December 6, 2023
Medical Device Evaluation Division
Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

Report on the Deliberation Results

Classification	Instrument & Apparatus 29, Electrosurgical Unit
Term Name	Percutaneous cardiac coagulation/ablation electrosurgical unit
Brand Name	TRUPULSE Generator
Applicant	Johnson & Johnson K.K.
Date of Application	February 1, 2023 (Application for marketing approval)

Results of Deliberation

In its meeting held on December 6, 2023, the Committee on Medical Devices and *In-vitro* Diagnostics reached the following conclusion, and decided that this conclusion should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

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

The use-results survey period should be 4 years. The following approval condition should be imposed.

Approval Condition

1. The applicant is required to take necessary actions such as; (i) disseminating information on the eligibility requirements for physicians who perform ablation and eligibility criteria for medical institutions prepared in cooperation with relevant academic societies; (ii) providing training workshops for physicians who have sufficient knowledge and experience in percutaneous catheter ablation for the treatment of arrhythmia including atrial fibrillation, so that the physicians would sufficiently acquire the required skills and adequate knowledge including procedural complications, etc. before using the product at medical institutions capable of providing appropriate medical care.

Review Report

November 13, 2023
Pharmaceuticals and Medical Devices Agency

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

Classification	1. Instrument & Apparatus 51, Suckers, Tubes and Catheters for Infusion or Drainage 2. Instrument & Apparatus 29, Electrosurgical Unit
Term Name	1. Catheter for cardiac ablation 2. Percutaneous cardiac coagulation/ablation electrosurgical unit
Brand Name	1. VARIPULSE Pulsed Field Ablation Catheter 2. TRUPULSE Generator
Applicant	Johnson & Johnson K.K.
Date of Application	February 1, 2023
Reviewing Office	Office of Medical Devices I

Review Results

November 13, 2023

Classification	1. Instrument & Apparatus 51, Suckers, Tubes and Catheters for Infusion or Drainage
	2. Instrument & Apparatus 29, Electrosurgical Unit
Term Name	1. Catheter for cardiac ablation
	2. Percutaneous cardiac coagulation/ablation electrosurgical unit
Brand Name	1. VARIPULSE Pulsed Field Ablation Catheter
	2. TRUPULSE Generator
Applicant	Johnson & Johnson K.K.
Date of Application	February 1, 2023

Results of Review

The VARIPULSE pulsed field ablation catheter (hereinafter referred to as "VARIPULSE Catheter") and TRUPULSE Generator are a pulsed field ablation (PFA) system intended to be used for the treatment of drug-refractory symptomatic paroxysmal atrial fibrillation (the VARIPULSE Catheter and TRUPULSE Generator are collectively referred to as the "VARIPULSE Platform"). PFA is an ablation method that applies short, high-voltage electric pulses to myocardial tissue, increasing cell membrane permeability of myocardial tissue, causing irreversible electroporation (IRE) of the membrane surface to induce cell death, thereby resulting in lesion formation.

The applicant submitted non-clinical data supporting physicochemical characterization, electrical safety and electromagnetic compatibility, biological safety, stability and durability, and performance; the data revealed no particular problem.

The applicant submitted clinical data from the interim analysis results of clinical studies conducted in Europe and Canada.

The primary efficacy endpoint is "freedom from documented symptomatic and asymptomatic atrial fibrillation, atrial tachycardia, or atrial flutter based on electrocardiogram (ECG) data (for ≥30 seconds using an arrhythmia monitoring device) during the efficacy assessment period (91-365 days postablation procedure)." The mean posterior distribution of freedom from recurrence at the time of interim analysis was 70.0% (two-sided 95% confidence interval [CI], 62.1%-77.4%).

The posterior probability of the freedom from recurrence exceeding the prespecified performance target of 50% was >99.9%, which is greater than the threshold of 99.75%, the early success criteria for the primary efficacy endpoint, demonstrating the efficacy of the VARIPULSE Platform.

The primary safety endpoint was the incidence of early-onset of primary adverse events (PAEs) within 7 days of initial mapping and ablation. No PAEs were reported before the interim analysis date. The mean posterior distribution for the incidence of PAEs at the interim analysis was 0.5% (a two-sided 95% CI, 0.0%-2.0%). The posterior probability of the PAE incidence being lower than the prespecified performance target of 14% was >99.9%, which exceeded the threshold of 97.5%, the early success criteria for the primary safety endpoint. Although the early success criteria were met, major safety issues in ablation such as cerebral embolism, oesophageal injury, atrio-oesophageal fistula, phrenic nerve paralysis, and pulmonary vein stenosis were investigated because the PFA is a novel technology of ablation. The results indicated that the VARIPULSE Platform has acceptable safety if necessary cautionary statements are provided and information is communicated to healthcare professionals.

The VARIPULSE Platform has different configuration and technology of ablation from those of approved radiofrequency ablation devices or balloon ablation devices. Therefore, it was concluded that the VARIPULSE Platform should be used at medical institutions capable of responding to various complications by physicians with sufficient experience in percutaneous ablation for the treatment of arrhythmia after participating in appropriate training workshops on the VARIPULSE Platform and appropriately understanding the involved risks. Because the VARIPULSE Platform is an ablation device based on a novel technology, and available clinical data are limited; it was concluded that a use-results survey should be conducted to collect safety and efficacy data in clinical use in Japan, and additional risk minimization measures should be taken as necessary.

On the basis of the results of review, PMDA has concluded that the VARIPULSE Platform may be approved for the following intended use with the approval condition below, and that the results should be presented to the Committee on Medical Devices and *In-vitro* Diagnostics for further deliberation.

Intended Use of VARIPULSE Catheter

The VARIPULSE Catheter is a multielectrode catheter intended to be used for pulsed field ablation and cardiac electrophysiologic examination for the treatment of drug-refractory symptomatic paroxysmal atrial fibrillation.

Intended Use of TRUPULSE Generator

The TRUPULSE Generator is a device that delivers pulsed field ablation energy for percutaneous myocardial catheter ablation in the treatment of tachyarrhythmia.

Approval Conditions

The applicant is required to take necessary actions such as; (i) disseminating information on the eligibility requirements for physicians who perform ablation and eligibility criteria for medical institutions prepared in cooperation with relevant academic societies; (ii) providing training workshops for physicians who have sufficient knowledge and experience in percutaneous catheter ablation for the treatment of arrhythmia including atrial fibrillation, so that the physicians would sufficiently acquire the required skills and adequate knowledge including procedural complications, etc. before using the product at medical institutions capable of providing appropriate medical care.

