June 12, 2023
Medical Device Evaluation Division
Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Report on the Deliberation Results

Classification	Instrument & Apparatus 29, Electrosurgical Unit
Term Name	Radio-frequency ablation system
Brand Name	Cool-tip RFA System E Series
Applicant	Covidien Japan Inc.
Date of Application	November 30, 2022

Results of Deliberation

In its meeting held on June 12, 2023, the Committee on Medical Devices and *In-vitro* Diagnostics reached the following conclusion, and decided that this conclusion should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is not designated as a medical device subject to a use-results survey. The partial change application for the product should be approved.

The following underlined condition should be newly imposed.

Approval Conditions

1. (Omitted)
2. <u>The applicant is required to report to the Pharmaceuticals and Medical Devices Agency the results of the final analysis of the clinical study included in the application to add a new indication of breast tumor and take appropriate action as needed.</u>

Review Report

May 19, 2023

Pharmaceuticals and Medical Devices Agency

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

Classification	Instrument & Apparatus 29, Electrosurgical Unit
Term Name	Radio-frequency ablation system
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Applicant	Covidien Japan Inc.
Date of Application	November 30, 2022
Reviewing Office	Office of Medical Devices II

Review Results

May 19, 2023

Classification	Instrument & Apparatus 29, Electrosurgical Unit
Term Name	Radio-frequency ablation system
Brand Name	Cool-tip RFA System E Series
Applicant	Covidien Japan Inc.
Date of Application	November 30, 2022

Results of Review

The Cool-tip radio frequency ablation (RFA) System E Series (Approval No. 22300BZX00335000; hereinafter referred to as "the Cool-tip RFA System") is a radio frequency ablation system used for coagulation and ablation of liver tumors, small renal malignancies, acardiac mass by stopping blood flow to the acardiac twin, and pulmonary malignancies and other tumors not indicated for or refractory to standard therapy. The Cool-tip RFA System consists of active electrodes, which are placed in the tissue for coagulation and ablation, a generator, which delivers power to the active electrodes, and other components.

The Cool-tip RFA System has already received approval on August 2, 2011 for the intended use of coagulation and ablation of liver tumors (approval number, 22300BZX00335000). Subsequently, the following indications have been added: "acardiac mass by stopping blood flow to the acardiac twin" on July 25, 2018; and "small renal malignancies" and "pulmonary malignancies, malignant bone tumors, osteoid osteoma, pelvic malignant tumors, and soft tissue tumors that developed in the extremities, thoracic cavity, and abdominal cavity that are not indicated for or refractory to standard therapy" on December 24, 2021. The objective of the present application for partial change approval is to add a new indication of "early-stage breast cancer."

The Japanese Breast Cancer Society submitted a petition requesting early introduction of the Cool-tip RFA System, and the Ministry of Health, Labour and Welfare designated the Cool-tip RFA System as a medical device with high medical need.

Non-clinical data of the Cool-tip RFA System were omitted because the data submitted at the initial approval can be used for evaluation of the new indication.

Clinical data of the Cool-tip RFA System were submitted based on the "multicenter collaborative study that aims to validate the efficacy of RFA therapy and to standardize its use for early-stage breast cancer" (Radiofrequency Ablation Therapy for Early Breast Cancer as Local Therapy [RAFAELO] study). The study was conducted under the Advanced Medical Care B Program to verify the long-term treatment effect of RFA therapy for localized, solitary, early-stage breast cancer with a tumor diameter of ≤1.5 cm, without axillary lymph node metastasis and other metastasis as confirmed by palpation and imaging diagnosis. After the Cool-tip RFA System was designated as a medical device with high medical need by the Ministry of Health, Labour and Welfare, the applicant revised the initial analysis plan and submitted the summarized results obtained up to a cut-off date of February 2, 2022, for the application of early regulatory approval with the results of the final analysis to be submitted later, instead of waiting for the completion of the 5-year follow-up period. In the results of the RAFAELO study summarized for the application, all 346 subjects of the full analysis set (FAS) completed the follow-up period up to 3 years, 324 subjects completed the follow-up period up to 4 years, and 183 subjects completed the follow-up period up to 5 years.

The 5-year ipsilateral breast tumor recurrence-free survival (IBTRFS) rate, the primary endpoint, was 98.5% (95% CI, 96.4%-99.4%), which was equivalent to that of the current standard of care in Japan. The incidence of Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥3 adverse events was 7.0% (95% CI, 4.6%-10.1%), and the incidence of Grade ≥3 adverse reactions (medical device-related adverse events) was 1.1% (95% CI, 0.3%-2.7%), indicating clinically acceptable safety.

Taking account of comments raised by the Expert Discussion, the Pharmaceuticals and Medical Devices Agency (PMDA) comprehensively reviewed the submitted data and concluded as follows: The RFA therapy with the Cool-tip RFA System would not replace surgical treatment, the current first-line standard therapy for early-stage breast cancer. However, the Cool-tip RFA System was designated as a medical device with high medical need by the Ministry of Health, Labour and Welfare, the Cool-tip RFA System can be introduced into the clinical practice as a treatment option for early-stage breast cancer provided that the Cool-tip RFA System is used in compliance with a proper use guideline to be prepared by the relevant academic society, is used only in precisely intended patients, and is used carefully after relevant information on the treatment is provided to the patient by the physician.

As a result of its regulatory review, PMDA has concluded that the Cool-tip RFA System may be granted a marketing approval for the intended use as described below with the following approval conditions, and that the application should be deliberated at the Committee on Medical Devices

and *In-vitro* Diagnostics. The intended use and approval conditions to be added in the present partial change application are underlined.

Intended Use

The Cool-tip RFA System is used for coagulation and ablation via the percutaneous route, laparoscopy, laparotomy, thoracoscopy, or thoracotomy of the following tissue:

- Coagulation and ablation of partial or complete liver tumors or small renal malignancies
- Coagulation and ablation for the treatment of breast tumor (localized, solitary, early-stage breast cancer with a tumor diameter of ≤1.5 cm, without axillary lymph node metastasis and metastasis as confirmed by palpation and diagnostic imaging)
- Coagulation and ablation of acardiac mass by stopping blood flow to the acardiac twin
- Coagulation and ablation for the treatment of following tumors not indicated for or refractory to standard therapy (including palliative care)
  - Pulmonary malignancies
  - Malignant bone tumors
  - Osteoid osteoma
  - Pelvic malignant tumor
  - Soft tissue tumors that developed in the extremities, thoracic cavity, and abdominal cavity

Approval Conditions

(1) The applicant is required to take necessary actions, including providing training sessions and disseminating a guideline for proper use prepared in cooperation with the relevant academic society, to ensure that the Cool-tip RFA System will be used by physicians with thorough knowledge and experience in providing treatment with a radio-frequency ablation system, who have acquired the skills required for using the Cool-tip RFA System, who have adequate knowledge of procedural complications, and that the Cool-tip RFA System will be used at medical facilities capable of providing adequate medical care.

(2) The applicant is required to report to the Pharmaceuticals and Medical Devices Agency the results of the final analysis of the clinical study included in the application to add a new indication of breast tumor and take appropriate action as needed.

Review Report

May 19, 2023

Product for Review

Classification	Instrument & Apparatus 29, Electrosurgical Unit
Term Name	Radio-frequency ablation system
Brand Name	Cool-tip RFA System E Series
Applicant	Covidien Japan Inc.
Date of Application	November 30, 2022
Proposed Intended Use	The Cool-tip RFA System is used for coagulation and ablation via the percutaneous route, laparoscopy, laparotomy, thoracoscopy, or thoracotomy of the following tissues: − Coagulation and ablation of partial or complete liver tumors, small renal malignancies or breast tumors − Coagulation and ablation of acardiac mass by stopping blood flow to the acardiac twin − Coagulation and ablation for the treatment of following tumors not indicated for or refractory to standard therapy (including palliative care) • Pulmonary malignancies • Malignant bone tumors • Osteoid osteoma • Pelvic malignant tumor • Soft tissue tumors that developed in the extremities, thoracic cavity, and abdominal cavity

Table of Contents

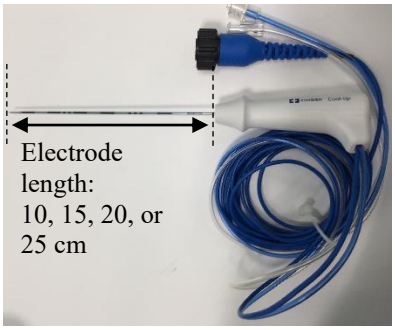
List of Abbreviations

CT	Computed Tomography
EN	European Norm
ER	Estrogen Receptor
FAS	Full Analysis Set
GCP	Good Clinical Practice
GVP	Good Vigilance Practice
HER2	Human Epidermal Growth Factor Receptor 2
IBTR rate	Ipsilateral Breast Tumor Recurrence rate
IBTRF rate	Ipsilateral Breast Tumor Recurrence Free rate
IBTRFS rate	Ipsilateral Breast Tumor Recurrence Free Survival rate
IDFS	Invasive Disease-free survival rate
IEC	International Electrotechnical Commission
ISO	International Organization for Standardization
MFS	Metastasis-free survival
MMG	Mammography
MRI	Magnetic Resonance Imaging
NCD	National Clinical Database
PgR	progesterone receptor
PS	Performance Status
QOL	Quality of life
RFA	Radio Frequency Ablation
SAS	Safety Analysis Set
SLNB	Sentinel lymph node biopsy

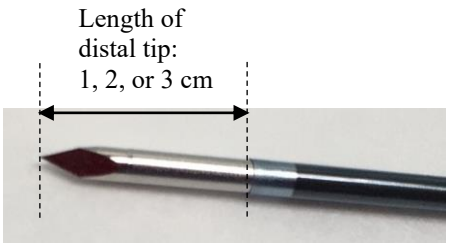
I. Product Overview

The Cool-tip RFA System E Series (Approval No. 22300BZX00335000; hereinafter referred to as "the Cool-tip RFA System") is a radio frequency ablation system used for coagulation and ablation of liver tumors, small renal malignancies, breast tumors, or other tissues. The device consists of active electrodes, which are placed in the tissue for coagulation and ablation, a generator, which delivers power to the active electrodes, and other components (Figure 1). In the RFA procedure for breast tumor, the active electrode shaft is inserted percutaneously under ultrasound guidance, equivalent to the procedure for liver and other tumors, to coagulate and ablate the target lesion.

Figure 1. Appearance of the Cool-tip RFA System



Active electrode (overall view)



Active electrode (distal tip of the electrode)

Generator

• Dimension

Height	Width	Depth
235 mm	433 mm	475 mm

• Electrical rating

Supply voltage	Frequency	Power input
100-120/220-240 VAC	50/60 Hz	Max. 385 W

• Radiofrequency specifications

Operating frequency	Power output characteristics	Timer setting
472 kHz ± 1%	Max. 200 W	0-30 minutes

The applicant submitted the present partial change application (hereinafter referred to as "the present application") to add a new indication of "breast-conserving local therapy in patients with early-stage breast cancer," with no changes in specifications or components of the Cool-tip RFA System.

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

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

The expert advisors present during the Expert Discussion on the Cool-tip RFA System declared that they did not fall under the Item 5 of the Rules for Convening Expert Discussions, etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/20 dated December 25, 2008).

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

1.A Summary of the data submitted

1.A.(1) History of development

The Cool-tip RFA System is intended for the treatment of solitary breast cancer Tis-T1 (≤1.5 cm tumor diameter), N0, M0, Stage 0-I, according to the TNM classification system, the staging system for breast cancer (Table 1).

Table 1. TNM classification system for breast cancer (General Rules for Clinical and Pathological Recording of Breast Cancer 18th edition,[1] edited by the Japanese Breast Cancer Society)

<table>
<tr><td>Presence/absence of metastasis</td><td colspan="4">No metastasis: M0</td><td>Metastasis: M1</td></tr>
<tr><td>Metastasis to lymph nodes / Size of primary focus</td><td>No metastasis: N0</td><td>Axillary lymph nodes (movable): N1</td><td>Axillary lymph nodes (fixed) or internal mammary lymph nodes: N2</td><td>Both the axillary and internal mammary OR medial to the pectoralis minor muscle/under the collarbone: N3</td><td></td></tr>
<tr><td>Within the duct: Tis</td><td>0</td><td>—</td><td>—</td><td>—</td><td>—</td></tr>
<tr><td>None: T0</td><td>—</td><td rowspan="2">IIA</td><td rowspan="3">IIIA</td><td rowspan="5">IIIC</td><td rowspan="5">IV</td></tr>
<tr><td>≤2 cm: T1</td><td>I*</td></tr>
<tr><td>>2 cm but ≤5 cm: T2</td><td>IIA</td><td>IIB</td></tr>
<tr><td>>5 cm: T3</td><td>IIB</td><td>IIIA</td></tr>
<tr><td>Spread into the chest wall or skin change, inflammatory: T4</td><td colspan="3">IIIB</td></tr>
</table>

* The Cool-tip RFA System is intended to be used for Stage I tumors ≤1.5 cm in diameter.

