE Transcarotid NPS and concluded that there was no particular problem.

2.(5) Performance

2.(5).A Summary of the data submitted

The applicant submitted the following data to support the performance of the components. The data demonstrated the conformity of these components with all criteria set.

- Transcarotid Arterial Sheath: data from the testing of sheath body kink (flexural durability), airtightness (air leakage, liquid leakage under pressure), tensile strength at the junctions, and corrosion
- Venous Return Sheath: data from the testing of sheath body kink (flexural durability), leak-tightness (air leakage, liquid leakage under pressure), and tensile strength at the junctions
- Flow Controller: data from the testing of High/Low Flow Switch cycling, Flow Stop Button cycling, leak-tightness (liquid leakage under pressure, venous pressure spike), and tensile strength at the junctions
- Overall system: data on flow characterization
- Arterial Dilator and Venous Dilator: data from the testing of dilator withdrawal force, leak-tightness (air leakage, liquid leakage under pressure), hub-luer separation force, hub stress crack resistance, and tensile strength
- Guidewire: data from the testing of break, bending, radiopacity, strength at the core wire/coil junction, coating delamination strength, particulates, and corrosion

To support the flow characterization of the product and the performance of capturing embolic materials by the Flow Controller filter, the applicant submitted the data from the studies using carotid artery models for small particle transport efficiency, large particle transport efficiency, and air emboli/clinical emboli simulation. The particle transport efficiency studies demonstrated filter capture performance of ≥[redacted]% for small particles and ≥[redacted]% for large particles. The air emboli/clinical emboli simulation demonstrated the conformity with the flow characterization criteria required for the ENROUTE Transcarotid NPS (≤[redacted]% of the flow resistance value under the condition of no embolic materials).

The applicant submitted data from an animal study (evaluation of acute thrombus formation) to evaluate safety including thrombus formation and vascular injury associated with the use of the ENROUTE Transcarotid NPS. In [redacted] animals, the product established flow reversal. A series of CAS procedures were performed while switching between high and low flow settings. After a total of continuous flow reversal time of ≥[redacted] minutes at the low flow rate, the ENROUTE Transcarotid NPS was removed before vascular suture. In this study, a throttle line was inserted between the Flow Controller and Venous Return Sheath so that the flow rate was maintained at [redacted] mL/min for the purpose of the evaluation of performance at the low flow rate under extremely severe conditions. Angiographic evaluation of thrombi and vascular injury, the evaluation of thrombus formation in the Flow Controller filter, visual pathological examination of (arterial and venous) vascular access sites, and visual pathological examination of peripheral organs (the brain, lungs, and heart) were performed.

Although the angiographic evaluation at the time of Transcarotid Arterial Sheath insertion identified moderate vasospasm (n = [redacted]), for being a commonly observed event in [redacted], vasospasm was not considered clinically relevant. In other animals (n = [redacted]), <1 mm thrombi were found inside the Flow Controller. This was caused by the Guidewire tip unintentionally placed at a distal branch vessel by the operator, and thus this event was not considered to have caused by the flow reversal created by the product. There was no thrombus formation nor vascular injury severer than that expected in the normal endovascular treatment, and there were no pathological findings raising concerns.

The applicant submitted data from a sheath insertion study using the carotid artery recovered from a donated body, and a sheath insertion study for guidewire validation. The safety of the ENROUTE Transcarotid NPS at its insertion was considered clinically acceptable.

2.(5).B Outline of the review conducted by PMDA

PMDA asked the applicant to explain the validity of embolization conditions in the small and large particle transport efficiency studies and air emboli/clinical emboli simulation study in light of appropriate assessment of the product's intended ability to prevent embolism.

The applicant's explanation:

The small particle transport efficiency study was performed with embolic materials of approximately [redacted] to [redacted] pieces of [redacted] fine particles that were available in diameter ranging from [redacted] to [redacted] μm without having to be condensed or disintegrated during the study. A total of [redacted] to [redacted] pieces of fine particles in diameter of [redacted] to [redacted] μm are equivalent to [redacted] Rapps (1 Rapp = embolic load per carotid artery angioplasty reported in studies[7,8]) of particles of [redacted] to [redacted] μm in diameter. The large particle transport efficiency study used [redacted] nylon particles of [redacted] μm in diameter. A total of [redacted] pieces of particles of [redacted] μm in diameter are equivalent to [redacted] Rapp of particles of [redacted] to [redacted] μm in diameter. The density of the small particles ([redacted] g/mL) and that of the large particles ([redacted] g/mL) are similar to the density of materials expected to pass through the system of ENROUTE Transcarotid NPS during procedure, namely, blood ([redacted] g/mL), thrombus ([redacted] ± [redacted] g/mL), connective tissue ([redacted] g/mL), and vessel walls ([redacted] g/mL). Therefore, the conditions are clinically appropriate.

In the air emboli simulation, [redacted] mL of air was injected. The volume of air bubbles contained in the [redacted]-cm Extension Tube of the Transcarotid Arterial Sheath is equivalent to approximately [redacted] mL. Air bubbles of this size are easily visible to the operator and are expected to be removed by aspiration or other means. The study showed that even an injection of [redacted]-mL air emboli ([redacted] times the volume of air bubbles [redacted] mL) would not have a significant impact on the flow rate of blood passing through the ENROUTE Transcarotid NPS.

In the clinical emboli simulation, [redacted], which was thought to be equivalent to clinical embolic material, was used to fabricate mock embolic material. The mock embolic material was separated into [redacted] groups by particle diameter using high-precision sieves. The size distribution and number of particles of embolic material used were specified in the same manner as those specified in the small and large particle transport efficiency studies. In this study, the amount of embolic material used was equivalent to that to be released in a total of [redacted] sessions of carotid angioplasty procedures ([redacted] Rapps).

PMDA's view:
The embolic materials used in the small and large particle transport efficiency studies and air emboli/clinical emboli simulation were specified taking account of the embolic materials that are expected to be encountered in the clinical setting. Therefore these embolic materials are acceptable. These studies suggested that the ENROUTE Transcarotid NPS captures embolic materials while maintaining a flow reversal rate required for cerebral embolic protection. The ROADSTER Plus study revealed no cases of peripheral embolism caused by poor emboli capture and demonstrated the efficacy of the product as a cerebral embolic protection device. Taken together, the product has embolic protection ability required in clinical practice.

Based on the above performance data, PMDA concluded that there were no particular problems.

2.(6) Directions for use

2.(6).A Summary of the data submitted

The applicant submitted data relating to directions for use of the ENROUTE Transcarotid NPS from studies using mock blood vessels and the product components for assessing the ease of passage of the Guidewire and for simulations. The data from these studies demonstrated conformity with the specified criteria.

2.(6).B Outline of the review conducted by PMDA

Based on the review of data relating to directions for use, PMDA concluded that there were no particular problems.

3. Conformity to the Requirements Specified in Paragraph 3 of Article 41 of Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices

3.A Summary of the data submitted

The applicant submitted a declaration of conformity declaring that the ENROUTE Transcarotid NPS meets the standards for medical devices as stipulated by the Minister of Health, Labour and Welfare in accordance with Paragraph 3 of Article 41 of Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (hereinafter referred to as "the Essential Principles") (MHLW Ministerial Announcement No. 122, 2005).

3.B Outline of the review conducted by PMDA

PMDA reviewed the conformity of the ENROUTE Transcarotid NPS to the Essential Principles. Details are shown below.

1) The conformity of the product to Article 1, which stipulates preconditions, etc. for designing medical devices (particularly requirements for users, such as the expected level of technical knowledge and experience, and the expected level of education and training for users)

   PMDA's view:

   As described in Sections "6.B Outline of the review conducted by PMDA" and "7.B Outline of the review conducted by PMDA," essential elements to balance the risks and benefits of the product are the selection of eligible patients as well as users and medical institutions that provide the procedure, the provision of training for healthcare professionals, and adherence to the proper use standard. Accordingly, approval conditions should be attached to ensure that these necessary measures are taken.