Review report

November 13, 2023

Product for Review	
Classification	1. Instrument & Apparatus 51, Suckers, Tubes and Catheters for Infusion or Drainage 2. Instrument & Apparatus 29, Electrosurgical Unit
Term Name	1. Catheter for cardiac ablation 2. Percutaneous cardiac coagulation/ablation electrosurgical unit
Brand Name	1. VARIPULSE Pulsed Field Ablation Catheter 2. TRUPULSE Generator
Applicant	Johnson & Johnson K.K.
Date of Application	February 1, 2023
Proposed Intended Use	1. The VARIPULSE Catheter is a multielectrode catheter intended to be used for pulsed field ablation and cardiac electrophysiologic examination for the treatment of drug-refractory symptomatic paroxysmal atrial fibrillation. 2. The TRUPULSE Generator is a device that delivers pulsed field ablation energy for percutaneous myocardial catheter ablation in the treatment of tachyarrhythmia.

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List of Abbreviations

AAD	antiarrhythmic drug
ACL	advanced catheter location
ACT	activated clotting time
BMI	body mass index
CT	computed tomography
ECG	electrocardiogram
FAS	full analysis set
HRS	Heart Rhythm Society
IEC	International Electrotechnical Commission
IRE	irreversible electroporation
ISO	International Organization for Standardization
mITT	modified intention-to-treat
MMSE	mini mental state examination
MRA	magnetic resonance angiography
MRI	magnetic resonance imaging
mRS	modified Rankin scale
NIH	National Institutes of Health
NIHSS	National Institutes of Health stroke scale
PAE	primary adverse events
PFA	pulsed field ablation
PP	per protocol
PT-INR	prothrombin time-international normalized ratio

I. Product Overview

The VARIPULSE pulsed field ablation catheter (hereinafter referred to as "VARIPULSE Catheter") and TRUPULSE Generator are a pulsed field ablation (PFA) system intended to be used for the treatment of drug-refractory symptomatic paroxysmal atrial fibrillation (the VARIPULSE Catheter and TRUPULSE Generator are collectively referred to as the "VARIPULSE Platform"). PFA is an ablation method that applies short, high-voltage electric pulses to myocardial tissue, increasing cell membrane permeability of myocardial tissue, causing IRE of the membrane surface to induce cell death, thereby resulting in lesion formation.

The VARIPULSE Catheter is a circular multielectrode catheter with an adjustable diameter ranging from approximately 25 to 35 mm to allow positioning of the catheter over various sizes of pulmonary vein ostia in each patient. The TRUPULSE Generator is a device that delivers a pulsed electric field to the VARIPULSE Catheter (Figure 1). After the sheath is inserted into the femoral vein, the VARIPULSE Catheter is introduced through the sheath to the left atrium. Ablation is performed by bringing the ring electrodes into contact with tissue in the pulmonary vein ostia. Then, the ring electrodes are moved to the pulmonary vein antrum to perform ablation (Figure 2). Before performing ablation, 6 to 10 adjacent ring electrodes are selected from the 10 ring electrodes located in the circular part of the VARIPULSE Catheter in which the pulsed electric field is applied. The TRUPULSE Generator delivers short, bipolar biphasic pulses in a configuration between alternate electrodes with an energy of 1760 V and between adjacent electrodes with an energy of 880 V (Figure 3 and Figure 4). Each ablation is composed of [redacted] as presented in Figure 4.