According to the Japanese Breast Cancer Society Clinical Practice Guidelines for systemic treatment of breast cancer, 2022 edition,[2] the standard treatments for Stage 0 breast cancer are mainly local therapies of the breast (surgery and postoperative radiation therapy). In some patients, subsequent pharmacotherapy may be added. The standard treatments for early-stage breast cancer other than Stage 0 (Stages I to IIIA) are intended to prevent and control potential micrometastasis

by local therapies for the primary foci and axillary lymph nodes (surgery and postoperative radiation therapy) and systemic therapy (pharmacotherapy).

As a local therapy for the primary foci in the breast, breast-conserving therapy consisting of partial mastectomy and postoperative radiation therapy, or total mastectomy (followed by, as necessary, breast reconstruction and radiation therapy) has been performed. For Stage 0 to Stage II breast cancer meeting the indication criteria,[1] breast-conserving therapy (partial mastectomy and postoperative radiation therapy) is often performed.[2]

Breast surgery is an invasive procedure. Both partial mastectomy and total mastectomy carry risks of procedure-associated events such as bleeding and hematoma. Breast surgery may impact on the patient's quality of life (QOL) because surgery causes pain at the surgical site or in other areas, and leaves some scarring and deformation of the breast.

In RFA therapy with the Cool-tip RFA System, instead of surgically resecting part of the breast, a thin, needle-like active electrode is inserted into the breast cancer tissue from the breast surface for coagulation and ablation under ultrasound guidance. Compared with surgical resection, RFA therapy is assumed to leave less deformation in the wound area of the breast, and is less invasive to healthy tissue. It is expected that the physical and psychological discomfort of patients are mitigated by minimizing the extent of the wound made to the breast.

RFA therapy with the Cool-tip RFA System has been provided at the physician's discretion as a treatment not covered by Japanese national medical insurance during the period when the device had not yet received regulatory approval for use. Under the circumstances, there were cases where some physicians with insufficient knowledge of the therapeutic characteristics of RFA therapy performed the therapy in patients regarded as ineligible for the therapy. This was because too much emphasis was placed on cosmetic factors, and there were cases that resulted in recurrence of breast cancer. In view of the situation, the Japanese Breast Cancer Society released a cautionary statement in July 2010, "except for the purpose of a clinical study, at this point in time, RFA therapy should not be used in Japan."

However, there were clinical study results [3-5] that suggested that RFA therapy can be performed effectively and safely in patients meeting certain criteria. Accordingly, the "multicenter

[1] According to the Japanese Breast Cancer Society Clinical Practice Guidelines for systemic treatment of breast cancer, 2022 edition, partial mastectomy is indicated when (1) cancer was removed with a negative margin with acceptable cosmetic outcome; and (2) radiotherapy to the conserved breast is possible. Specifically, it is not indicated for the cases in which multiple cancer affecting different lobes of the mammary gland or wide progression of breast cancer is observed, or breast-conserving therapy is not desired by the patient.

collaborative study that aims to validate the efficacy of RFA therapy and to standardize its use for early-stage breast cancer" (Radiofrequency Ablation Therapy for Early Breast Cancer as Local Therapy [RAFAELO] study) was started in August 2013 by the National Cancer Center Hospital Japan under the Advanced Medical Care B Program (Notification No.2) to determine intended patient population and to verify the long-term therapeutic effect. (After July 2018, when the Clinical Trials Act came into effect, the study falls under the category of specified clinical trials.)

Subsequently, based on the data from the RAFAELO study, the usefulness of RFA therapy with the Cool-tip RFA System was re-examined, leading to submission of a written request for designation as a medical device with high medical need by the Japanese Breast Cancer Society in January 2021. In November 2021, at the 32nd meeting of the Study Group on early introduction of medical devices with high medical need (hereinafter referred to as the "Study Group on devices with high medical need"), designation of the Cool-tip RFA System as a medical device with high medical need was requested along with other requests, namely, early regulatory approval and improvement of environments to facilitate RFA therapy for appropriate patients.

In this context, the applicant submitted a partial change application to add a new indication of "breast tumor."

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

In Japan, the Cool-tip RFA System was approved on August 2, 2011 with an intended use of coagulation and ablation of a liver tumor. The indication of "acardiac mass by stopping blood flow to the acardiac twin" was added on July 25, 2018; and "small renal malignancies" and "pulmonary malignancies, malignant bone tumors, osteoid osteoma, pelvic malignant tumor, and soft tissue tumors that developed in the extremities, thoracic cavity, and abdominal cavity that are not indicated for or refractory to standard therapy" were added on December 24, 2021. In Europe and the US, the Cool-tip RFA System was approved for the intended uses shown in Table 2.

For sales in and outside Japan, during the period between February 2021 and July 2022, [redacted] pieces of active electrodes and [redacted] sets of generators were sold in Japan while [redacted] pieces of active electrodes and [redacted] sets of generators were sold in Europe (Table 2).

Table 2. Approvals and sales in and outside Japan

Country/ region	Brand name	Approval date	Current intended use or indication	Sales (February 2021 to July 2022)
Japan	Cool-tip RFA System E Series (22300BZX00335000)	August 2011	The Cool-tip RFA System is used for coagulation and ablation via the percutaneous route, laparoscopy, laparotomy, thoracoscopy, or thoracotomy of the following tissue: – Coagulation and ablation of partial or complete liver tumors or small renal malignancies – Coagulation and ablation of acardiac mass by stopping blood flow to the acardiac twin – Coagulation and ablation for the treatment of following tumors not indicated for or refractory to standard therapy (including palliative care) • Pulmonary malignancies • Osteoid osteoma • Pelvic malignant tumor • Malignant bone tumors • Soft tissue tumors that developed in the extremities, thoracic cavity, and abdominal cavity	[redacted] sets of generators [redacted] pieces of active electrodes
Europe	Cool-tip RF Ablation System E series (CE mark)	March 2010	Percutaneous, laparoscopic, and abdominal intraoperative coagulation and ablation of soft tissue (e.g., partial or complete ablation of unresectable liver tumors, and osteoid osteoma within bone)	[redacted] sets of generators [redacted] pieces of active electrodes
US	Cool-tip RF Ablation system E Series 510k (K203150)	February 2022	Percutaneous, laparoscopic, and abdominal intraoperative coagulation and ablation of soft tissue (including partial or complete ablation of unresectable liver tumors)	No sales (As of July 2022)

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

Tables 3 through 6 show the incidence of malfunctions reported to the Japanese and foreign regulatory authorities.

Table 3. Malfunctions in Japan (Active and return electrodes)

(February 2021 to July 2022)

Malfunction/adverse event (including suspected cases)	Site	Number of cases
Occurrence of errors	Unknown, 5	5
Bending	Unknown, 1	1
Erroneous operation	Unknown, 8	8
Ablation failure	Liver, 1; Unknown, 1	2
Contact dermatitis	Unknown, 1	1
Electrical conduction failure	Unknown, 3	3
Heating of return electrode	Unknown, 2	2
Thermal burn	Unknown, 1	1
Removal of electrode	Unknown, 1	1
Damage to the part	Liver, 1; Unknown, 1	2
Redness	Unknown, 1	1
Tube water leak	Liver, 1	1
Cancer recurrence	Liver, 2	2
Postoperative haemorrhage	Liver, 2	2
Embolism	Liver, 1	1
Cerebral infarction	Liver, 1	1
Angina pectoris	Liver, 1	1
Tumor progression	Liver, 1	1
Bile duct injury	Liver, 1	1
Dissemination	Liver, 1	1
Abscess	Liver, 1	1
Total	(Total number of cases)	39

Table 4. Malfunctions in Japan (Generators) (February 2021 to July 2022)

Malfunction/adverse event (including suspected cases)	Site	Number of cases
Occurrence of errors	Unknown, 6	6
Cooling water circulation failure	Unknown, 1	1
Output turned off	Unknown, 1	1
Display failure	Unknown, 2	2
Total	(Total number of cases)	10

Table 5. Malfunctions in Europe (Active and return electrodes*)

(February 2021 to July 2022)

Malfunction/adverse event (including suspected cases)	Site	Number of cases
Thermal burn	Unknown, 1; liver, 4; lung, 1	6
Occurrence of errors	Liver, 1	1
Removal of electrode	Liver, 1	1
Infection	Bone, 1; liver, 4; lung, 1	6
Tissue injury	Bone, 1	1
Pain	Bone, 1; liver, 1; pelvis, 1	3
Cancer recurrence	Liver, 8; pelvis, 1; lung, 1	10
Haemothorax	Liver, 1	1
Pneumothorax	Liver, 4	4
Abscess	Liver, 1	1
Hepatic encephalopathy	Liver, 1	1
Hepatic infarction	Liver, 1	1
Bile duct stenosis	Liver, 1	1

Malfunction/adverse event (including suspected cases)	Site	Number of cases
Portal vein thrombosis	Liver, 1	1
Pleural effusion	Liver, 4	4
Ablation failure	Liver, 6; pelvis, 1; lung, 1	8
Postoperative haemorrhage	Liver, 5	5
Pyrexia	Liver, 4	4
Constipation	Liver, 1	1
Vomiting	Liver, 1	1
Cough	Liver, 1	1
Arrhythmia	Liver, 1	1
Fistula	Liver, 2	2
Respiratory failure	Liver, 1	1
Hepatic failure	Liver, 2	2
Renal failure	Liver, 1	1
Cardiac disorders	Liver, 1	1
Embolism in portal vein branch	Liver, 1	1
Feeling hot	Pelvis, 1	1
Urination impaired	Pelvis, 1	1
Tumor progression	Liver, 4	4
Perforation	Liver, 1	1
Residual foci	Liver, 1	1
Cyst	Liver, 1	1
Haematoma	Liver, 1	1
Total	(Total number of cases)	81

* Components to which malfunctioning was attributed were determined as follows: if it was a customer's complaint, the component that the customer complained of (e.g., the electrode, return electrode, or generator) was determined to be the malfunctioning component. For malfunctions reported in the literature, if a malfunctioning component was indicated, the indicated component was determined to be the malfunctioning component. If specific components to which malfunctioning was attributed were not indicated, the specific components were identified by the manufacturer overseas.

Table 6. Malfunctions in Europe (Generators*) (February 2021 to July 2022)

Malfunction/adverse event (including suspected cases)	Site	Number of cases
Occurrence of errors	Unknown, 1	1
Abscess	Liver, 1	1
Bile leak	Liver, 1	1
Biliary stenosis	Liver, 1	1
Infection	Liver, 1	1
Fistula	Liver, 1	1
Bacteraemia	Liver, 1	1
Haemorrhage	Liver, 1	1
Postoperative haemorrhage	Liver, 1	1
Haematoma	Liver, 1	1
Aneurysm	Liver, 1	1
Pulmonary embolism	Liver, 1	1
Pneumonia	Liver, 1	1
Bronchitis	Liver, 1	1
Pneumothorax	Liver, 1	1
Pleural effusion	Liver, 1	1
Thrombosis	Liver, 1	1
Tissue injury	Liver, 1	1
Emphysema	Liver, 1	1
Subcutaneous emphysema	Liver, 1	1
Suffering	Liver, 1	1

Malfunction/adverse event (including suspected cases)	Site	Number of cases
Syncope	Liver, 1	1
Vomiting	Liver, 1	1
Bradycardia	Liver, 1	1
Hyperglycaemia	Liver, 1	1
Pyrexia	Liver, 1	1
Ablation failure	Liver, 1	1
Total	(Total number of cases)	27

* Components to which malfunctioning was attributed were determined as follows: if it was a customer's complaint, the component that the customer complained of (e.g., the electrode, return electrode, or generator) was determined to be the malfunctioning component. For malfunctions reported in the literature, if a malfunctioning component was indicated, the indicated component was determined to be the malfunctioning component. If specific components to which malfunctioning was attributed were not indicated, the specific components were identified by the manufacturer overseas.

2. Design and Development

2.(1) Performance and safety specifications

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

The present application has the proposed performance and safety specifications presented below. These specifications are the same as those approved at the initial approval because no substantial changes have been made since then to the specifications or components of the Cool-tip RFA System.

