June 10, 2024
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	Central circulatory catheter for trapping embolus
Brand Name	SENTINEL Cerebral Protection System
Applicant	Boston Scientific Japan K.K.
Date of Application	November 10, 2023 (Application for marketing approval)

Results of Deliberation

In its meeting held on June 10, 2024, the Committee on Medical Devices and *In-vitro* Diagnostics reached the following conclusion and decided that the conclusion be presented to the Pharmaceutical Affairs 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 2 years. The following condition should be attached.

Approval Condition

1. The applicant is required to ensure that the product be used in patients whose eligibility has been confirmed by physicians with adequate knowledge and experience in transcatheter aortic valve replacement procedures who are fully skilled in the use of the product and acquainted with complications associated with the procedures, and at medical institutions with a well-established system for the treatment. To this end, dissemination of the guidelines for proper use jointly prepared with related academic societies, provision of training seminars, and other necessary measures should be implemented.

Review Report

May 20, 2024
Pharmaceuticals and Medical Devices Agency

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

Classification	Instrument & Apparatus 51, Suckers, Tubes and Catheters for Infusion or Drainage
Term Name	Central circulatory catheter for trapping embolus
Brand Name	SENTINEL Cerebral Protection System
Applicant	Boston Scientific Japan K.K.
Date of Application	November 10, 2023
Items Warranting Special Mention	Priority review
Reviewing Office	Office of Medical Devices I

Review Results

May 20, 2024

Classification	Instrument & Apparatus 51, Suckers, Tubes and Catheters for Infusion or Drainage
Term Name	Central circulatory catheter for trapping embolus
Brand Name	SENTINEL Cerebral Protection System
Applicant	Boston Scientific Japan K.K.
Date of Application	November 10, 2023

Results of Review

SENTINEL Cerebral Protection System (hereinafter referred to as the SENTINEL System) is a catheter with filters that are tentatively placed in the brachiocephalic artery and the left common carotid artery percutaneously to capture and remove embolic debris loosened during transcatheter aortic valve replacement (TAVR) procedures.

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

The clinical study data submitted were the results of the PROTECTED TAVR study (the P-TAVR study) that was conducted as a post-marketing study in patients with severe symptomatic aortic stenosis undergoing TAVR in the US, Europe, and Australia.

The incidence of all stroke within 72 hours after TAVR or at discharge (whichever came first), the primary endpoint of the P-TAVR study, was 2.3% in the SENTINEL group and 2.9% in the control group that did not receive the SENTINEL System therapy. The results failed to demonstrate the superiority of the SENTINEL System over the control (P = 0.2960). After start of the study, the indication of TAVR was expanded to patients with low surgical risks. This change led to the enrollment of patients with baseline characteristics different from those expected at the planning stage, and likely contributed to the failure in achieving the primary endpoint of the study. The SENTINEL group, however, had a significantly lower incidence of disabling stroke, of all stroke, than the control group (SENTINEL group 0.5%, control group 1.3%, P = 0.0225). A meta-analysis using the results of clinical studies with the SENTINEL System, including the P-TAVR study, and other relevant data also showed a statistically significantly lower incidence of disabling stroke as observed in the P-TAVR study (SENTINEL group 0.5%, control group 1.6%, P = 0.001). TAVR-related stroke is a clinical challenge that is suggested to affect quality of life (QOL) and postoperative mortality. Disabling stroke is a physically and mentally critical event for patients, and there is a high clinical need for a device that captures embolic debris during TAVR. The study revealed no noteworthy safety event related to the SENTINEL System. Given this, and taking into consideration the comments from the Expert

Discussion, PMDA has concluded that the clinical risk-benefit balance of the SENTINEL System will be maintained where the procedures are performed in eligible patients with high risks of stroke who are carefully selected by a heart team of specialists from various fields based on baseline and anatomical characteristics.

The SENTINEL System is Japan's first device that captures embolic debris loosened during TAVR. As mentioned earlier, the selection of eligible patients is essential to maintain the risk-benefit balance of the SENTINEL System. Despite the current difficulty in definitive identification of eligible patient population, it is important that the decision on the use of the SENTINEL therapy be de made by heart teams in a comprehensive manner after assessing the risk of stroke based on patients' concurrent illness, medical history (peripheral vascular disease, chronic kidney disease, and stroke), imaging findings (severe calcification of the aortic valve and atheromatous lesion in the ascending/arch aorta), etc. Taking into consideration the comments from the Expert Discussion, this view should be reflected in the guidelines for proper use that will be created by related academic societies.

A use-results survey should be conducted to assess the appropriateness of the proposed post-marketing safety measures, including product training, and patient selection according to the guidelines for proper use, etc. The survey will assess the outcome of the SENTINEL System in the clinical settings in Japan, based on which additional risk reduction measures should be taken as necessary.

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

Intended Use

The SENTINEL System is a distal embolic protection device that is tentatively placed in an aortic branch (brachiocephalic artery and the left common carotid artery) to capture and remove embolic debris loosened during transcatheter aortic valve replacement (TAVR) procedures.

Approval Condition

The applicant is required to ensure that the product be used in patients whose eligibility has been confirmed by physicians with adequate knowledge and experience in transcatheter aortic valve replacement procedures who are fully skilled in the use of the product and acquainted with complications associated with the procedures, and at medical institutions with a well-established system for the treatment. To this end, dissemination of the guidelines for proper use jointly prepared with related academic societies, provision of training seminars, and other necessary measures should be implemented.

Review Report

May 20, 2024

Product for Review

Classification	Instrument & Apparatus 51, Suckers, Tubes and Catheters for Infusion or Drainage
Term Name	Central circulatory catheter for trapping embolus
Brand Name	SENTINEL Cerebral Protection System
Applicant	Boston Scientific Japan K.K.
Date of Application	November 10, 2023
Proposed Intended Use	The SENTINEL System is tentatively placed in the aortic branch (brachiocephalic artery and the left common carotid artery) to capture and remove embolic debris for the purpose of preventing ischemic cerebrovascular disorders during transcatheter aortic valve replacement (TAVR) procedures.

Table of Contents

I. Product Overview 6
II. Summary of the Data Submitted and Outline of the Review Conducted by the Pharmaceuticals and Medical Devices Agency 7
1. History of Development, Use in Foreign Countries, and Other Information 7
2. Design and Development 9
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 15
4. Risk Management 16
5. Manufacturing Process 16
6. Clinical Data or Alternative Data Accepted by the Minister of Health, Labour and Welfare 16
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 34
8. Documents Relating to Information on Precautions, etc. Specified in Paragraph 1 of Article 63-2 of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices, in Relation to Notification Pursuant to the Same Paragraph of the Act 35
III. Results of Compliance Assessment Concerning the New Medical Device Application Data and Conclusion Reached by PMDA 35
IV. Overall Evaluation 35

List of Abbreviations

AKIN	Acute Kidney Injury Network
AS	Aortic Stenosis
BMI	Body Mass Index
BSA	Body Surface Area
CABG	Coronary Artery Bypass Grafting
CAM	Confusion Assessment Method
CAS	Carotid Artery Stenting
CEA	Carotid Endarterectomy
CEC	Clinical Events Committee
COPD	Chronic Obstructive Pulmonary Disease
CT	Computed Tomography
EQ-5D	EuroQol 5-dimensions
ICU	Intensive Care Unit
IEC	International Electrotechnical Commission
ISO	International Organization for Standardization
ITT	Intention-to-Treat
MACCE	Major Adverse Cardiac or Cerebrovascular Event
MAP	Mean Arterial Pressure
MoCA	Montreal Cognitive Assessment
MRI	Magnetic Resonance Imaging
mRS	modified Rankin Scale
NIH	National Institutes of Health
NIHSS	National Institutes of Health Stroke Scale
NeuroARC	Neurologic Academic Research Consortium
PCI	Percutaneous Coronary Intervention
QOL	Quality of Life
SAVR	Surgical Aortic Valve Replacement
STS	Society of Thoracic Surgeons
TAVR	Transcatheter Aortic Valve Replacement
THT	Transcatheter Heart Valve Therapy
TIA	Transient Ischemic Attack
TVT	Transcatheter Valve Therapies
VARC	Valve Academic Research Consortium

I. Product Overview

SENTINEL Cerebral Protection System (hereinafter referred to as the SENTINEL System) is a catheter with filters that are tentatively placed in the brachiocephalic artery and the left common carotid artery percutaneously through the right radial or brachial artery to capture and remove embolic debris loosened during transcatheter aortic valve replacement (TAVR) procedures (Figure 1). The SENTINEL System comprises 2 filters within a 6-Fr catheter. Before TAVR procedure, the catheter is delivered percutaneously from the right radial or brachial artery to deploy the proximal filter in the brachiocephalic artery and the distal filter in the left common carotid artery (Table 1 and Figure 2). During filter deployment, rotation of the articulating knob of the catheter's rear handle allows the articulating sheath ([redacted] ± [redacted] mm) at the tip of the catheter to run along the blood vessel. The filters can be retracted and deployed up to 2 times.

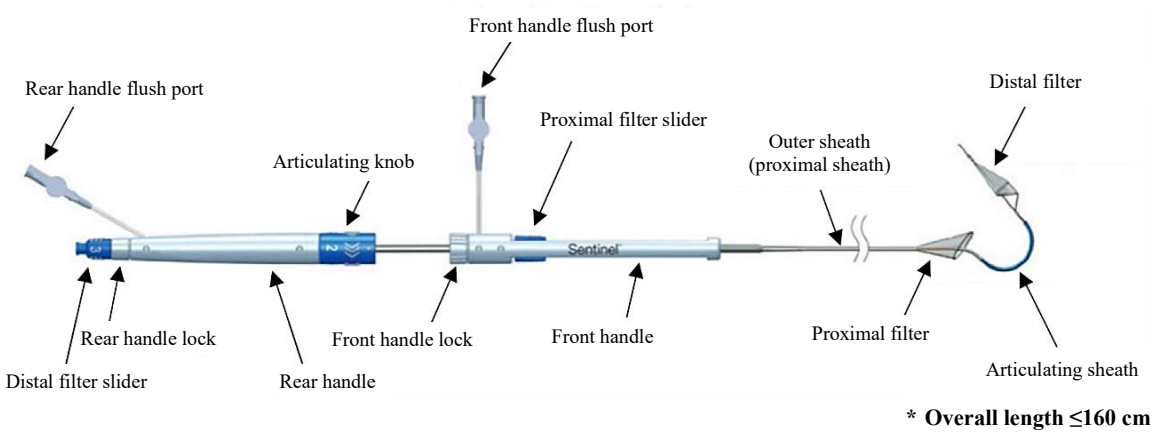

Figure 1. Composition of the SENTINEL System

Table 1. Filters and target blood vessels of the SENTINEL System

	Filter diameter (nominal)	Target blood vessel (diameter)	Filter pore size
Proximal filter	15.0 mm	Brachiocephalic artery (9.0-15.0 mm)	[redacted] µm
Distal filter	10.0 mm	Left common carotid artery (6.5-10.0 mm)	

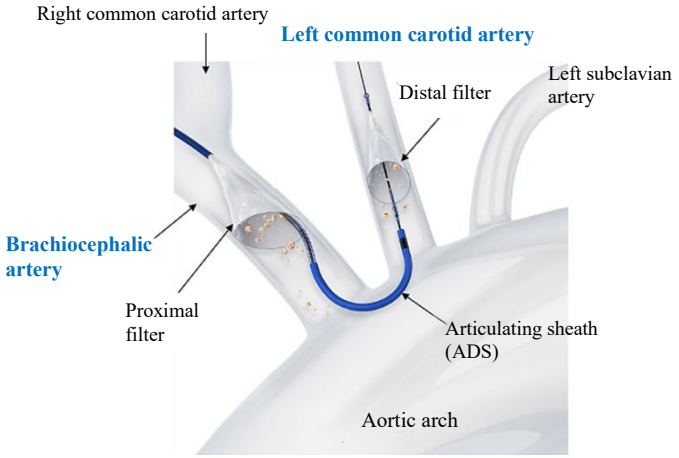

Figure 2. Image of the deployed filters of the SENTINEL System

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 in support of the application and the applicant's responses to the inquiries from the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined below.