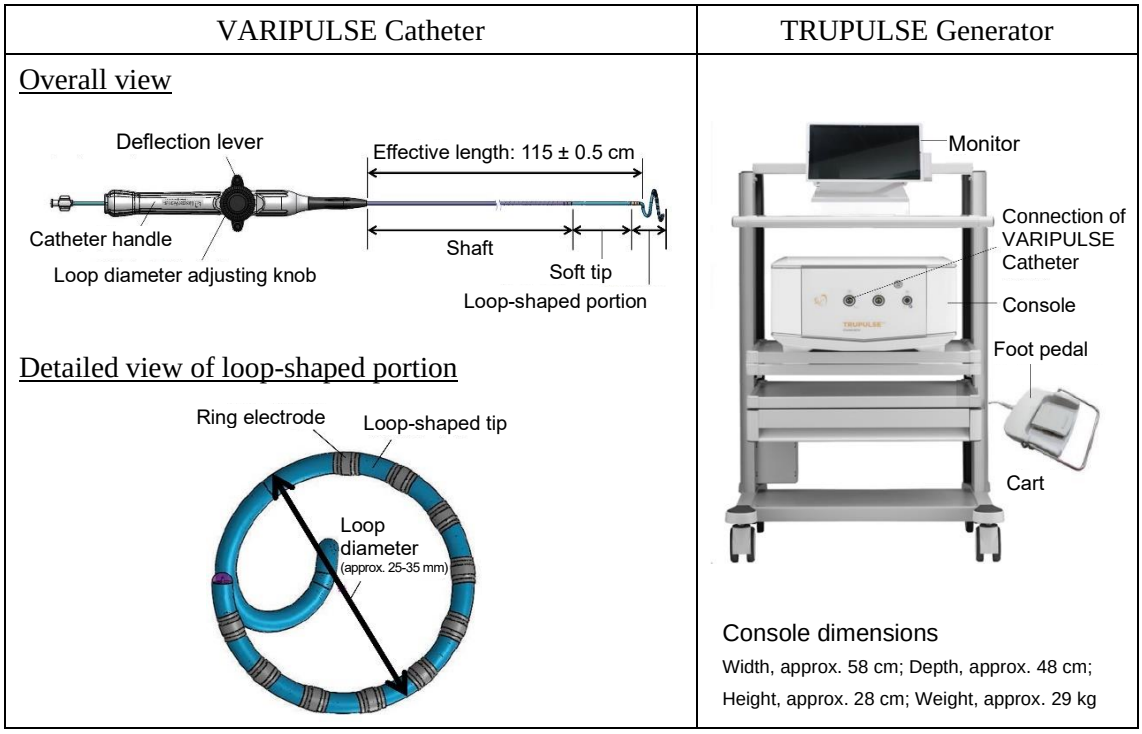

Figure 1. Appearance of VARIPULSE Platform

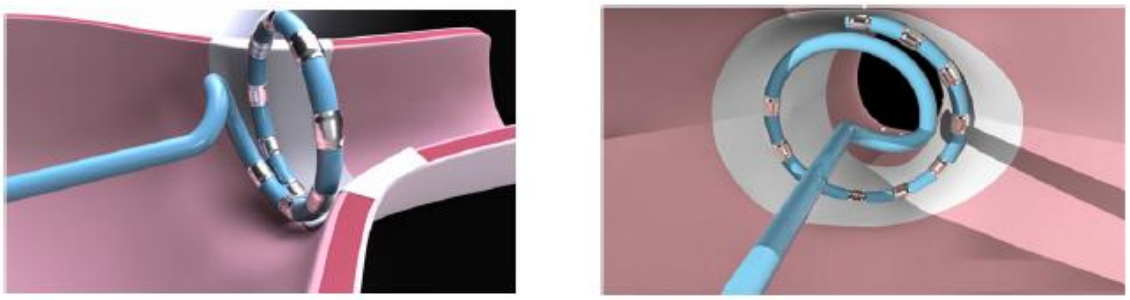

Figure 2. Schematic views of the VARIPULSE Catheter positioned at the pulmonary vein ostium (examples)

The catheter is positioned at the entrance of the pulmonary vein so that the ring electrodes achieve circumferential contact with the pulmonary vein wall (left); the catheter is positioned at the pulmonary vein antrum so that the ring electrodes achieve contact from the atrial side towards the pulmonary vein (right)

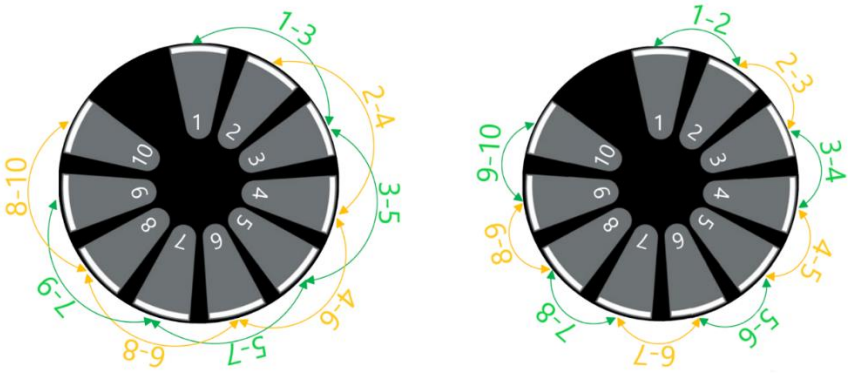

Figure 3. Selectable electrode pairs

Electrode pairs between skipped electrodes (left); electrode pairs between each of the adjacent electrodes (right)

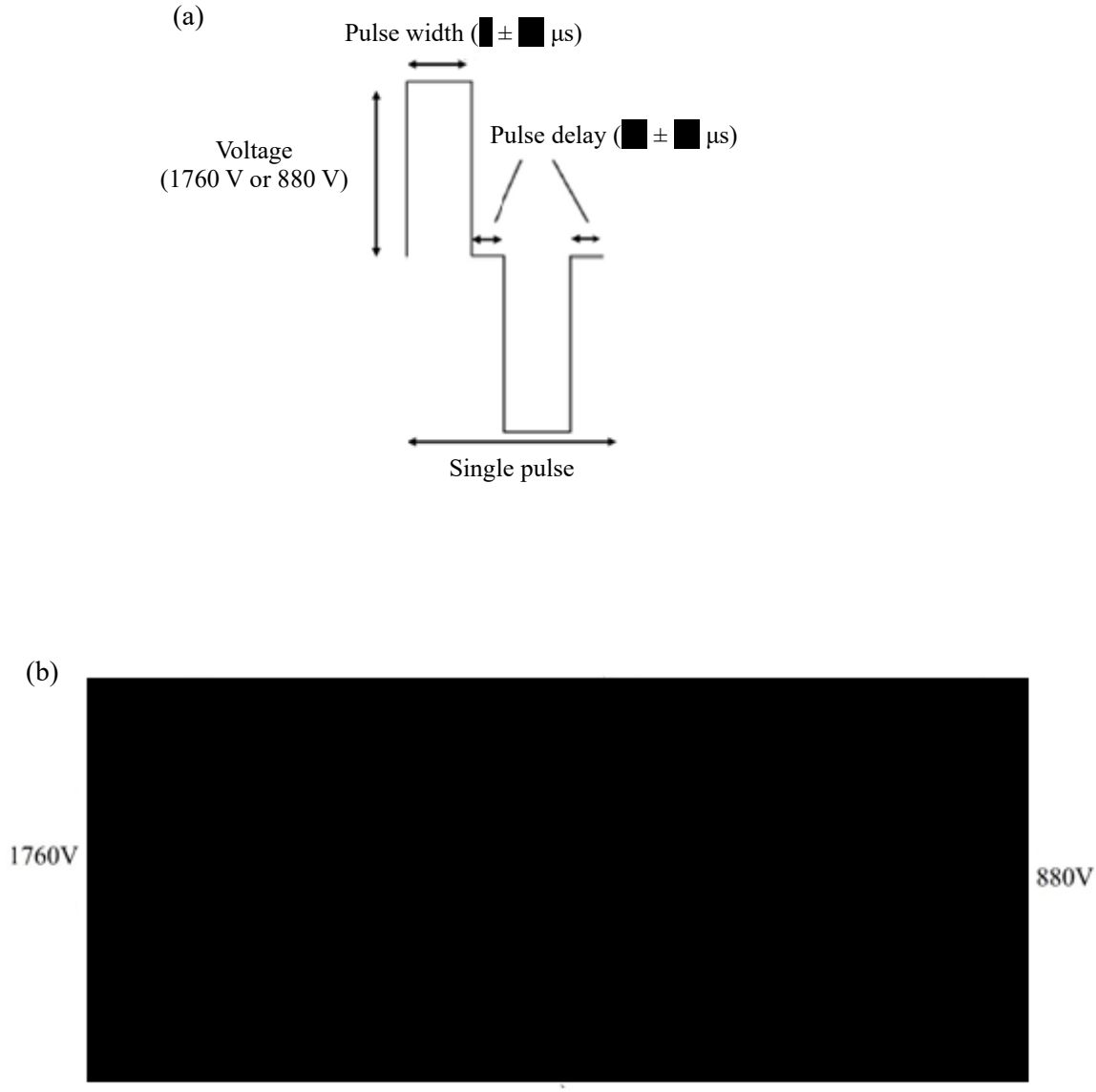

Figure 4. Output pulse of TRUPULSE Generator

(a) Single pulse specifications (b) a train of pulses (1 application)

- " " contains single pulses shown in (a).
- " " contains bursts of equivalent to (when electrodes are selected, for and for in Figure 3).
- " " is delivered from electrode pairs and contains burst cycles delivering pulses with an amplitude of 1760 V.
- " " is delivered from electrode pairs and contains burst cycles delivering pulses with an amplitude of 880 V.

