October 2, 2023
Medical Device Evaluation Division,
Pharmaceutical Safety 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 non-central circulatory embolectomy
Brand Name	ClotTriever Thrombectomy System
Applicant	Inari Medical, Inc.
Designated Marketing Authorization Holder	Vorpal Technologies K.K.
Date of Application	December 16, 2022 (Application for marketing approval of a medical device manufactured in a foreign country)

Results of Deliberation

In its meeting held on October 2, 2023, 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.

The product should be approved with designation 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 5 years. The product should be approved with the following conditions.

Approval Conditions

1. Treating physicians are expected to be adequately knowledgeable and experienced in the treatment of deep vein thrombosis so as to appropriately select patients to be treated with the product, and are required to have learned sufficient skills pertaining to the use of the product and knowledge about procedure-associated complications. The treatment with the product must be performed at medical institutions with an established system for the treatment. To this end, the applicant is required to take necessary measures such as dissemination of the guidelines for proper use prepared jointly with relevant academic societies and offering seminars.

2. The applicant is required to conduct a use-results survey covering all Japanese patients treated with the product until data are obtained from a certain number of patients, report survey results to the Pharmaceuticals and Medical Devices Agency, and take other appropriate measures as necessary.

Review Report

September 12, 2023
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).

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Reviewing Office	Office of Medical Devices II

Review Results

September 12, 2023

Classification	Instrument & Apparatus 51, Suckers, Tubes and Catheters for Infusion or Drainage
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Date of Application	December 16, 2022

Results of Review

ClotTriever Thrombectomy System (hereinafter referred to as the ClotTriever System) is a mechanical thrombectomy catheter system for percutaneous removal of venous thrombi in the treatment of deep vein thrombosis (DVT). The ClotTriever System consists of a ClotTriever Sheath, ClotTriever Catheter, dilator, pre-dilator, funnel loading tool, and 60-cc large bore syringe.

The applicant submitted non-clinical data supporting the physicochemical properties, biological safety, stability and durability, and performance of the ClotTriever System. There was no particular problem in the submitted data.

The clinical study data submitted were the results of hypothesis verification of the product's efficacy and safety in a cohort of patients with thrombi removed that were estimated to be ≤6 weeks old. It was a part of a multicenter, prospective study that evaluated outcomes of treatment with the ClotTriever System in patients with acute, subacute, and chronic proximal DVT extending above the popliteal vein (CLOUT Registry).

The primary efficacy endpoint of "technical success" (percentage of patients achieving ≥75% thrombus removal based on quantitative venographic scoring system) was 76.4% (68 of 89 subjects). The lower limit of the one-sided 97.5% confidence interval was 66.2%, which was higher than the predefined threshold (30%) ($P < 0.0001$). The secondary efficacy endpoints of "patency of the target vessel segment based on Duplex ultrasound" and "clinical symptoms (e.g., the Revised Venous Clinical Severity Score [rVCSS], etc.)" also indicated improvement from baseline at 30 days of the index procedure and later. These results demonstrated the efficacy of treatment with ClotTriever System comparable to that of conventional catheter-directed thrombolysis (CDT).

The primary safety endpoint of the "incidence of composite major adverse events within 30 days of the index procedure" was 20.0% (15 of 75 subjects). The upper limit of the one-sided 97.5% confidence

interval was 30.8%, which met the predefined threshold (34%) ($P < 0.0058$). While hemorrhagic complications are the challenges of CDT and valvular or vascular injury-associated event are concerns with the ClotTriever System, none of these occurred. Symptomatic pulmonary embolism, a significant complication of DVT, occurred in 1.4% (1 of 73) of subjects at 30 days of the index procedure, which was acceptable as compared with that with CDT. Rethrombosis, which may worsen clinical symptoms or cause post thrombotic syndrome, occurred in 17.8% of the study population (13 of 73 subjects). A causal relationship to the ClotTriever System or the index procedure could not be ruled out for only 2 events, and neither led to a serious outcome. Although the cause of rethrombosis remains unclear, thorough post-procedural management including anticoagulant therapy is essential to minimize the risk of rethrombosis, with a good understanding of various characteristics of patients experiencing rethrombosis.

In Japan, discontinued supply of urokinase, a thrombolytic drug, has been an obstacle to CDT. The ClotTriever System will be clinically useful, based on its efficacy and safety demonstrated to be comparable to CDT as mentioned earlier. Appropriate post-marketing safety measures will allow to maintain the risk-benefit balance of the ClotTriever System.

To assure effective and safe introduction of the ClotTriever System to Japan, physicians or medical teams must have sufficient experience and achievements in the standard treatment of the disease including CDT, learn necessary knowledge and skills pertaining to the product and the procedure through training, etc., and fully understand the pathological condition of patients eligible for the product so as to be able to select eligible patients. Treatment with the ClotTriever System may be followed by iliofemoral venous stenting or, where necessary, other emergency care including surgery to address complications such as pulmonary embolism. Medical institutions providing treatment with the ClotTriever System must have a system adequately prepared for such cases.

The clinical study enrolled only a limited number of subjects who would meet the eligibility criteria for ClotTriever System treatment in Japan. Because there is no option other than the ClotTriever System to replace CDT in the country, a change in therapeutic approach may affect patients' treatment outcomes. To address this issue, information about adverse events, procedures, patient characteristics, etc. should be collected through a use-results survey, and additional risk reduction measures should be taken as necessary.

As a result of its review, PMDA has concluded that the ClotTriever System may be approved for the following intended use, with the following approval conditions, and that the results should be presented to the Committee on Medical Devices and *In-vitro* Diagnostics for further deliberation.

Intended Use

The ClotTriever Thrombectomy System is intended for use to restart blood flow in patients with severe acute symptoms of deep vein thrombosis (excluding post thrombotic syndrome) who are difficult to undergo conventional treatment or are not expected to respond to conventional treatment.

Approval Conditions

1. Treating physicians are expected to be adequately knowledgeable and experienced in the treatment of deep vein thrombosis so as to appropriately select patients to be treated with the product, and are required to have learned sufficient skills pertaining to the use of the product and knowledge about procedure-associated complications. The treatment with the product must be performed at medical institutions with an established system for the treatment. To this end, the applicant is required to take necessary measures such as dissemination of the guidelines for proper use prepared jointly with relevant academic societies and offering seminars.
2. The applicant is required to conduct a use-results survey covering all Japanese patients treated with the product until data are obtained from a certain number of patients, report survey results to the Pharmaceuticals and Medical Devices Agency, and take other appropriate measures as necessary.

Review Report

September 12, 2023

Product for Review

Classification	Instrument & Apparatus 51, Suckers, Tubes and Catheters for Infusion or Drainage
Term Name	Catheter for non-central circulatory embolectomy
Brand Name	ClotTriever Thrombectomy System
Applicant	Inari Medical, Inc.
Designated Marketing Authorization Holder	Vorpal Technologies K.K.
Date of Application	December 16, 2022
Proposed Intended Use	The ClotTriever Thrombectomy System is a mechanical thrombectomy catheter system that percutaneously removes vein thrombosis in the treatment of deep vein thrombosis, and is intended for use to treat acute deep vein thrombosis.

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List of Abbreviations

BMI	Body Mass Index
CDT	Catheter-directed Thrombolysis
CEAP	Clinical manifestation‐Etiologic‐Anatomic distribution‐Pathophysiologic
CT	Computed Tomography
DVT	Deep Vein Thrombosis
IVC	Inferior Vena Cava
IVR	Interventional Radiology
MAE	Major Adverse Event
NPRS	Numeric Pain Rating Scale
PCDT	Pharmacomechanical CDT
PE	Pulmonary Embolism
PTS	Post-thrombotic Syndrome
QOL	Quality of Life
rt-PA	recombinant tissue-type Plasminogen Activator
rVCSS	the Revised Venous Clinical Severity Score
TVS	Target Vessel Segment

I. Product Overview

ClotTriever Thrombectomy System (hereinafter referred to as the ClotTriever System) is a mechanical thrombectomy catheter system for percutaneous removal of venous thrombi in the treatment of deep vein thrombosis (DVT). The ClotTriever System consists of a ClotTriever Sheath, ClotTriever Catheter, dilator, pre-dilator, funnel loading tool, and 60-cc large bore syringe. The ClotTriever Sheath, available in 2 sizes of 13 Fr and 16 Fr, is an introducer sheath consisting of a distal self-expanding nitinol (nickel-titanium alloy) mesh funnel, suction port, hemostatic hub, and others. The ClotTriever Catheter has a self-expanding nitinol coring element and a collection bag that collects clots at the tip of the 11-Fr catheter (Figure 1).

The ClotTriever Catheter is inserted through the ClotTriever Sheath and deployed distal to the occluding thrombus. As the coring element and the collection bag expand, the coring element removes clots mechanically when the catheter is pulled back.

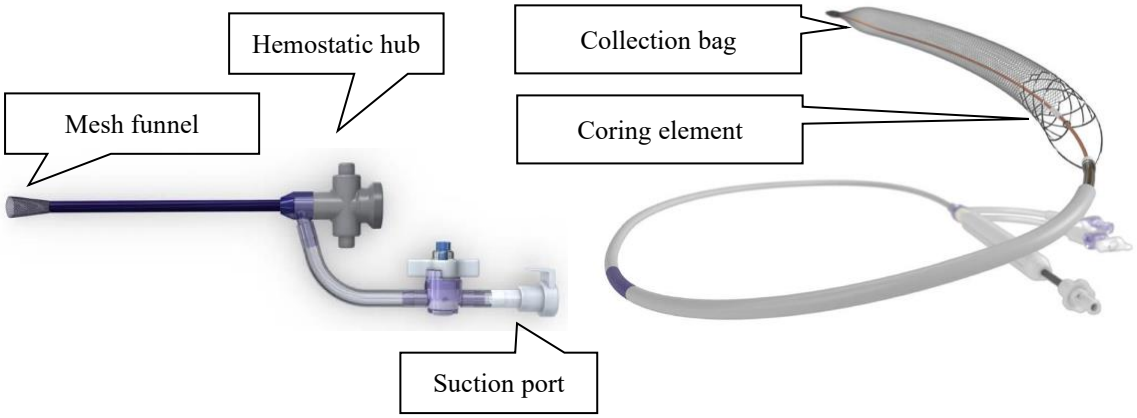

Figure 1. External view of the ClotTriever System (left, ClotTriever Sheath; right, ClotTriever Catheter)

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

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

The expert advisors present during the Expert Discussion on the ClotTriever System 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

DVT is a medical condition with thrombi developing in a deep vein in the extremities or pelvis. Thrombi can break free into the venous bloodstream, travel to the lungs, and occlude the pulmonary arteries. This is the main cause of pulmonary thromboembolism leading to cardiorespiratory impairment. Acute symptoms of DVT depend on the degree of the impairment of venous return, which is determined by the progression speed of thrombi and the extent of venous occlusion. In proximal DVT where thrombosis

occurs above the popliteal vein, a decrease in venous return in the acute phase is typically manifested as swelling, pain, and color change in the lower legs. In proximal DVT rapidly developing in the iliac vein with extensive occlusion, abnormal arterial perfusion associated with significantly decreased venous return may lead to venous necrosis. Clinically significant pathological conditions of DVT are phlegmasia alba dolens, phlegmasia cerulea dolens, and venous necrosis. Phlegmasia cerulea dolens is characterized by extensive venous thrombotic occlusion and congestion that induce severe cyanosis, and is a potential risk of compartment syndrome, venous necrosis, and leg amputation, particularly requiring attention as with venous gangrene. For early thrombectomy in severe DVT, catheter-directed thrombolysis (CDT), percutaneous mechanical thrombectomy, and surgical thrombectomy are available. Early thrombectomy, which can minimize early complications in proximal DVT with severe swelling or DVT accompanied by phlegmasia cerulea dolens, is said to be useful in patients with an estimated life expectancy of ≥1 year, and is also expected to prevent venous necrosis, an extremely rare complication. Venous stenosis lesions, including symptomatic iliofemoral venous outflow obstruction persisting after thrombectomy, are treated by expanding the narrowed section using a balloon catheter or iliofemoral venous stent (hereinafter referred to as the venous stent, which was granted approval based on the Pharmaceutical Affairs Law in 2022 and plans to be introduced to Japan in the future) to improve venous outflow.[1] The common complications of DVT are acute pulmonary thromboembolism, the most serious pathological condition, in the acute phase and post thrombotic syndrome (PTS) caused by venous valve destruction in the chronic phase. PTS is characterized by persistent venous congestive symptoms extensively present in the legs. It occurs post-acute DVT when remaining venous thrombi destroy the venous valves, making venous return sluggish and causing remaining thrombi to become organized. PTS commonly occurs frequently in proximal DVT at an incidence of approximately 20% to 50%.[2] This pathological condition substantially decreases the quality of life (QOL) of severe patients because of no appropriate therapeutic option. It is, therefore, crucial to select and administer proper treatment early after the onset of acute DVT.