2) The conformity of the product to Article 2, which stipulates risk management throughout the life cycle of medical devices

   PMDA's view:

   As described later in Sections "6.B Outline of the review conducted by PMDA" and "7.B Outline of the review conducted by PMDA," because of the lack of clinical data in Japan, the efficacy and safety of the product need to be evaluated in the clinical setting. Therefore, PMDA instructed the applicant to conduct a use-results survey.

3) The conformity of the product to Article 3, which stipulates the performance and function of medical devices, and to Article 6, which stipulates the efficacy of medical devices

   PMDA's view:

   As described later in Sections "6.B Outline of the review conducted by PMDA" and "7.B Outline of the review conducted by PMDA," the CAS performed with the product achieved favorable results in the clinical study, demonstrating that the use of the product is effective and safe in patients found as eligible based on a good understanding of the product characteristics. The review of conformity to Articles 3 and 6 indicated no problems.

4) The conformity of the product to Article 4, which stipulates the term of validity or lifetime of medical devices

   PMDA's view:

   As described earlier in Section "2.(4).B Outline of the review conducted by PMDA," in accordance with "Handling of stability studies related to the determination of the shelf life in the Application for Approvals (Certifications) for Marketing Medical Devices" (PFSB/ELD/OMDE Notification No. 1227-5, dated December 27, 2012, issued by the Office of Medical Devices Evaluation,

Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare), the applicant submitted a self-declaration stating that the shelf life for the product was selected after the stability evaluation required. The review of conformity to Article 4 indicated no problems.

5) The conformity of the product to Article 7, which stipulates the chemical properties, biological safety, and other aspects of medical devices
PMDA's view:
As described earlier in Sections 2.(2), 2.(3), 2.(5), and "4.B Outline of the review conducted by PMDA," the chemical properties of the product were validated. The review of conformity to Article 7 indicated no problems.

6) The conformity of the product to Article 8, which stipulates the prevention of microbial contamination of medical devices
PMDA's view:
As described later in Section "5.B Outline of the review conducted by PMDA," the ability of the product to prevent microbial contamination was validated. The review of conformity to Article 8 indicated no problems.

7) The conformity of the product to Article 17, which stipulates the general requirements for information provision to users, i.e., publicizing precautions and specifying such information in the package inserts (hereinafter referred to as "Information on Precautions, etc.")
PMDA's view:
As described later in Sections "6.B Outline of the review conducted by PMDA" and "7.B Outline of the review conducted by PMDA," to maintain the risk-benefit balance of the product, the most important is appropriate use of the product for appropriate patients according to users' understanding of product-associated risks. Relevant information should be disseminated through Information on Precautions, etc., proper use standard, training, and by other means.

Based on the above, PMDA comprehensively reviewed the conformity of the ENROUTE Transcarotid NPS to the Essential Principles and concluded that there was no particular problem.

4. Risk Management

4.A Summary of the data submitted

The applicant submitted a summary of risk management, risk management system, and its progress in accordance with EN ISO 14971: 2012 "Medical devices—Application of risk management to medical devices."

4.B Outline of the review conducted by PMDA

After a comprehensive review of the risk management documents taking into account the discussion presented in Section "3.B Outline of the review conducted by PMDA," PMDA concluded that there was no particular problem.

5. Manufacturing Process

5.A Summary of the data submitted

The applicant submitted data on the sterilization methods for the ENROUTE Transcarotid NPS (sterilization conditions for sterility assurance level, residue after ethylene oxide sterilization).

5.B Outline of the review conducted by PMDA

PMDA reviewed the documents on the manufacturing process and concluded that there was no particular problem.

6. Clinical Data or Alternative Data Accepted by the Minister of Health, Labour and Welfare

6.A Summary of the data submitted

For the clinical evaluation of the ENROUTE Transcarotid NPS, the applicant submitted data from the ROADSTER Plus study, which was conducted in Europe and the US using the previous-generation device.

6.A.(1) ROADSTER Plus study (Study period, November 1, 2012 to April 13, 2016)

Table 4 outlines the ROADSTER Plus study, a single-arm, prospective, multi-center study conducted to evaluate the efficacy and safety of the previous-generation device used for cerebral embolic protection during carotid artery angioplasty and CAS in patients at high risk of complications from CEA.

Table 4. Outline of ROADSTER Plus study

Item	Outline
Type of study	Single-arm, prospective, multi-center clinical study
Study population	Patients with atheromatous stenosis in the cervical internal carotid artery at high risk of complications from CEA
Main inclusion criteria	1. Patient meeting one of the following criteria regarding neurological symptoms and degree of stenosis Symptomatic: ≥50% stenosis as determined by angiography, history of stroke (minor or non-disabling stroke), transient ischemic attack, and/or amaurosis fugax within 180 days prior to procedure; or Asymptomatic: ≥70% stenosis as determined by angiography, without any neurological symptoms within the preceding 180 days 3. Patients having a discrete lesion in the internal carotid artery with or without lesions in the contiguous common carotid artery 8. Patients meeting at least one of the following criteria for high surgical risk factors: **Anatomic high-risk criteria** A. Contralateral carotid artery occlusion B. Tandem stenosis of >70% C. High cervical carotid artery stenosis D. Restenosis after CEA E. Bilateral stenosis requiring treatment (the contralateral vessel is due to be treated within 30 days of the procedure)

	F. Hostile neck that has been determined as safe for transcarotid access by the investigator including the following: I. History of neck irradiation II. Radical neck dissection III. Cervical spine immobility **Medical high-risk criteria** G. Aged ≥75 years H. ≥ 2-vessel coronary artery disease with history of angina I. Canadian Cardiovascular Society angina classification III or IV, or unstable angina J. New York Heart Association (NYHA) cardiac function classification III or IV K. Left ventricular ejection fraction (LVEF) of <30% L. Myocardial infarction between 72 hours and 6 weeks before the procedure M. Chronic obstructive pulmonary disease accompanied by one of the following ▪ A percent predicted forced expiratory volume in one second of <50% ▪ Long-term oxygen therapy ▪ Oxygen partial pressure at rest ≤60 mmHg (when breathing room air) N. Permanent contralateral cranial nerve injury O. Chronic renal insufficiency (serum creatinine ≥2.5 mg/dL)
Main exclusion criteria	15. Patients having neurologic illnesses within the past 2 years characterized by fleeting or fixed neurologic deficit which cannot be distinguished from transient ischaemic attack (TIA) or stroke (e.g. partial or secondarily generalized seizures, complicated or classic migraine, tumor or other space-occupying brain lesions, subdural hematoma, cerebral contusion or other post-traumatic lesions, intracranial infection, demyelinating disease, moderate to severe dementia, or intracranial hemorrhage) 16. Patients having a severe ipsilateral stroke (cerebrovascular accident [CVA] or retinal embolism) with major neurological deficit that is likely to confound study endpoints within 1 month of index procedure. 21. Patient has occlusion (Thrombolysis in Myocardial Infarction grade 0) or >1 cm “string sign” in the ipsilateral common or internal carotid artery. 25. Presence of extensive or diffuse atherosclerotic disease involving the proximal common carotid artery that would preclude the safe introduction of the study device. 26. Patients having a <5-cm distance between the clavicle and bifurcation, as assessed by duplex ultrasonography, computed tomography angiography, or magnetic resonance (MR) angiography. 31. Patients having a TIA or amaurosis fugax within 48 hours prior to the procedure.
Number of patients enrolled	141
Follow-up period	30 days post-procedure Patients suspected of having stroke were subjected to a follow-up neurological examination at 3 months post-procedure, and those suspected of having a procedure-related cranial nerve injury were subjected to a follow-up neurological examination at 6 months post-procedure.
Primary endpoint	A composite of any stroke, myocardial infarction, and death during a 30-day post-procedure period
Secondary endpoints	Technical success, acute device success, procedural success, access site complications, all death, all stroke, all myocardial infarction, cardiac death, ipsilateral stroke, contrast usage

A roll-in group with up to 5 patients was established per investigator in the ROADSTER Plus study. After the completion of the main registration, study centers continued to enroll patients in the extended-access phase so as to allow continuous use of the study device during the review process of 510 (k) submission in the US.