The VARIPULSE Catheter is equipped with a magnetic sensor, situated in its loop-shaped tip. The magnetic sensor is used to visualize the location of the VARIPULSE Catheter electrode using the three-dimensional (3D) mapping system "Biosense CARTO 3" (Approval No. 22200BZX00741000). The VARIPULSE Platform is used in combination with an irrigation

pump (nGEN Pump; Approval No. 30200BZX00043000) providing irrigation fluid during ablation. Figure 5 shows an example of the VARIPULSE Platform connected to other medical devices.

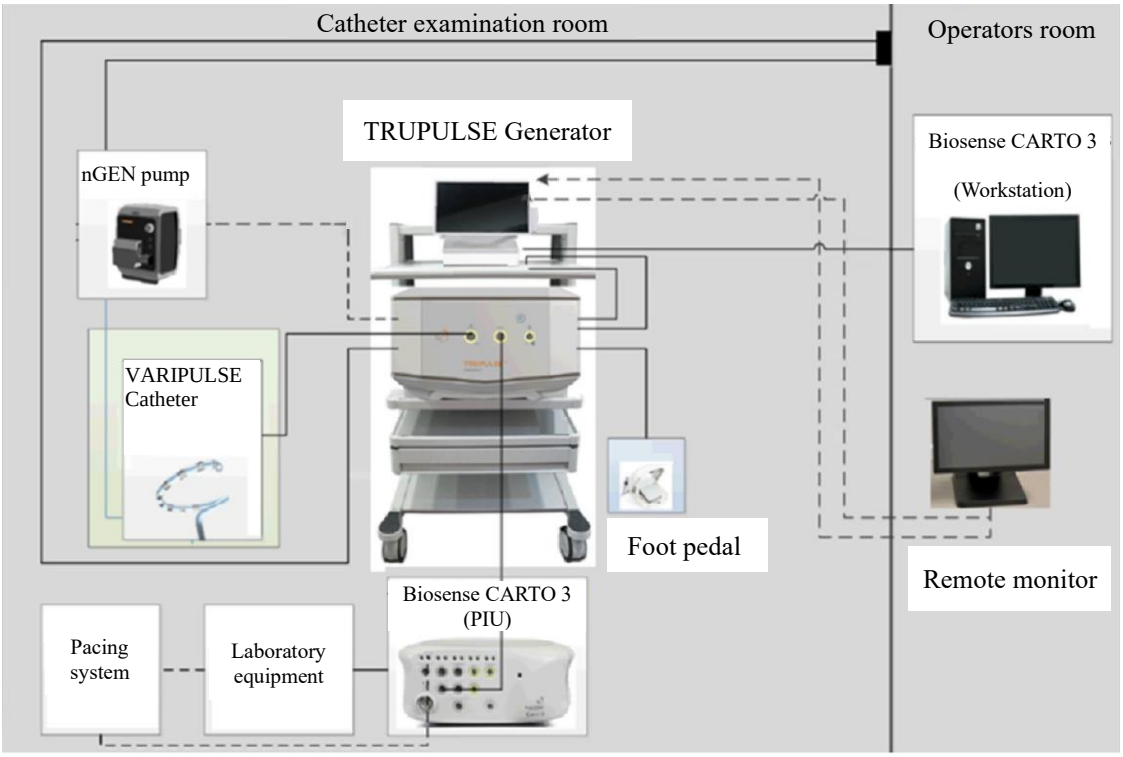

Figure 5. An example of the VARIPULSE Platform connected to other medical devices*

* Solid lines indicate required connections for operation of the VARIPULSE Platform, while dotted lines indicate other types of connections.

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

The data submitted for the current 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 VARIPULSE Platform declared that they did not fall under the Section 5, Chapter 3 of the Rules for Convening Expert Discussions, etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008, dated December 25, 2008).

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

1.A Summary of the data submitted

1.A.(1) History of development

Atrial fibrillation is the most common type of tachyarrhythmia. An estimated 716,000 people in Japan suffered from atrial fibrillation in 2005, with projections that this number will reach 1.03 million in 2050.[1] Atrial fibrillation is a cardiac condition in which abnormal electrical excitation occurs in the myocardial tissue of the atrium, causing rapid irregular heartbeat at a rate of ≥300 beats per minute, and can lead to subjective symptoms such as palpitations, shortness of breath, and malaise. Atrial fibrillation causes loss of sufficient atrial contraction, leading blood to stagnate in the atrium and making it more prone to the formation of blood clots, which may induce cardiogenic cerebral infarction. In addition, hemodynamic deterioration may lead to cardiac failure.

Treatment of paroxysmal atrial fibrillation, for which the VARIPULSE Platform is indicated, includes pharmacotherapies and non-pharmacotherapies. Antiarrhythmic drugs (AADs) are the main form of pharmacotherapies and long-term administration is required. In addition, many patients with paroxysmal atrial fibrillation who have been on pharmacotherapies eventually develop chronic atrial fibrillation.[2,3] Non-pharmacotherapies include surgical procedures and percutaneous myocardial ablation. Surgical procedures involve risks such as general anesthesia associated with thoracotomy and post-operative infections. Because it is less invasive compared to surgery, percutaneous myocardial ablation has been widely used as a treatment option since the late 1990s when it was found that the major trigger for initiation of paroxysmal atrial fibrillation is abnormal electrical impulses originating from the pulmonary vein.[4] Pulmonary vein isolation is a procedure in which myocardial tissue around the pulmonary vein-left atrial junction undergoes controlled destruction using an ablation catheter to prevent abnormal electrical impulses that originated from the pulmonary vein from entering the atrium. Pulmonary vein isolation is, therefore, regarded as a cornerstone in the effective treatment of paroxysmal atrial fibrillation (Figure 6).