The expert advisors present during the Expert Discussion on the SENTINEL System declared that they did not fall under the Item 5, Chapter 3 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

In Japan, the prevalence of aortic stenosis (AS) associated with age-related degeneration of the aortic valve leaflet is increasing. To treat patients with severe symptomatic AS, surgical aortic valve replacement (SAVR) or TAVR is selected based on age, surgical risk (e.g., Society of Thoracic Surgeons [STS] score), anatomical characteristics, etc. of each patient.[1]

TAVR was originally developed to treat patients with high surgical risks during SAVR. In Japan, "SAPIEN XT" (Approval number, 22500BZX00270000) was granted a marketing approval in 2013. After approval of other TAVR products and subsequent modification, TAVR has been increasingly indicated for patients with low surgical risks. In Japan, ≥10,000 patients undergo TAVR per year.[2]

Post-TAVR stroke is a critical issue that affects quality of life (QOL) and postoperative mortality of patients. The transcatheter valve therapies (TVT) Registry led by the American Association for Thoracic Surgery and the American College of Cardiology has shown that the mean incidence of symptomatic stroke over 30 days postoperative in approximately 100,000 patients (521 institutions in the US) was 2.3%, and most of these stroke cases occurred within 72 hours postoperative.[3-45] Post-TAVR stroke is related to an increased mortality at 30 days postoperative. A meta-analysis of 34 clinical studies involving 29,043 patients revealed an approximately 6-time increase in mortality risk at 30 days postoperative.[6,7]

Typical sources of emboli that may cause stroke include tissue fragments derived from calcified or atherosclerotic lesions of the aortic wall or arch aorta, those derived from the native aortic valve, and thrombi generated during procedures. Embolic debris derived from calcified or atherosclerotic lesions of the aortic wall or arch aorta forms when a TAVR delivery catheter scratches the aortic wall as it passes through the aortic arch or ascending aorta, causing the lesion to be peeled off. TAVR involves the placement of an artificial valve over the native aortic valve, which may chip the native aortic valve, causing tissue fragments, a source of emboli, to be released. Thrombolytic therapy is attempted in patients with cerebral infarction. However, the therapy is not always effective as it hardly works for tissue-derived debris, leading to an irreversible pathological condition.

The SENTINEL System, a device to capture embolic debris during TAVR procedures, was developed to address the TAVR-related safety issues. The Transcatheter Heart Valve Therapy Association (THT Association) submitted a written request on the early introduction of the medical devices for the SENTINEL System. At the thirty-third meeting of the Study Group on Early Introduction of Medical Devices, etc. of High Medical Need on August 5, 2022, the SENTINEL System was designated as a medical device with high medical need.

1.A.(2) Use in foreign countries

Table 2 presents the approval status of the SENTINEL System in major countries. A total of [redacted] units were sold between October 2018 and September 2023.

Table 2. Approval status in Europe and the US

Country/ region	Date of approval	Intended use
US	June 2017	The SENTINEL System is an embolic protection device to capture and remove thrombus/debris while performing transcatheter aortic valve replacement procedures. The brachiocephalic artery should be 9.0 to 15.0 mm and the left common carotid artery 6.5 to 10.0 mm in diameter for filter placement.
Europe	February 2013	The SENTINEL System is an embolic protection device to capture and remove embolic substances (thrombus/debris) while performing endovascular procedures. The proximal target artery should be 9.0 to 15.0 mm and the distal target artery 6.5 to 10.0 mm in diameter for filter placement.

The SENTINEL System has also been approved in Canada, Brazil, Chili, China, Venezuela, and Australia.

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

Table 3 and Table 4 present the incidence of major device malfunctions and adverse events (incidence of ≥0.01%), respectively, reported overseas after the use of the SENTINEL System from October 2018 to September 2023. A total of [redacted] deaths (0.0039%) were reported, all caused by stroke, for which a causal relationship to the SENTINEL System was unknown. More than one malfunction or adverse event might have been reported per patient.

Table 3. Malfunctions in foreign countries

Malfunction	Number of events	Incidence (%)*
Failure to capture and retrieve the distal filter	[redacted]	0.0547
Damage to the handle	[redacted]	0.0381
Failure to capture or retrieve the proximal filter	[redacted]	0.0254
Failure to deploy the proximal filter	[redacted]	0.0225
Difficulty in removal	[redacted]	0.0195
Failure to position the distal filter	[redacted]	0.0195
Failure to position the proximal filter	[redacted]	0.0146

* (Number of events/total number of units sold in foreign countries [redacted]) × 100

Table 4. Adverse events in foreign countries

Adverse event	Number of events	Incidence (%)*
Cerebrovascular disorder	[redacted]	0.0205

* (Number of events/total number of units sold in foreign countries [redacted]) × 100

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 SENTINEL System include leakage, torque integrity (torque rigidity), tensile strength, corrosion, deliverability [redacted], tip flexion, torque response [redacted], mock test [redacted], capture performance, blood flow pressure check [redacted], tip flexibility, kink resistance, introducer sheath compatibility, guidewire compatibility, radial force, deployment and retraction, stopcock lure compatibility, visibility, biological safety, sterility assurance, and bacterial endotoxins.

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

PMDA reviewed the proposed specifications based on the directions for use of the SENTINEL System, and asked the applicant to explain the justification of the bending angle ([redacted]°) of the articulating sheath at the tip of the catheter and of allowing filter placement up to 2 times.

The applicant's explanation:

The bending angle ([redacted]°) of the articulating sheath was determined based on the angle of [redacted] (approximately [redacted]°) in order to fit the expected anatomical structures of the brachiocephalic artery, aortic arch, left common carotid artery, etc. in TAVR patients.

The deployment and retraction testing on each filter up to [redacted] times caused no problem in the filters. Each filter was shown to be capable of being deployed and retracted for up to twice.

PMDA accepted the applicant's explanation about the design verification and proposed specifications for the SENTINEL System. The review on the proposed performance and safety specifications concluded that there was no particular problem in the tests and specification limits.

2.(2) Biological safety

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

To support the biological safety of the SENTINEL System, the applicant submitted the results of biological safety studies of the SENTINEL System conducted in accordance with the "Revision of Basic Principles of Biological Safety Evaluation Required for Marketing Application for Medical Devices (in Japanese)" (PSEHB/MDED Notification No. 0106-1, dated January 6, 2020) and International Organization for Standardization (ISO) 10993-1.

The following studies were conducted using a test sample which only differs in [redacted] from the SENTINEL System ([redacted] than the SENTINEL System): Cytotoxicity, sensitization, intracutaneous reactivity, acute systemic toxicity, material-derived pyrogenicity, hemocompatibility (material-related

hemolytic reaction and thrombogenicity), and genotoxicity. The results of these studies showed no problematic findings.

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

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

2.(3) Stability and durability

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

The applicant omitted the submission of stability data of the SENTINEL System and submitted a self-declaration that its shelf life had been determined based on 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 applicant also omitted the submission of test results on material deterioration due to radiation sterilization in accordance with the "Partial Revision of the 'Points to Consider in Preparing Summary Technical Documentation Submitted in Applications for Marketing Approval for Medical Devices (in Japanese)'" (PSEHB/MDED Notification No. 0228-7, dated February 28, 2018). Material deterioration was tested using appropriate test samples taking into consideration the maximum possible dose estimated from the dose distribution provided in the data on manufacturing method. On the basis of the results of this test, the applicant submitted a self-declaration assuring the product performance of the SENTINEL System.

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

PMDA reviewed the stability and durability data, and concluded that there was no particular problem.

2.(4) Performance

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

The applicant submitted the test results supporting the performance of the SENTINEL System, including leakage, torque integrity (torque rigidity), tensile strength, corrosion, deliverability, tip flexion/torque response, mock test, blood flow pressure check, tip flexibility, kink resistance, introducer sheath compatibility, guidewire compatibility, radial force, deployment and retraction, stopcock lure compatibility, and visibility. Leakage and the deployment/retraction of the proximal filter were tested with the SENTINEL System. The other tests were conducted with the same test sample as that used for the aforementioned biological safety test (which only differs in [redacted] from the SENTINEL System). All of the test results met the predefined acceptance criteria, assuring the performance of the SENTINEL System.

The applicant submitted the results of a capture performance test and an animal test that support the development concept of the SENTINEL System. The following summarizes the test results.

Capture performance

Capture performance of the SENTINEL System was tested to confirm the filters' embolic debris capture rates of ≥[redacted]% using through [redacted] as mock embolic debris, after the proximal and distal filters were deployed to [redacted]. To demonstrate that the SENTINEL System could capture and retrieve all embolic debris [redacted] were tested. All of the test results met the predefined acceptance criteria.

Animal test

To evaluate the performance and safety of the SENTINEL System, an *in vivo* mock test was conducted in animals. As shown in Table 5, a total of 4 pigs were tested, 2 each for 48 hours (acute phase) and 30 days postoperative (chronic phase), respectively.

A test sample (Device #1) was inserted in the pigs. The proximal and distal filters were deployed to the brachiocephalic artery and the left common carotid artery, respectively, and placed for 2 hours before removal. Deliverability, flexibility/kink resistance, positioning accuracy, visibility, blood pressure during filter placement, hemolytic reaction and thrombogenicity, and signs of damage to the test sample were assessed.

Subsequently, another test sample (Device #2) was inserted into the pigs in which Device #1 had been inserted and retracted. After the filters were deployed, thrombi (a total of 48 mm^3 for the proximal filter, a total of 24 mm^3 for the distal filter) were injected into the blood vessel to evaluate the capture performance of the test sample. At 5 minutes after the deployment of the filters, the test sample was removed with the proximal and distal filters retracted into the sheath fully or partially (for assessment under severe conditions). The animals underwent a pathological examination and necropsy at 48 hours or 30 days postoperative.

The distal filter of the test sample was either the 10-mm model used in the previous generation of the SENTINEL System ([redacted], hereinafter referred to as the "previous SENTINEL") or the [redacted]-mm model having a different filter size from that of the SENTINEL System (Device #2 for Animal #3). The SENTINEL System differs from the previous SENTINEL in the handle, [redacted], and [redacted]. Because the major changes to the previous SENTINEL were aimed to improve the operability of the handle, the results of this test were submitted to support the performance of the SENTINEL System.

Table 5. Test animal assignment

Evaluation	Animal 1 (#[redacted])	Animal 2 (#[redacted])	Animal 3[c] (#[redacted])	Animal 4 (#[redacted])
Acute phase (48 hours)	X	X		
Chronic phase (30 days)			X	X
Filter: Fully retracted[a]	X		X	
Filter: Partially retracted[b]		X		X

a, The distal and proximal filters were fully retracted into the sheath when the test sample was removed.
b, The distal and proximal filters were partially retracted into the sheath when the test sample was removed. (until approximately [redacted]% of the filter frame was retracted into the sheath.)
c, Device #2 was the test sample with the [redacted] mm distal filter.

All of the test samples successfully deployed the filters as intended, and the filters were retained at the deployed sites. There was no problem in their maneuverability, and embolic debris (thrombi) was successfully captured in both filters.

The safety evaluation demonstrated the survival of all animals at 48 hours or 30 days postoperative. The deployment and removal of 2 different test samples (Device #1 and Device #2) at the same site caused no macroscopic vascular damage. Histopathology showed mild histopathological changes in the 48-hour postoperative group (Animal #1 and Animal #2), but no abnormal findings in the 30-day postoperative group (Animal #3 and Animal #4). No procedure- or test sample-related adverse event was observed in any animal.

