May 22, 2025
Medical Device Evaluation Division
Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

Report on the Deliberation Results

Classification	Instrument & Apparatus 31, Medical Ablation Device
Term Name	General-purpose cryosurgical unit
Brand Name	Visual-ICE Cryoablation System
Applicant	Boston Scientific Japan K.K.
Date of Application	September 25, 2024 (Application for marketing approval)

Results of Deliberation

In its meeting held on May 22, 2025, 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 Council.

The product should be approved with no designation as a medical device subject to a use-results survey. The product is not classified as a biological product or a specified biological product.

The following approval condition must be satisfied.

Approval Conditions

1. The applicant is required to take necessary measures such as (i) disseminating the guidelines for proper use prepared in cooperation with related academic societies and (ii) providing training sessions, to ensure that the product will be used by physicians with adequate knowledge and experience in cryosurgical therapy who have acquired sufficient skills for using the product and adequate knowledge of possible complications associated with the procedure at medical institutions with a well-established system for the treatment.

Review Report

May 1, 2025
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 31, Medical Ablation Device
Term Name	General-purpose cryosurgical unit
Brand Name	Visual-ICE Cryoablation System
Applicant	Boston Scientific Japan K.K.
Date of Application	September 25, 2024 (Application for partial change approval of a medical device)
Items Warranting Special Mention	Priority review Orphan medical device
Reviewing Office	Office of Medical Devices II

Review Results

May 1, 2025

Classification	Instrument & Apparatus 31, Medical Ablation Device
Term Name	General-purpose cryosurgical unit
Brand Name	Visual-ICE Cryoablation System
Applicant	Boston Scientific Japan K.K.
Date of Application	September 25, 2024

Results of Review

The Visual-ICE Cryoablation System (Approval No. 30200BZX00289000) (hereinafter referred to as Visual-ICE) is a general-purpose cryosurgical unit intended for use to freeze and necrotize tissues for the treatment of small renal malignancies or liver tumors, as well as pulmonary malignant tumors that are ineligible for or refractory to standard therapy. The Visual-ICE consists of needles used to puncture and freeze or necrotize tissues, a main unit, etc.

The Visual-ICE was approved on September 2, 2020 for the intended use of freezing and necrotizing "small renal malignancies." Subsequently, it was approved on December 5, 2024 for the extended indications of "liver tumors, as well as pulmonary malignant tumors, malignant bone tumors, osteoid osteoma, intrapelvic malignant tumors, and soft tissue tumors that developed in the extremities, thoracic cavity, and abdominal cavity that are ineligible for or refractory to standard therapy." The present application for partial change approval (hereinafter referred to as the present application) has been submitted aiming to broaden the system's indication to tuberous sclerosis complex-angiomyolipoma that is ineligible for or refractory to standard therapy.

The applicant submitted non-clinical data for the cybersecurity, software lifecycle, and usability engineering. The data revealed no particular problem.

As data relating to the clinical study results of the Visual-ICE, the applicant submitted the results of a study (Cryo-tsc-study) that evaluated the efficacy and safety of cryotherapy as Advanced Medical Care B (renal tumor coagulation/ablation [limited to cryocoagulation] for the treatment of renal angiomyolipoma) in patients with tuberous sclerosis complex-angiomyolipoma (TSC-AML) with a tumor measuring ≥1 and ≤4 cm in longest diameter, regardless of whether patients were taking oral mammalian target of rapamycin (mTOR) inhibitors.

For efficacy, the primary efficacy endpoint of the Cryo-tsc-study "disease control rate (DCR) at 9 months after cryotherapy" was 100% (95% confidence interval [CI] [78.2%, 100.0%]). The sign test of the null hypothesis that DCR of 0.5 was statistically significant. A secondary endpoint "overall response rate (ORR) at 9 months after cryotherapy" was 93.3% (95% CI [68.1%, 99.8%]). The sign test of the null

hypothesis that ORR of 0.5 was also statistically significant. The results showed a certain degree of efficacy of Visual-ICE. For safety, Grade ≥3 adverse events occurred in 3 of 15 subjects (20%). Neither adverse events leading to death nor serious adverse events were reported. The results were clinically acceptable.

Pharmaceuticals and Medical Devices Agency (PMDA) comprehensively evaluated the submitted data on the basis of comments from the Expert Discussion. As a result, PMDA concluded as follows: Cryotherapy with the Visual-ICE should not be the first-line therapy replacing the current standard therapy for the treatment of TSC-AML. However, the Visual-ICE can be introduced to clinical practice as a treatment option for TSC-AML provided that the Visual-ICE therapy is carefully performed only in eligible patients in accordance with the guidelines for proper use created by related academic societies because the Visual-ICE is designated as an orphan medical device and there is a strong clinical need for its early introduction to clinical practice.

As a result of its review, PMDA has concluded that the Visual-ICE may be approved for marketing for the intended use shown below with the following approval conditions, and that the results should be presented to the Committee on Medical Devices and *In-vitro* Diagnostics for further deliberation. The underline denotes the intended use and approval condition added in the present application.

Intended Use
The Visual-ICE Cryoablation System is a cryosurgical unit that freezes and necrotizes biological tissues.

It is indicated for small renal malignancies and liver tumors.

It is also used for the treatment (including palliative intervention) of the following tumors that are ineligible for or refractory to standard therapy:
- Pulmonary malignant tumors
- Malignant bone tumors
- Osteoid osteoma
- Intrapelvic malignant tumors
- Soft tissue tumors that developed in the extremities, thoracic cavity, and abdominal cavity
- <u>Tuberous sclerosis complex-angiomyolipoma</u>

Approval Conditions
The applicant is required to take necessary measures such as (i) disseminating the guidelines for proper use prepared in cooperation with related academic societies and (ii) providing training sessions, to ensure that the product will be used by physicians with adequate knowledge and experience in cryosurgical therapy who have acquired sufficient skills for using the product and adequate knowledge of possible complications associated with the procedure at medical institutions with a well-established system for the treatment.

Review Report

May 1, 2025

Product for Review

Classification	Instrument & Apparatus 31, Medical Ablation Device
Term Name	General-purpose cryosurgical unit
Brand Name	Visual-ICE Cryoablation System
Applicant	Boston Scientific Japan K.K.
Date of Application	September 25, 2024
Proposed Intended Use (Underline denotes additions.)	The Visual-ICE Cryoablation System is a cryosurgical unit that freezes and necrotizes biological tissues. It is indicated for small renal malignancies and tuberous sclerosis complex-angiomyolipoma.
Items Warranting Special Mention	Priority review Orphan medical device

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List of Abbreviations

AML	Angiomyolipoma
AST	Aspartate Aminotransferase
CR	Complete Response
CRP	C-Reactive Protein
CT	Computed Tomography
DCR	Disease Control Rate
eGFR	estimated Glomerular filtration rate
FAS	Full Analysis Set
GCP	Good Clinical Practice
IEC	International Electrotechnical Commission
ISO	International Organization for Standardization
IVR	Interventional Radiology
MCS	Mental Component Summary
mRECIST	modified Response Evaluation Criteria in Solid Tumors
mTOR	mammalian Target Of Rapamycin
NE	Not Evaluable
ORR	Overall Response Rate
PCS	Physical Component Summary
PD	Progressive Disease
PR	Partial Response
QOL	Quality of life
RECIST	Response Evaluation Criteria in Solid Tumors
SAS	Safety Analysis Set
SD	Stable Disease
TSC	Tuberous Sclerosis Complex
TSC-AML	Tuberous Sclerosis Complex- Angiomyolipoma
Visual-ICE	Visual-ICE

I. Product Overview

Visual-ICE Cryoablation System (hereinafter referred to as Visual-ICE) is a successor to Cryosurgical Unit CryoHit (Approval No. 22200BZX00073000) (hereinafter referred to as the previous-generation product) that was approved on January 8, 2010. The Visual-ICE has the same basic mechanism of action and directions for use as those of the previous-generation product. The Visual-ICE is a cryosurgical unit that consists of a main unit that generates cold temperatures, etc., needles that puncture and freeze or necrotize target tissues, and multi-point thermal sensors that detect the temperature of tissue, etc. The principle of this system, which delivers cold temperatures from the needle tip and freezes its surrounding tissue, is based on the Joule–Thomson effect. By ejecting high-pressure (22.0-29.6 MPa) argon gas through a nozzle inside the needle tip, a temperature of approximately −80°C can be achieved at the needle tip. To thaw the tissue by the Joule-Thomson effect, the gas needs to be switched to helium gas. By ejecting high-pressure (12.4-20.1 MPa) helium gas from the same nozzle, the tissue can be thawed. The Visual-ICE is used under image guidance with X-ray computed tomography (CT) to ensure optimal freezing tissue coverage and to avoid unnecessary freezing of adjacent organs. (Figure 1, Table 1).

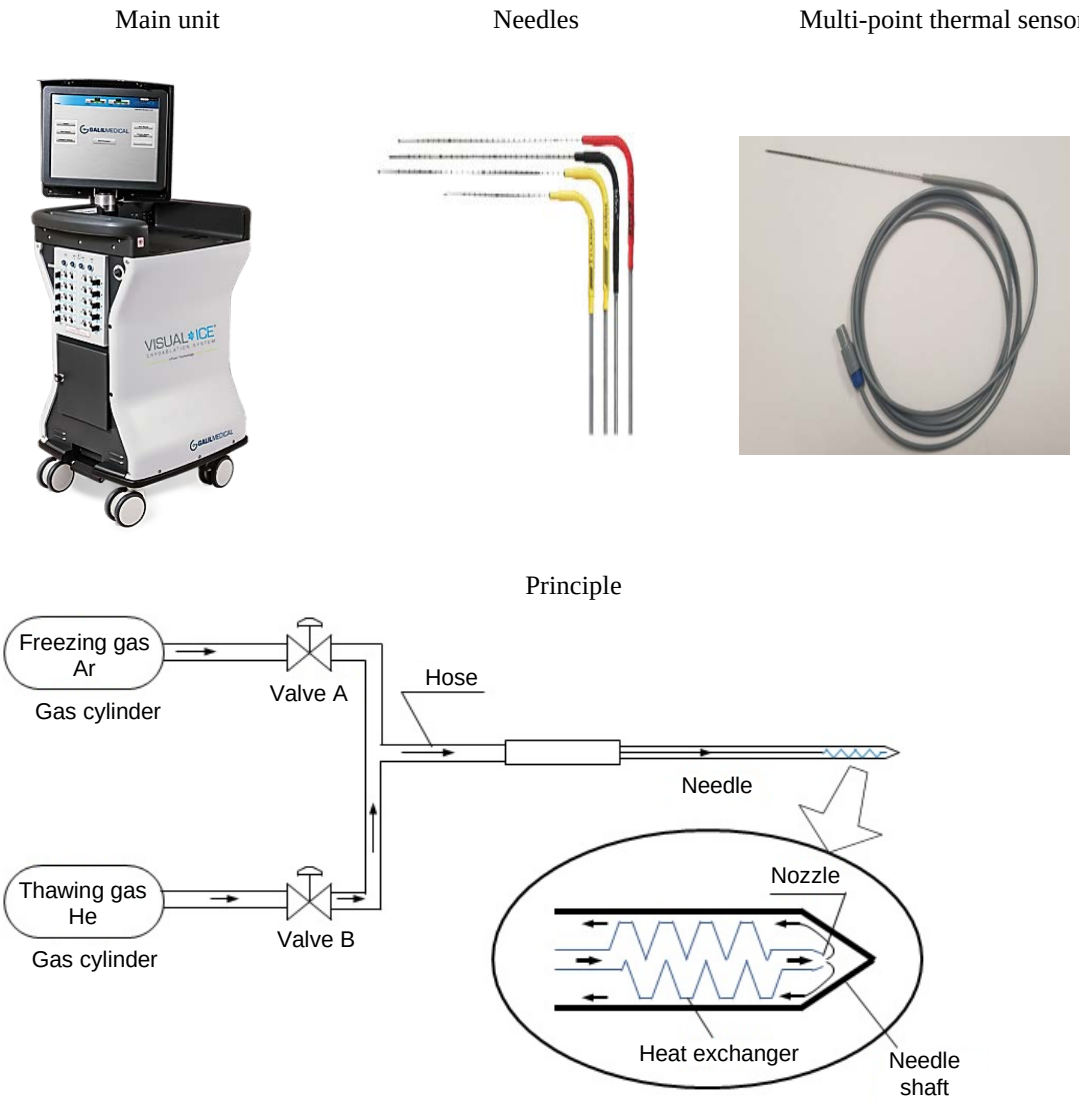

Figure 1. Appearance, structure, and principle of the Visual-ICE

Table 1. List of needles

Product name	Shape of handle	Shaft		Vacuum structure
		Length	Diameter	
Needle S-Plain Straight 175 mm	Straight	175 mm	1.5 mm	No
Needle S-Plain 90°175 mm	90°	175 mm	1.5 mm	No
Needle Sp Straight 175 mm	Straight	175 mm	1.5 mm	Yes
Needle Sp 90°175 mm	90°	175 mm	1.5 mm	Yes
Needle Sp 90°100 mm	90°	100 mm	1.5 mm	Yes
Needle I-Plus Straight 175 mm	Straight	175 mm	1.5 mm	Yes
Needle I-Plus 90°175 mm	90°	175 mm	1.5 mm	Yes

Non-clinical studies demonstrated that the Visual-ICE had similar efficacy and safety profiles to those of its previous-generation product, which was approved on January 8, 2010. The Visual-ICE was approved on September 2, 2020 for the same intended use (freezing and necrotizing small renal malignancies) (Approval No. 30200BZX00289000) (hereinafter referred to as the initial approval). Subsequently, the Visual-ICE was approved on December 5, 2024 for the extended indications of liver tumors, as well as pulmonary malignant tumors, malignant bone tumors, osteoid osteoma, intrapelvic malignant tumors, and soft tissue tumors that developed in the extremities, thoracic cavity, and abdominal cavity that are ineligible for or refractory to standard therapy.