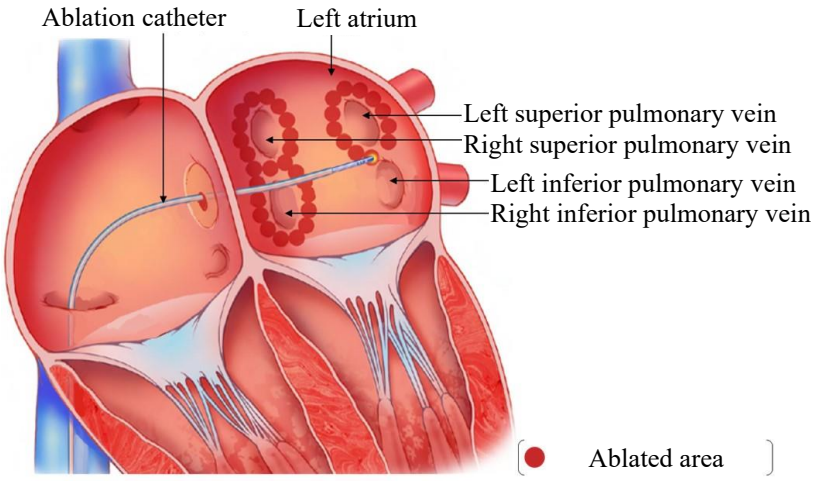

Figure 6. Schematic diagram of pulmonary vein isolation using a conventional ablation catheter

The modalities of ablation catheters that have been approved and used in Japan are radiofrequency ablation, cryoablation, thermal ablation, or laser ablation. In all ablation modalities, treatment is performed by damaging and causing necrosis of myocardial tissue that either sends abnormal electrical impulses or allows these impulses to pass through. Radiofrequency, thermal, and laser ablation destroy myocardial tissue by heating, and tissue carbonization and steam pops (intramyocardial steam explosion) due to excessive heating have been identified as issues associated with these techniques. Carbonization and steam pops may cause complications such as embolism and cardiac perforation. In all the ablation modalities mentioned above, during ablation near the ostium of the pulmonary vein in the posterior wall of the heart there is a risk that ablation energy may be delivered to structures adjacent to the heart, such as the esophagus and phrenic nerve, and this may lead to procedural complications such as atrio-oesophageal fistula and phrenic nerve injury.

The VARIPULSE Platform, which is used to perform PFA, was developed to address safety issues associated with ablation procedures by approved products. The strength and total delivery time of a pulsed electric field sufficient to cause cell death are known to be lower than those required for generating heat in tissue, suggesting that PFA can cause cell death by irreversible electroporation of the cell membrane without depending on a thermal effect.[5] Therefore, PFA with the VARIPULSE Platform is considered to reduce events associated with excessive heating such as tissue carbonization and steam pops, leading to a reduction in embolism, cardiac perforation, and other adverse events. A basic research on between-tissue variation in the strength of pulsed electric field required to induce cell death reported that myocardial tissue has a lower threshold compared with other tissues (Table 1). Although the thresholds for the esophagus and

phrenic nerve have not been determined, the thresholds are estimated to be comparable between vascular smooth muscle and the esophagus and between ordinary nerve tissue and the phrenic nerve based on the similarity of their tissue characteristics. Although the total delivery time of the pulsed electric field were not compared or investigated in these studies, the findings suggest that PFA can selectively target myocardial tissue while sparing surrounding tissue such as the esophagus and phrenic nerve by selecting the appropriate strength of the pulsed electric field using the VARIPULSE Platform, which is expected to have safety equivalent to or better than that of the approved ablation devices. In addition, although the VARIPULSE Platform has different technologies and mechanisms of ablation from those of the approved ablation devices, both devices cause tissue degeneration; therefore, the VARIPULSE Platform is expected to provide efficacy comparable to the approved ablation devices.

Table 1. Pulsed electric field required to induce cell death

Tissue type	Pulsed electric field required to induce cell death (V/cm)	Reference No. (Endnotes)
Myocardium	375	6
Red blood cells	1100-1600	7
Vascular smooth muscle	1750	8
Nerve	3800	9

The development history of the TRUPULSE Generator is as follows: the applicant submitted the results from a clinical study conducted in Europe and Canada (the inspIRE study) to support clinical data of the VARIPULSE Platform. In the inspIRE study, only the Generation I model generator was used. Improvements were made twice to the Generation I model over the course of developing the Generation III model (TRUPULSE Generator) (Table 2). The improvements from the Generation I model to the Generation II model were removal of the “min” mode, which were rarely used, and addition of a function to detect overlapping ring electrodes. In the inspIRE study, the Generation II model was used in only 4 subjects. The improvement from the Generation II model to the Generation III model (TRUPULSE Generator) was modification of application conditions in response to asymptomatic cerebral embolism that occurred in the inspIRE study [see Section 6 for details].

Table 2. Development of TRUPULSE Generator

Model	Changes from Generation I model (device model used in the inspIRE study)
Generation II model (Developed during the inspIRE study, and used for testing electrical safety and electromagnetic compatibility)	• Of the 2 output modes (min and MAX) provided in the Generation I model, only the MAX mode was retained. • A function was added based on the impedance measurements: with this function, when overlapping of the ring electrodes of the VARIPULSE Catheter is detected, output from the ring electrodes concerned is disabled.
Generation III model (TRUPULSE Generator) (Developed after an interim analysis that was conducted to confirm early success of the inspIRE study)	In addition to the modification to the Generation II model, the number of applications and ablations and their durations were fixed at the values below: • Pause between applications: [redacted] seconds • Number of applications: [redacted] • Preablation time: [redacted] seconds • Postablation time: [redacted] seconds

1.A.(2) Use in foreign countries

The VARIPULSE Catheter has not been approved or marketed in any countries outside Japan. Table 3 shows the approval and marketing status of the TRUPULSE Generator in countries outside Japan.