According to the protocol, the primary endpoint was analyzed using the Intention-To-Treat (ITT) population, which comprised all patients except those who were in the Roll-in group and those who were enrolled in the extended-access phase (Figure 3).

An achievement threshold of ≥11.0% was determined for the primary endpoint based on the data from the CREATE study,[9] which evaluated the efficacy and safety of the Spider Protection Device (Approval No. 22400BZX00174000) used in combination with the PROTEGE Carotid Stent Set (Approval No. 22400BZX00175000) in patients at high risk for CEA, a study population similar to that of the ROADSTER Plus study. The minimum number of patients required to reject the null hypothesis that the upper bound of the 95% confidence interval (CI) for the incidence of stroke, myocardial infarction, and death within 30 days post-procedure be ≥11.0% was calculated to be 140, based on the assumption of a one-sided significance level of 2.5% and a power of 80%. A total of 141 patients were enrolled.

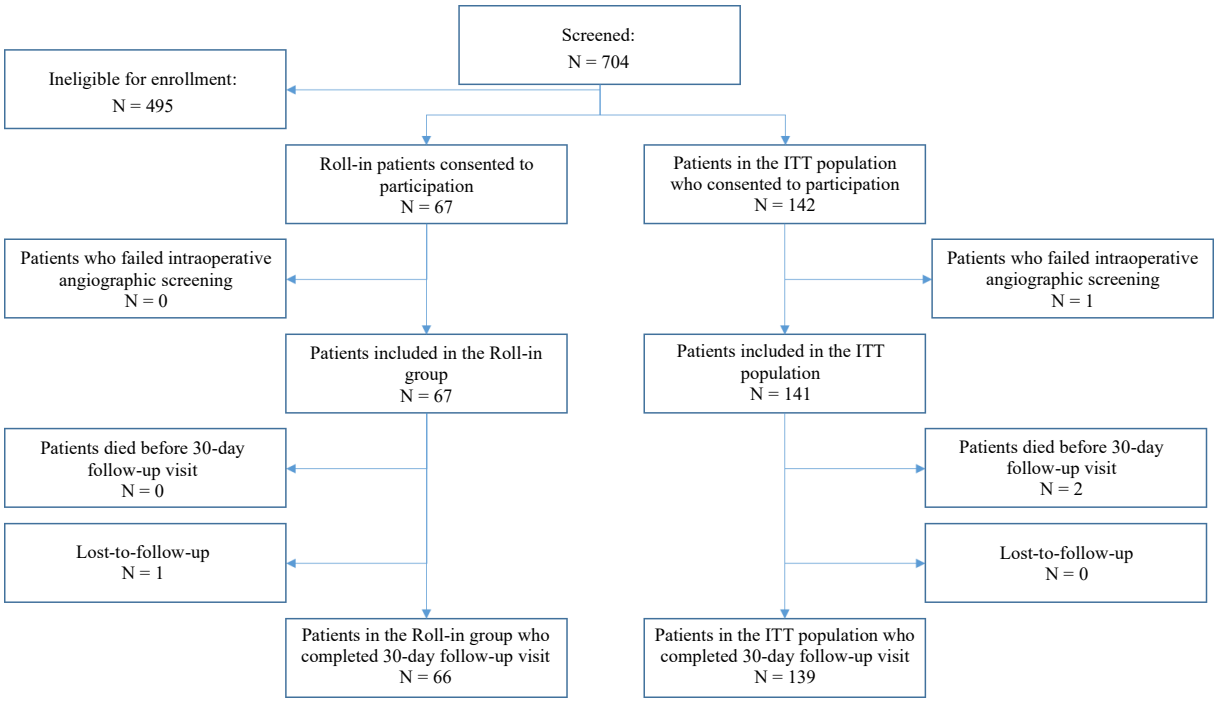

Figure 3. Flow chart of patient enrollment in the ROADSTER Plus study (ITT group)

6.A.(1).1) Patient characteristics

Table 5 shows patient characteristics in the ROADSTER Plus study. Table 6 shows risk factors for CEA in each patient.

Table 5. Patient characteristics

Observation		ITT (N = 141)	Extended-access phase (N = 78)
Age (years)	Mean ± SD	72.9 ± 8.89	71.14 ± 7.89
Height (cm)	Mean ± SD	169.7 ± 10.84	170.09 ± 9.86
Weight (kg)	Mean ± SD	80.0 ± 17.13	84.86 ± 18.53
Sex	Male	65.2% (92/141)	56.4% (44/78)
	Female	34.8% (49/141)	43.6% (34/78)
Medical history			
Smoking history		73.8% (104/141)	92.3% (72/78)
Current smoker		22.7% (32/141)	26.9% (21/78)
Drinking history		41.1% (58/141)	37.2% (29/78)

Observation		ITT (N = 141)	Extended-access phase (N = 78)
Current drinker		36.2% (51/141)	33.3% (26/78)
Diabetes mellitus		36.9% (52/141)	37.2% (29/78)
Diabetes mellitus type	type I	2.1% (3/141)	2.6% (2/78)
	type II	34.8% (49/141)	34.6% (27/78)
History of hypertension		86.5% (122/141)	91.0% (71/78)
Hyperlipidemia		77.3% (109/141)	96.2% (75/78)
Peripheral arterial disease		29.1% (41/141)	34.6% (27/78)
Coronary artery disease		41.8% (59/141)	53.8% (42/78)

Table 6. Applicable CEA high-risk criteria

Category	ITT (N = 141)	Extended-access phase (N = 78)
Contralateral carotid artery occlusion	7.8% (11/141)	12.8% (10/78)
Tandem stenosis of >70%	0.7% (1/141)	2.6% (2/78)
High cervical carotid artery stenosis	29.8% (42/141)	16.7% (13/78)
Restenosis after CEA	20.6% (29/141)	39.7% (31/78)
Bilateral stenosis requiring treatment	4.3% (6/141)	1.3% (1/78)
Hostile neck that is safe for transcarotid access	15.6% (22/141)	10.3% (8/78)
Aged ≥75 years	46.8% (66/141)	32.1% (25/78)
≥2-vessel coronary artery disease with history of angina	10.6% (15/141)	17.9% (14/78)
History of angina	1.4% (2/141)	3.8% (3/78)
Cardiac failure congestive—NYHA cardiac function classification III or IV	0.7% (1/141)	0.0% (0/78)
Known severe left ventricular dysfunction: LVEF <30%	1.4% (2/141)	1.4% (1/78)
MI between 72 hours and 6 weeks before the procedure	0.7% (1/141)	1.3% (1/78)
Severe pulmonary disease (COPD)	4.3% (6/141)	7.7% (6/78)
Permanent contralateral cranial nerve injury	0.0% (0/141)	0.0% (0/78)
Chronic renal insufficiency	0.7% (1/141)	0.0% (0/78)

6.A.(1).2) Study results

6.A.(1).2).(a) Primary endpoint

The incidence of events in the definition of the primary endpoint, "a composite of any stroke, myocardial infarction, and death during the 30-day post-procedural period (major adverse events [MAEs])," was 3.5% (5 of 141 subjects, 95% CI, 1.16-8.08), and the upper bound of the 95% confidence interval (8.08%) met the prespecified threshold (11.0%) (Table 7). The MAEs that occurred in the 5 subjects included death (2 subjects), stroke (2 subjects), and myocardial infarction (1 subject) (Table 8). The results of the extended-access phase group were similar to those of the ITT population (Table 7).