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

PMDA asked the applicant to explain the following issues on the capture performance test and the animal test:

(a) Validity of the capture performance results using [redacted]
(b) Effect of the differences between the test sample (previous SENTINEL) and the SENTINEL System used on the embolic debris capture performance of the SENTINEL System in animals
(c) Justification for the conclusion on the animal test that the effect of decreased mean arterial pressure (MAP) on hemodynamics during filter deployment was clinically acceptable

The applicant's explanation:

(a) A clinical study of the SENTINEL System (the SENTINEL study described later), where enrolled patients were divided into 4 groups according to the number particulates captured that were ≥500 μm in size, showed that a mean of 25 particulates were captured in the group having the largest number of particulates captured. In another clinical study using the previous SENTINEL (40 patients), grossly visible debris loosened during TAVR was captured in 30 of 40 patients (75%), with the size of captured debris ranging from 0.15 to 4.0 mm. The maximum filter pore size of the SENTINEL System is [redacted] μm. A separate test has confirmed that the capture performance does not depend on the size of [redacted] when the size of [redacted] is larger than the filter pore size. The capture performance ([redacted]) of the SENTINEL System is reasonable because that of an approved filter device "Filter Wire EZ" (Approval number, 22200BZX00139000), which captures and removes embolic debris such as thrombi during carotid artery stenting (CAS), is [redacted].

At the beginning of development, the SENTINEL System was intended for use in various intravascular treatments including [redacted], and the specification limits were determined based on [redacted]. The mean number of embolic particulates captured by the filters in combination with CAS was 7 (up to 13), and the mean particulate size was 248 ± 150 μm. Based on the maximum number of particulates and the maximum particulate size of [redacted], the maximum volume of embolic debris of [redacted] mm^3 was calculated.[8] Another literature reported that a mean of 34 particulates were captured by CAS, with the mean particulate size of 290 ± 512 μm in the long axis and 120 ± 187 μm in the short axis. Based on the maximum number of particulates and the maximum particulate size, the maximum volume of embolic debris is [redacted] mm^3.[9] On the basis of this calculation, the maximum embolic load on the filters in [redacted] was estimated to be approximately [redacted] mm^3. The rupture tolerance of the filters during removal of captured embolic debris is not thought to depend on procedures. Taking into consideration this theory and the maximum embolic load (approximately [redacted] mm^3) of [redacted], the capture performance test with mock TAVR was conducted to assure that the filters could capture [redacted]. The SENTINEL System has been used in Europe for intravascular treatment since 2013, without any reported malfunction due to inadequate capacity or tolerance of the filters. The filters of the SENTINEL System have adequate capture performance.

(b) In order to improve its manufacturing process, ergonomics, and usability, the previous SENTINEL was updated to the SENTINEL System with changes in the designs of the handle, [redacted], and [redacted]. Of these changes, [redacted] had the possibility to affect the capture performance (Figure 3). However, the filter pore size and the filter size (filter length and diameter) of the SENTINEL System remain the same as those in the previous SENTINEL. The mock use test confirmed that these changes did not affect the deployment performance and embolic debris capture performance of the filters.

[redacted]

Figure 3. [redacted] in the proximal filter of the SENTINEL System and the previous SENTINEL

(c) The lower mean limit of self-regulation of the cerebral blood flow in adults with normal blood pressure is reported to be ≥70 mmHg in MAP. The mean threshold for the development of the central nervous system ischemic symptoms is 45 to 55 mmHg in MAP, and the mean threshold for a change in brain waves is 57 mmHg in MAP.[10,11] On the basis of these reports, the

self-regulation of the cerebral blood flow does not function when the MAP decreases by approximately 18% to 22%. In order to ensure normal self-regulation of the cerebral blood flow in patients, the maximum acceptable decrease in MAP was specified conservatively as [redacted]%.

In the 4 tested animals, the placement of the proximal filter without thrombus injection only showed a gentle gradient in MAP, which was ≤5 mmHg at 2 hours after filter placement and ≤[redacted]% of the aortic pressure. After placement of the proximal filter in the presence of thrombi injected, the gradient in MAP was ≤5 mmHg in all of the animals except for Animal #3 (#[redacted]). Animal #3 (#[redacted]) had a MAP gradient of 15 mmHg, which did not meet the acceptance criterion ([redacted]%) for a percent decrease in MAP. This was likely related to the procedure for thrombus injection into the filter, etc. The MAP gradient was determined after distal filter placement in Animal #2 (#[redacted]) and Animal #3 (#[redacted]), which remained consistently within the range of [redacted]% (−3 to 3 mmHg) with or without thrombi.

Normal angiograms obtained during filter placement also showed no clinically significant change in pressure between proximal and distal to the filter of the test device. No test device-related adverse effect on blood pressure was observed.

In this animal test, each animal was treated at approximately 2.5 to 3 hours after the use of the test device. No pathological condition was reported in any animal, which indicates that the test device does not affect the blood flow or blood pressure proximal to distal to the filters, and that the effect of filter deployment on hemodynamics is clinically acceptable.

PMDA's view on the performance of the SENTINEL System:
The capture performance test showed a performance of approximately [redacted], with the measured capture rate of [redacted] of [redacted]% for the distal filter and [redacted]% for the proximal filter. The SENTINEL System is considered to have a satisfactory capture performance as compared with the other approved filter devices. The SENTINEL System has been used for intravascular treatment in Europe since 2013 and for TAVR in the US since 2017, without any malfunction reported or adverse event related to the rupture or inadequate capacity of the filters. The SENTINEL System is thus of no safety concern and able to capture embolic debris loosened expected during TAVR.

The key design elements that influence the capture performance (filter length and diameter) are common to the test sample (the previous SENTINEL) used in the animal test and the SENTINEL System. The capture performance of the SENTINEL System was evaluated in the capture performance test separately conducted using the SENTINEL System. Therefore, it was reasonable to extrapolate the results of the above animal test to the SENTINEL System as the applicant explained.

The reason remains unknown for the percent decrease in MAP not meeting the acceptance criterion in some animals. However, no test sample-related adverse event was observed in the animal test, and thus the safety of the SENTINEL System should be evaluated comprehensively based on the animal test findings and the later described clinical study results.

2.(5) Conformity to International Electrotechnical Commission (IEC) 62366-1

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

The applicant submitted data supporting the conformity of the SENTINEL System to the international standards specifying the usability engineering process of medical devices (IEC 62366-1).

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

PMDA reviewed the submitted data on the conformity to IEC 62366-1, and concluded that there was no particular problem.

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 SENTINEL 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 Public Notice No. 122, 2005).

3.B Outline of the review conducted by PMDA

PMDA reviewed the conformity of the SENTINEL System to the Essential Principles as shown below:

(1) PMDA's view on the conformity of the SENTINEL 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," user training, the selection of eligible patients according to the guidelines for proper use created jointly with related academic societies, and compliance with the requirements for medical institutions and physicians are important to maintain the risk-benefit balance of the SENTINEL System. To this end, an approval condition should be attached so that necessary measures are taken.

(2) PMDA's view on the conformity of the SENTINEL 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 SENTINEL System are available in Japan. Its efficacy and safety needs to be evaluated through clinical practice in Japan. On the basis of the findings from the survey, additional risk reduction measures should be taken as necessary. PMDA instructed the applicant to conduct a use-results survey.

(3) PMDA's view on the conformity of the SENTINEL 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 later in Section "6.B Outline of the review conducted by PMDA," the results of the clinical studies submitted suggest the possibility for the SENTINEL therapy to reduce the incidence of disabling stroke. The data demonstrated the efficacy and safety of the SENTINEL

System used in eligible patients selected based on the characteristics of the SENTINEL System. The SENTINEL System conforms to Articles 3 and 6.

(4) PMDA's view on the conformity of the SENTINEL 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," it is essential that the SENTINEL System be used by physicians with adequate knowledge and experience in TAVR, who select eligible patients with full understanding of the device characteristics so that risk-benefit balance of the device is maintained. To this end, treating physicians should be provided with necessary information through Information on Precautions, etc., the guidelines for proper use, training, and by other means.

PMDA comprehensively reviewed the conformity of the SENTINEL 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 a summary of risk management, the risk management system, and its progress 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 above 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 SENTINEL System (sterilization validation). The applicant also submitted data on the in-process tests of the SENTINEL System and explained that the manufacturing process of the SENTINEL System incorporates an in-process bacterial endotoxin test to control the risk of endotoxin contamination.

5.B Outline of the review conducted by PMDA

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

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

The applicant submitted clinical data of the PROTECTED TAVR study (P-TAVR study), an overseas post-marketing study. As the reference data, the applicant submitted the results from the overseas SENTINEL study.

6.A Summary of the data submitted

6.A.(1) P-TAVR study (evaluation data; Studied period, February 2020 to January 2022)

The P-TAVR study was a multicenter, prospective, randomized, controlled study conducted at 51 study sites in the US, Europe, and Australia to demonstrate that the SENTINEL System could significantly reduce the risk of perioperative stroke (within 72 hours postoperative) after TAVR in patients with AS undergoing TAVR. Table 6 presents a summary of the study.

Table 6. Summary of the P-TAVR study

Study objective	To demonstrate significant reduction of the risk of perioperative stroke (within 72 hours postoperative) after TAVR by the SENTINEL System
Study design	• Multicenter, prospective, randomized, controlled study (SENTINEL group or control group on a 1:1 basis) • SENTINEL group (protected with the SENTINEL System during TAVR) • Control group (not protected with the SENTINEL System during TAVR)
Sample size	3,000 (1,501 in the SENTINEL group, 1,499 in the control group)
Primary endpoints	All stroke (hemorrhagic, ischemic, or undetermined status; disabling or non-disabling) within 72 hours after TAVR or before discharge (whichever came first). All events were adjudicated by Clinical Events Committee (CEC) according to the Neurologic Academic Research Consortium (NeuroARC) definitions and the Valve Academic Research Consortium-2 (VARC-2) definitions.
Other endpoints	The following events occurring within 72 hours after TAVR or before discharge (whichever came first). Death (cardiovascular or non-cardiovascular), neurological endpoints (stroke, transient ischemic attack, and delirium), acute kidney injury, and major vascular complications at SENTINEL access site were adjudicated by the CEC. 1. All-cause death (cardiovascular or non-cardiovascular) 2. Neurological endpoints • Stroke (disabling and non-disabling) • Transient ischemic attack • Delirium 3. Safety composite of all-cause death and all stroke 4. Neurological status as determined by the following • Neurological physical examination • Modified Rankin Scale (mRS) • National Institutes of Health Stroke Scale (NIHSS) • Confusion Assessment Method for ICU Patients (CAM-ICU) • Montreal Cognitive Assessment (MoCA) 5. Neurological complications composite of all stroke, transient ischemic attack, and delirium 6. Acute kidney injury based on the AKIN System Stage 3 (including renal replacement therapy) and Stage 2 7. SENTINEL access site vascular complications related to the procedure (major and minor) 8. SENTINEL System delivery and retrieval (categorized as successful deployment of both filters, 1 filter, or no filter and retrieval of the system) 9. Baseline health status as evaluated by the EQ-5D QOL questionnaire
Inclusion criteria	1. Documented AS treated with an approved TAVR device via transfemoral access 2. Artery diameter at the filter placement site meeting recommendation (9-15 mm for the brachiocephalic artery and 6.5-10 mm for the left common carotid artery)
Exclusion criteria	1. >70% arterial stenosis in either the left common carotid artery or the brachiocephalic artery 2. Significant stenosis, ectasia, or dissection in brachiocephalic or left carotid artery, or aneurysm at the aortic ostium or within 3 cm of the aortic ostium 3. Compromised blood flow to the right upper extremity 4. Access vessels with excessive tortuosity 5. Uncorrected bleeding disorders 6. Contraindication for anticoagulant and antiplatelet therapies
Follow-up period	Through 72 hours or hospital discharge post-procedure (whichever comes first) 30 ± 7 days post-stroke for patients diagnosed with post-procedural stroke,

Figure 4 presents the breakdown of enrolled patients. A total of 3,000 patients (1,501 in the SENTINEL group, 1,499 in the control group) were enrolled. After enrollment, 95 patients (no valve replacement during TAVR in 12, no SENTINEL therapy in 83) in the SENTINEL group and 9 patients (no valve replacement during TAVR in 9) in the control group were not treated as assigned. Of 83 patients with no SENTINEL therapy, 42 patients had trans-radial/brachial artery access issues (spasm/tortuous artery) and 31 patients had tortuous brachiocephalic/subclavian artery, and registration error (not meeting the criteria for the carotid artery) was revealed in 2 patients, investigator's decision (details unknown) in 2 patients, study site's error (failure to obtain the SENTINEL System) in 2 patients, use in the radial artery for other purposes in 2 patients, anesthesia-related issue in 1 patient, and distal filter defect in 1 patient.

