October 16, 2015

Medical Device and Regenerative Medicine Product Evaluation Division
Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Report on the Deliberation Results

[Classification]	Instrument & Apparatus 51, Suckers, tubes and catheters for infusion or drainage
[Generic name]	Cardiac ablation catheter
[Brand name]	SATAKE-HotBalloon Catheter
[Applicant]	Toray Industries, Inc.
[Date of application]	November 26, 2014 (Application for marketing approval)

[Results of deliberation]
The results of deliberation of the Committee on Medical Devices and *In-vitro* Diagnostics on October 16, 2015 are as described below. It was concluded that the results should be reported to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

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

[Conditions for approval of the marketing application]
1. The applicant is required to take necessary measures to ensure the use of the product at medical institutions that meet the requirements established in cooperation with relevant academic societies, so that the product will be used at medical institutions which are staffed with physicians with adequate knowledge of and experience in percutaneous catheter ablation procedures for the treatment of arrhythmias including atrial fibrillation and which are prepared to manage procedural complications.
2. The applicant is required to take necessary measures to ensure that physicians attend appropriate training sessions to perform ablation procedures with the product in compliance with the requirements established in cooperation with relevant academic societies, so that the

product will be used, in compliance with the approved indication, by physicians with adequate knowledge of and experience in the technique of percutaneous catheter ablation using the product for the treatment of arrhythmias including atrial fibrillation, and the management of procedural complications, etc.

Review Report

September 29, 2015
Pharmaceuticals and Medical Devices Agency

The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following medical device submitted for registration are as follows.

[Classification]	:	Instrument & Apparatus 51, Suckers, tubes and catheters for infusion or drainage
[Generic name]	:	Cardiac ablation catheter
[Brand name]	:	SATAKE-HotBalloon Catheter
[Applicant]	:	Toray Industries, Inc.
[Date of application]	:	November 26, 2014
[Reviewing office]	:	Office of Medical Devices I

Review Results

September 29, 2015

[Classification]	:	Instrument & Apparatus 51, Suckers, tubes and catheters for infusion or drainage
[Generic name]	:	Cardiac ablation catheter
[Brand name]	:	SATAKE-HotBalloon Catheter
[Applicant]	:	Toray Industries, Inc.
[Date of application]	:	November 26, 2014

[Results of the review]

SATAKE-HotBalloon Catheter is a radiofrequency balloon ablation catheter system and indicated for the treatment of drug-refractory recurrent symptomatic paroxysmal atrial fibrillation. The system is composed of a balloon catheter, a mixing tube, a 16 Fr dilator, and a syringe and used in conjunction with other devices including a radiofrequency generator "SATAKE-HotBalloon Generator" and a guiding sheath "Treswaltz" (applications for these devices have been filed simultaneously). SATAKE-HotBalloon Catheter has a coil electrode within the balloon. Radiofrequency energy from the radiofrequency generator (a frequency of 1.8 MHz, a maximum power output of 150 W) is delivered between a coil electrode mounted inside the balloon and return electrodes placed on the patient's back to produce Joule's heat, which allows heating of a fluid filled in the balloon, leading to heating of the entire balloon. Furthermore, the fluid within the balloon is agitated by vibration from the mixing pump attached to the radiofrequency generator to maintain a uniform temperature of the balloon surface, and the myocardial tissue in contact with the balloon is ablated.

The applicant submitted the non-clinical data, namely the results of testing of physical and chemical properties, electrical safety and electromagnetic compatibility, biological safety, stability and durability, performance, and the results of studies to support the method of use. The submitted data showed no particular problems.

The applicant submitted the clinical data, namely the results from a Japanese clinical study using a previous generation of SATAKE-HotBalloon Catheter as an investigational device (the pivotal

study). Although the differences between SATAKE-HotBalloon Catheter and the investigational device affect bond strength and airtightness, non-clinical testing demonstrated that SATAKE-HotBalloon Catheter meets the requirements for bond strength and airtightness. For this reason, Pharmaceuticals and Medical Devices Agency (PMDA) considered that the efficacy and safety of SATAKE-HotBalloon Catheter can be evaluated based on the submitted pivotal study results. The pivotal study was a multicenter, randomized, antiarrhythmic drug therapy-controlled, open-label study intended to confirm the efficacy and safety of the investigational device in drug-refractory patients with symptomatic paroxysmal atrial fibrillation (17 sites in Japan; 100 subjects in the investigational device group, 43 subjects in the antiarrhythmic drug therapy group). "The chronic success rate," the primary efficacy endpoint, was 59.0% (59 of 100 subjects) in the investigational device group and 4.7% (2 of 43 subjects) in the antiarrhythmic drug therapy group, which demonstrated the statistically significant superiority of the investigational device over antiarrhythmic drug therapy. Furthermore, the chronic success rate with the investigational device in the pivotal study was non-inferior to the outcomes with a radiofrequency ablation catheter and a cryoablation catheter reported in foreign literature. The chronic success rate was slightly lower in the pivotal study than the data from the Japanese radiofrequency catheter ablation registry, possibly because additional ablation after pulmonary vein isolation or reablation was not permitted and recurrence was proactively detected in the pivotal study. Moreover, the pivotal study results suggested that a learning curve exists, and the procedure time with the SATAKE-HotBalloon Catheter is expected to be shorter than the data from the Japanese registry. Taking into account all of these findings, PMDA has concluded that the efficacy of the SATAKE-HotBalloon Catheter is clinically acceptable. The safety of the SATAKE-HotBalloon Catheter was evaluated, focusing on pulmonary vein stenosis, cerebral infarction, phrenic nerve paralysis, adverse events related to puncture site, esophageal injury, atrio-esophageal fistula, cardiac perforation, and cardiac tamponade, because none of the adverse events observed in the pivotal study were specific to SATAKE-HotBalloon Catheter and the product is an ablation device to treat atrial fibrillation. Malfunctions related to the balloon shape were assessed, focusing on balloon pinholes. PMDA has concluded that the safety of SATAKE-HotBalloon Catheter is acceptable, provided that appropriate precautions against each adverse event/malfunction are advised. Since these necessary precautions have been included in the label, PMDA has concluded that there is no particular problem with the information contained in the label at present. SATAKE-HotBalloon Catheter is different from conventional radiofrequency ablation catheters and a cryoballoon ablation catheter which has just been introduced into the Japanese market in terms of the procedures, shape, and the principle of ablation, and the number of patients assessed in the pivotal study was very limited. Therefore PMDA considers that a use-results survey should be conducted and information on the safety and efficacy of SATAKE-HotBalloon Catheter in routine clinical

settings should be promptly provided to healthcare professionals in clinical practice.

PMDA conducted an overall evaluation of the submitted data, taking into account the comments from the Expert Discussion. Consequently, PMDA has concluded that the efficacy and safety of SATAKE-HotBalloon Catheter are acceptable. PMDA has also concluded that after the market launch, physicians with adequate experience in percutaneous catheter ablation procedures, who have attended appropriate training sessions on SATAKE-HotBalloon Catheter, should use the product at medical institutions that are prepared to manage various complications.

As a result of its regulatory review, the PMDA has concluded that the SATAKE-HotBalloon Catheter may be approved for marketing for the following intended use, with the following conditions, and that this application should be subject to deliberation by the Committee on Medical Devices and *In-vitro* Diagnostics.

[Intended use]
The product is used for radiofrequency hot balloon ablation of cardiac tissue to treat drug-refractory recurrent symptomatic paroxysmal atrial fibrillation.

[Conditions for approval]
1. The applicant is required to take necessary measures to ensure the use of the product at medical institutions that meet the requirements established in cooperation with relevant academic societies, so that the product will be used at medical institutions which are staffed with physicians with adequate knowledge of and experience in percutaneous catheter ablation procedures for the treatment of arrhythmias including atrial fibrillation and which are prepared to manage procedural complications.
2. The applicant is required to take necessary measures to ensure that physicians attend appropriate training sessions to perform ablation procedures with the product in compliance with the requirements established in cooperation with relevant academic societies, so that the product will be used, in compliance with the approved indication, by physicians with adequate knowledge of and experience in the technique of percutaneous catheter ablation using the product for the treatment of arrhythmias including atrial fibrillation, and the management of procedural complications, etc.

Review Report

September 29, 2015

I. Product for Review

[Classification]	:	Instrument & Apparatus 51, Suckers, tubes and catheters for infusion or drainage
[Generic name]	:	Cardiac ablation catheter
[Brand name]	:	SATAKE-HotBalloon Catheter
[Applicant]	:	Toray Industries, Inc.
[Date of application]	:	November 26, 2014
[Proposed intended use]	:	SATAKE-HotBalloon Catheter is used for radiofrequency hot balloon ablation of cardiac tissue to treat drug-refractory recurrent symptomatic paroxysmal atrial fibrillation.

II. Product Overview

SATAKE-HotBalloon Catheter is a radiofrequency balloon ablation catheter system for the treatment of drug-refractory recurrent symptomatic paroxysmal atrial fibrillation. The system is composed of a balloon catheter, a mixing tube, a 16 Fr dilator, and a syringe (Figure 1). SATAKE-HotBalloon Catheter is used in conjunction with the medical devices as shown in Table 1. During the ablation procedure, the balloon is positioned at a target site and then inflated before being pressed against the tissue around the target site. The balloon diameter can be controlled, and the balloon can be inflated to diameters of 26 to 33 mm when the recommended volume of fluid (10 to 20 ml) is injected into the balloon. The principle of ablation is as follows: Radiofrequency energy from the radiofrequency generator (a frequency of 1.8 MHz and a maximum power output of 150 W) is delivered between a coil electrode mounted inside the balloon and return electrodes placed on the patient's back to produce Joule's heat, which allows heating of the fluid filled in the balloon, resulting in heating of the entire balloon. Furthermore, the fluid within the balloon is agitated by vibration created by the mixing tube squeezed by the roller in the mixing pump attached to the radiofrequency generator, to maintain a uniform temperature of the balloon surface (Figure 2). In an ablation procedure using a conventional radiofrequency ablation catheter, the tip electrode serves to deliver radiofrequency current to ablate the tissue contacted. On the other hand, an ablation procedure using SATAKE-HotBalloon Catheter allows the pulmonary vein ostium and the tissue around the antrum in contact with the hot balloon to be ablated (Figure 3).

"SATAKE-HotBalloon Generator" is used for radiofrequency energy delivery to the balloon and "Treswaltz" is used as a sheath that enables the balloon catheter to be inserted into the body and to be guided in the heart. Neither of them are included in this application, and separate applications have been filed for them.

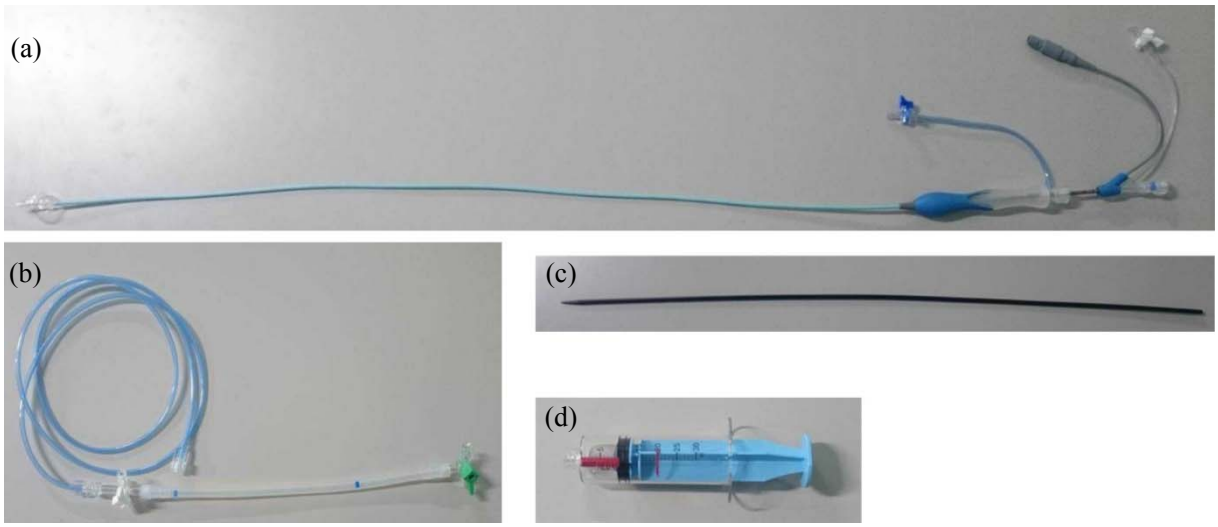

Figure 1. SATAKE-HotBalloon Catheter and its accessories
(a) balloon catheter, (b) mixing tube, (c) 16 Fr dilator, (d) syringe