The proposed specifications for the performance include power output characteristics, operating frequency, timer setting, impedance display, current display, power display, temperature display, and impedance control. The proposed specifications for the safety of the active electrode and other components include electrical safety (IEC 60601-1:2005/AMD1:2012, IEC 60601-2-2:2017), electromagnetic compatibility (IEC 60601-1-2:2014), sterility assurance, biological safety, and ethylene oxide sterilization residuals. The proposed specifications for the safety of the generator include electrical safety (IEC 60601-1:2005/AMD1:2012, IEC 60601-2-2:2017) and electromagnetic compatibility (IEC 60601-1-2:2014).

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

The proposed performance and safety specifications are the same as those approved at the initial approval. PMDA's view on using the same specifications:

The following is the performance required for the Cool-tip RFA System to perform RFA therapy of early-stage breast cancer: the active electrode shaft must be capable of being inserted into the lesion of interest, and the device must be capable of coagulating and ablating the target tissue as intended.

The area through which the electrode is inserted in the treatment of breast tumor consists of epithelial tissue, connective tissue, adipose tissue, and mammary tissue, which have similar characteristics to those involved in electrode insertion for the treatment of liver tumors, the

approved indication. In fact, the basic procedures of the Cool-tip RFA System for the proposed intended use (inserting the active electrode shaft into the target site and performing coagulation and ablation) is similar to those for the initially approved indication. The characteristics of the region around the coagulation/ablation site are unlikely to affect the performance and safety of the Cool-tip RFA System even when regional anatomical differences are taken into account.

PMDA therefore concluded that there is no particular problem in using the same performance and safety specifications as those approved in the initial approval.

2.(2) Safety specifications

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

The applicant omitted the submission of evaluation data on physicochemical properties, electrical safety, electromagnetic compatibility, mechanical safety, stability, and durability because no changes were made to the approved specifications or components of the Cool-tip RFA System for the present application. Given that no changes were also made to the raw materials or the directions for use, biological safety was evaluated based on the use results of the Cool-tip RFA System.

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

PMDA considered that the omission of evaluation data on physicochemical properties, electrical safety, electromagnetic compatibility, mechanical safety, stability, and durability was acceptable because no changes were made to the specifications or components of the Cool-tip RFA System for the present application. PMDA reviewed and accepted the data on biological safety.

2.(3) Performance

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

In the present application, no changes were made to the specifications or components of the Cool-tip RFA System from those approved earlier. The area through which the electrode is inserted in the treatment of breast tumor consists of epithelial tissue, connective tissue, adipose tissue, and mammary tissue, which have similar characteristics to those involved in electrode insertion for the treatment of liver tumor, the approved indication. In the intended coagulation/ablation site for the treatment of breast tumor, consisting of the tumor and surrounding soft tissue, the impedance is thought to differ from that of a liver tumor and surrounding healthy liver tissue; however, the difference is not significant enough to require a change in specifications. Furthermore, based on the results of the performance studies using the approved product submitted for the review for the initial approval (Table 7), the tissue insertion, coagulation, and ablation performance of the Cool-tip RFA System have already been evaluated.

On the basis of the above, the performance required for tissue insertion, coagulation, and ablation in the treatment of breast tumors is similar to that of liver tumors, therefore, the performance of the Cool-tip RFA System for the treatment of breast tumor is evaluable. Consequently, performance study data were omitted for the present application.

Table 7. List of performance tests for the approved product already evaluated during the review process for initial approval (for the approved range)

Performance tests
Study on the optimization of electrical conduction method for intermittent radio frequency (*ex vivo* study)
Comparison of the coagulation range using porcine muscle tissue (*in vivo* study)
Comparison of the coagulation range using porcine liver (*in vivo* study)
Study to evaluate the coagulation performance of the needle
Evaluation on application to large tumors
Evaluation of cooling water temperature
Determination of thermocouple measurement accuracy when cooling water is electrically conductive
Effects of cooling water temperature on ablation size

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

On the basis of the following points, PMDA concluded that submission of data on performance may be omitted.

- No changes were made to the specifications, components, or basic directions for use of the Cool-tip RFA System.
- The performance of the Cool-tip RFA System required for tissue insertion, coagulation, and ablation of breast tumor (the new indication to be added) is similar to that of liver tumor (approved indication).

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

3.A Summary of the data submitted

The applicant submitted a declaration of conformity explaining that the Cool-tip RFA System meets the standards for medical devices as stipulated by the Minister of Health, Labour and Welfare in accordance with Paragraph 3 of Article 41 of Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (hereinafter referred to as "the Essential Principles") (MHLW Public Notice No. 122, 2005).

3.B Outline of the review conducted by PMDA

PMDA reviewed the conformity of the Cool-tip RFA System to the Essential Principles.

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

PMDA's view:
As described later in Section "6.B Outline of the review conducted by PMDA," the precautions concerning appropriate selection of intended patients for the Cool-tip RFA System are critical and users are required to have sufficient knowledge and skills to meet the criteria; therefore, it was decided to continue to impose approval conditions so that the applicant takes necessary measures.

(2) The conformity of the Cool-tip RFA System to Article 3, which stipulates the performance and function of medical devices, and to Article 6, which stipulates the efficacy of medical devices

PMDA's view:
As described later in Section "6.B Outline of the review conducted by PMDA," it was demonstrated that the Cool-tip RFA System can be used effectively and safely if intended patients are selected appropriately and ablation is performed in an appropriate manner by the user after becoming fully familiar with the characteristics of the Cool-tip RFA System. Therefore, there is no problem with the conformity of the Cool-tip RFA System to Articles 3 and 6.

(3) The conformity of the Cool-tip RFA System to Article 17, which stipulates the general requirements for information provision to users, i.e., publicizing precautions and specifying such information in the package inserts (hereinafter referred to as "Information on Precautions, etc.")

PMDA's view:
As described later in Section "6.B Outline of the review conducted by PMDA," in order to ensure a favorable risk-benefit balance of the Cool-tip RFA System, it is essential for the user to select intended patients and use the device in an appropriate manner after becoming fully familiar with the risks associated with the Cool-tip RFA System. Therefore, relevant information should be disseminated through Information on Precautions, etc., proper use guidelines, training, and by other means.

PMDA comprehensively reviewed the conformity of the Cool-tip RFA System to the Essential Principles, and concluded that there was no particular problem.

4. Risk Management

4.A Summary of the data submitted

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

4.B Outline of the review conducted by PMDA

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

5. Manufacturing Process

5.A Summary of the data submitted

Data on the manufacturing process were omitted because no changes were made to the manufacturing process of the Cool-tip RFA System for the present application.

5.B Outline of the review conducted by PMDA

PMDA concluded that omission of data on the manufacturing process is acceptable.

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

6.A Summary of the data submitted

For the present application, the applicant submitted the results from the RAFAELO study, a clinical study conducted as the Advanced Medical Care B Program in patients with early-stage breast cancer with a tumor diameter of ≤1.5 cm, without axillary lymph node metastasis.

6.A.(1) RAFAELO study

6.A.(1).1) Outline

The RAFAELO study is a prospective, uncontrolled, multicenter collaborative study to validate the efficacy and safety based on the 5-year IBTRFS rate after RFA therapy, as well as adverse events and other relevant medical data in patients with early-stage breast cancer with a tumor diameter of ≤1.5 cm, without axillary lymph node metastasis. The RAFAELO study was initiated as the Advanced Medical Care B Program on August 1, 2013 at 9 study centers in Japan. The target sample size (N = 372) was reached on November 29, 2017, and follow-up is currently

underway. Since July 2018, when the Clinical Trials Act came into force, the study falls under the category of specified clinical trials.

As described earlier in Section "1.A.(1) History of development," the applicant revised the initial analysis plan instead of waiting for the completion of the 5-year follow-up period to apply for early regulatory approval based on the request by the Study Group on devices with high medical need, separately summarized the results obtained up to a cut-off date of February 2, 2022 for the application for regulatory approval, with the results of the primary and final analysis being submitted later, and filed a partial change application. From the results of the RAFAELO study summarized for the present application, all 346 subjects of the FAS completed the follow-up period up to 3 years, 324 subjects completed the follow-up period up to 4 years, and 183 subjects completed the follow-up period up to 5 years. Table 8 shows the outline of the study protocol.

Table 8. Outline of RAFAELO study protocol

Item	Outline
Objective	To investigate the efficacy and safety based on the 5-year IBTRFS rate after RFA, residual lesion rate after treatment, overall survival, distant recurrence-free survival, and adverse events in patients with early-stage breast cancer with a tumor diameter of ≤1.5 cm without axillary lymph node metastasis, thereby establishing the treatment method
Study type	Prospective, uncontrolled, multicenter study
Study population	Patients with solitary breast cancer Tis-T1 (tumor diameter: ≤1.5 cm), N0, M0, Stage 0-I, who are willing to participate in the clinical study, and tolerate postoperative chemotherapy, radiation therapy, and hormone therapy. Eligible patients have no past history of serious cerebral infarction, myocardial infarction, thromboembolism, and can tolerate general anesthesia.
Number of patients enrolled	372
Number of study centers	9 study centers in Japan
Primary endpoint	Primary efficacy evaluation: 5-year IBTRFS rate
Secondary endpoints	Secondary efficacy evaluation: Residual lesion rate after treatment, overall survival, and distant recurrence-free survival Secondary safety evaluation: CTCAE Grade ≥3 adverse events
Major inclusion criteria	• Patients with primary invasive or noninvasive ductal carcinoma of the breast histologically confirmed via needle biopsy • Patients with a single localized lesion with the greatest tumor diameter being ≤1.5 cm on all preoperative imaging examination • Patients with no prior treatment of this breast cancer (e.g., chemotherapy, hormone therapy, and radiation therapy) • Patients who do not have a previous history of cerebral infarction, myocardial infarction, or thromboembolism, and those who can tolerate general anesthesia

Item	Outline
	• Patients without axillary lymph node metastasis evident on palpation and diagnostic imaging
Major exclusion criteria	• Patients with a history of malignant tumors other than breast cancer. However, the following patients may be included in the study: – Patients who underwent radical treatment and have been free from recurrence for ≥5 years prior to enrollment and are determined by the physician to have a low risk of recurrence in the future • Patients with artificial bone or other implants that can prevent the application of a counter plate and that are contraindicated to RFA. • Patients with extensive intraductal breast lesions or suspected multiple lesions on imaging • Patients with extensive calcifications on mammography (MMG) • Patients with synchronous bilateral breast cancer or ectopic ipsilateral breast cancer with recurrence in the preserved breast • Patients with other organ metastases
Exam/follow-up period	Before, during, and within 1 week after RFA; approximately 3 months, 12 months, 1.5 years, 2 years, 2.5 years, 3 years, 3.5 years, 4 years, 4.5 years, and 5 years after completion of radiation

6.A.(1).2) Proposed target sample size

The primary endpoint of the RAFAELO study is the 5-year IBTRFS rate. In Study NSABP-06, a large-scale clinical study conducted in Europe and the US, the 5-year ipsilateral breast tumor recurrence (IBTR) rate was 5.7% in patients who had undergone partial mastectomy consisting of removal of cancer with a negative surgical margin with postoperative radiation therapy.[6] Although only patients with tumors ≤1.5 cm were included in the RAFAELO study, the IBTR rate in patients undergoing RFA (tumor not resected) was estimated to be approximately 10% higher than that reported in Study NSABP-B06, leading to an estimated 5-year IBTR rate of 6.3%. On the basis of the estimation, an expected 5-year IBTRFS rate of 93.7%, which was considered to assure safety, was selected. Conversely, assuming that the threshold for a clinically unacceptable 5-year IBTR survival rate is 90%, with a one-sided significance level of 5% and a statistical power of 80%, a sample size of 334 would be necessary. Taking into account that approximately 10% of patients would drop out of the study, a planned sample size of 372 was selected.

6.A.(1).3) Patient characteristics

The analysis sets and the patient characteristics for the RAFAELO study are presented in Tables 9 and 10, respectively.