The first-line therapy for DVT is anticoagulant therapy and is prescribed for all patients unless contradicted. Anticoagulant therapy prevents the progression of thrombi and thereby suppresses the occurrence and recurrence of pulmonary thromboembolism. Treatment options for extensive venous occlusion due to acute DVT in the iliofemoral veins include CDT, i.e., direct injection of a high-dose thrombolytic agent into clotting site using a catheter, in addition to anticoagulant therapy for severe cases. In recent years, catheter therapies such as CDT are mainstream in Japan. The decision of whether to select surgical thrombectomy or catheter therapy depends on adequacy of equipment and experience at medical facilities.[1]

Discontinuation of the supply of urokinase, a thrombolytic used for CDT, was publicly disclosed in February 2022, and medical institutions are projected to run out of urokinase by 2023. As CDT will no longer be performed in Japan, 4 related academic societies (the Japanese Society for Vascular Surgery, the Japanese Association of Cardiovascular Intervention and Therapeutics, the Japanese Society of Interventional Radiology, and the Japanese Society of Phlebology) submitted a joint request on the early introduction of venous thrombectomy devices to the Ministry of Health, Labour, and Welfare in August 2022. In line with this request, the applicant filed an application for a marketing approval for the ClotTriever System to replace CDT especially in the treatment of acute severe DVT.

1.A.(2) Use in foreign countries

In the US, the ClotTriever System received 510 (k) clearance for the primary intended use of thrombus or embolus removal from the peripheral vasculature in 2017 and additionally for the treatment of DVT in 2020. In Europe, the ClotTriever System received a CE Mark in 2020 (or 2023 according to the Medical Device Regulation). Table 1 shows the intended use and sales numbers in foreign countries.

Table 1. Intended use and sales numbers in foreign countries (as of the end of July 2023)

Country	Intended use	Date of approval	Sales number
US	The ClotTriever Thrombectomy System is indicated for: • The non-surgical removal of thrombi and emboli from blood vessels. • Injection, infusion, and/or aspiration of contrast media and other fluids into or from a blood vessel. The ClotTriever Thrombectomy System is intended for use in the peripheral vasculature including deep vein thrombosis.	February 16, 2017 September 9, 2020	[redacted]
Europe	The ClotTriever Thrombectomy System is indicated for thrombus removal in the peripheral vasculature and treatment of DVT. It is indicated for patients aged ≥18 years.	December 30, 2020 January 27, 2023	[redacted]

1.A.(3) Malfunctions and adverse events reported in foreign countries

Table 2 shows the number of post-marketing device malfunctions and adverse events reported in the US between July 2017 and July 2023. No device malfunction or adverse event has been reported in any countries other than the US.

Table 2. Malfunctions and adverse events reported in the US

Malfunction/adverse event	Number of events	Incidence*
Death	[redacted]	0.011464%
Intervention required to prevent permanent injury	[redacted]	0.010422%
Peripheral embolus	[redacted]	0.003127%
Extravasation	[redacted]	0.003127%
Vessel perforation	[redacted]	0.001042%
Prolonged hospitalization	[redacted]	0.001042%

* Calculated using [redacted] (number of devices used) as parameter

1.B Outline of the review conducted by PMDA

The applicant's explanation about the analysis of the causes of the malfunctions or adverse events reported in the foreign countries:

The causes of the deaths ([redacted] cases) were events related to pulmonary embolism (PE) in [redacted] cases and right cardiac failure in [redacted] cases. Common interventions required to prevent permanent injury ([redacted] cases) were phlebotomy and balloon angioplasty. Those interventions were required because of inappropriate device use including forcible pushing or drawing back of the device against resistance in [redacted] cases, and difficulty removing the device that has collected massive thrombi [redacted] cases. Peripheral embolism ([redacted] cases) occurred because of PE-related events in [redacted] cases and peripheral artery occlusion in [redacted] cases. Extravasation ([redacted] cases) and vessel perforation ([redacted] cases) occurred because of inappropriate device use (use in smaller vessels than specified) in [redacted] cases and user error in [redacted] cases. Prolonged hospitalization was due to a cerebrovascular accident.

PMDA's view:
The risks of the events owning to inappropriate device use and user errors can be reduced by providing users with a thorough understanding of the directions for use through training, etc. as mentioned later in Section 7. All cases with difficulty in the removal of a device collected massive thrombi, leading to phlebotomy, involved 13-Fr sheaths. Thus, it is also important to offer users training, etc. on sheath selection. The PE-related deaths and peripheral embolism are discussed later 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 ClotTriever Sheath include the tip and surface, radiopacity, deployment force of the ClotTriever Sheath from the dilator, kink resistance, leakage, air leakage, vacuum performance, tensile strength, liquid injection, particulates, corrosion resistance, and durability.

The proposed performance and safety specifications for the ClotTriever Catheter include the tip and surface, guidewire compatibility, deployment force of the collection bag/coring element from the delivery catheter, pull-in force of the ClotTriever Catheter handle, pull-in force of the collection bag/coring element into the delivery catheter, pull-out force of the ClotTriever Catheter from the ClotTriever Sheath, kink resistance, radiopacity, leakage, tensile strength, particulates, corrosion resistance, and durability.

The proposed performance and safety specifications for the dilator include the tip and surface, kink resistance, guidewire compatibility, pull-out force of the dilator from the ClotTriever Sheath, insertion force of the snap of the dilator handle into the sheath hub, pull-in force of the snap of the dilator handle from the sheath hub, leakage, tensile strength, and particulates.

The proposed performance and safety specifications for the predilator include the tip and surface, guidewire compatibility, leakage, kink resistance, tensile strength, durability, and particulates.

The proposed performance and safety specifications for the 60-cc large bore syringe include the leakage, vacuum performance, and tensile strength.

The proposed performance and safety specifications for the ClotTriever System include biological safety, bacterial endotoxins, and ethylene oxide sterilization residuals.

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

PMDA requested the applicant to add thrombus collection performance, which is essential to ensure the performance of the ClotTriever System, to the performance specifications.

The applicant agreed and added thrombus collection performance to the specifications based on the results of the [redacted] mock test described later in Section "2.(5) Performance."

PMDA reviewed the data supporting the proposed performance and safety specifications, including those added later, to evaluate the appropriateness of the tests and specification limits, and the test results, and concluded that there was no particular problem in the submitted data.

2.(2) Physicochemical properties

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

To support the physicochemical properties of the ClotTriever Sheath, the applicant submitted data on tests for the appearance and dimensions, the deployment force of the ClotTriever Sheath from the dilator, kink resistance of the ClotTriever Sheath and dilator, leakage, air leakage, vacuum performance, tensile strength (mock use), rotation breakage (mock use), insertion resistance and placement resistance, pushing force of the button on the hemostatic valve, hemostatic valve torque, hemostatic valve burst, flush stop cock torque, flush stop cock burst, flow from the sheath/dilator, and corrosion resistance.

To support the physicochemical properties of the ClotTriever Catheter, the applicant submitted data on tests for the appearance and dimensions, guidewire compatibility, conical fitting of the 6% lure taper, insertion of the ClotTriever Catheter through the ClotTriever Sheath, deployment force of the collection bag/coring element from the delivery catheter, pull-in force of the ClotTriever Catheter handle (expansion of the collection bag/coring element), pull-in force of the collection bag/coring element into the delivery catheter, pull-out force of the ClotTriever Catheter from the ClotTriever Sheath, kink resistance, leakage, tensile strength (mock use), rotation breakage (mock use), ClotTriever Catheter handle torque, and corrosion resistance.

To support the physicochemical properties of the dilator, the applicant submitted data on tests for the appearance and dimensions, guidewire compatibility, fitting force of the dilator handle (force required to fit the slide actuator of the dilator into the designated position), pull-out force of the dilator from the ClotTriever Sheath, pull-out force of the dilator from the ClotTriever Sheath (thrombus-like substances), insertion force of the snap of the dilator handle into the sheath hub (preparation for replacement), pull-in force of the snap of the dilator handle from the sheath hub (preparation for replacement), pull-in force of the dilator handle (force required to return the slide actuator of the dilator handle to the designated position) (preparation for replacement), leak, conical fitting of the 6% lure taper, tensile strength (mock use), and torque of the dilator handle/flush port.

To support the physicochemical properties of the predilator, the applicant submitted data on tests for the appearance and dimensions, guidewire compatibility, leakage, insertion and kink resistance (mock use), tensile strength, and the functions the predilator in a pig model.

To support the physicochemical properties of the funnel loading tool, the applicant submitted data on appearance and dimension tests.

To support the physicochemical properties of the 60-cc large bore syringe, the applicant submitted data on tests for the appearance and dimensions, leakage, vacuum performance, and tensile strength.

To support the physicochemical properties of the ClotTriever System, the applicant submitted data on tests for particulates and bacterial endotoxins.

The applicant explained that all test results met the predefined evaluation criteria, assuring the performance of the ClotTriever System clinically required.

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

PMDA asked the applicant to explain the justification of the tests for deployment frequency and the necessity of setting a maximum acceptable deployment frequency.

The applicant's explanation:
In a non-clinical study, the mesh funnel, collection bag, and coring element were deployed 5 times through the ClotTriever Sheath while their functions remained intact, and these components were demonstrated to have functionality and durability required for thrombus collection. Users will be informed of study outcomes, i.e., the number of times deployed was 5 in the non-clinical study, and the median, minimum, and maximum number of times deployed in the clinical study of the ClotTriever System were 4, 2, and 8, respectively. Users will also be advised that, if strong resistance is felt when moving forward or drawing back the ClotTriever Sheath, dilator, or ClotTriever Catheter, ensure to retrieve the collection bag and restore the coring element into the delivery catheter before removing the ClotTriever System. Accordingly, with necessary risk reduction measures taken, the maximum acceptable deployment times will not be determined.

PMDA accepted the applicant's explanation in view that no re-deployment-related malfunctions or adverse events were reported in the clinical study of the ClotTriever System and overseas post-marketing settings. PMDA reviewed the data on the physicochemical properties and concluded that there was no particular problem in the submitted data.

2.(3) Biological safety

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

To support the biological safety of the ClotTriever System, the applicant submitted data on tests for cytotoxicity, sensitization, intradermal reaction, acute systemic toxicity, pyrogenicity, genotoxicity, and blood compatibility, all of which are required for devices that are partly led into the body and transiently (≤24hours) come in contact with circulating blood while operated externally. The results of the tests showed no problem.

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

PMDA reviewed the data on the biological safety and concluded that there was no particular problem in the submitted data.

2.(4) Stability and durability

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

Since the ClotTriever System requires no specific storage condition, its quality will not deteriorate over time, and the results of stability study confirmed its stability for 2 years after sterilization, the applicant

omitted the submission of the results of stability studies required to determine shelf life and submitted a self-declaration stating that its shelf life was determined from the results of necessary stability studies in accordance with the "Handling of stability studies related to the determination of the shelf life in the application for marketing approvals (certifications) of medical devices (in Japanese)" (PFSB/ELD/OMDE Notification No. 1227-5, dated December 27, 2012).

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

PMDA reviewed the data supporting the stability and durability of the ClotTriever System, and concluded that there was no particular problem in the submitted data.

2.(5) Performance

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

To support the performance of the ClotTriever System, the applicant submitted data of [redacted] mock test and mock test [redacted]. In the mock test [redacted], [redacted], and thrombectomy was performed using the ClotTriever System and comparator "Fogarty venous thrombectomy catheter" (Approval No. 15100BZY00938000) according to the directions for use. After that, [redacted] was assessed. The tests showed no particular problem in insertion, deployment, retrieval, thrombi extraction performance of the ClotTriever System, and pathology. The blood vessels treated with the ClotTriever System had full-thickness injury penetrating the thin muscular media layer with the outer layer remaining intact. The blood vessels treated with the comparator showed partial-thickness injury of the outer fibromuscular layer. These findings indicate the possibility for both the ClotTriever System and the comparator to make small non-perforating injury to the vascular wall. The test demonstrated no significant macroscopic or histopathological difference in vascular injury between the ClotTriever System and the comparator.

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

PMDA reviewed the data on the performance and concluded that there was no particular problem in the submitted data.

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 ClotTriever System 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 ClotTriever System to the Essential Principles as shown below.

1) PMDA's view on the conformity of the ClotTriever System to Article 1, which defines preconditions, etc. for designing medical devices, (particularly, conditions for users, such as expected technical knowledge, experience, education, and training for users):
As described later in Section "6.B Outline of the review conducted by PMDA" and Section "7.B Outline of the review conducted by PMDA," the selection of patients eligible for the treatment, users, and medical institutions, training for users, and compliance with the guidelines for proper use are important to maintain the risk-benefit balance of the product. To this end, approval conditions should be attached so that necessary measures are taken.

2) PMDA's view on the conformity of the ClotTriever System to Article 2, which specifies requirements for risk management throughout the product life cycle of medical devices:
As described later in Section "6.B Outline of the review conducted by PMDA" and Section "7.B Outline of the review conducted by PMDA," no clinical efficacy or safety data of the ClotTriever System are available in Japan. The product's efficacy and safety needs to be evaluated in clinical settings in Japan, and thus PMDA instructed the applicant to conduct a use-results survey.

3) PMDA's view on the conformity of the ClotTriever System to Article 3, which specifies requirements for the performance and functions of medical devices, and to Article 6, which specifies the efficacy of medical devices:
As described earlier in Section 2.(5), the performance of the ClotTriever System has been reviewed. As described later in Section "6.B Outline of the review conducted by PMDA," the clinical study of the ClotTriever System showed a favorable outcome, demonstrating its efficacy and safety by selecting patients eligible for the therapy. The ClotTriever System conforms to Articles 3 and 6.