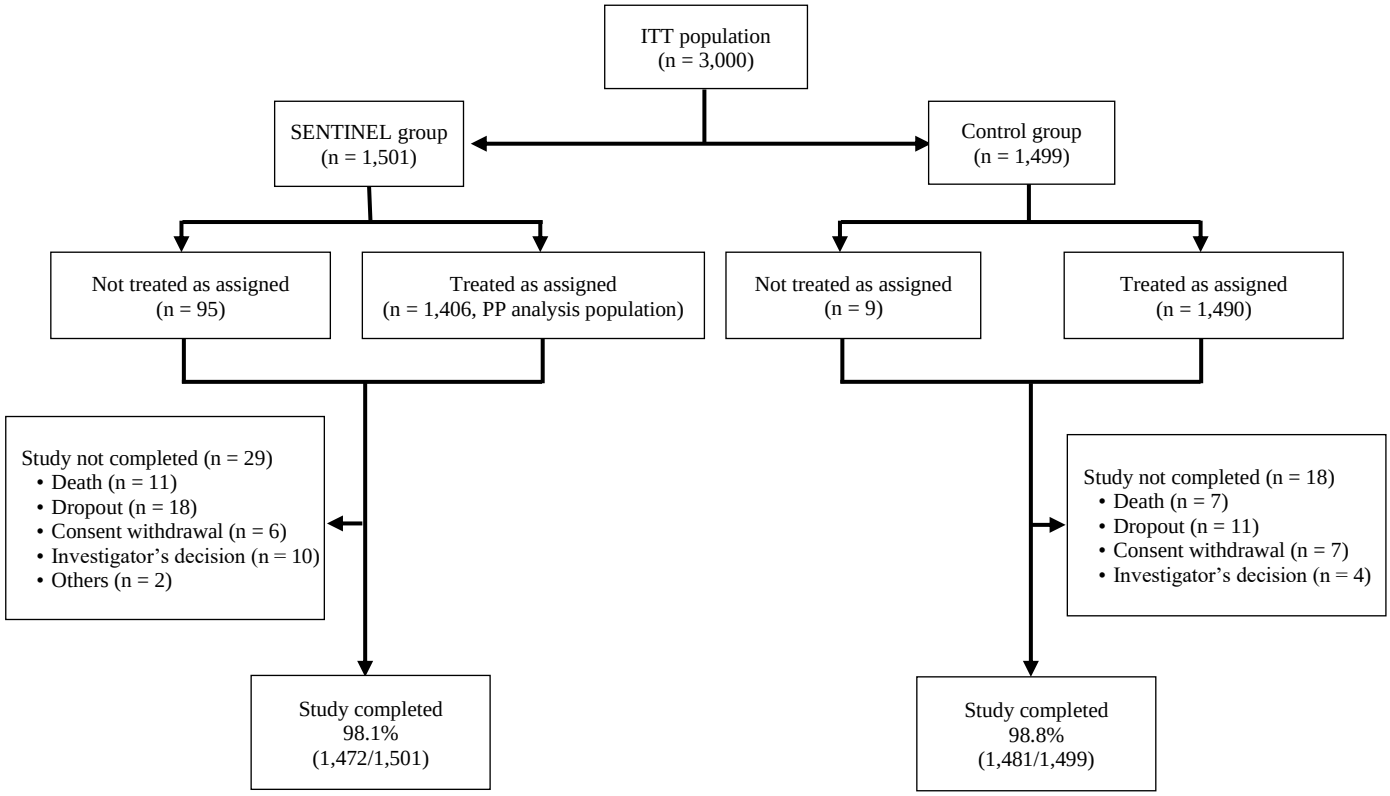

Figure 4. Breakdown for enrolled patients

With the primary endpoint of the study was "all stroke (hemorrhagic, ischemic, or undetermined status; disabling or non-disabling) within 72 hours after TAVR or before discharge (whichever came first)," the superiority of the SENTINEL therapy over the control therapy was assessed. The statistical approach employed an adaptive group sequential design, which allowed a planned modification according to interim analyses results and included 2 types of interim analyses, one to determine a sample size and the other to confirm early success of the study.

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

Table 7 and Table 8 present the patient characteristics in the intention-to-treat (ITT) analysis population (3,000 patients).

Table 7. Baseline characteristics, surgical risk assessment, and medical history

Endpoint	SENTINEL (n = 1,501)	Control (n = 1,499)	*P*-value
Female	42.0% (631/1,501)	37.8% (566/1,499)	0.0167
Age (years)	78.9 ± 8.0 (1,501) (30, 100)	78.9 ± 7.8 (1,499) (31, 101)	0.9543
Surgical risk assessment during SAVR			
STS score (%)	3.3 ± 2.7 (1,481) (0, 44)	3.4 ± 2.8 (1,482) (0, 25)	0.7056
STS score ≥3%	44.4% (658/1,481)	41.8% (620/1,482)	0.1540
STS score <3%	55.6% (823/1,481)	58.2% (862/1,482)	0.1540
EuroSCORE II (%)	4.6 ± 5.1 (1,175) (0, 54)	4.3 ± 5.2 (1,174) (0, 83)	0.2665
Other than low risk*	63.7% (956/1,501)	64.6% (968/1,499)	0.6131
Off-label use*	2.2% (33/1,501)	1.5% (23/1,499)	0.1790
High risk*	28.2% (424/1,501)	28.9% (433/1,499)	0.6989
Moderate risk*	33.2% (499/1,501)	34.2% (512/1,499)	0.5974
Low risk*	36.3% (545/1,501)	35.4% (531/1,499)	0.6131
CHA2DS2-VASc score	4.2 ± 1.3 (1,501) (0, 9)	4.2 ± 1.3 (1,499) (0, 9)	0.6740
General medical history			
Concurrent diabetes mellitus	33.4% (501/1,501)	34.8% (522/1,499)	0.4037
Current immunosuppressant therapy	3.5% (53/1,500)	4.4% (65/1,494)	0.2504
History of hyperlipidemia	75.5% (1,128/1,495)	74.6% (1,117/1,497)	0.5975
History of hypertension	87.1% (1,306/1,500)	87.6% (1,312/1,497)	0.6357
History of peripheral vascular disease	11.1% (165/1,484)	10.9% (162/1,481)	0.8757
History of COPD	13.9% (207/1,493)	13.4% (201/1,495)	0.7382
History of cardiovascular diseases			
History of coronary disease	56.9% (850/1,493)	58.9% (880/1,493)	0.2661
History of myocardial infarction	13.3% (198/1,488)	12.1% (179/1,485)	0.3048
History of cardiac failure congestive	58.6% (877/1,497)	57.9% (866/1,495)	0.7154
Prior PCI procedure	26.8% (401/1,495)	30.5% (456/1,493)	0.0246
Prior CABG procedure	11.1% (166/1,501)	11.7% (175/1,497)	0.5865
History of atrial fibrillation	34.1% (511/1,498)	31.4% (469/1,495)	0.1101
Prior pacemaker implantation	10.6% (159/1,501)	10.0% (150/1,499)	0.5973
History of neurological disease			
History of transient ischemic attack	5.2% (77/1,491)	5.4% (81/1,487)	0.7306
History of cerebrovascular accident	7.6% (114/1,496)	8.2% (122/1,491)	0.5691
Right carotid arterial stenosis (≥80%)	0.9% (11/1,269)	0.5% (6/1,267)	0.2249
Left carotid arterial stenosis (≥80%)	0.2% (2/1,268)	0.2% (2/1,264)	1.0000
Prior CEA/CAS procedure	2.4% (35/1,481)	2.9% (43/1,482)	0.3602

Continuous variables represent means ± standard deviations (SD) (minimum, maximum). Categorical variables represent percentages.

* Surgical risk was assessed by a heart team including a surgeon at each study site based on the STS scores and the anatomical or functional risk of patients (off-label use, STS score ≥15%; high risk, ≥8%; low risk, <3%).

Table 8. Baseline neurological evaluation

Endpoint	SENTINEL (n = 1,501)	Control (n = 1,499)	*P*-value
MoCA total score	24.5 ± 4.6 (1,445) (0.0, 31.0)	24.5 ± 4.5 (1,440) (0.0, 31.0)	0.9693
NIHSS total score	0.4 ± 1.0 (1,499) (0, 13)	0.3 ± 0.9 (1,494) (0, 10)	0.3005
mRS			
0: No symptoms	67.6% (1,014/1,501)	68.6% (1,027/1,497)	0.1564
1: No significant disability	15.9% (239/1,501)	17.4% (260/1,497)	
2: Slight disability	8.2% (123/1,501)	6.6% (99/1,497)	
3: Moderate disability	6.6% (99/1,501)	6.3% (94/1,497)	
4: Moderately severe disability	1.7% (26/1,501)	1.1% (17/1,497)	
5: Severe disability	0.0% (0/1,501)	0.0% (0/1,497)	
Overall CAM-ICU			
Positive	0.0% (0/1,499)	0.0% (0/1,497)	-
Negative	100% (1,499/1,499)	100% (1,497/1,497)	-

Continuous variables represent means ± SD (minimum, maximum). Categorical variables represent percentages.

6.A.(1).2) Surgical information

Table 9 presents the procedural characteristics in the P-TAVR study. The total time of the procedure from the insertion to removal of the SENTINEL System was 28.9 ± 16.6 minutes.

