September 05, 2022
Medical Device Evaluation Division
Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Report on the Deliberation Results

Classification	Instrument & Apparatus 7, Organ function replacement device
Term Name	Transcatheter bovine cardiac valve
Brand Name	Edwards SAPIEN 3
Applicant	Edwards Lifesciences Limited
Date of Application	September 29, 2021

Results of Deliberation

In its meeting held on September 5, 2022, the Committee on Medical Devices and *In-vitro* Diagnostics reached the following conclusion, and decided that this conclusion should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product applied for partial change is designated as a medical device subject to a use-results survey and should be approved.

The use-results survey period should be 7 years. The product should be approved with the following underlined condition.

Approval Conditions

1. Transcatheter aortic valve implantation
   (1) to (5) are omitted.
   (6) Treatment in patients with symptomatic valvular disease due to failing (stenosed, insufficient, or combined) of a transcatheter bioprosthetic aortic valve who are not eligible for surgery and of which treatment with the product is considered as their best therapeutic option
      1) The applicant is required to conduct a use-results survey covering all patients treated with the product, report the results of interannual analyses to the Pharmaceuticals and Medical Devices Agency, and take other appropriate measures as necessary.
2. Omitted.

Review Report

August 15, 2022
Pharmaceuticals and Medical Devices Agency

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

Classification	Instrument & Apparatus 7, Organ function replacement device
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Date of Application	September 29, 2021
Reviewing Office	Office of Medical Devices I

Review Results

August 15, 2022

Classification	Instrument & Apparatus 7, Organ function replacement device
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Results of Review

"Edwards SAPIEN 3" (Approval number 22800BZX00094000, hereinafter referred to as "SAPIEN 3") is a transcatheter heart valve system used for transcatheter aortic valve replacement (TAVR) or transcatheter pulmonary valve replacement. SAPIEN 3 mainly consists of a bioprosthetic valve, a delivery system, an introducer sheath set, and a balloon catheter.

SAPIEN 3 has been approved as a medical device used for TAVR in the treatment of "patients with severe symptomatic native aortic valve stenosis" or "patients with symptomatic valvular disease due to failing of a surgical bioprosthetic aortic valve who are not eligible for surgery." The application for partial change ("the partial change application") was submitted to add the indication "treatment for patients with symptomatic valvular disease due to failing of a transcatheter bioprosthetic aortic valve who are not eligible for surgery."

The applicant submitted non-clinical data supporting the physicochemical properties and performance. PMDA reviewed the submitted data and identified no particular problem.

The applicant submitted clinical data from patients who underwent transcatheter aortic valve in transcatheter aortic valve (TAV in TAV), which is a procedure that places a TAV on top of the existing transcatheter bioprosthetic aortic valve at the inner orifice, in Transcatheter Valve Therapies Registry (TVT Registry) conducted on the initiative of the Society of Thoracic Surgeons and the American College of Cardiology. The TVT Registry is a large-scale real-world database established in anticipation of TAVR to gain an expanded indication in the US. It is difficult to conduct a clinical study of SAPIEN 3 because of a limited number of patients who are eligible for TAV in TAV, which is proposed to be added to the indications of SAPIEN 3 in this partial change submission, and the age and other characteristics of this proposed target patient population. There is a great medical need for TAV in TAV. Since the medical environment, etc. of TAVR does not significantly differ between the US and Japan, it should be acceptable to use the data from the TVT Registry as the basis of evaluation of SAPIEN 3. The reliability of the TVT Registry data has been confirmed based on the results of compliance assessment concerning the new medical device application data.

In the TVT Registry, a total of 587 patients at 238 study sites in the US underwent TAV in TAV with SAPIEN 3, and SAPIEN 3 was implanted in a total of 584 patients. As of the time of data extract, 479 patients (89.0%) completed the 30-day follow-up, and 250 patients (66.5%) completed the 1-year follow-up.

The mean aortic-valve gradient was 33.5 ± 1.06 mmHg at baseline, 14.5 ± 0.42 mmHg at 30 days, and 13.8 ± 0.61 mmHg at 1 year, showing improvements in hemodynamics after TAV in TAV with SAPIEN 3, which was further demonstrated with improvements in New York Heart Association (NYHA) functional classification and the Kansas City Cardiomyopathy Questionnaire (KCCQ) score from baseline. These results confirmed that the therapeutic goal, which is to improve functional heart failure, was achieved. The data demonstrated the efficacy of TAV in TAV with SAPIEN 3 in patients for whom no other treatment options are available.

The Kaplan-Meier estimate of death was 5.0% at 30 days and 17.0% at 1 year. The Kaplan-Meier estimates of common adverse events were 2.7% for stroke, 1.7% for aortic valve reintervention, 9.2% for conduction disorder requiring pacemaker implantation, and 5.2% for valve-related readmission at 1 year. In the TVT Registry, transcatheter aortic valve in surgical aortic valve (TAV in SAV), which is a procedure that places TAV inside a failing surgical bioprosthetic valve in the aortic position, resulted in the Kaplan-Meier estimates of death of 2.8% at 30 days and 10.0% at 1 year. Publications reported that surgical valve replacement of a failed TAV device resulted in in-hospital mortality of 11.8% and in-hospital or within 30-day mortality of 17.1%. Taken together with comments from the Expert Discussion, PMDA concluded that the results of TAV in TAV with SAPIEN 3 in the TVT Registry were clinically comparable to the results of TAV in SAV in the TVT Registry and the literature data and acceptable. The application submitted to the regulatory authority in Japan specifies that TAV in TAV with SAPIEN 3 should be indicated for patients who are not eligible for surgery and have a failing TAV device made by the applicant. PMDA reviewed the clinical results from this patient population and found no particular problem.

The results of TAV in TAV in patients in Japan are not available. Information regarding TAV in TAV, including procedural success rate and incidences of adverse events in Japan, must be collected through a use-results survey. Additional risk mitigation measures should also be taken as necessary.

As a result of its review, PMDA has concluded that SAPIEN 3 may be approved for the intended use shown below with the following approval conditions, and that the results should be presented to the Committee on Medical Devices and *In-vitro* Diagnostics for further deliberation. The intended use and approval conditions proposed to be changed in this partial change application are underlined.

Intended Use

Edwards SAPIEN 3 is a balloon-expandable prosthetic cardiac valve (bovine pericardial tissue valve) system used for percutaneous cardiac valve implantation in the following patients:

- Patients with severe symptomatic aortic valve stenosis attributed to degenerative calcification of the native aortic valve cusp of which treatment with SAPIEN 3 is considered as their best therapeutic option. In the case of chronic dialysis patients, however, the treatment with SAPIEN 3 is limited to

patients who are not eligible for surgery and of which treatment with SAPIEN 3 is considered as their best therapeutic option.

- Patients with symptomatic valvular disease due to failing (stenosed, insufficient, or combined) of a surgical or transcatheter bioprosthetic aortic valve who are not eligible for surgery and of which treatment with SAPIEN 3 is considered as their best therapeutic option. Expect for the patients who have multiple bioprosthetic valves in the aortic position.
- Patients with failing (stenosed, insufficient, or combined) of a surgical right ventricular outflow tract extracardiac conduit or bioprosthetic valve in the pulmonic position that was implanted during surgery to treat congenital heart disease who are not eligible for surgery and of which treatment with SAPIEN 3 is considered as their best therapeutic option. Except for patients who have or need a stent in the target implant site of SAPIEN 3 and patients on chronic dialysis

Approval Conditions

1. Transcatheter aortic valve replacement

(1) Treatment in all eligible patients

1) The applicant is required to take necessary measures in cooperation with related academic societies to ensure that the product is used by surgeons with adequate knowledge and experience in the treatment of symptomatic severe aortic valve stenosis at medical institutions with a well-established system for possible complications in association with the treatment with the product.

2) The applicant is required to take necessary measures in cooperation with related academic societies to ensure that the product is used, in compliance with the indication, by surgeons as described in 1) in the treatment using the product after acquiring sufficient skills for using the product and adequate knowledge about procedure-related complications by attending relevant training courses or by other means.

3) The applicant is required to take necessary measures in cooperation with related academic societies to ensure that the product is used only in intended patients for the treatment with the product.

(2) Treatment in patients on chronic dialysis with severe symptomatic aortic valve stenosis attributed to degenerative calcification of the native aortic valve cusp who are not eligible for surgery and of which treatment with the product is considered as their best therapeutic option

1) The applicant is required to conduct a use-results survey covering all patients treated with the product, report the results of interannual analyses to the Pharmaceuticals and Medical Devices Agency, and take other appropriate measures as necessary until data from a certain number of patients have been accumulated.

(3) Treatment in patients not on chronic dialysis with severe symptomatic aortic valve stenosis attributed to degenerative calcification of the native aortic valve cusp who are eligible for surgery and of which treatment with the product is considered as their best therapeutic option

1) The applicant is required to submit reports on the results of analyses of long-term prognosis of patients in the clinical study included in this regulatory submission to Pharmaceuticals and Medical Devices Agency and to take appropriate measures as necessary.

(4) Treatment in patients not on chronic dialysis with symptomatic valvular disease due to failing (stenosed, insufficient, or combined) of a surgical bioprosthetic aortic valve who are not eligible for surgery and of which treatment with the product is considered as their best therapeutic option

1) The applicant is required to conduct a use-results survey covering all patients treated with the product, report the results of interannual analyses to the Pharmaceuticals and Medical Devices Agency, and take other appropriate measures as necessary until data from a certain number of patients have been accumulated.

2) The applicant is required to report the perioperative results with the 20-mm valve, which is to be investigated through the use-results survey, to Pharmaceuticals and Medical Devices Agency every certain number of patients in a timely manner and to take appropriate measures as necessary.

(5) Treatment in patients on chronic dialysis with symptomatic valvular disease due to failing (stenosed, insufficient, or combined) of a surgical bioprosthetic aortic valve who are not eligible for surgery and of which treatment with the product is considered as their best therapeutic option

1) The applicant is required to conduct a use-results survey covering all patients treated with the product, report the results of interannual analyses to the Pharmaceuticals and Medical Devices Agency, and take other appropriate measures as necessary until data from a certain number of patients have been accumulated.

(6) Treatment in patients with symptomatic valvular disease due to failing (stenosed, insufficient, or combined) of a transcatheter bioprosthetic aortic valve who are not eligible for surgery and of which treatment with the product is considered as their best therapeutic option

1) The applicant is required to conduct a use-results survey covering all patients treated with the product, report the results of interannual analyses to the Pharmaceuticals and Medical Devices Agency, and take other appropriate measures as necessary.

2. Transcatheter pulmonary valve replacement

(1) The applicant is required to develop and appropriately implement a post-marketing risk management plan.

(2) The applicant is required to take necessary measures in cooperation with related academic societies to ensure that the product is used by a heart team with adequate knowledge and experience in the treatment of congenital heart disorder and percutaneous aortic valve replacement at limited medical institutions with a well-established system for possible complications in association with the treatment with the product.

(3) The applicant is required to take necessary measures in cooperation with related academic societies to ensure that the product is used, in compliance with the indication, by surgeons of the heart team as described in (2) in the treatment using the product after acquiring sufficient skills for using the product and adequate knowledge about procedure-related complications by attending relevant training courses or by other means.

(4) The applicant is required to take necessary measures in cooperation with related academic societies to ensure that the product is used only in intended patients for the treatment with the product.

(5) The applicant is required to conduct a use-results survey covering all patients treated with the product, report the results periodically to the Pharmaceuticals and Medical Devices Agency, and

take other appropriate measures as necessary in cooperation with related academic societies until data from a certain number of patients have been accumulated.

Review Report

August 15, 2022

Product for Review

Classification	Instrument & Apparatus 7, Organ function replacement device
Term Name	Transcatheter bovine cardiac valve
Brand Name	Edwards SAPIEN 3
Applicant	Edwards Lifesciences Limited
Date of Application	September 29, 2021
Proposed Intended Use	Edwards SAPIEN 3 is a balloon-expandable prosthetic cardiac valve (bovine pericardial tissue valve) system used for percutaneous cardiac valve implantation in the following patients: • Patients with severe symptomatic aortic valve stenosis attributed to degenerative calcification of the native aortic valve cusp of which treatment with SAPIEN 3 is considered as their best therapeutic option. In the case of chronic dialysis patients, however, the treatment with SAPIEN 3 is limited to patients who are not eligible for surgery and of which treatment with SAPIEN 3 is considered as their best therapeutic option. • Patients with symptomatic valvular disease due to failing (stenosed, insufficient, or combined) of a surgical or transcatheter bioprosthetic aortic valve who are not eligible for surgery and of which treatment with SAPIEN 3 is considered as their best therapeutic option. Expect for the patients who have multiple bioprosthetic valves in the aortic position • Patients with failing (stenosed, insufficient, or combined) of a surgical right ventricular outflow tract extracardiac conduit or bioprosthetic valve in the pulmonic position that was implanted during surgery to treat congenital heart disease who are not eligible for surgery and of which treatment with SAPIEN 3 is considered as their best therapeutic option. Except for patients who have or need a stent in the target implant site of SAPIEN 3 and patients on chronic dialysis

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List of Abbreviations

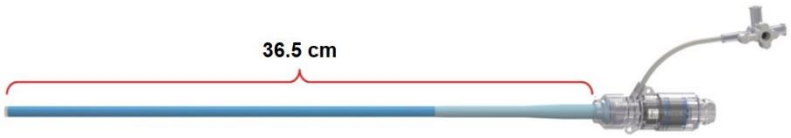
ACC	American College of Cardiology
AHA	American Heart Association
AI	Attempted Implant
FDA	Food and Drug Administration
GCP	Good Clinical Practice
KCCQ	Kansas City Cardiomyopathy Questionnaire
MRI	Magnetic Resonance Imaging
NYHA	New York Heart Association
QOL	Quality of Life
SAV	Surgical Aortic Valve
SAVR	Surgical Aortic Valve Replacement
SD	Standard Deviation
STS	Society of Thoracic Surgeons
TAV	Transcatheter Aortic Valve
TAVR	Transcatheter Aortic Valve Replacement
THT	Transcatheter Heart Valve Therapy
TVT Registry	Transcatheter Valve Therapies Registry
VI	Valve Implant

I. Product Overview

Edwards SAPIEN 3 (Approval number 22800BZX00094000, hereinafter referred to as "SAPIEN 3") is a balloon-expandable prosthetic cardiac valve (bovine pericardial tissue valve) system used for percutaneous cardiac valve implantation. SAPIEN 3 mainly consists of a bioprosthetic valve, a delivery system, an introducer sheath set, and a balloon catheter (Figure 1). The bioprosthetic valve is available in 3 models (9600TFX, 9750TFX, and 9755RSL) with different heights and fabric types of the outer skirt, methods of leaflet treatment, etc. (Table 1). SAPIEN 3 can be delivered via the iliofemoral arterial access, apical or ascending aortic access, or subclavian/axillary access. Different delivery systems are available for the transfemoral or trans-subclavian/axillary approach and for the transapical or transaortic approach.

(A) Bioprosthetic valve (model 9600TFX)

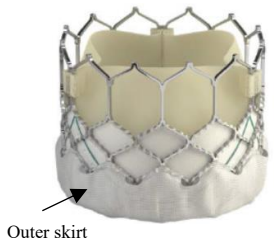
(B) Delivery system (transfemoral or trans-subclavian/axillary approach)



(C) Sheath (transfemoral or trans-subclavian/axillary approach)

Figure 1. Exterior appearance of the main components of SAPIEN 3

Table 1. Type of bioprosthetic valve of SAPIEN 3

Model No.	9600TFX	9750TFX	9755RSL
Exterior appearance	 Outer skirt		
Size	20/23/26/29 mm	20/23/26 mm	20/23/26/29 mm
Approach	Transfemoral or trans-subclavian/axillary Transapical or transaortic	Transfemoral or trans-subclavian/axillary Transapical or transaortic	Transfemoral or trans-subclavian/axillary
Outer skirt	Woven fabric	Knitted fabric	Knitted fabric
Leaflet treatment	ThermaFix	ThermaFix	RESILIA
Sterilization	Glutaraldehyde	Glutaraldehyde	Ethylene oxide

SAPIEN 3 is already approved as a medical device used for transcatheter aortic valve replacement (TAVR) or transcatheter pulmonary valve replacement. SAPIEN 3, as a medical device for TAVR, is

indicated for the treatment of (1) “patients with severe symptomatic aortic valve stenosis attributed to degenerative calcification of the native aortic valve cusp of which treatment with SAPIEN 3 is considered as their best therapeutic option (or chronic dialysis patients who are not eligible for surgery and of which treatment with SAPIEN 3 is considered as their best therapeutic option)” and (2) “patients with symptomatic valvular disease due to failing (stenosed, insufficient, or combined) of a surgical bioprosthetic aortic valve who are not eligible for surgery and of which treatment with SAPIEN 3 is considered as their best therapeutic option.” This application for partial change (“the partial change application”) was submitted to add the indication “treatment for patients with symptomatic valvular disease due to failing (stenosed, insufficient, or combined) of a transcatheter bioprosthetic aortic valve who are not eligible for surgery and of which treatment with SAPIEN 3 is considered as their best therapeutic option.” SAPIEN 3 is intended to be used in patients having a host transcatheter bioprosthetic aortic valve of SAPIEN 3 or SAPIEN XT (Approval number 22500BZX00270000), a previous generation product of SAPIEN 3, except for the patients who have multiple bioprosthetic valves in the aortic position.