4) PMDA's view on the conformity of the ClotTriever System to Article 4, which specifies the shelf-life or durability of medical devices:
As described earlier in Section 2.(4), the applicant submitted a self-declaration stating that the shelf-life of the ClotTriever System was determined from the results of necessary stability studies in accordance with the "Handling of stability studies related to the determination of the shelf life in the application for marketing approvals (certifications) of medical devices (in Japanese)" (PFSB/ELD/OMDE Notification No. 1227-5, dated December 27, 2012). The ClotTriever System conforms to Article 4.

5) PMDA's view on the conformity of the ClotTriever System to Article 7, which specifies requirements for the chemical properties, biological safety, and other aspects of medical devices:
As described earlier in Section 2.(2) and Section 2.(3), the biological safety and other aspects of the ClotTriever System were justified. The ClotTriever System conforms to Article 7.

6) PMDA's view on the conformity of the ClotTriever System to Article 8, which specifies the prevention of microbial contamination of medical devices:
As described later in Section "5.B. Outline of the review conducted by PMDA," prevention of microbial contamination of the ClotTriever System was justified. The ClotTriever System conforms to Article 8.

7) PMDA's view on the conformity of the ClotTriever System to Article 17, which specifies requirements for publicizing Information on Precautions, etc. or the communication of information to users via the instructions for use, etc. (hereinafter referred to as Information on Precautions, etc.):
As described later in Section "6.B Outline of the review conducted by PMDA" and Section "7.B Outline of the review conducted by PMDA," it is essential for users to fully understand the risks of the ClotTriever System, appropriately select eligible patients for the treatment with the ClotTriever System, and use the ClotTriever System properly so that its risk-benefit balance is maintained. To this end, necessary information should be provided through Information on Precautions, etc., the guidelines for proper use, training, and other measures. Accordingly, PMDA instructed the applicant to raise users' awareness, via Information on Precautions, etc., about compliance with the guidelines for proper use, which define patient eligibility and requirements for users, medical institutions, training, etc.

PMDA comprehensively reviewed the conformity of the ClotTriever System 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 data summarizing the risk management system and the risk management activities implemented for the ClotTriever System in accordance with ISO 14971:2019 "Medical devices – Application of risk management to medical devices."

4.B Outline of the review conducted by PMDA

PMDA comprehensively reviewed the document on risk management, taking into account the discussion presented in Section "3.B Outline of the review conducted by PMDA" and 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 ClotTriever System (conditions to assure sterility assurance level and ethylene oxide sterilization residuals).

5.B Outline of the review conducted by PMDA

PMDA reviewed the data on the manufacturing process and concluded that there was no particular problem in the submitted data.

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

6.A Summary of the data submitted

To support the clinical evaluation of the ClotTriever System, the applicant submitted the results from the CLOUT Registry study in the US. As shown in Table 3, the CLOUT Registry was a multicenter, prospective study that evaluated the real world use of the previous and current versions of the ClotTriever System in patients with acute, subacute, and chronic proximal DVT. The study included a cohort for verification of efficacy and safety hypotheses (Primary Analysis Population), with the intention to expand the indication of the ClotTriever System to DVT in the US.

Table 3. Outline of the CLOUT Registry

Item	Outline
Type of study	Multicenter, prospective study
Inclusion criteria	1. ≥18 years of age at consent 2. Proximal lower extremity DVT involving the femoral, common femoral, iliac veins, or inferior vena cava (IVC), alone or in combination 3. Willing and able to provide written informed consent after a full explanation on the details of the study
Exclusion criteria	1. Prior venous stent in the target vessel segment (TVS) 2. IVC aplasia/hypoplasia or other congenital anatomic anomalies of the IVC or iliac veins 3. IVC filter in place at the time of the planned index procedure 4. Allergy or hypersensitivity from heparin or iodinated contrast agents, except for mild to moderate contrast allergies, or thrombocytopenia 5. Life expectancy of <1 year 6. Chronic non-ambulatory status 7. Known hypercoagulable states that, in the opinion of the investigator, cannot be medically managed 8. Unavailability of a proximal lower extremity venous access site
Primary endpoints	Primary efficacy endpoint Technical success: Percentage of patients with complete or near complete (≥75%) removal of thrombi, as assessed based on a percent reduction in Marder score (assessed by the Core Lab). Primary safety endpoint Composite of major adverse events (MAEs), which is defined as at least one of the following MAEs, within 30 days of the index procedure; • All-cause mortality • Major bleeding • New symptomatic PE as diagnosed by pulmonary arteriography with CT • Rethrombosis of TVS
Secondary endpoints	• Individual MAEs among composite MAEs within 30 days of index procedure • Mild bleeding within 30 days of index procedure • Procedural complications (hematoma, false aneurysm, or perforation) at puncture site within 30 days of index procedure • Device-related death • Procedure-related death • The following assessments were conducted at each follow-up visit; − Patency of TVS by Duplex ultrasound − Rethrombosis of TVS − Rethrombosis of TVS due to the ClotTriever System − DVT in blood vessels other than TVS − Edema in the target leg compared with baseline (rVCSS edema scale) − Pain compared with baseline (NPRS) − EQ-5D, rVCSS, and Villalta scores (except for the time of hospital discharge) compared with baseline
Study period	[redacted], 20[redacted] (start of registration) to [redacted], 20[redacted] (end of registration) Currently, follow-up is ongoing.

The CLOUT Registry included 500 patients with proximal DVT treated with the ClotTriever System (Full Analysis Population). Of these, 91 patients with unilateral proximal DVT estimated to be ≤6 weeks old (by investigator) who were not treated by CDT or percutaneous mechanical thrombectomy in the past 3 months, found to have thrombi at baseline by the Core Lab, and treated with the ClotTriever System in ≥1 target vessel segment (TVS) were registered in the Primary Analysis Population (hereinafter referred to as the clinical study).

The primary efficacy endpoint of the clinical study was technical success (percentage of patients with complete or near complete [≥75%] removal of thrombi based on Marder score by the Core Lab). The Marder score is a quantitative scoring system used to assess venous patency by venography. The maximum score is defined for complete occlusion of each vessel segment (Table 4). Thrombus burden in each vessel segment is scored (Marder score is calculated by summing up the score for each vessel segment that is calculated by multiplying a percent stenosis determined from venograms by the maximum score of that segment).[i] The score indicates venous patency rate, while the percent reduction in Marder score refers to thrombus removal rate.

Table 4. Definition of Marder score

Vessel segment		Maximum score for complete occlusion
Iliac vein	Common iliac vein	3 points
	External iliac vein	3 points
Common femoral vein		4 points
Femoral vein	Proximal femoral vein	5 points
	Distal femoral vein	5 points
Popliteal vein		4 points
Sum		24 points

The primary safety endpoint was "composite of major adverse events (MAEs) within 30 days of the index procedure," which was defined as the occurrence of at least one of the following events; all-cause mortality, major bleeding, new symptomatic PE as diagnosed by pulmonary arteriography with computed tomography (CT), or rethrombosis of TVS. The thresholds for the primary efficacy and safety endpoints were determined with reference to 7 overseas publications reporting the outcomes of DVT treated with CDT or pharmacomechanical catheter directed thrombolysis (pharmacomechanical CDT [PCDT]).

The threshold for the efficacy endpoint was 30%, as calculated from the weighted mean of the "percentage of patients with complete or near complete (≥75%) removal of thrombi" determined from literature data (39.3%) and a margin of 10%. Assuming the expected performance of the ClotTriever System of 50%, significance level of 2.5%, power of 97%, and percentage of thrombus-free patients of 3%, 88 patients would be required to show that the value of ClotTriever System was higher than the threshold. The efficacy endpoint was evaluated in the Primary Effectiveness Cohort consisting of 89 subjects, excluding 2 subjects without venograms before or after the index procedure required for thrombus assessment by the Core Lab from the Primary Analysis Population. The threshold for the safety endpoint was 34%, as calculated from the weighted mean incidence of MAEs determined from the literature data (23.8%) and a margin of 10%. Assuming the incidence of MAEs within 30 days of the index procedure with the ClotTriever System as 20%, significance level of 2.5%, and power of 82%, 91 patients would be required to show that the incidence of MAE was lower than the threshold, allowing for a dropout of 5%. The safety endpoints were evaluated in the Primary Safety Cohort, which consisted of all subjects included in the Primary Analysis Population.

[i] For example, the Marder score for a 50% stenosis in the common femoral vein is 2 points as calculated by multiplying 4 points by 0.5. In the clinical study, a thrombus removal rate represents a percent reduction from baseline in Marder score before additional treatment following the index procedure.

Two-year follow-up was completed by 50.5% (46 of 91) of subjects, while 34.1% (31 of 91) of subjects discontinued the study (The study completion forms for the remaining 14 subjects were not completed at the time of data extraction). The reasons for study discontinuation were lost to follow-up in 23 subjects, refusal for follow-up in 1 subject, consent withdrawal in 1 subject, and death in 6 subjects. Table 5 shows the follow-up status in the clinical study.

Table 5. Follow-up status (Primary Analysis Population)

	Day 30	Month 6	Year 1	Year 2
Survival*[1]	81.3% (74/91)	74.7% (68/91)	67.0% (61/91)	33.0% (30/91)
Death*[2]	2.2% (2/91)	4.4% (4/91)	4.4% (4/91)	6.6% (6/91)
Consent withdrawal/lost to follow-up*[3]	16.5% (15/91)	20.9 (19/91)	26.4% (24/91)	26.4% (24/91)
Upcoming*[4]	0	0	0	4.4% (4/91)
Unknown*[5]	0	0	2.2% (2/91)	29.7% (27/91)

*1 Subject's survival was confirmed at the follow-up visit.
*2 Subject's death was confirmed at the follow-up visit.
*3 The subject's condition was unknown at the follow-up visit because of consent withdrawal.
*4 The subject has not reached the follow-up visit window.
*5 The subject has reached the follow-up visit window but has not been documented in the follow-up form.

6.A.(1) Patient characteristics

Table 6 shows the patient characteristics in the clinical study.

Table 6. Patient characteristics (Primary Analysis Population)

Item	N = 91
Age (years old), mean ± SD (minimum, maximum)	57.48 ± 15.927 (18.6, 89.8)
Sex	
Male	52.7% (48/91)
Female	47.3% (43/91)
BMI, mean ± SD (minimum, maximum)	31.084 ± 6.6491 (20.56, 54.52)
Race	
Caucasian	69.2% (63/91)
Black or African American	26.4% (24/91)
Native American or Alaska Natives	2.2% (2/91)
Others	2.2% (2/91)
Asian	0.0% (0/91)
History of DVT, yes	18.7% (17/91)
Contraindication for thrombotic, yes (relative contraindication)*[1]	39.6% (36/91)
Duration of limb symptom	
<7 days	51.6% (47/91)
7-14 days	20.9% (19/91)
2-4 weeks	17.6% (16/91)
4-6 weeks	5.5% (5/91)
>6 weeks	3.3% (3/91)
Unknown	1.1% (1/91)
Prior treatment for DVT, yes	20.9% (19/91)
Details of prior treatment	
Mechanical thrombectomy	0
Thrombolysis	0
Anticoagulant therapy for ≥7 days*[2]	94.7% (18/19)
Others	5.3% (1/19)
Provoked DVT,*[3] yes	35.2% (32/91)
CEAP C classification of target segment	
C0 (no visible or palpable signs of venous disease)	1.1% (1/91)
C1 (telangiectasia, reticular varicose veins, etc)	0
C2 (varicose veins)	2.3% (2/91)
C3 (edema)	80.7% (71/91)
C4a (pigmentation or eczema)	12.5% (11/91)
C4b (lipodermatosclerosis or atrophie blanche)	2.3% (2/91)
C5 (healed ulcers)	1.1% (1/91)
C6 (active ulcers)	0
Data missing	3

*1 The reasons for relative contraindications were recent bleeding, surgery, invasive intervention, anticoagulant therapy, age of >75 years, and body weight of >60 kg.
*2 Prior anticoagulant therapy for recent DVT (within the past 30 days) over ≥7 days
*3 DVT that is caused by a clear inciting or triggering factor, including oral contraceptives, pregnancy, surgery within 3 months, hormone replacement therapy, cancer, long-distance travel, and long-term bed rest

6.A.(2) Study results

6.A.(2).1) Information on device and procedure

All subjects completed the treatment with 1 session of the index procedure. The mean procedure duration was 64.0 minutes. The mean thrombectomy duration (total time from the insertion of the ClotTriever Sheath in the beginning of the procedure to the removal of the ClotTriever Catheter from subject at the end of the procedure) was 34.2 minutes. The mean blood loss was 58.5 mL. The investigational devices used in the clinical study were the 13-Fr sheath in 97.5% (78 of 80 subjects), the 16-Fr sheath in 2.5% (2 of 80 subjects), and unknown in 11 subjects. Table 7 shows the procedure information.