Table 9. Analysis sets

Analysis population	Number of patients
Enrolled patients	372
Safety analysis set (SAS)	370
Full analysis set (FAS)	346

Table 10. Patient characteristics

Item	N (%)
Age (years)	
Median	55
25%-75%	47-64
Min-Max	32-78
Mean	55.8
SD	10.5
Sex	
Male	0 (0.0)
Female	372 (100.0)
Body weight	
Median	53.6
25%-75%	48.6-59
Min-Max	36-100
Mean	54.7
SD	8.6
BMI	
Median	21.7
25%-75%	19.8-24.5
Min-Max	15.8-41
Mean	22.4
SD	3.5
Performance Status (excluding 1 patient whose data not entered)	
0	371 (100.0)
1	0 (0.0)
Tumor diameter by palpation (mm) (excluding 157 patients not examined by palpation, 158 patients whose data not entered)	
Median	10
25%-75%	8-13
Min-Max	0-24
Mean	10.7
SD	4.1
Tumor diameter by MRI (mm) (excluding 5 patients whose data not entered)	
Median	11
25%-75%	9-13
Min-Max	0-15
Mean	10.7
SD	2.8
Tumor diameter by ultrasound (mm) (excluding 1 patient whose data not entered)	
Median	10
25%-75%	8-12

Item	N (%)
Min-Max	1.2-16
Mean	9.8
SD	2.8
Tumor diameter by MMG (mm) (excluding 122 patients whose tumor was not visualized, 123 patients whose data not entered)	
Median	10
25%-75%	8-12
Min-Max	1.3-17
Mean	10.1
SD	2.7
Tumor diameter by CT (mm) (excluding 234 patients whose data not entered)	
Median	10
25%-75%	8-12
Min-Max	3-15
Mean	9.9
SD	2.7
Tissue type (excluding 1 patient whose data not entered)	
Ductal carcinoma in situ	40 (10.8)
Invasive ductal carcinoma	324 (87.3)
Ductal carcinoma	7 (1.9)
Hormone receptor: ER (excluding 1 patient whose data not entered)	
Negative	13 (3.5)
Positive	356 (96.0)
Unknown	2 (0.5)
Hormone receptor: PgR (excluding 1 patient whose data not entered)	
Negative	38 (10.2)
Positive	331 (89.2)
Unknown	2 (0.5)
HER2 expression status (excluding 1 patient whose data not entered)	
Negative	337 (90.8)
Positive	27 (7.3)
Unknown	7 (1.9)
Ki67 index (%) (excluding 42 patients who are unknown, 43 patients whose data not entered)	
Median	10.6
25%-75%	6.2-19.4
Min-Max	0.5-80
Mean	15.0
SD	12.8
Nuclear grade (excluding 1 patient whose data not entered)	
1	228 (61.5)
2	62 (16.7)
3	23 (6.2)
Unknown	58 (15.6)
Histological grade (excluding 1 patient whose data not entered)	
1	168 (45.3)
2	107 (28.8)
3	17 (4.6)
Unknown	79 (21.3)

Item	N (%)
Vascular invasion (excluding 1 patient whose data not entered)	
0	199 (53.6)
1+	12 (3.2)
2+	0 (0.0)
Unknown	160 (43.1)

The results for genetic status (Table 11) show that estrogen receptor (ER)-positive, progesterone receptor (PgR)-positive, and human epidermal growth factor receptor 2 (HER2)-negative are the most frequent (304 patients, 81.9%), followed by ER-positive, PgR-negative, and HER2-negative (24 patients, 6.5%).

Table 11. Genetic information

ER	PgR	HER2	N (%)
+	+	+	19 (5.1)
+	+	−	304 (81.9)
+	+	Unknown	6 (1.6)
+	−	+	2 (0.5)
+	−	−	24 (6.5)
+	Unknown	−	1 (0.3)
−	+	−	1 (0.3)
−	−	+	6 (1.6)
−	−	−	6 (1.6)
Unknown	+	−	1 (0.3)
Unknown	Unknown	Unknown	1 (0.3)

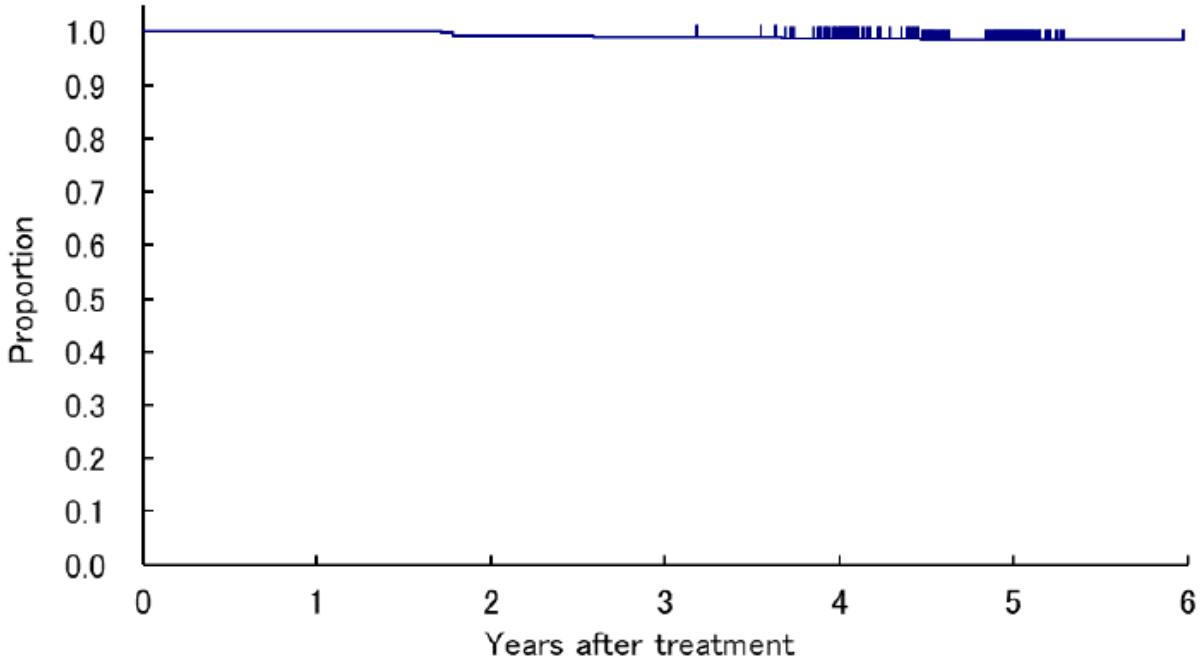
6.A.(1).4) Study results

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

6.A.(1).4).(a).i) Primary endpoint: 5-year IBTRFS rate

The Kaplan-Meier curve for recurrence-free survival time in patients with ipsilateral breast tumor in the FAS (346 patients) is shown below (Figure 2). The 5-year IBTRFS rate was 98.5% (95% CI, 96.4%-99.4%). The median follow-up period was 5 years, with 5 events (ipsilateral breast cancer [2 patients], deaths due to primary disease [2 patients], and death due to other disease [1 patient]).

Figure 2. The Kaplan-Meier curve for recurrence-free survival time in patients with ipsilateral breast tumor (FAS: 346 patients)



Analysis set		0	1	2	3	4	5	6
FAS	At risk	346	346	344	343	324	183	0
	Censoring	—	0	0	0	18	140	183

6.A.(1).4).(a).ii) Secondary endpoint: the residual lesion rate after treatment

RFA therapy and subsequent radiation therapy were performed in all patients in the FAS (N = 346). At 3 months after the completion of radiation therapy, all patients underwent vacuum-assisted needle biopsy. Table 12 shows the residual lesion rate after treatment in the 346 patients. Residual lesions were found in 10 patients, and the residual lesion rate after treatment was 2.9% (95% CI, 1.4%-5.3%).

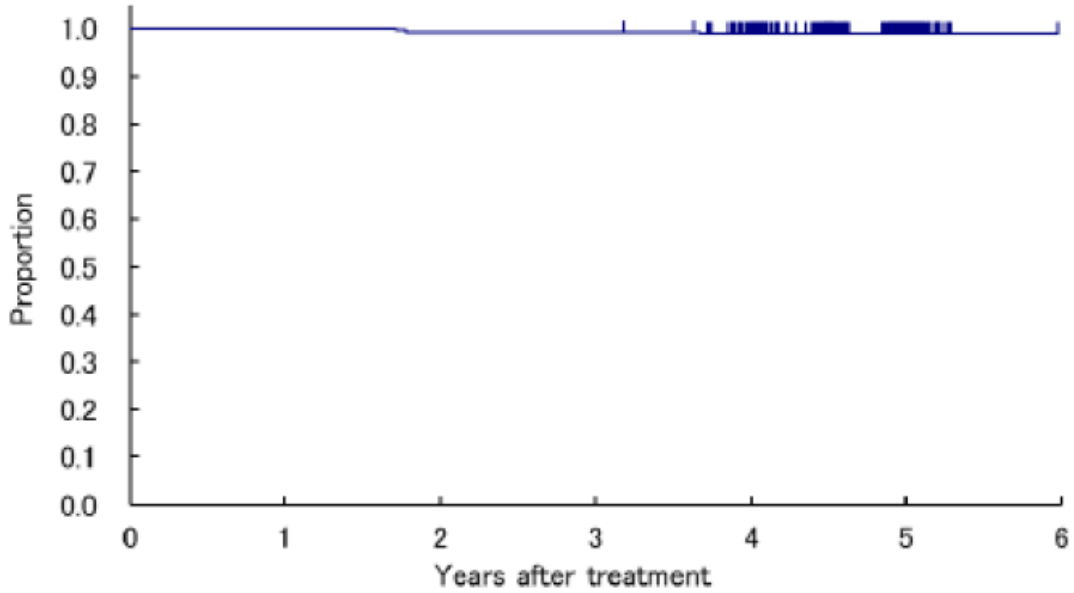
Table 12. Residual lesion rate after treatment

Presence of residual intraductal lesion only	Presence of residual invasive carcinoma only	No residual lesion	Unknown/missing measurement	The residual lesion rate after treatment (95% CI)
6	4	336	0	2.9% (1.4%-5.3%)

6.A.(1).4).(a).iii) Secondary endpoint: overall survival

Figure 3 shows the Kaplan-Meier curve for overall survival. Overall survival at 5 years was 99.1% (95% CI, 97.3%-99.7%) in the FAS (N = 346). The median follow-up period was 5 years with 3 events (deaths due to primary disease [2 patients], and death due to other disease [1 patient]).

Figure 3. Kaplan-Meier curve for overall survival (FAS, 346 patients)

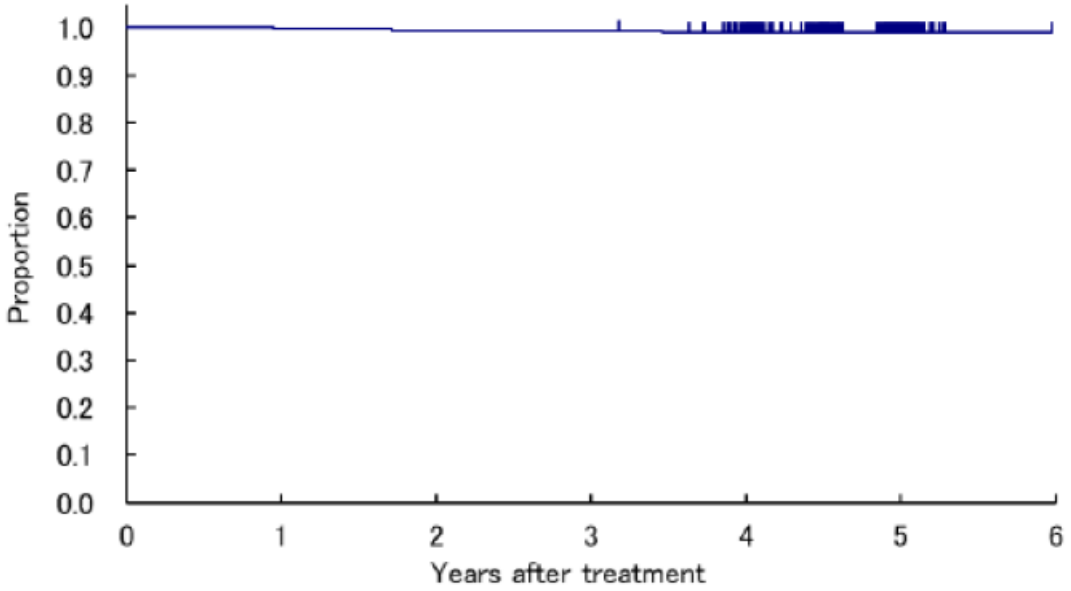


Analysis set		0	1	2	3	4	5	6
FAS	At risk	346	346	344	344	327	184	0
	Censoring	—	0	0	0	16	143	184

6.A.(1).4).(a).iv) Secondary endpoint: distant recurrence-free survival

Figure 4 shows the Kaplan-Meier curve for distant recurrence-free survival. Distant recurrence-free survival at 5 years was 99.1% (95% CI, 97.3%-99.7%) in the FAS (N = 346). The median follow-up period was 5 years with 3 events (recurrence in the lung/lymph nodes [1 patient], recurrence in the liver [1 patient], and death due to other disease [1 patient]).

Figure 4. Kaplan-Meier curve for distant recurrence-free survival (FAS, 346 patients)



Analysis set		0	1	2	3	4	5	6
FAS	At risk	346	345	344	344	327	184	0
	Censoring	—	0	0	0	16	143	184

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

In the SAS (N = 370), the incidence of CTCAE[2] Grade ≥3 adverse events was 7.0% (95% CI, 4.6%-10.1%), Grade ≥3 adverse reactions (medical device-related adverse events) was 1.1% (95% CI, 0.3%-2.7%).