Table 7. Primary endpoint

Parameter	ITT (N = 141)	Extended-access phase (N = 78)
MAE within 30 days post-procedure	3.5% (5/141)	3.8% (3/78)
(Exact 95% binomial CI), *P*-value	(1.16, 8.08), 0.0047	(0.80, 10.83)
– Death within 30 days post-procedure	1.4% (2/141)	0.0% (0/78)
– Stroke within 30 days post-procedure	1.4% (2/141)	1.3% (1/78)
– MI within 30 days post-procedure	0.7% (1/141)	2.6% (2/78)

Table 8. Causes and outcomes in patients who failed to achieve the primary endpoint

Patient ID.	Cause	Development/outcome	Relationship with the product or procedure (adjudicated by the independent committee)	
			The product	Procedure
ITT population				
[redacted]	Death	The patient died 15 days post-procedure due to diabetic ketoacidosis, pneumonia, and elevated cardiac enzymes.	Possibly related	Related
	Death	The patient died 22 days post-procedure due to respiratory failure caused by aspiration pneumonia after general anesthesia and epistaxis.	Possibly related	Related
	Stroke	No neurologic abnormalities were noted when the patient regained consciousness after the procedure. At 8 hours post-procedure, facial paralysis on the right side and speech disorder were noted, and the patient was diagnosed as having ipsilateral ischemic stroke. The symptoms improved 30 days later.	Probably related	Related
	Stroke	No neurologic abnormalities were noted when the patient regained consciousness after the procedure. At 2 days post-procedure, left-sided hemiparesis, drowsiness, and disorientation were noted. Diffusion weighted magnetic resonance imaging (MRI) confirmed dot-like changes in the right frontal lobe and ischemia in the bilateral watershed area but predominantly in the right hemisphere. The patient was diagnosed as having had a stroke. The patient had grade 4/5 muscle strength in all extremities 30 days later.	Possibly related	Related
	MI	Elevated troponin I levels were noted at 1-day post-procedure without accompanying chest symptoms. Coronary angiography revealed chronic left anterior descending coronary artery obstruction with well-developed collateral branches. Acute surgical intervention was not necessary, and the condition was managed medically. The event was confirmed as myocardial infarction.	Not related	Probably related
Extended-access phase group				
[redacted]	Stroke	No neurologic abnormalities were noted after the procedure. Left-sided hemiplegia was noted at 5 hours post-procedure, and diffusion weighted MRI	Possibly related	Related

[redacted]		confirmed restricted diffusion of multiple small foci in the right frontoparietal lobe, and the patient was diagnosed as having had a stroke. Minor sensory loss was still present 30 days later.		
	MI	At 3 days post-procedure, the patient returned to the office complaining of dyspnea. Pulmonary congestion, pleural effusion, decreased left ventricular systolic function, and increased troponin I levels were noted, and the patient was re-admitted to the hospital. Severe multivessel lesions were found by cardiac catheterization and emergency coronary artery bypass was performed. The event was confirmed as myocardial infarction.	Not related	Probably related
	MI	The patient experienced chest pain lasting ≤10 minutes twice on the day of procedure. The electrocardiogram indicated ST inversion in V3-V6, and increased troponin I levels were noted. Echocardiography indicated preserved left ventricular function, and additional intervention was not performed. The event was confirmed as myocardial infarction.	Not related	Probably related

6.A.(1).2).(b) Secondary endpoints

In the ITT population, acute device success (i.e., successful delivery of the device, establishment of reverse flow, and successful retrieval/removal from the vasculature) and technical success were both achieved in 99.3% of subjects (140 of 141 subjects). Success was not achieved in 1 subject whose procedure was terminated due to artery dissection (Patient No. [redacted]). Access site complications occurred in 15 subjects (10.6%) (**Table 9**).

Table 9. Secondary endpoints (30 days post-procedure)

Endpoint		ITT (N = 141)	Extended-access phase (N = 78)
Acute device success		99.3% (140/141)	100.0% (78/78)
Technical success		99.3% (140/141)	100.0% (78/78)
Procedural success (technical success and no MAEs)		95.7% (135/141)	96.2% (75/78)
All death		1.4% (2/141)	0.0% (0/78)
All stroke		1.4% (2/141)	1.3% (1/78)
All MI		1.4% (2/141)	2.6% (2/78)
All cardiac death		0.7% (1/141)	0.0% (0/78)
Ipsilateral stroke		1.4% (2/141)	1.3% (1/78)
Access site complications			
– Exudative hemorrhage		5.0% (7/141)	1.3% (1/78)
– Localized postoperative wound hematoma		4.3% (6/141)	1.3% (1/78)
– Postoperative wound hematoma*		0.7% (1/141)	5.1% (4/78)
– Artery access site hematoma**		0.0% (0/141)	0.0% (0/78)
– Femoral venous access site hematoma		0.7% (1/141)	3.8% (3/78)
– Rebleeding		0.0% (0/141)	1.3% (1/78)
Contrast usage (cc)	Mean ± SD (N)	72.0 ± 41.6 (135)	79.3 ± 77.82 (75)
	Min, Max	17, 250	15, 585

* Hematoma at access sites that requires postoperative intervention

**Hematoma at access sites that is considered life-threatening and requires emergency intervention

6.A.(1).2).(c) Adverse events at 30 days post-procedure

Adverse events were adjudicated by an independent clinical events committee. At 30 days post-procedure, 186 cases of adverse events occurred in 82 subjects (58.2%) in the ITT population and 68 cases of adverse events in 36 subjects (46.2%) in the extended-access phase group. A total 39 cases of serious adverse events occurred in 20 subjects (14.2%) in the ITT population and 11 cases of serious adverse events occurred in 9 subjects (11.5%) in the extended-access phase group. In the ITT population of the ROADSTER Plus study, procedure- and/or device-related serious adverse events occurred in 16 subjects (Table 10), and all these events resolved with additional treatment except for death due to anaemia and respiratory failure, exacerbation of anaemia, and stroke (1 subject each). During the extended-access phase, procedure- and/or device-related serious adverse events occurred in 9 subjects (Table 11), and all these events were resolving with treatment except for ischaemic stroke and myocardial infarction (1 subject each). An adverse event associated with insertion of a device such as the Sheath of ENROUTE Transcarotid NPS into the carotid artery, namely, “Serious artery dissection or artery dissection leading to procedure termination,” occurred in 4 subjects (2.8%) in the ITT population and 1 subject (1.3%) in the extended-access phase. These events were artery dissection requiring treatment (4 subjects) and artery dissection leading to procedure termination (1 subject). Table 12 shows the details.

One subject in the ITT population was suspected of having a procedure-related cranial nerve injury and underwent a 3-month or 6-month post-procedure follow-up examination. The subject was reported to

have non-serious cranial nerve disorder at 1-day post-procedure. At the 6-month follow-up examination, it was reported that cranial nerve paralysis had resolved.