Table 7. Procedure information (Primary Analysis Population)

Item	N = 91
Number of times deployed*[1] mean ± SD (minimum, maximum)	4.0 ± 1.42 (2, 8)
Age of oldest thrombus	
Acute/subacute/chronic*[2]	47.3% (43/91)/52.7% (48/91)/0
Iliac or iliofemoral DVT*[1,3]	77.8% (70/90)
Additional intervention after the index procedure with the ClotTriever System	
IVC filter	1.1% (1/91)
Balloon angioplasty	73.6% (67/91)
Venous stenting	42.9% (39/91)
Additional intervention with the ClotTriever System	1.1% (1/91)

*1 Based on data from 90 subjects

*2 Thrombus age was estimated and classified by the investigator based on the appearance and texture of the thrombus, subject's medical history, and relevant diagnostic images (Acute, fresh thrombus of ≤14 days; subacute, organized thrombus of 14 days to 6 weeks; chronic, fibrous thrombus of >6 weeks).

*3 It was defined as common iliac, external iliac and/or common femoral DVT based on a pre-procedural Marder score.

6.A.(2).2) Efficacy evaluation

The primary efficacy endpoint of "technical success" in 89 subjects in the Primary Effectiveness Cohort was 76.4% (68 of 89 subjects), with a lower limit of the one-sided 97.5% confidence interval of 66.2% meeting the predefined threshold ($P < 0.0001$) (Table 8). The Marder score before the index procedure was 9.47 ± 3.86 (min 2.5, max 18.0), which decreased to 1.39 ± 1.70 (min 0.0, max 7.5) after the index procedure. The percent reduction in Marder score (thrombus removal rate) from baseline was approximately 85% after the index procedure. The percent reduction in Marder score was ≥90% in 49.4% of the subjects and 100% in 42.7% the subjects. Of 21 subjects who failed to achieve the primary efficacy endpoint, 4 subjects had a percent reduction in Marder score of <50% (Table 9). Table 10 shows a summary of the results of the secondary efficacy endpoints.

Table 8. Results of the primary efficacy endpoint (Primary Effectiveness Cohort)

Item	N = 89
Technical success (≥75% thrombus removal, as assessed based on a percent reduction in Marder score)	76.4% (68/89)
97.5% confidence interval, *P* value	66.2%-100.0%, <0.0001

Table 9. details of subjects who failed to achieve the primary efficacy endpoint (Primary Effectiveness Cohort)

Subject ID	Time from symptom onset	Thrombus*1 age	Percent reduction in Marder score	Amount of residual thrombus		Adjunct treatment after the index procedure
				Pre-index procedure	Post-index procedure	
1	4-6 weeks	Subacute	56.5%	61%-70%	≤10%	Balloon angioplasty
2	7-14 days	Acute	30.8%	Occluded	≤10%	Balloon angioplasty
3	<7 days	Subacute	48.1%	Occluded	21%-30%	Balloon angioplasty
4	7-14 days	Subacute	71.9%	81%-90%	≤10%	Balloon angioplasty Stenting
5	<7 days	Subacute	70.8%	Occluded	21%-30%	Balloon angioplasty Stenting
6	<7 days	Acute	66.7%	Occluded	≤10%	Balloon angioplasty Stenting
7	2-4 weeks	Acute	70.2%	Occluded	≤10%	None
8*3	<7 days	Acute	58.8%	91%-99%	≤10%	Balloon angioplasty
9	<7 days	Subacute	69.4%	91%-99%	31%-40%	Balloon angioplasty
10	7-14 days	Subacute	51.7%	91%-99%	-*2	Balloon angioplasty
11	<7 days	Acute	57.7%	Occluded	21%-30%	Balloon angioplasty
12*3	<7 days	Subacute	35.7%	91%-99%	≤10%	None
13	>6 weeks	Subacute	66.7%	61%-70%	11%-20%	Balloon angioplasty
14	<7 days	Subacute	59.3%	Occluded	≤10%	Balloon angioplasty Stenting
15	7-14 days	Subacute	54.5%	Occluded	≤10%	Balloon angioplasty
16	7-14 days	Subacute	53.3%	71%-80%	≤10%	None
17	<7 days	Subacute	37.5%	91%-99%	≤10%	Balloon angioplasty
18	7-14 days	Acute	56.3%	Occluded	≤10%	Balloon angioplasty
19	<7 days	Acute	54.8%	Occluded	21%-30%	Balloon angioplasty
20	<7 days	Subacute	61.1%	Occluded	≤10%	None
21	<7 days	Subacute	63.2%	91%-99%	≤10%	None

*1 Age of oldest thrombus, *2 Not measured

*3 This subject failed to reach the follow-up visit window for assessment of the primary safety endpoint.

Table 10. Results of the secondary efficacy endpoints (Primary Effectiveness Cohort)

	Baseline	Day 30	Month 6	Year 1	Year 2
Patency of TVS,*[1,2] N (%)	83 (93.3%)	63 (70.8%)	54 (60.7%)	42 (47.2%)	34 (38.2%)
Patent	13.3% (11/83)	69.8% (44/63)	75.9% (41/54)	88.1% (37/42)	94.1% (32/34)
P-value*[3]		<0.0001	<0.0001	<0.0001	<0.0001
rVCSS score,*[7] N (%)	80 (89.9%)	71 (79.8%)	55 (61.8%)	46 (51.7%)	38 (42.7%)
Mean ± SD	6.3 ± 3.3	3.9 ± 2.8	2.9 ± 2.3	2.5 ± 2.0	2.6 ± 2.2
Min, Max	0, 19	0, 13	0, 10	0, 8	0, 8
P-value*[4]		<0.0001	<0.0001	<0.0001	<0.0001
rVCSS pain score N (%)	84 (94.4%)	72 (80.9%)	57 (64.0%)	47 (52.8%)	38 (42.7%)
Mean ± SD	2.0 ± 1.0	0.6 ± 0.8	0.6 ± 0.8	0.5 ± 0.8	0.3 ± 0.6
Min, Max	0, 3	0, 3	0, 3	0, 3	0, 2
P-value*[4]		<0.0001	<0.0001	<0.0001	<0.0001
Severity (rVCSS pain score)					
Non (0)	9.5% (8/84)	58.3% (42/72)	56.1% (32/57)	70.0% (31/47)	71.1% (27/38)
Mild (1)	19.0% (16/84)	26.4% (19/72)	31.6% (18/57)	23.4% (11/47)	23.7% (9/38)
Moderate (2)	33.3% (28/84)	12.5% (9/72)	10.5% (6/57)	6.4% (3/47)	5.3% (2/38)
Severe (3)	38.1% (32/84)	2.8% (2/72)	1.8% (1/57)	4.3% (2/47)	0
NPRS score,*[8] N (%)	80 (89.9%)	71 (79.8%)	51 (57.3%)	49 (55.1%)	39 (43.8%)
Mean ± SD	4.8 ± 3.2	1.5 ± 2.3	1.5 ± 2.2	1.4 ± 2.5	1.0 ± 1.8
Min, Max	0, 10	0, 10	0, 9	0, 8	0, 7
P-value*[5]		<0.0001	<0.0001	<0.0001	<0.0001
EQ-5D score,*[9] N (%)	83 (93.3%)	71 (79.8%)	57 (64.0%)	51 (57.3%)	39 (43.8%)
Mean ± SD	0.5866 ± 0.3062	0.8631 ± 0.1702	0.8471 ± 0.2226	0.8806 ± 0.1856	0.9294 ± 0.1024
Min, Max	-0.040, 1.000	0.106, 1.000	-0.109, 1.000	0.135, 1.000	0.628, 1.000
P-value*[5]		<0.0001	<0.0001	<0.0001	<0.0001
Villalta score*,[10] N (%)	83 (93.3%)	71 (79.8%)	55 (61.8%)	47 (52.8%)	38 (42.7%)
Mean ± SD	11.2 ± 5.7	4.3 ± 4.1	3.1 ± 4.1	2.9 ± 4.1	2.5 ± 2.9
Min, Max	1, 27	0, 16	0, 18	0, 21	0, 11
P-value*[4]		<0.0001	<0.0001	<0.0001	0.0001
Severity (Villalta score)					
Less than mild (1-4)	8.4% (7/83)	64.8% (46/71)	76.4% (42/55)	83.0% (39/47)	78.9% (30/38)
Mild (5-9)	34.9% (29/83)	23.9% (17/71)	14.5% (8/55)	8.5% (4/47)	18.4% (7/38)
Moderate (10-14)	31.3% (26/83)	7.0% (5/71)	7.3% (4/55)	6.4% (3/47)	2.6% (1/38)
Severe (≥15)	25.3% (21/83)	4.2% (3/71)	1.8% (1/55)	2.1% (1/47)	0
P-value*[6]		<0.0001	<0.0001	<0.0001	<0.0001

*1 "Patency" is determined by "the presence of blood flow" and "normal/partial compressibility."
*2 Subjects with available baseline and follow-up data underwent paired measurement.
*3 When the total of non-diagonal elements is ≥10, a *P*-value is calculated using McNemar test. When the total of non-diagonal elements is <10, a *P*-value is calculated using McNemar's exact test. The frequency limitations between a baseline value and a follow-up value are compared.
*4 Calculated using Wilcoxon Rank Sum test in comparison with a baseline value.
*5 Calculated using Wilcoxon signed-rank test in comparison with a baseline value.
*6 Calculated using McNemar-Bowker test of symmetry between a baseline value and a follow-up value.
*7 rVCSS score: The intensity of each of "Pain or other discomfort," "Varicose veins," "Venous edema," "Skin pigmentation," "Inflammation," "Skin induration," "Active ulcer number," "Active ulcer duration," "Active ulcer size," and "Use of compression therapy" is scored 0 (non), 1 (mild), 2 (moderate), or 3 (severe) and totaled (maximum score of 30 points).
*8 NPRS score: The intensity of pain is rated by patients themselves using a 11-point scale from 0 (no pain) to 10 (worst possible pain).
*9 EQ-5D score: Five health-related dimensions of "Mobility," "Self-care," "Usual activities," "Pain/discomfort," and "Anxiety/depression" are rated by patients themselves using a 5-point scale, 1 (no problems) to 2 (slight problems), 3 (moderate problems), 4 (severe problems), or 5 (extreme problems). The score ranges from 0.025 to 1.000.
*10 Villalta score: The severity of each symptoms (1, Pain; 2, Cramps; 3, Heaviness; 4, Paresthesia; 5, pruritus) and clinical signs (1, Pretibial edema; 2, Skin induration; 3, Hyperpigmentation; 4, Redness; 5, Venous ectasia; 6, Pain on calf compression) is scored 0 (non), 1 (mild), 2 (moderate), or 3 (severe). On the basis of the total score, the severity of PTS is assessed as mild (5-9), moderate (10-14), or severe (≥15).

6.A.(2).3) Safety evaluation

The primary safety endpoint of "composite MAEs within 30 days of the index procedure" was analyzed in 76 of 91 subjects in the Primary Safety Cohort, excluding 15 subjects who failed to reach the 30-day

follow-up visit window because of consent withdrawal/lost to follow-up. The analysis results showed that the primary safety endpoint was 20.0% (15 of 75 subjects, excluding 1 subject who reached the follow-up visit window but had missing data), with the upper limit of the one-sided 97.5% confidence interval of 30.8%, which met the predefined threshold (P = 0.0058) (Table 11). Composite MAEs (17 events in 15 subjects) reported in the clinical study were all-cause mortality (2 subjects), new symptomatic PE (1 event in 1 subject), and rethrombosis of TVS (14 events in 13 subjects) (Table 11). Table 12 shows a list of the 15 subjects who failed to reach the follow-up visit window for the assessment of the primary safety endpoint. In addition, all-cause mortality (7 events) and new symptomatic PE (2 events) were reported within 2 years of the index procedure, but a relationship to the ClotTriever System or the index procedure was ruled out for all events. No procedure-related events, such as major bleeding, mild bleeding, puncture site complications, and valvular or vasculature injury, occurred.

Table 11. Results of the safety endpoints (Primary Safety Cohort)

Item	N = 91*1
Primary safety endpoint	
Composite MAEs within 30 days	20.0% (15/75)
97.5% confidence interval, *P* value	0%-30.8%, 0.0058
Secondary safety endpoints	
Individual MAEs of primary safety endpoint	
All-cause mortality	2.6% (2/76)
Major bleeding*2	0
New symptomatic PE as diagnosed by pulmonary arteriography with CT	1.4% (1/73)
Rethrombosis of TVS*3	17.8% (13/73)
Mild bleeding within 30 days*4	0
Procedural complications at the puncture site within 30 days	0
Device-related death within 2 years	0
Procedure-related death within 2 years	0

*1 The percentage is calculated using the number of subjects who reached the follow-up visit window in the Primary Safety Cohort as the denominator.