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 with the partial change 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 SAPIEN 3 declared that they did not fall under the Item 5 of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

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

1.A Summary of the data submitted

1.A.(1) History of development

In Japan, more people have severe symptomatic aortic valve stenosis due to degenerative changes as the population ages. Surgical aortic valve replacement (SAVR) to treat aortic valve stenosis requires extracorporeal circulation and general anesthesia. This procedure is associated with high surgical risks, including perioperative death and complications, in elderly patients or have severe preoperative complications or severe cardiopulmonary dysfunction. To address these challenges of SAVR, TAVR, which is less invasive than the surgical approach, was developed as a treatment option for patients with aortic valve stenosis who are not eligible for SAVR because of age, a poor general condition, etc. In Japan, SAPIEN XT, a previous generation product of SAPIEN 3, was approved in 2013. Subsequently, with the aim of reducing the risks of paravalvular regurgitation and vascular complications, SAPIEN 3, having an outer skirt that prevents regurgitation and a smaller delivery system, was developed and approved in 2016.

SAPIEN 3 was also approved in January 2020 for use in transcatheter aortic valve in surgical aortic valve (TAV in SAV), which is a procedure that places a transcatheter aortic valve (TAV) inside a failing surgical bioprosthetic valve in the aortic position. SAPIEN 3 was approved in January 2021 for use in patients on chronic dialysis with severe symptomatic native aortic valve stenosis or symptomatic valvular disease due to failing of a surgical bioprosthetic aortic valve who are not eligible for surgery.

Further, SAPIEN 3 was approved in April 2021 in patients with severe symptomatic native aortic valve stenosis who are eligible for surgery, except for the patients on chronic dialysis.

Many patients with aortic valve stenosis have been treated by TAVR. Similar to surgical bioprosthetic valves implanted through open-heart surgery, transcatheter bioprosthetic valves have limited durability and fail.[1,2] In the early years after its introduction, TAVR was solely used in elderly patients who are not eligible for surgery. For this reason, only limited data are available regarding the long-term durability of TAV.[3,4,5,6] As TAVR becomes popular, more patients will require reintervention due to a failed TAV. Most of these patients are more likely to be at high surgical risk and not eligible for surgical reintervention. Surgical removal of a failed TAV is associated with the risk of aortic root damage because the valve adheres to the surrounding tissue.[7] Surgical intervention due to a failed TAV was associated with a high risk of death; indicating an operative mortality of 17.1% (in-hospital or within 30 days) according to the report by Jawitz et al.[8] and an in-hospital mortality of 11.8% according to the report by Fukuhara et al.[9] For these reasons, there is a growing medical need of treatment by transcatheter aortic valve in transcatheter aortic valve (TAV in TAV), which is a procedure that places a TAV on top of the existing transcatheter bioprosthetic aortic valve at the inner orifice, as an option for non-surgical reintervention.

SAPIEN 3 indicated for use in TAV in TAV received a CE mark in Europe in July 2019 and marketing approval from the Food and Drug Administration (FDA) in September 2020. The introduction of TAV in TAV in clinical practice in Japan has also been demanded as a treatment option, which is the basis of this partial change application.

1.A.(2) Use in and outside Japan

Table 2 shows the information regarding approvals of SAPIEN 3 in the US and Europe. A total of [redacted] SAPIEN 3 bioprosthetic valves were sold worldwide between January 1, 2015 and April 30, 2022.

Table 2. Indications in Europe and the US

Country/ region	Approved/authorized intended use	Time of approval/authorization for TAV in TAV
Europe	1) The Edwards SAPIEN 3 system is indicated for use in patients with heart disease due to native calcific aortic stenosis at any or all levels of surgical risk for open heart surgery. 2) The Edwards SAPIEN 3 system is indicated for use in patients with symptomatic heart disease due to a failing aortic bioprosthetic valve or a failing mitral surgical bioprosthetic valve (stenosed, insufficient, or combined) who are judged by a heart team to be at high or greater risk for open surgical therapy (i.e., predicted risk of surgical mortality ≥ 8% at 30 days, based on the Society of Thoracic Surgeons (STS) risk score and other clinical co-morbidities unmeasured by the STS risk calculator).	July 2019 CE mark (2103732CE01, 2103732DE12)
US	1) The Edwards SAPIEN 3 and SAPIEN 3 Ultra Transcatheter Heart Valve system is indicated for relief of aortic stenosis in patients with symptomatic heart disease due to severe native calcific aortic stenosis who are judged by a Heart Team, including a cardiac surgeon, to be appropriate for the transcatheter heart valve replacement therapy. 2) The Edwards SAPIEN 3 and SAPIEN 3 Ultra Transcatheter Heart Valve system is indicated for patients with symptomatic heart disease due to failing (stenosed, insufficient, or combined) of a surgical or transcatheter bioprosthetic aortic valve, a surgical bioprosthetic mitral valve, or a native mitral valve with an annuloplasty ring who are judged by a heart team, including a cardiac surgeon, to be at high or greater risk for open surgical therapy (i.e., predicted risk of surgical mortality ≥ 8% at 30 days, based on the Society of Thoracic Surgeons (STS) risk score and other clinical co-morbidities unmeasured by the STS risk calculator).	September 2020 PMA (P140031/S112)

1.A.(3) Malfunctions and adverse events in and outside Japan

Tables 3 to 10 show malfunctions of the key components of SAPIEN 3 reported between January 1, 2015, and April 30, 2022. The bioprosthetic valve model 9755RSL has not been sold either in or outside Japan as of July 2022.

Table 3. Common adverse events and malfunctions in and outside Japan (bioprosthetic valve model 9600TFX)

	Bioprosthetic valve [number of events (%)]				
Adverse event/malfunction	**20 mm**	**23 mm**	**26 mm**	**29 mm**	**Unknown**
Common adverse events					
Cardiac conduction disorder (heart block)	[redacted] (0.35)	[redacted] (0.61)	[redacted] (0.35)	[redacted] (0.23)	[redacted] (0.03)
Annulus rupture/dissociation	[redacted] (0.04)	[redacted] (0.07)	[redacted] (0.10)	[redacted] (0.14)	[redacted] (0.00)
Cerebrovascular disorder/stroke	[redacted] (0.09)	[redacted] (0.15)	[redacted] (0.08)	[redacted] (0.05)	[redacted] (0.01)
Coronary artery occlusion/thrombus	[redacted] (0.07)	[redacted] (0.10)	[redacted] (0.05)	[redacted] (0.03)	[redacted] (0.00)
Death (unknown cause)	[redacted] (0.09)	[redacted] (0.09)	[redacted] (0.05)	[redacted] (0.03)	[redacted] (0.01)
Endocarditis	[redacted] (0.06)	[redacted] (0.07)	[redacted] (0.05)	[redacted] (0.05)	[redacted] (0.00)
Bioprosthetic valve thrombus	[redacted] (0.07)	[redacted] (0.07)	[redacted] (0.04)	[redacted] (0.02)	[redacted] (0.00)
Wrong implantation site	[redacted] (0.04)	[redacted] (0.03)	[redacted] (0.04)	[redacted] (0.04)	[redacted] (0.00)
Common malfunctions					
Regurgitation	[redacted] (0.43)	[redacted] (0.23)	[redacted] (0.18)	[redacted] (0.23)	[redacted] (0.01)
Abnormal placement	[redacted] (0.22)	[redacted] (0.13)	[redacted] (0.10)	[redacted] (0.11)	[redacted] (0.00)
Damage/incorrect display of temperature indicator	[redacted] (0.15)	[redacted] (0.09)	[redacted] (0.09)	[redacted] (0.07)	[redacted] (0.00)
Embolus	[redacted] (0.05)	[redacted] (0.06)	[redacted] (0.07)	[redacted] (0.10)	[redacted] (0.00)
Increased pressure gradient	[redacted] (0.11)	[redacted] (0.07)	[redacted] (0.03)	[redacted] (0.02)	[redacted] (0.00)
Leaflet malfunction (Inside patients)	[redacted] (0.05)	[redacted] (0.04)	[redacted] (0.03)	[redacted] (0.03)	[redacted] (0.00)
Stenosis	[redacted] (0.09)	[redacted] (0.04)	[redacted] (0.02)	[redacted] (0.02)	[redacted] (0.00)
Difficulty in crimping	[redacted] (0.08)	[redacted] (0.04)	[redacted] (0.02)	[redacted] (0.01)	[redacted] (0.00)

* Malfunctions with an incidence of ≥0.05%. N = [redacted]

Table 4. Common adverse events and malfunctions in and outside Japan (bioprosthetic valve model 9750TFX)

Bioprosthetic valve [number of events (%)]					
Adverse event/malfunction	**20 mm**	**23 mm**	**26 mm**	**29 mm**	**Unknown**
Common adverse events					
Cardiac conduction disorder (heart block)	(0.01)	(0.05)	(0.05)	(0.00)	(0.00)
Wrong implantation site	(0.01)	(0.05)	(0.04)	(0.00)	(0.00)
Annulus rupture/dissociation	(0.01)	(0.02)	(0.05)	(0.08)	(0.00)
Coronary artery occlusion/thrombus	(0.05)	(0.02)	(0.01)	(0.00)	(0.00)
Common malfunctions					
Valve damage	(0.06)	(0.12)	(0.34)	(0.00)	(0.00)
Embolus	(0.06)	(0.13)	(0.13)	(0.00)	(0.00)
Regurgitation	(0.23)	(0.10)	(0.10)	(0.04)	(0.00)
Difficulty in crimping	(0.16)	(0.11)	(0.02)	(0.00)	(0.00)
Abnormal placement	(0.03)	(0.05)	(0.06)	(0.00)	(0.00)
Increased pressure gradient	(0.14)	(0.06)	(0.02)	(0.00)	(0.00)
Event related to leaflet contact during preparation	(0.08)	(0.03)	(0.01)	(0.00)	(0.00)

* Malfunctions with an incidence of ≥0.05%. N = [redacted]

Table 5. Common adverse events and malfunctions in and outside Japan (transfemoral delivery system)

Transfemoral delivery system [number of events (%)]					
Adverse event/malfunction	**20 mm**	**23 mm**	**26 mm**	**29 mm**	**Unknown**
Common adverse events					
Vascular/access site-related complication	(0.03)	(0.05)	(0.05)	(0.07)	(0.00)
Ventricular/cardiac perforation	(0.05)	(0.04)	(0.02)	(0.02)	(0.00)
Common malfunctions					
Difficulty in removal	(0.04)	(0.06)	(0.15)	(0.21)	(0.00)
Balloon rupture	(0.07)	(0.08)	(0.13)	(0.14)	(0.00)
Damage	(0.04)	(0.06)	(0.12)	(0.18)	(0.00)
Difficulty in valve alignment	(0.02)	(0.04)	(0.05)	(0.16)	(0.00)
Leak	(0.02)	(0.05)	(0.06)	(0.08)	(0.00)
Valve dislocation on balloon	(0.03)	(0.05)	(0.06)	(0.08)	(0.00)
Difficulty in preparation	(0.05)	(0.06)	(0.07)	(0.04)	(0.00)
Difficulty in fine adjustment	(0.02)	(0.03)	(0.04)	(0.12)	(0.00)
Separation	(0.01)	(0.01)	(0.05)	(0.04)	(0.00)

* Malfunctions with an incidence of ≥0.05%. N = [redacted] (including trans-subclavian/axillary system)

Table 6. Common adverse events and malfunctions in and outside Japan (transfemoral balloon catheter)

Transfemoral balloon catheter [number of events (%)]					
Adverse event/malfunction	**20 mm**	**23 mm**	**26 mm**	**29 mm**	**Unknown**
Common adverse events					
Cardiac conduction disorder (heart block)	(0.06)	(0.03)	(0.02)	(0.01)	(0.00)

* Malfunctions with an incidence of ≥0.05%. N = [redacted] (including trans-subclavian/axillary system)

Table 7. Common adverse events and malfunctions in and outside Japan (transfemoral introducer sheath set, model 914ES/916ES/9610ES14/9610ES16)

Transfemoral introducer sheath set [number of events (%)]			
Adverse event/malfunction	**20/23/26 mm**	**29 mm**	**Unknown**
Common adverse events			
Vascular/access site-related complication	(0.13)	(0.14)	(0.02)
Common malfunctions			
Inter-device resistance	(0.25)	(0.23)	(0.00)
Damage	(0.20)	(0.36)	(0.00)
Kink, bend	(0.04)	(0.09)	(0.00)
Difficulty in inserting into patient	(0.04)	(0.05)	(0.00)
Liner detachment	(0.03)	(0.05)	(0.00)

* Malfunctions with an incidence of ≥0.05%. N = [redacted] (including trans-subclavian/axillary system)

Table 8. Common adverse events and malfunctions in and outside Japan (transfemoral introducer sheath set, model 914ESP/916ESP)

Transfemoral introducer sheath set [number of events (%)]			
Adverse event/malfunction	**20/23/26 mm**	**29 mm**	**Unknown**
Common malfunctions			
Inter-device resistance	[redacted] (0.46)	[redacted] (0.27)	[redacted] (0.00)
Damage	[redacted] (0.42)	[redacted] (0.32)	[redacted] (0.00)
Kink, bend	[redacted] (0.09)	[redacted] (0.05)	[redacted] (0.00)
Difficulty in inserting into patient	[redacted] (0.09)	[redacted] (0.14)	[redacted] (0.00)

* Malfunctions with an incidence of ≥0.05%. N = [redacted] (including trans-subclavian/axillary system)

Table 9. Common adverse events and malfunctions in and outside Japan (transapical or transaortic delivery system)

Transapical or transaortic delivery system [number of events (%)]					
Adverse event/malfunction	**20 mm**	**23 mm**	**26 mm**	**29 mm**	**Unknown**
Common malfunctions					
Inter-device resistance	[redacted] (0.04)	[redacted] (0.19)	[redacted] (0.40)	[redacted] (0.18)	[redacted] (0.00)
Balloon rupture	[redacted] (0.17)	[redacted] (0.21)	[redacted] (0.25)	[redacted] (0.12)	[redacted] (0.00)
Difficulty in removal	[redacted] (0.09)	[redacted] (0.10)	[redacted] (0.16)	[redacted] (0.10)	[redacted] (0.00)
Valve dislocation on balloon	[redacted] (0.04)	[redacted] (0.05)	[redacted] (0.10)	[redacted] (0.16)	[redacted] (0.00)
Difficulty in passing through placement site	[redacted] (0.00)	[redacted] (0.09)	[redacted] (0.06)	[redacted] (0.09)	[redacted] (0.00)
Separation	[redacted] (0.09)	[redacted] (0.04)	[redacted] (0.08)	[redacted] (0.06)	[redacted] (0.00)
Kink, bend	[redacted] (0.00)	[redacted] (0.03)	[redacted] (0.05)	[redacted] (0.03)	[redacted] (0.00)
Difficulty in preparation	[redacted] (0.00)	[redacted] (0.07)	[redacted] (0.04)	[redacted] (0.01)	[redacted] (0.00)

* Malfunctions with an incidence of ≥0.05%. N = [redacted]

Table 10. Common adverse events and malfunctions in and outside Japan (transapical or transaortic introducer sheath set)

Transapical or transaortic introducer sheath set [number of events (%)]		
Adverse event/malfunction	**20/23/26 mm**	**29 mm**
Common adverse events		
Access site-related complication	[redacted] (0.05)	[redacted] (0.04)

* Malfunctions with an incidence of ≥0.05%. N = [redacted]

1.B Outline of the review conducted by PMDA

PMDA asked the applicant to explain whether any malfunctions or adverse events related to TAV in TAV occurred in foreign countries and whether any corrective measures were taken to address problems.

The applicant's explanation:

Reported malfunctions and adverse events associated with valve in valve, including TAV in SAV, TAV in TAV, and TAV in TAV implemented as a bailout of first TAVR, with SAPIEN 3 in the aortic position were common to TAVR and TAV in SAV in native valves. No issue specific to TAV in TAV has been identified. As sufficient risk mitigation measures are thought to exist already, no corrective measure has been taken as of the time of this application.

This partial change application includes no change in the current components of SAPIEN 3. Neither an adverse event nor a malfunction having a substantially high incidence has been reported. No issue specific to TAV in TAV has been identified. On the basis of the applicant's explanations, PMDA concluded that there is no particular problem at this point.

2. Design and Development

2.(1) Performance and safety specifications

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

This partial change application included no change in the current performance and safety specifications of SAPIEN 3. The applicant proposed to use the current performance and safety specifications.

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

PMDA concluded that the current performance and safety specifications of SAPIEN 3 can be used.

2.(2) Physicochemical properties

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

To support the physicochemical properties of SAPIEN 3, the applicant submitted the results of a finite element analysis of frame fatigue, dimension test of the bioprosthetic valve, and migration test, all of which were conducted taking into consideration the possibility of performing TAV in TAV with SAPIEN 3 in patients with SAPIEN 3 TAV or "SAPIEN XT" TAV. No issue was identified in the physicochemical properties of SAPIEN 3. The frame fatigue testing was [redacted]. No additional test was determined to be necessary. There is no galvanic corrosion risk because no dissimilar metal contact would occur during TAV in TAV with SAPIEN 3 in patients with SAPIEN 3 TAV or "SAPIEN XT" TAV. For this reason, no galvanic corrosion test was determined to be necessary. Magnetic resonance imaging (MRI) compatibility testing was [redacted]. No additional test was determined to be necessary. Balloon inflation/burst pressure testing was [redacted]. No additional test was determined to be necessary.