Table 10. List of procedure- and/or device-related serious adverse events in the ITT population (excluding MAEs)

Patient ID	Adverse event	Outcome	Relationship	Measure taken (details)
[redacted]	Anaemia	Recovered with treatment	Procedure	Transfusion
	Urinary retention	Recovered with treatment	Procedure	Hematuria also developed but recovered within 24 hours.
	Surgical wound haematoma	Recovered with treatment	Procedure	Surgery or other intervention
	Exacerbation of anaemia	Continued with treatment	Procedure	Transfusion
	Severe hypotension	Recovered with treatment	Procedure	Medication
	Artery dissection	Recovered with treatment	Device/ procedure	Switched to CEA
	Artery dissection	Recovered with treatment	Device/ procedure	Surgery or other intervention
	Stroke	Continued without treatment	Device/ procedure	The ability to find right words and facial paralysis improved without hospitalization.
	Artery dissection	Recovered with treatment	Device/ procedure	Surgery or other intervention
	Other neurological complications	Recovered with treatment	Procedure	Medication
	Anaemia	Recovered with treatment	Procedure	Hospitalization
	Anaemia requiring transfusion	Death	Procedure	4 units of red blood cell transfusion
	Epistaxis	Recovered with treatment	Procedure	Spontaneously resolved after reintubation for airway protection.
	Respiratory failure	Death	Procedure	Surgery or other intervention
	Severe hypotension	Recovered with treatment	Procedure	Hydration, treatment by drip infusion
	Pyrexia	Recovered with treatment	Procedure	Infusion of empiric antibiotic
	Other neurological complications	Recovered with treatment	Procedure	Hospitalization
	Renal failure	Recovered with treatment	Procedure	Hydration
	Increased troponin levels	Recovered with treatment	Procedure	Surgery or other intervention
	Severe hypotension	Recovered with treatment	Procedure	Medication
	Dyspnoea	Recovered with treatment	Procedure	Hospitalization

Table 11. List of procedure- and/or device-related serious adverse events in the extended-access phase group (excluding MAEs)

Patient ID	Adverse event	Outcome	Relationship	Actions taken (details)
[redacted]	Pneumothorax	Recovered with treatment	Procedure	Surgery or other intervention
	Surgical wound haematoma	Recovered with treatment	Procedure	Surgery or other intervention
	Artery dissection	Recovered with treatment	Device/ procedure	Surgery or other intervention
	Surgical wound haematoma	Recovered with treatment	Procedure	Surgery or other intervention
	Surgical wound haematoma	Recovered with treatment	Procedure	Medication
	Stroke, ischaemic	Continuation of treatment	Device/ procedure	Transferred to a rehabilitation facility for recovery
	MI	Continuation of treatment	Procedure	Hospitalization
	Urinary retention	Recovered with treatment	Procedure	Medication
	Respiratory failure	Recovered with treatment	Procedure	The patient was found apneic in the postoperative care ward. Resuscitation with bag-valve-mask ventilation was started, and BiPAP was used until recovery of physical strength.
	Surgical wound haematoma	Recovered with treatment	Procedure	Surgery or other intervention

Table 12. List of serious artery dissection or artery dissection leading to procedure termination

Patient ID	Outcome	Actions taken
ITT population		
[redacted]	Recovered	Termination of procedure (acute device success was not achieved)
	Recovered with artery therapy	Switched to CEA
	Recovered with artery therapy	A total of 2 stents were used to treat the dissection flap.
	Recovered with artery therapy	Surgical repair was performed during procedure.
Extended-access phase group		
[redacted]	Recovered with artery therapy	A total of 2 stents were used to treat the dissection flap.

6.B Outline of the review conducted by PMDA

6.B.(1) Appropriateness of using data from a foreign clinical study on the previous-generation device to evaluate the ENROUTE Transcarotid NPS

The applicant's explanation about the use of the data of the previous-generation device from the ROADSTER Plus study for the evaluation of the ENROUTE Transcarotid NPS, in view of equivalency between the 2 products:

One of the major differences between the ENROUTE Transcarotid NPS and the previous-generation device used in the study is the minimum permissible limit of flow resistance. The flow rate is inversely proportional to the flow resistance. The ENROUTE Transcarotid NPS has a lower minimum permissible limit of flow resistance to better accommodate flow loads. The lowered minimum permissible limit of

flow resistance may increase the flow rate of blood passing through the system (Increased by up to [redacted]% at the most severe permissible limit. This applies to both the low and high flow rate settings). The high flow setting can produce a flow rate that is [redacted]% of that obtained in the low flow rate setting. Therefore, a potential increase in flow rate by [redacted]% in the low flow rate setting would have a minimal impact on tolerability in the clinical use of the product. Furthermore, the ENROUTE Transcarotid NPS, which is the upgraded version of the previous-generation device, was evaluated in the ROADSTER 2 study conducted in the post-marketing clinical setting in Europe and the US. The ROADSTER 2 study enrolled a total of 692 patients at high risk for CEA to evaluate the efficacy and safety of the ENROUTE Transcarotid NPS in post-marketing clinical use (patients were enrolled from [redacted] to [redacted]). Patients' tolerance to flow reversal was demonstrated for both the previous-generation device (98.6% in the ROADSTER Plus study) and the ENROUTE Transcarotid NPS (98.4% in the ROADSTER 2 study). The increase in flow rate with decreased minimum permissible limit of flow resistance will provide embolic protection with enhanced flow reversal, and will not negatively affect the embolic protection performance of the ENROUTE Transcarotid NPS.

Taken together, the possible increase in the maximum permissible blood flow rate by up to [redacted]% will not lead to frequent patient intolerance to flow reversal and is clinically acceptable. In addition, taking account of other non-clinical study data, the embolic protection performance of the ENROUTE Transcarotid NPS is considered equivalent to that of the previous-generation device.

PMDA's view:
Among main upgrades from the previous-generation device to the ENROUTE Transcarotid NPS (Table 1), changes influential to the product's efficacy and safety are the increased reverse blood flow by up to [redacted]% achieved by decreased flow resistance and the modified shape of the Transcarotid Arterial Sheath tip. As the applicant explained, the increase in the blood flow rate will not deteriorate the embolic protection performance of the product. The data from the clinical studies of both devices demonstrated that patient tolerance to flow reversal with the ENROUTE Transcarotid NPS is equivalent to that with the previous-generation device at high rates (98.6% and 98.4%, respectively). In addition, as discussed later, the modified sheath tip shape is suggested to contribute to a decrease in serious artery dissection. Accordingly, PMDA concluded that the data from the ROADSTER Plus study with the previous-generation device were valid for the evaluation of the ENROUTE Transcarotid NPS.

6.B.(2) Applicability of data from the ROADSTER Plus study to the Japanese population

PMDA concluded that the use of data from the ROADSTER Plus study in Europe and the US to evaluate the efficacy and safety of the ENROUTE Transcarotid NPS in the Japanese population is acceptable for the following reasons:

- Ethnic factors (e.g., anatomical position of the carotid bifurcation) and different medical environment (e.g., treatment guidelines and available treatment options) do not differ substantially

enough to cause a significant impact on the clinical positioning of the product or the results of the ROADSTER Plus study.

- The level of technical difficulty in the CAS procedure using the product is comparable to that with the approved devices, and the procedure involves techniques for placing and removing the product to and from the carotid artery, which are similar to those in the conventional CEA. Therefore, another clinical study in Japan, even if conducted, is less likely to yield new findings.

Meanwhile, the ENROUTE Transcarotid NPS will be the first embolic protection device leveraging the flow reversal mechanism to be introduced in Japan, which warrants the establishment of a treatment system, selection of eligible patients, and measures against adverse events in ways that fit the product characteristics. As mentioned later, post-marketing safety measures such as offering appropriate training for surgeons and conducting a use-results survey will be important to assure the efficacy and safety of the product in Japan.

6.B.(3) Appropriateness of the design of the ROADSTER Plus study

The ENROUTE Transcarotid NPS is intended for cerebral embolic protection during the CAS procedure. The product was developed to minimize the onset of perioperative stroke, which is however difficult to be verified in a clinical study due to its practical infeasibility. Albeit its different operation theory, the ENROUTE Transcarotid NPS is used for the same purpose as the existing filter-type devices. PMDA thus concluded that the design of the ROADSTER Plus study was valid for the evaluation of the efficacy and safety of the ENROUTE Transcarotid NPS for the following reasons:

- The ENROUTE Transcarotid NPS targets patients at high risk for CEA, a patient population that is considered eligible for conventional CAS. The inclusion criteria of the ROADSTER Plus study specified high risk factors for CEA such as high cervical carotid artery stenosis, bilateral stenosis requiring treatment, etc.
- “MAEs occurring within 30 days post-procedure” was the primary endpoint, the same as in the clinical studies of the approved filter-type embolic protection devices for CAS, with the same achievement threshold as that for these approved devices.