*2 Clinically obvious bleeding accompanied by a ≥5 g/dL decrease in hemoglobin, transfusion of ≥2 units of red blood cells, or involvement of a significant region (intracranial or intraspinal)

*3 Occlusive thrombosis within the TVS that occurred after the patency of this segment was previously restored and was confirmed by diagnostic imaging (Duplex ultrasound, venography, CT venography, or contrast-enhanced magnetic resonance venography)

*4 Non-major bleeding excluding mild blood exudation at puncture site and hemoglobinuria with no complication

Table 12. Details of subjects who failed to reach the follow-up visit window for assessment of the primary safety endpoint (Primary Safety Cohort)

Subject ID	Time to onset	Causal event	Intervention to adverse events	Outcome	Relation to device	Relation to procedure
All-cause mortality						
1	Day 23	Non-small cell lung cancer stage IV	None	Death	Unrelated	Unrelated
2	Day 13	Spinal cord infection	None	Death	Unrelated	Unrelated
New symptomatic PE as diagnosed by pulmonary arteriography with CT						
3	Day 2	Aggravation of PE	Postoperative thrombolysis	Resolved*1	Unrelated	Unknown
Rethrombosis of TVS						
4	Day 13	Rethrombosis	ClotTriever, IVC filter, stent placement	Resolved*1	Unrelated	Unrelated
	Day 27	Rethrombosis	Switching of anticoagulant	Persisting	Unrelated	Unrelated
5	Day 26	Rethrombosis of TVS	None	Persisting	Unrelated	Unrelated
6	Day 4	Rethrombosis of TVS	Postoperative thrombolysis/venous angioplasty	Resolved	Unrelated	Related
7*2	Day 21	Recurrent DVT	ClotTriever, balloon angioplasty	Resolved	Unrelated	Unrelated
8	Day 21	Femoral thrombosis	None	Resolved	Unrelated	Unrelated
9	Day 30	Rethrombosis	None	Persisting	Unrelated	Unrelated
3	Day 8	Rethrombosis	None	Persisting	Unrelated	Unknown
10	Day 22	Right femoral rethrombosis	None	Resolved	Unrelated	Unrelated
11	Day 21	Femoral rethrombosis	None	Resolved	Unrelated	Unrelated
12*2	Day 19	Right femoral and popliteal rethrombosis	None	Resolved	Unrelated	Unrelated
13	Day 20	Rethrombosis	None	Persisting	Unrelated	Unrelated
14	Day 11	Acute occlusive DVT of the left leg	Switching of anticoagulant	Resolved	Unrelated	Unrelated
15	Day 29	Proximal venous rethrombosis of the left leg	Postoperative thrombolysis	Resolved	Unrelated	Unrelated

*1 The subject had sequela, the details of which are not available.
*2 This subject failed to achieve the primary efficacy endpoint.

Serious adverse events occurred in 9.2% (7 of 76 subjects) within 30 days of the index procedure, which were DVT (3 events in 3 subjects), and PE, non-small cell lung cancer, pulseless action potential, and spinal cord infection (1 event in 1 subject each). In addition, 41 adverse events occurred in 35 subjects within 2 years of the index procedure, including 20 serious adverse events in 20.9% (19 of 91 subjects). None of these events were related to the device, while 2 events in 2 subjects were related to the index procedure, and a causal relationship to the index procedure was unknown for 1 event in 1 subject (Table 13).

Table 13. Serious adverse events reported within 2 years of the index procedure (Primary Safety Cohort)

Classification	Event	Number of events	Causality		
			Relation to device	Relation to procedure	
				Related	Unknown
Vascular disorders	DVT	11	0	1	0
	PE	2	0	0	1
Cardiac diseases	Cardiac arrest	1	0	0	0
	Pulseless electrical activity	1	0	1	0
Infections	Septic shock	1	0	0	0
	Spinal cord infection	1	0	0	0
Neoplasms benign, malignant and unspecified	Non-small cell lung cancer	1	0	0	0
	Osteosarcoma	1	0	0	0
Respiratory, thoracic and mediastinal disorders	Respiratory failure	1	0	0	0

No device malfunctions resulted in death or aggravation, required intervention to prevent death or aggravation, or contributed to death or aggravation in the past 2 years.

All-cause mortality reported in the Full Analysis Population within 2 years of the index procedure included a device-related death in 1 subject, and a death of unknown causal relationship to the device or index procedure in 1 subject (Table 14). Within 2 years of the index procedure, 195 adverse events occurred in 150 subjects, including 115 serious adverse events in 91 subjects. Of these, 1 event in 1 subject was related to the device, while 1 event in 1 subject had unknown causal relationship to the device, 25 events in 25 subjects were related to the index procedure, and 9 events in 9 subjects had unknown causal relationship to the index procedure (Table 15).

Table 14. All-cause mortality reported within 2 years of the index procedure (Full Analysis Population)

Subject ID	Primary Analysis Population	Number of days from index procedure	Causal event	Relation to device or procedure
1	Not included	269 days	Atrial fibrillation	Unrelated
2	Included	159 days	Osteosarcoma	Unrelated
3	Not included	21 days	Cardiac failure congestive	Unrelated
4*[1]	Not included	866 days	Cerebrovascular disorder	Unrelated
5	Included	500 days	Dehydration	Unrelated
6	Not included	296 days	Acute respiratory failure	Unrelated
7	Not included	51 days	Metastatic small cell carcinoma	Unrelated
8	Not included	273 days	Meningitis	Unrelated
9	Not included	97 days	Sepsis	Unrelated
10	Included	23 days	Non-small cell lung cancer stage IV	Unrelated
11*[2]	Not included	51 days	Cerebrovascular disorder	Unknown
12	Included	36 days	Respiratory failure	Unrelated
13	Not included	412 days	Metastatic prostate cancer	Unrelated
14	Not included	3 months and 23 days	Cancer (stage IV)	Unrelated
15	Not included	309 days	Metastatic cervical cancer	Unrelated
16	Included	13 days	Spinal cord infection	Unrelated
17	Not included	326 days	Acute kidney disorder	Unrelated
18	Included	558 days	Septic shock	Unrelated
19	Not included	0 days	PE	Related to device
20	Not included	208 days	Septic shock	Unrelated
21	Not included	87 days	Death (details unknown)	Unrelated
22	Included	419 days	Cardiac arrest	Unrelated
23	Not included	192 days	Cancer, pneumonia, heart attack	Unrelated
24	Not included	123 days	Acute respiratory failure	Unrelated
25	Not included	210 days	Neoplasm malignant of pleura metastatic	Unrelated
26	Not included	11 days	Cardiac arrest	Unrelated
27	Not included	26 days	Respiratory failure	Unrelated
28*[2]	Not included	197 days	Leukaemia	Unrelated
29	Not included	159 days	Myocardial infarction	Unrelated
30	Not included	229 days	Cardiac failure congestive	Unrelated
31	Not included	83 days	Death (details unknown)	Unrelated

*1 The subject is not included as a death case in the analysis data because the subject died after the completion of 2-year follow-up.

*2 The subject is not included as a death case in the analysis data because the subject's death was reported after the data extraction on [redacted], 20[redacted].

Table 15. Serious adverse events reported within 2 years of the index procedure (Full Analysis Population)

Classification	Event	Number of events	Causality			
			Relation to device		Relation to procedure	
			Related	Unknown	Related	Unknown
Vascular disorders	DVT	62	0	0	14	6
	PE	8	1*[1]	0	0	3
	Cerebrovascular disorder	2	0	0	0	0
	Extrinsic iliac vein compression	1	0	0	0	0
	Haematoma	1	0	0	1	0
	PTS	1	0	0	1	0
	Spontaneous haematoma	1	0	0	0	0
Neoplasms benign, malignant and unspecified including cysts and polyps	Cervix carcinoma stage IV	1	0	0	0	0
	Malignant neoplasm of pleura metastatic	1	0	0	0	0
	Myelodysplastic syndrome	1	0	0	0	0
	Non-small cell lung cancer stage IV	1	0	0	0	0
	Osteosarcoma	1	0	0	0	0
	Prostate cancer metastatic	1	0	0	0	0
	Small cell carcinoma	1	0	0	0	0
Cardiac diseases	Cardiac arrest	2	0	0	0	0
	Atrial fibrillation	1	0	0	1	0
	Cardiac failure congestive	1	0	0	0	0
	Myocardial infarction	1	0	0	0	0
	Pulseless electrical activity	1	0	0	1	0
Blood and lymphatic system disorders	Anaemia	5	0	0	2	0
Infections	Septic shock	2	0	0	0	0
	Meningitis	1	0	0	0	0
	Sepsis	1	0	0	0	0
	Spinal cord infection	1	0	0	0	0
Respiratory, thoracic and mediastinal disorders	Acute respiratory failure	2	0	0	0	0
	Respiratory failure	2	0	0	0	0
	Epistaxis	1	0	0	1	0
General disorders and administration site conditions	Death	4	0	0	0	0
Gastrointestinal disorders	Gastrointestinal hemorrhage	2	0	0	1	0
Injury, poisoning and procedural complications	False aneurysm	2	0	1*[2]	2	0
Investigation	Haemoglobin decreased	1	0	0	1	0
Metabolism and nutrition disorders	Dehydration	1	0	0	0	0
Renal and urological diseases	Acute renal disorder	1	0	0	0	0

*1 The subject with Subject ID 19 in Table 14

*2 False right popliteal aneurysm. Angioplasty and stenting of the right popliteal artery were performed.

6.B Outline of the review conducted by PMDA

6.B.(1) Clinical positioning of the ClotTriever System

The applicant's explanation about the clinical positioning of the ClotTriever System:

Severe DVT with arterial ischemia such as phlegmasia cerulea dolens, for which catheter therapy is recommended as Class I therapy[1] in the Guidelines for Diagnosis, Treatment and Prevention of Pulmonary Thromboembolism and Deep Vein Thrombosis (Revised Version, 2017) (hereinafter referred to as the Guidelines), should be an absolute indication for treatment with the ClotTriever System. Phlegmasia cerulea dolens is the most severe form of DVT. The primary therapeutic objectives of the disease are improvement of ischemia, preservation of affected limbs, and symptom relief.[1,3] Delayed treatment may result in venous necrosis, and therefore patients usually undergo emergency intervention within 2 to 3 days after the onset of phlegmasia cerulea dolens.[4,5,6] Because of its recent onset, most cases are of acute thrombi, but subacute or chronic thrombi may also be present. According to a literature article, acute and subacute thrombi[6] were isolated from a patient, and acute and chronic thrombi[7] from a different patient. These patients had phlegmasia cerulea dolens and were treated by thrombectomy with the ClotTriever System. The Guidelines recommend CDT as a Class IIa therapy for acute-stage severe proximal DVT and a low of bleeding risk.[1] The ClotTriever System, which requires no thrombolytic, can be used in patients with a high risk of bleeding. The primary objectives of CDT in this patient population are the alleviation of acute clinical symptoms (e.g., pain, edema, and redness) caused by rapid dissolution of thrombi, improvement in symptoms, prevention of pulmonary thromboembolism, and prevention of PTS. Non-fresh thrombi may not adequately respond to CDT because of their altered characteristics, preventing sufficient infiltration of a drug solution into the thrombi. For this reason, CDT is better indicated for acute thrombi that are <14 days old.[1] The thrombi collected in the clinical study were roughly estimated to be ≤6 weeks old based on their characteristics. This finding suggests that the ClotTriever System can be indicated for acute-stage severe proximal DVT.

PMDA's view:

In Japan, discontinued supply of urokinase is posing an obstacle to CDT. Related academic societies have submitted a joint request on the early introduction of venous thrombectomy devices.

CDT, as explained by the applicant, is positioned as one of the standard therapies for acute-phase severe DVT with arterial ischemia (phlegmasia cerulea dolens), and its clinical significance in the restart of blood flow by intravascular therapy has been established. For acute-stage severe proximal DVT, CDT is also employed to treat severe symptoms persisting despite anticoagulant therapy or appropriate conservative therapies such as leg elevation and compression therapy. Considering the current difficulty with CDT, the ClotTriever System is a potentially useful substitution for CDT for patients who need to be treated by CDT mentioned above, if the product's efficacy and safety are clinically acceptable as compared with CDT.

Thrombus suction catheter "INDIGO System" (Approval No. 30500BZI00017000) was approved as of April 20, 2023, in response to the request by related academic societies as with the ClotTriever System. In order to address different characteristics of patients and thrombi, it is of clinical significance to introduce the ClotTriever System with a different mechanism for thrombectomy to Japan as another treatment option.

6.B.(2) Study design

6.B.(2).1) Validity as evaluation data

The clinical study was a multicenter, prospective study that evaluated the outcomes of patients with acute, subacute, and chronic proximal DVT treated with the previous and current versions of the ClotTriever System. Therefore, the study included some patients with undetermined status of arterial ischemia or with non-severe clinical symptoms at baseline, who were thus not completely consistent with eligibility for ClotTriever System treatment mentioned earlier in Section "6.B.(1) Clinical positioning of the ClotTriever System." However, PMDA concluded, weighing the feasibility of a clinical trial and medical needs for the ClotTriever System, that its efficacy and safety in eligible patients for ClotTriever System treatment would be evaluable based on the results of the clinical study for the following reasons:

- As mentioned in Section "6.B.(1) Clinical positioning of the ClotTriever System," the ClotTriever System is intended for patients who were supposed to be treated with CDT. The clinical significance of thrombectomy in intravascular treatment has already been established in terms of the restart of blood flow.
- The clinical study tested hypotheses on the performance of thrombectomy and safety of the previous version of the ClotTriever System in comparison with CDT and PCDT.
- The thrombi collected in the clinical study were roughly estimated to be ≤6 weeks old based on their characteristics, which are projected to be similar to those of thrombi in patients eligible for ClotTriever System treatment mentioned in Section "6.B.(1) Clinical positioning of the ClotTriever System."[6,7] Therefore, the clinical performance of the ClotTriever System in thrombectomy is evaluable based on the results of the clinical study.
- The major modifications from the previous to current versions of the ClotTriever System included changes in dimensions (catheter length, sheath length, and mesh funnel length), and the addition of a 16-Fr sheath. Those modifications will have a minimal impact on the efficacy and safety of the product.