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

PMDA reviewed the data on the physicochemical properties and concluded that there was no particular problem.

2.(3) Biological safety

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

The applicant determined that no additional study for biological safety was necessary because this partial change application includes no change in the current components of SAPIEN 3 and the environment (contact site and duration) to which the device is exposed is similar to that in implantation in a native valve or TAV in SAV. Accordingly, the applicant did not submit data supporting the biological safety of SAPIEN 3.

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

PMDA concluded that no data supporting the biological safety are required.

2.(4) Stability and durability

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

The applicant determined that no additional stability study was necessary because this partial change application includes no change in the current components of SAPIEN 3.

The applicant also determined that no new durability study was necessary because the historical durability data of SAPIEN 3 in TAV in SAV can be applied to SAPIEN 3 in TAV in TAV.

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

PMDA concluded that no data supporting the stability and durability are required.

2.(5) Performance

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

To support the performance of SAPIEN 3, the applicant submitted the results of a pulsatile flow test and a computational fluid analysis, all of which were conducted taking into consideration the possibility of performing TAV in TAV with SAPIEN 3 in patients with SAPIEN 3 TAV or "SAPIEN XT" TAV. The pulsatile flow test demonstrated that the effective orifice area and the regurgitation rate met their acceptance criteria in all size combinations. The computational fluid analysis showed no significant difference in the flow velocity distribution between TAV alone and TAV in TAV.

The applicant determined that no new tests of steady flow pressure gradient, regurgitant leak of steady flow, flow visualization, and [redacted] were necessary for TAV in TAV because the historical test data in TAV in SAV can be applied to TAV in TAV.

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

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

2.(6) Directions for use

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

The applicant submitted the data from a design validation study in TAV in TAV to support the direction for use of SAPIEN 3 as reference data. The direction for use of SAPIEN 3 in TAV in TAV is the same as that in TAVR in a native valve or TAV in SAV. For this reason, the applicant determined that the proposed direction for use could be verified by analyzing the data on the device implant success rate and the incidence of usage-related adverse events in TAV in TAV with SAPIEN 3 in the Transcatheter Valve Therapies Registry (TVT Registry) conducted on the initiative of the Society of Thoracic Surgeons (STS) and the American College of Cardiology (ACC).

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

PMDA reviewed the data supporting the directions for use and concluded that there was no particular problem. PMDA also concluded that this review should include the clinical results described later in Section "6 Clinical Data or Alternative Data Accepted by the Minister of Health, Labour and Welfare."

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

3.B Outline of the review conducted by PMDA

PMDA reviewed the conformity of SAPIEN 3 to the Essential Principles as shown below.

(1) PMDA's view on the conformity of SAPIEN 3 to Article 1, which defines preconditions, etc. for designing medical devices (particularly conditions for users, such as technical knowledge, experience, education, and training for intended users):
As described later in Section "6.B Outline of the review conducted by PMDA," selection of patients eligible for the treatment with SAPIEN 3 and compliance with precautions for the TAV in TAV procedure are important. To this end, users must have appropriate knowledge and skills. An approval condition should be imposed to ensure that necessary measures are taken to train users.

(2) PMDA's view on the conformity of SAPIEN 3 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," the efficacy and safety of SAPIEN 3 should be evaluated in clinical use in Japan. In addition, the eligibility of patients who have received SAPIEN 3 should be verified. On the basis of the results of these evaluations, additional risk mitigation measures should be taken as necessary. PMDA instructed the applicant to conduct a user-results survey.

(3) PMDA's view on the conformity of SAPIEN 3 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 efficacy and safety of SAPIEN 3 have been shown in patients who are not eligible for surgery when the users understood the characteristics of SAPIEN 3 and selected patients eligible for the procedure. SAPIEN 3 conforms to Articles 3 and 6.

(4) PMDA's view on the conformity of SAPIEN 3 to Article 17, which specifies requirements for publicizing information including precautionary advice or the communication of information to users via instructions for use, etc. (precautions and other information):
As described later in Section "6.B Outline of the review conducted by PMDA," it is essential for users to fully understand the risks of SAPIEN 3, select patients eligible for the treatment with SAPIEN 3, and use SAPIEN 3 properly in order to maintain its risk-benefit balance. To this end,

information should be provided through precautions and other information, proper use statements, training, and other measures.

PMDA comprehensively reviewed the conformity of SAPIEN 3 to the Essential Principles and concluded that there was no particular problem.

4. Risk Management

4.A Summary of the data submitted

The applicant submitted data summarizing the risk management system and risk management activities implemented for SAPIEN 3 in accordance with ISO 14971 "Medical devices – Application of risk management to medical devices."

4.B Outline of the review conducted by PMDA

PMDA comprehensively reviewed the document on risk management taking into account the discussion presented in Section "3.B Outline of the review conducted by PMDA" and concluded that there was no particular problem.

5. Manufacturing Process

5.A Summary of the data submitted

This partial change application included no change in the manufacturing process or raw materials of animal origin of SAPIEN 3. The applicant did not submit data on the manufacturing process and raw materials of animal origin.

5.B Outline of the review conducted by PMDA

PMDA concluded that no data regarding the manufacturing method are required.

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

6.A Summary of the data submitted

The applicant submitted the clinical data from patients who underwent TAV in TAV with SAPIEN 3 in the TVT Registry conducted on the initiative of the Society of Thoracic Surgeons (STS) and the American College of Cardiology (ACC).

The TVT Registry was initiated in the US in December 2011 to collect real-world clinical data on the safety and efficacy of TAVR in order to ensure the proper use of the device and optimize treatment of each patient, as well as to open the way to future expansion in the indication of TAVR. The FDA, Centers for Medicare & Medicaid Services, and Duke Clinical Research Institute also collaborate with this Registry. In the US, SAPIEN 3 received an FDA clearance in September 2020 on the basis of the clinical results of TAV in TAV with SAPIEN 3 in the TVT Registry (data extracted on August 9, 2019). The present partial change application in Japan is based on the updated results of the TVT Registry (data extracted on [redacted], 20[redacted]). A summary of Section "6.A.(1) Results of TAV in TAV with SAPIEN 3 in the TVT Registry" and Section "6.A.(2) Results in the proposed target population in Japan among the patients described in (1)" is presented below.

6.A.(1) Results of TAV in TAV with SAPIEN 3 in the TVT Registry

Table 11 shows a summary of the results of TAV in TAV with SAPIEN 3 in the TVT Registry.

Table 11. Summary of results of TAV in TAV with SAPIEN 3 in the TVT Registry

Item	Description
Type of study	Prospective, multicenter, registry research
Analysis population	Patients who underwent TAV in TAV which implanted SAPIEN 3 in a failed transcatheter bioprosthetic aortic valve, except for patients who had multiple bioprosthetic valves in the aortic position
Number of patients analyzed	587 Model 9600TFX: 529 Model 9750TFX: 58
Registration period	Date of first procedure: [redacted], 20[redacted] Date of final procedure: [redacted], 20[redacted]
Follow-up period	1 year after procedure
Date of data extraction	[redacted], 20[redacted]
Endpoints	Safety endpoints • Mortality • Incidence of adverse events Efficacy endpoints • Echocardiographic parameters ➢ Aortic regurgitation ➢ Paravalvular regurgitation ➢ Mean pressure gradient ➢ Left ventricular ejection fraction • NYHA functional classification • Admission period • QOL measured by KCCQ
Number of study sites	238 study sites across the US

Figure 2 shows the analysis population. A total of 647 patients underwent TAV in TAV with SAPIEN 3 at 238 study sites in the US between [redacted], 20[redacted] and [redacted], 20[redacted]. The data collected in the TVT Registry include the model numbers of previously implanted TAVs (hereinafter referred to as "host valves") in patients who underwent TAV in TAV with SAPIEN 3. However, this information is deleted when the data are transferred to the applicant. The applicant can identify whether the host valve was one of the applicant's products by cross-checking the data set of patients who underwent their first TAVR with one of the applicant's products as provided by the TVT Registry against the data set of patients who underwent TAV in TAV with SAPIEN 3. The host valves used in the analysis population include SAPIEN series and valves manufactured by other companies. Of 647 patients, 18 patients had their host valves implanted before the first patient underwent TAVR in the PARTNER-US study conducted in the US ([redacted], 20[redacted]) or on an unknown date. These patients were excluded from the analysis because there is no information that assures the proper use of SAPIEN 3. For 42 patients who received multiple bioprosthetic valves in the aortic position, including those who underwent TAV in TAV in TAV or TAV in TAV in SAV, these patients were also excluded from the analysis. The attempted implant (AI) population consisted of all 587 patients who were included in the analysis. The valve implant (VI) population consisted of 584 patients, excluding 3 patients for whom the implant procedure started but was converted to SAVR from the AI population. A total of 479 patients (89.0%) completed the visit within the 30-day follow-up window. A total of 250 patients (66.5%) completed the visit within the 1-year follow-up window.

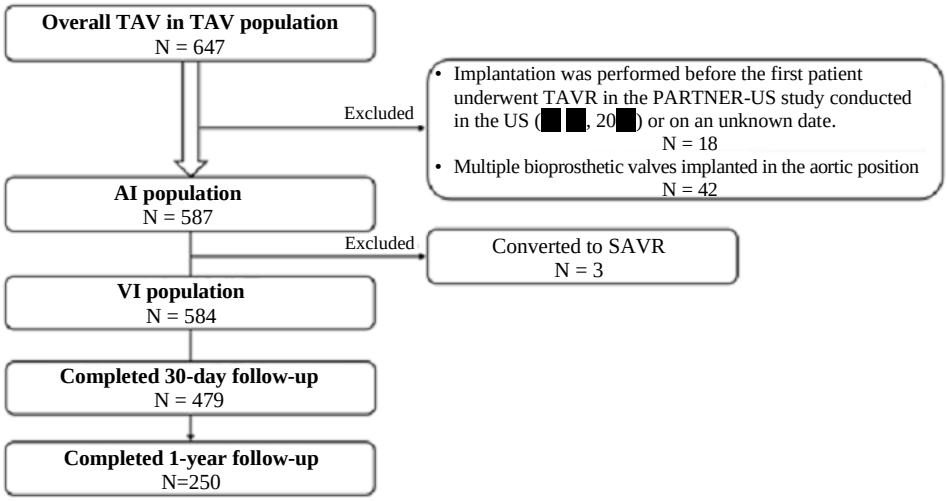


Figure 2. Analysis population

Table 12 shows the patient disposition at each follow-up visit up to 1 year in the AI population. A total of 376 patients were eligible for the 1-year visit. Of them, 66.5% (250 of 376) of patients completed the visit within the 1-year follow-up window. A total of 211 patients were withdrawn from the survey or had a visit not yet due (patients have not reached the follow-up visit window or patients have reached the visit window but have not completed the follow-up visit yet) by the time of the database extract; including visit not yet due in 96 patients, death in 77 patients, consent withdrawal in 6 patients, and lost to follow-up in 32 patients.

Table 12. Patient disposition at each follow-up visit up to 1 year (AI population)

Item	30 days	1 year
All follow-up patients	538	376
Follow-up visit completed within the defined window[1]	479 (89.0%)	250 (66.5%)
Follow-up visit completed outside of the defined window	59 (11.0%)	126 (33.5%)
Withdrawal or visit not yet due	49	211
Death before visit	ND	77
Consent withdrawal before visit	ND	6
Lost to follow-up	ND	32
Visit not yet due[2]	ND	96

ND, No Data

[1] The 30-day follow-up visit window was defined as the period between 21 and 75 days post-procedure. The 1-year follow-up visit window was defined as the period between 305 and 425 days post-procedure.

[2] Patients have not reached the follow-up visit window or patients have reached the visit window but have not completed the follow-up visit yet.

Table 13 shows the patient demographics and baseline characteristics in the AI population.

Table 13. Patient demographics and baseline characteristics (AI population)

Patient demographics and baseline characteristics	Summary statistics*
Age (years)	78.5 ± 9.7 (587)
Sex	
Male	55.2% (324/587)
Female	44.8% (263/587)
Race/ethnicity	
Caucasian	92.2% (541/587)
Black or African American	5.5% (32/587)
Asian	0.9% (5/587)
Other or unknown	1.5% (9/587)
STS score (%)	8.8 ± 7.6 (529)
NYHA class	
Class I/II	18.2% (106/581)
Class III/IV	81.8% (475/581)
Previous myocardial infarction	25.7% (151/587)
Prior intervention	
Coronary artery bypass	24.0% (141/587)
Percutaneous transluminal coronary angioplasty	34.6% (203/586)
Prior aortic valvuloplasty	11.8% (69/587)
Cerebrovascular disorder	15.2% (89/587)
Peripheral vascular disease	29.6% (173/585)
Atrial fibrillation/flutter	46.0% (270/587)
Permanent pacemaker	29.4% (172/585)
Circumferential aortic calcification	6.0% (35/586)
Chest deformity	7.7% (45/587)
Echocardiographic findings	
Valve area (cm^2)	1.0 ± 0.5 (308)
Mean pressure gradient (mmHg)	33.4 ± 19.7 (345)
Left ventricular ejection fraction (%)	51.0 ± 14.4 (582)
Moderate or severe aortic regurgitation	73.5% (431/586)
Moderate or severe mitral regurgitation	39.4% (204/518)

* Continuous variables are presented as mean ± standard deviation (SD) (number of patients). Categorical variables are presented as % (n/total number). The total number only counted the patients with valid data.

6.A.(1).1) Procedure information

Table 14 shows the procedure information in the AI population. Approximately 80% of patients who underwent TAV in TAV with SAPIEN 3 were inoperable, or at extreme or high risk for surgery. The most common delivery approach was transfemoral, which was used in 94.4% (554 of 587) of patients. The model of the biosynthetic valve implanted was 9600TFX in 90.1% (529 of 587) of patients and 9750TFX in 9.9% (58 of 587) of patients. The most common size of the valve was 23 mm in 35.4% (208 of 587) of patients, followed by 26 mm in 33.9% (199 of 587) of patients, 29 mm in 26.9% (158 of 587) of patients, and 20 mm in 3.7% (22 of 587) of patients. There was no aborted procedure, while 0.5% (3 of 587) of patients were converted to SAVR because of ventricle rupture in 1 patient, aortic annulus rupture in 1 patient, and other (details unknown) in 1 patient.

Table 14. Procedure information (AI population)

Item	Summary statistics*
Surgical risk	
Inoperable/extreme risk	16.6% (96/579)
High risk	62.2% (360/579)
Moderate risk	18.1% (105/579)
Low risk	3.1% (18/579)
Implant approach	
Transfemoral	94.4% (554/587)
Transapical	1.0% (6/587)
Transaortic	0.5% (3/587)
Trans-subclavian/axillary	2.0% (12/587)
Transiliac	0.2% (1/587)
Transseptal	0.2% (1/587)
Transcarotid	0.9% (5/587)
Other	0.5% (3/587)
Valve model implanted	
9600TFX	90.1% (529/587)
9750TFX	9.9% (58/587)
Size of valve implanted	
20 mm	3.7% (22/587)
23 mm	35.4% (208/587)
26 mm	33.9% (199/587)
29 mm	26.9% (158/587)
Cardiopulmonary bypass	0.9% (5/586)
Cardiopulmonary bypass status	
Elective	40.0% (2/5)
Emergent	60.0% (3/5)
Cardiopulmonary bypass Time (min)	101.0 ± 40.7 (5)
Type of anesthesia	
General anesthesia	60.6% (355/586)
Conscious sedation	38.9% (228/586)
Combination	0.5% (3/586)
Procedure time (min)	104.6 ± 2.8 (587)
Device implanted successfully[1]	99.0% (581/587)
Procedure aborted	0.0% (0/587)
Conversion to SAVR	0.5% (3/587)
Ventricle rupture	1
Aortic annulus rupture	1
Other	1
Mechanical assist device in place at start of procedure	0.7% (4/586)
Intra-aortic balloon pump	2
Catheter based assist device	2

* Continuous variables are presented as mean ± SD (number of patients). Categorical variables are presented as % (n/total number). The total number only counted the patients with valid data.

[1] Device implanted successfully was defined as placement of a bioprosthetic valve in an intended site without requiring more than 1 valve.

6.A.(1).2) Safety endpoints

6.A.(1).2).(a) Death

Table 15 shows the mortality up to 1 year in the AI population. A total of 28 patients died within 30 days and 69 patients died within 1 year. The Kaplan-Meier estimate of death was 5.0% at 30 days and 17.0% at 1 year. The causes of death in 69 patients who died within 1 year were cardiac disease other than valve disease in 19 patients, neurological disease in 4 patients, renal disease in 4 patients, infection in 3 patients, respiratory disease in 4 patients, vascular disease in 1 patient, valve disease in 1 patient, others in 9 patients, and unknown in 24 patients.