Table 9. Surgical characteristics

Endpoint	SENTINEL (n = 1,501)	Control (n = 1,499)	*P*-value
Total procedural time (min)[a]	71.4 ± 44.1 (1,466) (0.0, 549.0)	53.0 ± 30.1 (1,490) (0.0, 440.0)	<0.0001
Total SENTINEL procedural time (min)[b]	28.9 ± 16.6 (1,456) (0.0, 174.0)	NA	-
Total fluoroscopy time (min)	15.2 ± 14.4 (1,430) (0.0, 97.0)	ND	-
Total amount of contrast media used (cc)	51.2 ± 54.5 (1,432) (0.0, 491.0)	ND	-
Type of anesthesia			
Local anesthesia	27.6% (411/1,489)	27.4% (408/1,490)	0.8931
General anesthesia	26.8% (399/1,489)	26.4% (393/1,490)	0.7950
Conscious sedation	45.6% (679/1,489)	46.2% (689/1,490)	0.7258
Pre-dilatation performed	38.5% (573/1,489)	41.9% (624/1,490)	0.0586
1 balloon expansion	92.0% (526/572)	93.4% (583/624)	0.3277
2 balloon expansions	5.6% (32/572)	5.1% (32/624)	0.7204
≥3 balloon expansions	2.1% (12/572)	1.4% (9/624)	0.3885
Post-dilatation performed	26.2% (390/1,489)	25.7% (383/1,490)	0.7616
1 balloon expansion	83.1% (324/390)	78.9% (302/383)	0.1344
2 balloon expansions	13.3% (52/390)	18.3% (70/383)	0.0594
≥3 balloon expansions	3.1% (12/390)	2.6% (10/383)	0.6969
Switching to thoracotomy	0.2% (3/1,489)	0.3% (5/1,490)	0.7262
Use of unplanned cardiopulmonary bypass	0.1% (2/1,489)	0.1% (2/1,490)	1.0000
TAV-in-TAV placement performed	1.7% (26/1,489)	1.5% (22/1,490)	0.5589
Prosthetic valve type placed in the test procedures[c]			
Patients deemed at high risk			
Balloon expandable valves	37.9% (569/1,501)	38.6% (578/1,499)	0.7137
Non-balloon expandable valves	25.8% (387/1,501)	26.0% (390/1,499)	0.8834
Patients deemed at low risk			
Balloon expandable valves	22.9% (344/1,501)	22.4% (336/1,499)	0.7421
Non-balloon expandable valves	13.4% (201/1,501)	13.0% (195/1,499)	0.7570
Length of hospitalization			
Overall (days)	3.3 ± 4.1 (1,477) (0, 75)	3.3 ± 3.5 (1,483) (0, 30)	0.7137
Patients discharged within 72 hours	69.5% (1,027/1, 477)	68.0% (1,008/1,483)	0.3591
Length of hospitalization (days)	1.5 ± 0.7 (1,027) (0, 4)	1.5 ± 0.8 (1,008) (0, 5)	0.5526
Patients discharged beyond 72 hours	30.5% (450/1,477)	32.0% (475/1,483)	0.3591
Length of hospitalization (days)	7.3 ± 5.5 (450) (0, 75)	7.1 ± 4.1 (475) (1, 30)	0.6062

Continuous variables represent means ± SD (minimum, maximum). Categorical variables represent percentages.
a, Time from the initial punctuation/incision to vascular closure
b, Time from insertion to removal of the SENTINEL System
c, Prosthetic valves finally placed

6.A.(1).3) Status of use

6.A.(1).3).(a) Status of use of the SENTINEL System

Table 10 presents the use status of the SENTINEL System. In 31 patients, the package of the SENTINEL System was opened, but some access problems, etc. prevented the insertion of the device into the blood vessel, resulting from excessive tortuosity or spasms of the radial or brachial artery. In 41 patients, the insertion of the SENTINEL System into the blood vessel was successful, but the deployment was prevented by tortuous brachiocephalic or subclavian artery, etc.

Table 10. Status of use of the SENTINEL System

Status of use of the SENTINEL System	SENTINEL System (N = 1,481)
Opened but not inserted	2.1% (31/1,481)
Inserted but not deployed	2.8% (41/1,481)
Inserted and deployed	95.1% (1,409/1,481)[a]

a, A total of 3 patients required 2 units of the SENTINEL System. The use status of the second unit was reported as "Inserted and deployed" after the first unit was removed.

6.A.(1).3).(b) SENTINEL procedural information

Table 11 presents the information on the procedures with the SENTINEL System. The deployment of the 2 filters succeeded in 98.2% (1,381 of 1,406) of patients. In patients in whom only 1 filter (proximal filter) was deployed, the deployment of the distal filter was prevented by anatomical problems.

Table 11. SENTINEL procedural information

Endpoint	Use of SENTINEL System (n = 1,406)
Successful delivery and retrieval[a]	98.2% (1,380/1,406)
Delivery	
2 filters deployed	98.2% (1,381/1,406)
1 filter deployed	1.8% (25/1,406)
No filter deployed	0.0% (0/1,406)
Retrieval	99.9% (1,405/1,406)

a, Successful deployment of 2 filters and system retrieval

6.A.(1).3).(c) Malfunctions of the SENTINEL System

Table 12 presents device malfunctions reported with the SENTINEL System. There was no device malfunction resulting in serious adverse events.

Table 12. Malfunctions reported with the SENTINEL System

Endpoint	Incidence of malfunctions (N = 1,450[a])
Distal filter	
Deployment failure	0.9% (13/1,450)
Filter dislocation/separation	0.1% (2/1,450)
Bend/kink	0.1% (2/1,450)
Capture/retrieval of failed filter	0.1% (2/1,450)
Proximal filter	
Deployment failure	0.2% (3/1,450)
Handle	
Drop/separation	0.1% (2/1,450)
Shaft bend/kink/breakage	0.1% (1/1,450)
Articulating sheath bend/kink	0.1% (1/1,450)
Difficult tracing of anatomical structure	0.1% (2/1,450)
Others	0.8% (12/1,450)

a, The number of opened SENTINEL System (N = 1,450) that failed to be deployed after insertion, or successfully deployed after insertion In 31 units opened but not inserted into subjects' bodies, 4 malfunctions were reported including shaft bend/kink/breakage, etc. These units were replaced with new ones.

6.A.(1).4) Study results

6.A.(1).4).(a) Efficacy

The planned interim analysis was performed by the Independent Safety and Statistical Monitor Committee on the first 70% of enrolled patients (n = 2,100). The analysis failed to show a significant difference in the primary endpoint in favor of the SENTINEL group (SENTINEL group 2.2%, control

group 2.4%, $P = 0.7652$). Accordingly, patient enrollment was continued until the sample size of 3,000 was reached as originally planned.

The incidence of all stroke (hemorrhagic, ischemic, or undetermined status; disabling or non-disabling) within 72 hours after TAVR or before discharge (whichever came first), the primary endpoint of the study, was 2.3% (34 of 1,501 patients) in the SENTINEL group and 2.9% (43 of 1,499 patients) in the control group ($P = 0.2960$). The study failed to demonstrate the pre-specified hypothesis (superiority of the SENTINEL therapy over the control therapy) (Table 13). The SENTINEL group, however, showed a statistically significantly lower incidence of disabling stroke than the control group (SENTINEL group 0.5%, control group 1.3%, $P = 0.0225$).

Table 13. Stroke at discharge

Endpoint	SENTINEL	Control	Difference [95% CI]	*P*-value
All stroke	2.3% (34/1,501)	2.9% (43/1,499)	-0.6% [-1.7%, 0.5%]	0.2960
Day of index procedure	0.8% (12/1,501)	0.9% (14/1,499)	-0.1% [-0.8%, 0.5%]	0.6911
1 day post-procedure	1.2% (18/1,501)	1.1% (16/1,499)	0.1% [-0.6%, 0.9%]	0.7331
2 days post-procedure	0.3% (4/1,501)	0.7% (10/1,499)	-0.4% [-0.9%, 0.1%]	0.1074
3 days post-procedure	0.1% (2/1,501)	0.3% (4/1,499)	-0.1% [NA]	0.4524
Disabling	0.5% (8/1,501)	1.3% (20/1,499)	-0.8% [-1.5%, -0.1%]	0.0225
Non-disabling	1.7% (26/1,501)	1.5% (23/1,499)	0.2% [-0.7%, 1.1%]	0.6691

6.A.(1).4).(b) Safety

Other endpoints include all-cause death (cardiovascular or non-cardiovascular) within 72 hours after TAVR or before discharge (whichever came first), neurological endpoints, acute kidney injury, and SENTINEL access site major vascular complications. These events were adjudicated by the independent CEC. A major vascular complication (0.1%, 1 of 1,501 patients) in the SENTINEL group was introducer sheath-associated bleeding at the trans-radial artery access site, which was unrelated to the SENTINEL System. The incidence of all-cause death (SENTINEL group 0.5%, control group 0.3%, $P = 0.2482$), composite of stroke, transient ischemic attack (TIA), and delirium (SENTINEL group 3.1%, control group 3.7%, $P = 0.3587$), and acute kidney injury (SENTINEL group 0.5%, control group 0.5%, $P = 0.7978$) did not significantly differ between the groups (Table 14). Deaths occurred in 8 patients in the SENTINEL group, which were reported as unrelated to the SENTINEL System by investigators or sub-investigators.

Table 14. CEC-adjudicated adverse events reported before discharge

CEC events	SENTINEL (n = 1,501)	Control (n = 1,499)	*P*-value
All-cause death or all stroke	2.7% (41/1,501)	3.0% (45/1,499)	0.6571
All-cause death	0.5% (8/1,501)	0.3% (4/1,499)	0.2482
Cardiovascular	0.5% (8/1,501)	0.3% (4/1,499)	0.2482
Non-cardiovascular	0.0% (0/1,501)	0.0% (0/1,499)	-
All stroke	2.3% (34/1,501)	2.9% (43/1,499)	0.2960
Disabling	0.5% (8/1,501)	1.3% (20/1,499)	0.0225
Ischemic	0.4% (6/1,501)	1.1% (17/1,499)	0.0211
Hemorrhagic	0.1% (2/1,501)	0.2% (3/1,499)	0.6871
Non-disabling	1.7% (26/1,501)	1.5% (23/1,499)	0.6691
Ischemic	1.7% (26/1,501)	1.5% (23/1,499)	0.6691
Hemorrhagic	0.0% (0/1,501)	0.0% (0/1,499)	-
Neurological complications composite[a]	3.1% (46/1,501)	3.7% (55/1,499)	0.3587
All stroke	2.3% (34/1,501)	2.9% (43/1,499)	0.2960
Transient ischemic attack	0.1% (1/1,501)	0.1% (2/1,499)	0.6246
Delirium	0.8% (12/1,501)	0.7% (11/1,499)	0.8367
All-cause death or disabling stroke	1.0% (15/1,501)	1.5% (22/1,499)	0.2452
Cardiac death or disabling stroke	1.0% (15/1,501)	1.5% (22/1,499)	0.2452
SENTINEL access site vascular complication	0.1% (1/1,501)	NA	1.0000
Acute kidney injury[b]	0.5% (8/1,501)	0.5% (7/1,499)	0.7978
Acute kidney injury, Stage 2[b]	0.3% (4/1,501)	0.3% (5/1,499)	0.7534
Acute kidney injury, Stage 3[b]	0.3% (4/1,501)	0.1% (2/1,499)	0.6872

a, Including stroke, transient ischemic attack, and delirium
b, Within 72 hours postoperative. Stage 3 includes renal replacement therapy

6.A.(2) SENTINEL study (reference data; Studied period, October 2014 to March 2016)

The SENTINEL study was a multicenter, prospective, randomized, controlled study conducted at 19 study sites in the US and Germany to evaluate the efficacy and safety of the SENTINEL System in patients with severe symptomatic calcified AS, for which TAVR is indicated.

A total of 363 patients were enrolled in the study and randomized to the following 3 groups.

Safety group: Used the SENTINEL System during TAVR and had safety evaluation at 30 and 90 days postoperative

Efficacy group: Used the SENTINEL System during TAVR, had safety evaluation at 30 and 90 days postoperative, magnetic resonance imaging (MRI) for stroke assessment at 2 to 7 days and 30 days postoperative, and neurocognitive evaluation at 2 to 7 days, 30 days, and 90 days postoperative

Control group: Received TAVR without the SENTINEL System, had safety evaluation, MRI, and neurocognitive evaluation as in the efficacy group

The primary safety endpoint of the study was the "incidence of major adverse cardiac or cerebrovascular event (MACCE, defined as all-cause death, all stroke, and acute kidney injury [Class 3]) confirmed within 30 days postoperative." The incidence of MACCE was 7.4% (18 of 244 patients; upper limit of 95% confidence interval [CI], 10.7%) in the SENTINEL group, consisting of the safety group and the efficacy group. The result met the pre-specified performance goal of 18.3%.

The study had the following 2 primary efficacy endpoints:

- A significant reduction in the median total new lesion volume in protected territories (brain territories perfused by the brachiocephalic artery and the left common carotid artery) as measured by MRI at 2 to 7 days postoperative in the efficacy group in comparison with the control group (evaluation of superiority)
- A ≥30% reduction in the median total new lesion volume in protected territories in the efficacy group in comparison with the control group (evaluation of therapeutic effect)

The primary safety and efficacy endpoints (evaluation of superiority) of the study were analyzed in an imputed ITT population. (For patients whose clinical or/and MRI data were partially missing, the values were stochastically calculated using data of other patients with similar characteristics, such as the total new lesion volume as measured by diffusion weighted MRI at baseline and/or 2 to 7 days postoperative, the number of days before MRI, etc.)