The present application is an application for partial change approval (hereinafter referred to as the present partial change application) aiming to broaden the indication of the Visual-ICE to the freezing or necrotizing renal angiomyolipoma associated with tuberous sclerosis complex (TSC-AML) that is ineligible for or refractory to standard therapy. The present partial change application includes no change in the specifications or constituent parts of the Visual-ICE.

The intended use, as of December 5, 2024, when the Visual-ICE was approved is shown below.

Intended Use

The Visual-ICE Cryoablation System is a cryosurgical unit that freezes and necrotizes biological tissues.

It is indicated for small renal malignancies, liver tumors, and tuberous sclerosis complex-angiomyolipoma.

It is also used for the treatment (including palliative intervention) of the following tumors that are ineligible for or refractory to standard therapy:

- Pulmonary malignant tumors
- Malignant bone tumors
- Osteoid osteoma
- Intrapelvic malignant tumors
- Soft tissue tumors that developed in the extremities, thoracic cavity, and abdominal cavity

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

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

The expert advisors present during the Expert Discussion on the Visual-ICE declared that they did not fall under the Item 5 in Chapter 3 of the Rules for Convening Expert Discussions, etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

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

1.A Summary of the data submitted

1.A.(1) History of development

Tuberous sclerosis complex (TSC) is a congenital genetic disease causing benign tumors, called hamartomas, to form throughout the whole body. It is a rare disease with complications including psychoneurotic symptoms such as "epilepsy" and "mental retardation," pulmonary "lymphangioleiomyomatosis," and facial "angiofibroma." TSC results from a loss-of-function mutation in either *TSC1* (chromosome *9q34*) or *TSC2* (chromosome *16p13.3*). Genetic analysis detects either gene mutation in 80% of patients with TSC (60% in Japan).[1)]

The Visual-ICE is intended for use in the treatment of renal angiomyolipoma (AML) among TSC. Patients with TSC-AML start experiencing an increase in tumor frequency and size in their 10's. Tumors >4 cm in diameter are associated with an increased risk of bleeding due to tumor rupture.[2)] The development of many AML lesions may lead to decreased kidney function. An increased risk of death from renal disease with age has been a significant problem in patients with TSC.[2)]

The Clinical Practice Guidelines for tuberous sclerosis complex-associated renal angiomyolipoma 2023 (hereinafter referred to as the Japanese guidelines) currently recommend arterial embolism (first-line) or surgery (partial nephrectomy and nephrectomy) as standard therapy to treat TSC-AML when symptoms, such as bleeding from tumor blood vessels, feeling of abdominal compression, and haematuria, are present. However, this standard therapy does not provide a sufficient therapeutic effect in prevention of AML rupture and preservation of renal function. In addition, repeating surgery is technically difficult. The Japanese guidelines weakly recommend pharmacotherapy in patients with a tumor >4 cm or at high risk of tumor rupture who are under clinical follow-up. For pharmacotherapy of TSC-AML, everolimus, which is a mammalian target of rapamycin (mTOR) inhibitor, was approved under the pharmaceutical affairs in November 2012. Because of adverse drug reactions such as interstitial pneumonia and impacts on fertility, some patients are not eligible for treatment with everolimus. Even in patients eligible for the everolimus therapy, disease control is limited (e.g., limited tumor shrinks).[1)3)] Patients need to continue the everolimus therapy for an extended period of time. Patients exhibit various symptoms. As it is a rare disease, the patient population is small and only limited

clinical data are available. Currently, there is no clear consensus about the timing of interruption or reduction of everolimus, or its dose.[1)]

On the basis of the current situation, there is a clinical need for more local treatment options available, especially to patients with a problematic urinary organ property due to increased AMLs. Cryotherapy with the Visual-ICE involves percutaneous puncture of a fine needle into TSC-AML under guidance with X-ray CT to freeze and necrotize the tissue, without surgical excision of the kidney. Therefore, this therapy is less invasive and has less impact on renal function than surgical excision. In addition, the Visual-ICE therapy can be repeated.

A medical device for cryotherapy was approved in 2010 in Japan for the indication of small renal malignancies. Some reports on cryotherapy to treat TSC-AML were published overseas around 2016. These reports suggest the potential effectiveness of cryotherapy in the treatment of TSC-AML. In Japan, a study (Clinical research registration No. jRCTs072200039) (Cryo-tsc-study) was conducted as Advanced Medical Care B (Public Notice No. 42) from October 2020 in order to evaluate the efficacy and safety of cryotherapy with the previous-generation product as Advanced Medical Care (renal tumor coagulation/ablation [limited to cryocoagulation] for the treatment of renal angiomyolipoma) in patients with TSC-AML. Subsequently, the Visual-ICE was designated as an orphan medical device for the expanded indication in April 2024 based on the results of the Cryo-tsc-study as mentioned above.

The present partial change application has been submitted aiming to broaden the indication of the Visual-ICE to “tuberous sclerosis complex-angiomyolipoma that is ineligible for or refractory to standard therapy.” The key differences between the previous-generation product and the Visual-ICE are presented in the table below (Table 2, Table 3).

Table 2. Comparison between the previous-generation product and the Visual-ICE

Item	Visual-ICE Cryoablation System (Visual-ICE)	Cryosurgical Unit CryoHit (previous-generation product)
Main unit	Rated supply voltage: Single-phase AC 100-240 V Rated supply frequency: 50/60 Hz Power input: 250 VA	Rated supply voltage: Single-phase AC 100-120 V Rated supply frequency: 50/60 Hz Power input: 360 VA
Needles	Needle type: 7 types Shaft outer diameter: 1.5 mm Shaft length: 100, 175 mm Shape of handle: Straight, 90° Number of heat exchangers: [redacted] or [redacted] Vacuum structure: Yes or no	Needle type: 4 types Shaft outer diameter: 1.5 mm Shaft length: 175 mm Shape of handle: Straight, 90° Number of heat exchangers: [redacted] or [redacted] Vacuum structure: No
Other constituent parts	• Multi-point thermal sensor Shaft outer diameter: 1.5 mm Shaft length: 175 mm	• Thermal sensor Outer diameter: 1.5 mm Length of insertion: 175 mm • Distribution panel • MRI kit • Remote control unit
Raw materials (parts contacting blood)	Needle shaft: Stainless steel Handle heat-shrinkable tube: Polyolefin	Probe tube: Chrome plating Needle shaft: Nickel superalloy Handle heat-shrinkable tube: Polyolefin
Directions for use	The needle is punctured into a tumor under image guidance with X-ray CT.	The probe (or needle) is punctured into a tumor under image guidance with MR or X-ray CT.

Table 3. Comparison of needle shape and frozen area between the previous-generation product and the Visual-ICE

Brand name	Product name	Handle	Shaft		Shaft internal structure		0°C frozen area specification*	
		Shape	Diameter [mm]	Length [mm]	Vacuum structure	No. of heat exchangers	Diameter [mm]	Length [mm]
Visual-ICE Cryoablation System	Needle S-Plain Straight 175 mm	Straight	1.5	175	No	[redacted]	33 ± [redacted]	38 ± [redacted]
	Needle S-Plain 90°175 mm	90°	1.5	175	No	[redacted]	33 ± [redacted]	38 ± [redacted]
	Needle Sp Straight 175 mm	Straight	1.5	175	Yes	[redacted]	39 ± [redacted]	45 ± [redacted]
	Needle Sp 90°175 mm	90°	1.5	175	Yes	[redacted]	39 ± [redacted]	45 ± [redacted]
	Needle Sp 90°100 mm	90°	1.5	100	Yes	[redacted]	39 ± [redacted]	45 ± [redacted]
	Needle I-Plus Straight 175 mm	Straight	1.5	175	Yes	[redacted]	43 ± [redacted]	60 ± [redacted]
	Needle I-Plus 90°175 mm	90°	1.5	175	Yes	[redacted]	43 ± [redacted]	60 ± [redacted]
Cryosurgical Unit CryoHit	Needle 1.5 mm S Straight	Straight	1.5	175	No	[redacted]	37 ± [redacted]	43 ± [redacted]
	Needle 1.5 mm S 90°	90°	1.5	175	No	[redacted]	37 ± [redacted]	43 ± [redacted]
	Needle 1.5 mm I Straight	Straight	1.5	175	No	[redacted]	42 ± [redacted]	61 ± [redacted]
	Needle 1.5 mm I 90°	90°	1.5	175	No	[redacted]	42 ± [redacted]	61 ± [redacted]

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

In Japan, the Visual-ICE was approved on September 2, 2020 for the intended use of freezing and necrotizing “small renal malignancies.” Subsequently, the Visual-ICE was approved on December 5,

2024 for the extended indications of liver tumors, as well as pulmonary malignant tumors, malignant bone tumors, osteoid osteoma, intrapelvic malignant tumors, and soft tissue tumors that developed in the extremities, thoracic cavity, and abdominal cavity that are ineligible for or refractory to standard therapy. In Europe and the US, the Visual-ICE was authorized for the intended use shown in Table 4.

Table 4 presents the sales volume in and outside Japan from June 2022 to May 2024. In Japan, [redacted] main units, [redacted] needles, and [redacted] multi-point thermal sensors were sold. In the US, [redacted] main units, [redacted] needles, and [redacted] multi-point thermal sensors were sold. In Europe, [redacted] main units, [redacted] needles, and [redacted] multi-point thermal sensors were sold.

Table 4. Approval status and sales volume in and outside Japan (June 2022 to May 2024)

Country	Brand name	Date of authorization	Present intended use or effect	Sales results		
				Main unit	Needle	Multi-point thermal sensor
Japan	Visual-ICE	September 2, 2020 (initial approval) December 5, 2024 (partial change approval for the expanded indication)	The Visual-ICE Cryoablation System is a cryosurgical unit that freezes and necrotizes biological tissues. It is indicated for small renal malignancies, liver tumors, and tuberous sclerosis complex-angiomyolipoma. It is also used for the treatment (including palliative intervention) of the following tumors that are ineligible for or refractory to standard therapy: • Pulmonary malignant tumors • Malignant bone tumors • Osteoid osteoma • Intrapelvic malignant tumors • Soft tissue tumors that developed in the extremities, thoracic cavity, and abdominal cavity	[redacted]	[redacted]	[redacted]
US	Visual-ICE	March 12, 2012 (K113860)	The Visual-ICE Cryoablation System is intended for cryoablative destruction of tissue during surgical procedures. The Visual-ICE Cryoablation System is intended for use as a cryosurgical tool in the fields of general surgery, dermatology, neurology (including cryoanalgesia), thoracic surgery (with the exception of cardiac tissue), otorhinolaryngology, gynecology, oncology, proctology, and urology. This system is designed to destroy tissue (including prostate and kidney tissue, liver metastases, tumors, and skin lesions) by the application of extremely cold temperatures.	[redacted]	[redacted]	[redacted]
Europe	Visual-ICE	June 24, 2013 (CE mark)	The Visual-ICE Cryoablation System is intended for cryoablative destruction of tissue during surgery. The Visual-ICE Cryoablation System is intended for use as a cryosurgical tool in the fields of general surgery, dermatology, neurology (including cryoanalgesia), thoracic surgery (with the exception of cardiac tissue), gynecology, oncology, and urology. This system is designed to destroy tissue (including prostate and kidney tissue, liver metastases, tumors, and skin lesions) by the application of extremely cold temperatures.	[redacted]	[redacted]	[redacted]

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

Tables 5 to 7 present the incidences of malfunctions or adverse events reported to the Japanese and foreign regulatory authorities. Since the main unit is reusable, the incidence of its malfunctions or events relative to the sales volume cannot be determined accurately. The numbers of malfunctions or events alone are presented in the table. Neither device-related deaths nor malfunctions of the multi-point thermal sensor were reported.

Table 5. Malfunctions of the needle in Japan (June 2022 to May 2024)

Malfunctions and adverse events	Number of events	Incidence
Frozen shaft	[redacted]	0.154
Haemorrhage	[redacted]	0.077
Total	[redacted]	0.231

Table 6. Malfunctions of the main unit overseas (June 2022 to May 2024)

Adverse events	Number of events
Pulmonary embolism	[redacted]
Total	[redacted]
Malfunctions	**Number of events**
System, insufficient freezing	[redacted]
System, failure to reach intended temperature	[redacted]
System, connecting port defect	[redacted]
Main unit, display defect	[redacted]
System, unexpected reboot/reset	[redacted]
Unrelated to the product	[redacted]
Total	[redacted]

Table 7. Malfunctions of the needle overseas (June 2022 to May 2024)

Adverse events	Number of events	Incidence*
Haemorrhage	[redacted]	0.010
Thermal burn, third degree	[redacted]	0.010
Total	[redacted]	0.020
Malfunctions	**Number of events**	**Incidence***
Frozen shaft	[redacted]	0.061
Needle, unexpected operation	[redacted]	0.031
Needle, insufficient freezing	[redacted]	0.031
Label mistake	[redacted]	0.020
Needle, gas/air leakage	[redacted]	0.010
Total	[redacted]	0.153

*(Number of events/sales volume overseas: [redacted] units) × 100

2. Design and Development

2.(1) Performance and safety specifications

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

Since the present application contains no change in the specifications or constituent parts of the Visual-ICE, there is no substantial change in the performance or safety specifications. The following specifications were proposed.