Table 15. Mortality up to 1 year (AI population)

Item	Kaplan-Meier estimate[1]	
	30 days (Patients at risk = 467)	1 year (Patients at risk = 191)
Death	5.0% (28)	17.0% (69)

[1] The Kaplan-Meier estimates up to 30 days and 1 year using the time to the first event in each patient. The figures in parentheses represent the number of patients with event.

6.A.(1).2).(b) Incidence of site-reported adverse events

Table 16 shows the incidence of adverse events in the AI population reported by each study site up to 1 year. The most common site-reported adverse event up to 1 year was non-valve related readmission, the Kaplan-Meier estimate of which was 29.9%, followed by conduction disorder requiring pacemaker implantation with a Kaplan-Meier estimate of 9.2%, valve-related readmission with a Kaplan-Meier estimate of 5.2%, and unplanned other cardiac surgery or intervention with a Kaplan-Meier estimate of 3.5%. The Kaplan-Meier estimates of other site-reported adverse events at 1 year were 2.7% for stroke, 1.7% for aortic valve reintervention, 1.5% for transient ischaemic attack, 0.5% for valve thrombosis, and 0.5% for coronary artery occlusion or coronary artery compression.

Table 16. Incidence of site-reported adverse events up to 1 year (AI population)

Item	Kaplan-Meier estimate[1]	
	30 days	1 year
Non-valve related readmission	6.2% (34, 32)	29.9% (143, 107)
Conduction disorder requiring pacemaker implantation	6.9% (39, 39)	9.2% (46, 46)
Valve-related readmission	0.9% (5, 5)	5.2% (21, 18)
Unplanned other cardiac surgery/intervention	2.0% (11, 11)	3.5% (15, 15)
Unplanned vascular surgery/intervention	2.0% (12, 12)	3.2% (16, 16)
Minor vascular complication	3.1% (18, 18)	3.1% (18, 18)
Cardiac arrest	2.9% (17, 17)	2.9% (17, 17)
All stroke	2.5% (14, 14)	2.7% (15, 15)
Severe haemorrhage	0.9% (5, 5)	2.6% (12, 10)
Other haemorrhage	2.5% (14, 14)	2.5% (14, 14)
Ischaemic stroke	2.1% (12, 12)	2.3% (13, 13)
Myocardial infarction	0.7% (5, 4)	2.3% (9, 8)
Percutaneous coronary intervention	0.9% (5, 5)	2.1% (9, 9)
New requirement for dialysis	0.5% (3, 3)	2.0% (7, 7)
Aortic valve reintervention	0.7% (4, 4)	1.7% (7, 7)
Haematoma at access site	1.6% (9, 9)	1.6% (9, 9)
Conduction disorder requiring implantable cardioverter defibrillator (ICD)	0.6% (3, 3)	1.5% (6, 6)
Transient ischaemic attack	0.9% (5, 5)	1.5% (7, 7)
Atrial fibrillation	1.4% (8, 8)	1.4% (8, 8)
Haemorrhage of digestive tract	1.1% (6, 6)	1.1% (6, 6)
Major vascular complication	0.7% (4, 4)	1.0% (5, 5)
Haemorrhage at access site	1.0% (6, 6)	1.0% (6, 6)
Perforation with or without cardiac tamponade	0.7% (4, 4)	0.7% (4, 4)
Valve thrombosis	0.2% (1, 1)	0.5% (2, 2)
Coronary artery occlusion or coronary artery compression	0.5% (3, 3)	0.5% (3, 3)
Ventricle rupture	0.3% (2, 2)	0.3% (2, 2)
Valve removal	0.3% (2, 2)	0.3% (2, 2)
Endocarditis	0.0% (0, 0)	0.3% (2, 1)
Life threatening haemorrhage	0.0% (0, 0)	0.2% (1, 1)
Unknown stroke	0.2% (1, 1)	0.2% (1, 1)
Haemorrhagic stroke	0.2% (1, 1)	0.2% (1, 1)
Urogenital haemorrhage	0.2% (1, 1)	0.2% (1, 1)
Aortic dissection	0.2% (1, 1)	0.2% (1, 1)
Transapical related event	0.2% (1, 1)	0.2% (1, 1)

[1] The Kaplan-Meier estimates up to 30 days and 1 year. The figures in parentheses represent the number of events and the number of patients with event. The time to the first event in each patient was used in the summarization.

6.A.(1).3) Efficacy endpoints

6.A.(1).3).(a) Primary echocardiographic parameters

Table 17 shows the primary echocardiographic parameters at baseline, 30 days, and 1 year in the VI population. Table 18 shows the results by the size of the valve of SAPIEN 3. The mean pressure gradient was 33.5 ± 1.06 mmHg at baseline, 14.5 ± 0.42 mmHg at 30 days, and 13.8 ± 0.61 mmHg at 1 year, showing improvements in hemodynamics after TAV in TAV with SAPIEN 3. The mean pressure gradient exceeded 20 mmHg in 67.9% (233 of 343) of patients at baseline, which decreased to 18.5% (69 of 373) of patients at 30 days and 19.7% (28 of 142) of patients at 1 year.

Table 17. Primary echocardiographic parameters (VI population)

Endpoints	Summary statistics*		
	Baseline	30 days	1 year
Mean pressure gradient (mmHg)	33.5 ± 1.06 (343)	14.5 ± 0.42 (373)	13.8 ± 0.61 (142)
Valve area (cm^2)	1.0 ± 0.03 (306)	NA	NA
Left ventricular ejection fraction (%)	51.0 ± 0.60 (579)	52.1 ± 0.70 (380)	54.2 ± 0.98 (144)
Mean pressure gradient >20 mmHg	67.9% (233/343)	18.5% (69/373)	19.7% (28/142)
Mean pressure gradient >40 mmHg	36.2% (124/343)	1.6% (6/373)	0.0% (0/142)

* Continuous variables are presented as mean ± SD (number of patients). Categorical variables are presented as % (n/total number). The total number only counted the patients with valid data.
NA, Not Applicable. No data regarding the post-operative valve area are collected in the TVT Registry.

Table 18. Echocardiographic parameters by valve size of SAPIEN 3 (VI population)

Endpoints	Summary statistics*			
	20 mm (N = 22)	23 mm (N = 207)	26 mm (N = 199)	29 mm (N = 156)
Baseline				
Mean pressure gradient (mmHg)	36.7 ± 4.42 (18)	39.4 ± 1.54 (157)	30.6 ± 1.80 (109)	22.3 ± 2.24 (59)
Left ventricular ejection fraction (%)	56.7 ± 2.86 (22)	55.5 ± 0.85 (207)	49.9 ± 1.07 (195)	45.6 ± 1.16 (155)
30 days				
Mean pressure gradient (mmHg)	20.7 ± 2.73 (12)	17.2 ± 0.76 (149)	13.9 ± 0.67 (116)	10.2 ± 0.45 (96)
Left ventricular ejection fraction (%)	62.1 ± 1.53 (12)	55.8 ± 0.96 (149)	51.5 ± 1.31 (120)	46.1 ± 1.40 (99)
1 year				
Mean pressure gradient (mmHg)	17.5 ± 2.50 (2)	17.7 ± 1.05 (57)	12.4 ± 0.84 (46)	9.2 ± 0.67 (37)
Left ventricular ejection fraction (%)	60.0 ± 2.00 (2)	58.2 ± 1.23 (57)	53.4 ± 1.90 (46)	48.9 ± 1.91 (39)

* Continuous variables are presented as mean ± SD (number of patients). Categorical variables are presented as % (n/total number). The total number only counted the patients with valid data.

6.A.(1).3).(b) Aortic regurgitation

Figure 3 shows changes in the severity of aortic regurgitation up to 1 year in the VI population. Moderate or severe aortic regurgitation was observed in 73.6% (429 of 583) of patients at baseline, which decreased to 3.4% (13 of 383) of patients at 30 days and 2.8% (4 of 145) of patients at 1 year.

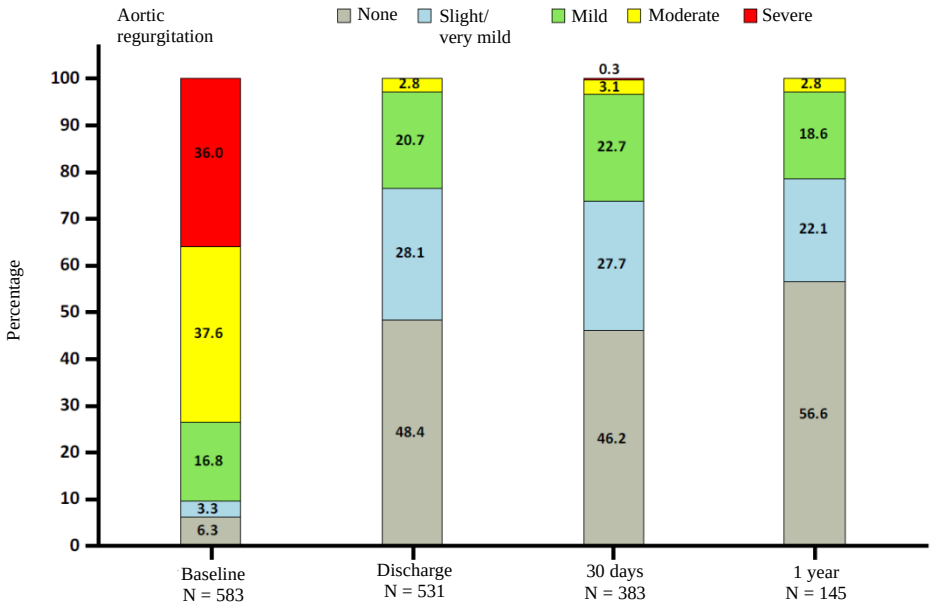


Figure 3. Aortic regurgitation up to 1 year (VI population)

6.A.(1).3).(c) Paravalvular regurgitation

Figure 4 shows changes in the severity of paravalvular regurgitation up to 1 year in the VI population. Moderate or severe paravalvular regurgitation was observed in 2.9% (14 of 485) of patients at discharge, 3.5% (12 of 344) of patients at 30 days, and 1.5% (2 of 131) of patients at 1 year, showing no substantial change.

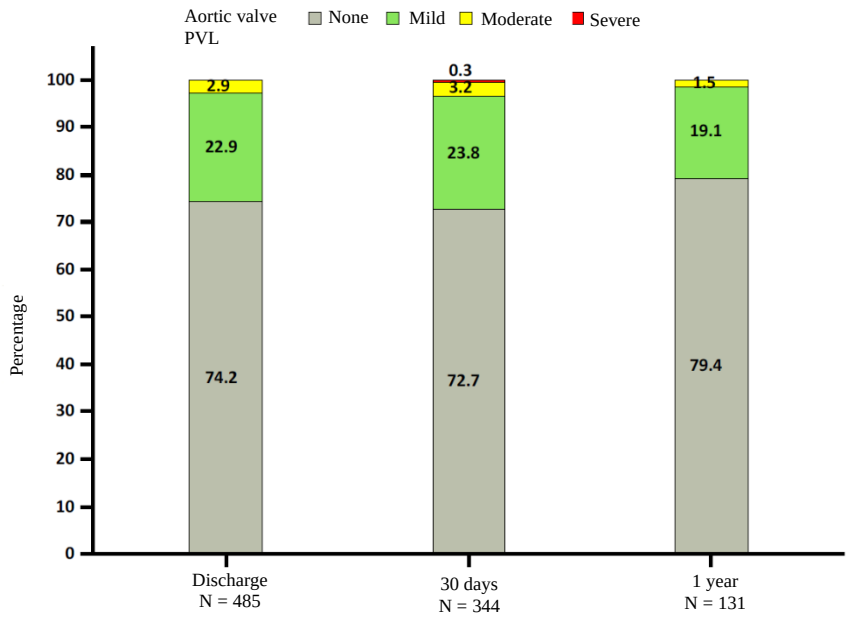


Figure 4. Paravalvular regurgitation up to 1 year (VI population)

6.A.(1).3).(d) New York Heart Association (NYHA) classification

Figure 5 shows NYHA class distributions up to 1 year in the VI population. The NYHA class was Class III or IV in 81.7% (472 of 578) of patients at baseline. The majority of patients (≥85%) had an improved NYHA class to Class I or II after implantation of SAPIEN 3. The NYHA class was Class III in 14.2% (56 of 393) of patients at 30 days and IV in 12.8% (23 of 180) of patients at 1 year.

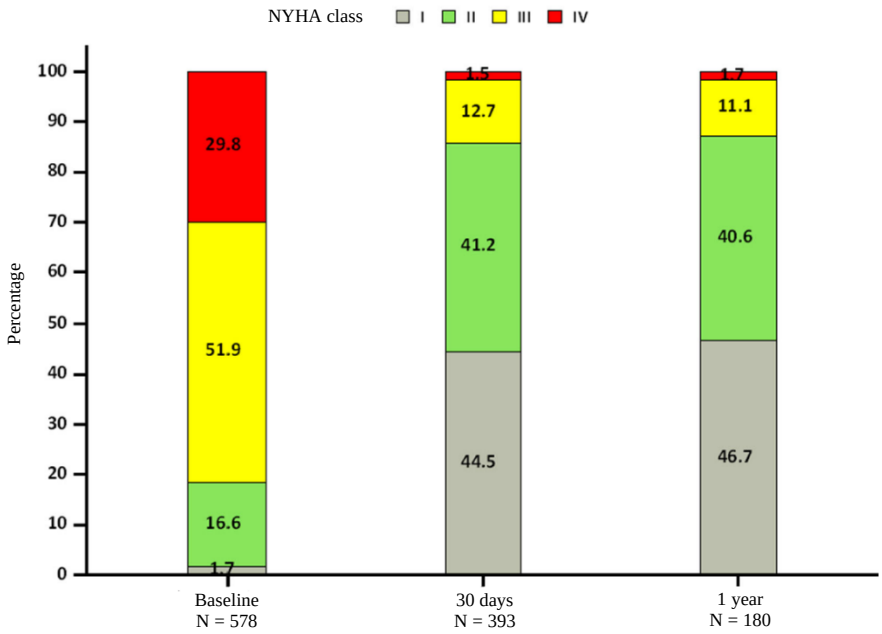


Figure 5. NYHA class distributions (VI population)

6.A.(1).3).(e) Quality of Life (QOL) measured by Kansas City Cardiomyopathy Questionnaire (KCCQ)

The KCCQ score in the VI population improved from 39.1 ± 1.2 (N = 467) at baseline to 70.1 ± 1.3 (N = 368) at 30 days and 73.7 ± 1.8 (N = 167) at 1 year, showing that the improvement was maintained.

6.A.(2) Results in the proposed target population in Japan

Approximately 80% of patients who underwent TAV in TAV with SAPIEN 3 in the TVT Registry were inoperable, or at extreme or high risk for surgery. However, the TVT Registry also included some patients at moderate or low risk. The Guideline on the Management of Valvular Heart Disease[10] in Japan recommends the transcatheter valve-in-valve approach to symptomatic patients at high surgical risk with severe bioprosthetic valve stenosis or regurgitation. The same guideline defines bioprosthetic valve stenosis with a mean pressure gradient of ≥35 mmHg as significant stenosis. In accordance with this guideline, the proposed target population of TAV in TAV with SAPIEN 3 in Japan is defined as patients who are inoperable, or at extreme or high risk for surgery with a mean baseline pressure gradient of ≥35 mmHg or severe aortic regurgitation. Thus, the efficacy and safety of TAV in TAV with SAPIEN 3 were evaluated in this patient population.

The host valves included in this partial change application are either SAPIEN 3 or "SAPIEN XT." The TVT Registry provides information to verify whether the host valves in patients are the applicant's product. Thus, patients who had a SAPIEN series host valve were extracted from patients who met the definition of the proposed target population of SAPIEN 3 in Japan to evaluate its efficacy and safety. A total of 276 patients, who met the definition of the proposed target population in Japan, were extracted from patients who were registered in the TVT Registry and underwent TAV in TAV. Table 19 shows the results in 116 patients with a SAPIEN series host valve and patients in the overall population who underwent TAV in TAV (N = 587).