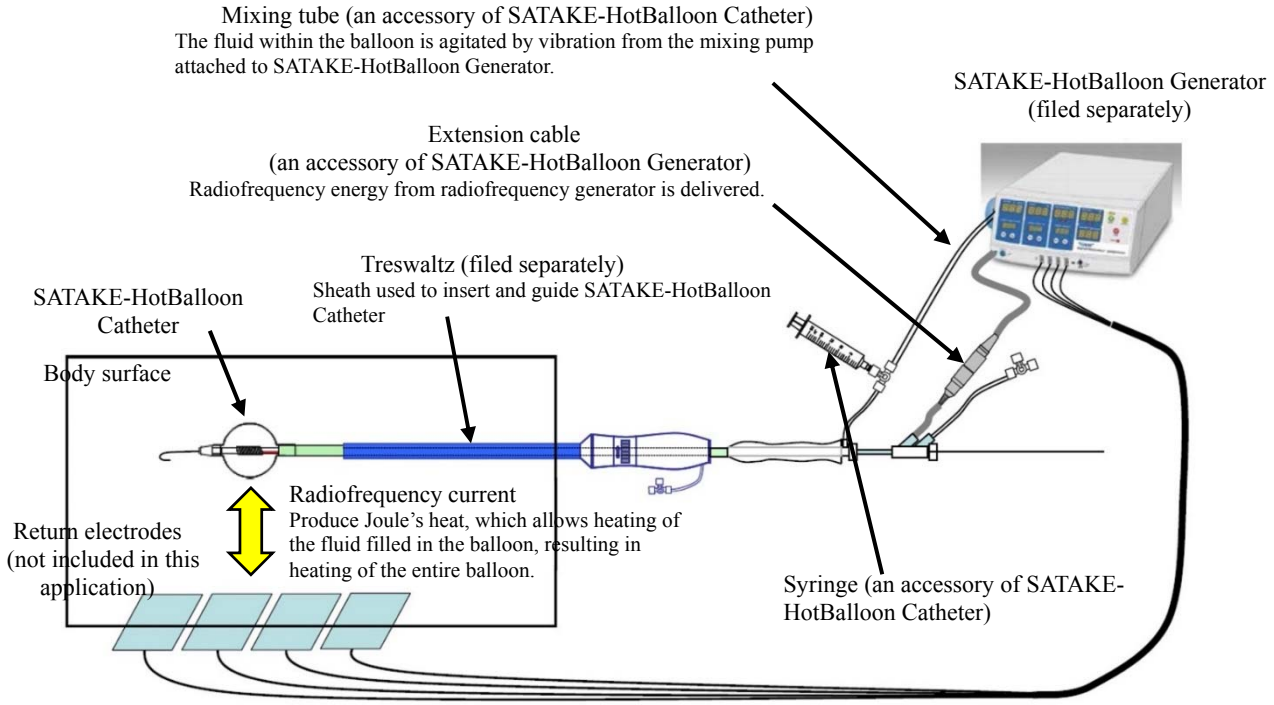

Figure 2. SATAKE-HotBalloon Catheter system

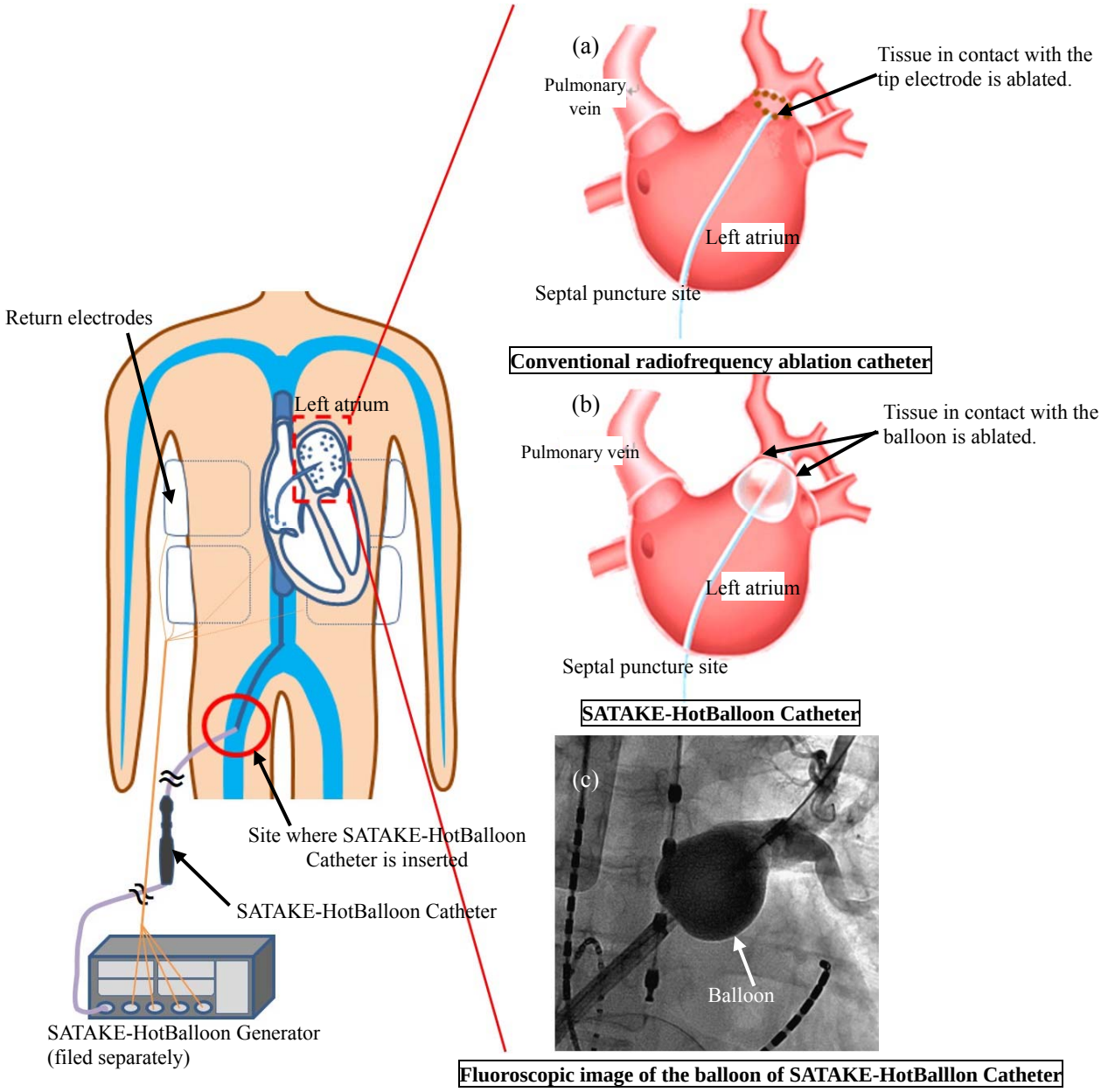

Figure 3. Principle of ablation using conventional radiofrequency ablation catheter and SATAKE-HotBalloon Catheter

(a) Conventional radiofrequency ablation catheter, (b) SATAKE-HotBalloon Catheter, (c) Fluoroscopic image of the balloon of SATAKE-HotBalloon Catheter

Table 1. Medical devices to be used in conjunction with SATAKE-HotBalloon Catheter

Brand name	Components	Approval number
SATAKE-HotBalloon Generator	Radiofrequency generator, mixing pump head, extension cable, power cord	Filed separately
Treswaltz	Deflectable guiding sheath, dilator	Filed separately
Accessories of the electric scalpels (Non-sterile)	Return electrodes	20800BZG00059000
Spring guidewire	Spring guidewire	21100BZY00391000

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

The data submitted in this application and the applicant's responses to the inquiries from the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined below. As this application was received during the period of interim measures ending on March 31, 2015 after the enforcement of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics (PMD Act), the format of the submitted data is in accordance with Article 40, Item 5 of the Ordinance for Enforcement of the Pharmaceutical Affairs Act.

The relevant expert advisors for the Expert Discussion have declared that they do not fall under Item 5 of the "Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency" (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1. Origin or history of discovery and usage conditions in foreign countries etc.

1.(1) Origin or history of discovery

Atrial fibrillation is the most common tachyarrhythmia. The number of patients is estimated at ≥700,000 in Japan. Drug therapy or non-drug therapy is used for the treatment of atrial fibrillation. Although multiple anti-arrhythmic drugs have been approved for the treatment of atrial fibrillation, drug therapy does not necessarily result in complete cure. Unlike drug therapy, complete cure can be expected with surgical procedures.[i, ii, iii] In the late 1990s, it was found that the majority of patients with paroxysmal atrial fibrillation had the episodes triggered by abnormal impulses originating in the pulmonary veins, and treatment with a radiofrequency ablation catheter (the catheter tip electrode is brought into contact with myocardial tissue to be ablated by radiofrequency energy in order to block abnormal impulses) was introduced as a minimally invasive alternative to surgical intervention.[i, iv] Radiofrequency catheter ablation is widely used as a minimally invasive technique also in Japan, whereas some issues have been noted. The issues are described below.

Since the tip electrode of a conventional radiofrequency ablation catheter only allows point-by-point ablation, a high number of radiofrequency energy applications are required to create ablation lesions encircling the pulmonary vein ostium. This results in longer procedure time and fluoroscopy time, which have been considered as issues. In addition, since the tip electrode of a radiofrequency ablation catheter is cooled by blood flow, excessive radiofrequency current may be delivered to increase the electrode temperature. As a result, deep myocardial tissue may be

heated to temperatures exceeding the preset value for the electrode.[v] Subsequently, irrigated catheters were developed. Irrigated catheters allow myocardial tissue and the ablation catheter electrode to be cooled with irrigating solutions such as normal saline during ablation in order to avoid excessive ablation.

Considering the above situation, the applicant developed SATAKE-HotBalloon Catheter whose heated balloon could create a circular lesion on the tissue around the circumference of the pulmonary vein ostium with a single application of energy. Since the balloon of SATAKE-HotBalloon Catheter can produce an ablated area of the tissue and can ablate an extensive area of the tissue with a single application of energy, the simplification of the procedure is expected to reduce procedure time and fluoroscopy time. The heat transmitted from the balloon surface ablates myocardial tissue, which is less likely to cause a reduction in temperature by blood flow. Complications related to superheating of deep myocardial tissue due to excessive energy delivery are expected to be reduced. Moreover, because SATAKE-HotBalloon Catheter has no irrigation system, fluid loading due to irrigation does not occur.

The prototype went through multiple improvements before leading to the final product (Table 2). In [redacted], a pilot study was conducted using the prototype ablation catheter (NTA-1) and the prototype of "SATAKE-HotBalloon Generator" (RFX-1) (a medical device to be used in conjunction with SATAKE-HotBalloon Catheter) to evaluate the safety and efficacy of NTA-1/RFX-1. The clinical data from the pilot study were submitted as the reference data in this application (the details are described in "8. Clinical data"). [redacted]. TSB-001 (the prototype) consists of NTA-1, an improved version of RFX-1 radiofrequency generator (SRF-1), and a sheath (DGS). Then, improvements were made primarily to increase the efficacy of TSB-001, and TSB-002 was developed. TSB-002 consists of an improved version of NTA-1 ablation catheter (NTA-2), SRF-1, and an improved version of DGS sheath (DGS-1, which is "Treswaltz," a medical device to be used in conjunction with SATAKE-HotBalloon Catheter). In [redacted], another pilot study was conducted using TSB-002 to evaluate its efficacy and safety. The clinical data from the study were submitted as the reference data in this application (the details are described in "8. Clinical data"). The pilot study identified issues such as maneuverability and the occurrence of device malfunctions including balloon pinholes. [redacted]

[redacted]. The investigational device (TSB-002C) consists of an improved version of NTA-2 ablation catheter (NTA-2C), an improved version of SRF-1 radiofrequency generator (SRF-2C), and DGS-1. After [redacted], a pivotal study was conducted using TSB-002C in [redacted]. The study intended to assess the efficacy and safety of TSB-002C versus antiarrhythmic drug therapy for the treatment of patients with drug-refractory, symptomatic paroxysmal atrial fibrillation. The clinical data from the pivotal study were submitted in this application (the details are described in "8. Clinical data"). Since device malfunction (output stop) occurred in the pivotal study, improvements were made in order to address this device malfunction, improve maneuverability, and simplify the manufacturing process. This led to the development of TSB-002E. TSB-002E consists of an improved version of NTA-2C ablation catheter (NTA-2E), an improved version of SRF-2C radiofrequency generator ("SRF-2E," which is "SATAKE-HotBalloon Generator," a medical device to be used in conjunction with SATAKE-HotBalloon Catheter), and DGS-1. In response to the requests from healthcare professionals in Japan and the US, further improvements were made to improve maneuverability and simplify the manufacturing process, thus resulting in the development of TSB-002F. TSB-002F consists of an improved version of NTA-2E ablation catheter (NTA-2F, which is the proposed product, i.e., SATAKE-HotBalloon Catheter), SRF-2E, and DGS-1. [redacted].

Table 2. History of improvements; Changes from the previous model

Model	Balloon catheter	Radiofrequency generator	Sheath
NTA-1/RFX-1 ∗ Used in the pilot study of NTA-1/RFX-1	NTA-1	RFX-1	[redacted]
TSB-001		SRF-1 [redacted]	DGS [redacted]
TSB-002 ∗ Used in the pilot study of TSB-002	NTA-2 [redacted]	SRF-1 [redacted]	DGS-1 (Treswaltz, a medical device to be used in conjunction with SATAKE-HotBalloon Catheter) [redacted]
TSB-002B	NTA-2B [redacted]	SRF-2B [redacted]	
TSB-002C (Investigational device) ∗ Used in the pivotal study	NTA-2C [redacted]	SRF-2C [redacted]	
TSB-002E	NTA-2E [redacted]	SRF-2E (SATAKE-HotBalloon Generator, a medical device to be used in conjunction with SATAKE-HotBalloon Catheter) [redacted]	
TSB-002F	NTA-2F (SATAKE-HotBalloon Catheter) [redacted]		

1.(2) Usage conditions in foreign countries

SATAKE-HotBalloon Catheter has not been licensed or marketed in any foreign country.

2. Setting of specifications (performance and safety specifications)

2.A Summary of the submitted data

The proposed product specifications include surface (the external surface of the catheter should appear free from extraneous matter and surface defects which may cause minimum trauma to vessels during use), radiopacity, corrosion resistance, maximum guidewire diameter, airtightness and damage on inflation, catheter shaft strength, electrical resistance (resistance between the electrodes in the connector), leakage current, sterility assurance level (SAL), bacterial endotoxins, ethylene oxide sterilization residuals, and biological safety (JIS T 0993-1:2012).

The proposed specifications for the mixing tube, an accessory of SATAKE-HotBalloon Catheter, include airtightness and sterility assurance level (SAL).

The proposed specifications for the 16 Fr dilator, an accessory of SATAKE-HotBalloon Catheter, include surface (the external surface should appear free from extraneous matter and surface defects which may cause minimum trauma to vessels during use), maximum guidewire diameter, sterility assurance level (SAL), bacterial endotoxins, ethylene oxide sterilization residuals, and biological safety (JIS T 0993-1:2012).

The specifications for the syringe, an accessory of SATAKE-HotBalloon Catheter, include sterility assurance level (SAL).

2.B Outline of the review by PMDA

PMDA instructed the applicant to include the following requirements in the product specifications: balloon rupture (the balloon dose not rupture when filled with [redacted] mL of fluid), air leakage under reduced pressure (no ingress of air occurs when a reduced pressure is applied to the catheter lumen), catheter elongation (the elongated balloon catheter can be inserted into and withdrawn from the sheath), torque, temperature control (balloon surface temperature is controlled to a preset value, the difference in surface temperature [redacted] is within a range of ±[redacted]°C, and the preset surface temperature is reached within [redacted] minutes), current overload (no damage to the catheter after [redacted] applications of energy, the difference in the maximum balloon surface temperature between the first and [redacted]th applications of energy is within a range of ±[redacted]°C), and balloon compliance. The proposed device was tested for these requirements in non-clinical studies.

The applicant included balloon rupture, air leakage under reduced pressure, catheter elongation,

torque, temperature control, current overload, and balloon compliance in the product specifications.

PMDA checked the additional specifications, reviewed the data on the setting of specifications, including "5. Performance," which is described later, and then concluded that there is no particular problem.

3. Stability and durability

3.A Summary of the submitted data

The applicant submitted real-time stability and durability data, namely the results of the following tests using TSB-002E stored for [redacted] months: dimensional test, repeated balloon inflation/deflation test, bond strength test, test for air leakage under reduced pressure, mixing tube leakage test, electrical test, appearance test, sterility test, and catheter elongation test. TSB-002E, instead of TSB-002F (SATAKE-HotBalloon Catheter), was used in these tests. [redacted] differ between TSB-002E and TSB-002F, but these differences are not related to the dimensions, airtightness, balloon performance, etc. The use of the submitted data in the evaluation of SATAKE-HotBalloon Catheter was considered acceptable.

Tests were selected so as to ensure that the specification requirements for SATAKE-HotBalloon Catheter after storage are met, and as a result of testing, all acceptance criteria were met. The test results after [redacted]-month storage were comparable to those immediately after sterilization, demonstrating [redacted]-month stability of the test device. Based on these results, a shelf life of 10 months was proposed. A stability study protocol for a [redacted]-month study was submitted. The test results after [redacted]-month storage and those immediately after sterilization both met the acceptance criteria and there were no time-dependent changes in test results. For these reasons, the shelf life can be extended by conducting a study according to the protocol.

3.B Outline of the review by PMDA

PMDA concluded from the review of stability and durability data that the proposed shelf life of 10 months is acceptable at present. Moreover, PMDA concluded that the shelf life can be extended if a study for extending the shelf life is completed according to the protocol and if the test results demonstrate the stability of SATAKE-HotBalloon Catheter.

4. Conformity to the requirements specified in Article 41, Paragraph 3 of the Pharmaceutical Affairs Act

4.A Summary of the submitted data

A declaration of conformity declaring that the product meets the requirements for medical devices as stipulated by the Minister of Health, Labour and Welfare in accordance with Article 41, Paragraph 3 of the Pharmaceutical Affairs Act (MHLW Ministerial Announcement No.122 of 2005, i.e., "old Essential Principles"[1]) was submitted.

4.B Outline of the review by PMDA

The product application was filed after the enforcement of the PMD Act, but during the period of interim measures (ending on November 24, 2015) following the implementation of the new Essential Principles for medical devices (November 25, 2014). According to the Notification No. 1105-5 of the Counselor of Minister's Secretariat, MHLW, dated November 5, 2014, the old Essential Principles is applicable to products submitted during the period of interim measures. Therefore, PMDA used the submitted data to review the conformity of SATAKE-HotBalloon Catheter to the old Essential Principles.

Since PMDA's review identified the following issues in the initial results of assessment by the applicant, PMDA instructed the applicant to address these issues.

(a) Article 1 specifies the assumptions, etc., for the design of medical devices (especially, the assumed level of technical knowledge and experience that the user of the medical device has, and to what extent education and training should be given to the user). The conformity of SATAKE-HotBalloon Catheter to the above provisions was assessed. As later described in "8.B.(3).1) Pulmonary vein stenosis," users should be informed of specific risks, e.g., lower balloon inflation volume, which was identified as a risk factor for pulmonary vein stenosis, etc., in the pivotal study. The risk-related information initially proposed by the applicant was considered inadequate, and PMDA thus instructed the applicant to take additional risk reduction measures, i.e., provision of information about specific procedural precautions against pulmonary vein stenosis and training on these precautions. The applicant accepted it.