The proposed performance specifications were ice-ball size (needle), system pressure resistance and leakage, needle pressure resistance and gas leakage, and measurement precision of the multi-point thermal sensor. The proposed safety specifications were electrical safety (International Electrotechnical Commission [IEC]60601-1:2005/AMD1:2012), electromagnetic compatibility (IEC60601-1-2:2014, AMD:2020), biological safety (International Organization for Standardization [ISO] 10993-1:2018), ethylene oxide sterilization residuals (ISO 10993-7:2008), and software lifecycle process (IEC 62304:2006+A1:2015).

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

PMDA' view on the proposed performance and safety specifications of the Visual-ICE:

TSC-AML, which is the new indication proposed in the present application, has different disease characteristics from those of small renal malignancies, which was the initial indication approved for the Visual-ICE. For both indications, however, the intended use of the Visual-ICE is to freeze and necrotize the kidney tissue. Consequently, the puncture site and tissue are similar for the proposed indication and the initial-approved indication. No change has been made to the principle of the Visual-ICE, which is to freeze the needle tip by ejecting high-pressure (22.0-29.6 MPa) argon gas through a nozzle inside the needle tip and to thaw the tissue using high-pressure (12.4-20.1 MPa) helium gas. The addition of the proposed indication will not affect the performance or safety of the Visual-ICE.

PMDA concluded that there was no particular problem in the proposed performance and safety specifications of the Visual-ICE.

2.(2) Safety specifications

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

Since the present application contains no change in the specifications or constituent parts of the Visual-ICE, the applicant omitted the submission of evaluation data regarding the physicochemical properties, electrical safety and electromagnetic compatibility, mechanical safety, and stability and durability of the Visual-ICE. The biological safety of the Visual-ICE was evaluated based on its clinical use experience since there is no change in the raw materials or directions for use.

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

Since the present application contains no change in the specifications or constituent parts of the Visual-ICE, PMDA concluded that evaluation data regarding the physicochemical properties, electrical safety and electromagnetic compatibility, mechanical safety, and stability and durability could be omitted. PMDA reviewed the data on biological safety and concluded that there was no particular problem.

2.(3) Performance

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

The present application contains no change in the specifications or constituent parts of the Visual-ICE. The intended use of the Visual-ICE in the treatment of TSC-AML is to freeze and necrotize renal tumors as in the initial-approved indication. Consequently, the puncture site and tissue are similar for both indications. The tissue puncture and freezing/necrotizing performance of the Visual-ICE was evaluated based on the results of the performance test, which were submitted for the initial approval (Table 8). Since no change has been made to the principle of the Visual-ICE from the initial approval, the addition of the proposed indication will not affect the performance or safety of the Visual-ICE.

The performance required for the Visual-ICE to puncture and freeze/necrotize tissues is similar in the treatment of TSC-AML and small renal malignancies and the data submitted for the initial approval suffice to evaluate the performance of the Visual-ICE in the treatment of TSC-AML. Thus, performance data were omitted in the present application.

Table 8. List of performance tests evaluated in the initial approval (approved range)

Test	
Performance	Area of freezing (ice-ball size)
	System pressure resistance and leakage
	Needle pressure resistance and gas leakage
	Temperature measurement precision of multi-point thermal sensor
Main software functions	Freezing, thawing, and stopping
	Needle test
	Gas flow control
	Display of freezing, thawing, and stopping time
	Sequence setting of freezing and thawing time
	Display of supply gas pressure
	Display of the temperature of multi-point thermal sensor
Others	Temperature of needle shaft with vacuum structure
	Bending strength during puncture
	Monitoring of the puncture site and frozen area under image guidance with X-ray CT
	Expected frozen area with needle
	Thawing with helium gas
	Injury caused by thawing with helium gas

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

For the following reasons, PMDA concluded that performance data could be omitted:

- There is no change in the specifications, constituent parts, or basic directions for use of the Visual-ICE.
- The performance required for the Visual-ICE to puncture and freeze/necrotize tissues is similar in the treatment of small renal malignancies, which is the initial-approved indication, and TSC-AML, which is the proposed new indication.

2.(4) Directions for use

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

The present application contains no change in the specifications or constituent parts of the Visual-ICE. The intended use of the Visual-ICE in the treatment of TSC-AML is to freeze and necrotize renal tumors as in the initial-approved indication. Consequently, the puncture site and tissue are similar for both indications. Data regarding directions for use were omitted in the present application.

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

For the following reasons, PMDA concluded that performance data could be omitted:

- There is no change in the specifications, constituent parts, or basic directions for use of the Visual-ICE.
- TSC-AML has different disease characteristics from those of small renal malignancy, which was the initial-approved indication. For both indications, however, the target organs and basic directions for use are the same. Consequently, there appears to be no significant procedural safety concern.

2.(5) Conformity to IEC62304

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

The applicant submitted data supporting the conformity of the Visual-ICE to the international standard that defines the software lifecycle process for medical device software (IEC62304:2006+Amd. 1:2015).

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

PMDA reviewed the submitted data on the conformity to IEC62304 and concluded that there was no particular problem.

2.(6) Cybersecurity

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

The applicant submitted the results of cybersecurity tests that complied with "Confirmation of Compliance with Article 12, Paragraph 3 of the Essential Principles for Medical Devices" (PSEHB/MDED Notification No.0523-1 dated May 23, 2023).

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

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

2.(7) Usability

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

The applicant submitted data supporting the conformity of the Visual-ICE to the international standard that defines usability engineering process (IEC62366-1).

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

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

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

3.A Summary of the data submitted

The applicant submitted a declaration of conformity declaring that the Visual-ICE 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 Visual-ICE to the Essential Principles as shown below.

(1) PMDA's view on the conformity of the Visual-ICE 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):
As described later in Sections "6.B Outline of the review conducted by PMDA" and "7.B Outline of the review conducted by PMDA," selection of eligible patients, users, and medical institutions, provision of information to users, compliance with the guidelines for proper use, etc. are important to maintain a risk-benefit balance of the Visual-ICE. To this end, an approval condition will be attached to ensure that necessary measures are taken.

(2) PMDA's view on the conformity of the Visual-ICE to Article 3, which stipulates requirements for the performance and functions of medical devices, and to Article 6, which stipulates the efficacy of medical devices:
As described later in Sections "6.B Outline of the review conducted by PMDA" and "7.B Outline of the review conducted by PMDA," the Advanced Medical Care B Study demonstrated a certain degree of efficacy and safety of the Visual-ICE. The Visual-ICE conforms to Articles 3 and 6.

(3) PMDA's view on the conformity of the Visual-ICE to Article 17, which stipulates requirements for publicizing information on precautions or providing such information through the instructions for use, etc. (the Information on Precautions, etc.):
As described later in Section "6.B Outline of the review conducted by PMDA," users must understand the risk of the Visual-ICE, select eligible patients, and ensure proper use to maintain its risk-benefit balance. To this end, information should be provided through the Information on Precautions, etc., the guidelines for proper use, training, and other measures.

PMDA comprehensively reviewed the conformity of the Visual-ICE 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 the document summarizing the risk management, the risk management system, and its implementation status in accordance with ISO 14971:2019 "Medical devices—Application of risk management to medical devices."

4.B Outline of the review conducted by PMDA

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

5. Manufacturing Process

5.A Summary of the data submitted

The present application contains no change in the manufacturing process of the Visual-ICE. Data on the manufacturing process were omitted in the present application.

5.B Outline of the review conducted by PMDA

PMDA concluded that the data on the manufacturing process of the Visual-ICE could be omitted.

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

6.A Summary of the data submitted

This study was conducted to evaluate the efficacy and safety of cryotherapy with the previous-generation product of the Visual-ICE, which shares the same mechanism of freezing and a similar freezing performance with the Visual-ICE, in patients with TSC-AML.

The applicant submitted the clinical evaluation of the Visual-ICE from the results of the Cryo-tsc-study, which was Advanced Medical Care B clinical research conducted in patients with TSC-AML with a tumor measuring ≥1 and ≤4 cm in longest diameter, regardless of whether patients were taking oral mTOR inhibitors in the present application. In addition, the applicant submitted the reference data from a report on “Clinical outcomes of other cryotherapies and treatment with similar medical devices in TSC-AML” and “Clinical outcomes of cryotherapy in small renal malignancies” based on published literature.

6.A.(1) Cryo-tsc-study

6.A.(1).1) Summary

The Cryo-tsc-study (the study) was a multi-center, prospective, single-arm clinical study that evaluated the efficacy and safety of the Visual-ICE based on disease control rate of AML at 9 months after cryotherapy, adverse events, etc. in patients with TSC-AML with a tumor measuring ≥1 and ≤4 cm in longest diameter, regardless of whether patients were taking oral mTOR inhibitors. The study, designated as Advanced Medical Care B clinical research, was initiated at 5 study sites in Japan on October 1, 2020 and completed on December 31, 2022. Table 9 presents an outline of the study protocol.

Table 9. Outline of the Advanced Medical Care B Study

Item	Outline
Study objective	Evaluation of the efficacy and safety of cryotherapy in patients with tuberous sclerosis complex with renal angiomyolipoma that tended to grow
Study design	Prospective, open-label, non-controlled, single-arm, multi-center (5 study sites), Japanese study
Study population	Tuberous sclerosis complex (TSC)-angiomyolipoma (AML)
Major inclusion criteria	• Patients aged ≥16 years at the time of informed consent • Patients with confirmed diagnosis of tuberous sclerosis complex based on the modified Gomez criteria or TSC clinical consensus Guideline for Diagnosis 2012 at the time of enrollment • Patients with AML measuring ≥1 and ≤4 cm in longest diameter, as confirmed by diagnostic imaging within 4 months prior to enrollment, regardless of whether patients were taking oral mTOR inhibitors • Written informed consent was provided by: ➢ the patient alone (when the patient aged ≥20 years, fully understands explanations), ➢ the patient and his/her legally acceptable representative (parent or legal guardian) (when the patient aged <20 years, fully understands explanations), or ➢ legally acceptable representative alone.
Major exclusion criteria	• Patients who are unable to withdraw from mTOR inhibitor therapy • Patients who are unable to maintain a resting state during cryotherapy • Patients with platelet $<6 \times 10^4/\mu L$ (within 28 days prior to enrollment) • Patients with history of serious allergy to contrast media or obstructing materials • Patients with infection requiring systemic treatment • Patients with comorbid malignancy • Women who are pregnant, possibly pregnant, or within 28 days post-partum • Patients with disabling complicating psychological disease or psychiatric symptom that makes participation in the study difficult • Patients with uncontrolled complicating hypertension • Patients with ineligibility for participation in the study as deemed by the investigator
Sample size	15
Primary endpoint	• Disease control rate (DCR) of AML at 9 months after cryotherapy DCR was calculated as the percentage of subjects with CR, PR, or SD with tumor shrinkage. SD with tumor shrinkage was defined as SD with a longest diameter at the follow-up visit smaller than the baseline longest diameter.
Secondary endpoints	Efficacy evaluation • Overall response rate of AML at 9 months after cryotherapy • Renal function (change from baseline in renal function [serum creatinine and eGFR] after cryotherapy) • Change from baseline in QOL (QOL [SF-36v2]) at 3 and 9 months after cryotherapy • Additional treatment Safety evaluation criteria • Safety (safety after initiation of cryotherapy)
Study period	• Enrollment period: October 1, 2020 to September 30, 2021 (1 year) • Follow-up period: October 1, 2021 to June 30, 2022 (9 months after the date of the last treatment) • Analysis and clinical study report preparation period: December 31, 2022 (6 months after the end of the follow-up period) • Study period: October 1, 2020 to December 31, 2022 (including the analysis period)

6.A.(1).2) Sample size determination

The primary endpoint of the study was disease control rate of AML at 9 months after cryotherapy. Without therapeutic intervention, patients with TSC-AML cannot achieve tumor shrinkage or disease control, and will experience tumor growth over time. Even when tumor shrinkage is achieved with a mTOR inhibitor, tumors are most likely to regrow once the medication is stopped, although the growth rate varies among patients. Untreated TSC-AML will progress over time, i.e., progressive disease (PD) or stable disease (SD) with an increasing trend of tumor size (a longest diameter at the follow-up visit

larger than the baseline longest diameter). Its disease control rate is approximately 0%. If cryotherapy provides disease control (disease control rate [DCR]; complete response [CR], partial response [PR], or SD with a trend of tumor shrinkage) in half (50%) the study population, reduction in bleeding risk and freedom from decreased kidney function which are the therapeutic goals of TSC-AML, can be achieved. This is considered of adequate clinical significance. In this study, therefore, DCR was assessed using a sign test under the null hypothesis that DCR of 0.5, at a significance level of 5%. This means that when at least 12 of 15 subjects achieve disease control, the result is statistically significant. When the true value of DCR is 80%, 85%, and 90%, the probabilities that AML is assessed as SD or better in at least 12 of 15 subjects were 64.8%, 82.3%, and 94.4%, respectively. Assuming a true DCR of ≥85%, a sample size of 15 achieves a power of ≥80%. Since TSC-AML, the target disease of the study, is a rare disease, it is challenging to accrue subjects. In this study, medical institutions that actively engaged in multidisciplinary treatment of TSC participated. A preliminary survey showed that approximately 3 patients per year might be eligible for the study at each site. Accordingly, the sample size of 15, a total at 5 sites, was determined.