Table 19. Results in the proposed target population in Japan

Item	Proposed target population in Japan		TVT Registry TAV in TAV Overall population (N = 587)
	All valves (N = 276)	SAPIEN series (N = 116)	
Patient demographics and baseline characteristics			
Age (years)	78.6 ± 10.47 (276)	78.7 ± 10.21 (116)	78.5 ± 9.7 (587)
Female %	53.3% (147/276)	68.1% (79/116)	44.8% (263/587)
STS score (%)	11.2 ± 9.06 (251)	12.4 ± 11.51 (106)	8.8 ± 7.6 (529)
NYHA class III/IV	86.4% (236/273)	81.7% (94/115)	81.8% (475/581)
Mean pressure gradient (mmHg)	43.0 ± 1.34 (175)	45.7 ± 1.74 (83)	33.4 ± 19.7 (345)
Moderate or severe aortic regurgitation	75.9% (208/274)	75.0% (87/116)	73.5% (431/586)
Left ventricular ejection fraction (%)	50.1 ± 0.90 (272)	51.3 ± 1.32 (116)	51.0 ± 14.4 (582)
Procedure information			
Procedure time (min)	109.5 ± 4.19 (276)	101.6 ± 4.76 (116)	104.6 ± 2.8 (587)
Device implanted successfully[1]	98.9% (273/276)	98.3% (114/116)	99.0% (581/587)
Conversion to SAVR	0.4% (1/276)	0.0% (0/116)	0.5% (3/587)
Key results at 30 days			
Kaplan-Meier estimate of common adverse events[2]			
Death	6.5% (17, 17)	8.9% (10, 10)	5.0% (28,28)
Aortic valve reintervention	0.4% (1, 1)	0.9% (1, 1)	0.7% (4, 4)
Conduction disorder requiring pacemaker implantation	9.1% (24, 24)	7.3% (8, 8)	6.9% (39, 39)
Myocardial infarction	1.2% (4, 3)	1.9% (3, 2)	0.7% (5, 4)
Stroke	4.9% (13, 13)	4.4% (5, 5)	2.5% (14, 14)
Transient ischaemic attack	1.1% (3, 3)	1.8% (2, 2)	0.9% (5, 5)
Valve-related readmission	0.4% (1, 1)	1.0% (1, 1)	0.9% (5, 5)
Severe haemorrhage	2.0% (5, 5)	1.0% (1, 1)	0.9% (5, 5)
Major vascular complication	1.5% (4, 4)	2.6% (3, 3)	0.7% (4, 4)
Valve thrombosis	0.4% (1, 1)	0.0% (0, 0)	0.2% (1, 1)
NYHA class III/IV	16.1% (30/186)	15.0% (12/80)	14.2% (56/393)
Improvement in NYHA class from baseline	83.8% (155/185)	83.5% (66/79)	80.1% (313/391)
Mean pressure gradient (mmHg)	15.0 ± 0.63 (183)	16.5 ± 0.80 (82)	14.5 ± 0.42 (373)
Moderate or severe aortic regurgitation	2.7% (5/187)	1.2% (1/82)	3.4% (13/383)
Key results at 1 year			
Kaplan-Meier estimate of common adverse events[2]			
Death	18.8% (37, 37)	23.0% (20, 20)	17.0% (69,69)
Aortic valve reintervention	2.6% (4, 4)	0.9% (1, 1)	1.7% (7, 7)
Conduction disorder requiring pacemaker implantation	11.3% (27, 27)	9.1% (9, 9)	9.2% (46, 46)
Myocardial infarction	1.9% (5, 4)	1.9% (3, 2)	2.3% (9, 8)
Stroke	5.3% (14, 14)	4.4% (5, 5)	2.7% (15, 15)
Transient ischaemic attack	1.9% (4, 4)	1.8% (2, 2)	1.5% (7, 7)
Valve-related readmission	6.2% (10, 9)	1.0% (2, 1)	5.2% (21, 18)
Severe haemorrhage	3.4% (8, 7)	2.5% (2, 2)	2.6% (12, 10)
Major vascular complication	1.5% (4, 4)	2.6% (3, 3)	1.0% (5, 5)
Valve thrombosis	1.1% (2, 2)	0.0% (0, 0)	0.5% (2, 2)
NYHA class III/IV	12.8% (10/78)	13.3% (4/30)	12.8% (23/180)
Improvement in NYHA class from baseline	87.0% (67/77)	86.2% (25/29)	77.5% (138/178)
Mean pressure gradient (mmHg)	14.7 ± 0.99 (67)	18.1 ± 1.48 (30)	13.8 ± 0.61 (142)
Moderate or severe aortic regurgitation	0.0% (0/69)	0.0% (0/30)	2.8% (4/145)

[1] Device implanted successfully was defined as placement of a bioprosthetic valve in an intended site without requiring more than 1 valve.
[2] The Kaplan-Meier estimates up to 30 days and 1 year. The figures in parentheses represent the number of events and the number of patients with event. The time to the first event in each patient was used in the summarization.

Table 20 shows the results of the primary echocardiographic parameters at 30 days and 1 year in all registry patients who met the definition of the proposed target population in Japan. Table 21 shows the results in patients with a SAPIEN series host valve.

Table 20. Echocardiographic parameters by valve size (overall proposed target population in Japan)

Endpoints		Summary statistics*			
		20 mm	23 mm	26 mm	29 mm
Overall proposed target population in Japan (N = 276)	Baseline				
	Mean pressure gradient (mmHg)	47.8 ± 7.62 (8)	47.0 ± 1.65 (92)	42.3 ± 2.36 (47)	29.4 ± 3.67 (28)
	Moderate or severe aortic regurgitation	80.0% (8/10)	65.2% (75/115)	79.0% (64/81)	89.9% (62/69)
	Left ventricular ejection fraction (%)	56.3 ± 5.39 (10)	55.4 ± 1.12 (115)	46.3 ± 1.74 (79)	44.7 ± 1.80 (68)
	30 days				
	Mean pressure gradient (mmHg)	22.2 ± 4.63 (6)	17.8 ± 0.99 (85)	13.9 ± 1.16 (44)	10.3 ± 0.69 (48)
	Moderate or severe aortic regurgitation	0.0% (0/6)	3.5% (3/86)	2.2% (1/46)	2.0% (1/49)
	1 year				
	Mean pressure gradient (mmHg)	ND	18.5 ± 1.56 (32)	13.1 ± 1.38 (19)	8.9 ± 0.98 (16)
	Moderate or severe aortic regurgitation	ND	0.0% (0/32)	0.0% (0/19)	0.0% (0/18)

ND, No Data
* Continuous variables are presented as mean ± SD (number of patients). Categorical variables are presented as % (n/total number). The total number only counted the patients with valid data.

Table 21. Echocardiographic parameters by valve size (SAPIEN series)

Endpoints		Summary statistics*			
		20 mm	23 mm	26 mm	29 mm
SAPIEN series (N = 116)	Baseline				
	Mean pressure gradient (mmHg)	36.2 ± 6.61 (5)	46.5 ± 2.07 (51)	45.4 ± 3.95 (20)	48.4 ± 7.33 (7)
	Moderate or severe aortic regurgitation	80.0% (4/5)	68.8% (44/64)	84.8% (28/33)	78.6% (11/14)
	Left ventricular ejection fraction (%)	46.4 ± 7.34 (5)	55.0 ± 1.60 (64)	47.6 ± 2.60 (33)	44.4 ± 3.74 (14)
	30 days				
	Mean pressure gradient (mmHg)	21.3 ± 3.90 (4)	18.1 ± 1.10 (46)	14.6 ± 1.55 (18)	12.4 ± 1.41 (14)
	Moderate or severe aortic regurgitation	0.0% (0/4)	2.2% (1/46)	0.0% (0/18)	0.0% (0/14)
	1 year				
	Mean pressure gradient (mmHg)	ND	20.8 ± 1.81 (19)	15.3 ± 2.58 (6)	10.8 ± 2.52 (5)
	Moderate or severe aortic regurgitation	ND	0.0% (0/19)	0.0% (0/6)	0.0% (0/5)

ND, No Data
* Continuous variables are presented as mean ± SD (number of patients). Categorical variables are presented as % (n/total number). The total number only counted the patients with valid data.

6.B Outline of the review conducted by PMDA

6.B.(1) Justification of evaluating the efficacy and safety of SAPIEN 3 in Japan based on TVT Registry data

6.B.(1).1) Justification of using TVT Registry data

The applicant's explanation about the justification of using TVT Registry data to evaluate the efficacy and safety of TAV in TAV with SAPIEN 3:

The TVT Registry was initiated in the US in December 2011 to collect real-world clinical data regarding the safety and efficacy of TAVR in order to ensure the proper use of the device and optimize treatment of each patient, as well as to open the way to future expansion in the indication of TAVR. The FDA and other organizations also collaborate with this Registry. The quality of the TVT Registry data is controlled on the computer system through quality inspection to ensure data integrity and consistency. Only data that meet the quality criteria are accepted as registry data. Data auditing by the third party is also conducted annually. No significant data accuracy or integrity issue has been identified. In the US, SAPIEN 3 received an FDA clearance in September 2020 based on the clinical results of TAV in TAV with SAPIEN 3 in the TVT Registry. Prior to the marketing application in Japan, the applicant signed a data provision agreement with the STS and the ACC, which own this registry, so that the applicant can

use the TVT Registry database and confirmed the reliability of the data. It is reasonable to use the registry data for the purpose of this regulatory submission.

Since the TVT Registry is not a study intended for hypothesis verification, it should be noted that no success criteria are specified in this registry to evaluate the efficacy and safety of TAV in TAV with SAPIEN 3. Nevertheless, it is possible to evaluate whether the efficacy and safety of TAV in TAV with SAPIEN 3 are similar to those of TAV in SAV, a conventional treatment, with a certain degree of certainty by comparing the results and descriptive statistics of the 2 procedures.

Table 22 shows the results from patients registered in the TVT Registry who underwent TAV in SAV with SAPIEN 3 (data extracted on [redacted], 20[redacted]) and those who underwent TAV in TAV with SAPIEN 3 (data extracted on [redacted], 20[redacted]) at 30 days and 1 year.

Table 22. Comparison of results between TAV in SAV and TAV in TAV

	TVT Registry	
	TAV in SAV (N = 6,382)	TAV in TAV (N = 587)
Device	SAPIEN 3	SAPIEN 3
Patient demographics and procedure information		
Age (years)	73.8 ± 11.26	78.5 ± 9.7
Male %	66.8%	55.2%
STS score (%)	6.8 ± 6.08	8.8 ± 7.6
NYHA class III/IV	77.4%	81.8%
Surgical risk		
Inoperable/extreme risk	12.8%	16.6%
High risk	52.1%	62.2%
Moderate risk	28.6%	18.1%
Low risk	6.4%	3.1%
Mean pressure gradient (mmHg)	38.9 ± 16.97	33.4 ± 19.7
Implant approach		
Transfemoral	94.1%	94.4%
Valve model implanted		
9600TFX	87.2%	90.1%
9750TFX	12.8%	9.9%
Size of valve implanted		
20 mm	12.9%	3.7%
23 mm	49.6%	35.4%
26 mm	29.0%	33.9%
29 mm	8.5%	26.9%
Procedure time (min)	95.2 ± 0.67	104.6 ± 2.8
Results at 30 days		
Kaplan-Meier estimate of common adverse events		
Death	2.8%	5.0%
Stroke	1.3%	2.5%
Aortic valve reintervention	0.4%	0.7%
Conduction disorder requiring pacemaker implantation	2.2%	6.9%
Myocardial infarction	0.5%	0.7%
Transient ischaemic attack	0.2%	0.9%
Valve-related readmission	0.5%	0.9%
Severe haemorrhage	0.4%	0.9%
Major vascular complication	1.0%	0.7%
Valve thrombosis	0.2%	0.2%
Improvement in NYHA class from baseline	85.4%	80.1%
Mean pressure gradient (mmHg)	19.9 ± 0.13	14.5 ± 0.42
Moderate or severe aortic regurgitation	0.9%	3.4%
Results at 1 year		
Kaplan-Meier estimate of common adverse events		
Death	10.0%	17.0%
Stroke	2.4%	2.7%
Aortic valve reintervention	1.8%	1.7%
Conduction disorder requiring pacemaker implantation	3.6%	9.2%
Myocardial infarction	1.3%	2.3%
Transient ischaemic attack	0.3%	1.5%
Valve-related readmission	2.3%	5.2%
Severe haemorrhage	2.2%	2.6%
Major vascular complication	1.3%	1.0%
Valve thrombosis	0.9%	0.5%
Improvement in NYHA class from baseline	85.4%	77.5%
Mean pressure gradient (mmHg)	19.8 ± 0.20	13.8 ± 0.61
Moderate or severe aortic regurgitation	1.3%	2.8%

The mean pressure gradient was 19.9 ± 0.13 mmHg at 30 days and 19.8 ± 0.20 mmHg at 1 year in patients who underwent TAV in SAV, and 14.5 ± 0.42 mmHg at 30 days and 13.8 ± 0.61 mmHg at 1 year in patients who underwent TAV in TAV. The mean pressure gradient was lower in the TAV in TAV cohort than the TAV in SAV cohort, showing better hemodynamics in the TAV in TAV cohort. The all-

cause mortality was 2.8% at 30 days and 10.0% at 1 year in the TAV in SAV cohort, and 5.0% at 30 days and 17.0% at 1 year in the TAV in TAV cohort. The all-cause mortality was higher in the TAV in TAV cohort than the TAV in SAV cohort. This was likely explained by the fact that the TAV in TAV cohort included more patients who were older and therefore at higher surgical risk than the TAV in SAV cohort. Cohort B NR3 in the PARTNER II study, where TAV in SAV with "SAPIEN XT" was evaluated in patients who were at extreme risk of surgery (mean STS score, 9.9%), had a 1-year mortality of 19.7%. On the basis of these findings, TAV in TAV appeared not to be associated with a substantially higher mortality than TAV in SAV.

The medical therapy cohort in the PARTNER-US study in patients who were not eligible for surgery had a 1-year mortality of 50.2%. Patients with a failed TAV who received palliative treatment are expected to have a comparable or higher mortality. Considering this estimation, the mortality after TAV in TAV with SAPIEN 3 should be clinically acceptable. A report by Jawitz et al.[8] shows a mortality within 30 days after surgical valve replacement in patients with a failed TAV of 17.1%. The therapeutic outcome of TAV in TAV with SAPIEN 3 is unlikely to be remarkably inferior to surgical valve replacement.

In conclusion, although the TVT Registry is not a study intended for hypothesis verification, the efficacy and safety of TAV in TAV with SAPIEN 3 can be sufficiently evaluated by comparing the results of TAV in SAV, which is an approved treatment approach in Japan, and the clinical results in the TVT Registry. The data used as the basis of the supplemental application decision in the US have been updated. This current regulatory submission included the data from 587 patients collected over approximately 5 years, which is enough in terms of the sample size and the period for analysis.

PMDA's view:
Recently, increasing efforts have been made to utilize real-world data obtained in actual clinical practice in the development of pharmaceuticals and medical devices in Japan and other countries. The Japanese regulatory authorities have also issued the "Basic principles on Utilization of Registry for Applications" (PSEHB/PED Notification No. 0323-1 and PSEHB/MDED Notification No. 0323-1 dated March 23, 2021) and the "Points to Consider in Ensuring Reliability for Utilization of Registry Data for Applications" (PSEHB/PED Notification No. 0323-2 and PSEHB/MDED Notification No. 0323-2 dated March 23, 2021). When the sample size is too small to conduct a clinical study aiming to expand the indication of a drug or medical device because of the rarity or urgency of a disease, registry data, instead of data from a clinical study, may be used to evaluate the efficacy and safety of the drug or medical device. Since there are not many patients who are candidates for TAV in TAV and because of the age of the proposed target patient population, it would be extremely difficult to conduct a prospective clinical study. The TVT Registry is a large-scale real-world database established to open the way to future expansion in the indication of TAVR in the US. This database was also the basis of the supplemental approval decision for TAV in TAV in the US. It is, therefore, understandable that the applicant uses the registry data as the basis of the partial change application in Japan.

Although the TVT Registry is not a Good Clinical Practice (GCP)-compliant clinical study, the reliability of the TVT Registry database as a data source for the application is assured as described later

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

TAVR with SAPIEN 3 has been established as the standard treatment in Japan. With its demonstrated efficacy and safety, TAV in SAV with SAPIEN 3 is also approved in Japan. Although TAV in SAV and TAV in TAV are different in the shape of the host valve and implantation procedure, they are similar in terms of using a valve-in-valve technique in the aortic position. Considering the similarity of these approaches, the applicant’s explanation that TAV in TAV with SAPIEN 3 can be evaluated with a certain degree of certainty by comparing the results of TAV in TAV and TAV in SAV is acceptable. It is also appropriate to use the endpoints of the TVT Registry in this evaluation.

6.B.(1).2) Extrapolation of the US registry data to Japan

The applicant’s explanation about the justification of extrapolating the US registry data to Japan:

- Target patient population of TAV in TAV with SAPIEN 3

  In the US, surgical valve replacement is the first-line retreatment option for patients with prosthetic valve dysfunction. The ACC/American Heart Association (AHA) guidelines [11] recommend considering a transcatheter approach for patients at extreme or high surgical risk. The Guideline on the Management of Valvular Heart Disease[10] in Japan also recommends the transcatheter valve in valve approach to symptomatic patients at high surgical risk with severe prosthetic valve dysfunction. There appears to be no difference in the retreatment strategy for patients with prosthetic valve dysfunction between the US and Japan.

  A variety of factors, including anatomical features of the chest not suitable for surgery, old age, decreased cardiopulmonary function, a poor general condition due to dialysis, may make surgical valve replacement difficult in the treatment of patients with prosthetic valve dysfunction. Among them, age is an important factor in selecting a treatment. In accordance with the Japanese guideline, TAVR should be considered first in patients with aortic valve stenosis aged ≥80 years, and SAVR in those aged <75 years. The US guidelines recommend TAVR as the first-line treatment in patients aged ≥80 years, similarly to the Japanese guideline, but gives a Class I recommendation to both TAVR and SAVR in patients aged ≥65 years. For this reason, patients in the US may undergo a first TAV placement at younger ages than those in Japan. In the US, however, TAV in TAV with SAPIEN 3 is also limited to patients who are not eligible for surgery or high risk for surgery. In addition, the ethnicity of patients is unlikely to affect the durability of bioprosthetic valves. Therefore, the age of the target patient population of TAV in TAV with SAPIEN 3 should not substantially differ between the US and Japan.