6.B.(4) Efficacy and safety

6.B.(4).1) Efficacy

The ENROUTE Transcarotid NPS met the prespecified threshold for the primary endpoint and provided clinical study results similar to existing similar medical devices including the approved filter-type embolic protection devices (Table 13). PMDA considers that the product provides effective embolic protection during CAS procedure.

Table 13. Results of clinical studies on the ENROUTE Transcarotid NPS and similar medical devices including approved devices

	ROADSTER Plus ITT	Covidien SpideRx (CREATE)[10]	Boston Scientific Wallstent (BEACH)[11]	Covidien Protégé (CREATE)[9]	Cordis Precise (SAPPHIRE)[12]
Primary endpoint (MAEs occurring within 30 days post-procedure)	3.5%	5.6%	6.3%	6.3%	4.8%
Death within 30 days post-procedure	1.4%	2.5%	1.6%	1.9%	1.2%
Stroke within 30 days post-procedure	1.4%	5.0%	4.5%	4.6%	3.6%
MI within 30 days post-procedure	0.7%	0.6%	1.0%	1.0%	2.4%
Serious dissection	2.1%	Unreported	0.4%	1.2%	Unreported
Serious wound/groin hematoma	0.7%	Unreported	2.1%	Unreported	Unreported
Serious access site complications	0.7%	1.3%	Unreported	2.6%	5.4%

The cases with MAEs of subjects who failed to achieve the primary efficacy endpoint (**Table 8**) are also considered clinically acceptable for the following reasons:

- Death occurred only in the ITT population, and 1 of the 2 subjects died had developed diabetic ketoacidosis while the other had had pneumonia. These events can be prevented by appropriate postoperative management. The incidence of death was comparable with those in the clinical studies of similar devices (1.2%-2.5%).
- Stroke occurred in 2 subjects (1.4%) in the ITT population and 1 subject (1.3%) in the extended-access phase group. The comparison of point estimates shows that these incidences are lower than that in the representative conventional CAS data (4.1%, all stroke in the CAS group in the CREST study[4]). In the subject who developed myocardial infarction, the event was non-serious and had a favorable outcome.

As shown above, the incidence of perioperative stroke in transcarotid CAS using the ENROUTE Transcarotid NPS tends to be lower than that in transfemoral CAS reported, indicating that the product can reduce the onset of perioperative stroke, a remaining issue in transfemoral CAS, for which the product is intended.

In view of possible impact of anesthetic modality used on MAEs, PMDA asked the applicant to explain the incidences of MAEs by anesthetic modality during procedure.

The applicant's explanation:
Table 14 shows the incidences of MAEs by anesthetic modality during the procedure. The incidence of MAEs was 2.7% (95% CI, 0.33-9.42; 2 of 74 subjects) under local anesthesia or conscious sedation, and 4.5% (95% CI, 0.93-12.53; 3 of 67 subjects) under general anesthesia. Although based on a point estimate comparison, the incidence was higher under general anesthesia. The MAEs under general

anesthesia were death in 2 subjects and myocardial infarction in 2 subjects (1 of these is the 1 of the subjects who died). Given the low incidences with the difference of only 1 subject between the groups, and no difference in the incidences based on the overlapping 95% confidence intervals, surgeons are required to choose the best appropriate anesthetic modality for each patient.

PMDA's view:
The applicant's explanation is reasonable. However, the incidence of MAEs and that of each event are critical in the assessment of an embolic protection device and may show different trends depending on the anesthetic modality used, although only insignificant difference was shown with the small sample size of the ROADSTER Plus study. Therefore, it is important that the surgeons operating the ENROUTE Transcarotid NPS are fully aware this possibility before treatment planning for each patient, including eligibility for the use of the product. The results by anesthetic modality from the ROADSTER Plus study should be provided as "Information on Precautions, etc.," and users of the product should be thoroughly instructed of careful decision making on the use of the product through training, etc.

Table 14. Incidence of MAEs by anesthetic modality

Major adverse event	Local anesthesia (N = 74)	General anesthesia (N = 67)
MAE	2 (2.7%)	3 (4.5%)
Stroke	2 (2.7%)	0 (0.0%)
Death	0 (0.0%)	2 (3.0%)
MI	0 (0.0%)	2 (3.0%)

The secondary endpoints, i.e., "acute device success rate," "technical success rate," and "procedural success rate" were 99.3%, 99.3%, and 95.7%, respectively in the ITT population and 100.0%, 100.0%, and 96.2%, respectively, in the extended-access phase group, indicating favorable results. The incidence of all death, all stroke, and ipsilateral stroke was 1.4% in the ITT population and 0.0%, 1.3%, and 1.3%, respectively, in the extended-access phase group, indicating low incidence. The results of procedures using the ENROUTE Transcarotid NPS have raised no particular concerns.

6.B.(4).2) Safety

Because the ENROUTE Transcarotid NPS is an embolic protection device used for transcarotid artery stenting in patients at high risk for CEA, serious adverse events other than MAEs defined in the primary endpoint, i.e., artery dissection associated with direct carotid access, and access site complications and hypotension, both observed frequently in CAS, should be evaluated.

The applicant's explanation about artery dissection defined as a serious adverse event in the ROADSTER Plus study:
Artery dissection is a procedural complication associated with the use of the ENROUTE Transcarotid NPS. The event can be prevented through training and improvement of the product. The training

program covers suggestions for the prevention of artery dissection and other complications, and troubleshooting of complications. Based on the results from the ROADSTER Plus study, the rigidity of Guidewire body was increased to facilitate the insertion and delivery of the Transcarotid Arterial Sheath into the vessel, and the Transcarotid Arterial Sheath was modified with an angled tip (Table 1). In the foreign post-marketing study (ROADSTER 2 study), the incidence of artery dissection decreased to 1.3%, which is considered acceptable.

PMDA's view:
Serious artery dissection or artery dissection leading to procedure termination occurred in 4 subjects (2.8%) in the ITT population and 1 subject (1.3%) in the extended-access phase group. Three of the subjects required surgical procedures including CEA and had favorable outcomes. With these results taken into account, the provision of training and cautionary advice to healthcare professionals about complications associated with the ENROUTE Transcarotid NPS is important to minimize the onset of artery dissection and associated risks. In addition, treatment using the product should be performed by surgeons or medical teams capable of surgical procedures equivalent to CEA so that appropriate actions are taken in the event of artery dissection.

PMDA concluded that other adverse events associated with the ENROUTE Transcarotid NPS in the ROADSTER Plus study were acceptable for the following reasons:

- A total of 15 subjects (10.6%) in the ITT population developed access site complications in the neck and femoral vein, which do not occur in transfemoral CAS, but only 1 subject (0.7%) who developed postoperative wound hematoma required additional treatment. The other cases of access site complications, namely, exudative haemorrhage, localized postoperative wound hematoma, and femoral venous access site hematoma, did not require additional treatment. In the extended-access phase group, access site complications occurred in 10 subjects (12.8%), and 4 subjects (5.1%) developed postoperative wound hematoma and required additional treatment. Of these, 2 subjects received transfusions and the other 2 underwent surgical treatment, with favorable outcomes. Although the access site is different from the existing embolic protection devices, there were no events specific to the ENROUTE Transcarotid NPS. As shown in Table 13, the incidence of serious access site complications did not differ significantly from that of similar devices.
- Serious hypotension requiring treatment occurred only in 4 subjects (2.8%) in the ITT population, and in 3 subjects it was classified as procedure-related event. All resolved in several days with treatment. Hypotension is recognized as a common risk with CAS. The incidence of serious hypotension was lower than that with the existing product "PRECISE for the Carotid Artery" (Approval No. 21900BZX00781000), 9.3%, reported in the re-examination report.[13]
- The rest of the serious adverse events were not specific to the product, and there were no events occurring at a higher incidence as compared to those associated with other common CAS.