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

Table 10 presents the analysis sets in this study. Table 11 presents the patient characteristics.

Table 10. Analysis set

Disposition	n (%)
Enrolled	15
Treated with cryotherapy	15 (100.0)
Discontinued after cryotherapy	0 (0.0)
Efficacy analysis set (FAS)	15 (100.0)
Safety analysis set (SAS)	15 (100.0)

Table 11. Patient characteristics

Characteristics		N = 15
Sex	Male (%)	3 (20.0)
Age (years)	Mean (SD)	34.0 (12.5)
Height (cm)	Mean (SD)	162.2 (5.5)
Body weight (kg)	Mean (SD)	60.2 (9.1)
Medical history	Yes (%)	6 (40.0)
Complication	Yes (%)	12 (80.0)
Drug allergy	Yes (%)	5 (33.3)
Prior embolization	Yes (%)	4 (26.7)
Prior surgery	Yes (%)	2 (13.3)
Prior treatment with everolimus	Yes (%)	12 (80.0)
Other prior treatment	Yes (%)	1 (6.7)

Table 12-1 presents target lesion data assessed by the central review committee. The response of each target lesion of the study was evaluated in accordance with the modified Response Evaluation Criteria in Solid Tumors (mRECIST) in principle. Alternatively, the RECIST was used for efficacy evaluation in the case that the target lesion was not contrasted enough because of its high fat content or that contrast CT could not be performed because subjects were found to have contrast media allergy after enrollment.

Table 12-1. List of target lesion data assessed by the central review committee

Patient ID	RECIST (central review) Size (mm)	mRECIST (central review) Size (mm)	Evaluation criteria
[redacted]	16.66	16.66	modified RECIST
	29.49	29.49	modified RECIST
	34.86	34.86	modified RECIST
	25.65	-	RECIST v1.1
	17.6	-	RECIST v1.1
	19.37	-	RECIST v1.1
	24.23	24.23	modified RECIST
	17.39	17.39	modified RECIST
	32.08	32.08	modified RECIST
	33.66	33.66	modified RECIST
	20.49	20.49	modified RECIST
	25.34	25.34	modified RECIST
	20.93	20.93	modified RECIST
	28.03	28.03	modified RECIST
	21.06	21.06	modified RECIST

In this study, embolization was performed before cryotherapy in order to increase the visibility of target lesions. Table 12-2 presents prior embolization status. A total of 13 subjects underwent embolization. The remaining 2 subjects were excluded because they had contrast media allergy or decreased kidney function due to complicating chronic kidney disease and IgA nephropathy.

Table 12-2. Dates of admission and discharge, and angiography/embolization status

Patient ID	Date of admission	Date of discharge	Angiography/ embolization	Date of angiography/ embolization	Procedural adverse drug reaction
[redacted]	20[redacted]	20[redacted]	Yes	20[redacted]	No
	20[redacted]	20[redacted]	Yes	20[redacted]	No
	20[redacted]	20[redacted]	Yes	20[redacted]	No
	20[redacted]	20[redacted]	Yes	20[redacted]	Yes
	20[redacted]	20[redacted]	No	-	-
	20[redacted]	20[redacted]	No	-	-
	20[redacted]	20[redacted]	Yes	20[redacted]	No
	20[redacted]	20[redacted]	Yes	20[redacted]	No
	20[redacted]	20[redacted]	Yes	20[redacted]	No
	20[redacted]	20[redacted]	Yes	20[redacted]	No
	20[redacted]	20[redacted]	Yes	20[redacted]	No
	20[redacted]	20[redacted]	Yes	20[redacted]	No
	20[redacted]	20[redacted]	Yes	20[redacted]	No
	20[redacted]	20[redacted]	Yes	20[redacted]	No
	20[redacted]	20[redacted]	Yes	20[redacted]	No

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

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

i) Primary endpoint: DCR (DCR was the percentage of subjects with CR, PR, or SD with a trend of tumor shrinkage) of AML at 9 months after cryotherapy

Tumor response (DCR) at 9 months after cryotherapy was CR in 12 subjects (80.0%), PR in 2 subjects (13.3%), and SD with a trend of tumor shrinkage in 1 subject (6.7%). The DCR was 100%. The sign test of the null hypothesis that DCR of 0.5 was statistically significant with a *P*-value of <0.001 (Table 13).

Table 13. Target lesion response (DCR)

Response	Month 9 (N = 15)
CR	12 (80.0)
PR	2 (13.3)
SD with a trend of tumor shrinkage	1 (6.7)
SD with an increasing trend of tumor size	0 (0.0)
PD	0 (0.0)
NE	0 (0.0)
DCR	15 (100.0)
95% CI	78.2, 100.0
P-value of sign test	<0.001

ii) Secondary endpoint: ORR (ORR was the percentage of subjects with CR or PR) of AML at 9 months after cryotherapy

Tumor response (overall response rate [ORR]) at 9 months was PR or better in 14 subjects. The ORR was 93.3%. The sign test of the null hypothesis that ORR of 0.5 was also statistically significant with a *P*-value of <0.001 (Table 14).

Table 14. Target lesion response (ORR)

Response	Month 9 (N = 15)
CR	12 (80.0)
PR	2 (13.3)
SD with a trend of tumor shrinkage	1 (6.7)
SD with an increasing trend of tumor size	0 (0.0)
PD	0 (0.0)
NE	0 (0.0)
ORR	14 (93.3)
95% CI	68.1, 99.8
P-value of sign test	<0.001

iii) Secondary endpoint: Change in renal function (serum creatinine and eGFR)

At and after 1 month following cryotherapy, serum creatinine significantly increased. The median change at 9 months was 0.06 mg/dL. The point estimate of median was 0.05, with its 95% confidence interval of (0.03, 0.09). Estimated Glomerular filtration rate (eGFR) also significantly decreased. The median change at 9 months was −5.0 mL/min/1.73 m^2. The point estimate of median was −6.9 with its 95% confidence interval of (−14.8, −3.8) (Table 13-2). No change was observed in the grade of serum creatinine. The eGFR grade increased by 1 level in 3 subjects (20%) at 9 months following cryotherapy (Tables 15-3 and 15-4).

Table 15-1. Serum creatinine and eGFR

Evaluation timing	Summary statistics	Serum creatinine (mg/dL)	eGFR (mL/min/1.73 m^2)
Baseline	N	15	15
	Mean (SD)	0.73 (0.28)	89.4 (29.4)
	Median (min, max)	0.65 (0.42, 1.53)	89.2 (30.8, 143.8)
1-day post-procedure	N	15	15
	Mean (SD)	0.73 (0.26)	88.2 (26.3)
	Median (min, max)	0.63 (0.48, 1.45)	95.6 (32.4, 124.3)
1-month post-procedure	N	15	15
	Mean (SD)	0.83 (0.36)	78.3 (24.3)
	Median (min, max)	0.68 (0.57, 1.97)	76.3 (23.2, 109.4)
3-month post-procedure	N	15	15
	Mean (SD)	0.81 (0.34)	79.7 (25.3)
	Median (min, max)	0.71 (0.53, 1.86)	77.9 (24.7, 121.5)
6-month post-procedure	N	15	15
	Mean (SD)	0.81 (0.30)	78.9 (24.6)
	Median (min, max)	0.70 (0.54, 1.67)	77.5 (27.8, 119.1)
9-month post-procedure	N	15	15
	Mean (SD)	0.79 (0.31)	79.9 (23.1)
	Median (min, max)	0.67 (0.56, 1.73)	79.4 (26.7, 114.4)

Table 15-2. Change in serum creatinine and eGFR

Evaluation timing	Summary statistics	Serum creatinine (mg/dL)	eGFR (mL/min/1.73 m^2)
1-day post-procedure	N	15	15
	Mean (SD)	-0.01 (0.05)	-1.2 (9.8)
	Median (min, max)	0.00 (-0.08, 0.06)	0.0 (-21.5, 14.5)
	95% CI of median*	-0.00 (-0.03, 0.02)	-0.7 (-5.4, 3.2)
1-month post-procedure	N	15	15
	Mean (SD)	0.09 (0.12)	-11.2 (13.6)
	Median (min, max)	0.06 (-0.04, 0.44)	-6.5 (-48.2, 7.6)
	95% CI of median*	0.07 (0.04, 0.14)	-7.9 (-16.0, -4.5)
3-month post-procedure	N	15	15
	Mean (SD)	0.08 (0.09)	-9.7 (10.0)
	Median (min, max)	0.05 (-0.02, 0.33)	-7.9 (-32.3, 1.7)
	95% CI of median*	0.06 (0.04, 0.11)	-7.8 (-15.5, -4.4)
6-month post-procedure	N	15	15
	Mean (SD)	0.07 (0.05)	-10.6 (11.0)
	Median (min, max)	0.06 (-0.03, 0.15)	-7.6 (-37.8, 4.3)
	95% CI of median*	0.07 (0.05, 0.10)	-8.1 (-16.8, -5.3)
9-month post-procedure	N	15	15
	Mean (SD)	0.06 (0.06)	-9.5 (11.6)
	Median (min, max)	0.06 (-0.01, 0.20)	-5.0 (-43.8, 1.1)
	95% CI of median*	0.05 (0.03, 0.09)	-6.9 (-14.8, -3.8)

* Point estimate of median by Hodges-Lehmann method and its 95% confidence interval by Bootstrap method

Table 15-3. Shift table of serum creatinine grades

Evaluation timing		Baseline				
		0	1	2	3	4
1-day post-procedure	0	13 (86.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	1	0 (0.0)	1 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)
	2	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1-month post-procedure	0	11 (73.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	1	2 (13.3)	1 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)
	2	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
3-month post-procedure	0	11 (73.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	1	2 (13.3)	1 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)
	2	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
6-month post-procedure	0	11 (73.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	1	2 (13.3)	1 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)
	2	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
9-month post-procedure	0	13 (86.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	1	0 (0.0)	1 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)
	2	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Table 15-4. Shift table of eGFR grades

Evaluation timing		Baseline				
		0	1	2	3	4
1-day post-procedure	0	9 (60.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	1	3 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	2	0 (0.0)	1 (6.7)	2 (13.3)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1-month post-procedure	0	10 (66.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	1	2 (13.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	2	0 (0.0)	1 (6.7)	1 (6.7)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
3-month post-procedure	0	11 (73.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	1	1 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	2	0 (0.0)	1 (6.7)	1 (6.7)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
6-month post-procedure	0	11 (73.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	1	1 (6.7)	1 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)
	2	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
9-month post-procedure	0	11 (73.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	1	1 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	2	0 (0.0)	1 (6.7)	1 (6.7)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

iv) Secondary endpoint: Change in quality of life (QOL)

The mean baseline physical component summary (PCS) and mental component summary (MCS) were 53.3 and 50.5, respectively, which are close to the mean value (50) in the Japanese general population. The mean changes (95% CI) in PCS and MCS at 9 months were 1.1 (−3.9, 6.2) and 0.5 (−4.5, 5.4), respectively (Tables 16-1 and 16-2). Patient ID [redacted] did not receive the test as decided by the attending physician because of mild intellectual disability. The data from Patient ID [redacted] were excluded from analyses because no source document was available.

Table 16-1. Summary SF-36 scores (PCS, MCS)

Evaluation timing	Summary statistics	PCS	MCS
Baseline	N	13	13
	Mean (SD)	53.3 (5.0)	50.5 (11.7)
	Median (min, max)	54.1 (41.5, 59.2)	47.8 (33.9, 69.2)
3-month post-procedure	N	13	13
	Mean (SD)	52.7 (7.8)	51.9 (10.0)
	Median (min, max)	52.7 (29.6, 60.5)	51.3 (32.6, 69.2)
9-month post-procedure	N	13	13
	Mean (SD)	54.5 (4.5)	51.0 (11.0)
	Median (min, max)	55.3 (46.7, 59.8)	50.3 (25.3, 69.2)

PCS, Physical Component Summary; MCS, Mental Component Summary

Table 16-2. Change in summary SF-36 scores (PCS, MCS)

Evaluation timing	Summary statistics	PCS	MCS
3-month post-procedure	N	13	13
	Mean (SD)	-0.6 (9.6)	1.3 (6.0)
	Median (min, max)	-0.7 (-27.4, 11.2)	1.0 (-13.1, 9.9)
	95% CI of mean	(-6.4, 5.2)	(-2.3, 5.0)
9-month post-procedure	N	13	13
	Mean (SD)	1.1 (8.4)	0.5 (8.2)
	Median (min, max)	0.7 (-10.8, 18.3)	1.0 (-17.0, 19.4)
	95% CI of mean	(-3.9, 6.2)	(-4.5, 5.4)

PCS, Physical Component Summary; MCS, Mental Component Summary

v) Secondary endpoint, Additional treatment

No subject received additional treatment, such as initiation of pharmacotherapy with an mTOR inhibitor, embolization or surgical therapy of other lesions on the ipsilateral kidney, due to regrowth of target lesions after cryotherapy.

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

i) Haematology

No noteworthy change was observed from 1 day to 9 months after cryotherapy (Tables 17-1 and 17-2).