  In summary, there appears not to be a substantial difference in the target patient population of TAV in TAV with SAPIEN 3 between the US and Japan.

- Host valves to be managed through TAV in TAV with SAPIEN 3

  The host valves to be managed through TAV in TAV with SAPIEN 3 must be Edwards SAPIEN series. Valves of other companies are excluded from the indication because it was difficult to conduct a similar design verification to that of the SAPIEN series. The SAPIEN series approved in the US

includes “SAPIEN XT” and SAPIEN 3, both of which are approved in Japan, as well as its first generation “Edwards SAPIEN.” The major difference of “Edwards SAPIEN” from “SAPIEN XT” and SAPIEN 3 is the material of the stent frame. It has been shown that implantation of a TAV does not over-expand the host valve of “Edwards SAPIEN.” Although the SAPIEN series has some differences in the type of host valve between the US and Japan, these differences are unlikely to affect the results of TAV in TAV with SAPIEN 3 because the devices of “Edwards SAPIEN” are similar to those of the SAPIEN series approved in Japan. In summary, there appears to be no difference in the host valves to be managed through TAV in TAV with SAPIEN 3 that might affect the treatment outcome between the US and Japan. Some SAPIEN series available in the US uses a delivery system, loader, and introducer sheath set that have not been approved in Japan, but such differences in the shape and structure do not influence the operability during the expansion of a bioprosthetic valve or the performance of the implanted valve. Thus, the clinical results in the US can be extrapolated to Japan.

- Difference in the medical environment in TAV in TAV with SAPIEN 3
  There is no difference in the recommended diagnostic criteria for prosthetic valve dysfunction between the US and Japanese guidelines. In addition, the results of the previous clinical studies in the US and Japan have demonstrated no difference in the medical environment of TAVR with SAPIEN 3 that might affect the treatment outcome between the 2 countries. The medical environment of TAV in TAV with SAPIEN 3 in Japan is unlikely to be different from that in the US. Considering the similarity of the procedures in TAV in TAV and TAV in SAV with SAPIEN 3, TAV in TAV with SAPIEN 3 can be performed safely in Japan, similarly to TAV in SAV.

PMDA’s view:
The treatment method and diagnostic criteria for aortic valve disease are similar in the US and Japan, and no substantial difference has been identified in the results of the previous clinical studies of TAVR between the 2 countries. The technical elements, including the implantation method and procedure, of transcatheter aortic valve placement in an implanted TAV are basically the same as those of TAVR in a native aortic valve or TAV in SAV. The proficiency of TAVR procedure, treatment outcome, type of host valve to be managed with SAPIEN 3 are similar in the US and Japan. The applicant’s explanation that there will be no new difference in the medical environment of the TAV in TAV procedure is, therefore, acceptable. Since the efficacy and safety of TAV in TAV may depend on the type of host valve, the applicant has appropriately proposed to use the Edwards SAPIEN series, whose compatibility with SAPIEN 3 has been confirmed based on the results of the previous nonclinical and clinical studies, and whose information about implantation procedure, etc. can be provided to users, as host valves to be managed through TAV in TAV with SAPIEN 3.

As explained by the applicant, however, a use-results survey in patients who were not eligible for surgery and received “SAPIEN XT” in the native aortic valve in Japan revealed that the mean age of the patients was 86.5 ± 3.67 years old for the 20 mm valve, 84.4 ± 7.99 years old for the 23/26 mm valve, and 82.1 ± 6.63 years old for the 29 mm valve. Taking the time to failing of a TAV into consideration, patients who are expected to undergo TAV in TAV in Japan will be older than the mean age of the TAV in TAV

cohort in the TVT Registry (78.5 ± 9.7 years old). This must be noted in the evaluation [see Section "6.B.(2).2).(c) Evaluation considering use in oldest-old patients"].

6.B.(2) Efficacy and safety of SAPIEN 3

6.B.(2).1) Overall outcome

The efficacy evaluation showed the device implant success rate in TAV in TAV with SAPIEN 3 of 99.0% (Table 14) and an improvement in mean pressure gradient from 33.5 ± 1.06 mmHg at baseline to 14.5 ± 0.42 mmHg at 30 days (Table 17), which was further demonstrated with improvements in the NYHA class (Figure 5). The satisfactory improvements in hemodynamics and the NYHA class were maintained up to 1 year. The safety evaluation showed the mortality at 1 year of 10.0% in the TAV in SAV cohort and 17.0% in the TAV in TAV cohort, being higher in the TAV in TAV cohort than the TAV in SAV cohort (Table 22).

PMDA's view on the higher mortality in the TAV in TAV cohort than the TAV in SAV cohort:
In the early years after the introduction of TAVR, it was used only in patients who were not eligible for this procedure. Therefore, many patients who require reintervention are more likely to be at higher surgical risk than those patients with a surgical bioprosthetic valve who later required TAV in SAV for reintervention and will not be eligible for surgical reintervention. The TVT Registry has also demonstrated a higher mean age, STS score, and surgical risk of patients in the TAV in TAV cohort than the TAV in SAV cohort, indicating that TAV in TAV is generally indicated for patients in a more critical condition. This appears to explain, at least partially, the higher mortality in the TAV in TAV cohort. Considering these patient characteristics and the incidence of valve-related adverse events, the TAV in TAV intervention is unlikely to have resulted in the high mortality in the TAV in TAV cohort.

Conservative medical management or surgical intervention is a current treatment option available for patients who require reintervention due to a failing host valve. The present application is intended to expand the indications to patients requiring TAV in TAV who are not eligible for surgery. Considering that no other useful treatment is available for these patients, TAV in TAV with SAPIEN 3 is effective with a clinically acceptable safety. There is a risk-benefit balance.

6.B.(2).2) Efficacy and safety in the proposed target population in Japan and patients with a SAPIEN series host valve

As shown in Table 19, PMDA asked the applicant to explain the reason that the risk of stroke in 1 year tended to be higher in the patients in the registry who met the definition of the proposed target population in Japan* (5.3% [4.4% with the host valves of SAPIEN series]) than the overall TVT Registry population (2.7%). PMDA also asked the applicant to explain the high 1-year mortality of 23.0% with the host valves of SAPIEN series although the sample size was limited. As aforementioned, the mean age of the proposed target population of TAV in TAV in Japan is expected to be higher than that in the overall population who underwent TAV in TAV with SAPIEN 3 in the TVT Registry. PMDA asked the applicant to explain the efficacy and safety in the proposed target population of TAV in TAV with SAPIEN 3 in Japan in the context of age.

* Patients who are inoperable, or at extreme or high risk for surgery with a mean baseline pressure gradient of ≥35 mmHg or severe aortic regurgitation

6.B.(2).2).(a) Risk of stroke

The applicant's explanation:

The proposed target population in Japan is patients in whom surgery is difficult to perform. Their STS score (11.2% ± 9.06%) was naturally higher than that in the overall TVT Registry population (8.8% ± 7.6%). In addition, more patients have risk factors of stroke, such as peripheral arterial disease and dialysis, than the overall TVT Registry population (peripheral arterial disease, 33.0% in the proposed target population in Japan and 29.6% in the overall registry population; dialysis, 9.4% and 7.7%, respectively). The medical therapy cohort in the previous clinical study in patients with severe native aortic valve stenosis who were not eligible for surgery (Cohort B of the PARTNER-US study) had a 1-year severe stroke-free rate of 95.1%. In patients who were not eligible for surgery and have to receive palliative treatment, the incidence of stroke at 1 year is estimated to be at least 4.9%. Considering these results and the higher STS score in the proposed target population in Japan than that in the overall TVT Registry population, the incidence of stroke (5.3% [4.4% with the host valves of SAPIEN series]) at 1 year in patients in this registry who met the definition of the proposed target population in Japan is clinically acceptable.

PMDA concluded that the applicant's explanation about the risk of stroke was reasonable.

6.B.(2).2).(b) Mortality with a host valve of SAPIEN series

The applicant's explanation:

Table 23 shows the causes of death in the registry patients who met the definition of the proposed target population in Japan. Of 37 patients who died within 1 year, 7 patients died from cardiac disease, other than valvular disease. Of patients who met the definition of the proposed target population in Japan, 20 patients with a host valve of SAPIEN series died within 1 year, including cardiac disease (other than valvular disease) in 6 patients. This figure is not particularly higher than that in the overall registry population that met the definition of the proposed target population in Japan. TAV in TAV with SAPIEN 3 in a SAPIEN series TAV in Japan appears to be not associated with a higher mortality.

Table 23. Causes of death in patients who died within 1 year (all patients and patients with a host valve of SAPIEN series who met the definition of the proposed target population in Japan)

Cause of death	Proposed target population in Japan	
	SAPIEN series (N = 20)	All valves (N = 37)
Cardiac disease (other than valvular disease)	6	7
Neurological disease	2	4
Renal disease	1	2
Infection	0	2
Respiratory disease	2	4
Vascular disease	1	1
Valvular disease	0	0
Other	1	2
Unknown	7	15

On the basis of the applicant's explanation and for the following reason, PMDA concluded that the above outcome was acceptable: Having a host valve of SAPIEN series is unlikely to be associated with a higher mortality because there is no difference among the types of host valves in the incidences at 1 year of

aortic valve reintervention, myocardial infarction, valve-related readmission, and valve thrombosis, which were rather lower in patients with a host valve of SAPIEN series.

6.B.(2).2).(c) Evaluation considering use in oldest-old patients

The applicant's explanation:

The efficacy and safety of TAV in TAV with SAPIEN 3 in Japan were evaluated by stratified analysis using the cut-off age of 85 years, which was selected to ensure that a sufficient sample size was available for the analysis taking into consideration the mean age of patient candidates for TAV in TAV in Japan (approximately 90 years old). Table 24 shows the results of the stratified analysis in registry patients aged ≥85 years who met the definition of the proposed target population in Japan, together with the analysis results in patients with a host valve of SAPIEN series.

Table 24. Results of TAV in TAV in patients aged ≥85 years who met the definition of the proposed target population in Japan

Item	Proposed target population in Japan: ≥85 years		Proposed target population in Japan (overall) (N = 276)
	All valves (N = 98)	SAPIEN series (N = 43)	
Patient demographics and baseline characteristics			
Age (years)	88.8 ± 2.83 (98)	88.9 ± 3.06 (43)	78.6 ± 10.47 (276)
Female %	59.2% (58/98)	76.7% (33/43)	53.3% (147/276)
STS score (%)	11.8 ± 7.63 (92)	12.2 ± 9.52 (41)	11.2 ± 9.06 (251)
NYHA class III/IV	89.6% (86/96)	83.3% (35/42)	86.4% (236/273)
Mean pressure gradient (mmHg)	40.8 ± 15.40 (62)	47.6 ± 12.78 (32)	43.0 ± 1.34 (175)
Moderate or severe aortic regurgitation	78.6% (77/98)	76.7% (33/43)	75.9% (208/274)
Left ventricular ejection fraction (%)	53.6 ± 13.20 (97)	55.5 ± 12.36 (43)	50.1 ± 0.90 (272)
Procedure information			
Procedure time (min)	102.6 ± 6.69 (98)	95.8 ± 7.31 (43)	109.5 ± 4.19 (276)
Device implanted successfully[1]	100.0% (98/98)	100.0% (43/43)	98.9% (273/276)
Conversion to SAVR	0.0% (0/98)	0.0% (0/43)	0.4% (1/276)
Key results at 30 days			
Kaplan-Meier estimate of common adverse events[2]			
Death	7.5% (7, 7)	4.7% (2, 2)	6.5% (17, 17)
Aortic valve reintervention	0.0% (0, 0)	0.0% (0, 0)	0.4% (1, 1)
Conduction disorder requiring pacemaker implantation	6.4% (6, 6)	4.9% (2, 2)	9.1% (24, 24)
Myocardial infarction	0.0% (0, 0)	0.0% (0, 0)	1.2% (4, 3)
Stroke	5.4% (5, 5)	5.0% (2, 2)	4.9% (13, 13)
Transient ischaemic attack	1.0% (1, 1)	2.3% (1, 1)	1.1% (3, 3)
Valve-related readmission	0.0% (0, 0)	0.0% (0, 0)	0.4% (1, 1)
Severe haemorrhage	0.0% (0, 0)	0.0% (0, 0)	2.0% (5, 5)
Major vascular complication	3.1% (3, 3)	4.7% (2, 2)	1.5% (4, 4)
Valve thrombosis	0.0% (0, 0)	0.0% (0, 0)	0.4% (1, 1)
NYHA class III/IV	10.1% (7/69)	6.3% (2/32)	16.1% (30/186)
Improvement in NYHA class from baseline	89.7% (61/68)	87.1% (27/31)	83.8% (155/185)
Mean pressure gradient (mmHg)	13.1 ± 0.81 (62)	14.1 ± 0.86	15.0 ± 0.63 (183)
Moderate or severe aortic regurgitation	1.6% (1/62)	0.0% (0/27)	2.7% (5/187)
Key results at 1 year			
Kaplan-Meier estimate of common adverse events[2]			
Death	20.9% (14, 14)	26.8% (7, 7)	18.8% (37, 37)
Aortic valve reintervention	0.0% (0, 0)	0.0% (0, 0)	2.6% (4, 4)
Conduction disorder requiring pacemaker implantation	6.4% (6, 6)	4.9% (2, 2)	11.3% (27, 27)
Myocardial infarction	2.3% (1, 1)	0.0% (0, 0)	1.9% (5, 4)
Stroke	6.9% (6, 6)	5.0% (2, 2)	5.3% (14, 14)
Transient ischaemic attack	1.0% (1, 1)	2.3% (1, 1)	1.9% (4, 4)
Valve-related readmission	4.6% (2, 2)	0.0% (0, 0)	6.2% (10, 9)
Severe haemorrhage	0.0% (0, 0)	0.0% (0, 0)	3.4% (8, 7)
Major vascular complication	3.1% (3, 3)	4.7% (2, 2)	1.5% (4, 4)
Valve thrombosis	2.2% (1, 1)	0.0% (0, 0)	1.1% (2, 2)
NYHA class III/IV	3.3% (1/30)	11.1% (1/9)	12.8% (10/78)
Improvement in NYHA class from baseline	89.7% (26/29)	75.0% (6/8)	87.0% (67/77)
Mean pressure gradient (mmHg)	11.7 ± 1.34 (21)	16.7 ± 2.85 (7)	14.7 ± 0.99 (67)
Moderate or severe aortic regurgitation	0.0% (0/21)	0.0% (0/5)	0.0% (0/69)

[1] Device implanted successfully was defined as placement of a bioprosthetic valve in an intended site without requiring more than 1 valve.
[2] The Kaplan-Meier estimates up to 30 days and 1 year. The figures in parentheses represent the number of events and the number of patients with event. The time to the first event in each patient was used in the summarization.

A total of 14 patients aged ≥85 years died within 1 year. The Kaplan-Meier estimate of death was 7.5% at 30 days and 20.9% at 1 year, which were slightly higher than the mortalities in all patients who met the definition of the proposed target population in Japan (6.5% at 30 days, 18.8% at 1 year). However, no patient required aortic valve reintervention within 1 year. The incidence of valve-related readmission was 4.6% at 1 year, which was lower than that in all patients who met the definition of the proposed target population in Japan (6.2%). The NYHA class improved in 89.7% (26 of 29) of patients at 1 year.

The mean pressure gradient substantially improved from 40.8 ± 15.40 mmHg at baseline to 13.1 ± 0.81 mmHg at 30 days and 11.7 ± 1.34 mmHg at 1 year. No patient had moderate or severe aortic regurgitation at 1 year.

Furthermore, neither a new safety nor an efficacy issue that needed to be examined was identified in patients aged ≥85 years with a host valve of SAPIEN series. The mortality in this population was 26.8% at 1 year, which was not substantially different from that in all patients with a host valve of SAPIEN series who met the definition of the overall proposed target population in Japan (23.0%) (Table 19).

PMDA's view:
The results of the TVT Registry have suggested no particular concern about the efficacy and safety of TAV in TAV with SAPIEN 3 in the age group of patients who met the definition of the proposed target population in Japan. Its efficacy and safety appear to be clinically acceptable in the proposed target population in Japan. Nevertheless, it is essential to evaluate the efficacy and safety of SAPIEN 3 in clinical practice in Japan through a use-results survey and take appropriate measures if necessary.

6.B.(2).3) Efficacy and safety of smaller-diameter valves

The TVT Registry has demonstrated that the pressure gradient tends to be higher as the TAV diameter is smaller. In addition, the sample size and long-term data with the 20-mm valve of SAPIEN 3 are limited compared with the other valve sizes. PMDA asked the applicant to explain the efficacy and safety of TAV in TAV with the 20-mm valve of SAPIEN 3.

The applicant's explanation:
Since the proposed target population in Japan have a smaller body size than the patient populations in the US and Europe, relatively more patients require a smaller-diameter valve. It is, therefore, essential to introduce small-diameter valves into Japan. TAV in TAV, which places another TAV inside a host valve, is associated with a higher post-procedural pressure gradient than TAVR with a native aortic valve, as in TAV in SAV. In particular, the remaining pressure gradient is a challenge with small-diameter valves. However, TAV in TAV that places SAPIEN 3 inside a TAV having no ring is expected to secure a larger effective orifice area than TAV in SAV, which is an approved procedure in Japan, that is commonly performed to place SAPIEN 3 inside a surgical bioprosthetic valve with a stent having a stiff ring. With a large orifice area, TAV in TAV is expected to be associated with a lower risk of the remaining pressure gradient than TAV in SAV.