Table 3. Approval and marketing status of TRUPULSE Generator in countries outside Japan

Country/ Region	Brand name	Date approved	Intended use	Quantity sold
Europe	TRUPULSE™ Generator	October 25, 2023	The TRUPULSE™ Generator is indicated for cardiac electrophysiological procedures. The TRUPULSE™ Generator delivers pulsed field ablation during cardiac ablation procedures.	0
US	Not approved			

2. Design and Development

2.(1) Performance and safety specifications

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

The proposed performance and safety specifications for the VARIPULSE Catheter include the following: electrical continuity, leakage current, water leak, tensile strength, magnetic sensor calibration, biological safety, ethylene oxide sterilization residuals, bacterial endotoxins, radiopacity, and corrosion resistance. The proposed performance and safety specifications for the TRUPULSE Generator include output accuracy, impedance measurement accuracy, irrigation

pump control, safety device, and electrical safety and electromagnetic compatibility.

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

PMDA requested the applicant to include the following items, which were tested in the non-clinical studies of the VARIPULSE Catheter, in the performance and safety specifications: durability against repeated energy delivery (the catheter should withstand pulsed field ablations being repeated [redacted] times with the TRUPULSE Generator); durability against expansion/contraction of the loop-shaped portion (the catheter should withstand expansion/contraction of the loop-shaped tip being repeated [redacted] times); and bending durability (the catheter should withstand bending of the soft tip being repeated [redacted] times).

The applicant included the durability against repeated energy delivery, durability against expansion/contraction of the loop-shaped portion, and bending durability in the performance and safety specifications.

After reviewing the appropriateness of other proposed performance and safety specifications, tests, and specification limits for the VARIPULSE Catheter and TRUPULSE Generator, PMDA concluded that there was no particular problem.

2.(2) Physicochemical properties

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

To support the physicochemical properties of the VARIPULSE Catheter, the applicant submitted data from the appearance test, electrical test, irrigation flow rate test, loop-shaped tip buckling test, rigidity test, lateral force test, catheter impregnation test, operation test in the vascular model, rotation/contraction/bending test in the water tank, handle-shaft bending fatigue test, catheter initialization test, ablation cycle test, torque test, loop-shaped tip-housing tensile test, soft tip-shaft tensile test, shaft-handle tensile test, side arm-hub torque test, and side arm-hub tensile test. All test results met the prespecified acceptance criteria, indicating that the physicochemical properties of the VARIPULSE Catheter are assured.

Data relating to physicochemical properties were not submitted because physicochemical properties would not affect the performance and safety of the TRUPULSE Generator.

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

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

2.(3) Electrical safety and electromagnetic compatibility

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

To support the electrical safety and electromagnetic compatibility of the VARIPULSE Platform, the applicant submitted data indicating that the VARIPULSE Platform conforms to the standards. These standards specify the general requirements for basic safety and essential performance of medical electrical equipment (IEC 60601-1:2005/AMD1:2012), electromagnetic compatibility of medical electrical equipment (IEC 60601-1-2:2014), and particular requirements for the basic safety and essential performance of high frequency surgical equipment and high frequency surgical accessories (IEC 60601-2-2:2017). The Generation II model, the previous model of the TRUPULSE Generator, was used as the test specimen. The difference between Generation II model and TRUPULSE Generator (Generation III model) is a modification in the software caused by fixing some parameters on ablation and application. The hardware of these devices are identical for both models. The applicant explained that it is reasonable to extrapolate the test results obtained using the Generation II model as the test specimen as the test results for the TRUPULSE Generator, because no modifications were made to affect the electrical safety and electromagnetic compatibility.

All results conformed to the standards, indicating that the electrical safety and electromagnetic compatibility of the VARIPULSE Platform are assured.

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

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

2.(4) Biological safety

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

The applicant submitted the results of a biological safety study of the VARIPULSE Catheter conducted in accordance with the "Amendment of Basic Principles of Biological Safety Evaluation Required for Application for Approval to Market Medical Devices" (PSEHB/MDED Notification No. 0106-1, dated January 6, 2020) and ISO 10993-1.

The following studies were conducted: cytotoxicity, sensitization, irritation/intracutaneous reactivity, material-derived pyrogen, acute systemic toxicity, and hemocompatibility (hemolysis and thrombus formation caused by materials). The results of these studies showed no problematic findings.

The applicant omitted the submission of data supporting the biological safety of the TRUPULSE

Generator because it is not a medical device involving contact with blood or tissue.

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

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

2.(5) Stability and durability

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

The applicant omitted the submission of test results supporting the stability of the VARIPULSE Catheter and submitted a self-declaration with a statement that its shelf life was determined based on the results of the required safety evaluations conducted in accordance with the "Handling of Stability Studies Related to the Determination of the Shelf Life in the Application for Marketing Approvals (Certifications) of Medical Devices" (PFSB/ELD/OMDE Notification No. 1227-5, dated December 27, 2012).

The applicant omitted the submission of data supporting the stability and durability of the TRUPULSE Generator because its quality does not deteriorate over time.

A shelf life of 1 year has been proposed for the VARIPULSE Catheter while no shelf life for the TRUPULSE Generator was proposed.

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

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

2.(6) Performance

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

To support the performance of the VARIPULSE Platform, the applicant submitted the results of a study using the device in combination with Biosense CARTO 3 and the swine workflow study, in which the VARIPULSE Catheter and the Generation I model of the VARIPULSE Generator were used. As described in Table 2, although the Generation I model differs from the VARIPULSE Generator, the applicant explained that ablation procedures were performed using settings that provides conditions identical to those with the VARIPULSE Generator, and therefore, the results with the Generation I model can be extrapolated to the VARIPULSE Generator.

The study using the device in combination with Biosense CARTO 3 evaluated the following: calibration accuracy of magnetic sensor, position accuracy of magnetic sensor, noise of magnetic sensor, effect of PFA on magnetic sensor position, effect of pacing on magnetic sensor position,

anomalies in magnetic sensor coil, position and noise of advanced catheter location (ACL), ACL leakage current, effect of PFA on ACL position, effect of pacing on ACL position, ECG gain accuracy, ECG signal noise, ECG signal recovery from ablation, and ECG crosstalk. All test results met the prespecified criteria, indicating that the performance of the VARIPULSE Platform is assured.

The swine workflow study was conducted to evaluate the performance and safety of the VARIPULSE Platform on a swine beating heart model for [redacted] ± [redacted] days post-procedure, and operability of the VARIPULSE Platform. There were 3 study procedure groups performing PFA, each group having different PFA conditions, and 1 control group performing radiofrequency ablation. In the study, [redacted] pigs per group were used, and Table 4 and Table 5 show the conditions for PFA and radiofrequency ablation, respectively. In each of the PFA groups, the conditions concerning the number of total ablations for each ablation target site and the number of applications for the same site were changed.