Table 17-1. Haematology

Evaluation timing	Summary statistics	White blood cell count (/mm^3)	Platelet count (×10^4/mm^3)	Haemoglobin (g/dL)
1-day post-procedure	N	15	15	15
	Mean (SD)	3916.0 (1817.0)	-3.2 (2.2)	-0.6 (0.6)
	Median (min, max)	3190 (1800, 7890)	-2.9 (-7.9, 0.0)	-0.5 (-1.7, 0.2)
	95% CI of mean	(2909.8, 4922.2)	(-4.4, -2.0)	(-0.9, -0.2)
1-month post-procedure	N	15	15	15
	Mean (SD)	-242.7 (1508.8)	-0.3 (3.2)	-0.4 (0.6)
	Median (min, max)	500 (-4380, 1710)	-0.9 (-5.2, 5.0)	-0.2 (-1.8, 0.4)
	95% CI of mean	(-1078.2, 592.9)	(-2.1, 1.5)	(-0.7, -0.1)
3-month post-procedure	N	15	15	15
	Mean (SD)	366.7 (1258.1)	0.3 (3.3)	0.0 (0.6)
	Median (min, max)	260 (-1900, 2220)	0.9 (-8.1, 6.4)	0.0 (-0.7, 1.6)
	95% CI of mean	(-330.1, 1063.4)	(-1.5, 2.1)	(-0.3, 0.4)
6-month post-procedure	N	15	15	15
	Mean (SD)	-146.7 (1237.0)	0.6 (4.7)	0.1 (0.7)
	Median (min, max)	-200 (-2600, 2500)	-0.1 (-8.5, 9.6)	0.0 (-1.0, 1.4)
	95% CI of mean	(-831.7, 538.4)	(-2.0, 3.2)	(-0.3, 0.5)
9-month post-procedure	N	15	15	15
	Mean (SD)	25.3 (907.0)	1.6 (2.3)	0.1 (0.7)
	Median (min, max)	200 (-1280, 1300)	1.7 (-1.5, 4.7)	0.2 (-1.1, 1.4)
	95% CI of mean	(-476.9, 527.6)	(0.3, 2.8)	(-0.2, 0.5)

Table 17-2. Change in haematology

Evaluation timing	Summary statistics	White blood cell count (/mm^3)	Platelet count (×10^4/mm^3)	Haemoglobin (g/dL)
1-day post-procedure	N	15	15	15
	Mean (SD)	3916.0 (1817.0)	-3.2 (2.2)	-0.6 (0.6)
	Median (min, max)	3190 (1800, 7890)	-2.9 (-7.9, 0.0)	-0.5 (-1.7, 0.2)
	95% CI of mean	(2909.8, 4922.2)	(-4.4, -2.0)	(-0.9, -0.2)
1-month post-procedure	N	15	15	15
	Mean (SD)	-242.7 (1508.8)	-0.3 (3.2)	-0.4 (0.6)
	Median (min, max)	500 (-4380, 1710)	-0.9 (-5.2, 5.0)	-0.2 (-1.8, 0.4)
	95% CI of mean	(-1078.2, 592.9)	(-2.1, 1.5)	(-0.7, -0.1)
3-month post-procedure	N	15	15	15
	Mean (SD)	366.7 (1258.1)	0.3 (3.3)	0.0 (0.6)
	Median (min, max)	260 (-1900, 2220)	0.9 (-8.1, 6.4)	0.0 (-0.7, 1.6)
	95% CI of mean	(-330.1, 1063.4)	(-1.5, 2.1)	(-0.3, 0.4)
6-month post-procedure	N	15	15	15
	Mean (SD)	-146.7 (1237.0)	0.6 (4.7)	0.1 (0.7)
	Median (min, max)	-200 (-2600, 2500)	-0.1 (-8.5, 9.6)	0.0 (-1.0, 1.4)
	95% CI of mean	(-831.7, 538.4)	(-2.0, 3.2)	(-0.3, 0.5)
9-month post-procedure	N	15	15	15
	Mean (SD)	25.3 (907.0)	1.6 (2.3)	0.1 (0.7)
	Median (min, max)	200 (-1280, 1300)	1.7 (-1.5, 4.7)	0.2 (-1.1, 1.4)
	95% CI of mean	(-476.9, 527.6)	(0.3, 2.8)	(-0.2, 0.5)

ii) Clinical chemistry (CRP)

C-reactive protein (CRP) increased from 0.14 mg/dL at baseline to 1.98 mg/dL at 1 day after cryotherapy and decreased to 0.16 mg/dL at 1 month after cryotherapy (Table 18).

Table 18. Clinical chemistry (CRP)

Evaluation timing	Summary statistics	CRP (mg/dL)
Baseline	N	14
	Mean (SD)	0.14 (0.13)
	Median (min, max)	0.07 (0.02, 0.37)
1-day post-procedure	N	15
	Mean (SD)	1.98 (2.13)
	Median (min, max)	1.20 (0.10, 8.30)
1-month post-procedure	N	15
	Mean (SD)	0.16 (0.25)
	Median (min, max)	0.09 (0.02, 1.03)
3-month post-procedure	N	15
	Mean (SD)	0.06 (0.04)
	Median (min, max)	0.04 (0.02, 0.16)
6-month post-procedure	N	15
	Mean (SD)	0.05 (0.02)
	Median (min, max)	0.04 (0.02, 0.09)
9-month post-procedure	N	15
	Mean (SD)	0.07 (0.05)
	Median (min, max)	0.06 (0.02, 0.18)

The baseline number of subjects was 14 because [redacted] was missing.

iii) Urinalysis

The urinalysis parameters changed to positive at 1 day after cryotherapy but almost returned to negative at 1 month after cryotherapy. Urinary occult blood did not resolve in 7 subjects in 1 month (Table 19).

Table 19. Urinalysis data

Evaluation timing	Assessment	Glucose	Protein	Leukocyte	Occult blood	Nitrite
Baseline	-	14 (100.0)	8 (57.1)	11 (78.6)	6 (42.9)	10 (90.9)
	±	0 (0.0)	3 (21.4)	0 (0.0)	1 (7.1)	0 (0.0)
	1+	0 (0.0)	2 (14.3)	1 (7.1)	4 (28.6)	1 (9.1)
	2+	0 (0.0)	1 (7.1)	1 (7.1)	0 (0.0)	0 (0.0)
	3+	0 (0.0)	0 (0.0)	1 (7.1)	3 (21.4)	0 (0.0)
1-day post-procedure	-	15 (100.0)	1 (6.7)	9 (60.0)	0 (0.0)	14 (93.3)
	±	0 (0.0)	3 (20.0)	1 (6.7)	0 (0.0)	0 (0.0)
	1+	0 (0.0)	6 (40.0)	1 (6.7)	0 (0.0)	1 (6.7)
	2+	0 (0.0)	5 (33.3)	4 (26.7)	1 (6.7)	0 (0.0)
	3+	0 (0.0)	0 (0.0)	0 (0.0)	14 (93.3)	0 (0.0)
1-month post-procedure	-	15 (100.0)	10 (66.7)	10 (66.7)	4 (26.7)	11 (91.7)
	±	0 (0.0)	3 (20.0)	1 (6.7)	4 (26.7)	0 (0.0)
	1+	0 (0.0)	1 (6.7)	2 (13.3)	1 (6.7)	1 (8.3)
	2+	0 (0.0)	1 (6.7)	0 (0.0)	3 (20.0)	0 (0.0)
	3+	0 (0.0)	0 (0.0)	2 (13.3)	3 (20.0)	0 (0.0)
3-month post-procedure	-	15 (100.0)	10 (66.7)	11 (73.3)	13 (86.7)	11 (91.7)
	±	0 (0.0)	3 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)
	1+	0 (0.0)	1 (6.7)	2 (13.3)	1 (6.7)	1 (8.3)
	2+	0 (0.0)	1 (6.7)	2 (13.3)	0 (0.0)	0 (0.0)
	3+	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)
6-month post-procedure	-	15 (100.0)	11 (73.3)	13 (86.7)	11 (73.3)	11 (91.7)
	±	0 (0.0)	3 (20.0)	0 (0.0)	2 (13.3)	0 (0.0)
	1+	0 (0.0)	1 (6.7)	1 (6.7)	1 (6.7)	0 (0.0)
	2+	0 (0.0)	0 (0.0)	1 (6.7)	1 (6.7)	1 (8.3)
	3+	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
9-month post-procedure	-	15 (100.0)	12 (80.0)	13 (86.7)	12 (80.0)	12 (100.0)
	±	0 (0.0)	2 (13.3)	0 (0.0)	2 (13.3)	0 (0.0)
	1+	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)	0 (0.0)
	2+	0 (0.0)	1 (6.7)	1 (6.7)	0 (0.0)	0 (0.0)
	3+	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)

Note) There was no data in subject with urine protein of 4+.

iv) Laboratory test grades

No noteworthy change was observed after cryotherapy (Table 20).

Table 20. Laboratory test grades

Evaluation timing	Grade	White blood cell count	Platelet count	Haemoglobin	Proteinuria
Baseline	0	15 (100.0)	15 (100.0)	13 (86.7)	11 (78.6)
	1	0 (0.0)	0 (0.0)	2 (13.3)	2 (14.3)
	2	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.1)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	-
1-day post-procedure	0	15 (100.0)	15 (100.0)	12 (80.0)	4 (26.7)
	1	0 (0.0)	0 (0.0)	3 (20.0)	6 (40.0)
	2	0 (0.0)	0 (0.0)	0 (0.0)	5 (33.3)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	-
1-month post-procedure	0	15 (100.0)	15 (100.0)	11 (73.3)	13 (86.7)
	1	0 (0.0)	0 (0.0)	4 (26.7)	1 (6.7)
	2	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	-
3-month post-procedure	0	14 (93.3)	15 (100.0)	13 (86.7)	13 (86.7)
	1	0 (0.0)	0 (0.0)	2 (13.3)	1 (6.7)
	2	1 (6.7)	0 (0.0)	0 (0.0)	1 (6.7)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	-
6-month post-procedure	0	14 (93.3)	15 (100.0)	13 (86.7)	14 (93.3)
	1	1 (6.7)	0 (0.0)	1 (6.7)	1 (6.7)
	2	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	-
9-month post-procedure	0	15 (100.0)	15 (100.0)	13 (86.7)	14 (93.3)
	1	0 (0.0)	0 (0.0)	2 (13.3)	0 (0.0)
	2	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	-

v) Vital signs

No noteworthy change was observed after cryotherapy (Table 21).

Table 21. Vital signs

Evaluation timing	Summary statistics	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)	Body temperature (°C)	Pulse (bpm)	SpO_2 (%)
Date of admission	N	15	15	15	15	13
	Mean (SD)	116.8 (11.8)	73.5 (11.6)	36.6 (0.5)	75.1 (12.0)	98.2 (0.9)
	Median (min, max)	114 (100, 143)	70 (55, 99)	36.6 (35.9, 37.7)	75 (58, 92)	99 (97, 99)
Date of treatment	N	15	15	15	15	15
	Mean (SD)	117.3 (11.5)	76.7 (10.5)	36.5 (0.4)	74.9 (10.2)	97.9 (1.0)
	Median (min, max)	113 (101, 133)	78 (59, 94)	36.5 (35.9, 37.0)	75 (59, 88)	98 (97, 100)
1-day post-procedure	N	15	15	15	15	14
	Mean (SD)	115.1 (11.2)	71.1 (10.7)	36.9 (0.7)	75.8 (11.8)	97.5 (1.1)
	Median (min, max)	115 (101, 141)	69 (50, 87)	36.8 (35.6, 38.2)	73 (60, 98)	98 (96, 99)

vi) Adverse events

All adverse events reported at the trial sites through 9 months after cryotherapy were collected. A total of 79 adverse events were reported in 15 subjects. Neither serious adverse events nor deaths occurred. A total of 63 adverse events in 14 subjects were causally related to cryotherapy. Of them, 3 adverse events (aspartate aminotransferase [AST] increased, haematuria, and chronic kidney disease) in 3 subjects were Grade 3. The AST increased and haematuria in 1 subject each were naturally resolving without intervention. One subject with chronic kidney disease had decreased kidney function (Grade 2) at baseline. The subject had a slight decrease in eGFR at 9 months, which was reported as a Grade 3 adverse event (Tables 22-1 and 22-2).