(b) Article 2, Item 4 specifies disclosure of any residual risks observed after risk reduction measures were taken. The conformity of SATAKE-HotBalloon Catheter to the above provisions was assessed. As later described in "8.B.(3).5) Esophageal injury and atrio-esophageal fistula," adverse events for which a relationship to esophageal cooling could not be ruled out occurred and aspiration pneumonia is a noteworthy adverse event. Therefore,

[1] Differences between the old and new Essential Principles: changes and additions were made regarding considerations for design and manufacture, considerations for use environment, considerations for medical devices using programs, considerations for medical devices intended for use by lay persons, and information to be provided to users by labels or other materials.

the adverse event-related information initially proposed by the applicant was considered inadequate. PMDA instructed the applicant to take additional risk reduction measures, namely assessment of the details of esophageal cooling (infused volume of cooling water, the number of infusions, esophageal temperature before and after infusion) and associated adverse events in the use-results survey, leading to further safety measures. The applicant accepted it.

As later described in "8.B.(4).1) Post-marketing safety measures," the balloon inflation volume was below the recommended level in many subjects in the pivotal study. This may be related to the occurrence of adverse events, and the information proposed initially by the applicant was considered inadequate. Therefore, PMDA instructed the applicant to take additional risk reduction measures, namely assessment of the distribution of the balloon inflation volumes and the detailed report of patients treated with the device with low balloon inflation volume (the cause and the occurrence of adverse events) in the use-results survey, leading to further safety measures. The applicant accepted it.

Based on the above, PMDA comprehensively reviewed the conformity of SATAKE-HotBalloon Catheter to the old Essential Principles. PMDA concluded that there is no particular problem.

5. Performance

5.(1) Physical and chemical properties

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

The applicant submitted the data on the physical and chemical properties of SATAKE-HotBalloon Catheter, namely the results of radiopacity test, corrosion resistance test, dimensional test, balloon rupture test, bacterial endotoxins test, repeated balloon inflation/deflation test, bond strength test, test for air leakage under reduced pressure, catheter elongation test, torsional bond strength test, torque test, mixing tube leakage test, catheter tube temperature measurements, and test to assess agitating volume. TSB-002E, instead of TSB-002F (SATAKE-HotBalloon Catheter), was used in these tests. [redacted] differ between TSB-002E and TSB-002F, but these differences are not related to the tests. The use of the submitted data in the evaluation of SATAKE-HotBalloon Catheter was considered appropriate.

The test results met all the acceptance criteria, demonstrating assurance of the physical and chemical properties of SATAKE-HotBalloon Catheter.

5.(1).B Outline of the review by PMDA

PMDA reviewed the data on physical and chemical properties, and concluded that there is no particular problem.

5.(2) Electrical safety and electromagnetic compatibility

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

The submitted data on the electrical safety and electromagnetic compatibility of SATAKE-HotBalloon Catheter consisted of the results of electrical test (resistance between the electrodes in the connector) and leakage current test. TSB-002E, instead of TSB-002F (SATAKE-HotBalloon Catheter), was used in the electrical test. [redacted] differ between TSB-002E and TSB-002F, but these differences are not related to the resistance between the electrodes. The use of the submitted data in the evaluation of SATAKE-HotBalloon Catheter was considered appropriate. TSB-002, instead of TSB-002F (SATAKE-HotBalloon Catheter), was used in the leakage current test. [redacted] differ between TSB-002E and TSB-002F. The leakage current test is performed to monitor leakage currents between return electrodes and the ground and between the electrodes in the balloon and the ground. The differences between TSB-002 and TSB-002F are involved in the parts that do not affect the results of the leakage current test. For these reasons, the use of the submitted data in the evaluation of SATAKE-HotBalloon Catheter was considered appropriate.

The test results met all the acceptance criteria, demonstrating assurance of the electrical safety and electromagnetic compatibility of SATAKE-HotBalloon Catheter.

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

PMDA reviewed the data on electrical safety and electromagnetic compatibility, and concluded that there is no particular problem.

5.(3) Biological safety

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

The submitted biological safety data consist of the results of testing of TSB-002B in accordance with the "Reference data concerning the basic principles of biological safety testing" (Administrative Notice on medical device review No. 36, dated March 19, 2003) (hereinafter referred to as "Review Guideline No. 36"). The TSB-002B catheter, instead of TSB-002F (SATAKE-HotBalloon Catheter), was used in these tests. The components of the TSB-002B catheter in contact with fluid or drug solution, and treatment of these components in the

manufacturing process (the method of sterilization, the method of integrating the components into the finished product) are the same as those for SATAKE-HotBalloon Catheter. For this reason, the use of the submitted test data in the evaluation of SATAKE-HotBalloon Catheter was considered appropriate.

The tests required for external communicating devices in contact with circulating blood for a limited duration (≤24 hours) were selected for SATAKE-HotBalloon Catheter and the results of these tests were submitted. The catheter was tested for cytotoxicity, sensitization, intracutaneous reactivity, acute toxicity, pyrogenicity, hemolysis, thrombogenicity, and complement activation. The test results showed no findings of concern.

The 16Fr dilator is identical to the dilator as an accessory device used with the approved catheter of [redacted] in term of the manufacturing process including raw materials, method of use, insertion time, and sterilization. In addition, the dilator used with the approved catheter has had no malfunctions attributable to its raw materials since it was marketed. These facts were considered to support the biological safety of SATAKE-HotBalloon Catheter. As a result, the biological safety test was omitted.

After completion of the tests, Review Guideline No. 36 was abolished upon the issuance of the "Basic Principles of Biological Safety Evaluation Required for Application for Approval to Market Medical Devices" (PFSB/ELD/OMDE Notification No. 0301-20 of the Office of Medical Device Evaluation, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated March 1, 2012) (hereinafter referred to as "Notification No. 20"). All test results were confirmed to meet the requirements of Notification No. 20.

5.(3).B Outline of the review by PMDA

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

5.(4) Mechanical safety

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

The applicant explained that the mechanical safety of SATAKE-HotBalloon Catheter is covered by the data on physical and chemical properties, and thus the data for mechanical safety was not submitted.

5.(4).B Outline of the review by PMDA

Since mechanical safety data can be reviewed as part of the data for physical and chemical properties of SATAKE-HotBalloon Catheter, PMDA concluded that there is no particular problem.

5.(5) Tests to support performance

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

The submitted data on the performance of SATAKE-HotBalloon Catheter included the results from the following tests/studies: the appearance test, balloon compliance test, balloon preparation test (a test for verifying the preparation including air aspiration, temperature measurement accuracy test, temperature control test (a test for verifying that balloon surface temperature is controlled to a preset value and for verifying the difference in surface temperature [redacted] and the time the preset surface temperature is reached), current overload test (a test for verifying that no damage to the catheter is made after [redacted] applications of energy and that the difference in the maximum balloon surface temperature between the first and [redacted]th applications of energy is within the range of ± [redacted]°C), and test for conformability to the inner wall of the atrium (around the antra) (a test for verifying the relationship of the radius of the area in contact with the balloon and the contact pressure and a test for verifying that balloon surface temperature is controlled to a preset value), study to evaluate ablation characteristics in pigs, study to evaluate balloon surface temperatures of TSB-001 and TSB-002E, and study to evaluate contact areas of TSB-001 and TSB-002E.

TSB-002E, instead of TSB-002F (SATAKE-HotBalloon Catheter), was used in the appearance test, balloon compliance test, balloon preparation test, temperature measurement accuracy test, temperature control test, current overload test, and test for conformability to the inner wall of the atrium (around the antra). [redacted] differ between TSB-002E and TSB-002F, but these differences are not related to the appearance, balloon performance, or temperature sensor. For this reason, the use of the submitted data in the evaluation of SATAKE-HotBalloon Catheter was considered appropriate.

The test results met all the acceptance criteria, demonstrating assurance of the performance of SATAKE-HotBalloon Catheter.

TSB-001, instead of TSB-002F (SATAKE-HotBalloon Catheter), was used in the study to evaluate ablation characteristics in pigs. The results of this study conducted to verify the basic manipulation of SATAKE-HotBalloon Catheter and the basic ablation technique was considered

acceptable for the evaluation of SATAKE-HotBalloon Catheter for the following reasons: (1) [redacted] differ between TSB-001 and TSB-002F, but the basic structures and the principles of heating of the devices are identical; (2) the study results showed no differences in [redacted]; (3) the studies comparing TSB-001 and TSB-002E (the study to evaluate balloon surface temperatures of TSB-001 and TSB-002E and the study to evaluate contact areas of TSB-001 and TSB-002E) revealed that the balloon surface temperatures and contact areas of the two catheters were comparable; and (4) the same balloon is used in TSB-001E and TSB-002F.

In the study to evaluate ablation characteristics in pigs, 6 pigs underwent pulmonary vein ablation procedure (acute [the day of procedure] assessment, 4 pigs; chronic [30 days after procedure] assessment, 2 pigs), and the tissue was heated to 70°C for [redacted] minutes. After the ablation procedure was completed, histological assessment of the pulmonary veins, heart, lungs, brain, and others was performed. The size of the balloon for ablation ranged from [redacted] mm to [redacted] mm. In the study, electrical isolation of all but one ablated pulmonary vein was achieved. No findings such as hemodynamic instability, death, cardiac and vascular perforation, pulmonary vein stenosis, pericarditis, myocardial infarction, pericardial effusion, atrioventricular block, disorders involving the proximate tissues such as the lungs, esophagus, trachea, and aorta, thromboembolus in the brain, lungs, kidneys, and liver, phrenic nerve disorder, vomiting, or any sign of burn caused by abnormal heating of deep tissue were observed during ablation.

The above study results verified the basic ablation technique with SATAKE-HotBalloon Catheter, demonstrating assurance of its efficacy and safety.

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

PMDA reviewed the data from the tests to support performance and concluded that there is no particular problem.

5.(6) Tests to support efficacy

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

The applicant explained that the efficacy of SATAKE-HotBalloon Catheter is covered by the data from tests to support performance, and thus the data from tests to support efficacy was not submitted.

5.(6).B Outline of the review by PMDA

Since data from tests to support efficacy can be reviewed as part of the data from tests to support

performance, PMDA concluded that there is no particular problem.

5.(7) Tests to support method of use

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

The submitted data on the method of use of SATAKE-HotBalloon Catheter consist of the results from tests for compatibility with the sheath and the guidewire. TSB-002E, instead of TSB-002F (SATAKE-HotBalloon Catheter), was used in these tests. [redacted] differ between TSB-001 and TSB-002F, but these differences are not related to the balloon inserted into the sheath, shaft, or guidewire lumen. For this reason, the use of the submitted data in the evaluation of SATAKE-HotBalloon Catheter was considered appropriate.

The test results met all established acceptance criteria.

5.(7).B Outline of the review by PMDA

PMDA reviewed the data from the tests to support usage method, and concluded that there is no particular problem.

6. Risk analysis

6. A Summary of the submitted data

The applicant submitted the documents summarizing the risk management system and its implementation status in reference to ISO 14971 “Medical devices - Application of risk management to medical devices.”

6.B Outline of the review by PMDA

PMDA reviewed the risk analysis data, and concluded that there is no particular problem.

7. Manufacturing process

7. A Summary of the submitted data

The submitted manufacturing process data consisted of data on manufacturing process and facilities, quality control data, and data on sterilization method.

7.B Outline of the review by PMDA

PMDA reviewed the manufacturing process data, and concluded that there is no particular problem.

8. Clinical data

8.A Summary of the submitted data

The submitted clinical data consisted of the results from a Japanese clinical study (a pivotal study of TSB-002C for the treatment of paroxysmal atrial fibrillation). TSB-002C (the investigational device) was used instead of TSB-002F (SATAKE-HotBalloon Catheter) in the pivotal study.

The applicant's explanation:

The data from a clinical study using TSB-002C, instead of TSB-002F, can be submitted as the data from a pivotal study of TSB-002F because the differences between TSB-002C and TSB-002F [Table 2] are related to the parts that are not in contact with body fluids or drug solution and do not affect the efficacy or safety of SATAKE-HotBalloon Catheter. Thus, the applicant considered that the data from a clinical study using TSB-002C can be extrapolated to TSB-002F (SATAKE-HotBalloon Catheter).

PMDA's view:

The differences between TSB-002C used in the pivotal study and TSB-002F affect bond strength, the airtightness of the inner lumen through which the guidewire passes, and the airtightness of the balloon lumen to be filled with inflation fluid, but should not affect clinical study results as long as certain requirements are met. Since non-clinical testing results (bond strength test, test for compatibility with the guidewire, repeated balloon inflation/deflation test, test for air leakage under reduced pressure) demonstrated that SATAKE-HotBalloon Catheter meets the requirements for bond strength and airtightness, the efficacy and safety of the product can be evaluated based on the submitted pivotal study data.

8.A.(1) Pivotal study of TSB-002C for the treatment of paroxysmal atrial fibrillation] (Study period, [redacted] to [redacted])

The investigational device (TSB-002C) used in the pivotal study consists of a previous model of the ablation catheter used in SATAKE-HotBalloon Catheter (NTA-2C), a previous model of "SATAKE-HotBalloon Generator" (a device to be used in conjunction with SATAKE-HotBalloon Catheter) (SRF-2C), and "Treswaltz" (a device to be used in conjunction with SATAKE-HotBalloon Catheter) (DGS-1). The pivotal study was a multicenter, randomized, antiarrhythmic drug therapy-controlled, open-label study intended to confirm the efficacy and safety of the investigational device in drug-refractory patients with symptomatic paroxysmal atrial fibrillation. The study was conducted at 17 study sites in Japan (target sample size of 111 subjects [74 in the investigational device group and 37 in the antiarrhythmic drug therapy group for analysis of the

primary efficacy endpoint]). The key inclusion and exclusion criteria for the pivotal study are as shown in Table 3. Patients in the antiarrhythmic drug therapy group were deemed to have failed to achieve the primary efficacy endpoint of chronic success if their ECG data obtained between the end of the drug titration period (Day 29) and Week 16 visit indicated that the drug therapy was ineffective (the occurrence of a core-laboratory-confirmed atrial fibrillation episode lasting ≥30 seconds documented by a 12-lead ECG, mobile ECG, or Holter monitor, etc.) or the drug therapy could not be continued as planned due to adverse drug reactions and other reasons. Then the patients were given the option to undergo ablation using the investigational device ("crossover subjects"). However, patient crossover into the investigational device group was not permitted if the patient had an unresolved adverse drug reaction and its resolution was considered medically necessary.

Table 3. Inclusion and exclusion criteria

Inclusion criteria
[Tentative enrollment[2]] 1. Aged ≥20 years and <75 years at the time of giving consent 2. Diagnosis of symptomatic paroxysmal atrial fibrillation 3. Refractory or intolerant to ≥1 Class I, II, III or IV antiarrhythmic drug at the time of giving consent [Formal enrollment[3]] 4. At least 2 atrial fibrillation episodes between 6 months prior to giving consent and formal enrollment documented in the medical record, etc. 5. At least 1 atrial fibrillation episode lasting ≥30 seconds between 6 months prior to giving consent and formal enrollment documented by a 12-lead ECG, mobile ECG, or Holter monitor, etc.
Exclusion criteria
[Tentative enrollment] 1. Previous left atrial ablation or surgical treatment for atrial fibrillation 2. Refractory or intolerant to all of pilsicainide, cibenzoline, propafenone, disopyramide, and flecainide 3. NYHA Class III or IV heart failure 4. History of (within 6 months prior to enrollment) or current myocardial infarction or unstable angina 5. Severe ischemic heart disease or valvular disease 6. Use of a left atrial appendage occlusion device 7. Cannot take any anticoagulant drug 8. Previous participation in the present clinical study [Formal enrollment] 9. Left atrial diameter ≥50 mm 10. Left ventricular ejection fraction (LVEF) <35% 11. Presence of a left atrial thrombus 12. Deemed unsuitable for participation in the study by the investigator or sub-investigator

In the pivotal study, 153 patients were tentatively enrolled and randomized. In the end, a total of 143 patients (100 in the investigational device group, 43 in the antiarrhythmic drug therapy group) were enrolled and included in the primary efficacy analysis (Figure 4).