Table 4. The PFA conditions in swine workflow study

Group	Ablation target site	Number of ring electrodes delivering PFA energy	Total number of ablations in ablation target sites	Number of applications for the same site	Pause between applications [seconds]
1	Left atrium	[redacted]			
	Right atrium				
2	Left atrium				
	Right atrium				

Group	Ablation target site	Number of ring electrodes delivering PFA energy	Total number of ablations in ablation target sites	Number of applications for the same site	Pause between applications [seconds]
3	Left atrium	[redacted]			
	Right atrium				

Table 5. The radiofrequency ablation conditions in swine workflow study

Group	Ablation target site	Output [W]	Cut-off temperature [°C]	Irrigation flow rate [mL/min]	Energy delivery time [seconds]	Number of ablations (minimum)
4	Left atrium	[redacted]				
	Right atrium					

Myocardial ablation was performed in pigs. The VARIPULSE Catheter is intended to be used only for pulmonary vein isolation in clinical practice; however, in the study, ablation was performed not only on the pulmonary vein ostium, but also other areas in the left atrium, as well as in the right atrium, to study the characteristics of PFA. Of the [redacted] animals in Group 1 through 3, which underwent PFA, ablation of the right atrium was performed intentionally in the areas adjacent to the phrenic nerve rather than avoiding these areas in [redacted] animals. The follow-up period was [redacted] ± [redacted] days after ablation.

The overall success rate for pulmonary vein isolation in the acute phase (immediately after ablation) in Groups 1 through 4 was [redacted]% ([redacted] in Group 1, [redacted] in Group 2, [redacted] in Group 3, and [redacted] in Group 4), indicating that the results met the acceptance criteria ([redacted]%). At the time of follow-up, [redacted]% of pulmonary vein isolation was maintained in Groups 1 through 3, which underwent PFA ([redacted] in Group 1, [redacted] in Group 2, and [redacted] in Group 3), while the corresponding percentage was [redacted]) in Group 4, which underwent radiofrequency ablation, meeting the acceptance criteria ([redacted]%). After the procedure, none of the following events were reported in animals in Groups 1 through 4: thrombus and/or carbonization on the tip of the catheter, clinically serious steam pops (may lead to pericardial effusion and/or cardiac tamponade), mural thrombus in ablated myocardial tissue, pulmonary vein stenosis (>70% reduction in pulmonary vein diameter at the ostium), damage to surrounding tissue such as the lung, esophagus, or phrenic nerve, mechanical injury of myocardial tissue caused by the catheter, and peripheral thromboembolism in the upstream/downstream tissue.

The total number of ablations per pulmonary vein was [redacted] in Group 1, [redacted] in Group 2, and [redacted] in Group 3. Since the number of applications per ablation was set as 1, 3, and 6 in Groups 1, 2, and 3, respectively, the total number of applications per pulmonary vein was [redacted], [redacted], and [redacted] in Groups 1, 2, and 3, respectively. It was recommended that at least a total of 12 applications per pulmonary vein should be specified for the inspIRE study so that the number of total applications would be aligned with the results of the above study.

The applicant also conducted software tests (output, pump, CARTO 3 compatibility), an output accuracy test, and impedance measurement accuracy test to support the performance of the TRUPULSE Generator. All results met the prespecified acceptance criteria, demonstrating that the performance of the TRUPULSE Generator is assured.

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

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

2.(7) Conformity to IEC 62304

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

The applicant submitted data demonstrating that the TRUPULSE Generator meets the international standards (IEC 62304:2006+Amd. 1:2015) that specify the software life cycle processes of medical device software.

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

PMDA reviewed the data supporting the conformity of the TRUPULSE Generator to IEC 62304,

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 VARIPULSE Platform meets the standards for medical devices as stipulated by the Minister of Health, Labour and Welfare in accordance with the provisions in 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 VARIPULSE Platform to the Essential Principles.

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

PMDA's view:

As described later in Section "6.B Outline of the review conducted by PMDA," essential elements to maintain the risk-benefit balance of the VARIPULSE Platform include the following: (i) trainings provided to healthcare professionals, and (ii) adherence to requirements for medical facilities and performing physicians which are prepared in cooperation with relevant academic societies. Accordingly, approval condition should be attached to ensure that these necessary measures are taken.

(2) The conformity of the VARIPULSE Platform to Article 2, which stipulates risk management throughout the life cycle of medical devices

PMDA's view:

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 VARIPULSE Platform is a device based on a novel ablation technology, and available clinical data on the device are limited. Therefore, the efficacy and safety in clinical practice in Japan need to be evaluated, and additional risk minimization measures should be taken as necessary; therefore, PMDA instructed the applicant to conduct a use-results survey.

(3) The conformity of the VARIPULSE Platform to Article 3, which stipulates the performance and function of medical devices, and to Article 6, which stipulates the efficacy of medical devices

PMDA's view:

As described later in Section "6.B Outline of the review conducted by PMDA," the submitted clinical study data demonstrated that the VARIPULSE Platform can be effective and safe as those of the approved devices in patients with drug-refractory symptomatic paroxysmal atrial fibrillation; therefore, there is no problem with the conformity of the VARIPULSE Platform to Articles 3 and 6.

(4) The conformity of the VARIPULSE Platform to Article 17, which stipulates general requirements on provision of information to users, i.e., publicizing precautions and specifying such information in the package inserts (hereinafter referred to as "Information on Precautions, etc.")

PMDA's view:

As described later in Section "6.B Outline of the review conducted by PMDA," it is essential that users should operate the VARIPULSE Platform after understanding its characteristics to maintain the risk-benefit balance of the VARIPULSE Platform. Therefore, the applicant is required to provide information through Information on the Precautions, training, and by other means.

4. Risk Management

4.A Summary of the data submitted

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

4.B Outline of the review conducted by PMDA

PMDA comprehensively reviewed the documents 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 applicant submitted data on the sterilization methods for the VARIPULSE Catheter (status of sterilization validation, residues after ethylene oxide sterilization). The applicant also submitted data relating to in-process testing during manufacture of the VARIPULSE Platform,

and explained that bacterial endotoxin testing for the VARIPULSE Catheter is performed during the manufacturing process to control endotoxin contamination.