Table 25 shows the mean pressure gradient in TAVR in a native aortic valve, TAV in SAV, and TAV in TAV with the 20-mm valve of SAPIEN 3.

Table 25. Comparison of the mean pressure gradient (mmHg) with the 20-mm valve

	TAVR in a native aortic valve[1] (N = 11)	TAV in SAV[2] (N = 82)	TAV in TAV[3] (N = 10)
Baseline	50.6 ± 12.7 (11)	44.3 ± 15.27 (72)	47.8 ± 7.62 (8)
30 days	15.7 ± 6.0 (11)	26.8 ± 10.50 (47)	22.2 ± 4.63 (6)
1 year	22.6 ± 5.6 (6)	ND	ND

ND, No Data
[1] Inoperable/high-risk patient group in the PARTNER II study SAPIEN 3 cohort
[2] Results from inoperable/high-risk patients in the TAV in SAV cohort in the TVT Registry
[3] Results from patients who met the definition of the proposed target population in Japan (i.e., patients who are inoperable, or at extreme or high risk for surgery with a mean baseline pressure gradient of ≥35 mmHg and/or severe aortic regurgitation) in the TAV in TAV cohort in the TVT Registry

The mean pressure gradient at 30 days was lower in patients who underwent TAVin TAV than patients who underwent TAV in SAV. The mean pressure gradient at 1 year could not be determined because none of the 10 patients who underwent TAVin TAV shown in Table 25 had mean pressure gradient data at 1 year. As shown in Table 18, however, pressure gradient data were available at 30 days in 12 patients and at 1 year in 2 patients among all 22 patients in the TVT Registry who received the 20-mm valve of SAPIEN 3. The mean pressure gradient was satisfactory at both 30 days and 1 year (20.7 ± 2.73 mmHg at 30 days, 17.5 ± 2.50 mmHg at 1 year). Although even the overall TVT Registry does not provide a sample size large enough to evaluate the mean pressure gradient at 1 year, TAV in TAV resulted in an almost constant mean pressure gradient, which was rather lower than that in TAV in SAV at 30 days. For these reasons, the mean pressure gradient at 1 year is unlikely to be substantially worse than TAV in SAV. In addition, among the 22 patients in the TVT Registry who received the 20-mm valve of SAPIEN 3, 8 patients had a mean pressure gradient of ≥20 mmHg at 30 days or 1 year. Neither death nor valve-related readmission was reported in any of these 8 patients within 1 year. One patient underwent aortic valve reintervention, which was balloon aortic valvuloplasty because of valve damage at 4 days. This aortic valve reintervention was not because of the remaining pressure gradient after TAV in TAV.

To ensure the safe introduction of TAV in TAV with SAPIEN 3 in Japan, information regarding the remaining pressure gradient with the small-diameter valve will be provided in precautions and other information, and training materials as when TAV in SAV was introduced. In addition, in order to reduce the risk of using the small-diameter valve, appropriate information will be provided to healthcare professionals to ensure that patients are selected after full consideration of the therapeutic purpose of TAV in TAV. Furthermore, there are plans to conduct a use-results survey to collect and evaluate data in clinical practice so that safety measures can be installed in a timely manner if necessary.

PMDA's view:
Since the TVT Registry collects no data regarding the effective orifice area, whether a sufficient effective orifice area was secured in each patient in the TAV in TAV cohort is unknown. There is also a concern that only very limited data are available regarding the mean pressure gradient with the 20-mm valve of SAPIEN 3. On the other hand, the applicant explained that the structural characteristics of the host valves provide a larger effective orifice area in TAV in TAV than that in TAV in SAV and that TAV in TAV was associated with a lower risk for the remaining pressure gradient than TAV in SAV since the valve size of SAPIEN 3 was selected according to the ring diameter of the patient's native aortic valve. Those explanations are understandable. The efficacy and safety of TAV in TAV with the 20-mm valve of SAPIEN 3 appear to be assured to some extent. Nevertheless, since there are only limited data with

the 20-mm valve of SAPIEN 3 and whether the procedure should be performed must be determined carefully for each patient, PMDA instructed the applicant to provide relevant information in precautions and other information, and training materials. The applicant agreed.

6.B.(2).4) Efficacy and safety in patients on chronic dialysis

The applicant's explanation:

There are concerns of early calcification and failing of bioprosthetic valves in patients on chronic dialysis, who are generally prone to calcium deposition compared with patients not on dialysis. In addition, patients on chronic dialysis have multiple comorbidities and a poor general condition because of bleeding tendency, being easily infectible, etc. Since those conditions render them at extreme risk for surgery, many patients may require TAV in TAV with SAPIEN 3, which is less invasive than surgical valve replacement, to manage a failed TAV. For this reason, patients on chronic dialysis are included in the proposed target population of TAV in TAV with SAPIEN 3 in this application. The efficacy and safety of TAV in TAV with SAPIEN 3 were evaluated in patients who are not eligible for surgery on chronic dialysis. Table 26 shows a comparison of the results between 45 patients on chronic dialysis and 542 patients not on dialysis who underwent TAV in TAV with SAPIEN 3 in the TVT Registry. Table 27 shows the causes of death in patients who died within 1 year.

Table 26. Results of TAV in TAV with SAPIEN 3 in patients on chronic dialysis

Item	TVT Registry	
	Chronic dialysis patients (N = 45)	Non-dialysis patients (N = 542)
Patient demographics and baseline characteristics		
Age (years)	68.9 ± 10.06 (45)	79.3 ± 9.22 (542)
Female %	33.3% (15/45)	45.8% (248/542)
STS score (%)	16.2 ± 15.23 (40)	8.2 ± 6.28 (489)
NYHA class III/IV	82.2% (37/45)	81.7% (438/536)
Mean pressure gradient (mmHg)	39.6 ± 15.94 (33)	32.7 ± 20.01 (312)
Moderate or severe aortic regurgitation	60.0% (27/45)	74.7% (404/541)
Procedure information		
Surgical risk		
Inoperable/extreme risk	17.8% (8/45)	16.5% (88/534)
High risk	73.3% (33/45)	61.2% (327/534)
Moderate risk	8.9% (4/45)	18.9% (101/534)
Low risk	0.0% (0/45)	3.4% (18/534)
Implant approach		
Transfemoral	93.3% (42/45)	94.5% (512/542)
Transapical	0.0% (0/45)	1.1% (6/542)
Transaortic	2.2% (1/45)	0.4% (2/542)
Trans-subclavian/axillary	2.2% (1/45)	2.0% (11/542)
Others	2.2% (1/45)	1.7% (9/542)
Procedure time (min)	104.6 ± 7.04 (45)	104.6 ± 2.94 (542)
Device implanted successfully[1]	97.8% (44/45)	99.1% (537/542)
Conversion to SAVR	0.0% (0/45)	0.6% (3/542)
Key results at 30 days		
Kaplan-Meier estimate of common adverse events[2]		
Death	7.0% (3, 3)	4.9% (25, 25)
Aortic valve reintervention	0.0% (0, 0)	0.8% (4, 4)
Conduction disorder requiring pacemaker implantation	13.8% (6, 6)	6.3% (33, 33)
Myocardial infarction	2.5% (2, 1)	0.6% (3, 3)
Stroke	4.6% (2, 2)	2.3% (12, 12)
Transient ischaemic attack	0.0% (0, 0)	1.0% (5, 5)
Valve-related readmission	2.5% (1, 1)	0.8% (4, 4)
Severe haemorrhage	0.0% (0, 0)	1.0% (5, 5)
Major vascular complication	0.0% (0, 0)	0.7% (4, 4)
Valve thrombosis	0.0% (0, 0)	0.2% (1, 1)
NYHA class III/IV	5/27 (18.5%)	51/366 (13.9%)
Improvement in NYHA class from baseline	22/27 (81.5%)	291/364 (79.9%)
Mean pressure gradient (mmHg)	16.2 ± 1.57 (26)	14.3 ± 0.44 (347)
Moderate or severe aortic regurgitation	1/26 (3.8%)	12/357 (3.4%)
Key results at 1 year		
Kaplan-Meier estimate of common adverse events[2]		
Death	26.2% (8, 8)	16.3% (61, 61)
Aortic valve reintervention	0.0% (0, 0)	1.9% (7, 7)
Conduction disorder requiring pacemaker implantation	13.8% (6, 6)	8.7% (40, 40)
Myocardial infarction	2.5% (2, 1)	2.2% (7, 7)
Stroke	4.6% (2, 2)	2.5% (13, 13)
Transient ischaemic attack	0.0% (0, 0)	1.6% (7, 7)
Valve-related readmission	7.1% (3, 2)	5.1% (18, 16)
Severe haemorrhage	4.5% (1, 1)	2.4% (11, 9)
Major vascular complication	0.0% (0, 0)	1.1% (5, 5)
Valve thrombosis	0.0% (0, 0)	0.5% (2, 2)
NYHA class III/IV	2/10 (20.0%)	21/170 (12.4%)
Improvement in NYHA class from baseline	6/10 (60.0%)	132/168 (78.6%)
Mean pressure gradient (mmHg)	15.3 ± 2.37 (10)	13.6 ± 0.63 (132)
Moderate or severe aortic regurgitation	0/10 (0.0%)	4/135 (3.0%)

[1] Device implanted successfully was defined as placement of a bioprosthetic valve in an intended site without requiring more than 1 valve.

[2] The Kaplan-Meier estimates up to 30 days and 1 year. The figures in parentheses represent the number of events and the number of patients with event. The time to the first event in each patient was used in the summarization.

Table 27. Causes of death in patients who died within 1 year (chronic dialysis patients and non-dialysis patients)

Cause of death	Chronic dialysis patients (N = 8)	Non-dialysis patients (N = 61)
Cardiac disease (other than valvular disease)	0	19
Neurological disease	0	4
Renal disease	2	2
Infection	1	2
Respiratory disease	2	2
Vascular disease	0	1
Valvular disease	0	1
Other	1	8
Unknown	2	22

The mortality at 1 year was 26.2% in chronic dialysis patients and 16.3% in non-dialysis patients, being substantially higher in chronic dialysis patients. The causes of death shown in Table 27, however, indicate no attribution of these deaths to the TAV in TAV procedure. Taking the difference in the STS score between the 2 patient groups into consideration, the above result is clinically acceptable. In addition, the mortality at 1 year after first surgical aortic valve replacement was 21% to 25.5% in patients who were eligible for surgery on chronic dialysis.[12,13] TAV in TAV with SAPIEN 3 can be a useful treatment option in patients on chronic dialysis.

The mean pressure gradient was 16.2 ± 1.57 mmHg at 30 days and 15.3 ± 2.37 mmHg at 1 year in chronic dialysis patients, and 14.3 ± 0.44 mmHg at 30 days and 13.6 ± 0.63 mmHg at 1 year in non-dialysis patients, being slightly higher in chronic dialysis patients. On the other hand, the mean pressure gradient after TAVR in the Japanese clinical study of SAPIEN 3 in patients on chronic dialysis was 11.87 ± 3.5 mmHg at 30 days and 12.42 ± 3.6 mmHg at 1 year, showing no trend of the mean pressure gradient to increase over the year. The mean pressure gradient is unlikely to increase over time substantially more in patients on chronic dialysis than patients not on dialysis.

In summary, TAV in TAV with SAPIEN 3 can be an effective, safe, and useful treatment available to patients on chronic dialysis who are not eligible for surgery.

PMDA's view:
Patients on chronic dialysis had a substantially higher 1-year mortality than patients not on dialysis. Taking the difference in the STS score between the 2 patient groups into consideration, however, these patient's factors are likely to have mainly contributed to the difference in the mortality. As reported in the publications, the mortality was 21% to 25.5% at 1 year after first SAVR in patients who were eligible for surgery on chronic dialysis. Compared with this mortality, the above result is clinically acceptable. TAV in TAV with SAPIEN 3 can be a useful treatment option available for patients on chronic dialysis. There is a risk-benefit balance. Nevertheless, careful decision by a heart team based on the patient's prognosis is required in selecting patients for this treatment since patients on chronic dialysis have a poor outcome compared to patients not on dialysis. In Japan, there are many patients on long-term dialysis, and their patient characteristics may be different from those in the US. It is, therefore, essential to evaluate SAPIEN 3, including the appropriateness of patient's selection, through a use-results survey and to take appropriate measures if necessary.

6.B.(3) Potential risk of TAV in TAV and risk mitigation measures

PMDA asked the applicant to provide detailed explanations about the risks shown below based on the characteristics of TAV in TAV with SAPIEN 3.

6.B.(3).1) Coronary artery occlusion

The applicant's explanation:

TAV in TAV appears to be associated with a relatively low risk of coronary artery occlusion because the leaflets of the host valve do not extend outwards in this procedure, unlike TAVR in a native aortic valve or TAV in SAV. To investigate whether the risk of coronary artery occlusion is higher in TAV in TAV than TAVR in a native aortic valve or TAV in SAV, the incidence of coronary artery occlusion at 30 days after each procedure with SAPIEN 3 was compared.

As shown in Table 28, the incidence of coronary artery occlusion was 0.2% in TAVR with a native aortic valve and 1.0% in TAV in SAV with SAPIEN 3. Coronary artery occlusion or coronary artery compression occurred in 3 patients who underwent TAV in TAV with SAPIEN 3 by 30 days (host valve; SAPIEN series in 1 patient, other than SAPIEN series in 2 patients). The Kaplan-Meier estimates of these events (0.5%) did not substantially differ from the other procedures. Information on preoperative angiography to ensure the absence of coronary artery occlusion and the use of the proper method of valve placement in TAV in TAV, as in TAVR in a native aortic valve or TAV in SAV, will be provided in training materials to reduce the risk of coronary artery occlusion.

Table 28. Comparison of the risk of coronary artery occlusion among the procedures

	TAVR in a native aortic valve	TAV in SAV	TAV in TAV
	PARTNER II study S3HR[1] (N = 583)	TVT Registry (N = 6,382)	TVT Registry (N = 587)
Coronary artery occlusion at 30 days[2]	0.2%	1.0%[3]	0.5%[3]

[1] Inoperable/high-risk patient group in the PARTNER II study SAPIEN 3 cohort
[2] Kaplan-Meier estimate
[3] "Coronary artery occlusion or coronary artery compression" cases in the TVT Registry

PMDA concluded that the applicant's explanation that appropriate information would be provided through training to reduce the risk of coronary artery occlusion was agreeable because TAV in TAV with SAPIEN 3 was not shown to be associated with a substantially high risk of coronary artery occlusion.

6.B.(3).2) Difficult coronary access after TAV in TAV

The applicant's explanation:

In placement of SAPIEN 3 alone in a native aortic valve, coronary access appears to be relatively easy after the procedure as the mesh of the stent frame is open. On the other hand, TAV in TAV where SAPIEN 3 is placed on top of the host valve may make future coronary intervention difficult because the mesh of the stent frame is blocked by the leaflets of the host valve, which makes catheterization challenging. It is, therefore, important to assess the position of the coronary ostium and the diameter of the Valsalva sinus appropriately prior to the procedure, and carefully make a decision on whether the patient should undergo TAV in TAV with SAPIEN 3. If the patient has coronary artery stenosis prior to TAV in TAV, it is also critical for a heart team to carefully examine a treatment strategy, including the treatment of the affected coronary artery such as coronary intervention prior to TAV in TAV.

The following information on preoperative assessment and precautions on the placement of SAPIEN 3 to reduce the above risk will be provided in precautions and other information, and training materials: Coronary access may be difficult after the procedure, which can make the treatment of coronary artery disease challenging; and the position of the coronary ostium and the diameter of the Valsalva sinus must be appropriately assessed prior to the procedure, based on which whether the procedure should be conducted must be carefully decided.

PMDA concluded that the applicant's explanation that detailed preoperative anatomical assessment of the area around the coronary artery and consideration of preoperative coronary intervention by a heart team would be provided in precautions and other information, and training materials was agreeable because SAPIEN 3 used in TAV in TAV makes coronary access difficult due to its structure.

6.B.(3).3) Thrombosis

The applicant's explanation:

Overlapping bioprosthetic valves after TAV in TAV, which places a TAV in a host valve, may increase the incidence of thromboembolism events, i.e., thrombosis due to activated platelets caused by a disturbed flow and thrombosis due to platelet aggregation caused by blood retention. Of the overall TAV in TAV cohort in the TVT Registry, only 2 patients experienced valvular thrombosis by 1 year, and the incidence of thrombosis was as low as 0.5% at 1 year. Although the outcome of the valvular thrombosis in these 2 patients is unknown, neither of them required aortic valve reintervention and their survival throughout the follow-up period is confirmed. Both patients had a host valve other than the SAPIEN series. No valvular thrombosis is reported in patients who underwent the placement of SAPIEN 3 in a host valve of SAPIEN series.