[2] For tentative enrollment, patients were screened by routine clinical examination (the criteria at the time of obtaining consent) and randomized to either treatment group.
[3] For formal enrollment, patients were screened by examination specific to ablation clinical trials (the criteria at formal enrollment).

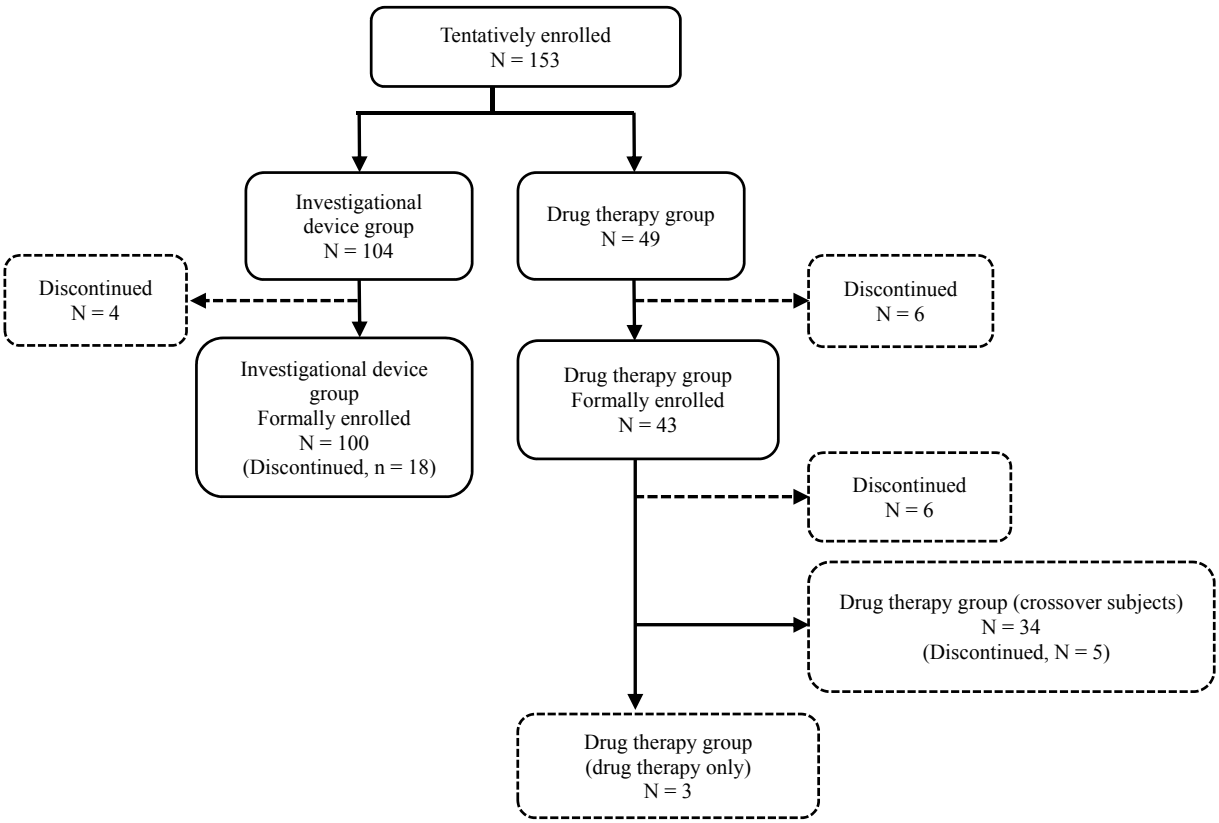

Figure 4. Subject disposition

The primary efficacy endpoint was the chronic success rate. Chronic success is as defined below.

Investigational device group:

Patients who were free from any atrial fibrillation episode lasting ≥30 seconds documented by a 12-lead ECG, mobile ECG, or Holter monitor from the end of the blanking period[4] to Week 48 visit (at 36 weeks after the blanking period) in the absence of prohibited/restricted drugs[5] and restricted therapy.[6]

Antiarrhythmic drug therapy group:

Patients who were free from any atrial fibrillation episode lasting ≥30 seconds documented by a 12-lead ECG, mobile ECG, or Holter monitor, etc., from the end of the drug titration period to Week 40 visit (at 36 weeks after the drug titration period) in the absence of prohibited/restricted drugs[7] and restricted therapy.

[4] A period for ablation lesion stabilization

[5] Class I-IV antiarrhythmic drugs for the treatment of atrial fibrillation. Class I-IV antiarrhythmic drugs considered ineffective before the ablation procedure were allowed to be used, but a drug change or a dose increase was not permitted. Where Class II or IV antiarrhythmic drugs were used for indications other than the treatment of atrial fibrillation, the use of a new drug, a drug change, and a dose increase were permitted.

[6] Cardioversion for the treatment of atrial fibrillation

[7] Changes of antiarrhythmic drugs (Classes I-IV) selected during the drug titration period and dose increases. Where Class II or IV antiarrhythmic drugs were used for indications other than the treatment of atrial fibrillation, the use of a new drug, a drug change, and a dose increase were permitted.

The chronic success rate was 59.0% (59 of 100 subjects; 95% confidence interval [CI], 48.7%-68.7%) in the investigational device group and 4.7% (2 of 43 subjects; 95% CI, 0.6%-15.8%) in the antiarrhythmic drug therapy group. The superiority of the investigational device over antiarrhythmic drug therapy was demonstrated by Fisher's exact test ($P < 0.0001$).

The secondary endpoint was the acute success rate in the investigational device group: the percentage of subjects with all pulmonary veins [PVs] (right superior pulmonary vein [RSPV], right inferior pulmonary vein [RIPV], left superior pulmonary vein [LSPV], and left inferior pulmonary vein [LIPV]) isolated and the percentage of isolated PVs among ablated PVs (RSPV, RIPV, LSPV, LIPV). Successful isolation was defined as "the achievement of an electrogram amplitude of ≤0.1 mV or dissociation of PV potentials from left atrial potentials." The percentage of subjects with all PVs (RSPV, RIPV, LSPV, LIPV) isolated was 93.0% (93 of 100 subjects; 95% CI, 86.1%-97.1%). The percentages of isolated PVs among ablated PVs (RSPV, RIPV, LSPV, LIPV) were 100.0% for RSPV (100 of 100 PVs; 95% CI, 97.0%-100.0%), 100.0% for RIPV (100 of 100 PVs; 95% CI, 97.0%-100.0%), 94.0% for LSPV (94 of 100 PVs; 95% CI, 87.4%-97.8%), and 98.0% for LIPV (98 of 100 PVs; 95% CI, 93.0%-99.8%).

Safety endpoints were major complications, adverse events, and investigational device malfunctions. Major complications were defined as the following events occurring in subjects in the investigational device group or crossover subjects.

1) A serious adverse event occurring within 7 days after the procedure
2) Any severe pulmonary vein stenosis (>70%) or esophageal perforation, cardiac tamponade, phrenic nerve paralysis, or cerebral infarction accompanied by clear neurological symptoms occurring after the procedure
3) Mild (<50%) or moderate (50%-70%) pulmonary vein stenosis (PVS) that occurred after the procedure and met one of the following criteria:
   (a) PVS requiring invasive intervention, such as PV stenting
   (b) PVS resulting in significant clinical symptoms

The incidences of major complications were 12.0% (12 of 100 subjects, 14 events) in the investigational device group and 11.2% (15 of 134 subjects, 17 events) in the combined group consisting of subjects in the investigational device group and crossover subjects. The major complications in the investigational device group were pulmonary vein stenosis (>70%) (5 subjects), phrenic nerve paralysis (5 subjects), cerebral infarction (2 subjects), atrioventricular block complete (1 subject), and sick sinus syndrome (1 subject). The major complications in the

combined group consisting of subjects in the investigational device group and crossover subjects were pulmonary vein stenosis (>70%) (7 subjects), phrenic nerve paralysis (5 subjects), cerebral infarction (2 subjects), atrioventricular block complete (1 subject), sick sinus syndrome (1 subject), and vascular pseudoaneurysm (1 subject). Esophageal perforation, cardiac tamponade, cerebral infarction accompanied by clear neurological symptoms, or pulmonary vein stenosis as listed in 3) above was not reported.

The incidences of adverse events were 96.0% (96 of 100 subjects) in the investigational device group, 27.9% (12 of 43 subjects) in the antiarrhythmic drug therapy group, and 97.1% (33 of 34 subjects) in the group of crossover subjects. Adverse events reported by ≥10% of subjects in any group are as shown in Table 4.

Table 4. Adverse events reported by ≥10% of subjects in any group

	Investigational device (N = 100) Follow-up period, 48 weeks	Antiarrhythmic drug therapy (N = 43) Follow-up period, 40 weeks	Crossover subjects (N = 34) Follow-up period, 48 weeks
C-reactive protein increased	34.0% (n = 34)	0.0% (n = 0)	23.5% (n = 8)
Nasopharyngitis	22.0% (n = 22)	2.3% (n = 1)	11.8% (n = 4)
Back pain	17.0% (n = 17)	2.3% (n = 1)	23.5% (n = 8)
Vessel puncture site haemorrhage	15.0% (n = 15)	0.0% (n = 0)	23.5% (n = 8)
Blood creatine phosphokinase increased	15.0% (n = 15)	2.3% (n = 1)	14.7% (n = 5)
White blood cell count increased	14.0% (n = 14)	0.0% (n = 0)	0.0% (n = 0)
Vomiting	10.0% (n = 10)	0.0% (n = 0)	2.9% (n = 1)
Pyrexia	10.0% (n = 10)	0.0% (n = 0)	8.8% (n = 3)

The incidences of serious adverse events were 10.0% (10 of 100 subjects, 12 events) in the investigational device group, 4.7% (2 of 43 subjects) in the antiarrhythmic drug therapy group, and 11.8% (4 of 34 subjects) in the group of crossover subjects. The serious adverse events reported in the investigational device group were cerebral infarction (2 subjects) and bronchitis, pneumonia, bladder cancer, colon cancer, gastric cancer, anxiety disorder, loss of consciousness, atrioventricular block complete, bradycardia, and sick sinus syndrome (1 subject each) (follow-up period, 48 weeks). The serious adverse events reported in the antiarrhythmic drug therapy group were back pain and laceration (1 subject each) (follow-up period, 40 weeks). The serious adverse events experienced by crossover subjects were cardiac failure acute, prinzmetal angina, sick sinus syndrome, and vascular pseudoaneurysm (1 subject each) (follow-up period, 48 weeks).

The incidences of adverse events of concern associated with a catheter ablation procedure for atrial fibrillation are described below.

Pulmonary vein stenosis was assessed by comparing 3D-CT images at 24 weeks after the procedure or at 48 weeks after the procedure/discontinuation with pre-procedural 3D-CT images. The percent of PV stenosis was defined as follows: “Percent of PV stenosis (%) = (1 − [post-procedural PV diameter/pre-procedural PV diameter]) × 100.” As a result, the incidences of pulmonary vein stenosis (>70%) were 5.0% (5 of 100 subjects) in the investigational device group and 5.2% (7 of 134 subjects) in the combined group consisting of subjects in the investigational device group plus crossover subjects. The events reported are broken down as follows: LIPV stenosis (>70%) experienced by 3 subjects, RSPV stenosis (>70%) experienced by 2 subjects, RIPV stenosis (>70%) experienced by 1 subject, and LSPV stenosis (>70%) experienced by 1 subject.

The incidence of cerebral infarction was 2.0% (2 of 100 subjects) in the investigational device group. Cerebral infarction was not reported by crossover subjects. Transient ischaemic attack (TIA) did not occur in the investigational device group or crossover subjects.

The incidence of phrenic nerve paralysis was 5.0% (5 of 100 subjects [asymptomatic in 2 subjects]) in the investigational device group. All those events were transient and resolved during the study period. Phrenic nerve paralysis was not reported by crossover subjects.

The incidences of adverse events related to puncture site were 21.0% (21 of 100 subjects) in the investigational device group and 23.1% (31 of 134 subjects) in the combined group consisting of subjects in the investigational device group plus crossover subjects. The adverse events related to puncture site in the investigational device group included vessel puncture site haemorrhage **(**12.0%, 12 of 100 subjects), vessel puncture site swelling (3.0%, 3 of 100 subjects), vessel puncture site bruise (3.0%, 3 of 100 subjects), vessel puncture site pain (2.0%, 2 of 100 subjects), and vessel puncture site induration (2.0%, 2 of 100 subjects).

Esophageal injury or atrio-esophageal fistula did not occur in the investigational device group or crossover subjects.

Neither cardiac perforation nor cardiac tamponade occurred in the investigational device group or crossover subjects.

Investigational device malfunctions were defined as “effects of malfunctioning of the investigational device, such as device damage and device’s failure to operate as intended,

regardless of whether the malfunctioning occurs during the design, supply, storage, or use phase." The incidences of investigational device malfunctions were 6.0% (6 of 100 subjects) in the investigational device group and 7.5% (10 of 134 subjects) in the combined group consisting of subjects in the investigational device group plus crossover subjects. The investigational device malfunctions related to SRF-2C were reported by 4 subjects (output stop [3 subjects] and energy delivery failure [1 subject]). Those related to NTA-2C were reported by 5 subjects (balloon pinholes [3 subjects]; and accidental removal of the balloon tip, difficulty in performing occlusive venography, and air entry into the infusion line [1 subject each]). Those related to DGS-1 were reported by 1 subject (twist [1 subject]). The use of the investigational device was discontinued in 9 subjects (5 subjects due to NTA-2C device malfunctions, 3 subjects due to SRF-2C device malfunctions, and 1 subject due to DGS-1 device malfunctions). There were no adverse events related to any of these investigational device malfunctions. Table 5 shows the causes of investigational device malfunctions, corrective actions, and occurrence of events after corrective actions taken.

In the pivotal study, the total fluoroscopy time (mean ± standard error [SE]) was 49.5 ± 27.4 minutes, and the procedure time was 113.8 ± 33.2 minutes.

Table 5. Details of investigational device malfunctions

Event	Cause	Corrective action	Occurrence of events after corrective action taken
SRF-2C			
3 cases of output stop	• Electric noise associated with movement of the balloon due to a sparsely coiled electrode inside the balloon • Electric noise due to a change in the position of metal wires inside the balloon	• A catheter appearance test was added (to check a sparsely or densely coiled electrode and/or the position of metal wires) • Precautions regarding the procedure for using the catheter were given • A noise cut filter was added.	None
1 case of energy delivery failure	• Deployment of cables such as the return electrode cables and the extension cable • Electric noise associated with the method of connecting the power cord	• Precautions regarding the deployment of cables were given • Precautions regarding the method of connecting the power cord were given	None
NTA-2C			
3 cases of a balloon pinhole	Damage caused by friction on the balloon	A thorough leakage test in the manufacturing process was conducted after the first case of a balloon pinhole was reported. Procedural precautions were given.	Similar cases were reported (2 cases of a pinhole).
1 case of accidental removal of the balloon tip	The tip got caught in the sheath's hemostasis valve when the catheter was removed from the sheath in the event of a pinhole	The method of removing the catheter in the event of a pinhole was communicated	None
1 case of difficulty in performing occlusive venography	Deformation of the inner lumen of the catheter caused by excessive compressive force when the balloon was stretched	Precautions regarding stretching of the balloon were given	None
1 case of air entry into the infusion line	Strong negative pressure induced by air aspiration in the syringe when the guidewire was inserted	Advise on careful manipulation of the syringe was given	None
DGS-1			
1 case of twist	The deflected tip of DGS-1 was rotated	Precautions regarding torque manipulation were given	None

[Pilot study of TSB-002 for the treatment of atrial fibrillation] (Study period, [redacted] to [redacted]) (Reference data)

TSB-002, which was used in a pilot study of TSB-002 for the treatment of atrial fibrillation ("pilot study of TSB-002"), consists of a previous model of NTA-2C ablation catheter (NTA-2), a previous model of SRF-2C radiofrequency generator (SRF-1), and DGS-1.