The following ranges of adverse events were collected in the RAFAELO study:

- For adverse events associated with RFA therapy or vacuum-assisted needle biopsy, Grade ≥1 adverse events were collected.
- For adverse events other than the above, Grade ≥3 adverse events, or Grade ≥1 adverse events that required ≥24 hours of hospitalization or extension of hospitalization were collected.

Adverse event that occurred during RFA procedure was thermal burns (Table 13) at an incidence <5%. No Grade ≥3 adverse events occurred.

[2] CTCAE ver.4.0 Japanese Clinical Oncology Group (JCOG) version
Grade 1. Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2. Moderate: minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
Grade 3. Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self-care activities of daily living
Grade 4. Life-threatening consequences; urgent intervention indicated
Grade 5. Death related to adverse events

Table 13. CTCAE adverse events during RFA procedure (SAS, 370 patients)

	Grade 1	Grade 2	Grade 3	Grade 4	Grade unknown	Total
Thermal burn	4 (1.1%)	3 (0.8%)	0	0	0	7 (1.9%)

The most frequently occurring adverse event after RFA before the start of radiation therapy was induration (7 patients, 1.9%). Induration occurred most frequently (1 patient, 0.3%) during the period of radiation therapy. After radiation therapy, the most frequently occurring adverse event was wound infection (4 patients, 1.1%). All of these events occurred at an incidence of <5%. No adverse events lead to death and there were no serious adverse events.

6.B Outline of the review conducted by PMDA

PMDA mainly reviewed the following points, taking account of comments raised in the Expert Discussion.

(1) Justification for using the RAFAELO study as a confirmatory study for the present partial change application of the Cool-tip RFA System rather than conducting a new clinical trial
(2) Efficacy and safety of the Cool-tip RFA System
(3) Clinical positioning of the Cool-tip RFA System
(4) Post-marketing safety measures for the Cool-tip RFA System

6.B.(1) Justification for using the RAFAELO study as a confirmatory study for the present partial change application of the Cool-tip RFA System rather than conducting a new clinical trial

The RAFAELO study was initiated on August 1, 2013 as the Advanced Medical Care B Program. The enrollment of 372 patients (target sample size) was completed on November 29, 2017, and follow-up is currently ongoing.

Instead of waiting for the completion of the 5-year follow-up period, the applicant revised the analysis plan to add the details summarized in Table 14, and filed an application based on the results obtained up to a cut-off date of February 2, 2022, with the interim, primary, and final analyses to be submitted separately, for early regulatory approval taking into account the request made by the Study Group on devices with high medical need.

Table 14. Summary of analysis plan added to the RAFAELO study

Primary endpoint: 5-year IBTRFS rate	The analyses were performed in the FAS as outlined below: • No tests are performed in accordance with the statistical analysis plan for regulatory application. • Generate the 5-year IBTRFS curve using the Kaplan-Meier method. − Obtain the annual number of patients at risk − Obtain the annual number of patients censored • Calculate the annual IBTRFS rate using the Kaplan-Meier method. Calculate the corresponding 95% CI using Greenwood's formula. Use 365.25 days per year and 365.25/12 days per month. • Calculate the median recurrence-free survival time in patients with ipsilateral breast tumor using the Kaplan-Meier method. Calculate the corresponding 95% CI using the Brookmeyer and Crowley method. Use 365.25 days per year and 365.25/12 days per month. • For the recurrence-free survival time in patients with ipsilateral breast tumor, calculate the follow-up period for each patient according to the following definition, and calculate the summary statistics (i.e., minimum value, 25th percentile, median, 75th percentile, and maximum value). − Follow-up period (days) = (date of confirmed IBTR, or date of death, or date of 3 months biopsy[for patients with event] or date of the last confirmed tumor recurrence-free survival [for patients who achieved recurrence-free survival]) − date of RFA + 1 day
Secondary endpoint: residual lesion rate after treatment	The residual lesion rate after treatment with the corresponding 95% CI was obtained in the FAS. The exact CI based on the binomial distribution (Clopper and Pearson method) was used for interval estimation.
Secondary endpoint: overall survival, recurrence-free survival	The analyses were performed in the FAS as outlined below. Results of metastasis on imaging were assessed locally at the study centers. • Generate the overall survival curve and distant recurrence-free survival curve using the Kaplan-Meier method. − Obtain the annual number of patients at risk − Obtain the annual number of patients censored • Calculate the annual overall survival rate and annual distant recurrence-free survival rate using the Kaplan-Meier method. Calculate the corresponding 95% CI using Greenwood's formula. Use 365.25 days per year and 365.25/12 days per month. • Calculate the median for overall survival and distant recurrence-free survival using the Kaplan-Meier method. Calculate the corresponding 95% CI using the Brookmeyer and Crowley method. Use 365.25 days per year and 365.25/12 days per month. • For overall survival and distant recurrence-free survival, calculate the follow-up period for each patient according to the following definitions, and calculate the summary statistics (i.e., minimum value, 25th percentile, median, 75th percentile, and maximum value). − Follow-up period (days) = (date of death [for patients with event] or date of the last confirmed survival) − date of RFA + 1 day − Follow-up period (days) = (date of confirmed distant recurrence or date of death [for patients with event] or date of the last confirmed distant recurrence-free survival [for patients who achieved recurrence-free survival]) − date of RFA + 1 day
Data cut-off date	February 2, 2022
Number of patients included by duration in years	Of the patients included in the FAS (N = 346), all 346 patients completed the 3-year follow-up period, 324 patients completed the 4-year follow-up period, and 183 patients completed the 5-year follow-up period.

The applicant's explanation about the justification for using data from the RAFAELO study for the present application rather than conducting a new clinical trial:

- Detailed conditions have been specified for implementation of the RAFAELO study, which is designated as a study of the Advanced Medical Care B Program. The treatment protocol defines subjects' eligibility and exclusion criteria, preoperative and postoperative examinations as well as adjuvant therapy in detail. Therefore, if a new clinical trial were to

be planned, it was expected that the resultant study would be similar to the RAFAELO study, and therefore, it was considered unlikely that a new study would provide new safety and efficacy findings.

- While the RAFAELO study was conducted as a single-arm study, the breast-conserving therapy (partial mastectomy plus radiation therapy to the conserved breast) is an established standard therapy in the patient population of the RAFAELO study, and the 5-year recurrence free rate is 94.3% based on the historical data [6] obtained from a large-scale clinical study. Because the rate is nearly 100%, there is no room for further improvement in the group included in the single-arm study, therefore it is unlikely that selection bias would have an adverse effect on inference. Accordingly, it is considered justifiable to demonstrate the efficacy of RFA based on the study results from the single-arm study rather than conducting an additional randomized study.
- It is expected to take 7 to 8 years if a new clinical trial is planned, conducted, analyzed, and filed for regulatory approval. Given that the Cool-tip RFA System was designated as a medical device with high medical need, and a prompt filing for regulatory approval is needed, patients would benefit more if regulatory application is submitted based on available data from the study under the Advanced Medical Care B Program rather than conducting a new clinical trial, and the Cool-tip RFA System is introduced into the market early to provide appropriate RFA therapy to appropriate patients.

PMDA considers that, in principle, clinical evaluation data required for application for regulatory approval must be evaluated based on the results obtained according to the prescribed protocol for a clinical study as a "clinical trial," as defined in the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. In the present application, however, PMDA concluded that based on the factors shown below, it is acceptable not to request the applicant to conduct a confirmatory comparative study with the standard therapy as a control and to perform the necessary clinical evaluation using the study results from the RAFAELO study submitted for the present application:

- As described later in Section "III. Results of Compliance Assessment Concerning the New Medical Device Application Data and Conclusion Reached by PMDA," the Good Clinical Practice (GCP) inspection has confirmed that data from the RAFAELO study were accrued in a manner that ensures compliance with the criteria in the GCP for medical devices or ISO 14155 (Clinical investigation of medical devices for human subjects—Good clinical practice).
- Given that a 5-year recurrence-free rate of close to 100% has already been established for the standard therapy and the objective of the RAFAELO study is to demonstrate that the

efficacy of RFA is comparable to that of the standard therapy, appropriate evaluation is possible based on data from a single-arm study.

- Given that the Cool-tip RFA System was designated as a medical device with high medical need, and early introduction of the device into clinical use is desirable, to file an application early based on the available data is more beneficial for patients in terms of providing appropriate environments for RFA therapy for eligible patients, rather than conducting a new clinical trial.

The applicant's explanation about the justification for submitting the results of the analysis not planned in the initial study as data for application documents for regulatory approval:

- Since the data cut-off date was selected considering the regulatory submission schedule, no specific changes occurred before and after that date to patients participating in the study, and therefore, the risk for IBTR or death will not differ significantly between before and after the cut-off date.
- Of the patients included in the FAS (N = 346), 324 patients completed the 4-year follow-up period and 183 patients completed the 5-year follow-up period. Patients in the FAS who had not completed the 5-year follow-up period (those with ongoing follow-up and those who dropped out) are indicated by tick marks on the Kaplan-Meier curve for recurrence-free survival time in patients with ipsilateral breast tumor, and taken into account as an estimated value in the calculation of the 5-year IBTRFS rate; therefore, it was concluded that statistical reliability and precision are sufficiently assured.

PMDA's view:

On the basis of the applicant's view and the factors shown below, PMDA concluded that the justification for submitting the results of the analysis not planned in the initial study as data for application documents for regulatory approval is acceptable:

- The data cut-off was conducted in response to the need for early application for regulatory approval after being designated as a medical device with high medical need. It is clear that data cut-off was not an arbitrary act of the person conducting the study.
- Many patients have already completed the 4-year follow-up and more than half of patients have completed the 5-year follow-up. In addition, those who have not completed the 5-year follow-up are incorporated in the calculation of the 5-year IBTRFS rate.

Although the results of all patients after completion of 5-year follow-up are not submitted in the present application, PMDA concluded that data submitted for the present application are evaluable on the premise that the following approval condition is imposed: when the final analysis results of all patients after completion of 5-year follow-up become available, the applicant is

required to submit the results, which will be reviewed by PMDA, and to take appropriate measures as necessary.

6.B.(2) Efficacy and safety of the Cool-tip RFA System

6.B.(2).1) Efficacy (primary endpoint)

The 5-year IBTRFS rate in the FAS (N = 346) was 98.5% (95% CI, 96.4%-99.4%). The median follow-up period was 5 years with 5 events (ipsilateral breast cancer [2 patients], deaths due to primary disease [2 patients], and death due to other disease [1 patient]).

The applicant's discussion of efficacy in clinical practice based on the published literature on partial mastectomy in Japan (Table 15):

In the literature, the 5-year ipsilateral breast tumor recurrence-free (IBTRF) rate ranged from 96.9% (Min) to 99.1% (Max), and the 10-year IBTRF rate ranged from 90.5% (Min) to 98.4% (Max). Although the number of literature is limited, the 4-year IBTRFS rate ranged from 95.5% (Min) to 98.9% (Max). The 5-year IBTRFS rate was 98%. The 5-year IBTRFS rate in the RAFAELO study (98.5%) is equivalent to that of surgical treatment by partial mastectomy in clinical practice in Japan.