6.B.(2).2) Endpoints and thresholds

The applicant's explanation about the justification of the primary endpoints and thresholds:

The primary efficacy endpoint of the clinical study was assessed based on vascular patency, which is the best efficacy index of thrombectomy in treatment of DVT. The Marder scoring system has been used overseas to assess the patency of vessels treated by CDT or PCDT in patients with DVT,[8] and it was therefore selected to evaluate the performance of the ClotTriever System in the clinical study. A thrombus removal rate with the ClotTriever System was defined as a percent reduction from baseline in Marder score after the index procedure. The thrombus removal rate (based on a percent reduction in Marder score) for PCDT using a thrombectomy system (overseas approved product) was 76% in the ATTRACT study, a randomized controlled study using PCDT with anticoagulant therapy,[9] suggesting alleviated PTS and improved acute clinical symptoms and QOL.

The primary safety endpoint was set considering the following risks: 15% to 32% of DVT cases may lead to PE,[10] the concurrence of DVT and PE increases mortality within 1 month to 30%,[11] the estimated cumulative incidence of the first recurrence of venous thromboembolism is high in several

months after the start of treatment, reaching 5% by 30 days after the start of treatment in some cases,[12] and most patients with DVT undergo anticoagulant therapy, which may cause major bleeding in 10 days after the start of anticoagulant therapy at a reported highest incidence of 1.5%.[9] Based on these data, all-cause mortality, major bleeding, new symptomatic PE diagnosed by pulmonary arteriography using CT, and rethrombosis of TVS were defined as MAEs.

The thresholds for the primary efficacy and safety endpoints were determined in reference to 7 foreign articles on the outcomes of DVT treated with CDT or PCDT (Table 16). Out of 6 articles used to determine the threshold for the primary efficacy endpoint, 3 reported thrombus removal rates lower than the calculated weighted mean (39.3%). These results are assumed to have been based on the percentages of subjects with complete thrombolysis (100%). There were 2 articles reporting the outcomes of CDT using urokinase as in Japan. Of these, particularly the one reported more favorable outcome yielded a technical success rate (percentage of subjects with 100% thrombolysis) of 30.8%,[13] showing near consistency with the weighted mean (39.3%) determined for the clinical study. While the definition of MAEs varied among these articles used to set the primary safety endpoint threshold, events reported with similar outcomes to those of MAEs in the clinical study were regarded as MAEs. In the 2 articles reporting on CDT with urokinase, the incidence of rethrombosis at 1 month after treatment was 24.0% and the incidence of major bleeding within 7 days after treatment was 2.0%.[13,14] These results are almost consistent with the weighted mean (23.8%).

Table 16. List of literature references used to determine the thresholds for the primary endpoints

Author	Patient (duration of disease)	Treatment	Definition of technical success and outcome	Definition of MAEs and outcome
Mewissen et al.[13] (1999)	Symptomatic lower limb DVT	CDT (urokinase)	100% Thrombolysis: The thrombolysis rate was assessed on a 3-point scale*[1] based on the thrombus score determined for each vascular segment using venography.	1. Major bleeding and PE at 12 months post-procedure 2. Rethrombosis at 1 month post-procedure
			30.8% (96 of 312 patients*[2])	1. 12.7% (60 of 473 patients*[2]) 2. 24.0% (75 of 312 patients*[2])
Schweitzer et al.[14] (2000)	Acute leg or pelvic thrombosis (<9 days)	CDT (urokinase)	100% Thrombolysis: The thrombolysis rate was classified into 5 levels*[3] by visual quantification using venography and ultrasound (Duplex).	Adverse event (major bleeding) within 7 days after treatment requiring early termination of treatment
			20.0% (10 of 50 patients)	2.0% (1 of 50 patients)
Elsharawy et al.[15] (2002)	Acute proximal DVT (<10 days)	CDT (streptokinase)	Complete thrombolysis: The thrombolysis rate was classified into 3 levels*[4] by venography and ultrasound (Duplex).	Complications (e.g., bleeding and PE) during the 6-month follow-up period from the end of treatment through hospital discharge
			61.1% (11 of 18 patients)	0% (0 of 18 patients)
Enden et al.[16] (2011)	New-onset proximal DVT (≤21 days)	CDT (rt-PA)	70% Thrombolysis: The thrombolysis rate was assessed on a 3-point scale*[1] based on the thrombus score determined for each vascular segment using venography.	CDT-related clinical bleeding frequency, recurrent thromboembolism, death, and PE within 24 months post-procedure
			75.6% (68 of 92 patients*[5][17])	14.4% (13 of 90 patients)
Engelberger et al.[18] (2015)	Acute proximal DVT (<2 weeks)	EKOS*[6]/ CDT (rt-PA)	≥50% Thrombolysis: The thrombolysis rate was calculated from the thrombus score determined for each vascular segment using ultrasound.	Adverse events observed (early rethrombosis and major bleeding)
			60.4% (29 of 48 patients)	4.2% (2 of 48 patients)
Vedantham et al.[9] *[8] (2017)	Symptomatic acute proximal DVT (<14 days)	PCDT*[7] (rt-PA)	100% Thrombolysis: The thrombolysis rate was calculated from Marder score determined using venography.	Major bleeding, recurrent thromboembolism, and death within 10 days post-procedure
			34.2% (69 of 202 patients[13])*[8]	3.6% (12 of 336 patients)
Lin et al.[19] *[9] (2017)	Proximal DVT in 93% of the patients	CDT (rt-PA)		Bleeding (major bleeding), death, and PE at 3 months post-procedure
				39.3% (35 of 89 patients)
Total Weighted mean			283 of 720 patients 39.3%	198 of 1140 patients 23.8%*[10]

*1 <50%, 50%–99%, 100% (complete thrombolysis)
*2 Patients with acute DVT (n = 312) are a subset of patients with symptomatic leg DVT (n = 473).
*3 Progression of thrombosis, no reduction in thrombus, partial thrombolysis of <50%, partial thrombolysis of ≥50%, complete thrombolysis (100%)
*4 No thrombolysis, partial thrombolysis, complete thrombolysis
*5 Includes 2 patients who were excluded from the Intention-to-Treat (ITT) analysis population in Article 16.
*6 Ultrasound-assisted thrombolysis system
*7 Includes AngioJet (a system that creates local negative pressure using water pressure of jet stream to suction thrombi) and Trellis (a system that expands a balloon on the proximal and distal sides of a thrombi to inject thrombolytics, and destroys and aspirates thrombi through a rotating catheter), neither of which is approved in Japan.
*8 To prepare for a presentation at an academic conference, these data were excluded from a sensitivity analysis that re-calculated a weighted mean as planned, which was confirmed to have no impact on the analysis.
*9 This reference was used only to determine the threshold for the primary safety endpoint.
*10 The weighted mean incidence of MAEs was calculated by totaling the values determined using a random-effects model of each component of the composite endpoint. This is not a simple weighted mean incidence of MAEs reported in respective literature articles.

PMDA's view:
The ClotTriever System is expected to substitute for CDT in Japan. Thus, the ClotTriever System should demonstrate its efficacy by itself by restoring blood flow (good vascular patency) and improving clinical symptoms without prior or add-on treatment such as CDT. The safety assessment of the product should demonstrate that the occurrence of important safety events (PE, DVT, vascular injury, catheter puncture site complications, etc.) after the treatment with ClotTriever System is similar or acceptable as compared with CDT. The clinical study employed the primary efficacy endpoint of thrombus removal rate and secondary efficacy endpoints relevant to clinical symptoms. These primary and secondary safety endpoints allows for the assessment of above-mentioned important safety events, thus they are reasonable

The definition of technical success, "a ≥75% reduction in Marder score," for the evaluation of the primary efficacy endpoint is acceptable for the following reasons:

- Currently, there is no standard index for the restart of blood flow by CDT or other thrombectomy systems in severe DVT. In most sources consulted to determine the thresholds, the restart of blood flow was assessed based on a quantitative thrombus removal rate or thrombolysis rate determined by diagnostic imaging, such as angiography and ultrasound. Thrombus removal rates can be roughly converted to Marder scores.
- Although there is no established evidence on a clinically significant thrombus removal rate, the ATTRACT study and other articles reported improved clinical symptoms when ≥50% thrombus removal was achieved,[9,20] suggesting a certain clinical significance of ≥75% thrombus removal.

Because the ClotTriever System is expected substitute for CDT in Japan, it is reasonable to determine the thresholds of efficacy and safety based on articles on CDT or PCDT. The efficacy and safety thresholds of 30% and 34%, respectively, are also acceptable because these foreign literature consulted for threshold setting included key articles on large-scale randomized control studies of CDT and PCDT (CaVenT study[16] and ATTRACT study[9]).

6.B.(3) Use of foreign clinical study results

The applicant's explanation about the justification of evaluating the ClotTriever System based on the results of the foreign clinical study:
No ethnic difference has been reported on the characteristics of thrombi. While the incidence of DVT is reported to be lower in Japan than in Europe and the US,[21] there is no report on an ethnic difference in the natural course of DVT after onset. Thus, ethnicity is not considered to affect the efficacy or safety of the ClotTriever System. Japanese people are generally known to have higher risk of bleeding, and thus the types and doses of thrombolytics are a major difference between Japan and overseas in CDT treatment for acute severe DVT. Recombinant tissue-type plasminogen activator (rt-PA), streptokinase, and urokinase are available overseas, while low-dose urokinase is the only thrombolytic for the treatment of DVT covered by public health insurance in Japan. The limited thrombolytic types and urokinase available only at lower dose than other countries contribute to the low incidences of CDT-associated hemorrhagic complications, etc. in Japan, and the incidences of MAEs also tend to be lower in Japan as compared with those reported in foreign articles. Nevertheless, the primary safety outcome in the clinical study was clinically acceptable as compared with the outcomes of CDT in Japan (Table

17). The primary efficacy outcome can be extrapolated to results in Japan if the threshold set based on the foreign articles is met. The impact on the efficacy or safety of the ClotTriever System due to different medical environment is also considered acceptable.

PMDA's view:
As explained by the applicant, the incidences of DVT are indicative of ethnicity-associated differences. Because of similar characteristics of thrombi, however, such differences will not affect the efficacy or safety of the ClotTriever System. In addition, the following observations also support efficacy and safety evaluations of the ClotTriever System in patients to be treated in Japan based on the results of the clinical study conducted in the US:

- Baseline clinical symptoms in the clinical study were classified according to clinical manifestation–etiologic–anatomic distribution–pathophysiologic (CEAP). C3 and C4a accounted for 90.1% (82 of 91 subjects), with a rVCSS pain score of ≥2 in 71.4% (60 of 84 subjects), and a Villalta score of ≥10 indicating clinical symptoms and signs corresponding to moderate PTS in 56.6% (47 of 83 subjects). The study population included similar patient groups eligible for CDT reported in articles in and outside Japan.[9,22] The clinical study also included a small percentage of severe patients with rVCSS pain score of 3 (38.1%, 32 of 84 subjects) and a Villalta score of ≥15 (25.3%, 21 of 83 subjects).
- While the clinical study included no patient with prior CDT, the study data are valid for the efficacy and safety evaluations of the ClotTriever System in Japan where CDT will no longer be performed.
- The incidence of CDT-associated hemorrhagic complications tends to be lower in Japan than overseas because of different type and dose of thrombolytic used. However, the ClotTriever System requires no thrombolytic, the difference in the incidences of hemorrhagic complications minimally affect the evaluation of the ClotTriever System.

6.B.(4) Efficacy and safety

6.B.(4).1) Efficacy

The primary efficacy endpoint of the clinical study of "technical success" was 76.4% (68 of 89 subjects), which met the predefined threshold determined from the outcomes of CDT and PCDT. The Marder score was 9.47 ± 3.86 before the index procedure and reduced to 1.39 ± 1.70 after the index procedure, showing a thrombus removal rate of approximately 85%. According to Japanese and foreign articles, 88%[23] and 82%[24] of subjects achieved ≥50% thrombolysis after CDT, and the thrombus removal rate of CDT or PCDT was 76%[9], 85%,[25] and 70.1%[22] (Tables 16 and 17). These results do not substantially differ from the results of the clinical study. PMDA concluded that the results of the clinical study demonstrated a comparable clinical performance (restart of blood flow or vascular patency) of mechanical thrombectomy with the ClotTriever System to that of CDT.

Table 17. Outcomes of treatment with CDT and PCDT in Japan

Author		Yamada et al.[25] (2006)	Mizuno et al.[22] (2015)	Nakamura et al.[24] (2021)
Patient (duration of disease)		Symptomatic acute proximal DVT (<30 days)	Symptomatic proximal DVT	Acute proximal DVT (≤21 days)
Number of patients		31	35	52
Type of treatment		PCDT	CDT	CDT
Thrombolytic		Urokinase, 720,000 units/day Total, 1,710,000 units (range, 720,000–3,600,000 units) on average Duration, 2.4 days (range, 1–5 days) on average	Urokinase, 413,300 ± 30,100 units/day	Urokinase, 480,000–720,000 units/day Total, 2,670,000 ± 1,060,000 units Duration, 5.1 ± 1.8 days
Efficacy	**Percentage of patients with ≥50% thrombolysis**	-	-	82%
	Thrombolysis rate	85% (22%-100%)	70.1%	-
Safety	**Severe bleeding**	0	2.9% (1 of 35 patients)	6% (3 of 52 patients)
	PE	No life-threatening event	0	0

The clinical study evaluated the "patency of TVS assessed by Duplex ultrasound" as a secondary efficacy endpoint and confirmed that improved blood flow after thrombectomy was maintained over 2 years. Thrombectomy with the ClotTriever System improved baseline clinical symptoms (rVCSS score, numeric pain rating scale (NPRS) score, EQ-5D score, and Villalta score) at and after 30 days of the index procedure. Pain, a key symptom in acute-phase treatment of severe DVT, as assessed based on rVCSS pain score and NPRS score also tended to improve from baseline at and after 30 days of the index procedure. The baseline mean Villalta score of 11.2 ± 5.7 equivalent to "moderate," improved to 4.3 ± 4.1 equivalent to "Absent" at 30 days of the index procedure, which lasted over 2 years. These results suggest that thrombectomy with the ClotTriever System contributes to the restart of blood flow and improved clinical symptoms (Table 10).