The pilot study of TSB-002 was a multicenter, non-randomized, open-label study intended to evaluate the efficacy and safety of TSB-002 in patients with paroxysmal or persistent atrial fibrillation (target sample size of 30). The study was conducted at 3 study sites in Japan. In the

pilot study of TSB-002, 32 patients were enrolled. TSB-002 was used in 31 patients, but 1 patient discontinued participation in the study due to SRF-1 device malfunctions before the procedure. All of the 31 patients treated with TSB-002 were included in the efficacy and safety analyses. Of the 31 patients, 6 discontinued participation in the study. Specifically, 2 subjects discontinued because conventional ablation was performed due to atrial fibrillation recurrence; 1 subject discontinued because the subject had to be treated for prostate cancer; 1 subject discontinued because the subject had to receive radiation therapy; 1 subject discontinued because of SRF-1 start-up failure; and 1 subject discontinued at the subject's own request. The 1 subject experiencing SRF-1 start-up failure discontinued the study treatment on the day of procedure and the other 5 subjects discontinued the study treatment beyond 6 months after the procedure.

The primary efficacy endpoints were the acute success rate and the chronic success rate at 6 months after ablation.

Acute success was defined as elimination of PV potentials (the PV-left atrial junction) (an electrogram amplitude of <0.1 mV) or dissociation of PV potentials from left atrial potentials at the end of the ablation procedure. The acute success rate was 91.7% (111 of 121 PVs; 95% CI, 85.3%-96.0%).

Chronic success at 6 months post-ablation was defined as "freedom from any atrial fibrillation episode lasting ≥30 seconds at 6 months post-ablation (excluding the blanking period)." The chronic success rate at 6 months post-ablation was 71.0% (22 of 31 subjects; 95% CI, 52.0%-85.8%).

The primary safety endpoint was the incidence of major complications at 6 months post-ablation, and major complications were defined as any of the following:

1) A serious adverse event occurring within 7 days after the procedure
2) Any severe pulmonary vein stenosis (>70%) or esophageal perforation occurring after the procedure
3) Any mild (<50%) or moderate (50%-70%) pulmonary vein stenosis occurring after the procedure and meeting one of the following criteria:
   (a) Requires an invasive intervention, such as PV stenting
   (b) Results in significant clinical symptoms

The incidence of major complications at 6 months post-ablation was 0% (0 of 31 subjects).

The incidence of adverse events was 80.6% (25 of 31 subjects) and the incidence of serious adverse events was 12.9% (4 of 31 subjects). Adverse events reported by ≥5% of subjects were C-reactive protein increased (8 subjects), back pain (6 subjects), aspartate aminotransferase increased (6 subjects), γ-glutamyltransferase increased (5 subjects), and white blood cell count increased (5 subjects). The reported serious adverse events were sudden hearing loss, anaplastic astrocytoma, colon adenoma, and prostate cancer (1 subject each), all of which were considered causally unrelated to TSB-002.

A total of 10 device malfunctions for TSB-002 (including 2 device malfunctions occurring prior to the use of TSB-002) were reported. The malfunctions consist of 6 for NTA-2 (balloon pinhole [2 malfunctions], pinhole caused by external damage [1], inner lumen leakage [1], contact failure of electrode lead wires in the connector [1], and separation between the catheter tube, and the luer lock [1]) and 4 for SRF-1 (connector failure for the temperature monitor line [2] and connector failure for the on-board power supply [2]).

[Pilot study of NTA-1/RFX-1 for the treatment of atrial fibrillation] (Study period, [redacted], [redacted] to [redacted], [redacted]) (Reference data)

NTA-1/RFX-1, which was used in a pilot study of NTA-1/RFX-1 for the treatment of atrial fibrillation (a pilot study of NTA-1/RFX-1), consists of the prototype ablation catheter (NTA-1) and the prototype of "SATAKE-HotBalloon Generator" (RFX-1, a device to be used in conjunction with SATAKE-HotBalloon Catheter). The study was an open-label study conducted at 2 sites in Japan (target sample size, 20 subjects). The primary objective of the study was to evaluate the safety of NTA-1/RFX-1 in patients with atrial fibrillation and an additional objective was to evaluate its efficacy.

All of 20 enrolled patients were included in the efficacy analysis for ablation success immediately after the procedure. Of the 20 patients, 14 were included in the efficacy analysis of freedom from atrial fibrillation at 12 weeks post-ablation. The remaining 6 patients were excluded from the analysis because their use of a new antiarrhythmic drug or other therapies was considered to affect evaluation. Twenty patients were included in the safety analysis.

The primary efficacy endpoints were ablation success immediately after the procedure and freedom from atrial fibrillation at 12 weeks post-ablation. Ablation success immediately after the procedure was assessed as follows: First, the effect of ablation of the left atrial tissue surrounding the four pulmonary vein ostia was classified as "isolation" (elimination or dissociation of PV potentials after the procedure), "a decrease in electrogram amplitude" (the electrogram amplitude

decreased after the procedure compared with before the procedure), "no change" (the electrogram amplitude did not decrease after the procedure compared with before the procedure), or "unassessable" (not ablated). Next, subjects were assessed as "success" ("no change" for 0 PVs and "isolation" for ≥3 PVs), "markedly effective" ("no change" for 0 PVs and "isolation" for ≤2 PVs), "effective" ("no change" for 1 or 2 PVs), "slightly effective" ("no change" for 3 PVs), or "failure" ("no change" for all four PVs), and the percentage of "success," "markedly effective," and "effective" was calculated as the efficacy rate. As a result, 17 subjects were assessed as success, 1 subject as markedly effective, 2 subjects as effective, and 0 subjects as slightly effective or failure, resulting in the efficacy rate of 100% (20 of 20 subjects; 95% CI, 86.1%-100.0%). Freedom from atrial fibrillation at 12 weeks post-ablation was assessed by the presence or absence of an episode of palpitation at 12 weeks post-ablation, and the percentage of patients with no episodes of palpitation was defined as the efficacy rate. Analysis showed that 9 subjects had no palpitation episodes and 5 subjects had a palpitation episode. The efficacy rate was 64.3% (9 of 14 subjects; 95% CI, 35.1%-87.2%).

The primary safety endpoint was the occurrence of complications and NTA-1/RFX-1 device malfunctions at 14 weeks post-ablation. Subjects were classified as having no problem,[8] having little problem,[9] having minor problem,[10] or having major problem.[11] As a result, 19 subjects were found to have no problem, 1 subject was found to have little problem, and no subjects were found to have minor or major problem.

Adverse events occurred in 11 of 20 subjects (16 events). The events included sputum bloody (6 subjects); white blood cell increased (2 subjects); and CPK increased, cough/pharynx strange sensation of, hepatic function abnormal, cardiac tamponade, pericarditis, pyrexia, pulmonary vein stenosis (PV stenosis of 60% reduction in diameter), and vomiting (1 subject each). The pericarditis was reported as a serious event. Only pulmonary vein stenosis was considered causally related to NTA-1/RFX-1.

[8] There were neither adverse events considered related to NTA-1/RFX-1 nor NTA-1/RFX-1 device malfunctions, nor adverse effects of NTA-1/RFX-1 device malfunction (if any) on the patient.
[9] A "mild adverse event" considered related to NTA-1/RFX-1 was noted, or the adverse effect of NTA-1/RFX-1 device malfunction on the patient was classified as a "mild adverse event."
[10] A "moderate adverse event" considered related to NTA-1/RFX-1 was noted, or the adverse effect of NTA-1/RFX-1 device malfunction on the patient was classified as a "moderate adverse event."
[11] A "severe adverse event" (e.g., death) considered related to NTA-1/RFX-1 was noted, or the adverse effect of NTA-1/RFX-1 device malfunction on the patient was classified as a "severe adverse event."

8.B Outline of the review by PMDA

PMDA reviewed the data by focusing on the following points.

8.B.(1) Clinical positioning

PMDA's view on the clinical positioning of SATAKE-HotBalloon Catheter:

In Japan, some cardiac ablation techniques are currently available for treatment of drug-refractory patients with symptomatic paroxysmal atrial fibrillation. Isolation of pulmonary veins using a radiofrequency ablation catheter has already been performed and a technique using a cryoballoon ablation catheter has also been initiated. The applicant claims that reduced procedure time is an advantage of the balloon catheter employed in SATAKE-HotBalloon Catheter. However, no head-to-head studies have been performed to compare SATAKE-HotBalloon Catheter with a conventional radiofrequency ablation catheter, and conditions such as the number of centers and the number of patients are different between the Japanese radiofrequency catheter ablation registry [vi] and the pivotal study. However, reduced procedure time can be expected with SATAKE-HotBalloon Catheter in principle and in comparison with the data from the Japanese registry [see "8.B.(2) Efficacy"]. Reduced fluoroscopy time, reduction of complications related to superheating of deep myocardial tissue, and decreased fluid loading can also be expected in principle, though no head-to-head studies have been performed.

The advantage of the balloon catheter employed in SATAKE-HotBalloon Catheter has not been studied thoroughly. However, based on the efficacy and safety of SATAKE-HotBalloon Catheter versus conventional radiofrequency ablation catheters used for the isolation of pulmonary vein, PMDA concluded that making SATAKE-HotBalloon Catheter available for routine clinical use as an option for ablation in patients with atrial fibrillation is of significance if the efficacy and safety of the product are clinically acceptable [see "8.B.(2) Efficacy and 8.B.(3) Safety"].

PMDA also concluded that the intended patient population as specified in "Intended use" is appropriate because this patient population reflects patients included in the pivotal study and is consistent with the patient population for whom ablation is indicated by the current Japanese guideline.

8.B.(2) Efficacy

PMDA asked the applicant to provide a justification for selecting the chronic success rate as the primary endpoint for the pivotal study.

The applicant's explanation:
The FDA Guidance[vii] recommends "freedom from symptomatic atrial fibrillation at one year" as a primary efficacy endpoint for clinical studies of ablation catheter devices intended to treat atrial fibrillation. This could justify the selection of chronic success rate as the primary endpoint for the pivotal study. On the other hand, 34 subjects in the antiarrhythmic drug therapy group who met the criteria pre-specified in the protocol (recurrence of atrial fibrillation, adverse reactions to antiarrhythmic drugs) were classified as treatment failures, which should be appropriate because these subjects did not meet "the definition of success."

PMDA's view:
Selection of the chronic success rate as the primary endpoint for the pivotal study is justified, given that the goal was the treatment of symptomatic paroxysmal atrial fibrillation. Meanwhile, 33 subjects who experienced recurrence of atrial fibrillation and then underwent ablation were classified as treatment failures because they did not meet the definition of success and responded inadequately to drug therapy clinically. This would be appropriate. Although 1 subject who underwent ablation due to adverse reactions to an antiarrhythmic drug is not necessarily incompatible with the definition of success, the success rate in the drug therapy group would be 4.8% (2 of 42 subjects) even if this subject is excluded, which does not make a difference in terms of comparison with the investigational device group. Thus, this does not preclude the efficacy of SATAKE-HotBalloon Catheter. Since exclusion of this patient with adverse reactions does not affect the study results, classification as treatment failures is acceptable for subjects who crossed over to ablation treatment from the antiarrhythmic drug therapy group.

Moreover, PMDA asked the applicant to provide a justification for selecting patients receiving antiarrhythmic drug therapy as a control group in the pivotal study.

The applicant's explanation:
When the pivotal study was being planned, there was no radiofrequency ablation catheter intended for the treatment of atrial fibrillation (specified in the "Intended use") in Japan. At the time of submission of clinical trial notification, there were radiofrequency ablation catheters intended for the treatment of atrial fibrillation (specified in the "Intended use"). However, the method and technique for the treatment of atrial fibrillation using these devices had not been established and ablation using these devices had not been positioned as standard treatment in Japan. The applicant therefore considered that patients receiving antiarrhythmic drug therapy should be selected as a control group. A radiofrequency ablation catheter was compared with antiarrhythmic drug therapy in a foreign clinical trial for the treatment of atrial fibrillation, and the choice of the control group

in the pivotal study was considered appropriate. As a result, the chronic success rate (the primary endpoint) was 59.0% (59 of 100 subjects) in the investigational device group and 4.7% (2 of 43 subjects) in the antiarrhythmic drug therapy group (control group). The chronic success rate was statistically significantly higher with the investigational device, thus demonstrating the efficacy of SATAKE-HotBalloon Catheter.

PMDA's view:
In light of the situation at the time when the pivotal study was being planned (a radiofrequency ablation catheter intended for the treatment of atrial fibrillation [as specified in the "Intended use"] had just been marketed in Japan), selection of patients receiving antiarrhythmic drug therapy as a control group in the pivotal study was unavoidable. On the other hand, ablation therapy for the treatment of drug-refractory symptomatic paroxysmal atrial fibrillation is becoming more widespread in Japan at present. Thus, PMDA asked the applicant to explain the efficacy of SATAKE-HotBalloon Catheter compared with conventional radiofrequency ablation catheters.

The applicant's explanation:
First, the Japanese registry was used to compare the currently available outcome of ablation therapy for paroxysmal atrial fibrillation in Japan with the data from the study using SATAKE-HotBalloon Catheter. A total of 2137 patients were registered in the registry between September 2011 and March 2012 and the 1-year follow-up data were collected from 1208 patients (including 777 patients with paroxysmal atrial fibrillation) at 119 centers. The chronic success rate at 1 year post-ablation in patients with paroxysmal atrial fibrillation was 70.9% (551 of 777 subjects). The proportion of successful outcome in this report was numerically higher than the chronic success rate in the pivotal study (59.0%, 59 of 100 subjects). The Japanese registry included patients who underwent left atrial linear ablation in addition to conventional pulmonary vein isolation (15.4%, 120 of 777 patients), those who underwent complex fractionated atrial electrogram (CFAE) ablation in addition to conventional pulmonary vein isolation (4.9%, 38 of 777 patients), and those who underwent reablation after recurrence of atrial fibrillation (11.3%, 88 of 777 patients). In the pivotal study, such additional procedures were not permitted, and recurrence of atrial fibrillation was detected more rigorously using a mobile ECG or Holter monitor. These differences were likely to have affected the outcome. The Japanese registry consists of the data obtained after the market launch of conventional radiofrequency ablation catheters in Japan. Generally, the operators are expected to be more familiar with the procedure in routine clinical practice than in clinical trials, resulting in a higher success rate in the registry than in a clinical trial. Despite the fact that there are limitations in the assessment of the relationship between accumulation of experience and the success rate based on the data from the pivotal study because the number of

patients enrolled is limited, the chronic success rate was 52.9% (9 of 17 patients) among the first patients at each site and 64.7% (11 of 17 patients) among the last patients at each site. The entire study population was divided into two halves (50 vs. 50 patients) to be analyzed. The chronic success rate was 56.0% (28 of 50 patients) among the first half of patients and 62.0% (31 of 50 patients) among the second half of patients. Thus, the pivotal study data suggested the possibility that a learning curve exists. The mean procedure time was 3.36 ± 1.15 hours in the Japanese registry and 1.90 ± 0.55 hours in the pivotal study. According to the literature comparing a cryoablation catheter (Arctic Front or Arctic Front Advance) vs. a radiofrequency ablation catheter (Thermocool)[viii] for the treatment of paroxysmal atrial fibrillation in a foreign study, the chronic success rate at 1 year after the procedure was 60.3% for the cryoablation catheter and 61.1% for the radiofrequency ablation catheter. The results were both similar to the chronic success rate in the pivotal study of SATAKE-HotBalloon Catheter. The applicant therefore considers that the success rate in the pivotal study of SATAKE-HotBalloon Catheter is clinically adequate.