Table 15. Results of Japanese literature search

Literature	5-year IBTRF rate (%)	10-year IBTRF rate (%)	IBTR rate (%)	N	Median follow-up period (years)	Remarks
Yoshida-Ichikawa 2021 [7]	98.7	95.9	—	186	9.4	• Hypofractionation • pTis, pT1-3, pN0-2
	98.3	95.3	—	186		• Conventional fractionation • pTis, pT1-3, pN0-2
Ohsumi 2022 [8]	97.0	90.5	—	321	7.83	• No irradiation • Adjuvant endocrine therapy • Median tumor dimeter = 1.5 cm
Sawaki 2019 [9]	96.9	—	—	129	4.96	• Single high-dose intraoperative irradiation • Stage 0-IIA • Reported as 5-year IBTR rates in the literature
Ono 2019 [10]	—	96.0	—	419	9.3	• pT0, pTis, pT1-4 • Reported as 10-year IBTR rates in the literature
Inoue 2019 [11]	99.1	95.2	—	84	6.1	• No irradiation • Stage 0-IIA, Tis, T1-2 • Reported as 5-year IBTR rates and 10-

Literature	5-year IBTRF rate (%)	10-year IBTRF rate (%)	IBTR rate (%)	N	Median follow-up period (years)	Remarks
						year IBTR rates in the literature
	98.4	98.4	—	119	6.3	• Irradiation • Stage 0-IIA, Tis, T1-2 • Reported as 5-year IBTR rates and 10-year IBTR rates in the literature
Nozaki 2021 [12]	98 (5-year IBTRFS rate)	—	—	306	5.88	• Hypofractionation • Stage I-IIb, pT1-2, N0-1
Takahashi 2016 [13]	—	97.9	3.6	306	12	• pTis, pT1-2, pN0-3 • Reported as 10-year IBTR rates in the literature
Sato 2017 [14]	98.9 (4-year IBTRFS rate)	—	—	301	4.17	• Partial breast irradiation • pTis, pT1-2 • 297 patients, 301 tumors (The number of patients [N] indicates the number of tumors.)
	98.0 (4-year IBTRFS rate)	—	—	200	4.5	• Whole breast irradiation • pTis, pT1-2 • 196 patients, 200 tumors (N indicates the number of tumors.)
Sato 2018 [15]	—	—	1.97	407	4.25	• Partial breast irradiation • pTis, pT1-2 • 403 patients, 407 tumors (N indicates the number of tumors.)
	—	—	2.92	240	4.86	• Whole breast irradiation • pTis, pT1-2 • 238 patients, 240 tumors (N indicates the number of tumors.)
Sato 2017 [16]	97.6 (4-year IBTRFS rate)	—	—	99	3.85	• Partial breast irradiation • pTis, pT1-2 • 98 patients, 99 tumors (N indicates the number of tumors.)
	95.5 (4-year IBTRFS rate)	—	—	85	3.82	• Whole breast irradiation • pTis, pT1-2 • 85 patients, 85 tumors (N indicates the number of tumors.)

At the time of filing the present application, the 5-year follow-up results in the RAFAELO study have not been obtained from all patients. The applicant's explanation about the long-term recurrence rate and survival rate following RFA therapy is based on data in the literature from in and outside Japan (Table 16):

- In the Japanese and overseas literature, the survival rates and IBTR rates [17-28] in patients with tumors ≤2 cm in diameter do not significantly differ from the IBTRFS rate (98.5%) and IBTR rate (0.6% [2 of 346] of patients in the FAS) in the RAFAELO study, respectively. Studies that enrolled patients with advanced lesions, however, have high recurrence rates including IBTR rates and low survival rates.[17,27,29,30]
- Although the number of evaluated patients was limited, the results of <5 years after RFA therapy tended to be similar to those of ≥5 years.[17-20]

Table 16. Literature from in and outside Japan on RFA therapy

Literature	IBTR rate	Survival rate	Median follow-up period (range)	Tumor diameter
Ito T, 2018 [17]	Tumor diameter ≤2.0 cm 2.3% (8 of 355 patients) Tumor diameter >2.0 cm 10% (3 of 30 patients)	Tumor diameter 1.0 cm: 97% Tumor diameter 1.1-2.0 cm: 94% Tumor diameter >2.0 cm: 87%	50 months (range, 3-92)	≤3.5 cm
Noguchi M, 2012 [18]	0% (0 of 19 tumors)	94.4% (1 of 18 patients)	60 months (range, 37-82)	≤2.0 cm
Nagashima T, 2015 [19]	0% (0 of 26 tumors)	—	88 months (range, 58-108)	≤2.0 cm
van de Voort, 2021 [20]	0.41% (1 in 243 patients)	—	(range, 15-61)	≤2.0 cm
Oura S, 2007 [21]	0% (0 of 52 patients)	—	15 months (range, 6-30)	≤2.0 cm
Yamamoto N, 2011 [22]	0% (0 of 30 tumors)	100% (29 of 29 patients)	17 months (range, 2-41)	≤2.0 cm
Yoshinaga Y, 2013 [23]	0% (0 of 14 patients)	100% (14 of 14 patients)	39.9 months	≤2.0 cm
Susini T 2007 [24]	0% (0 of 3 patients)	—	18 months	<2.0 cm
Nagashima T, 2009 [25]	0% (0 of 17 patients)	100% (17 of 17 patients)	19 months (range, 12–28)	≤2.0 cm
Xia LY, 2021 [26]	0% (0 of 136 patients)	—	29 months	≤2.0 cm
Motoyoshi A, 2010 [27]	0% (0 of 17 patients) (1 patient with extensive axillary lymph node metastasis developed metastasis)	—	23 months (range, 3-36)	≤2.0 cm
Sato T 2010 [28]	0% (0 of 5 patients)	—	22 months (range, 21-24)	≤2.0 cm
Santoro G 2012 [29]	—	83.3% (5 of 6 patients)	24 months	Median: 3.85 cm (range, 2.5-6.0 cm)
Mercy PY 2007 [30]	20% (1 of 5 tumors)	100% (4 of 4 patients)	29.4 months	—

PMDA concluded that the following applicant's explanation is acceptable: the 5-year IBTRFS rate in the RAFAELO study is 98.5% (95% CI, 96.4%-99.4%) and is equivalent to the current outcome of partial mastectomy in Japan.

Although the 5-year follow-up results in the RAFAELO study have not been obtained from all patients at the time of filing the present application, based on the applicant's additional discussions, the long-term recurrence rate and survival rate are unlikely to radically worsen provided that the Cool-tip RFA System is used only in patients who meet the eligibility criteria as those in the RAFAELO study. Therefore, on the basis of the present explanation by the applicant, PMDA concluded that the efficacy required for the Cool-tip RFA System to be introduced into Japan as a treatment option for early-stage breast cancer can be assured. However, this is on the condition that the applicant submits the final analysis results of the RAFAELO study to PMDA when the results become available, and PMDA will review the details, as described earlier in Section II. 6.B.(1).

6.B.(2).2) Safety

Of the SAS (N = 370), the incidence of CTCAE Grade ≥3 adverse events was 7.0% (95% CI, 4.6%-10.1%) and the incidence of Grade ≥3 adverse reactions (device-related adverse events) was 1.1% (95% CI, 0.3%-2.7%).

The adverse event of thermal burn occurred during the RFA procedure with an incidence <5%. No Grade ≥3 adverse events occurred.

The most frequently occurring adverse event after RFA before the start of radiation therapy was induration (7 patients, 1.9%). Induration occurred most frequently (1 patient, 0.3%) during the period of radiation therapy. After radiation therapy, the most frequently occurring adverse event was wound infection (4 patients, 1.1%). All of these events occurred at an incidence of <5%. No adverse events resulted in death and there were no serious adverse events.

On the basis of the above, PMDA concluded that the safety of the Cool-tip RFA System and the RFA procedure is clinically acceptable provided that the Cool-tip RFA System is used only in patients who meet the eligibility criteria equivalent to those in the RAFAELO study.

6.B.(2).3) Residual lesion rate after treatment

RFA therapy was followed by radiation therapy, and 3 months later, all of the patients in the FAS (N = 346) underwent vacuum assisted biopsy. Table 17 shows the residual lesion rate after

treatment. Residual lesions were found in 10 patients, and the residual lesion rate after treatment was 2.9% (95% CI, 1.4%-5.3%).

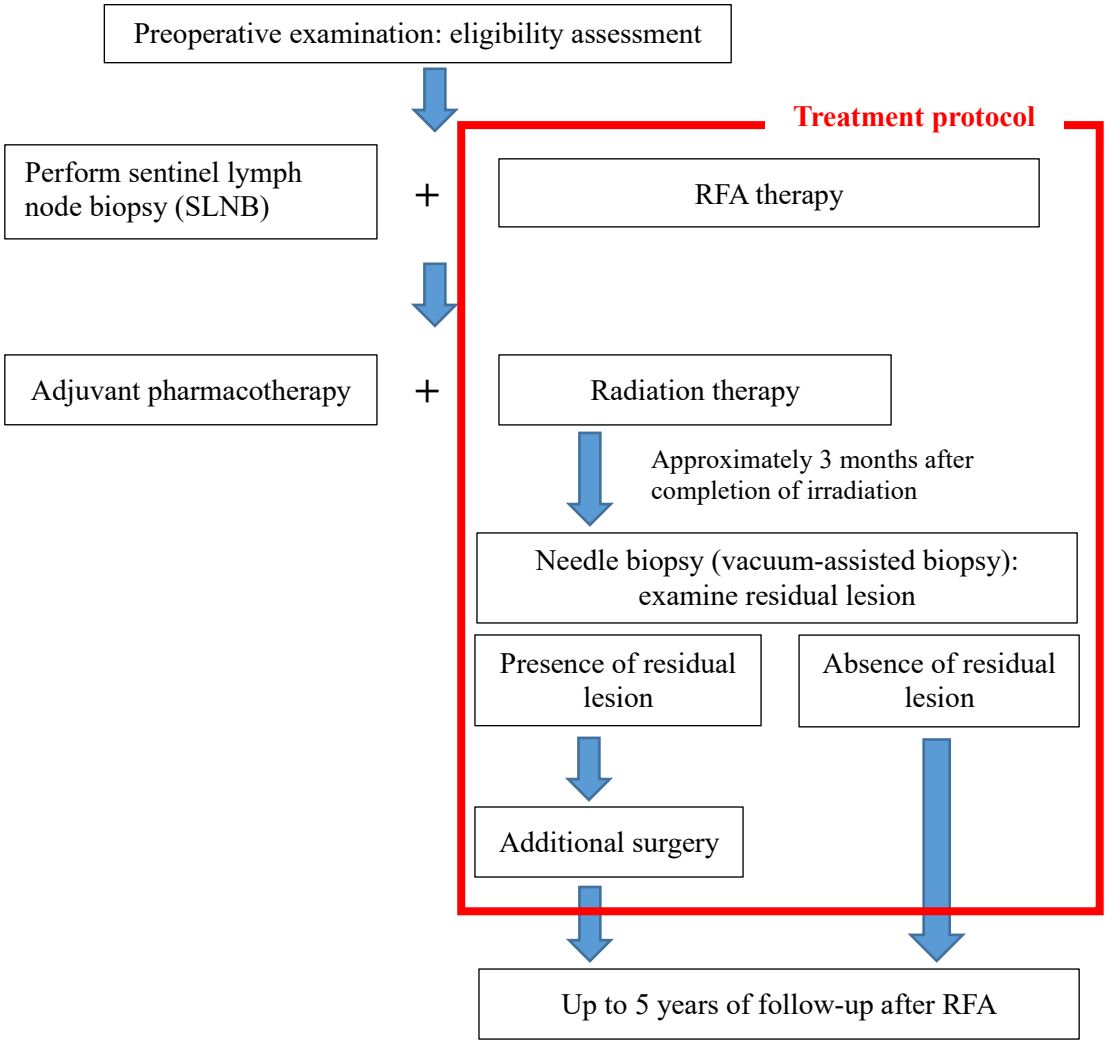
Table 17. Residual lesion rate after treatment

Residual intraductal lesion only	Residual invasive carcinoma only	No residual lesion	Unknown/ missing measurement	The residual lesion rate after treatment
6	4	336	0	2.9% (95% CI, 1.4%–5.3%)

The applicant's explanation:

As shown above, residual lesions are possibly present in a certain number of patients after RFA therapy. Therefore, a treatment protocol was defined for the post-marketing setting (Figure 5) to confirm the presence of residual lesions using vacuum-assisted biopsy approximately 3 months after radiation therapy following RFA, and to perform additional surgery if residual lesions were present.

Figure 5. Post-marketing treatment protocol



PMDA considers that a similar treatment protocol as that of the RAFAELO study need to be followed after the market launch, as stated by the applicant, because residual lesions are possibly present in a certain number of patients after RFA therapy even if the patients meet the eligibility criteria equivalent to those in the RAFAELO study. Therefore, PMDA asked the applicant to explain what measures would be taken after the launch to ensure that the Cool-tip RFA System would be used by following the treatment protocol similar to that of the RAFAELO study.

The applicant's response:

A treatment protocol similar to that of the RAFAELO study will be defined in the training program for the proper use guidelines prepared by the Japanese Breast Cancer Society. After the approval of the device, the website of the Japanese Breast Cancer Society will promptly disseminate information emphasizing that it is necessary to comply with the proper use guidelines and to participate in the training program before using the Cool-tip RFA System. Information

material containing cautionary statements to the effect similar to those appearing on the website will also be inserted into the shipping package of the Cool-tip RFA System after approval to ensure that users comply with the proper use guidelines.

PMDA's view on the applicant's response:
The proper use guidelines to be developed by the relevant academic society should specify a treatment protocol which includes needle biopsy for the assessment of presence/absence of residual tumor. As one of the approval conditions, it is appropriate to impose the need to comply with the proper use guidelines.