The primary efficacy endpoint in superiority evaluation (median total new lesion volume in protected territories) showed no statistically significant difference between the efficacy group (109.1 mm^3) and the control group (174.0 mm^3) (P = 0.2354). The therapeutic effect was shown by a 42% reduction in the total new lesion volume in protected territories in the efficacy group as compared to the control group, which met the pre-specified performance goal (≥30% reduction). Histopathology showed embolic debris captured by either filter in 99% of patients treated with the SENTINEL System, which included acute thrombi containing tissue and foreign materials (98%), arterial wall (94%), valve tissue (50%), calcification (50%), foreign materials (35%), and myocardium (15%).

The effect of differences in TAVR access site on the efficacy and safety of the SENTINEL System was as follows:
TAVR was performed via transfemoral access in 94.2% of the enrolled patients in the safety group (114 of 121 patients) and the efficacy group (113 of 120 patients), and 95.8% in the control group (113 of 118 patients), while transapical access was employed in 3.3% (4 of 121 patients) in the safety group, 2.5% (3 of 120 patients) in the efficacy group, and 1.7% (2 of 118 patients) in the control group, aortic access in 1.7% (2 of 121 patients) in the safety group, 2.5% (3 of 120 patients) in the efficacy group, and 0.8% (1 of 118 patients) in the control group, subclavian arterial access in 0% in the safety group, 0.8% (1 of 120 patients) in the efficacy group, and 1.7% (2 of 118 patients) in the control group; and other (unknown) in 0.8% (1 of 121 patients) in the safety group, 0% in the efficacy group, and 0% in the control group. Meanwhile, the SENTINEL System is meant for right brachial or radial arterial access, and cannot be used for TAVR via right subclavian or axillary arterial access.

None of the patients with non-transfemoral access experienced stroke by 30 days postoperative. Stroke (disabling stroke) occurred by 90 days postoperative only in 1 patient in the control group but not in the SENTINEL group.

6.B Outline of the review conducted by PMDA

6.B.(1) Extrapolation of the results of the foreign clinical study to Japanese patients

The applicant's explanation about the appropriateness of evaluation of the SENTINEL System using the results of the P-TAVR study conducted in the US, Europe, and Australia:
To assess the extrapolability of results from the P-TAVR study to Japanese patients, ethnic factors and differences in medical environment were investigated.

Ethnic differences between Japan and foreign countries include the causes of AS and the anatomical structure of patients. However, in TAVR-eligible patients for whom the SENTINEL System is indicated, the causes of AS do not differ substantially between the US/Europe and Japan. From an anatomic point of view, a possible concern is the difference in vascular size and vascular network due to the different physique between Caucasian patients and Japanese patients. However, in the P-TAVR study enrolling 14 Asians including 3 Japanese (mean body mass index [BMI] of 23.5, mean body surface area [BSA] of 1.63) and small patients (minimum BMI of 12.0), no device delivery problem was reported. Various clinical studies on percutaneous coronary angioplasty, mostly via the radial artery, reported no difference in the arterial vascular network. Thus, there is no noteworthy difference in vascular network or vascular diameter between Caucasian patients and Japanese patients.

Differences in medical environment between Japan and outside Japan include the prevalence of TAVR and TAVR-specific equipment and manpower. However, the difference in the prevalence of TAVR is not significant between Japan and other countries, because the eligibility for TAVR is assessed from various perspectives by a heart team consisting of specialists from different fields. The results of clinical studies, etc. conducted in and outside Japan indicate no substantial difference in the frequency of stroke during TAVR between Japan and other regions.[12131415161718192021-22]

These findings suggest that the extrapolation of the foreign clinical study results to Japanese patients is possible.

PMDA's view on the extrapolation of the results of the P-TAVR study to Japanese patients:
The use of the SENTINEL System depends on the anatomy of the vascular diameter and network of the branchial artery, etc., and thus there is no ethnic factor affecting the outcome of the SENTINEL therapy. According to the medical practice guidelines in and outside Japan, the treatment and evaluation criteria for AS, causes of AS, frequency of strokes, and the implementation system for TAVR are similar in Japan and the US. The clinical outcome of TAVR is also comparable in and outside Japan.[1] The procedure for the insertion of the SENTINEL System (trans-radial artery access) has been commonly employed in percutaneous coronary angioplasty in Japan as well. As described later, the clinical treatment system will be established through product training, etc. as a part of post-marketing safety measures in a joint effort with related academic societies to support the proper use of the SENTINEL System. Taken all together, the efficacy and safety evaluations of the SENTINEL System are feasible in Japanese patients based on the foreign clinical study data.

6.B.(2) Efficacy and safety of the SENTINEL System

PMDA's view:

The incidence of all stroke within 72 hours after TAVR or before discharge (whichever came first), the primary endpoint in randomized comparison with the control group that did not use the SENTINEL System, is considered a reasonable index for the evaluation of therapeutic effect of the SENTINEL System against the target disease, in the aim of the risk reduction in stroke. Meanwhile, PMDA asked the applicant to explain the cause of the failure to meet the primary endpoint of the P-TAVR study (incidence of all stroke), and reasons for presenting the results of the P-TAVR study to demonstrate the efficacy and safety of the SENTINEL System.

The applicant's explanation:
Cause of the failure to meet the primary endpoint of the P-TAVR study (incidence of all stroke)
The possible major causes of the failure to meet the primary endpoint in the P-TAVR study include "the incidence of stroke in the P-TAVR study that was lower than that expected at the study planning phase" and "baseline characteristics of the enrolled patients that could not be anticipated at the study planning phase"

The P-TAVR study was designed based on the assumption that the primary endpoint (the incidence of all stroke) be 2% in the SENTINEL group and 4% in the control group (Table 15). The expected incidence of all stroke (4%) in the control group was determined based on the incidence of stroke (approximately 1.5%-7%) in the control group treated without the SENTINEL System in previous clinical studies, etc. that evaluated the performance of the SENTINEL System during TAVR procedures,[23-24252627] as well as the incidence of stroke before discharge (the test device, 4.4%; control devices from other companies, 4.3%) in the REPRISE III study, which evaluated the efficacy and safety of Lotus Edge Valve System (Approval number, 30100BZX00270000), a transcatheter aortic valve replacement system.[28] The SENTINEL Study was conducted to evaluate the usefulness of the SENTINEL System and showed the incidence of perioperative stroke of 3.0% (7 of 231 patients) in the SENTINEL group and 8.2% (9 of 110 patients) in the control group, with a 63%-relative reduction in the incidence of perioperative stroke. For the P-TAVR study, the expected incidence of stroke in the SENTINEL group was determined based on these outcomes, with an estimated efficacy of the SENTINEL System in the P-TAVR study as a "50%-relative risk reduction." The control group in the P-TAVR study revealed an incidence of all stroke (2.9%) lower than expected (4%), which was likely explained by the inconsistency in diagnostic methodology for stroke and the characteristics of the enrolled patients that could not be anticipated at the study planning phase.

The P-TAVR study required post-TAVR neurological evaluation by specialists such as neurologists. The study, however, for being a post-marketing clinical study, did not require diffusion-weighted MRI that is not common in clinical practice. On the contrary, in most of the above-mentioned clinical studies referenced in determining the expected incidence of stroke, diffusion-weighted MRI was required. Diffusion-weighted MRI can detect even mild asymptomatic cerebral infarction, and this could lead to the high overall incidence of stroke in these studies, possibly contributing to the gap between the expected and observed incidences of stroke in the P-TAVR study.

Table 15. Rationale for the expected incidences of all stroke in the P-TAVR study and comparison of results

	Clinical study referenced	P-TAVR study	
	Control	Control	SENTINEL
Expected incidence of all stroke	-	4%	2% (assuming a 50% relative risk reduction)
Incidence of all stroke	Approximately 1.5%-7%	2.9%	2.3% (21% relative risk reduction)
Incidence of disabling stroke	Approximately 2.4%-7%	1.3%	0.5% (60% relative risk reduction)

The difference in the incidences between expected and observed stroke is attributable to the indication of TAVR extended to patients with low surgical risks in SAVR and the characteristics of enrolled patients that could not be anticipated at the study planning phase. The control group of the P-TAVR study yielded the mean STS score of 3.3%, which is lower than the literature data (approximately 5%-6%) referenced in determining the expected incidence of stroke in the control group (Table 16). Many patients with high surgical risks in SAVR have concurrent pathological conditions such as coronary artery disease, a history of stroke, etc. that are known to be relatively high-risk factors of stroke. A greater number of patients with low surgical risks associated with SAVR were enrolled in the P-TAVR study, and that may explain the lower incidence of stroke observed than expected in the control group.

Table 16. Literature articles referenced in the determination of the expected incidence of stroke in the control group

Author	Study design	Sample size (N)	STS score	Incidence of stroke (%)	Timing of stroke assessment
Seeger J et al.[23]	All-comer, prospective research	SENTINEL: 280 Non-SENTINEL: 522 Propensity score matching population: 280/group	SENTINEL: 6.2 ± 4.2 Non-SENTINEL: 6.9 ± 5.0 (mean ± SD)	SENTINEL: 1.4 Non-SENTINEL: 4.6 (propensity score matching analysis) Disabling stroke SENTINEL: 0.4 Non-SENTINEL: 3.2	Within 7 days post-procedure
Seeger J et al.[24]	Patient-level pooled analysis[a]	SENTINEL: 717 Non-SENTINEL: 589 Propensity score matching population: 533/group	SENTINEL: 6.2 ± 4.2 Non-SENTINEL: 6.6 ± 4.9 (mean ± SD)	SENTINEL: 1.88 Non-SENTINEL: 5.44 (propensity score matching analysis) Disabling stroke SENTINEL: 0.38 Non-SENTINEL: 2.44	Within 72 hours post-procedure
Butala NM et al.[25]	Observational research using TVT Registry data	SENTINEL: 12,409 Non-SENTINEL: 110,777	-	SENTINEL: 1.3 Non-SENTINEL: 1.5 (unadjusted analysis) SENTINEL: 1.3 Non-SENTINEL: 1.58 (propensity score-based model)	On admission
Van Mieghem NM et al.[26]	Multicenter, double-blind, randomized study	SENTINEL: 32 Non-SENTINEL: 33	SENTINEL: 4.6 Non-SENTINEL: 5.8 (median)	Disabling stroke SENTINEL: 0 Non-SENTINEL: 7	30 days post-procedure
Ndunda PM et al.[27]	Meta-analysis using literature search	SENTINEL: 606 Non-SENTINEL: 724	-	Symptomatic stroke SENTINEL: 3.5 Non-SENTINEL: 6.1	30 days post-procedure

a, The data from the SENTINEL study, CLEAN-TAVI study, and SENTINEL-Ulm study were used.

Demonstration of the efficacy and safety of the SENTINEL System based on the results of the P-TAVR study

As described earlier, the incidence of all stroke, the primary endpoint of the P-TAVR study, was lower than expected in the control group, revealing the sample size of 3,000 was insufficient for the evaluation of between-group difference in the incidence of all stroke. Having said that, a point-estimate comparison showed, although statistically insignificant, a lower incidence of all stroke in the SENTINEL group (2.3%) than in the control group (2.9%) with a 21%-relative risk reduction (Table 15). The incidence of disabling stroke was significantly lower in the SENTINEL group (0.5%) than in the control group (1.3%) with a 60%- relative risk reduction (Table 15). There was no between-group difference in the safety outcomes with death, composite of stroke, TIA, and delirium, and acute kidney injury. A major vascular complication at the device access site occurred in 1 patient in the SENTINEL group. However, the event was unrelated to the SENTINEL System, and the risk of the event can be minimized through a series of procedural training. These findings suggest that the SENTINEL System is safe and possibly reduce the risk of disabling stroke, although the P-TAVR study failed to demonstrate a reduced risk of all stroke with the SENTINEL System.