Table 22-1. Summary of adverse events

Item	Number of subjects (%)	Number of events
Number of subjects	15	-
All adverse events	15 (100.0)	79
Serious	-	-
Non-serious	15 (100.0)	79
Serious	0 (0.0)	0
Severity	-	-
Grade 1	14 (93.3)	54
Grade 2	11 (73.3)	22
Grade 3	3 (20.0)	3
Grade 4	0 (0.0)	0
Causal relationship	-	-
Unrelated	10 (66.7)	16
Related	14 (93.3)	63
Intervention	-	-
No	15 (100.0)	60
Yes	10 (66.7)	19
Outcome	-	-
Resolved	15 (100.0)	74
Resolving	1 (6.7)	1
Resolved with sequela	0 (0.0)	0
Not resolved	4 (26.7)	4
Death	0 (0.0)	0
Unknown	0 (0.0)	0

Table 22-2. Frequency of adverse events

Adverse events	Number of subjects (%)	Number of events
Number of subjects	15	-
All adverse events	15 (100.0)	79
Gastrointestinal disorders	6 (40.0)	11
Nausea	4 (26.7)	4
Retroperitoneal haemorrhage	5 (33.3)	5
Vomiting	2 (13.3)	2
General disorders and administration site conditions	11 (73.3)	16
Pyrexia	5 (33.3)	5
Pain	10 (66.7)	11
Infections and infestations	1 (6.7)	1
COVID-19	1 (6.7)	1
Musculoskeletal and connective tissue disorders	1 (6.7)	1
Rhabdomyolysis	1 (6.7)	1
Blood and lymphatic system disorders	4 (26.7)	4
Anaemia	4 (26.7)	4
Vascular disorders	4 (26.7)	4
Haematoma	4 (26.7)	4
Injury, poisoning and procedural complications	1 (6.7)	1
Discomfort at puncture site	1 (6.7)	1
Nervous system disorders	2 (13.3)	2
Neuralgia	1 (6.7)	1
Hyposensitivity	1 (6.7)	1
Renal and urinary disorders	15 (100.0)	33
Haematuria	14 (93.3)	14
Proteinuria	11 (73.3)	11
Cystitis noninfective	1 (6.7)	1
Chronic kidney disease	5 (33.3)	7
Investigations	6 (40.0)	6
AST increased	1 (6.7)	1
Creatinine increased	3 (20.0)	3
White blood cell decreased	2 (13.3)	2

Table 22-3. Frequency of adverse events (causal relationship, related)

Adverse events	Number of subjects (%)	Number of events
Number of subjects	15	-
All adverse events	14 (93.3)	63
Gastrointestinal disorders	6 (40.0)	11
Nausea	4 (26.7)	4
Retroperitoneal haemorrhage	5 (33.3)	5
Vomiting	2 (13.3)	2
General disorders and administration site conditions	11 (73.3)	16
Pyrexia	5 (33.3)	5
Pain	10 (66.7)	11
Musculoskeletal and connective tissue disorders	1 (6.7)	1
Rhabdomyolysis	1 (6.7)	1
Blood and lymphatic system disorders	1 (6.7)	1
Anaemia	1 (6.7)	1
Vascular disorders	4 (26.7)	4
Haematoma	4 (26.7)	4
Injury, poisoning and procedural complications	1 (6.7)	1
Discomfort at puncture site	1 (6.7)	1
Nervous system disorders	2 (13.3)	2
Neuralgia	1 (6.7)	1
Hyposensitivity	1 (6.7)	1
Renal and urinary disorders	11 (73.3)	24
Haematuria	10 (66.7)	10
Proteinuria	7 (46.7)	7
Chronic kidney disease	5 (33.3)	7
Investigations	3 (20.0)	3
AST increased	1 (6.7)	1
Creatinine increased	2 (13.3)	2

6.A.(2) Evaluation of literature data

As presented on the following pages, the reports on “Clinical outcomes of other cryotherapies and treatment with similar medical devices in TSC-AML” and “Clinical outcomes of cryotherapy in small renal malignancies” based on published literature show no evidence that refutes the efficacy of the Visual-ICE therapy in the treatment of TSC-AML. The reports indicate no therapy-related serious adverse events. In addition, there was no significant adverse event reported in patients having multiple treated lesions or those who underwent cryotherapy more than once.

(a) Efficacy evaluation in TSC-AML

- “Literature report on cryotherapy in the treatment of TSC-AML”[4] demonstrated that all of the 8 AMLs (including 7 TSC-AMLs) with a median diameter of 3.9 (2.1-7.7) cm in 5 patients with AMLs (including 4 patients with TSC-AML) who underwent cryotherapy shrank at 37 (20-62)-month median follow-up without regrowth.
- “Literature report on microwave ablation in the treatment of TSC-AML”[5] demonstrated that all of the 10 AMLs with a mean diameter of 6.3 (4.5-8.5) cm in 9 patients with TSC-AML (with 10 tumors) who underwent microwave ablation shrank at 9 (3-12)-month mean follow-up.
- “Literature report on radiofrequency ablation in the treatment of TSC-AML”[6] demonstrated that radiofrequency ablation reduced the longest tumor diameter of 4 AMLs (from 6.1-32.4 cm to 5.1-31.5 cm) at 48-month follow-up in 4 patients with AML (including 2 patients with TSC-AML). The tumor size did not substantially decrease but did not increase.

(b) Safety evaluation in TSC-AML

- "Literature report on cryotherapy in the treatment of TSC-AML"[4] demonstrated a satisfactory tolerability of cryotherapy, with few peri-procedural complications such as puncture site haemorrhage and no post-procedural complications. The long-term safety evaluation with the median follow-up period of 37 (20-62) months indicated normal serum creatinine and eGFR values, showing that renal function was maintained.
- "Literature report on microwave ablation in the treatment of TSC-AML"[5] showed neither peri-procedural serious complications nor delayed adverse events (defined as events occurring after 30 days) at maximum follow-up of 12 months.
- "Literature report on radiofrequency ablation in the treatment of TSC-AML"[6] showed neither peri-procedural complications nor new haemorrhage or renal symptoms during the 48-month follow-up period, with serum creatinine within the normal range (48-90 μmol/L), showing that renal function was maintained.

(c) Safety evaluation in small renal malignancies

- "Literature report on cryotherapy in 609 patients with small renal malignancies" demonstrated the overall incidence of complications of 8.3% and the incidence of serious complications of 3.4%. In patients with a tumor diameter of ≤4 cm, the incidence of serious complications was ≤3%. The most common adverse event was haemorrhage (3.2%), which required treatment in 1.4% of the patients.
- "Literature report on cryotherapy in 117 patients with small renal malignancies" demonstrated the incidence of complications of 11% and the incidence of serious complications of 3%. Complications occurred within 30 days after cryotherapy in as small as 4% of the patients. Most complications were mild in severity.
- "Literature report on cryotherapy in 78 patients with anterior renal tumors" demonstrated the incidence of serious complications of 4%. Mild adverse events occurred in 27% of the patients and all of the events were managed conservatively. No patients required dialysis or had severe decreased kidney function.
- Post-marketing information on the Visual-ICE and its previous-generation product in the treatment of small renal malignancies also suggests no particular safety concerns.

(d) Treatment of multiple lesions with 1 session of cryotherapy

- "Literature report on cryotherapy in the treatment of TSC-AML" described the experience of simultaneous cryotherapy of 2 neighboring tumor lesions in 3 patients with TSC-AML (including 1 patient with lesions in both kidneys). All of the treated tumors shrank in size, without a substantial change in serum creatinine or eGFR, showing that renal function was maintained well. Another "Literature report on cryotherapy in the treatment of TSC-AML"[10] described the experience of simultaneous cryotherapy of 3 lesions (size of 4.5, 2.5, and 1.5 cm), which was performed because it was technically feasible. All of the treated tumors shrank in size. Creatinine was 0.6 mg/dL peri-procedural and 0.8 mg/dL post-procedural, showing that renal function was maintained well.
- "Literature report on microwave ablation in the treatment of TSC-AML"[5] included the experience of ablation in 2 lesions in 1 patient. Both tumors shrank in size, without any serious peri-procedural complications or adverse events.

- "Literature report on laparoscopic partial nephrectomy (LPN) and laparoscopic cryotherapy (LCA) in the treatment of multiple unilateral renal tumors"[11] showed that the LCA group tended to have a smaller amount of bleeding and shorter admission period than the LPN group. Both groups had similar intermediate-term cancer-specific survival rates, as well as a similar incidence of complications and post-procedural changes in renal function.
- "Literature report on laparoscopic partial nephrectomy and cryotherapy in the treatment of synchronous multiple unilateral renal tumors"[12] showed that the group that received cryotherapy for all tumor lesions experienced neither tumor recurrence at the treatment sites nor peri-procedural or post-procedural complications.
- "Literature report on cryotherapy in the treatment of multiple renal lesions"[13] described the experience of cryotherapy of 2 lesions in 5 patients, 3 lesions in 1 patient, and 4 lesions in 1 patient. The mean lesion size was 2.0 cm. The mean serum creatinine was 1.5 mg/dL pre-procedural and 1.7 mg/dL post-procedural. Follow-up showed no tumor recurrence, minimum complications, and rare short-term loss of renal function.
- "Literature report on cryotherapy in the treatment of bilateral multiple renal cell carcinoma"[14] showed that 3 of 5 tumors were completely frozen, without significant complications, and that renal function was maintained.

(e) Repeat cryotherapy in patients with prior cryotherapy

- "Literature report on cryotherapy in the treatment of local recurrent renal cell carcinoma"[15] described the experience of repeat cryotherapy in 20 patients, with successful outcomes of all surgeries. Neither complications nor deaths were reported. Three patients experienced local recurrence again. One of them had a new tumor 13 months later, underwent the third cryotherapy, and experienced no recurrence during the 26-month follow-up period.
- "Literature report on cryotherapy in the treatment of Von Hippel-Lindau (VHL)"[16] described the experience of cryotherapy of 5 lesions in 4 patients. No recurrence was observed during the follow-up period. Two patients underwent the treatment again for remaining tumors, without any significant complications. One patient underwent cryotherapy for 2 tumors every 3 months. In any case, BUN and creatinine values were stable, showing no significant effect on renal function.
- "Literature report on cryotherapy in the treatment of bilateral multiple renal cell carcinoma"[14] described the experience of a 35-year-old female patient with VHL having 2 tumors in the left kidney and 3 tumors in the right kidney. The patient received the first cryotherapy for 2 tumors in the left kidney and was discharged from hospital 2 days after the procedure. Six weeks later, the patient received the second cryotherapy for 3 tumors in the right kidney and was discharged from hospital 2 days after the procedure. No significant peri-procedural or post-procedural complications were observed. The renal function was maintained.

6.B Outline of the review conducted by PMDA

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

(1) Justification for not conducting a new clinical study and instead including the Cryo-tsc-study as the confirmatory study in the present application of the Visual-ICE

(2) Efficacy and safety of the Visual-ICE

(3) Clinical positioning and intended use
(4) Directions for use of the Visual-ICE approved under pharmaceutical regulations
(5) Post-marketing safety measures of the Visual-ICE

6.B.(1) Justification of not conducting a new clinical study and instead including the Cryo-tsc-study as the confirmatory study in the present application of the Visual-ICE

The Cryo-tsc-study was a multi-center, single-arm, open-label study, designated as Advanced Medical Care B clinical research, was initiated in October 2020. Treatment and follow-up of 15 subjects, i.e., the planned sample size, were completed by June 2022.

The applicant' explanation about the justification for not conducting a new clinical study and submitting the present application based on the results of this Advanced Medical Care B study:

- This study complies with the Clinical Trials Act and provides reliable data equivalent to those collected in clinical studies.
- TSC is designated as an intractable disease (158) under the Act on Medical Care for Patients with Intractable Diseases. Approximately 1,269 to 3,806 patients with TSC-AML are estimated to be possibly treated with the Visual-ICE therapy.[18)19)] This small patient population makes it difficult to conduct a new clinical study.
- The Visual-ICE is a medical device with particularly high medical necessity and is designated as an orphan medical device ("Designation of orphan medical devices [in Japanese]" [PSB/MDED Notification No. 0327-1 dated March 27, 2024]).
- In Japan, the Visual-ICE is approved for cryotherapy of small renal malignancies with established safety of renal tissue. In the expanded indication, the needle is punctured into a target tumor to freeze it. The basic mechanism of action and directions for use of the Visual-ICE are the same for the new and approved indications.

PMDA's view:

Clinical evaluation required for application for approval under the pharmaceutical regulations should be based on the results of "clinical studies," as stipulated under the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices, that have been conducted according to predefined protocols, in principle. For the following reasons, however, the present application requires no new standard therapy-controlled confirmation study. The study results submitted in the present application can be used for clinical evaluation required under the regulations.

- As described later in "III. Results of Compliance Assessment Concerning the New Medical Device Application Data and Conclusion Reached by PMDA," Good Clinical Practice (GCP) inspection confirmed that data collection in the Cryo-tsc-study fully complied with the standards stipulated in the GCP of medical devices or ISO14155 (Clinical investigation of medical devices for human subjects - Good clinical practice).
- The Visual-ICE therapy is intended to treat tuberous sclerosis complex-angiomyolipoma that is ineligible for or refractory to standard therapy. Considering that no conventional treatment with a similar clinical positioning is available, the data from this study, although it was a single-arm study, are sufficient for clinical evaluation of the therapy to a certain degree.

- The Visual-ICE is designated as an orphan medical device. There is a strong need for its early introduction to clinical practice. The number of patients with TSC-AML eligible for the Visual-ICE therapy is limited, which makes it difficult to conduct a new confirmatory clinical study. Taking these situations into consideration, the present application for early introduction of the Visual-ice into clinical practice in Japan is acceptable provided that a regulatory review is conducted based on the appropriate existing data and adequate post-marketing measures are in place.

6.B.(2) Efficacy and safety of the Visual-ICE

6.B.(2).1) Validity of extrapolating the clinical study data of the previous-generation product into the Visual-ICE

PMDA asked the applicant to explain the justification of extrapolating the clinical study data of the previous-generation product (Cryosurgical Unit CryoHit), which has the same basic mechanism of action and directions for use as those of the Visual-ICE, into the Visual-ICE.

The applicant's explanation:

The key differences between the Visual-ICE and the previous-generation product lie in the needle (3 types of needles with different shaft lengths and vacuum structure available for the Visual-ICE) and the compatibility with diagnostic imaging modalities. The shaft length is the distance from the heat exchanger to the handle. The different shaft lengths are available with the Visual-ICE to improve convenience for operators. The vacuum structure of the Visual-ICE is intended to ease a temperature drop around the shaft to reduce the risk of frostbite at the needle puncture site. None of these features are likely to affect the area of freezing. The area of freezing with the Needle S-Plain type of the Visual-ICE is slightly smaller than that of the previous-generation product. However, both have the same directions for use in that the freezing area is monitored under diagnostic imaging guidance during freezing sessions. The difference is not clinically significant. In the Cryo-tsc-study, cryotherapy was performed under X-ray CT guidance, which can be used with the Visual-ICE and the previous-generation product. There is no particular problem in extrapolating the results with the previous-generation product into the Visual-ICE.