Iliac venous stenosis interrupting blood flow requires venous stenting because thrombectomy alone does not provide sufficient vascular patency. As shown in Table 7, 42.9% (39 of 91) of subjects in the clinical study required venous stenting after the index procedure. The threshold of technical success was achieved in 89.5% (34 of 38) of subjects with venous stenting and 66.7% (34 of 51) of subjects without venous stenting. The tendency of improvement in clinical symptoms did not differ between the 2 subgroups. These results indicate a marginal impact of stenting on the efficacy of the ClotTriever System.

Treatment with the ClotTriever System is intended for patients who are candidates for CDT. The clinical significance of the restart of blood flow by thrombectomy with CDT has already been established. The clinical study demonstrated that the ClotTriever System had a performance level in thrombus removal comparable to that of CDT, improving blood flow and clinical symptoms. PMDA therefore concluded that the ClotTriever System has efficacy on the basis of the comments from the Expert Discussion.

6.B.(4).2) Safety

PMDA asked the applicant to explain the details of rethrombosis reported in the clinical study and risk reduction measures to prevent rethrombosis, a risk for recurrence of severe clinical symptoms or PTS in a remote phase.

The applicant's explanation:

In the clinical study, compliance with anticoagulant therapy guidelines was unknown in all 13 subjects experiencing rethrombosis. Of these, 10 subjects received no venous stenting during the index procedure (percentage of subjects with stenting, 23.1% in subjects with rethrombosis, 46.2% in subjects with no rethrombosis, 42.9% in the whole study population). A total of 2 subjects had a history of cancer, 1 of whom had a severe clotting disorder. These multiple factors were considered to have contributed to the high incidence of rethrombosis. None of these cases was associated with thrombectomy with the ClotTriever System or its outcome, and were highly likely due to inadequate response or noncompliance with the post-index procedural anticoagulant therapy, stenting, subject's thrombotic predisposition, or other factors. Careful attention to patient characteristics, appropriate anticoagulant therapy administered after the treatment with the ClotTriever System, compliance enhancement, proper stenting as necessary, etc. will prevent rethrombosis. Thus, the incidence of rethrombosis reported is acceptable (Table 18).

Table 18. Subjects with rethrombosis of TVS within 30 days (Primary Safety Cohort)

Subject ID*1	Thrombus removal rate	Compliance with anticoagulant therapy (30 days post-index procedure)	Cause of DVT	Medical history at baseline	Venous stenting
4	100.0%	Not reported	Not provoked	PE	None
5	88.4%	Not reported	Not provoked	None	Yes
6	100.0%	Not reported	Not provoked	Cancer*2	Yes
7	58.8%	Not reported	Not provoked	None	None
8	100.0%	Not reported	Not provoked	None	None
9	100.0%	Not reported	Not provoked	None	None
3	84.8%	Not reported	Immobility	PE, cancer*2	None
10	100.0%	Not reported	Not provoked	None	None
11	90.2%	Not reported	Pregnancy	Cerebrovascular disorder, hyper-anticoagulation	None
12	35.7%	Not reported	Recent long-term trip	PE	None
13	80.0%	Not reported	Not provoked	None	None
14	91.9%	Not reported	Not provoked	PE	None
15	100.0%	Not reported	Not provoked	PE	Yes

*1 Same Subject IDs as in Table 12 indicate the same subjects.
*2 Cancer was inactive at baseline.

PMDA's view:

Of 13 subjects with rethrombosis of TVS within 30 days after the index procedure, 84.6% (11 of 13 subjects) achieved ≥80% thrombus removal. Given this, rethrombosis in these subjects was unlikely to be primarily attributable to residual thrombi left by the ClotTriever System. The applicant' remark on the importance of appropriate post-procedural management including anticoagulant therapy is reasonable. Rethrombosis of TVS for which a causal relationship to the ClotTriever System or index procedure could not be ruled out occurred only in 2 subjects (Table 12). It has resolved in 1 subject after

intravascular treatment but is persisting in the other subject. Nevertheless, the cases neither required additional intervention nor led to any serious event, and are thus considered clinically acceptable. The applicant's explanation about rethrombosis and risk reduction measures are also acceptable. On the basis of the comments from the Expert Discussion, PMDA concluded that anticoagulant therapy and venous stenting following the treatment with the ClotTriever System should be tailored to patient characteristics, and this post-marketing safety measure must be clearly and thoroughly communicated through Information on Precautions, etc., training, and by other means.

The applicant's explanation about the risk of PE, which is one of the therapeutic purposes of severe DVT and is an event of interest in safety evaluation of the ClotTriever System:
In the Full Analysis Population, 1 subject experienced PE on the day of the index-procedure, which was causally related to the device as assessed by an independent medical monitor. The event resulted in death. In this subject, the deployed ClotTriever System was moved without fluoroscopic guidance. The subsequent fluoroscopically guided examination found that the end part of the dilator tip of the ClotTriever System was caught by the mesh funnel, causing the dilator tip to be reversed and pulled into the left common iliac vein. At this point, there was no change in the hemodynamics of the subject. The end part of the ClotTriever System was successfully removed from the vein without causing extensive damage to the mesh funnel. Later, however, the subject's condition suddenly changed. Pulmonary arteriography showed extensive PE. A causal analysis by the manufacturer concluded that the use of the ClotTriever System without fluoroscopic guidance was the cause of the event.

PMDA's view on the risk of PE associated with treatment with the ClotTriever System:
PE occurred within 30 days after thrombectomy with the ClotTriever System in 1 of 73 subjects (1.4%) as moderate PE because of the progression of the underlying disease and 10 of 500 subjects (2.0%) in the Full Analysis Population in the clinical study. PE related to the ClotTriever System or index procedure occurred only in 1 subject in the Full Analysis Population. On the other hand, the incidence of PE after CDT or PCDT was 0% to 34% (Table 16). The risk of PE associated with the ClotTriever System is similar to that with conventional therapies, and is therefore clinically acceptable. However, PE in 1 subject that was related to the ClotTriever System was due to mishandling of the product, and resulted in the death (serious event) of subject. It must be ensured that the ClotTriever System be used by physicians who have learned skills and knowledge for the operation and the procedure through training, etc. and at medical institutions adequately prepared for emergency. All-cause deaths and symptomatic PE within 2 years of the index procedure were reported in 7 and 2 of 91 subjects in the clinical study and 31 and 10 of 500 subjects in the Full Analysis Population, respectively. Other than the 1 case mentioned above, neither device- or procedure-related death nor symptomatic PE occurred. Considering the incidence of the serious adverse events within 2 years of the index procedure, the results of the clinical study showed no particular difference in the safety profile between the analysis populations.

On the basis of the above and for the following reasons, PMDA concluded that the ClotTriever System has an acceptable safety profile:

- The primary safety endpoint of "composite MAEs within 30 days of the index procedure" was achieved in the clinical study.

- None of the deaths reported within 2 years of the index procedure was related to the ClotTriever System or procedure (Table 14).
- None of the devices - and/or procedure-related serious adverse events within 2 years of the index procedure had a higher incidence than that reported in articles on CDT or PCDT in Japan or overseas (Tables 13 and 15).
- Rethrombosis for which a causal relationship to the ClotTriever System or index procedure could not be ruled out occurred only in 2 subjects. None of the cases resulted in a serious outcome. The risk of rethrombosis can be reduced by thorough post-procedural management including anticoagulant therapy. Thrombi that remained in TVS because of inadequate clot removal with the ClotTriever System was unlikely to have caused rethrombosis (Tables 12 and 18).
- Neither device - or procedure-related PE was reported other than 1 case that resulted from the inappropriate operation of the ClotTriever System. The incidence of PE after treatment with the ClotTriever System in the clinical study, etc. does not substantially differ from the data on CDT or PCDT reported.
- Valvular or vascular injury has been a concern with the mechanical thrombectomy, but no such event occurred.

PMDA's view:
As discussed in Sections 6.B.(4).1) and 6.B.(4).2), the clinical study has demonstrated that the ClotTriever System is as efficacious and safe as CDT in patients with severe DVT, who are conventionally candidates for CDT. As the supply problem of urokinase, a thrombolytic drug, has been an obstacle to CDT in Japan, related academic societies have submitted a joint request on the early introduction of venous thrombectomy devices that can replace CDT. The ClotTriever System has been shown to have efficacy and safety as CDT as mentioned, and thus is expected to be clinically useful in Japan. The ClotTriever System is also expected to reduce hemorrhagic complications, the challenges of CDT, by removing thrombi without using a thrombolytic, as demonstrated with no hemorrhagic complication occurring in the clinical study. Effective and safe introduction of the ClotTriever System to Japan in line with the post-marketing safety measures, as explained later in Section "6.B.(5) Post-marketing safety measures," will assure the risk-benefit balance of the product in eligible patients.

On the basis of the clinical positioning of the ClotTriever System, its intended use or effects should be modified as follows. (Underline denotes additions and changes.)

Intended Use or Effects
The ClotTriever Thrombectomy System is <u>intended for use to restart blood flow in patients with severe acute symptoms of</u> deep vein thrombosis <u>(excluding post thrombotic syndrome) who are difficult to undergo conventional treatment or are not expected to respond to conventional treatment</u>.

6.B.(5) Post-marketing safety measures
The ClotTriever System is the first mechanical thrombectomy catheter system to be introduced to Japan for the treatment of severe DVT to replace CDT because of discontinued supply of urokinase. The product's introduction will nearly coincide with the introduction of thrombus suction catheter "INDIGO System." On the basis of the results of the clinical study and other information, PMDA considers that

the following safety measures need to be taken for effective and safe introduction of the ClotTriever System to Japan:

1) The ClotTriever System must be used by physicians who are competent to determine patient eligibility and appropriate time to perform catheterization in mechanical thrombectomy, including the use of the ClotTriever System, and adequately knowledgeable about a series of procedures for DVT including concurrent therapies and post-procedural management (e.g., anticoagulant therapy).
2) The ClotTriever System must be used by physicians or at medical institutions that are competent to appropriately determine the clinical need for venous stenting after thrombectomy with the ClotTriever System and to perform stenting safely.
3) The ClotTriever System must be used by physicians adequately knowledgeable and skilled in diagnosis and procedures that assure the safe use of the ClotTriever System.
4) The ClotTriever System must be used at medical institutions staffed by physicians who are prepared for emergencies including surgery to address complications and serious procedure-related PE or other adverse events, or in partnership with a medical institution qualified as such.
5) On the basis of post-marketing treatment outcome, the guidelines for proper use must be reviewed as necessary, and additional safety measures must be taken.

Table 19 outlines the training programs on the ClotTriever System drafted by the applicant. Table 20 presents the draft guidelines for proper use proposed by the related academic societies (the Japanese Society for Vascular Surgery, the Japanese Association of Cardiovascular Intervention and Therapeutics, the Japanese Society of Interventional Radiology, and the Japanese Society of Phlebology).

Table 19. Outline of training programs

Item	Description
Classroom lecture	Appointed manufacturer's staff members or trainers will give a classroom lecture aimed at deepening the understanding of the features of the ClotTriever System and thrombectomy procedures with the ClotTriever System (3 hours). Contents Anatomy, pathological condition, indications, contraindications, product summary (structure and composition), clinical study results including complications, product usage, and case reviews (3 hours)
Hands-on training	Training staff members will give hands-on training aimed at the acquisition of a series of procedural skills using vascular models (2 hours).

Table 20. Summary of guidelines for proper use (Draft)

Eligibility criteria for patients	Patients who meet all of the following criteria: 1) Deep vein thrombosis including iliac vein occlusion 2) 1) Severe deep vein thrombosis (phlegmasia cerulea dolens, phlegmasia alba dolens, and venous gangrene) with arterial ischemia or 2) deep vein thrombosis with constant pain that substantially interferes with daily activities despite anticoagulant therapy and adequate conservative therapies, such as leg elevation and compression therapy (VCSS pain score 3)
Eligibility criteria for medical institutions	1) Providing medical care for deep vein thrombosis 2) Being cooperative in all-patient registration 3) Certified by the Japanese Society of Interventional Radiology, the Japanese Association of Cardiovascular Intervention and Therapeutics, or the Japanese Board of Cardiovascular Surgery 4) Certified for venous compression therapy or having a partnership with a certified medical institution
Eligibility criteria for treating physicians	1) IVR specialists, cardiovascular surgery specialists, physicians certified for cardiovascular intervention, or physicians certified for intravascular treatment by the Japanese Society for Vascular Surgery 2) Completed training programs required

In terms of safety measures in 1) and 3), the knowledge and skills pertaining to the ClotTriever System mentioned are provided in the training programs drafted by the applicant. Thus, the proposed training programs are reasonable. The safety measures in 1) to 4) can be addressed by adhering to the eligibility criteria for medical institutions and treating physicians in the guidelines for proper use drafted by related academic societies. These safety measures and the provision of training programs should be attached as Approval condition 1. To address the safety measure in 5), it is important to implement a use-results survey for evaluations at 6 months of index procedure as explained later in Section 7, as well as further longer-term assessment of the risk-benefit balance of the ClotTriever System treatment in addressing PE, PTS, and other complications, based on the registry that is to be developed by related academic societies.