PMDA's view on the efficacy of SATAKE-HotBalloon Catheter:
Whether or not the chronic success rate of 59.0% (59 of 100 subjects) in the pivotal study is adequate as compared with conventional radiofrequency ablation catheters cannot be assessed rigorously because the study was not designed to include patients treated with a conventional radiofrequency ablation catheter as the control. The chronic success rate in the pivotal study was slightly lower than the success rate in the Japanese registry. As the applicant argued, it is theoretically possible that prohibition of adding ablation to PV isolation and re-ablation and the method of detecting recurrence in the pivotal study affected the outcome. The applicant discussed that the pivotal study data suggested the existence of a learning curve. The discussion is also understandable though a definitive conclusion cannot be made. The efficacy of SATAKE-HotBalloon Catheter is considered clinically acceptable based on the overall review of the following findings: (1) The pivotal study demonstrated statistically significant superiority of SATAKE-HotBalloon Catheter over antiarrhythmic drug therapy in terms of the chronic success rate; (2) the chronic success rate with SATAKE-HotBalloon Catheter is not lower than the outcomes of catheter ablation using similar devices in a foreign study; (3) the lower chronic success rate with SATAKE-HotBalloon Catheter than that in the Japanese registry is considered attributable to the above-mentioned factors; and (4) reduced procedure time is expected with SATAKE-HotBalloon Catheter as compared with the data from the Japanese registry. However, as SATAKE-HotBalloon Catheter was studied in a limited number of patients at a limited number of sites in Japan, information on successful outcome should be collected in the use-results survey to assess whether the product is adequately effective in clinical practice in Japan. If a new finding

becomes available, the information should be provided to healthcare professionals in clinical practice. According to the draft use-results survey protocol proposed by the applicant, acute and chronic success rates are to be analyzed. The draft protocol is considered appropriate.

8.B.(3) Safety

8.B.(3).1) Pulmonary vein stenosis

Considering that pulmonary vein stenosis is a significant complication and that a 5% incidence of >70% stenosis is clinically relevant, PMDA asked the applicant to explain the incidence of pulmonary vein stenosis in patients treated with SATAKE-HotBalloon Catheter versus conventional radiofrequency ablation catheters.

The applicant's explanation:

The data from the study of SATAKE-HotBalloon Catheter were compared with the data from the Japanese registry, the foreign registry,[ix] and an US study of NaviStar ThermoCool[x] all of which involved patients treated with conventional radiofrequency ablation catheters. The incidence of serious pulmonary vein stenosis requiring invasive intervention was 0.08% (1 of 1208 patients) in the Japanese registry and 0.29% (48 of 16,309 patients) in the foreign registry, and such event was not reported in the pivotal study of SATAKE-HotBalloon Catheter or the US study of NaviStar ThermoCool. It is presumed that CT scanning of all patients was not performed in these surveys or study, unlike in the pivotal study of SATAKE-HotBalloon Catheter. This fact makes accurate comparison difficult. Pulmonary vein stenosis observed in the pivotal study of SATAKE-HotBalloon Catheter was asymptomatic and did not require invasive intervention. The event occurred possibly because the balloon was inserted too deeply in the pulmonary vein. Since the risk can be reduced by training users, the risk of pulmonary vein stenosis associated with SATAKE-HotBalloon Catheter should be clinically acceptable.

PMDA asked the applicant to explain factors associated with the development of pulmonary vein stenosis.

The applicant's explanation:

Data from 127 subjects, excluding 7 subjects with missing post-procedural PV measurements (96 subjects in the investigational device group, 31 crossover subjects), in the pivotal study were used to investigate the association of the following factors with the development of severe (>70%) pulmonary vein stenosis for each of the four pulmonary veins: total fluoroscopy time, total ablation time, procedure time, the number of energy applications, the mean highest set ablation temperature, myocardial thickness, the mean balloon inflation volume (the mean volume of fluid

in the balloon inflated for ablation of the PV ostium and the tissue around the PV antrum), the mean balloon inflation volume for ablation of the PV ostium, and left atrial volume. The analysis of all pulmonary veins identified the following factors associated with the development of severe pulmonary vein stenosis: lower mean balloon inflation volume, lower mean balloon inflation volume for ablation of the PV ostium, reduced total fluoroscopy time, and larger left atrial volume. Among these factors identified, reduced total fluoroscopy time and larger left atrial volume are not apparent risk factors because total fluoroscopy time is the time for the entire procedure and is unlikely to be related to balloon manipulation, and because analysis of individual pulmonary veins also identified smaller left atrial volume as a risk factor. On the other hand, the balloon inflation volume is considered an important risk factor. Analysis of individual pulmonary veins identified longer total ablation time and increased number of energy applications as risk factors for some of the pulmonary veins. These risk factors should also be noted.

PMDA asked the applicant to explain each of the identified risk factors in more details.

The applicant's explanation:
The recommended balloon inflation volume was determined as follows:
In the pilot study of NTA-1/RFX-1, [redacted] types of balloons with diameters of [redacted] mm were used. [redacted] mm was most commonly used and the mean balloon diameter (measured value) was [redacted] mm. Based on these results, a balloon with a reference diameter of 26 mm was developed and the size of the balloon was adjusted by the volume of diluted contrast medium injected into the balloon.

A maximum balloon diameter of 33 mm (a balloon inflation volume of 20 mL) was chosen so that the balloon can have full contact with the pulmonary vein of [redacted] mm in diameter, which was the largest pulmonary vein in the pilot study of NTA-1/RFX-1. In non-clinical testing (balloon compliance test), balloon inflation volumes of 10 to 20 mL were required to achieve balloon diameters of 26 to 33 mm. A balloon with a small diameter is likely to be inserted deeply in the pulmonary vein, which could result in pulmonary vein stenosis or phrenic nerve paralysis. Although non-clinical testing (balloon rupture test) demonstrated that a balloon inflation volume of [redacted] mL does not result in balloon rupture, a balloon inflation volume of >20 mL may result in balloon damage. Therefore, a balloon inflation volume of 10 to 20 mL was recommended.

Although the recommended balloon inflation volume was 10 to 20 mL in the pivotal study, the actual balloon inflation volume (mean ± SD, [Min., Max.]) was 8.52 ± 2.21 (3.0, 16.0) mL for ablation of the PV ostium and 9.44 ± 2.30 (3.0, 18.0) mL for ablation of the PV ostium and the

tissue around the antrum. The mean balloon inflation volume (mean ± SD) by severity of pulmonary vein stenosis (mild [<50%, including subjects without pulmonary vein stenosis], moderate [50%-70%], severe [>70%]) was 9.343 ± 1.896 mL, 9.213 ± 2.029 mL, and 7.487 ± 2.433 mL, respectively, and the mean balloon inflation volume for ablation of the PV ostium was 8.469 ± 2.073 mL, 8.262 ± 2.007 mL, and 6.357 ± 2.249 mL, respectively.

The balloon inflation volume was ≥10 mL in 44 of 134 subjects for RSPV, 16 of 134 subjects for RIPV, 61 of 134 subjects for LSPV, and 28 of 134 subjects for LIPV, and these subjects did not develop pulmonary vein stenosis (>70%). Therefore, the risk of pulmonary vein stenosis can be reduced by injecting ≥10 mL into the balloon.

The risk factors identified for some of the pulmonary veins were analyzed by severity of pulmonary vein stenosis. The total ablation time was 28.5 ± 4.7 minutes in subjects experiencing mild stenosis, 27.4 ± 3.4 minutes in subjects experiencing moderate stenosis, and 32.5 ± 3.3 minutes in subjects experiencing severe stenosis for LIPV. The total number of energy applications was 2.3 ± 0.7, 2.1 ± 0.3, and 2.7 ± 1.2, respectively, for LIPV. Accordingly, caution against excessive ablation will be advised.

PMDA's view on the risk of pulmonary vein stenosis associated with the use of SATAKE-HotBalloon Catheter:
Although pulmonary vein stenosis associated with pulmonary vein isolation has been reported also with conventional radiofrequency ablation, due attention should paid to the possibility that the risk of pulmonary vein stenosis may be higher with SATAKE-HotBalloon Catheter than with conventional radiofrequency ablation catheters because SATAKE-HotBalloon Catheter has a balloon and the principle of ablation is different. All events of pulmonary vein stenosis reported in the pivotal study were asymptomatic and required no intervention, but the possibility of the occurrence of clinically relevant pulmonary vein stenosis associated with the use of SATAKE-HotBalloon Catheter cannot be ruled out since the number of patients studied was very limited. For this reason, precautions are needed to reduce the risk. Risk reduction measures proposed by the applicant include appropriate control of the balloon inflation volume, total ablation time, and the number of energy applications, which is important, in principle, in terms of avoiding excessive ablation. The proposed risk reduction measures are appropriate at present.

Even though the recommended balloon inflation volume was 10 to 20 mL in the pivotal study, the mean balloon inflation volume was less than 10 mL. According to the applicant, the balloon inflation volume was adjusted for each patient. However, given that adjustment was left up to the

operator, risk reduction by complying with the recommended balloon inflation volume is preferable at present. After the market launch, information on the specific risk (e.g., lower balloon inflation volume was identified as a risk factor for pulmonary vein stenosis, etc., in the pivotal study) should be made available for clinical practice and then healthcare professionals should be thoroughly informed of the recommended volume.

For avoidance of excessive ablation, appropriate precautions should be advised, taking into account that the usage of SATAKE-HotBalloon Catheter is characterized by ablation at the PV ostium and at the PV antrum. At present, it should be ensured that the recommended balloon inflation volume is advised and that training or other measures are provided. Then, detailed information on the occurrence of pulmonary vein stenosis in clinical practice should be collected in the use-results survey and if a new finding becomes available, the information should be provided to healthcare professionals in clinical practice.

Accordingly, PMDA instructed the applicant to provide information about specific procedural precautions, to provide training on these precautions, and to take action regarding use-results evaluation.

The applicant's response:
Information about specific procedural precautions will be offered and training on these precautions will be provided. Information will be collected in the use-results survey and the obtained findings will be offered to healthcare professionals in clinical practice appropriately.

PMDA concluded that the applicant's view is acceptable.

8.B.(3).2) Cerebral infarction

In the pivotal study, the incidence of cerebral infarction was 2.0% (2 of 100 subjects) in the investigational device group, and cerebral infarction was not reported in the crossover subjects. Transient ischemic attack (TIA) did not occur in the investigational device group or crossover subjects.

PMDA asked the applicant to explain the incidence of cerebral infarction in patients treated with SATAKE-HotBalloon Catheter versus conventional radiofrequency ablation catheters.

The applicant's explanation:
The incidence of stroke and cerebral infarction was 0.4% (5 of 1208 patients) in the Japanese

registry, 0.23% (37 of 16,309 patients) in the foreign registry, and 0.0% (0 of 139 patients) in the US study of NaviStar ThermoCool. Although comparison is difficult due to differences in patient characteristics and assessment method, among the studies, the incidence of cerebral infarction associated with an ablation procedure using SATAKE-HotBalloon Catheter is not markedly different from that associated with an ablation procedure using a conventional radiofrequency ablation catheter. There should be no clinical problem.

Cerebral infarction is a significant complication and adequate comparison of its incidence cannot be made based on the data from the pivotal study. PMDA asked the applicant to explain the details of the cases of cerebral infarction, including its causality to SATAKE-HotBalloon Catheter.

The applicant's explanation on cerebral infarction experienced by 2 subjects:
One case of cerebral infarction occurred in a 6[redacted]-year-old woman who was taking rivaroxaban 15 mg/day until the day before the procedure. When sedation was stopped after the ablation procedure, paralysis of the left upper limb was noted, which resolved following the administration of infusions. The operator heard the sound of air suction when inserting a mapping catheter (not the investigational device) into the sheath. For this reason, among others, the event was considered to be caused by air embolism and its causal relationship to SATAKE-HotBalloon Catheter was ruled out. Another case of cerebral infarction occurred in a 6[redacted]-year-old woman who stopped warfarin 2 days before the procedure and was then using heparin. After the compressed femoral puncture site was released following the ablation procedure, muscle weakness in the right lower limb was noted. The head MRI on the following day revealed cerebellar infarction. The patient received infusions and then underwent rehabilitation. The patient eventually recovered. The event was considered causally unrelated to SATAKE-HotBalloon Catheter because the event was likely to be caused by a thrombus at the puncture site. In the pivotal study protocol, anticoagulant therapy prior to the procedure was not specified but anticoagulant therapy during the procedure was specified as follows: activated coagulation time (ACT) after septal puncture should be measured and heparin injection should be administered with a target ACT of 300 to 400 seconds.

PMDA asked the applicant to explain measures to reduce the risk of cerebral infarction.

The applicant's explanation:
In order to prevent air embolism, general precautions should include selection of the appropriate size of the devices to be used in conjunction with SATAKE-HotBalloon Catheter (e.g., the guiding sheath), careful maneuver, and adequate sedation/analgesia. In addition, appropriate air aspiration when inserting SATAKE-HotBalloon Catheter is essential. Accordingly, these precautions will be

advised. The following actions are important to prevent left atrial thrombus: the proper use of anticoagulants before and after the procedure, appropriate assessment of the left atrium for thrombus before the procedure, control of ACT within a proper range by anticoagulants during the procedure, and checking for the absence of a thrombus on the balloon surface after catheter removal. For the prevention of puncture site thrombosis, excessive compression after hemostasis should be avoided, and the appropriate use of elastic stocking and other measures may be needed. Thus, these precautions will be advised to reduce the risk appropriately.

PMDA's view on the risk of cerebral infarction associated with the use of SATAKE-HotBalloon Catheter:
In a non-clinical study (a pig study to evaluate the characteristics of ablation procedure), pulmonary vein ablation was performed using a previous model of SATAKE-HotBalloon Catheter in 6 pigs to determine the basic manipulation of the product and the ablation technique. As a result, no thromboembolus was observed in the brain, lungs, kidneys, or liver. The investigator denied the causal relationship of cerebral infarction (2 subjects) reported in the pivotal study to SATAKE-HotBalloon Catheter based on the situation at onset, but the risk of cerebral infarction was not compared between SATAKE-HotBalloon Catheter and conventional radiofrequency ablation catheters, thus, adequate caution should be provided. At present, the usual precautions (e.g. appropriate use of perioperative anticoagulant therapy [before and after the procedure]; and precautions regarding the manipulation of SATAKE-HotBalloon Catheter and the devices to be used in conjunction with the product) should be ensured, and detailed information should be collected on the implementation of measures against the risk of cerebral infarction and the occurrence of cerebral infarction and TIA, etc., in the use-results survey. If a new finding becomes available, the information should be provided to healthcare professionals in clinical practice.

Accordingly, PMDA instructed the applicant to take action regarding use-results evaluation, in addition to the measures proposed by the applicant (e.g. appropriate use of perioperative anticoagulant therapy [before and after the procedure]; and precautions regarding the manipulation of SATAKE-HotBalloon Catheter and the devices to be used in conjunction with the product).

The applicant responded that information will be collected in the use-results survey and that the obtained findings will be offered to healthcare professionals in clinical practice appropriately.

PMDA concluded that the applicant's view is acceptable.