PMDA's view, taking account of the applicant's explanations:

The Visual-ICE and the previous-generation product (Cryosurgical Unit CryoHit) have the same basic mechanism of action and directions for use. Their differences lie in the needle and the compatibility with diagnostic imaging modalities. The results of the non-clinical studies submitted for the initial approval have demonstrated the equivalence of the area of freezing with the needles of the Visual-ICE and the previous-generation product. The difference in the needles appears not to affect clinical efficacy and safety substantially. In the Cryo-tsc-study, cryotherapy was performed under X-ray CT guidance, which can be used with the Visual-ICE and the previous-generation product. The Visual-ICE could be evaluated based on the results of the clinical study submitted in the present application.

6.B.(2).2) Efficacy

TSC-AMLs grow relatively quickly. Since tumor growth is associated with risks of haemorrhage and decreased kidney function, not only tumor shrinkage but also growth suppression has clinical significance. Accordingly, the primary efficacy endpoint "DCR of AML at 9 months after cryotherapy"

was selected for the Cryo-tsc-study. The primary endpoint was 100% (95% CI [78.2%, 100.0%]). The sign test of the null hypothesis that DCR of 0.5 was statistically significant. The Cryo-tsc-study, although it was a single-arm study, achieved the primary endpoint. A secondary endpoint of ORR was 93.3% (95% CI [68.1%, 99.8%]). The sign test of the null hypothesis that ORR of 0.5 was also statistically significant. PMDA concluded that the results demonstrated the efficacy of Visual-ICE.

6.B.(2).3) Safety

Since the Cryo-tsc-study showed a significant increase in serum creatinine and a decrease in eGFR at 9 months, PMDA asked the applicant to explain the risk of decreased kidney function associated with the Visual-ICE therapy.

The applicant's explanation:

The median change in serum creatinine was +0.06 mg/dL at 9 months. The eGFR grade increased by 1 level in 3 of 15 subjects (20%). The median change in eGFR was −5.0 mL/min/1.73 m^2. The literature report on cryotherapy in the treatment of renal tumors demonstrated that the change in serum creatinine in 30 patients treated with cryotherapy was 0.2 ± 0.3 mg/dL at 3 months.[20] The literature report on cryotherapy in 95 patients with renal tumors demonstrated that the grade increased by 1 level or more in 19.0% to 25.9% of the patients at or after Month 6.[21] A systematic review on cryotherapy in the treatment of renal tumors demonstrated that a post-procedural change in eGFR ranged from −7 to −23.6 mL/min/1.73 m^2.[22] The level of decreased kidney function after cryotherapy in the study is within the clinically acceptable range.

PMDA's view, taking account of the applicant's explanations:

Decreased kidney function observed in the Cryo-tsc-study was also reported in cryotherapy of renal tumors. It is not a new risk potentially associated with the expanded indication. The Cryo-tsc-study showed no particular safety issues other than renal function. Neither serious adverse events nor deaths were reported. The safety results of the study are clinically acceptable. Although there are some concerns about performing the Visual-ICE therapy in patients with renal impairment due to chronic kidney disease, etc., the package insert of the Visual-ICE includes a cautionary statement that the therapy should be carefully indicated for patients with renal impairment. In addition, guidelines for proper use have been created mainly by the Japanese Urological Association. The safety measures taken by the applicant are appropriate.

On the basis of the discussion in Sections 6.B.(2).2) and 6.B.(2).3) above, PMDA concluded that the Cryo-tsc-study, although it was a single-arm study, suggested the efficacy and safety of the Visual-ICE in patients with TSC-AML. The Visual-ICE therapy is indicated for patients who are ineligible for or refractory to standard therapy. Since there is a strong clinical need for new treatment options available to this patient population, PMDA concluded that the Visual-ICE is useful.

6.B.(3) Clinical positioning and intended use of the Visual-ICE

The standard therapies of TSC-AML in Japan recommended in the Japanese guidelines are arterial embolization, surgery (partial nephrectomy and nephrectomy), and mTOR inhibitors. In clinical practice, TSC-AMLs of ≤4 cm in longest diameter that are ineligible for or refractory to the standard therapy and

are not accompanied by TSC symptoms in any organ are typically just observed without intervention because of the invasiveness of surgical therapy, adverse drug reactions to mTOR inhibitors, etc. Accordingly, the study enrolled "patients with TSC-AML measuring ≥1 and ≤4 cm in longest diameter, regardless of whether patients were taking oral mTOR inhibitors."

However, a certain number of patients with small TSC-AMLs that are ineligible for or refractory to standard therapy require some therapeutic intervention because of potential tumor haemorrhage or rupture. The Japanese guidelines state that "cryotherapy is a minimally invasive and repeatable therapy, and has the least impact on renal function" in general. In addition, a report describes as follows: Although cryotherapy has limited benefits in the treatment of diffuse TSC-AML measuring >4 cm in tumor diameter, this therapy is possibly minimally invasive in small, localized tumors compared with arterial embolization and surgery (partial nephrectomy and nephrectomy).[17] The Visual-ICE therapy has the potential to suppress the progression of small tumors in a minimally invasive manner.

PMDA's view on the clinical positioning of the Visual-ICE:
No results of a direct comparison between cryotherapy with the Visual-ICE and standard therapy in the treatment of TSC-AML are available. Since the efficacy and safety of the Visual-ICE therapy in comparison with the standard therapy is unknown, the Visual-ICE therapy should not be the first-line option replacing the current standard therapy. In clinical practice, however, a certain number of patients require the Visual-ICE therapy. In addition, the Visual-ICE is designated as an orphan medical device and there is a strong clinical need for its early introduction to clinical practice. Taken all together and on the basis of the discussion in Section "6.B.(2) Efficacy and safety of the Visual-ICE," the Visual-ICE can be introduced to clinical practice in Japan as a treatment option provided that the Visual-ICE therapy is carefully performed only in eligible patients in accordance with the guidelines for proper use created by related academic societies.

The package insert includes the cautionary statement that the Visual-ICE is indicated for tumors of 1 to 4 cm in diameter. In addition, it provides the information on the area of freezing based on the results of non-clinical studies. For these reasons, tumor size does not need to be described in the intended use. The intended use should be "Tuberous sclerosis complex-angiomyolipoma that is ineligible for or refractory to standard therapy."

6.B.(4) Directions for use of the Visual-ICE approved under pharmaceutical regulations

The Cryo-tsc-study included no patients who had multiple lesions treated with the Visual-ICE or those who underwent the Visual-ICE therapy more than once. Taking account of comments from the Expert Discussion and for the following reasons, however, PMDA concluded that no particular restrictions on use (e.g., Contraindications of the package insert) needed to be included in the directions for use:

- TSC-AML, which is a genetic disease, develops in early ages. Patients may have AMLs one after another with aging or have many AMLs at once. Since patients require treatment of multiple lesions or repeat treatment, there is a strong need for a minimally invasive and repeatable therapy in clinical practice.

- TSC-AML has different disease characteristics from those of small renal malignancy, which was the initial-approved indication. For both indications, however, the target organs and basic directions for use are the same. Consequently, there appears to be no significant procedural safety concern.
- No literature reports showed serious complications or adverse events after cryotherapy of multiple lesions (2-4 per session) or repeat cryotherapy in patients with TSC-AML or small renal malignancies, indicating no particular major concerns about cryotherapy of multiple lesions or repeat cryotherapy.
- The package insert includes cautionary information that the Cryo-tsc-study did not evaluate the efficacy and safety of cryotherapy of multiple lesions or repeat cryotherapy. As described later in Section 6.B.(5).1), guidelines for proper use created mainly by the Japanese Urological Association also include precautions, etc. about cryotherapy of multiple lesions or repeat cryotherapy. These measures can assure procedural safety in clinical practice. The applicant's measures are appropriate.

6.B.(5) Post-marketing safety measures of the Visual-ICE

6.B.(5).1) Guidelines for proper use

Certain criteria need to be established for the expanded indication of the Visual-ICE to ensure its proper use. To this end, guidelines for proper use are being prepared in cooperation with 4 academic societies, the Japanese Urological Association, the Japanese Society of Endourology and Robotics, the Japanese Society of Interventional Radiology, and the Japanese Society of Tuberous Sclerosis Complex. The purpose of the guidelines is to define criteria and supplementary items regarding selection of eligible patients, procedural skills of treating physicians, and medical institutions that can appropriately manage emergencies or adverse events potentially occurring during treatment. To standardize the Visual-ICE therapy, training sessions are also planned for physicians certified by the Japanese Society of Interventional Radiology and urologists who treat patients with the Visual-ICE.

Table. Summary of guidelines for proper use (draft)

Guidelines for proper use of cryotherapy of TSC-AML (draft)

- Background of the guidelines for proper use

Cryotherapy has already been covered by public health insurance for the treatment of small renal cancer. Cryotherapy is now also available for the treatment of tuberous sclerosis complex (TSC)-angiomyolipoma (TSC-AML). For one reason behind this new option, repeat surgery, etc. to treat AMLs, which develop one after another in patients with TSC-AML as they age, is technically challenging and not realistic. Everolimus, which is an mTOR inhibitor, demonstrated to shrink TSC-AML, is also available. However, discontinuing everolimus leads to tumor regrowth, while continuous administration of everolimus affects the growth of young patients, pregnancy, etc.

Cryotherapy has promising efficacy and safety in the treatment of TSC-AML. To maximize the efficacy and safety of cryotherapy, certain criteria are required. Given this, 4 academic societies relevant to this therapy (the Japanese Urological Association, the Japanese Society of Endourology and Robotics, the Japanese Society of Interventional Radiology [IVR], and the Japanese Society of Tuberous Sclerosis Complex) have decided to establish guidelines for proper use of cryotherapy for TSC-AML.

- Intended use
  - Growth suppression of tuberous sclerosis complex-angiomyolipoma
  - Long-term renal function maintenance and haemorrhage prophylaxis

- Criteria for patient selection

Eligibility criteria
- Patients with a confirmed diagnosis of tuberous sclerosis complex
- Patients must have a lesion of ≥10 mm and ≤40 mm in long diameter.

Exclusion criteria
- Pregnant women or women who may possibly be pregnant

- Patients who are unable to maintain rest or receive general anesthesia for treatment
- Patients with uncontrolled epileptic attacks
- Patients with blood clotting abnormality (platelet count <50000/mm^3).

● Qualification for medical institutions
- Eligible departments: Urology or radiology
- Number of physicians per department: At least 2 full-time physicians
- Medical institutions must have an appropriate follow-up system,
- have an appropriate treatment system for emergencies, and
- have a coordinated medical care system for the treatment of tuberous sclerosis complex.

● Qualification for treating physicians
- The therapy must be performed by specialists certified by the Japanese Society of IVR and urologists who have adequate specialized knowledge and experience in diagnostic imaging and percutaneous cryotherapy required for the treatment of tuberous sclerosis complex. Treating physicians must take training sessions for percutaneous cryotherapy held by the Japanese Society of IVR.

● Supplementary items
- The frozen needle must be punctured under imaging guidance to monitor the target area of treatment in images. Members of multidisciplinary conferences who assess patient's eligibility for the therapy must include radiodiagnostic specialists certified by the Japan Radiological Society and medical specialists certified by the Japanese Society of IVR.
- Localized tumors: In the treatment of tumors adjacent to renal hilus, it is essential to use adequate image monitoring during cryotherapy to prevent damage to the vascular structure, renal pelvis, and ureter.
- When both kidneys have lesions, cryotherapy should, in principle, be performed on 1 kidney at a time.
- When multiple lesions exist, it is recommended that approximately 3 lesions of 30 mm in diameter be treated per session.
- Patients with and without prior treatment with everolimus are eligible for the therapy.
- Repeat treatment: In the case of inadequate response to the frozen tumor, repeat treatment is permitted. As this disease is benign, the appropriate treatment interval is 6 months or more. For patients with many tumors requiring treatment multiple times, the treatment interval must be fully discussed at a multidisciplinary conference.
- The applicant must cooperate in follow-up investigation conducted by academic societies, etc.

Since cryotherapy with the Visual-ICE for the treatment of TSC-AML must be carefully indicated to eligible patients appropriately selected by physicians, it is necessary for the applicant to work with the related academic societies in preparing guidelines for proper use that include criteria for patient selection and medical institutions, and requirement for treating physicians, as well as to provide training for physicians. PMDA concluded that this applicant's policy is appropriate. To mandate compliance with the guidelines for proper use, this should also be attached as an approval condition for this expanded indication.

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

For the following reasons, the applicant explained that no use-results survey was necessary because there were no concerns that needed to be investigated through a use-results survey:

● The Cryo-tsc-study confirmed the efficacy and safety of the Visual-ICE in Japanese subjects although their number was limited. The literature reports on clinical research of other cryotherapy and similar medical devices showed no data that contradicted the results of the Cryo-tsc-study. There is no issue that should be investigated in the post-marketing setting.

- To ensure the same procedural quality as that in the study, training for treating physicians will be provided. In addition, related academic societies have planned to establish requirements for physicians and medical institutions.
- Further information will be collected in the post-marketing setting in cooperation with a related academic society, the Japanese Society of Tuberous Sclerosis Complex, so as to revise the Information on Precautions, etc., the guidelines for proper use, and other guidelines as necessary, and to provide relevant information to healthcare professionals.