Disabling stroke occurred in 8 patients in the SENTINEL group in the P-TAVR study. Further investigation in these patients revealed that, of 6 patients with disabling ischemic stroke, only 1 had infarction in the territories protected by the SENTINEL System, possibly due to an inappropriate filter positioning by the SENTINEL System or sizes of embolic debris that could not be captured by the filters (Table 17). The remaining 2 patients had infarction outside the protected territories of the SENTINEL System, which was attributable to the area of the left subclavian artery that is not covered by the SENTINEL System.

Table 17. Disabling stroke cases in the SENTINEL group in the P-TAVR study

Disabling ischemic stroke	**Number of patients**
Within the protected territories (middle cerebral artery infarction)	1
Outside the protected territories (occipital lobe infarction)	2
The SENTINEL System was not used (difficulty in guidewire insertion due to the narrow and tortuous radial artery, the access site of the SENTINEL System.)	1
Unknown location	2
Disabling hemorrhagic stroke	**Number of patients**
Cerebellar hemorrhage of unknown cause unrelated to the SENTINEL System (reported as unrelated the SENTINEL System because of no problem in the ability to capture embolic debris by the filters.)	1
Cerebral hemorrhage (cerebellar hemorrhage was reported as unrelated to the SENTINEL System.)	1

After the data of the P-TAVR study were publicized, a meta-analysis was conducted using data from 4,066 patients, including the results of the P-TAVR study and other clinical studies of the SENTINEL System. The meta-analysis showed device success in 92% of the patients in the SENTINEL group, indicating a statistically significantly lower risk of disabling stroke as demonstrated in the P-TAVR study (SENTINEL group 0.5%, control group 1.6%, relative risk 0.33, 95% CI 0.17-0.65, $P = 0.001$).[29] The risk of all stroke was also lower in the SENTINEL group than in the control group (SENTINEL group 2.7%, control group 3.7%, relative risk 0.67, 95% CI 0.48-0.95, $P = 0.02$). Patients who underwent TAVR and experienced perioperative ischemic stroke showed significantly high in-hospital mortality, i.e., approximately 3 times that in patients who did not experience the event. The occurrence of stroke was reported to have led to prolonged hospitalization by a mean number days of 6.[30] Post-TAVR stroke was related to increased mortality at 30 days postoperative. The data from patients treated by TAVR and the meta-analysis also revealed an approximately 6-time increase in mortality risk at 30 days postoperative.[7] These reports suggest that stroke progression can be irreversible. The sequelae of stroke may interfere with daily activities or social activities of patients even with improved AS post- TAVR, posing a serious problem for patients.

Technically, the P-TAVR study was not designed to demonstrate a significant between-group difference in the incidence of disabling stroke. However, the results of the P-TAVR study and the meta-analysis have shown the effect of the SENTINEL System in reducing the risk of disabling stroke associated with TAVR.

PMDA's view on the efficacy and safety of the SENTINEL System:
The safety profile of the SENTINEL System is clinically acceptable based on the results of the P-TAVR study and the meta-analysis suggesting no noteworthy safety issue related to the device.

The efficacy results of the SENTINEL System are subject to careful interpretation, in view that the primary endpoint of the P-TAVR study (the incidence of all stroke) was not met and that the specified sample size in the P-TAVR study was not intended for the analysis of disabling stroke, although it showed a statistically significant between-group difference in the study.

At the same time, TAVR-related stroke is a clinical issue that is suggested to lead to impaired QOL and postoperative mortality. Currently, there is no technique to capture embolic debris loosened during TAVR in Japan. Such device is of high clinical need, which has brought to the designation of the SENTINEL System as a high-need medical device. Disabling stroke is a physically and mentally critical event for patients. The meta-analysis, including the P-TAVR study, showed a reduced risk of disabling stroke with the use of the SENTINEL System. Furthermore, the SENTINEL study demonstrated the competence of the SENTINEL System in capturing embolic debris during TAVR.

Taking into consideration the issues and clinical need in dealing with stroke during TAVR in Japan, and in light of the comments from the Expert Discussion, PMDA has concluded that the clinical risk-benefit balance of the SENTINEL System will be maintained where the SENTINEL therapy is provided to patients at high risk of stroke strictly selected by a heart team of specialists from various fields, with careful attention to their baseline and anatomical characteristics. (Patient eligibility for the SENTINEL therapy is discussed later in 6.B.[3]).

6.B.(3) Patient eligibility for the SENTINEL therapy
The applicant's explanation about the eligible patient population for the use of the SENTINEL System:
In the written request the THT Association submitted to the Study Group on the Early Introduction of Medical Devices, etc. of High Medical Need, potential post-TAVR high risk factors, for which the SENTINEL therapy is indicated, include a history of stroke, low kidney function, low body weight, and peripheral arterial diseases, according to the meta-analysis of many clinical studies. Approximately 5% of all patients who had undergone TAVR were considered to have those factors.[31] The transcatheter aortic valve replacement in-hospital stroke (TASK) study was conducted to determine risk predictors for TAVR-related perioperative cerebral vascular disorders and to establish a scoring model for risk stratification. The study identified the 4 independent risk predictors for cerebral vascular disorders including a history of stroke, the use of an artificial valve other than balloon-expandable valves, chronic kidney disease, and peripheral vascular disease, and a TASK scoring system based on these factors has been proposed.[32] In an additional analysis of the P-TAVR study, patients were scored by giving 1 point each to the 4 parameters of the TASK scoring system. When the cutoff was set at 2 points in the TASK score, there was no significant between-group difference in the incidence of all stroke. However, the incidence of disabling stroke tended to be lower in the SENTINEL group than in the control group in both subgroups of TASK score (score <2,

SENTINEL group 0.9%, control group 4.7%, $P = 0.1097$; score ≥2, SENTINEL group 0.5%, control group 1.1%, $P = 0.0884$) (Table 18).

Table 18. Incidence of stroke by TASK score category

Endpoint	SENTINEL	Control	*P*-value
All stroke	2.3% (34/1,501)	2.9% (43/1,499)	0.2960
TASK score ≥2	3.5% (4/113)	8.5% (9/106)	0.1213
TASK score <2	2.2% (30/1,388)	2.4% (34/1,393)	0.6232
Disabling stroke	0.5% (8/1,501)	1.3% (20/1,499)	0.0225
TASK score ≥2	0.9% (1/113)	4.7% (5/106)	0.1097
TASK score <2	0.5% (7/1,388)	1.1% (15/1,393)	0.0884

Assuming that the TASK score alone would not adequately serve to assess eligibility for the SENTINEL therapy in a certain number of patients, further investigation was conducted on the patient population eligible for the SENTINEL therapy.

Embolic debris derived from calcified or atherosclerotic lesions of the aortic wall or arch aorta builds up when the delivery catheter for TAVR passes through the aortic arch or ascending aortic wall. Also, tissue fragments are loosened from the aortic valve when an artificial valve is replaced in TAVR. According to the findings reported, an arteriosclerotic lesion in the aorta is a risk factor of ischemic stroke, and the calcification of the aortic valve can also be a predictive factor of post-TAVR stroke.[33,34,3536,-37] Given these findings, an arteriosclerotic lesion around the ascending aorta and aortic valve calcification should be taken into consideration in eligibility assessment.

Thus, the selection of patients for the SENTINEL therapy should involve careful assessment on "the risk factors included in the TASK scoring system" and "the presence of an arteriosclerotic lesion around the ascending aorta or aortic valve calcification," and decision making by a heart team (of specialists from various fields, including cardiovascular internal medicine and cardiovascular surgery) on a patient-by-patient basis as required by the THT Association. In Europe and the US, where the SENTINEL System has already been used in clinical practice, patients at high risk of stroke are identified based on risk factors i.e., age, kidney function, peripheral vascular disease, calcification patterns of blood vessels, etc. in association with TAVR, and a history of stroke, to receive the SENTINEL therapy.

To ensure the proper use of the SENTINEL System, the related academic societies will investigate the proportion of patients who use the SENTINEL System to patients who undergo TAVR at each medical institution, and the proper way of using the SENTINEL System will be discussed based on future evidence, with a view to the revision of the guidelines for proper use, in a joint effort with the related academic societies.

PMDA's view:
As explained by the applicant, the selection of eligible patients is essential to maintain the risk-benefit balance of the SENTINEL System. Currently, however, it is difficult to clearly identify eligible population for the SENTINEL therapy based on the results of the P-TAVR study, etc. Even in Europe and the US, where the SENTINEL System has already been used in clinical practice, medical practice

guidelines, etc. do not specify definite risk factor of stroke during TAVR. Thus, the applicant should discuss with the related academic societies based on the currently available evidence. The best approach in patient selection for the SENTINEL therapy should involve the assessment of the risk of stroke by a heart team, with concurrent illness, medical history (peripheral vascular disease, chronic kidney disease, and stroke), imaging findings (severe aortic valve calcification and atheromatous lesion in the ascending/arch aorta), etc. taken into consideration, and determine the use of the SENTINEL system in a comprehensive manner. In view of the comments from the Expert Discussion, this conclusion should be reflected in the guidelines for proper use created by related academic societies. To ensure that eligible patients be selected strictly according to the guidelines for proper use, PMDA instructed the applicant to provide relevant advice in the instructions for use, and the applicant agreed. Taking into consideration the comments from the Expert Discussion, the applicant's joint effort with the related academic societies in assuring the proper use of the SENTINEL System, i.e. the investigation of the proportion of patients treated with the device and evidence collection with a view to future revision of the guidelines, is considered appropriate.

6.B.(4) Post-marketing safety measures

The applicant's explanation about a post-marketing safety measures for the SENTINEL System:
Product training will be provided to physicians who will be using the SENTINEL System in cooperation with the THT Association. The training will provide the programs outlined below, which basically model after those provided overseas. In the early stage of introduction of the SENTINEL System to Japan, product specialists with expert knowledge about the device will give on-site advice on the operation procedure, etc. as practiced in other countries. A system for learning curve effect minimization is to be established (Table 19).

Table 19. Outline of the product training program in Japan

Description
Classroom training
• Product summary (e.g., product characteristics, operating principle, basic operation procedure, and troubleshooting)
• Product preparation flow (e.g., preparation of other devices, product setup)
• Patient selection (e.g., explanation about how to select eligible patients based on CT data of actual cases)
• Clinical data (e.g., the results of the major clinical studies, including the P-TAVR study)
Hands-on training
• Simulation of the general procedure (blood vessel model)
• Virtual simulation*

* A procedural training for the SENTINEL therapy on PCs using a demonstration handle that simulates the handle part of the SENTINEL System

The applicant, in cooperation with the THT Association, plans to create the guidelines for proper use, which will advise patient selection as mentioned earlier and requirements for physicians and medical institutions. From the viewpoint of assurance of the proper use of the SENTINEL System, the THT Association will investigate the proportion of patients who use the SENTINEL System per medical institution and revise the guidelines for proper use as necessary, which will also be mentioned in the guidelines.

PMDA's view on the proposed post-marketing safety measures:

The SENTINEL System should be used by physicians who have been adequately trained on the device and have adequate experience in earlier-mentioned patient selection and TAVR, and at medical institutions capable of dealing with various complications. In a joint effort with the related academic societies, the guidelines for proper use, which will include requirements for physicians and medical institutions, will be created. The post-marketing safety measures will include training and the on-site advice by product specialists. These approaches by the applicant are considered reasonable and should be attached as approval condition.

6.B.(5) Intended use

Based on the above discussions, the SENTINEL System is intended for use to capture and remove embolic debris loosened during TAVR. Accordingly, PMDA concluded that the proposed intended use be modified as follows.

Intended use (Underline denotes changes.)

The SENTINEL System is a distal embolic protection device that is tentatively placed in an aortic branch (brachiocephalic artery and the left common carotid artery) to capture and remove embolic debris loosened during transcatheter aortic valve replacement (TAVR) procedures.

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 20 outlines the draft use-results survey plan submitted by the applicant.