8.B.(3).3) Phrenic nerve paralysis

The applicant's explanation on phrenic nerve paralysis associated with the use of SATAKE-HotBalloon Catheter:

In the pivotal study, all subjects were required to receive diaphragm pacing with an electrode placed in the superior vena cava under fluoroscopic imaging in order to monitor the movement of the diaphragm during the application of energy for ablation of RSPV and RIPV, thereby preventing phrenic nerve paralysis. In the pivotal study, the incidence of phrenic nerve paralysis was 5.0% (5 of 100 subjects [asymptomatic in 2 subjects]) in the investigational device group. All those events were transient and resolved during the study period. Phrenic nerve paralysis did not occur in the crossover subjects. The data from subjects in the investigational device group plus crossover subjects (N = 134) were analyzed to identify the factors associated with the occurrence of phrenic nerve paralysis. The association of the following factors with phrenic nerve paralysis was investigated: total fluoroscopy time, total ablation time, procedure time, and left atrial volume; and for each pulmonary vein, total ablation time, the number of energy applications, the mean highest set ablation temperature, myocardial thickness, the mean balloon inflation volume, and the mean balloon inflation volume for ablation of the PV ostium. As a result, the mean balloon inflation volume for ablation of the RSPV ostium was 6.700 ± 1.718 mL in 5 subjects with phrenic nerve paralysis and 8.895 ± 1.679 mL in 129 subjects without phrenic nerve paralysis. The mean balloon inflation volume for RSPV was 7.934 ± 1.497 mL in 5 subjects with phrenic nerve paralysis and 9.737 ± 1.654 mL in 129 subjects without phrenic nerve paralysis. Thus, lower balloon inflation volume was considered a risk factor. Since (1) all events of phrenic nerve paralysis observed in the pivotal study were mild in severity and resolved, and (2) the risk of ablation deep in the pulmonary vein can be reduced by training users, the risk of phrenic nerve paralysis associated with the use of SATAKE-HotBalloon Catheter is clinically acceptable. Precautions on the recommended balloon inflation volume (as with measures against pulmonary vein stenosis), phrenic nerve pacing, etc., will be advised as safety measures.

PMDA's view on the risk of phrenic nerve paralysis associated with the use of SATAKE-HotBalloon Catheter:

In the pivotal study, 5 subjects experienced phrenic nerve paralysis. These events were non-serious and resolved. However, as some of these subjects had symptoms, appropriate risk reduction measures should be implemented. A risk reduction measure proposed by the applicant (avoidance of ablation deep in the pulmonary vein) is appropriate and it is important to advise this risk reduction measure appropriately. Moreover, detailed information on the occurrence of phrenic nerve paralysis in clinical practice should be collected in the use-results survey. If a new

finding becomes available, the information should be provided to healthcare professionals in clinical practice.

PMDA instructed the applicant to take action regarding the use-results evaluation, in addition to the measures proposed by the applicant (precautions regarding the balloon inflation volume [information about specific procedural precautions and training on these precautions should be provided] and phrenic nerve pacing).

The applicant responded that information will be collected in the use-results survey and that the obtained findings will be offered to healthcare professionals in clinical practice appropriately.

PMDA concluded that the applicant's view is acceptable.

8.B.(3).4) Adverse events related to puncture site

The applicant's explanation on puncture site-related adverse events associated with the use of SATAKE-HotBalloon Catheter:

In the pivotal study, the incidences of adverse events related to puncture site were 21% (21 of 100 subjects) in the investigational device group and 23.1% (31 of 134 subjects) in the combined group consisting of subjects in the investigational device group and crossover subjects. No serious adverse events or significant adverse events requiring surgical intervention or transfusion were reported. In clinical studies with currently approved devices, significant adverse events related to puncture site requiring surgical intervention or transfusion have been reported.[x,xi] The sheath for SATAKE-HotBalloon Catheter has an external diameter of 17 Fr, which is larger than currently approved devices. Thus, the risk of adverse events related to puncture site may be increased.

However, the risk can be reduced by advising the following precautions: (1) pre-dilation with a 16 Fr dilator should be performed as done in the pivotal study; (2) femoral vein and insertion site injuries should be minimized by exercising special caution when inserting, manipulating, and removing the sheath (to be used with SATAKE-HotBalloon Catheter) and when performing hemostasis at the insertion site; and (3) close attention should be paid to hemorrhage-related events at the puncture site.

PMDA's view on puncture site-related adverse events associated with the use of SATAKE-HotBalloon Catheter:

Although none of the adverse events related to puncture site reported in the pivotal study were considered serious, the possibility of a slightly higher incidence with SATAKE-HotBalloon

Catheter cannot be ruled out because no head-to-head studies against a conventional radiofrequency ablation catheter have been conducted. Taking also into account that eligible patients are likely to be on anticoagulant therapy, close attention should be paid to hemorrhage during and after the procedure. It is important to continue to take usual precautions for veinpuncture.

As proposed by the applicant, information on pre-dilation with a 16 Fr dilator should also be provided, but this was specified also in the pivotal study protocol. Thus, close attention must be paid to hemorrhage, even when pre-dilation with a 16 Fr dilator is performed. Moreover, detailed information on the occurrence of puncture site-related adverse events associated with the use of SATAKE-HotBalloon Catheter in clinical practice should be collected in the use-results survey. If a new finding becomes available, the information should be provided to healthcare professionals in clinical practice.

PMDA instructed the applicant to take action regarding the use-results evaluation, in addition to the measures proposed by the applicant (information on pre-dilation with a 16 Fr dilator should be provided and precautions against puncture site haemorrhage should be advised).

The applicant responded that information will be collected in the use-results survey and that the obtained findings will be offered to healthcare professionals in clinical practice appropriately.

PMDA concluded that the applicant's view is acceptable.

8.B.(3).5) Esophageal injury and atrio-esophageal fistula

The applicant's explanation on esophageal injury and atrio-esophageal fistula associated with the use of SATAKE-HotBalloon Catheter:

In the pivotal study, esophageal injury or atrio-esophageal fistula did not occur in the investigational device group or crossover subjects. In the pivotal study, the esophageal temperature was monitored during the ablation of the pulmonary vein ostium or the tissue around the antrum in close proximity to the esophagus in order to prevent these complications. The esophagus was cooled, the pressure of pressing the balloon or the balloon position was adjusted, and energy delivery was discontinued, etc., in order to ensure that the esophageal temperature remains <40°C. A gastric tube was placed into the esophagus and cooling water was infused for esophageal cooling, as appropriate. Ablation was performed while ensuring that the esophageal temperature remains <40°C. A similar method will be recommended also after the market launch.

Since esophageal cooling is not necessarily a common method, PMDA asked the applicant to explain whether adverse events possibly related to this method occurred in the pivotal study and measures to reduce the risk of aspiration of cooling water.

The applicant's explanation:
Although causal relationship between the reported adverse events and esophageal temperature monitoring or esophageal cooling (the Method) was not assessed in the pivotal study, events for which a causal relationship to the Method could not be ruled out were analyzed. The incidence of those events was 18.7% (25 of 134 subjects) in the combined group consisting of subjects in the investigational device group and crossover subjects. Adverse events reported by ≥3 subjects were foreign body aspiration (13 subjects), pyrexia (4 subjects), aspiration pneumonia (3 subjects), and vomiting (3 subjects). The three episodes of aspiration pneumonia were non-serious. Since the event resolved within 3 days in 2 subjects and the event resolved without treatment in 1 subject, these were not considered significant events. The patients with aspiration pneumonia had no common background factors. The applicant therefore considers that there are no subgroups of patient characteristics who should avoid the use of SATAKE-HotBalloon Catheter to prevent this risk. However, since aspiration pneumonia occurred on the day of, or the day after the ablation procedure, general inflammation/infection control is needed to treat inflammation occurring immediately after ablation. In the pivotal study, the Method was implemented under sedation in 133 subjects excluding 1 subject. The risk of foreign body aspiration, which causes aspiration pneumonia, was controlled as follows: The infused cooling water was aspirated through a gastric catheter if the patient was at risk of aspiration of refluxed cooling water due to deep sedation and supine position; and the patient was called and urged to swallow.

Therefore, the safety of the Method can be assured also during ablation using SATAKE-HotBalloon Catheter by advising the above two measures against foreign body aspiration and general inflammation/infection control before and after the ablation procedure in the label.

PMDA's view on the risk of esophageal injury and atrio-esophageal fistula associated with the use of SATAKE-HotBalloon Catheter:
Since (a) the pivotal study did not compare SATAKE-HotBalloon Catheter with a conventional radiofrequency ablation catheter, and (b) the limited number of patients was assessed in the pivotal study, specific data such as incidence of esophageal injury and atrio-esophageal fistula associated with the use of SATAKE-HotBalloon Catheter cannot be assessed. Yet, adequate caution is needed in the same way as with conventional radiofrequency ablation catheters. Although esophageal cooling performed in the pivotal study is not necessarily a common method,

there is no choice but to recommend this method since the efficacy and safety of SATAKE-HotBalloon Catheter was evaluated under this condition. In this regard, information should be provided appropriately. Although the applicant's measures against aspiration associated with esophageal cooling are acceptable, aspiration pneumonia occurred even when these measures were implemented. For this reason, precautions regarding the applicant's measures should be included in the label to ensure information provision. Then the Method should be implemented carefully.

Furthermore, given that (a) ablation procedures were performed in a limited number of subjects by a limited number of physicians at a limited number of sites in the pivotal study, (b) esophageal cooling is not a common preventive measure, (c) subjects experienced adverse events for which a causal relationship to the Method could not be ruled out, and (d) aspiration pneumonia is a noteworthy adverse event, PMDA concluded that the applicant should take the following post-marketing measures: the applicant should collect post-marketing information carefully and should take safety measures as soon as any problem is detected concerning the incidence and seriousness of adverse events.

PMDA instructed the applicant to assess the details of esophageal cooling (infused volume of cooling water, the number of infusions, esophageal temperature before and after infusion) and related adverse events in the use-results survey and to consider the need for further safety measures. Furthermore, PMDA concluded that detailed information on the occurrence of esophageal injury and atrio-esophageal fistula should also be collected in the use-results survey and that if a new finding becomes available, the information should be provided to healthcare professionals in clinical practice. Accordingly, PMDA instructed the applicant to take action regarding the use-results evaluation, in addition to the precautions proposed by the applicant, e.g. esophageal temperature monitoring.

The applicant's response:
Information on the details of esophageal cooling (infused volume of cooling water, the number of infusions, esophageal temperature before and after infusion) will be collected in the use-results survey, and related adverse events will be assessed. Then, further safety measures will be considered. Information on the occurrence of esophageal injury and atrio-esophageal fistula will also be collected in the use-results survey and the obtained findings will be offered to healthcare professionals in clinical practice appropriately.

PMDA concluded that the applicant's view is acceptable.

8.B.(3).6) Cardiac perforation and cardiac tamponade

The applicant's explanation on cardiac perforation and other risks associated with the use of SATAKE-HotBalloon Catheter:

In the pilot study using the prototype of the ablation system (NTA-1/RFX-1) [8.A Summary of the submitted data (Reference data)], cardiac tamponade occurred in 1 subject. Since a commercial guidewire used in the pilot study of NTA-1/RFX-1 was straight and rigid, the pulmonary vein, etc., was possibly injured by the guidewire advanced ahead of the balloon, resulting in cardiac tamponade. Besides cardiac tamponade, bloody sputum (6 subjects) and pericarditis (1 subject) were also considered related to injuries caused by the guidewire. For these reasons, a spring guidewire with a more flexible tip (Approval Number, 21100BZY00391000) was selected for the pilot study of TSB-002 and the pivotal study, both of which were conducted after the completion of the pilot study of NTA-1/RFX-1. As a result, in the pilot study of TSB-002 and the pivotal study, cardiac tamponade, bloody sputum, cardiac perforation, or pericarditis did not occur. In light of this development history, the spring guidewire will be selected also for SATAKE-HotBalloon Catheter after the market launch.

PMDA's view on the risk of cardiac perforation and cardiac tamponade associated with the use of SATAKE-HotBalloon Catheter:

As the measure against cardiovascular injury-related complications observed during the early development phase, the applicant decided to pre-specify the guidewire, taking account of differences in manipulation between SATAKE-HotBalloon Catheter and conventional radiofrequency ablation catheters because guidewire manipulation in the pulmonary vein during the use of the product is assumed. The applicant's decision is acceptable at present. On the other hand, detailed information on the occurrence of these events associated with the use of SATAKE-HotBalloon Catheter in clinical practice should be collected in the use-results survey. If a new finding becomes available, the information should be offered to healthcare professionals in clinical practice.

PMDA instructed the applicant to take action regarding use-results evaluation, in addition to the measure proposed by the applicant (requirements for the guidewire).

The applicant responded that information will be collected in the use-results survey and that the obtained findings will be offered to healthcare professionals in clinical practice appropriately.

PMDA concluded that the applicant's view is acceptable.

8.B.(3).7) Balloon pinholes

The applicant's explanation on balloon pinholes, namely device malfunctions reported in 3 subjects in the pivotal study:

In all events, a pinhole in the balloon was not detected immediately before use but developed during use. No health hazard was reported. Its cause was explored and was considered to be abrasion of the balloon surface. Additional procedural precautions and thorough leakage test in the manufacturing process were chosen as preventive measures.

The additional procedural precautions are as follows: injection of diluted contrast medium into the unfolded balloon, insertion of the balloon into the sheath in water or while flushing with water, retaining of the balloon at the stiff portion of the guidewire, and straightening of the deflected sheath when the balloon is removed from or inserted into the tip of the sheath.

[redacted].

These measures were taken after the occurrence of the first malfunction (balloon pinhole). The remaining 2 malfunctions were reported after the procedural precautions were advised. The events were also considered to be caused by abrasion of the balloon surface as with the first event, and thus the same measures were continued. After these 3 malfunctions were reported, no similar event was observed in 19 subjects. When thorough leakage test was started in the manufacturing process, production of the investigational device was completed. Consequently, the devices that passed this test were not used in the clinical study. A defect caused by abrasion of the balloon surface can be prevented by complying with these precautions.

For early detection of pinholes, it is important to check the shape of the balloon under fluoroscopic imaging. Thus, physicians will be advised to check the shape of the balloon at least every 30 seconds under fluoroscopic imaging. Physicians will be advised to take the following actions in the event of a pinhole leak: "elongate the balloon and remove the catheter carefully while applying full suction, and if resistance is felt, remove the catheter and the sheath together." There were no cases of a balloon pinhole leading to balloon rupture, and non-clinical testing (balloon rupture test) also indicated that the possibility of balloon rupture is low in normal use of SATAKE-HotBalloon Catheter. Even if balloon rupture occurs, diluted contrast medium in the balloon will be diffused and cooled rapidly, which should have no adverse effects on the body.

PMDA's view on balloon pinholes:
A balloon pinhole is a serious safety concern about SATAKE-HotBalloon Catheter. Even if no health hazard was reported in clinical studies, appropriate risk reduction measures should be taken. The additional procedure for leakage test needs to be performed as described by the applicant. However, given that the pre-use checks of the devices identified no problems for all the malfunctions (balloon pinhole) reported in the pivotal study, this issue is unlikely to be solved solely by conducting the thorough leak test.

The procedural precautions for avoiding abrasion of the balloon surface as proposed by the applicant are rational and users should be fully informed of the precautions. However, the 2 malfunctions (balloon pinhole) were reported after these precautions were advised. The risk may not be excluded completely by taking these precautions.

First, these measures should be taken, and then if a pinhole is found, actions such as removal of the catheter is recommended as in the pivotal study. The applicant should ensure that users are informed of the measures for early detection and the actions to be taken in the event of a balloon pinhole and then should collect post-marketing information on the occurrence of balloon pinholes appropriately.

According to the draft use-results survey protocol submitted by the applicant, the information on device malfunctions is to be collected. Thus, the survey protocol as well as information provision about the measures for early detection and the actions to be taken in the event of a balloon pinhole as proposed by the applicant are acceptable.

As a result of the above safety evaluation, PMDA concluded that the safety of SATAKE-HotBalloon Catheter is clinically acceptable.

8.B.(4) Post-marketing safety measures and use-results evaluation

8.B.(4).1) Post-marketing safety measures

The applicant's explanation on the requirements for physicians to use SATAKE-HotBalloon Catheter and their medical institutions:
The requirements for physicians and medical institutions established in cooperation with the Japanese Heart Rhythm Society are currently as follows: Lecture and hands-on training will be conducted for physicians who use SATAKE-HotBalloon Catheter for the first time. Lecture will provide the product overview, comparison with previously approved devices, precautions for safe

use, and factors contributing to the occurrence of adverse events such as pulmonary vein stenosis and phrenic nerve paralysis (the factors include the position of the balloon during ablation, injected volume, and shape). Hands-on training will offer hands-on experience, training facility tour, and training under the supervision of the expert instructor. The appropriate requirements for medical institutions where SATAKE-HotBalloon Catheter would be used were established, based on "the Requirements for Medical Institutions that Undertake Percutaneous Cardiac Catheter Cryoablation" (June 25, 2014) published by the Ablation Committee of the Japanese Heart Rhythm Society.