7.B Outline of the review conducted by PMDA

PMDA' view on the safety of the Visual-ICE, in addition to the applicant's explanations:

There are no significant concerns about the post-marketing procedural safety of the Visual-ICE because the target organ (kidneys) to be punctured with the needle and the procedures for needle puncture are the same in the Visual-ICE therapy and treatment of small renal malignancies, which has already been widely performed. The literature reports indicated no substantial difference in the renal safety of cryotherapy between TSC-AML and small renal malignancies. The Cryo-tsc-study also suggests no particular safety concerns about the Visual-ICE therapy. In addition, the planned post-marketing safety measures proposed by the applicant include training for treating physicians and preparation of the guidelines for proper use in cooperation with the related academic societies. These measures ensure selection of eligible patients and technical requirement. Since no new safety concerns are likely to arise in the post-marketing setting, no use-results survey was required. The applicant has planned to collect information regularly in compliance with the Ministerial Ordinance on Good Vigilance Practice (GVP), as well as collect post-marketing information in cooperation with the related academic societies.

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

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

The medical device application data (6-1-2 Periodic/clinical study report of advanced medical care*) 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 the on-site GCP inspection

The medical device application data (6-1-2 Periodic/clinical study report of advanced medical care*) were subjected to an on-site GCP inspection, 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, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

* Data to be subjected to this inspection and assessment are based on the clinical research conducted in compliance with the following; "Declaration of Helsinki (2013)," "Points to Consider in the Implementation of Advanced Medical Care and Institutional Standards Specified by the Minister of

Health, Labour, and Welfare, and the Handling of Notifications Related to Advanced Medical Care (in Japanese) (MHLW/HPB Notification No. 0304-2, MHLW/PSEHB Notification No. 0304-2, MHLW/HIB Notification No. 0304-16 dated March 4, 2016, including subsequent revisions)," "Act on the Protection of Personal Information (Act No. 57, 2003)," "Clinical Trials Act (Act No. 16, 2017), and "Ministerial Ordinance for Enforcement of the Clinical Trials Act (MHLW Ordinance No. 17, 2018)."

IV. Overall Evaluation

The present partial change application is an application for partial change intended to expand the indication of the Visual-ICE to TSC-AML. The review of the Visual-ICE focused primarily on (1) the justification for not conducting a new clinical study and instead including the Cryo-tsc-study as the confirmatory study in the present application, (2) the efficacy and safety of the Visual-ICE, (3) the clinical positioning of the Visual-ICE, (4) post-marketing safety measures for the Visual-ICE, and (5) the necessity of use-results survey. PMDA has reached the following conclusions, taking account of discussion at the Expert Discussion.

(1) Justification for not conducting a new clinical study and instead including the Cryo-tsc-study as the confirmatory study in the present application

Clinical evaluation required for application for approval under the pharmaceutical regulations should be based on the results of clinical studies, etc. that have been conducted according to their predefined protocols, in principle. The clinical study submitted in the present application was conducted as an Advanced Medical Care B Study. The study has been shown to meet the standards of the Medical Device GCP or ISO14155 (Clinical investigation of medical devices for human subjects - Good clinical practice).

The Visual-ICE is designated as an orphan medical device. There is a strong need for its early introduction to clinical practice. However, the number of patients with TSC-AML eligible for the Visual-ICE therapy is limited. This makes it difficult to conduct a new confirmatory clinical study. For these reasons, PMDA concluded that it was acceptable to use the existing data, including the results of the above clinical study submitted, in clinical evaluation of the Visual-ICE.

(2) Efficacy and safety of the Visual-ICE

The efficacy of the Visual-ICE was evaluated in 15 subjects using the primary endpoint "DCR of AML at 9 months after cryotherapy." The primary endpoint was 100% (95% CI [78.2%, 100.0%]). The sign test of the null hypothesis that DCR of 0.5 was statistically significant and the primary endpoint was achieved. A secondary endpoint of ORR was 93.3% (95% CI [68.1%, 99.8%]). The sign test of the null hypothesis that ORR of 0.5 was also statistically significant. Although the sample size was limited, the results showed a certain degree of efficacy of Visual-ICE. PMDA concluded that the Visual-ICE demonstrated efficacy as a treatment option for TSC-AML in Japan.

In the study, the following Grade ≥3 adverse events occurred in 3 of 15 subjects (20%): AST increased, haematuria, and chronic kidney disease. Of them, AST increased and haematuria were naturally resolving without intervention. Chronic kidney disease occurred in a subject with decreased kidney function at baseline. The package insert of the Visual-ICE includes a cautionary statement that the

therapy is carefully indicated for patients with renal impairment as a risk reduction measure. The study showed no particular safety risk other than renal function. Neither adverse events leading to death nor serious adverse events were reported. Since remaining risks of the adverse events, malfunctions, etc. reported in the study are clinically acceptable, PMDA concluded that the safety of the Visual-ICE was also acceptable.

(3) Clinical positioning of the Visual-ICE

The cryotherapy with the Visual-ICE should not be the first-line option for the treatment of TSC-AML replacing the current standard therapy. In clinical practice, however, a certain number of patients who have small tumors that are ineligible for or refractory to standard therapy or those who are at high risk of tumor haemorrhage or rupture require the Visual-ICE therapy. Since the Visual-ICE is designated as an orphan medical device and there is a strong clinical need for its early introduction to clinical practice, PMDA concluded that the Visual-ICE could be introduced to clinical practice as a treatment option for TSC-AML provided that the Visual-ICE therapy is carefully performed only in eligible patients in accordance with the guidelines for proper use created by the related academic societies.

(4) Post-marketing safety measures of the Visual-ICE

Cryotherapy with the Visual-ICE for the treatment of TSC-AML must be carefully performed in appropriately selected eligible patients to ensure that the Visual-ICE is adequately used in clinical practice. The Visual-ICE therapy must also be performed at medical institutions that can appropriately manage emergencies or adverse events potentially occurring during treatment. If treating physicians do not adequately understand the characteristics or directions for use of the Visual-ICE, or have no adequate knowledge about the treatment protocol, the Visual-ICE may not be used properly, which may lead to the onset of adverse events such as decreased kidney function.

In order to ensure the proper use of the Visual-ICE, some post-marketing safety measures need to be taken. PMDA concluded that the applicant was required to work with the related academic societies in creating guidelines for proper use that include criteria for patient selection and requirements of treating physicians and medical institutions, as well as to provide training for treating physicians. To mandate compliance with the guidelines for proper use, this should be attached as an approval condition for this expanded indication.

(5) Necessity of use-results survey

There appear to be no significant concerns about the procedural safety of the Visual-ICE because the target organ (kidneys) to be punctured with the needle and the procedures for needle puncture are the same in the Visual-ICE therapy and treatment of small renal malignancies, which has already been widely performed. The safety of cryotherapy is not expected to differ substantially between small renal malignancies and TSC-AML, which is the expanded indication proposed in the present application. The literature reports on cryotherapy in the treatment of TSC-AML or the Cryo-tsc-study suggests no particular safety concerns specific to the Visual-ICE therapy. In addition, the planned post-marketing safety measures proposed by the applicant include training for treating physicians and preparation of the guidelines for proper use in cooperation with the related academic societies. These measures ensure

selection of eligible patients and technical requirements. Since no new safety concerns are likely to arise in the post-marketing setting, PMDA concluded that no use-results survey was required.

The applicant has planned to collect information regularly in compliance with the Ministerial Ordinance on GVP, as well as collect post-marketing information on treatment outcomes using a registry in cooperation with the related academic societies.

As a result of its review, PMDA has concluded that the Visual-ICE may be approved for the intended use shown below, with the following approval conditions. The underline denotes the intended use and approval condition added in the present application.

Intended Use
The Visual-ICE Cryoablation System is a cryosurgical unit that freezes and necrotizes biological tissues.

It is indicated for small renal malignancies and liver tumors.

It is also used for the treatment (including palliative intervention) of the following tumors that are ineligible for or refractory to standard therapy:
- Pulmonary malignant tumors
- Malignant bone tumors
- Osteoid osteoma
- Intrapelvic malignant tumors
- Soft tissue tumors that developed in the extremities, thoracic cavity, and abdominal cavity
- Tuberous sclerosis complex-angiomyolipoma

Approval Conditions
The applicant is required to take necessary measures such as (i) disseminating the guidelines for proper use prepared in cooperation with related academic societies and (ii) providing training sessions, to ensure that the product will be used by physicians with adequate knowledge and experience in cryosurgical therapy who have acquired sufficient skills for using the product and adequate knowledge of possible complications associated with the procedure at medical institutions with a well-established system for the treatment.

The product is not classified as a biological product or a specified biological product.

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

References

[1] Clinical Practice Guidelines for tuberous sclerosis complex-associated renal angiomyolipoma 2023

[2] Shepherd, Charles W, Gomez, et al. Causes of death in patients with tuberous sclerosis. *Mayo Clin Proc.* 1991;66:792-796.

[3] Bissler JJ, McCormack FX, Young LR, et al. Sirolimus for angiomyolipoma in tuberous sclerosis complex or lymphangioleiomyomatosis. *N Engl J Med.* 2008;358:140-151.

[4] Karina Trelborg, Tommy Kjærgaard Nielsen, Ernst Øyvind Østraat, et al. Laparoscopic cryoablation of adults: A report of four cases associated with tuberous sclerosis and 1 case of sporadic origin. *J Pediatr Urol*. 2016 Dec;12(6):384.e1-384.e6.

[5] Anna Maria Ierardi, Mario Petrillo, Andrea Coppola, et al. Percutaneous microwave ablation of renal angiomyolipomas in tuberous sclerosis complex to improve the quality of life: preliminary experience in an Italian center. *Radiol Med.* 2019 Mar;124(3):176-183.

[6] S M Gregory, C J Anderson, U Patel. Radiofrequency ablation of large renal angiomyolipoma: median-term follow-up. *Endosc Int Open. Cardiovasc Intervent Radiol*. 2013 Jun;36(3):682-9.

[7] Garnon J, Van Strijen MJ, Nielsen TK, et al. Safety of percutaneous renal cryoablation: an international multicentre experience from the EuRECA retrospective percutaneous database. *Eur Radiol.* 2019;29(2):660-671.

[8] Duus LA, Junker T, Rasmussen BS, et al. Safety, efficacy, and mid-term oncological outcomes of computed tomography-guided cryoablation of T1 renal cancer. *Acta Radiol.* 2023;64(2):814-820.

[9] Raja J, Pigg R, Li Y, et al. Percutaneous cryoablation of 100 anterior renal tumors: safety and technical success. *Abdom Radiol (NY).* 2024;49(3):919-926.

[10] Gregory F. Byrd, Eric J. Lawatsch, Hrair-George Mesrobian, et al. Laparoscopic cryoablation of renal angiomyolipoma. *J Urol.* 2006 Oct;176(4 Pt 1):1512-6; discussion 1516.

[11] Yi-Chia Lin, Burak Turna, Rodrigo Frota, et al. Laparoscopic Partial Nephrectomy versus Laparoscopic Cryoablation for Multiple Ipsilateral Renal Tumors. *European Urology*. 2008;53:1210-1218.

[12] Andrew P. Steinberg, Mete Kilciler, Sidney C. Abreu, et al. Laparoscopic Nephron-Sparing Surgery for Two or More Ipsilateral Renal Tumors. *UROLOGY*. 2004;Volume 64, Issue 2:255-258.

[13] Guarionex Joel DeCastro, Mantu Gupta, Ketan Badani, et al. Synchronous Cryoablation of Multiple Renal Lesions: Short-term Follow-up of Patient Outcomes. *UROLOGY*. 2010;75:303-306.

[14] Yoshihisa Kodama, Daisuke Abo, Yusuke Sakuhara, et al. MR-guided Percutaneous Cryoablation for Bilateral Multiple Renal Cell Carcinomas. *Radiation Medicine*. 2005;Vol. 23 No. 4:303-307.

[15] Zhamshid Okhunov, Joshua Chamberlin, Daniel M. Moreira, et al. Salvage Percutaneous Cryoablation for Locally Recurrent Renal-Cell Carcinoma After Primary Cryoablation. *Journal of Endourology*. June 2016:Volume 30, Number 6.

[16] W. Bruce Shingleton, Patrick E. Sewell, Jr. Percutaneous Renal Cryoablation of Renal Tumors in Patients with Von Hippel-Lindau Disease. *The Journal of Urology*. March 2002;Vol. 167:1268-1270.

[17] Fernandez-Pello S, Hora M, Kuusk T, et al. Management of sporadic renal angiomyolipomas: A systematic review of available evidence to guide recommendations from European association of urology renal cell carcinoma guidelines panel. *Eur Urol Oncol.* 2020;3:57-72.

[18] Japan Intractable Diseases Information Center, Intractable disease 158 Tuberous sclerosis complex

[19] Wataya-Kaneda M, Tanaka M, Hamasaki T et al. Trends in the Prevalence of Tuberous Sclerosis Complex Manifestations: An Epidemiological Study of 166 Japanese Patients: an epidemiological study of 166 Japanese Patients. *PLOS ONE*. 2013;e63910.

[20] Georges-Pascal Haber, Michael C. Lee, Sebastien Crouzet,et al. Tumor in Solitary Kidney: Laparoscopic Partial Nephrectomy vs Laparoscopic Cryoablation. *BJU International*. 2012;Vol 110 (1).

[21] Buy Xavier, Hervé Lang, Julien Garnon, et al. Percutaneous renal cryoablation: prospective experience treating 120 consecutive tumors. *American Journal of Roentgenology*. 2013;201.6:1353-1361.
[22] Deng Wen, Luyao Chen, Yibing Wang,et al. Cryoablation versus partial nephrectomy for clinical stage T1 Frenal masses: a systematic review and meta-analysis. *Journal of Cancer*. 2019;10.5:122.