Table 20. Outline of the draft use-results survey plan

Objective	To detect and verify information on malfunctions by type occurring in post-marketing clinical practice, and the quality, safety, and efficacy of the SENTINEL System
Planned sample size	200
Rationale	Taking into consideration the incidence of all stroke (2.27%, 95% CI 1.57%-3.15%) in the SENTINEL group in the P-TAVR study, the sample size of 200 was determined to detect ≥1 patient experiencing an adverse event or malfunction occurring at the incidence of 1.5% with a probability of ≥95%.
Survey period	2-year continuous survey (including preparation, 6 months; registration, 12 months; follow-up, 1 month; evaluation/analysis, 5 months)
Survey items	1. Surgical success (product delivery, filter deployment/retraction, and removal) 2. Follow-up 1) Follow-up at discharge (day of discharge) Whether follow-up is performed, NIHSS, mRS 2) Follow-up at 30 days postoperative Whether follow-up is performed, NIHSS, mRS 3. Malfunctions/adverse events, including disabling and non-disabling stroke (ischemic and hemorrhagic) (from product placement through follow-up at 30 days postoperative) The reasons for selecting patients based on the guidelines for proper use will also be collected as patient characteristics.

7.B Outline of the review conducted by PMDA

PMDA's view:

The SENTINEL System has not been used in Japan, and a post-marketing use-results survey is essential to verify the appropriateness of the proposed post-marketing safety measures, including product training and patient selection based on the guidelines for proper use. Additional risk reduction measures should be taken as necessary.

The sample size for the use-results survey of 200, proposed by the applicant based on the incidence of all stroke in the P-TAVR study, is reasonable. Because post-TAVR stroke occurs within 72 hours post-procedure in most cases, a 1-month follow-up period for each patient and a 2-year use-results survey period with the follow-up period taken into consideration, are thus acceptable. The survey items selected to evaluate each process in the procedure including delivery, placement, and removal of the SENTINEL System, and neurological assessments including the incidence of stroke, are reasonable.

PMDA has concluded that the draft use-results survey plan proposed by the applicant is appropriate.

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

8.A Summary of the data submitted

The applicant submitted instructions for use (draft) as an attachment in accordance with the Notification titled "Application for Marketing Approval of Medical Devices" (PFSB Notification No. 1120-5, dated November 20, 2014).

8.B Outline of the review conducted by PMDA

On the basis of the conclusion of the Expert Discussion, PMDA concluded that there were no particular problems with the proposed instructions for use where necessary caution is advised.

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

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

The 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 SENTINEL System focused on (1) the efficacy and safety of the SENTINEL System and (2) the post-marketing safety measures, including the selection of eligible

patients. Taking account of comments raised in the Expert Discussion, PMDA reached the following conclusions.

(1) Efficacy and safety of the SENTINEL System

The P-TAVR study, which was conducted overseas in patients undergoing TAVR to demonstrate the SENTINEL System's ability to reduce the risk of perioperative stroke after TAVR significantly, failed to meet the primary endpoint. The SENTINEL group, however, had a significantly lower incidence of disabling stroke than in the control group. Although the P-TAVR study had no specific sample size set to analyze the incidence of disabling stroke, the meta-analysis including the P-TAVR study suggested a reduced risk of disabling stroke with the use of the SENTINEL System. The pre-marketing SENTINEL study conducted in the US and Europe demonstrated the ability of the SENTINEL System to capture embolic debris during TAVR.

No noteworthy safety event has been reported. TAVR-related stroke is a significant clinical challenge that increases mortality and impairs QOL. Given that the SENTINEL System is expected to have a certain degree of efficacy, PMDA has concluded that its clinical risk-benefit balance is maintained where the device is used in patients with high risks of stroke strictly selected by a heart team of specialists from various fields based on baseline and anatomical characteristics, diagnostic imaging findings, etc., and that the introduction of the SENTINEL System to Japan is of significance.

(2) Post-marketing safety measures including the selection of eligible patients

The SENTINEL System, is Japan's first device to capture and remove embolic debris loosened during TAVR. As mentioned earlier, the selection of eligible patients is important to ensure the effective and safe introduction, and device- or procedure-related complications must be addressed appropriately. PMDA, therefore, has concluded that the SENTINEL System be used by physicians and at medical institutions that have full knowledge about the device, adequate experience in TAVR, and skills to deal with complications. To this end, compliance with the guidelines for proper use to be created by the related academic societies is essential, and this advice should be attached as approval condition.

The SENTINEL System has never been used in Japan. The appropriateness of patient selection based on the guidelines for proper use, etc. is subject to assessment. The applicant should, therefore, investigate the outcome of the SENTINEL System at clinical settings in Japan through a use-results survey and take additional risk reduction measures as necessary. The period of the use-results survey should be 2 years (preparation, 6 months; registration, 12 months; follow-up, 1 month; evaluation/analysis, 5 months).

As a result of the above review, PMDA has concluded that the SENTINEL System may be approved for marketing after modifying the intended use as shown below, with the following condition.

Intended Use

The SENTINEL System is a distal embolic protection device that is tentatively placed in an aortic branch (brachiocephalic artery and the left common carotid artery) to capture and remove embolic debris loosened during transcatheter aortic valve replacement (TAVR) procedures.

Approval Condition

The applicant is required to ensure that the product be used in patients whose eligibility has been confirmed by physicians with adequate knowledge and experience in transcatheter aortic valve replacement procedures who are fully skilled in the use of the product and acquainted with complications associated with the procedures, and at medical institutions with a well-established system for the treatment. To this end, dissemination of the guidelines for proper use jointly prepared with related academic societies, provision of training seminars, and other necessary measures should be implemented.

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 2 years.

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

References

[1] JCS/JSCS/JATS/JSVS 2020 Guidelines on the Management of Valvular Heart Disease

[2] The Japanese Circulation Society. The Japanese Registry Of All cardiac and vascular Diseases (JROAD) Annual Report 2022

[3] Huded CP, et al., Association between transcatheter aortic valve replacement and early postprocedural stroke. *JAMA*. 2019;321(23):2306-2315.

[4] Tchetche D, et al., Cerebrovascular events post-transcatheter aortic valve replacement in a large cohort of patients: a FRANCE-2 registry substudy. *JACC Cardiovasc Interv*. 2014;7(10):1138-45.

[5] Nombela-Franco L., et al., Timing, predictive factors, and prognostic value of cerebrovascular events in a large cohort of patients undergoing transcatheter aortic valve implantation. *Circulation.* 2012;126(25):3041-3053.

[6] Vlastra W. et al., Predictors, incidence, and outcomes of patients undergoing transfemoral transcatheter aortic valve implantation complicated by stroke. *Circ Cardiovasc Interv.* 2019;12:e007546.

[7] Muralidharan A., et al., Meta-analysis of perioperative stroke and mortality in transcatheter aortic valve implantation. *Am J Cardiol.* 2016;118(7):1031-1045.

[8] DeRubertis B., et al., Determining the quantity and character of carotid artery embolic debris by electron microscopy and energy dispersive spectroscopy. *Journal of Vascular Surgery.* 2007;45(4):716-725.

[9] Annalisa A., et al., Cerebral protection during carotid artery stenting. *Stroke.* 2022;33:456-461.

[10] Drummond J. C. Blood pressure and the brain: How low can you go? *Anesth Analg.* 2019;128(4):759-771.

[11] Thomas W. A., et al., Electrical activity of the cerebral cortex during induced hypotension in man: A comparison of sodium nitroprusside and trimetaphan, *British Journal of Anaesthesia.* 1985;57 (2):134-141.

[12] Medtronic Japan, Co., Ltd. Summary of product application in Marketing Application for CoreValve

[13] Pharmaceuticals and Medical Devices Agency. Review Report on SAPIEN XT. April 26, 2013.

[14] Edwards Lifesciences Limited. Summary of product application in Marketing Application for SAPIEN XT.

[15] Leon, M. B. et al., Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. *N. Engl. J. Med.* 2016;374,1609-1620.

[16] Thourani, V. H. et al., Transcatheter aortic valve replacement versus surgical valve replacement in intermediate-risk patients: a propensity score analysis. *Lancet.* 2016;387,2218-2225.

[17] Pharmaceuticals and Medical Devices Agency. Review Report on Edwards SAPIEN 3. January 22, 2021.

[18] Edwards Lifesciences Limited. Attached document in Partial Change Application for Edwards SAPIEN 3.

[19] Pharmaceuticals and Medical Devices Agency. Review Report on CoreValve. February 2, 2015.

[20] Reardon M. J. et al. Surgical or transcatheter aortic-valve replacement in intermediate-risk patients. *N. Engl. J. Med.* 2017;376,1321-1331.

[21] Pharmaceuticals and Medical Devices Agency. Review Report on CoreValve Evolut R. January 22, 2021.

[22] Medtronic Japan, Co., Ltd. Attached document in Partial Change Application for CoreValve Evolut R

[23] Seeger J., et al., Cerebral embolic protection during transcatheter aortic valve replacement significantly reduces death and stroke compared with unprotected procedures. *J Am Coll Cardiol Intv.* 2017;10:2297-2303.

[24] Seeger J., et al., Rate of peri-procedural stroke observed with cerebral embolic protection during transcatheter aortic valve replacement: a patient- level propensity-matched analysis. *Eur Heart J.* 2019;40:1334-1339.

[25] Butala N. M., et al., Cerebral embolic protection and outcomes of transcatheter aortic valve replacement: Results from the Transcatheter Valve Therapy registry. *Circulation.* 2021;143:2229-2240.

[26] Van Mieghem N., et al., Filter-based cerebral embolic protection with transcatheter aortic valve implantation: the randomised MISTRAL-C trial. *EuroIntervention.* 2016;12:499-507.

[27] Ndunda P. M., et al., Clinical outcomes of Sentinel Cerebral Protection System use during transcatheter aortic valve replacement: A systematic review and meta-analysis. *Cardiovasc Revasc Med.* 2020;21:717-722.

[28] Boston Scientific Japan K.K. Attached Document in Marketing Application for Lotus Edge Valve System

[29] Wolfrum M., et al., Cerebral embolic protection during transcatheter aortic valve replacement: a systematic review and meta-analysis of propensity score matched and randomized controlled trials using the Sentinel cerebral embolic protection device. *BMC Cardiovasc Disord.* 2023;23(1):306.

[30] Fahad A., et al., Clinical and economic burden of acute ischemic stroke following transcatheter aortic valve replacement. *Structural Heart.* 2019;3(1):72-73.

[31] 33rd meeting of the Study Group on the Early Introduction of Medical Devices, etc. of High Medical Need, Material 2-2, Written request from academic societies [2021-3], https://www.mhlw.go.jp/content/11121000/000972944.pdf

[32] Berkovitch A., et al., Clinical predictors for procedural stroke and implications for embolic protection devices during TAVR: Results from the multicenter transcatheter aortic valve replacement in-hospital stroke (TASK) study. *J Pers Med.* 2022;12(7):1056.

[33] French Study of Aortic Plaques in Stroke Group; Amarenco P, et al., Atherosclerotic disease of the aortic arch as a risk factor for recurrent ischemic stroke. *N Engl J Med.* 1996;334(19):1216-1221.

[34] Fujimoto S, et al., Aortic arch atherosclerotic lesions and the recurrence of ischemic stroke. *Stroke.* 2004;35(6):1426-1429.

[35] Jones EF, et al., Proximal aortic atheroma. An independent risk factor for cerebral ischemia. *Stroke.* 1995;26(2):218-24.

[36] Pollari F, et al., Aortic valve calcification as a risk factor for major complications and reduced survival after transcatheter replacement. *J Cardiovasc Comput Tomogr*. 2020;14(4):307-313.

[37] Foley M, et al., Aortic valve calcium score is associated with acute stroke in transcatheter aortic valve replacement patients. *J Soc Cardiovasc Angiogr Interv.* 2022;1(4):100349.