6.B.(3) Clinical positioning of the Cool-tip RFA System

6.B.(3).1) Clinical positioning and intended use

The patients included in the RAFAELO study was "patients with localized, solitary, early-stage breast cancer with a tumor diameter of ≤1.5 cm, without axillary lymph node metastasis and metastasis as confirmed by palpation and diagnostic imaging," and currently, the standard first-line therapy is breast-conserving therapy according to the Japanese Breast Cancer Society Clinical Practice Guidelines for systemic treatment of breast cancer, 2022 edition. Breast-conserving therapy has been implemented by combining surgical partial mastectomy and postoperative radiation therapy. Although breast-conserving therapy involving surgery is considered to be a reliable treatment in clinical practice, there are problems including issues on the patient's QOL, because of the invasive nature of surgery, and difficulty in determining a suitable amount of tissue to be removed in relation to the size of tumor.

In RFA therapy for early-stage breast cancer using the Cool-tip RFA System, the active electrodes are placed in the tumor lesion to deliver RF energy to the tissue being ablated. It is assumed that RFA therapy causes less deformation in the wound area and is less invasive of healthy tissue compared with partial mastectomy. It is expected that the physical and psychological discomfort of patients will be mitigated by minimizing the wound to the breast and maintaining a cosmetically acceptable appearance. However, there are concerns, such as risks of recurrence due to incomplete ablation, caused by lesions not being removed from the body. In addition, histopathological findings and immunohistochemical findings of resected specimens cannot be used as references to decide the suitable type of adjuvant therapy, as performed in the conventional therapy instead, prior biopsy findings need to be used as references.

On the basis of the above, PMDA made the conclusion that the clinical positioning of the Cool-tip RFA System should be as follows:

The RFA therapy with the Cool-tip RFA System would not replace surgical treatment, the current first-line standard therapy for early-stage breast cancer. However, the Cool-tip RFA System was designated as a medical device with high medical need by the Ministry of Health, Labour and Welfare, as per the request from the relevant academic society. Given the circumstances, and based on the discussion in Section "6.B.(2) Efficacy and safety of the Cool-tip RFA System," PMDA concluded that the Cool-tip RFA System can be introduced into clinical practice as a treatment option provided that the device is used with caution only in the intended patients, in compliance with the proper use guidelines (which are to be prepared by the relevant academic society), and only after relevant information on the treatment is provided to the patient by the physician.

The intended use should be limited to the scope in which the efficacy and safety have been demonstrated in the RAFAELO study: "coagulation and ablation of breast tumor (localized, solitary, early-stage breast cancer with a tumor diameter of ≤1.5 cm, without axillary lymph node metastasis and metastasis as confirmed by palpation and diagnostic imaging)."

6.B.(3).2) Intended patients

6.B.(3).2).(a) The applicability of neoadjuvant pharmacotherapy prior to RFA with the Cool-tip RFA System

In the RAFAELO study, patients who had received neoadjuvant pharmacotherapy prior to RFA with the Cool-tip RFA System were excluded and thus were not studied. PMDA asked the applicant to explain whether neoadjuvant pharmacotherapy is allowed prior to RFA with the Cool-tip RFA System.

The applicant's response:

Tumor diagnostic imaging method after neoadjuvant pharmacotherapy has not been established. Therefore, RFA therapy, which is performed under ultrasound guidance, is inappropriate in patients who have undergone neoadjuvant pharmacotherapy. A cautionary statement to that effect will be included in the "Precautions concerning intended use or indication" section in the "Information on Precautions, etc."

PMDA's view on the applicant's response:

The method for tumor imaging diagnosis after neoadjuvant pharmacotherapy has not been established, and in RFA therapy with the Cool-tip RFA System, suitable areas for electrode insertion are obscured on imaging in patients who have undergone neoadjuvant pharmacotherapy. The applicant considers that RFA using the Cool-tip RFA System is not appropriate in patients who have undergone neoadjuvant pharmacotherapy. PMDA considers the applicant's standpoint

is reasonable. The applicant plans to include a cautionary statement to this effect in the "Precautions concerning intended use or indication" section in the "Information on Precautions, etc." and PMDA considers this action is also appropriate.

6.B.(3).2).(b) Use in patients who may be considered eligible for neoadjuvant chemotherapy or patients with familial breast cancer

The applicant explained that, at this point, whether the device can be used in patients who may be considered eligible for neoadjuvant pharmacotherapy (e.g., patients with HER2-positive breast cancer) or patients with familial breast cancer will not be uniformly determined for the following reasons:

- A series of treatment plans, including the choice of neoadjuvant pharmacotherapy and local therapy, is determined by the physician taking into consideration the suitability of patients and patient request. At present, strong recommendations have not been made in the treatment guidelines for HER2-positive breast cancer or familial breast cancer. Uniformly specifying the use of Cool-tip RFA System in these patients will narrow their treatment options.
- The RAFAELO study included patients with HER2-positive breast cancer. The current results are based on data from such patients who did not undergo neoadjuvant pharmacotherapy and treated in accordance with the protocol.
- In the *Guidelines for Diagnosis and Treatment of Hereditary Breast and Ovarian Cancer 2021* [in Japanese], the results of meta-analyses in patients with familial breast cancer indicated that "the breast-conserving therapy in patients with breast cancer harboring BRCA pathogenic variants has a higher IBTR rate compared with the therapy in patients with sporadic breast cancer." However, the guidelines also state that "there is a lack of data indicating an association between breast-conserving therapy and worsening of survival rates." The guidelines "do not necessarily rule out the use of RFA therapy if patient strongly request breast-conserving therapy after fully understanding the risk of new breast cancer developing in the conserved breast and the necessity of continued screening in the conserved breast." Therefore, in patients with familial breast cancer, the use of RFA therapy should be determined only after the specific nature and risks of familial breast cancer are thoroughly explained to the patient through informed consent.

PMDA's view:

For patients who may be considered eligible for neoadjuvant pharmacotherapy (e.g., patients with HER2-positive breast cancer) or patients with familial breast cancer, priority should be given to providing the current standard therapy. However, this does not necessarily rule out the use of RFA therapy with the Cool-tip RFA System, provided that RFA therapy is chosen by a physician who satisfy the appropriate requirements, only after providing information to patients regarding the

risks and benefits of both the standard therapy and RFA therapy, and after taking the patient's views into account. PMDA asked the applicant to explain the measures designed to address such cases.

The applicant's response:
It is important that the use of Cool-tip RFA System is determined by the physician based on the patient's request after the risks and benefits of each therapy are understood by the patient. The following cautionary statements will be included in the "Warnings" section in the "Information on Precautions, etc.":

- "According to the proper use guidelines prepared by the relevant academic society, the physician should present to the patient the Cool-tip RFA System and other treatment options. The Cool-tip RFA System can be used after thoroughly explaining the risks and benefits of each treatment option to the patient, and confirming that the patient has understood the information."

Patients with familial breast cancer have increased risk of developing new breast cancer in the conserved breast and continued screening in the conserved breast is important; therefore, the following cautionary statement is to be included also in the "Important precautions" section in the "Information on Precautions, etc."

- "For patients with familial breast cancer, the use of Cool-tip RFA System should be determined after thoroughly explaining the increased risk of developing new breast cancer in the conserved breast and need for continued screening in the conserved breast to the patient in a manner equivalent to that provided to patients who have selected partial mastectomy."

In addition, the proposed requirements for operators include "breast surgeons or breast specialists" and "completion of the RFA e-learning session supervised by the Japanese Breast Cancer Society." Since the operators are highly knowledgeable regarding breast cancer treatment, they are considered to be capable of responding to the above precautions.

PMDA's view on the applicant's response:
The applicant's plan to include cautionary statements in the "Warnings" and "Important precautions" sections in the "Information on Precautions, etc." is appropriate. The applicant's explanation that the operators can respond to measures specified in the cautionary statements because the requirements for operators will be included in the proper use guidelines to be prepared by the relevant academic society is acceptable.

When relevant clinical data associated with the use of the Cool-tip RFA System in patients who may be considered eligible for neoadjuvant pharmacotherapy or patients with familial breast cancer become available in the future, the proper use guidelines and other guidelines should be revised as necessary.

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

6.B.(4).1) Proper use guidelines

The applicant's explanation:

When the indication is expanded, the following issues are important to ensure proper use of the Cool-tip RFA System: selection of eligible patients; the operator's skills and knowledge regarding the therapy; and the medical facility having the capacity to respond appropriately to emergencies and adverse events that may occur during the procedure. In addition, if the operator lacks an accurate understanding of the characteristics and directions for use of RFA devices, and has deficient knowledge of the treatment protocol, this will result in improper use of the device, leading to adverse events such as thermal burn. Alternatively, residual tumors may result in recurrence of breast cancer or metastasis. Accordingly, training of operators regarding proper use before introduction of the device is necessary. Currently, the draft for proper use guidelines (Table 18) and an outline of the training program (Table 19) have been deliberated by the Japanese Breast Cancer Society.

Table 18. Proper use guidelines (draft)

Facility requirements

- Clinical departments: Surgery or breast surgery
- ≥2 physicians work full-time in the department that performs RFA
- A pathology department has been established and is staffed with pathologists.
- ≥1 anesthesiologist is allocated.
- The facility has been certified by the Japanese Breast Cancer Society.
- The National Clinical Database (NCD) for breast cancer registration has been implemented.
- The facility has a system in which physicians from different departments who have expert knowledge on the disease under treatment discuss as a team whether patients are being selected appropriately based on the indication.
- The facility has an appropriate follow-up system to support patients after treatment.
- The facility is capable of providing appropriate treatments in case of emergency.

Operator requirements

- Breast surgeons or breast specialists
- ≥5 years of experience in the department
- Completion of the RFA e-learning session supervised by the Japanese Breast Cancer Society
- Number of RFA ablation performed: ≥3 patients as an operator or assistant
- Other requirements: RAF must be performed under the supervision/instruction of an experienced physician for up to 3 patients (experienced physician: RFA experience in ≥3 patients).

Registration of patients:

When RFA is performed for early-stage breast cancer, the responsible physician of the facility will register the patient for inclusion in the survey to be conducted by the Japanese Breast Cancer Society, and confirm the information required.

The information on the outcome of the patient is entered into the NCD for breast cancer registration.

Training program:

Lecture: e-learning (implemented by the company; a certificate of completion is issued and information is registered to the Japanese Breast Cancer Society)

Clinical program: the proof of performing RFA in 3 patients is submitted to the Japanese Breast Cancer Society and registered

Table 19. Outline of training program

Training program: outline of e-learning

1. Patient selection criteria

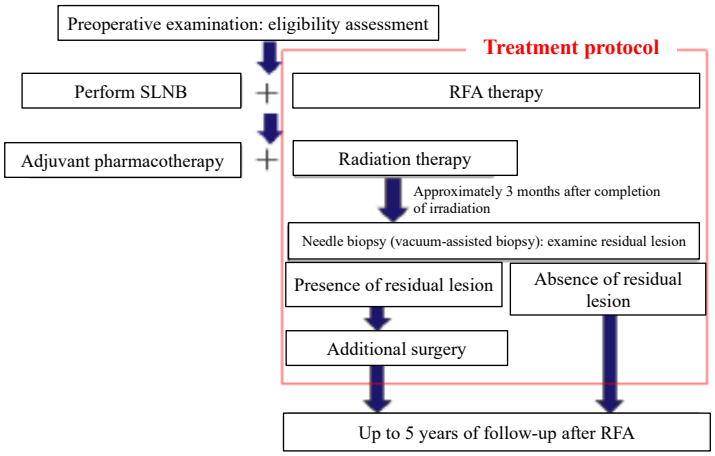
Eligibility criteria

- Patients with needle biopsy-proven, histologically graded normal primary ductal carcinoma.
- Patients with a single localized lesion with the greatest tumor diameter being ≤1.5 cm on all preoperative imaging examinations including contrast-enhanced magnetic resonance imaging (MRI).
- Patients without skin invasion or other skin findings (Delle).
- Patients with no prior treatment of this breast cancer (e.g., chemotherapy, hormone therapy, and radiation therapy).
- Females aged ≥20 years.
- Patients who can undergo postoperative radiation therapy.
- Patients who have organ functions that can tolerate surgery and systemic anesthesia.
- Patients without axillary lymph node metastasis evident on preoperative diagnosis.

Exclusion criteria

- Patients who are pregnant or possibly pregnant.
- Patients with a cardiac pacemaker or implantable cardioverter-defibrillator.
- Patients with complicated local active inflammation or infection.
- Patients with major cardiac or cerebral disease.
- Patients with artificial bone or other implants that can prevent the application of a counter plate and that are contraindicated to RFA.
- Patients receiving treatment, such as antiplatelet and anticoagulation therapy, that can affect hemostasis.
- Patients with extensive intraductal breast lesions or suspected multiple lesions on imaging.
- Patients with extensive calcifications on MMG.
- Patients with ectopic ipsilateral breast cancer with recurrence in the preserved breast.
- Patients with other organ metastasis.