PMDA's view on post-marketing safety measures:
Special requirements are needed for safety use of SATAKE-HotBalloon Catheter because (a) SATAKE-HotBalloon Catheter is different from conventional radiofrequency ablation catheters in terms of the shape and the principle of ablation, (b) SATAKE-HotBalloon Catheter is different from an approved cryoballoon ablation catheter in terms of the details of the procedure involving balloon manipulation and the principle of ablation, and (c) there are procedural precautions specific to SATAKE-HotBalloon Catheter. Specifically, physicians who understand the risk of SATAKE-HotBalloon Catheter appropriately should use the product carefully at medical institutions that are prepared to manage adverse events.

Physicians who already have adequate experience in percutaneous catheter ablation procedures for the treatment of arrhythmias should attend appropriate training on SATAKE-HotBalloon Catheter and then use the product at medical institutions that are prepared to manage various complications. These requirements should be imposed on this application as conditions for approval (Conditions 1 and 2).

The applicant should continue to discuss training content with the Japanese Heart Rhythm Society, etc., to establish the requirements appropriately. Moreover, post-marketing commitments are necessary for the following reasons (a) ablation procedures were performed in a limited number of subjects by a limited number of physicians at a limited number of sites in the pivotal study; (b) no head-to-head studies were conducted to compare SATAKE-HotBalloon Catheter and a conventional radiofrequency ablation catheter; (c) as described in "Section 8.B.(3).1)," the balloon inflation volume was below the recommended level in many subjects in the pivotal study and the relationship of the lower balloon inflation volume to the occurrence of adverse events cannot be ruled out; and (d) the possibility of an increased incidence of pulmonary vein stenosis and other adverse events associated with SATAKE-HotBalloon Catheter compared with conventional catheters cannot be ruled out. Therefore, post-marketing information should be

collected carefully, and safety measures should be taken as soon as any problem is detected concerning the incidence and seriousness of adverse events.

PMDA instructed the applicant to assess the distribution of the balloon inflation volumes and the details of subjects with low balloon inflation volume (the reason for the low balloon inflation volume and the occurrence of adverse events) and to consider whether further safety measures are necessary.

The applicant's response:
Information on the balloon inflation volume will be collected in the use-results survey. If the balloon inflation volume is less than the recommended level, its cause will be found out. Based on the collected information, the occurrence of adverse events by the balloon inflation volume will be assessed to consider the need for further safety measures.

PMDA concluded that the applicant's view is acceptable.

8.B.(4).2) Use-results evaluation

PMDA's view:
Since (a) the procedural characteristics of ablation therapy with SATAKE-HotBalloon Catheter are substantially different from those with conventional radiofrequency ablation catheters; (b) an approved cryoballoon ablation catheter for the treatment of atrial fibrillation is available, which has just been introduced into the Japanese market; and (c) SATAKE-HotBalloon Catheter is a device developed in Japan and the number of patients assessed in Japanese clinical studies was very limited, PMDA concluded that information on patients treated with SATAKE-HotBalloon Catheter should be collected in routine clinical settings until data from a specific number of patients will be accumulated, so that the safety and efficacy of SATAKE-HotBalloon Catheter can be assessed.

A summary of the draft use-results survey protocol submitted by the applicant is presented in Table 6.

Table 6. Summary of the draft use-results survey protocol

Objective	To evaluate the safety and efficacy of ablation procedure with SATAKE-HotBalloon Catheter in drug-refractory patients with recurrent symptomatic paroxysmal atrial fibrillation.
Planned sample size	400 patients ([redacted] consecutive patients, starting from the first patient, will be enrolled at each site. If enrollment does not reach [redacted] patients, all patients treated within the relevant period will be enrolled.)
Planned number of sites	[redacted] clinical study sites and [redacted] new sites
Survey period	3.5 years (preparatory period for marketing, 8 months; patient enrollment period, 12 months; patient follow-up period, 12 months; case report form (CRF) collection period, 6 months [including the formal examination period[12]]; and data lock and analysis period, 4 months)
Information to be collected	· Priority items: severe pulmonary vein stenosis, cerebral infarction, phrenic nerve paralysis · Other main information to be collected: patient characteristics, actual use of SATAKE-HotBalloon Catheter, previous/concomitant treatment for paroxysmal atrial fibrillation, concomitant treatment for other medical conditions, 12-lead ECG, 24-hour Holter monitoring, clinical laboratory tests, adverse events · Medical device malfunctions

The applicant's explanation on the sample size for use-results evaluation:
Among the priority items of adverse events (severe pulmonary vein stenosis, cerebral infarction, and phrenic nerve paralysis), cerebral infarction had the lowest incidence (1.5% [2 of 134 subjects]). Considering a broad range of patients and physicians in clinical practice after marketing, the target sample size was determined to be 400, which is double the number of patients (199 patients) needed to provide a 95% probability of detecting an adverse event with an incidence of 1.5%.

Consecutive patient enrollment are planned. This may result in the enrollment of a high proportion of patients treated with SATAKE-HotBalloon Catheter at specific sites. It is preferable to collect information on patients enrolled at different sites. SATAKE-HotBalloon Catheter will be used at approximately [redacted] sites in the first year, and [redacted] to [redacted] patients/year are expected to be treated with the product at most of the sites. Thus, the applicant decided to collect information on up to [redacted] consecutive patients at each site.

The applicant considered that adequate post-marketing information should be collected at not only clinical study sites but also new sites where SATAKE-HotBalloon Catheter has never been used. Thus, the applicant decided to conduct the survey at [redacted] clinical study sites and [redacted] new sites.

PMDA's view on the use-results survey plan proposed by the applicant:

[12] Inquiries about a lack of information and inconsistencies between the items, etc., in the CRFs collected will be made to the physicians who made the entries and then addition or correction will be made.

The use-results survey should be conducted to ensure that post-marketing data collected in routine clinical settings in Japan show the adequately reduced risk of adverse events such as pulmonary vein stenosis, cerebral infarction, and phrenic nerve paralysis, thereby indicating no safety concern, and to demonstrate that the efficacy of SATAKE-HotBalloon Catheter is adequate in clinical practice. The information to be collected through the survey is largely appropriate.

The sample size was determined so that an adverse event with the lowest incidence (among adverse events of severe pulmonary vein stenosis, cerebral infarction, and phrenic nerve paralysis, the incidence of cerebral infarction was lowest at 1.5% in the pivotal study) can be detected in the use-results survey. Thus, the sample size presented by the applicant is appropriate. The survey was designed to observe up to [redacted] consecutive patients enrolled per site in order to widely collect information at multiple sites where SATAKE-HotBalloon Catheter is used. The survey design is acceptable.

Since a very novel technique is needed to manipulate SATAKE-HotBalloon Catheter and there are specific precautions to take, it is also important to collect sufficient data at sites (medical institutions) where the product has never been used. Thus, the survey will be conducted at [redacted] clinical study sites and a maximum of [redacted] patients will be enrolled per clinical study sites (the target sample size, [redacted]). This survey plan are appropriate.

Moreover, taking into account that the target disease is paroxysmal atrial fibrillation, an observation period of 12 months for each patient is appropriate.

At present, there is no particular problem with the proposed use-results evaluation period of 3.5 years (preparatory period for marketing, 8 months; patient enrollment period, 12 months; patient follow-up period, 12 months; CRF collection period, 6 months; data lock and analysis period, 4 months) based on this observation period.

8.B.(5) Information contained in the label

The information contained in the label initially proposed by the applicant was considered inadequate. However, in the course of the regulatory review, as discussed above, information about necessary precautions such as the measures against foreign body aspiration and the actions to be taken in the event of a balloon pinhole was added to the label by the applicant. Thus, taking account of the comments from the Expert Discussion, PMDA concluded that there is no particular problem at present.

IV. Results of Compliance Assessment Concerning the Data Submitted in the Medical Device Application

Document-based inspection and data integrity assessment were conducted in accordance with the provisions of the PMD Act for the data submitted in the medical device application. PMDA concluded that there should be no problems with conducting a regulatory review based on the submitted product application documents.

V. Overall Evaluation

SATAKE-HotBalloon Catheter is a balloon ablation catheter system using radiofrequency energy. The key issues discussed in the review of SATAKE-HotBalloon Catheter were (1) clinical positioning and efficacy, (2) safety, and (3) post-marketing safety measures and use-results evaluation, and PMDA's conclusions taking account of the comments from the Expert Discussion are as shown below.

(1) Clinical positioning and efficacy

Regarding myocardial ablation in drug-refractory patients with symptomatic paroxysmal atrial fibrillation in Japan, isolation of pulmonary veins using a radiofrequency ablation catheter has already been performed and a technique using a cryoballoon ablation catheter has also been initiated. The applicant explained that shorter procedure time is an advantage of the balloon of SATAKE-HotBalloon Catheter. Although no head-to-head study comparing SATAKE-HotBalloon Catheter with a conventional radiofrequency ablation catheter has been performed, shorter procedure time with the product can be expected in principle and in comparison with the data from the Japanese registry. Reduced fluoroscopy time, reduction of complications related to superheating of deep myocardial tissue, and decreased fluid loading can also be expected in principle, though no head-to-head studies have been performed. Therefore, based on the efficacy and safety of SATAKE-HotBalloon Catheter versus conventional radiofrequency ablation catheters used for isolation of the pulmonary vein, PMDA concluded that making SATAKE-HotBalloon Catheter available for routine clinical use as an option for ablation in patients with atrial fibrillation is of significance if the efficacy and safety of the product are clinically acceptable.

The pivotal study demonstrated the statistically significant superiority of the investigational device over antiarrhythmic drug therapy for "chronic success rate" as the primary endpoint. Comparison with a conventional radiofrequency ablation catheter using a literature report demonstrated the superiority of SATAKE-HotBalloon Catheter to the control. In addition, the chronic success rate with SATAKE-HotBalloon Catheter in the pivotal study is not low as

compared with the outcomes of catheter ablation using similar devices in a foreign study. Although the chronic success rate with SATAKE-HotBalloon Catheter in the pivotal study was slightly lower than the success rate in the Japanese registry, the outcome may have been affected by some differences in treatment conditions, namely, the prohibition of adding ablation to pulmonary vein isolation and re-ablation, and active detection of recurrence in the pivotal study.

Moreover, the pivotal study suggested that a learning curve exists and reduced procedure time is expected with SATAKE-HotBalloon Catheter as compared with the Japanese registry. Taking account of the totality of these findings, the efficacy of SATAKE-HotBalloon Catheter is clinically acceptable at present.

However, since SATAKE-HotBalloon Catheter was studied in a limited number of patients at a limited number of sites in Japan, information should be collected through the use-results survey.

(2) Safety

None of the adverse events observed in the pivotal study were specific to SATAKE-HotBalloon Catheter. The assessment results for individual events of safety interest associated with the use of SATAKE-HotBalloon Catheter are described below.

Although all events of pulmonary vein stenosis were asymptomatic and required no intervention, the possibility of the occurrence of clinically relevant pulmonary vein stenosis associated with the use of SATAKE-HotBalloon Catheter cannot be ruled out because the number of patients studied was limited. At present, it should be ensured that precautions regarding the recommended balloon inflation volume are advised and that thorough training, etc., is provided.

The risk of cerebral infarction was not compared between SATAKE-HotBalloon Catheter and a conventional radiofrequency ablation catheter, but adequate caution is needed. At present, the usual precautions (e.g., appropriate use of perioperative anticoagulant therapy [before and after the procedure]) should be fully ensured.

Although all events of phrenic nerve paralysis were non-serious and resolved, appropriate risk reduction measures should be taken. Thus, precautions regarding the balloon inflation volume and measures such as phrenic nerve pacing should be advised.

Although none of the adverse events related to puncture site were considered serious, the incidence of adverse events associated with SATAKE-HotBalloon Catheter is slightly higher than

with conventional radiofrequency ablation catheters. For this reason, information on pre-dilation with a 16 Fr dilator should be provided, and precautions against puncture site haemorrhage should be advised.

The incidences of esophageal injury and atrio-esophageal fistula cannot be assessed specifically, since SATAKE-HotBalloon Catheter was not compared with a conventional radiofrequency ablation catheter. As in the case with conventional radiofrequency ablation catheters, adequate caution is necessary. Information on esophageal temperature monitoring, esophageal cooling, etc., should be provided appropriately.

Because guidewire manipulation in the pulmonary vein during the use of SATAKE-HotBalloon Catheter is assumed, the guidewire to be used with the product should be pre-specified in order to prevent cardiac perforation and cardiac tamponade.

Concerning balloon pinholes reported as malfunctions in the pivotal study, the measures proposed by the applicant should be implemented, i.e., leakage test and the procedural precautions for avoiding abrasion of the balloon surface. In addition, the measures for early detection and the actions to be taken in the event of a balloon pinhole should also be advised.

As described above, the applicant should advise the precautions and implement the measures against adverse events and device malfunctions and then collect information through the use-results survey.

(3) Post-marketing safety measures and use-results evaluation

Since (a) SATAKE-HotBalloon Catheter is different from conventional radiofrequency ablation catheters in terms of the shape and the principle of ablation, (b) SATAKE-HotBalloon Catheter is different from a cryoballoon ablation catheter in terms of the details of the procedure involving balloon manipulation and the principle of ablation, and (c) there are procedural precautions specific to SATAKE-HotBalloon Catheter, physicians who already have adequate experience in percutaneous catheter ablation procedures for the treatment of arrhythmias should attend appropriate training sessions on SATAKE-HotBalloon Catheter in order to use the product at medical institutions that are prepared to manage various complications.

Based on the above, the conditions for approval 1 and 2 should be imposed on this application. Since the balloon inflation volume was below the recommended level in many subjects in the pivotal study and its relationship to the occurrence of adverse events cannot be ruled out, etc.,

post-marketing information should be collected on the balloon inflation volume and the safety of SATAKE-HotBalloon Catheter in patients with low balloon inflation volume.

Furthermore, (a) the procedural characteristics of ablation therapy with SATAKE-HotBalloon Catheter are substantially different from those with conventional radiofrequency ablation catheters, (b) a cryoballoon ablation catheter has just been introduced into the Japanese market, and (c) SATAKE-HotBalloon Catheter is a device developed in Japan and the number of patients assessed in Japanese clinical studies was very limited. Therefore, it is necessary to collect information in routine clinical settings until data from a specific number of patients will be accumulated.

The use-results evaluation period should be 3.5 years.

Based on the above results, PMDA concluded that SATAKE-HotBalloon Catheter may be approved for the following intended use, with the following conditions.

[Intended use]
The product is used for radiofrequency hot balloon ablation of cardiac tissue to treat drug-refractory recurrent symptomatic paroxysmal atrial fibrillation.

[Conditions for approval]

1. The applicant is required to take necessary measures to ensure the use of the product at medical institutions that meet the requirements established in cooperation with relevant academic societies, so that the product will be used at medical institutions which are staffed with physicians with adequate knowledge of and experience in percutaneous catheter ablation procedures for the treatment of arrhythmias including atrial fibrillation and which are prepared to manage procedural complications.
2. The applicant is required to take necessary measures to ensure that physicians attend appropriate training sessions to perform ablation procedures with the product in compliance with the requirements established in cooperation with relevant academic societies, so that the product will be used, in compliance with the approved indication, by physicians with adequate knowledge of and experience in the technique of percutaneous catheter ablation using the product for the treatment of arrhythmias including atrial fibrillation, and the management of procedural complications, etc.

The product is not classified as a biological product or a specified biological product. The product should be designated as a medical device subject to the use-results survey and the use-results evaluation period should be 3.5 years.

This application should be deliberated by the Committee on Medical Devices and *In-vitro* Diagnostics.

VI. References

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