In the US, the combination of aspirin and clopidogrel is recommended according to the risk of stroke as an anticoagulation/antiplatelet therapy in TAVR with SAPIEN 3 in a native aortic valve and TAV in SAV with SAPIEN 3. Since the results from the TVT Registry indicate that the risk of thromboembolic complications is unlikely to increase in TAV in TAV with SAPIEN 3, the same anticoagulation/antiplatelet therapy as that in TAVR in a native aortic valve and TAV in SAV is recommended in TAV in TAV. In Japan, as in the US, the same anticoagulation/antiplatelet therapy as that in TAVR in a native aortic valve and TAV in SAV should be recommended in TAV in TAV.

PMDA concluded that the applicant's explanation about postoperative antithrombotic therapy is acceptable because the incidence of valvular thrombosis is low in the TVT Registry and no valvular thrombosis has been reported in patients with a host valve of SAPIEN series. PMDA also concluded that the use of antithrombotic therapy and adverse events in Japan should be fully investigated through the use-results survey described later to reduce the risk of this event.

6.B.(3).4) Conduction disorder

The applicant's explanation:

Table 29 shows the incidence of implantation of a permanent pacemaker after TAVR in a native aortic valve, TAV in SAV, and TAV in TAV with SAPIEN 3. The incidence of this event was higher in TAV in TAV than TAV in SAV but similar to that in TAVR with a native aortic valve. TAV in TAV appears to be

not associated with a higher risk of implantation of a permanent pacemaker. This risk related to TAV in TAV with SAPIEN 3 can be tolerated provided that information on appropriate sizing, placement depth, and preoperative assessment of the host valve is provided.

Table 29. Comparison of the risk of implantation of a permanent pacemaker among the procedures

Implantation of a permanent pacemaker[1]	TAVR in a native aortic valve			TAV in SAV	TAV in TAV	
	PARTNER II study S3HR[2] (N = 583)	PARTNER 3 study[3] (N = 496)	Clinical study in patients on dialysis[4] (N = 28)	TVT Registry (N = 6,382)	TVT Registry (N = 587)	TVT Registry SAPIEN series (N = 116)
30 days	14.1%	6.5%	7.1%	2.2%	6.9%	7.3%
1 year	16.8%	7.3%	7.1%	3.6%	9.2%	9.1%

[1] Kaplan-Meier estimate
[2] The previous clinical study in patients with severe native aortic valve stenosis who were not eligible for surgery
[3] The previous clinical study in patients with severe native aortic valve stenosis who were eligible for surgery
[4] A previous clinical study in patients on chronic dialysis with severe native aortic valve stenosis who were not eligible for surgery

PMDA asked the applicant to explain the reason for the higher incidence of implantation of a permanent pacemaker in TAV in TAV than TAV in SAV.

The applicant's explanation:
The lower incidence of conduction disorder in TAV in SAV can be explained by the position of the host valve. All host valves that are expected to be managed through TAV in TAV with SAPIEN 3 are placed within the annulus (intra-annular). On the other hand, many stented surgical bioprosthetic valves that are managed through TAV in SAV are placed on the annulus (supra-annular). When the host valve is a stented surgical bioprosthetic valve, a TAV valve is placed high (depth of the frame in the left ventricular outflow tract). The recommended placement depth of SAPIEN 3 is based on the position of the host valve. When the host valve is positioned supra-annular, the SAPIEN 3 valve is placed high, with the frame of the planted valve pressing the impulse conducting system running through the intraventricular septum, which reduces the risk of conduction disorder. This means, in relative terms, TAV in TAV is associated with a higher risk of conduction disorder than TAV in SAV.

PMDA's view:
TAV in TAV with SAPIEN 3 is associated with a certain level of risk (not low risk) of conduction disorder. However, there is no substantial difference from the risk of conduction disorder in TAVR in a native aortic valve, and the proposed target population of TAV in TAV with SAPIEN 3 is patients who are not eligible for surgery. In conclusion, the above result is acceptable.

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

The applicant's explanation:
Table 30 shows the post-marketing safety measures to be taken. The introduction of TAV in TAV is not intended to loosen the conventional facility criteria, etc. for TAVR. In selecting the first-line treatment for patients with aortic valve stenosis, SAVR, a conventional procedure, should be carefully considered by a heart team. In addition, since the proposed target population of TAV in TAV may include the oldest-old patients, the possible therapeutic interventions must be thoroughly discussed by a heart team based on the patient's opinion. It is critical to select appropriate patients. Information to ensure compliance

with the proper use statements in the expanded indication of TAV in TAV issued by relevant academic societies will be published in cooperation with those relevant academic societies.

Table 30. Post-marketing safety measures for TAV in TAV with SAPIEN 3

Facility criteria		• The facility is qualified as a supervisory TAVR facility and expert TAVR facility, as well as having an Edwards's TAVR system device supervisory doctor. • Full data from all patients who have undergone TAVR at the facility are registered in the registry. • Physicians have received a series of training sessions on TAV in TAV provided by Edwards. (To be qualified for performing TAV in TAV in patients on chronic dialysis, surgeons must fulfill the facility criteria for TAVR in patients on chronic dialysis.)
Training	Group training	Physicians experienced in TAV in TAV will be invited from the US to the group training and give training on the following issues, including the training manual: • Guidance on size selection of a valve to be used in TAV in TAV and position of valve placement • Assessment of the host valve's position and mechanism of valve failing • Screening criteria for coronary access Evidence on the relative position of the coronary artery and a host valve (e.g., Valve to Aorta distance)
	On-site training	Support of risk evaluation and procedure planning using the training manual as necessary
Technical support	Patient screening	Risk evaluation of TAV in TAV in at least first 4 patients by a screening proctor
	Support of procedure selection	Consultation with a Japanese proctor is available as necessary.
	A company's representative is present at each procedure.	Consultation with a Japanese proctor is available as necessary.

PMDA's view:

While the procedural aspect of TAV in TAV with SAPIEN 3 is similar to that of TAV in SAV, age and other characteristics of target patients are expected to differ between the 2 procedures. To optimize the risk-benefit balance of SAPIEN 3 in the proposed target population, it is most critical for surgeons to acquire necessary skills through training, proctor system, etc., fully understand the characteristics of the treatment with SAPIEN 3, and determine whether TAV in TAV with SAPIEN 3, or conservative medical or surgical therapy should be performed for patients. The applicant has proposed the facility criteria, training, and technical support system, and planned to take necessary measures to ensure that users comply with the proper use statements issued by relevant academic societies. The applicant's policy is acceptable.

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 31 shows a summary of the use-results survey plan (draft) of SAPIEN 3. Since SAPIEN 3 is expected to be used in a small number of patients in Japan, all patients who undergo this procedure during the registration period are planned to be registered in the survey. Because of differences in body size and the environment of dialysis between Japanese patients and US patients, data from patients who

receive the 20-mm valve and patients on chronic dialysis are of particular importance. To register as many of them as possible, a longer registration period (5 years) than other patients has been determined.

Table 31. Summary of the use-results survey plan (draft)

Item	Description
Objective	To evaluate the safety and efficacy of SAPIEN 3 in clinical practice in the proposed target population of TAV in TAV with SAPIEN 3
Target sample size	All patients who undergo the procedure during the registration period
Rationale	In the TVT Registry, the Kaplan-Meier estimate of a serious adverse event related to death, which was used as a safety endpoint, was 17.0% at 1 year in patients who received SAPIEN 3. A total of 17 patients are needed to detect an event with the incidence of 17.0% in at least 1 patient with a probability of ≥95%. On the basis of this number and considering the number of candidate patients expected from the market share of SAPIEN 3, all patients registered during the 3-year registration period will be included in the survey. To collect as much data as possible from patients who receive the 20-mm valve and patients on chronic dialysis, all patients in these cohorts registered during the 5-year registration period will be included in the survey.
Survey period	Survey period: 7 years (preparation for marketing, 0.5 years; registration + follow-up, 6 years; data entry/analysis, 0.5 years) Registration period: 3 years 5 years for patients who receive the 20-mm valve and patients on chronic dialysis Follow-up period: Up to 5 years
Key survey items	• All-cause death • Stroke • Remaining pressure gradient (mean pressure gradient >20 mmHg) • Moderate or severe aortic regurgitation

7.B Outline of the review conducted by PMDA

PMDA's view:

For the following reasons, information should be collected from all patients who undergo TAV in TAV with SAPIEN 3, the safety and efficacy should be evaluated, the eligibility of patients who have received SAPIEN 3 should be verified, and additional risk mitigation measures should be taken as necessary.

- Since no clinical results of TAV in TAV are available in Japan, use results in Japan should be promptly provided to healthcare professionals to support the proper use of SAPIEN 3.
- Whether the proposed post-marketing safety measures are sufficient should be determined to take additional measures as necessary.

The applicant has established a longer registration period for patients who receive the 20-mm valve and patients on chronic dialysis in order to collect as much data/information as possible during the survey period because of possible differences in body size and the environment of dialysis between Japanese patients and US patients. This applicant's strategy is acceptable.

PMDA concluded that the draft plan of the use-results survey is acceptable and that this should be added as an approval condition.

8. Documents Related to Precautions and Other Information Specified in Paragraph 1 of Article 63-2 of 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 precautions and other information (draft) as attachment in accordance with the Notification "Marketing Applications for 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 comments from the Expert Discussion, as described in Section "6.B Outline of the review conducted by PMDA," PMDA concluded that there were no particular problems with the proposed precautions and other information, provided that the applicant would provide necessary precautions.

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 compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. Prior to this application, [redacted] consultation was also conducted. 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

This partial change approval application was submitted to add an indication (TAV in TAV) of SAPIEN 3 as a medical device used in TAVR. The key issues in the review of SAPIEN 3 were (1) the efficacy and safety of TAV in TAV with SAPIEN 3 and (2) post-marketing safety measures. PMDA's view based on the comments from the Expert Discussion are described in the sections below.

(1) Efficacy and safety of TAV in TAV with SAPIEN 3

The TVT Registry has demonstrated a comparable efficacy of TAV in TAV with SAPIEN 3 to TAV in SAV. The safety evaluation showed higher mortality in the TAV in TAV cohort than the TAV in SAV cohort. Considering the results of surgical valve replacement of a failing TAV, however, the above mortality is clinically acceptable. The application submitted to the regulatory authority in Japan specifies that TAV in TAV with SAPIEN 3 should be indicated for patients who are not eligible for surgery and have a failing TAV device manufactured by the applicant. PMDA reviewed the clinical results from this patient population and found no particular problem. In summary, the benefits of SAPIEN 3 exceed its risks as a new treatment option available for patients with symptomatic cardiac disease due to a failing transcatheter bioprosthetic aortic valve who are not eligible for surgery in Japan.

(2) Post-marketing safety measures

While the procedural aspect of TAV in TAV is similar to that of TAV in SAV, age and other characteristics of target patients are expected to differ between the 2 procedures. To optimize the risk-benefit balance of SAPIEN 3 in the proposed target population, it is most critical for surgeons to acquire necessary skills through training, proctor system, etc., fully understand the characteristics of the treatment with SAPIEN 3, and determine whether TAV in TAV with SAPIEN 3, or conventional medical or surgical therapy should be performed for patients. In addition, since complications associated with SAPIEN 3 or implantation procedure must be treated appropriately, the procedure must be performed by surgeons with adequate experience in TAVR for the treatment of severe aortic valve stenosis at medical institutions with a well-established system for possible complications (Approval Condition 1 [1]). The results of Japanese clinical studies of TAV in TAV are not available. Information, including treatment results and incidence of adverse events in clinical practice in Japan, must be collected through a use-results survey, and additional risk mitigation measures should also be taken as necessary (Approval Condition 1 [6]). The use-results survey period should be 7 years (preparation for marketing, 0.5 years; registration + follow-up, 6 years; analysis period, 0.5 years).

As a result of the above review, PMDA has concluded that SAPIEN 3 may be approved for the intended use shown below. The intended use and approval conditions proposed to be changed in this partial change application are underlined.

Intended Use

Edwards SAPIEN 3 is a balloon-expandable prosthetic cardiac valve (bovine pericardial tissue valve) system used for percutaneous cardiac valve implantation in the following patients:

- Patients with severe symptomatic aortic valve stenosis attributed to degenerative calcification of the native aortic valve cusp of which treatment with SAPIEN 3 is considered as their best therapeutic option. In the case of chronic dialysis patients, however, the treatment with SAPIEN 3 is limited to patients who are not eligible for surgery and of which treatment with SAPIEN 3 is considered as their best therapeutic option.
- Patients with symptomatic valvular disease due to failing (stenosed, insufficient, or combined) of a surgical <u>or transcatheter</u> bioprosthetic aortic valve who are not eligible for surgery and of which treatment with SAPIEN 3 is considered as their best therapeutic option. <u>Expect for the patients who have multiple bioprosthetic valves in the aortic position.</u>
- Patients with failing (stenosed, insufficient, or combined) of a surgical right ventricular outflow tract extracardiac conduit or bioprosthetic valve in the pulmonic position that was implanted during surgery to treat congenital heart disease who are not eligible for surgery and of which treatment with SAPIEN 3 is considered as their best therapeutic option. Except for the patients who have or need a stent in the target implant site of SAPIEN 3 and patients on chronic dialysis

Approval Conditions

1. Transcatheter aortic valve replacement

(1) Treatment in all eligible patients

1) The applicant is required to take necessary measures in cooperation with related academic societies to ensure that the product is used by surgeons with adequate knowledge and experience in the treatment of symptomatic severe aortic valve stenosis at medical institutions

with a well-established system for possible complications in association with the treatment with the product.

2) The applicant is required to take necessary measures in cooperation with related academic societies to ensure that the product is used, in compliance with the indication, by surgeons as described in 1) in the treatment using the product after acquiring sufficient skills for using the product and adequate knowledge about procedure-related complications by attending relevant training courses or by other means.

3) The applicant is required to take necessary measures in cooperation with related academic societies to ensure that the product is used only in intended patients for the treatment with the product.

(2) Treatment in patients on chronic dialysis with severe symptomatic aortic valve stenosis attributed to degenerative calcification of the native aortic valve cusp who are not eligible for surgery and of which treatment with the product is considered as their best therapeutic option

1) The applicant is required to conduct a use-results survey covering all patients treated with the product, report the results of interannual analyses to the Pharmaceuticals and Medical Devices Agency, and take other appropriate measures as necessary until data from a certain number of patients have been accumulated.

(3) Treatment in patients not on chronic dialysis with severe symptomatic aortic valve stenosis attributed to degenerative calcification of the native aortic valve cusp who are eligible for surgery and of which treatment with the product is considered as their best therapeutic option

1) The applicant is required to submit reports on the results of analyses of long-term prognosis of patients in the clinical study included in this regulatory submission to Pharmaceuticals and Medical Devices Agency and to take appropriate measures as necessary.

(4) Treatment in patients not on chronic dialysis with symptomatic valvular disease due to failing (stenosed, insufficient, or combined) of a surgical bioprosthetic aortic valve who are not eligible for surgery and of which treatment with the product is considered as their best therapeutic option

1) The applicant is required to conduct a use-results survey covering all patients treated with the product, report the results of interannual analyses to the Pharmaceuticals and Medical Devices Agency, and take other appropriate measures as necessary until data from a certain number of patients have been accumulated.

2) The applicant is required to report the perioperative results with the 20-mm valve, which is to be investigated through the use-results survey, to Pharmaceuticals and Medical Devices Agency every certain number of patients in a timely manner and to take appropriate measures as necessary.

(5) Treatment in patients on chronic dialysis with symptomatic valvular disease due to failing (stenosed, insufficient, or combined) of a surgical bioprosthetic aortic valve who are not eligible for surgery and of which treatment with the product is considered as their best therapeutic option

1) The applicant is required to conduct a use-results survey covering all patients treated with the product, report the results of interannual analyses to the Pharmaceuticals and Medical Devices Agency, and take other appropriate measures as necessary until data from a certain number of patients have been accumulated.

(6) Treatment in patients with symptomatic valvular disease due to failing (stenosed, insufficient, or combined) of a transcatheter bioprosthetic aortic valve who are not eligible for surgery and of which treatment with the product is considered as their best therapeutic option

1) The applicant is required to conduct a use-results survey covering all patients treated with the product, report the results of interannual analyses to the Pharmaceuticals and Medical Devices Agency, and take other appropriate measures as necessary.

2. Transcatheter pulmonary valve replacement

(1) The applicant is required to develop and appropriately implement a post-marketing risk management plan.

(2) The applicant is required to take necessary measures in cooperation with related academic societies to ensure that the product is used by a heart team with adequate knowledge and experience in the treatment of congenital heart disorder and percutaneous aortic valve replacement at limited medical institutions with a well-established system for possible complications in association with the treatment with the product.

(3) The applicant is required to take necessary measures in cooperation with related academic societies to ensure that the product is used, in compliance with the indication, by surgeons of the heart team as described in (2) in the treatment using the product after acquiring sufficient skills for using the product and adequate knowledge about procedure-related complications by attending relevant training courses or by other means.

(4) The applicant is required to take necessary measures in cooperation with related academic societies to ensure that the product is used only in intended patients for the treatment with the product.

(5) The applicant is required to conduct a use-results survey covering all patients treated with the product, report the results periodically to the Pharmaceuticals and Medical Devices Agency, and take other appropriate measures as necessary in cooperation with related academic societies until data from a certain number of patients have been accumulated.

The product is classified as a biological product. The product is designated as a medical device subject to a use-results survey. The use-results survey period should be 7 years.

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

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