Based on the above, the efficacy and safety of the ENROUTE Transcarotid NPS, as demonstrated in the ROADSTER Plus study, are considered comparable with the existing devices used in CAS for the same purpose. Furthermore, for its safe and effective launch in Japan, it is important to implement post-marketing safety measures in a way that fits the characteristics of the product such as embolic protection mechanism and access site, which differentiate it from the existing devices. As discussed later in Section "6.B.(6) Post-marketing safety measures including the proper use of the product," and taking account of the comments from the Expert Discussion, PMDA have concluded that the ENROUTE Transcarotid NPS would be clinically meaningful as a new option of embolic protection devices during CAS, when used properly with risk minimization measures taken, such as the selection of eligible patients and the establishment of a treatment system capable of coping with adverse events.

6.B.(5) Clinical positioning and intended use

The applicant's explanation about the clinical positioning of the ENROUTE Transcarotid NPS and its intended use:

Flow reversal is the basis of the product mechanism as embolic protection device, which is not a new concept. Flow reversal employing Parodi's technique has been used in Japan to provide proximal protection and minimize plaque embolization.[14,15,16] Because of its target patient population same as the approved devices', the ENROUTE Transcarotid NPS is one of the options to be used in CAS procedure. Its transcarotid approach is useful not only in difficult CEA cases but also applicable to challenging transfemoral CAS.

In the ROADSTER Plus study, 5 types of stents for carotid artery, which have been approved by the US FDA, were used in combination the study device (Table 15). Therefore, it is not necessary to limit the types of stents to be used in combination with the ENROUTE Transcarotid NPS.

Table 15. Results of the ROADSTER Plus study by stent type

	Acculink	Xact	Wallstent*	Precise* ProRx	Protégé*	Unknown
Number of subjects	17	45	36	34	7	2
MAE (95% CI)	1 (5.89%) (0.15-28.69)	2 (4.45%) (0.54-15.15)	2 (5.56%) (0.68-18.66)	0 (0.00%) (0-10.28)	0 (0.00%) (0-40.96)	0 (0.00%) (0-84.19)
Acute device success	100%	100%	100%	100%	100%	50%
Technical success	100%	100%	100%	100%	100%	50%
Procedural success (95% CI)	94.12% (71.31-99.85)	95.56% (84.85-99.46)	94.45% (81.34-99.32)	100% (89.72-100.00)	100% (59.04-100.00)	50% (1.26-98.74)

* Stents approved in Japan: Wallstent ("Carotid Wallstent Monorail Endoprosthesis" [Approval No. 22200BZX00138000])
Precise ProRx ("PRECISE for the Carotid Artery" [Approval No. 21900BZX00781000])
Protégé ("PROTEGE RX for Carotid Artery System" [Approval No. 22400BZX00175000])

PMDA's view on the clinical positioning of the ENROUTE Transcarotid NPS:
According to a report in Cochrane's Systematic Review,[17] the incidence of perioperative death or stroke was higher with CAS than with CEA in patients with symptomatic lesions. Thus, CAS is currently performed in patients at high risk for CEA. In the CREST study,[4] which directly compared CEA and CAS, yielded comparable results between the procedures. However, the results show that CEA posed higher risks of myocardial infarction and cranial nerve paralysis, while CAS posed higher risks of stroke. Accordingly, the decision whether to perform CEA or CAS for patients at high risk for CEA should be made with the risk-benefit balance of the respective procedures weighed based on patient condition.

The ENROUTE Transcarotid NPS was developed to minimize the onset of perioperative stroke, which has been a problem associated with conventional transfemoral CAS. Although not compared with transfemoral CAS in the ROADSTER Plus study, the results of CAS using the product have been shown to be comparable with transfemoral CAS (Table 13). Together with the reports on transfemoral CAS in literature, the product is suggested to decrease the incidence of stroke as intended.[18] Therefore, taking into account the comments from the Expert Discussion, the ENROUTE Transcarotid NPS should be clinically recognized as a device to be used for patients at high risk for CEA like the conventional transfemoral CAS, and as a new option of embolic protection devices to treat carotid artery stenosis with its own unique feature that is expected to minimize cerebral infarction. The treatment methodology should be determined by weighing the benefits and risks with CEA, transfemoral CAS, and transcarotid CAS using the ENROUTE Transcarotid NPS.

The applicant's intention not to limit the types of carotid artery stents to be used with the ENROUTE Transcarotid NPS is reasonable because stent type is not likely to affect the cerebral embolic protection performance of the product, and no such limitation is necessary as long as the stent can be placed in the artery using the sheath of the product. However, the suitability of each approved stent for use with the product should be determined based on their specifications.

Based on the above, the “Intended use or indication” of the ENROUTE Transcarotid NPS should be modified as follows:

Intended use or indication

The ENROUTE Transcarotid NPS provides transcarotid vascular access and embolic protection during carotid artery angioplasty and stenting procedures for patients with carotid artery stenosis.
Intended patients are those who have

- a common carotid artery greater than 6 mm in reference diameter
- a carotid bifurcation located at least 5 cm above the clavicle

6.B.(6) Post-marketing safety measures including the proper use of the product

CEA and transfemoral CAS for the treatment of carotid artery stenosis, in which the ENROUTE Transcarotid NPS will be used, are highly-proven established treatments in Japan. The product is a new embolic protection device to be used in stenting for patients with carotid artery stenosis at high risk with CEA. While the data suggest that the product may reduce perioperative stroke, safe use of the product warrants particular considerations, including the effect of anesthesia on treatment performance and measures to be taken against carotid artery dissection. Given this, for the product to be launched in Japan in an effective and safe manner, its use should be limited to medical teams of surgeons sufficiently experienced in CEA and transfemoral CAS with a full understanding of the product’s efficacy and safety and the skills for these procedures, and at facilities capable of providing surgical and medical treatments including emergency CEA.

The proper use guidelines (Table 16), which define the requirements for operating surgeons of the ENROUTE Transcarotid NPS and for medical institutions, were discussed by relevant academic societies (the Japan Stroke Society, the Japan Neurosurgical Society, Japanese Society for Neuroendovascular Therapy, and the Japanese Society for Vascular Surgery). Table 17 outlines the training program implemented by the applicant.

Table 16. Outline of proper use guidelines (draft)

Item	Outline
Requirements for operators	The procedure must be performed by a team of surgeons who meet the following requirements and have completed the training program for the ENROUTE Transcarotid NPS, unless 1 surgeon satisfies both requirements. ➢ A neurosurgeon, cardiovascular surgeon, or surgeon-angiologist with experiences in CEA in ≥5 patients ➢ A CAS specialist with experiences in CAS in ≥10 patients
Requirements for medical institutions	• Being well-equipped and -systematized for a surgical carotid artery procedure and concurrent CAS. • Having an angiography room that accommodates clean technique or an operation room with an angiography device. Besides operating surgeons, an anesthesiologist, medical staff, etc. are available.

Table 17. Overview of product training program

Category	Detail
Lecture	
How to use	Explanation covering the pre-procedural preparation and the thorough procedure using the ENROUTE Transcarotid NPS up to the end
Carotid artery angioplasty	The background to the development of the transcarotid CAS program using the ENROUTE Transcarotid NPS
Prevention of complications	Troubleshooting
Hands-on training	
Hands-on training	A series of procedural operations using blood vessel models • Vessel exposure technique • Ultrasound operation • Stenting under flow reversal

The training program proposed by the applicant covers sufficient lectures and hands-on training, and the course is mandatory for surgeons regardless of the number of CEA procedures they may have performed. PMDA concluded that the training program was appropriate.

Currently, the standard requirements for operating surgeons and medical institutions performing CAS are specified in the "Carotid artery stenting practice standards"[19] authorized by 11 related academic societies. Surgeons or medical teams performing transcarotid CAS using the ENROUTE Transcarotid NPS must have not only CAS technique but also surgical skills for exposure of the common carotid artery, blood vessel suturing, and CEA to deal with adverse events such as artery dissection. The submitted standard requirements for operating surgeons and medical institutions satisfy these criteria. Taking into account the comments from the Expert Discussion, PMDA concluded that the requirements were appropriate.