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

Table 21 outlines the use-results survey plan of the ClotTriever System.

Table 21. Outline of the use-results survey plan

Objective	To collect and evaluate the safety and efficacy findings on the ClotTriever System in post-marketing clinical use in Japan
Survey population	DVT with severe acute symptoms, excluding PTS
Survey period	5 years after approval date (preparation for marketing, 12 months; registration, 36 months; follow-up, 6 months; analysis, 6 months)
Sample size	All patients (at least 100 patients who have completed the follow-up period)
Rationale	The sample size was determined to detect the incidence of respective events of the primary safety endpoint (MAEs within 30 days) in Japan comparable to that reported in the clinical study, and to allow for dropouts, etc.
Survey items	Key survey items • MAEs within 30 days of the post-index procedure (all-cause mortality, major bleeding, new symptomatic PE diagnosed by pulmonary arteriography with CT, and rethrombosis of TVS). • Technical success (The success rate of thrombectomy is determined based on the amount of residual thrombus assessed at medical institutions using venograms before and after the index procedure.) * MAEs will be determined by third parties such as medical monitors. Other survey items • Medical history, demography, and details of DVT • Information on the procedure (e.g., details of lesions and information on products used) • Clinical symptoms (e.g., NPRS, CEAP classification, QOL, rVCSS, and Villalta scores) • Duplex ultrasound • Anticoagulant and compliance with anticoagulant therapy • Procedure-related information (duration of thrombectomy, frequency of deployment, predicted blood loss, and concurrent treatment) • Procedural imaging before and after the index procedure to assess the amount of residual thrombus (e.g., venography and intravascular ultrasound) • Adverse events • Device malfunctions

7.B Outline of the review conducted by PMDA

Although the clinical study was designed with s some limitations in the sample size and population, the study revealed no serious concerns about the efficacy and safety of the ClotTriever System. For the following reasons, however, a use-results survey should be conducted in all patients treated with the ClotTriever System until the target sample size is reached, and additional risk reduction measures should be taken as necessary.

- Because the clinical study enrolled only a limited number of subjects who would meet the eligibility criteria for ClotTriever System treatment in Japan, the safety and efficacy of the ClotTriever System should be assessed in Japan.
- In Japan, there are no options other than the ClotTriever System as a substitute for CDT. The change in therapeutic approach may affect treatment outcomes in some patients.

The applicant proposed a target sample size of 100, which is similar to that of the clinical study. The proposed sample size is large enough to detect respective MAEs, including significant events that may occur in mechanical thrombectomy to treat this disease, at a certain level of accuracy, and is thus acceptable. The follow-up period of 6 months after the index procedure is reasonable since the purpose of treatment with the ClotTriever System is to restart blood flow and improve clinical symptoms during the acute-phase treatment of severe DVT. As mentioned earlier in Section "6.B.(5) Post-marketing safety measures," to address the improvement in safety and proper use of the ClotTriever System, it is

important to assess differences between the ClotTriever System and CDT and the risk-benefit balance of thrombectomy with the ClotTriever System, including long-term outcomes, by means of utilizing the registry that is to be developed by related academic societies and in industry-university-government collaborations.

PMDA concluded that the draft use-results survey plan proposed by the applicant, including the survey items, was appropriate and that this should be attached as Approval condition 2.

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 inspection and data integrity assessment

The medical device application data were subjected to a document-based 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 review of the application for the ClotTriever System focused on (1) the efficacy and safety of the ClotTriever System and (2) post-marketing safety measures. Taking account of comments raised in the Expert Discussion, PMDA reached the conclusions shown below.

(1) Efficacy and safety of the ClotTriever System

The clinical study evaluated the efficacy and safety of the ClotTriever System as a mechanical thrombectomy catheter system for patients with proximal DVT. The primary efficacy endpoint of the clinical study, "technical success" (percentage of patients with ≥75% thrombus removal based on quantitative venographic scoring system) was 76.4%. The result met the threshold (30%) determined from the outcomes of CDT, etc. The secondary efficacy endpoints of "the patency of the TVS based on Duplex ultrasound" and "clinical symptoms (rVCSS score, NPRS score, EQ-5D score, and Villalta score)" also improved from baseline at and after 30 days of the index procedure. The clinical study demonstrated the ClotTriever System's performance level comparable to that of CDT in thrombus removal and contribution to improvement in clinical symptoms, indicating promising efficacy of the product.

The primary safety endpoint of the clinical study, "incidence of composite MAEs within 30 days of the index procedure" was 20.0%. The result met the threshold (34%) determined from the outcomes of CDT, etc., showing the clinically acceptable safety of the ClotTriever System. There were neither haemorrhagic complications, which are challenges of CDT, nor events associated with valvular or vascular injury, a concern with the ClotTriever System. No particular concern about other adverse events including symptomatic PE (1.4%), a critical complication in severe DVT, was raised as compared to CDT.

In Japan, discontinued supply of the thrombolytic drug, urokinase, has been an obstacle to CDT, and eventually there will be no effective therapeutic approach for thrombus removal in DVT. Given this situation, the ClotTriever System has been shown to be as efficacious and safe as CDT and thus is clinically useful.

(2) Post-marketing safety measures

The ClotTriever System is the first mechanical thrombectomy catheter system to be introduced with "the INDIGO System," a thrombus suction catheter. In order to assure the product's effective and safe introduction, physicians or medical teams must have sufficient experience and achievements in the standard treatment of the disease including CDT, learn necessary knowledge and skills pertaining to the product and the procedure through training, etc., and fully understand the pathological condition of patients meeting eligibility for the product so as to be able to select patients appropriately. Where necessary, treatment with the ClotTriever System need to be followed by venous stenting or other emergency care including surgery to address complications such as PE. Medical institutions providing treatment with the ClotTriever System must have a system adequately prepared for such cases. Compliance with the guidelines for proper use issued by related academic societies is important, and this should be attached as Approval condition 1. The clinical study enrolled only a limited number of subjects who would meet the eligibility criteria for ClotTriever System treatment in Japan. The ClotTriever System will be used in Japan, where CDT is no longer an option. The applicant should collect post-marketing information on adverse events, procedures, patient characteristics, etc. in Japan through a use-results survey, and take additional risk reduction measures as necessary. The period of the use-results survey of the product should be 5 years (preparation for marketing, 12 months; registration, 36 months; follow-up, 6 months; analysis, 6 months). This requirement should be attached as Approval condition 2.

As a result of the above review, PMDA has concluded that the ClotTriever System may be approved for the intended use shown below.

Intended Use

The ClotTriever Thrombectomy System is intended for use to restart blood flow in patients with severe acute symptoms of deep vein thrombosis (excluding post thrombotic syndrome) who are difficult to undergo conventional treatment or are not expected to respond to conventional treatment.

Approval Conditions

1. Treating physicians are expected to be adequately knowledgeable and experienced in the treatment of deep vein thrombosis so as to appropriately select patients to be treated with the product, and are required to have learned sufficient skills pertaining to the use of the product and knowledge about procedure-associated complications. The treatment with the product must be performed at medical institutions with an established system for the treatment. To this end, the applicant is required to take necessary measures such as dissemination of the guidelines for proper use prepared jointly with relevant academic societies and offering seminars.

2. The applicant is required to conduct a use-results survey covering all Japanese patients treated with the product until data are obtained from a certain number of patients, report survey results to the Pharmaceuticals and Medical Devices Agency, and take other appropriate measures as necessary.

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 5 years.

PMDA has concluded that this application should be subjected to deliberation by the Committee on Medical Devices and *In-vitro* Diagnostics.

References

[1] The Japanese Circulation Society. Guidelines for Diagnosis, Treatment and Prevention of Pulmonary Thromboembolism and Deep Vein Thrombosis (Revised Version, 2017)

[2] Kahn SR et al. The post-thrombotic syndrome. *Hematol Am Soc Hematol Educ Progr.* 2010;216–220.

[3] Hagiwara et al. Treatment and diagnosis of deep vein thrombosis [in Japanese]. *Japanese Journal of Thrombosis and Hemostasis*. 2019;30(1):47-53.

[4] Erdoes LS et al. Pharmacomechanical thrombolysis for phlegmasia cerulea dolens. *Am Surg.* 2011 Dec;77(12):1606-1612.

[5] Kutsukata N et al. Surgical venous thrombectomy for Japanese patients with acute deep vein thrombosis: a review of 5 years' experience. *J Nippon Med Sch.* 2010 Jun;77(3):155-159.

[6] Mouawad NJ. Effective single-session percutaneous nonpharmacologic mechanical thrombectomy for phlegmasia cerulea dolens. *J Vasc Surg Cases Innov Tech.* 2020 Apr 15;6(2):212-215.

[7] Nezami N et al. Vertebroplasty-associated cement leak leading to iatrogenic venous compression and thrombosis. *J Vasc Surg Cases Innov Tech.* 2019 Nov 22;5(4):561-565.

[8] Vedantham S, et al. Reporting standards for endovascular treatment of lower extremity deep vein thrombosis. *J Vasc Interv Radiol.* 2009 Jul;20(7 Suppl):S391-408.

[9] Vedantham S et al. Pharmacomechanical Catheter-Directed Thrombolysis for Deep-Vein Thrombosis. *N Engl J Med.* 2017 Dec 7;377(23):2240-2252.

[10] Turetz M et al. Epidemiology, Pathophysiology, and Natural History of Pulmonary Embolism. *Semin Intervent Radiol.* Jun 2018;35(2):92-98.

[11] Heit JA et al. The epidemiology of venous thromboembolism. *J Thromb Thrombolysis.* 2016 Jan;41(1):3-14.

[12] Linkins LA, Choi PT, Douketis JD. Clinical impact of bleeding in patients taking oral anticoagulant therapy for venous thromboembolism: a meta-analysis. *Ann Intern Med.* 2003;139(11):893-900.

[13] Mewissen MW et al. Catheter-directed thrombolysis for lower extremity deep venous thrombosis: report of a national multicenter registry. *Radiology.* 1999 Apr;211(1):39-49.

[14] Schweizer J et al. Short- and long-term results after thrombolytic treatment of deep venous thrombosis. *J Am Coll Cardiol.* 2000 Oct;36(4):1336-43.

[15] Elsharawy M et al. Early results of thrombolysis vs anticoagulation in iliofemoral venous thrombosis. A randomised clinical trial. *Eur J Vasc Endovasc Surg.* 2002 Sep;24(3):209-14.

[16] Enden T et al. Long-term outcome after additional catheter-directed thrombolysis versus standard treatment for acute iliofemoral deep vein thrombosis (the CaVenT study): a randomised controlled trial. *Lancet.* 2012 Jan 7;379(9810):31-8.

[17] Haig Y et al. Determinants of early and long-term efficacy of catheter-directed thrombolysis in proximal deep vein thrombosis. *J Vasc Interv Radiol.* 2013 Jan;24(1):17-24.

[18] Engelberger RP et al. Ultrasound-assisted versus conventional catheter-directed thrombolysis for acute iliofemoral deep vein thrombosis. *Circ Cardiovasc Interv.* 2015 Jan;8(1):e002027.

[19] Lin M et al. Evaluation of thrombolysis using tissue plasminogen activator in lower extremity deep venous thrombosis with concomitant femoral-popliteal venous segment involvement. *J Vasc Surg Venous Lymphat Disord.* 2017 Sep;5(5):613-620.

[20] Comerota AJ et al. Postthrombotic morbidity correlates with residual thrombus following catheter-directed thrombolysis for iliofemoral deep vein thrombosis. *J Vasc Surg.* 2012 Mar;55(3):768-73.

[21] Ota S et al. Incidence, Characteristics and Management of Venous Thromboembolism in Japan During 2011. *Circ J.* 2018 Jan 25;82(2):555-560.

[22] Mizuno A et al. Real clinical practice of catheter therapy for deep venous thrombosis: periprocedural and 6-month outcomes from the EDO registry. *Cardiovasc Interv Ther*. 2015 Jul;30(3):251-9.

[23] Enden T et al. Catheter-directed thrombolysis vs. anticoagulant therapy alone in deep vein thrombosis: results of an open randomized, controlled trial reporting on short-term patency. *J Thromb Haemost.* 2009 Aug;7(8):1268-75.

[24] Nakamura H et al. Less frequent post-thrombotic syndrome after successful catheter-directed thrombolysis for acute iliofemoral deep vein thrombosis. *Cardiovasc Interv Ther.* 2021 Apr;36(2):237-245.

[25] Yamada N et al. Pulse-spray pharmacomechanical thrombolysis for proximal deep vein thrombosis. *Eur J Vasc Endovasc Surg.* 2006 Feb;31(2):204-11.