2. Treatment protocol



3. Outline of patient informed consent form and other information

1) Patient's condition (diagnosis and clinical condition)
2) Target and details of proposed medical treatment (preoperative examinations, treatment protocol including RFA therapy, adjuvant pharmacotherapy, and postoperative follow-up)
3) Results and efficacy expected from RFA
4) Possible complications and adverse events caused by RFA

5) Options other than RFA: availability and advantages/disadvantages
6) Expected result if medical treatment is not undertaken
7) The patient's right to seek an opinion of a physician from other medical institution (second opinion)
8) The right to disagree and right to withdraw consent
9) Other information deemed necessary for medical reasons

4. Needle biopsy method used to determine residual tumor
Collect several specimens from the center and peripheral areas of the tumor to detect residual unablated tumor.

5. Adjuvant pharmacotherapy
Adjuvant pharmacotherapy is proposed as necessary according to the guidelines based on the information on preoperative needle biopsy and diagnostic imaging and the status of sentinel lymph node metastasis.

6. Recurrence screening and actions to be taken in case of recurrence
Follow-up surveillance screening for recurrence is implemented on a regular basis. In principle, surgical resection is performed in case of recurrence.

In RFA therapy for early-stage breast cancer using the Cool-tip RFA System, intended patients should be selected in an appropriate manner and RFA should be performed with caution in proper patients. The applicant's policy puts importance on development of the proper use guidelines including the patient eligibility criteria and the requirements for operators and facilities as well as implementation of the training program, in cooperation with the relevant academic society. PMDA considers the applicant's policy is appropriate and also concluded that it is reasonable to continue to impose approval conditions for the new indication and to require compliance with the proper use guidelines.

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

7.A Summary of the data submitted

The applicant explained that there are no particular concerns left to be identified by a use-results survey and therefore a post-marketing use-results survey is unnecessary for the following reasons:

- Data from the RAFAELO study comprise data from ≥300 patients over 4 years, a sample size considered to be sufficient to assess the efficacy and safety of the Cool-tip RFA System. No particular concerns are raised by the safety data; therefore, there are no particular issues left to be addressed in post-marketing settings.
- Patients for whom the Cool-tip RFA System is intended after the market launch are essentially similar to the patient population of the RAFAELO study.
- The requirements for operators and facilities are to be specified by the relevant academic society to ensure that a procedure similar to that used in the RAFAELO study will be conducted.

7.B Outline of the review conducted by PMDA

PMDA's view:

The applicant's explanation is reasonable and a use-results survey is unlikely to identify new safety concerns, and therefore, no use-results survey is necessary. On the basis of the comments from the Expert Discussion concerning the need to accrue post-marketing information as shown below, PMDA asked the applicant to address the following issues:

- The rate of incomplete ablation of breast tumor after RFA therapy, local recurrence rate, localized adverse events, short-term adverse events, complications, cosmetic appearance

The applicant's response:

The measures to collect post-marketing data currently under consideration in cooperation with the relevant academic society (Japanese Breast Cancer Society) are shown below.

- RFA will be added to the procedures on the NCD for breast cancer registration, and physicians will be requested to enter prognostic data including IBTR.
- Short-term incomplete ablation will be added to the registry items of the academic society.

Information on localized adverse events, short-term adverse events, and cosmetic appearance leading to adverse events can be collected in the routine post-marketing activities for good vigilance practice (GVP).

Under the framework of the patient-proposed healthcare services, treatment has been provided to patients who wish to undergo RFA therapy after completion of enrollment in the RAFAELO study and meet the eligibility criteria equivalent to those applied in the RAFAELO study. Data on the effectiveness of RFA therapy and complications are collected and stored by the National Cancer Center Hospital. In the immediate future, when the final report on the data obtained from the RAFAELO study and data on the patient-proposed healthcare services are published, the revision of the "Information on Precautions, etc.," the proper use guidelines, and guidelines will be considered based on the results as necessary.

PMDA's view on the applicant's response:

The applicant explained that the applicant and the Japanese Breast Center Society will cooperate in collecting post-marketing data on the treatment using the Cool-tip RFA System. PMDA considers this applicant's plan is appropriate. The applicant should plan ahead so that collected information can be analyzed in a timely manner. On the basis of the information so obtained, the applicant should revise the "Information on Precautions, etc.," the proper use guidelines, and the guidelines as necessary, and provide information to healthcare professionals.

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

PMDA's conclusion concerning the results of document-based compliance assessment

The medical device application data in Section 6.A.(1) Clinical trial report were subjected to a document-based inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

PMDA's conclusion concerning the results of GCP on-site inspection and data integrity assessment

The medical device application data in Section 6.A.(1) Clinical trial report* were subjected to an on-site GCP inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

* The data subjected to the inspection and assessment are based on the clinical studies conducted in accordance with the following: "Declaration of Helsinki (2013)," "Practical considerations associated with advanced medical care services and establishment of facility criteria specified by the Minister of Health, Labour and Welfare and handling of notifications on advanced medical care services (Health Policy Bureau Notification No. 0731-2, Pharmaceutical and Food Safety Bureau Notification No. 0731-2, Health Insurance Bureau Notification No. 0731-7, dated on July 31, 2012, including subsequent revisions)," "Act on the Protection of Personal Information (Act No. 57 of 2003)," "Japanese Ethical Guidelines for Clinical Research (enacted on July 30, 2003, including subsequent revisions)." On and after December 22, 2014, "Ethical Guidelines for Medical and Health Research Involving Human Subjects (enacted on December 22, 2014, including subsequent revisions)" and on and after April 1, 2018, "Clinical Trials Act (Act No. 16 of 2017)."

IV. Overall Evaluation

The present application is a partial change application for medical devices to add a new indication of early-stage breast cancer. When conducting the review, PMDA primarily focused on (1) justification for using the RAFAELO study as a confirmatory study for the present partial change application of the Cool-tip RFA System rather than conducting a new clinical trial; (2) efficacy and safety of the Cool-tip RFA System; (3) clinical positioning of the Cool-tip RFA System; (4)

post-marketing safety measures for the Cool-tip RFA System; and (5) necessity of a use-results survey. PMDA reached the following conclusions, taking account of deliberations at the Expert Discussion:

(1) Justification for using the RAFAELO study as a confirmatory study for the present partial change application of the Cool-tip RFA System rather than conducting a new clinical trial

PMDA considers that in principle, clinical evaluation data required for application for regulatory approval must be evaluated based on the results obtained according to the prescribed clinical study protocol as a "clinical trial" defined in the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. In the present application, however, the GCP inspection has confirmed that data from the RAFAELO study were gathered in a manner that ensures compliance with the criteria in the GCP for medical devices or ISO 14155 (Clinical investigation of medical devices for human subjects—Good clinical practice).

The data was cut-off in response to the need for immediate application for regulatory approval after being designated as a medical device with high medical need. It is clear that data cut-off was not an arbitrary act of the person conducting the study. Furthermore, many patients have already completed the 4-year follow-up period and half or more patients have completed the 5-year follow-up period. In addition, those who have not completed the 5-year follow-up period are incorporated in the calculation of the 5-year IBTRFS rate. Given the situation, it is acceptable to submit the results for the analysis that was not planned initially as data in support of the application for regulatory approval. Additionally, although the results for up to 5 years of all patients are not submitted in the present application, the following approval condition is to be imposed: when the final results of the analysis including the 5-year follow-up period are obtained for all patients, the applicant is required to submit the results, which will be reviewed by PMDA, and to take appropriate measures as necessary.

PMDA concluded that necessary clinical evaluation is possible for the Cool-tip RFA System on the basis of the study results from the RAFAELO study submitted for the present application.

(2) Efficacy and safety of the Cool-tip RFA System

The efficacy results of the RAFAELO study show that the 5-year IBTRFS rate of 98.5% (95% CI, 96.4%-99.4%), which is equivalent to the outcomes of partial mastectomy, the current conventional treatment in Japan. While 5-year follow-up results in the RAFAELO study have not been obtained from all patients at the time of filing the present application, the long-term recurrence rate and survival rate are unlikely to worsen rapidly. Therefore, PMDA concluded that

the efficacy required for the Cool-tip RFA System to be introduced into Japan as a treatment option for early-stage breast cancer can be assured based on the current results.

The safety results of the RAFAELO study show that the adverse event of thermal burn occurred during the RFA procedure with an incidence <5%. No CTCAE Grade ≥3 adverse events occurred. For all the periods: after RFA before the start of radiation therapy, during the period of radiation therapy, and after radiation therapy, the incidence of CTCAE Grade ≥3 adverse events was <5%, and no adverse events resulted in death and no adverse events were classified as serious. On the basis of the above, PMDA concluded that the safety of the Cool-tip RFA System and the RFA procedure is clinically acceptable provided that the Cool-tip RFA System is used only in patients who meet the eligibility criteria equivalent to those in the RAFAELO study.

(3) Clinical positioning of the Cool-tip RFA System

The RFA therapy with the Cool-tip RFA System would not replace surgical treatment, the current first-line standard therapy for early-stage breast cancer. However, the Cool-tip RFA System was designated as a medical device with high medical need by the Ministry of Health, Labour and Welfare, as per the request from the relevant academic society. Given the circumstances, PMDA concluded that the Cool-tip RFA System can be introduced into clinical practice as a treatment option provided that the device is used with caution only in the intended patients, in compliance with the proper use guidelines (which are to be prepared by the relevant academic society), and only after relevant information on the treatment is provided to the patient by the physician.

(4) Post-marketing safety measures for the Cool-tip RFA System

In RFA therapy for early-stage breast cancer using the Cool-tip RFA System, intended patients should be selected in an appropriate manner and RFA should be performed with caution in proper patients. The facilities should be capable of responding appropriately in cases of emergency and adverse events that may occur during the procedure. In addition, if the operator lacks an accurate understanding of the characteristics and directions for use of RFA devices, and has deficient knowledge of the treatment protocol, this will result in improper use of the device, leading to adverse events such as thermal burn. Alternatively, residual tumors may result in recurrence of breast cancer or metastasis.

To implement post-marketing safety measures, the applicant should develop, in cooperation with the relevant academic society, the proper use guidelines which comprise the patient eligibility criteria and the requirements for operators and facilities, and then implement the training program and other measures to ensure proper use of the device. PMDA concluded that it is reasonable to

continue to impose approval conditions for the new indication and to require compliance with the proper use guidelines.

(5) Necessity of a use-results survey

As described earlier in Section "II.7. Plan for Post-marketing Surveillance etc. Stipulated in Paragraph 1 of Article 2 of Ministerial Ordinance on Good Post-marketing Study Practice for Medical Devices," PMDA concluded that a use-results survey is unlikely to identify new safety concerns, and therefore, no use-results survey is necessary.

On the basis of the results of the above review, PMDA has concluded that the Cool-tip RFA System may be approved for the following intended use by imposing the following approval conditions. The intended use and approval conditions to be added in the present partial change application are underlined.

Intended Use

The Cool-tip RFA System is used for coagulation and ablation via the percutaneous route, laparoscopy, laparotomy, thoracoscopy, or thoracotomy of the following tissue:

- Coagulation and ablation of partial or complete liver tumors or small renal malignancies
- Coagulation and ablation of breast tumor (localized, solitary, early-stage breast cancer with a tumor diameter of ≤1.5 cm, without axillary lymph node metastasis and metastasis as confirmed by palpation and diagnostic imaging) for the purpose of treatment
- Coagulation and ablation of acardiac mass by stopping blood flow to the acardiac twin
- Coagulation and ablation for the treatment of following tumors not indicated for or refractory to standard therapy (including palliative care)
  - Pulmonary malignancies
  - Malignant bone tumors
  - Osteoid osteoma
  - Pelvic malignant tumor
  - Soft tissue tumors that developed in the extremities, thoracic cavity, and abdominal cavity

Approval Conditions

(1) The applicant is required to take necessary actions, including providing training sessions and disseminating a guideline for proper use prepared in cooperation with the relevant academic society, to ensure that the Cool-tip RFA System will be used by physicians with thorough knowledge and experience in providing treatment with a radio-frequency ablation system, who have acquired the skills required for using the Cool-tip RFA System, who have adequate

knowledge of procedural complications, and that the Cool-tip RFA System will be used at medical facilities capable of providing adequate medical care.

(2) The applicant is required to report to the Pharmaceuticals and Medical Devices Agency the results of the final analysis of the clinical study included in the application to add a new indication of breast tumor and take appropriate action as needed.

The Cool-tip RFA System is not classified as a biological product or a specified biological product.

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

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