The applicant expressed their intention to work with relevant academic societies for the formulation of the proper use guidelines including the requirements for operators and institutions, and take necessary measures to ensure adherence to these requirements, e.g., providing training opportunities for operating surgeons. PMDA concluded that these steps were acceptable and should be designated as approval conditions 1 and 2.

7. Plan for Post-marketing Surveillance etc. Stipulated in Paragraph 1 of Article 2 of Ministerial Ordinance on Good Post-marketing Study Practice for Medical Devices

7.A Summary of the data submitted

To evaluate the efficacy and safety of the ENROUTE Transcarotid NPS in clinical use after the product launch in Japan, the applicant submitted a plan for a use-results survey that evaluates the incidences of MAEs, procedural success, and serious artery dissection, with an observation period of 30 days as was in the ROADSTER Plus study.

7.B Outline of the review conducted by PMDA

PMDA's view:

The applicant is required to perform post-marketing surveillance for the following reasons:

- There is no experience in the use of the product in Japan. The proper use of the product need to be facilitated by providing healthcare professionals with data on clinical use in Japan promptly.
- The applicant should verify the sufficiency of post-marketing safety measures set, and take additional steps if necessary.

The applicant's post-marketing surveillance plan is designed to collect data at a certain accuracy on MAEs, which are critical for the embolic protection device, and artery dissection as a complication of concern associated with the procedure employing the product. PMDA thus concluded that the plan is acceptable. The key survey items should be "incidences of MAEs," "incidence of artery dissection," and "procedural success," and other survey items should be "access site complications" and "cranial nerve injury." PMDA instructed the applicant to specify these survey items, and the applicant agreed (Table 18).

Table 18. Outline of use-results survey (draft)

Objective	Identification or verification of information regarding quality, safety, and efficacy of the product in post-marketing use
Planned sample size	Number of patients to be analyzed, N = 140 (continuous survey)
Rationale for sample size	A sample size of 140 will allow the detection, at a probability of ≥95%, of ≥1 patient experiencing an event reported at an incidence comparable to that of serious artery dissection in the ROADSTER Plus study (2.1%), the lowest among MAEs, artery dissection, and unachieved procedural success, which made up the combined incidence of 8.5% in the study.
Survey period	3 years from approval (registration, 18 months; follow-up period, 30 days; preparation/analysis period, 17 months)
Key survey items	• Incidences of MAEs • Incidence of artery dissection • Procedural success
Other survey items	• Patient characteristics • Characteristics of lesions • Procedure information (including anesthetic modality) • Malfunction/adverse events

8. Documents Relating to Information for Precautions, etc. Specified in Paragraph 1 of Article 63-2 of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices, in Relation to Notification Pursuant to the Same Paragraph of the Act

8.A Summary of the data submitted

The applicant submitted Information on Precautions, etc. (draft) as attachments in accordance with the Notification titled "Application for Marketing Approval of Medical Device" (PFSB Notification No. 1120-5, dated November 20, 2014).

8.B Outline of the review conducted by PMDA

On the basis of the conclusion of the Expert Discussion, as described earlier in Section "6.B Outline of the review conducted by PMDA," PMDA concluded that there was no particular problem at that time with the descriptions of Information on Precautions, etc., as long as necessary precautions are given.

III. Results of Compliance Assessment Concerning the New Medical Device Application Data and Conclusion Reached by PMDA

PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment,

PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

IV. Overall Evaluation

The ENROUTE Transcarotid NPS is used in combination with a carotid artery stent in patients with carotid artery stenosis to provide cerebral embolic protection during carotid artery angioplasty and stenting procedures. The review of the product focused primarily on: (1) product efficacy and safety and (2) post-marketing safety measures. Taking account of comments raised at the Expert Discussion, PMDA reached the following conclusions:

(1) Efficacy and safety of the ENROUTE Transcarotid NPS

The efficacy and safety of the ENROUTE Transcarotid NPS as a cerebral embolic protection device in transcarotid CAS in patients at high risk for CEA were evaluated in the ROADSTER Plus study. The primary endpoint of the study, "a composite of any stroke, myocardial infarction, and death during 30-day post-procedural period" was 3.5%. This met the prespecified achievement threshold and demonstrated the efficacy of the product. Considering the results from clinical studies of conventional transfemoral CAS, the product is expected to lower the incidence of stroke in patients undergoing CAS as intended.

In the ROADSTER Plus study, serious artery dissection or artery dissection leading to procedure termination occurred in 2.8% of subjects but these events had favorable outcomes after the surgical procedure including CEA, demonstrating that the risks can be reduced through training and improvements to the device. In addition, none of other serious adverse events reported were specific to the product, and there were no particular problems with the incidence of events, etc. as compared to other transfemoral CAS. Therefore, PMDA has concluded that the product has clinically acceptable safety.

Based on the above, the risk-benefit balance of transcarotid CAS employing the ENROUTE Transcarotid NPS is generally similar to that of conventional transfemoral CAS. The use of product in the procedure is clinically meaningful because it will broaden treatment options for patients with carotid artery stenosis. PMDA thus has concluded that the product is beneficial.

(2) Post-marketing safety measures

Although the efficacy and safety of transcarotid CAS employing the ENROUTE Transcarotid NPS do not significantly differ from established transfemoral CAS in Japan, it is critical to address adverse events attributable to its different access site and techniques the treatment with the product. For the ENROUTE Transcarotid NPS, which will broaden the treatment options for carotid arterial stenosis in patients at high risk for CEA, to be launched in Japan in an effective and safe manner, (1) patients' eligibility for treatment involving the product should be determined by surgeons or medical team

members with sufficient experience in CEA and transfemoral CAS who have gained a full understanding of the product's efficacy, safety, and the procedure through training or workshop, with due consideration of conventional options as well; and (2) the product should be used only by surgeons or at medical institutions with sufficient experience in the treatment of transfemoral CAS, adequate skills for these procedures, and capability to provide surgical or medical treatments including CEA for complications of the treatment with the product.

The ENROUTE Transcarotid NPS is the first embolic protection device for transcarotid artery stenting to be launched in Japan. Through the use-results survey, the applicant should gather information on patient characteristics, devices used in combination, adverse events and other data associated with the use of the product, and to take additional risk minimization measures as necessary. PMDA has concluded that the duration of the use-results survey be 3 years (registration, 18 months; follow-up period, 30 days; preparation/analysis period, 17 months).

As a result of the above review, PMDA has concluded that ENROUTE Transcarotid NPS may be approved for the intended use below.

Intended Use

The ENROUTE Transcarotid Neuroprotection System provides transcarotid vascular access and embolic protection during carotid artery angioplasty and stenting procedures for patients with carotid artery stenosis.

Intended patients are those who have

- a common carotid artery greater than 6 mm in reference diameter
- a carotid bifurcation located at least 5 cm above the clavicle

Approval Conditions

1. The applicant is required to take necessary measures to ensure that the product is used in compliance with the indication, only by surgeons with sufficient knowledge and experience in the procedure and in handling complications associated with the treatment. The surgeons also must have gained full understanding of the product's efficacy and safety through training on the surgical procedures and endovascular treatment for carotid artery stenosis using the product.
2. The applicant is required to take necessary measures to ensure that the product is used at medical institutions having surgeons experienced in the treatment of carotid artery stenosis and a system responsive to various cases including complications associated with treatment involving the product.

The product is not classified as a biological product or a specified biological product. The product is designated as a medical device subject to a use-results survey. The use-results survey period should be 3 years.

PMDA has concluded that this application should be deliberated at the Committee on Medical Devices and *In-vitro* Diagnostics.

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