5.B Outline of the review conducted by PMDA

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

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

The applicant submitted the results from the inspIRE study conducted in foreign countries as clinical study data of the VARIPULSE Platform. In the inspIRE study, the IRE circular catheter (identical to the VARIPULSE Catheter) and IRE Generator (identical to the Generation I model of TRUPULSE Generator) were used as test devices [see Table 2 in Section 1.A.(1). The combination of the VARIPULSE Catheter and IRE Generator are hereinafter referred to as "IRE System"].

6.A Summary of the data submitted

The inspIRE study is a multicenter, prospective, single-arm study conducted at 11 study centers in Europe and 2 study centers in Canada to evaluate the efficacy and safety of the IRE System in patients with drug-refractory symptomatic paroxysmal atrial fibrillation. Table 6 outlines the inspIRE study, which consisted of the following 2 phases (Wave I and II).

Wave I: Wave I assessed initial safety and efficacy of the IRE System in advance by enrolling up to 40 subjects. In addition, neurological evaluation, pulmonary vein stenosis, and esophageal lesions were assessed to compare the safety results with those of Wave II.

Wave II: Wave II is comprised of the Roll-In cohort, which was established to minimize the effect of learning curves, and the Main cohort, which was to acquire data used for hypothetical testing. A Bayesian adaptive design was adopted. This design allows previously planned modifications, based on the interim analysis results. Two types of interim analyses were to be performed, an interim analysis for sample size selection and an interim analysis for determining the early success of the study.

Table 6. Outline of the inspIRE study

Item	Outline
Objective	To assess the safety and long-term efficacy of the IRE System for pulmonary vein isolation in patients with paroxysmal atrial fibrillation
Study design	Multicenter, prospective, single-arm study
Study population	Patients with drug-refractory symptomatic paroxysmal atrial fibrillation

Item	Outline
Sample size	Wave I: 40 subjects, Wave II Roll-In: 30 subjects, Wave II Main: 186 subjects* * The interim analysis for sample size selection identified a sample size sufficient to assess the primary efficacy endpoint; therefore, enrollment was discontinued, leading to a total sample size of 186 subjects.
Inclusion criteria	1. Patients diagnosed as having symptomatic paroxysmal atrial fibrillation. 2. Patients selected for atrial fibrillation ablation procedure by pulmonary vein isolation. 3. Patients who failed antiarrhythmic drugs (AADs) (Class I to IV). Treatment failure is one of the following: recurrent symptomatic atrial fibrillation, intolerant to or contraindicated to the AADs. 4. Patients aged 18 to 75 years. 5. Patients who are willing to and capable of providing consent. 6. Patients who are willing to and capable of complying with pre-, post-, and follow-up testing and requirements.
Exclusion criteria	1. Patients with atrial fibrillation secondary to electrolyte imbalance, thyroid disease, or reversible or non-cardiac cause. 2. Patients with previous left atrium ablation or surgery. 3. Patients known to require ablation outside the pulmonary vein region (e.g., cavotricuspid isthmus region, atrioventricular reentrant tachycardia, atrioventricular nodal reentry tachycardia, atrial tachycardia, ventricular tachycardia, and Wolff-Parkinson-White syndrome). 4. Patients previously diagnosed as having persistent atrial fibrillation (>7 days). 5. Patients with severe dilatation of the left atrium (left atrial diameter >50 mm in case of transthoracic echocardiography). 6. Patients with left atrial thrombus. 7. Patients with severely reduced left ventricular ejection fraction (<40%). 8. Patients with poorly controlled cardiac failure or New York Heart Association class III or IV. 9. Patients with a history of blood clotting, bleeding abnormalities, or contraindication to anticoagulation (heparin, warfarin, or dabigatran) 10. Patients with a history of thromboembolic events within the past 6 months (including transient ischaemic attack). 11. Patients with previous percutaneous coronary intervention or myocardial infarction within the past 2 months. 12. Patients who anticipate undergoing coronary artery bypass graft surgery combined with valvular operation, cardiac operation (e.g., ventriculotomy, atriotomy), or valvular cardiac (surgical or percutaneous) procedure. 13. Patients with unstable angina within the past 6 months. 14. Patients who anticipate undergoing cardiac transplantation, cardiac surgery, or other major surgery within the next 12 months. 15. Patients with significant pulmonary disease (e.g., restrictive pulmonary disease, constrictive or chronic obstructive pulmonary disease), or any other disease or disfunction of the lungs or respiratory system that produces severe chronic symptoms.

Item	Outline
	16. Patients with identified significant anomaly in the pulmonary vein that, in the opinion of the investigator of the inspIRE study, would preclude enrollment in the inspIRE study. 17. Patients with pulmonary vein stenosis. 18. Patients with acute illness, active systemic infection, or sepsis. 19. Patients with intracardiac thrombus, myxoma, tumor, interatrial baffle or patch or other abnormality that precludes catheter introduction or manipulation. 20. Patients with severe mitral regurgitation. 21. Patients using an implanted pacemaker or implantable cardioverter-defibrillator or other implanted metal cardiac device that may interfere with the pulsed energy field. 22. Patients with a condition that precludes vascular access (e.g., inferior vena cava filter). 23. Patients with a significant congenital anomaly or medical problem that, in the opinion of the investigator of the inspIRE study, would preclude enrollment in the inspIRE study. 24. Patients classified as socially vulnerable and require special care in terms of assuring welfare. 25. Patients currently enrolled in another investigational study evaluating another device or drug. 26. Women who are pregnant (confirmed by pregnancy test for premenopausal women), lactating, or who are of child-bearing age and plan on becoming pregnant during the course of the clinical investigation of inspIRE study. 27. Patients with life expectancy of less than 12 months. 28. Patients for whom the devices used in the inspIRE study are contraindicated according to the instruction manuals. Additional exclusion criteria for Wave I: 29. Patients in whom magnetic resonance imaging (MRI) is contraindicated because contrast media cannot be used due to advanced renal disease, or other reasons such as claustrophobia (in the opinion of the investigator of the inspIRE study). 30. Patients with iron-containing metal implants. 31. Patients with unresolved neurological deficit. 32. Patients with poorly controlled significant gastro esophageal reflux disease.
Primary endpoint	**Primary efficacy endpoint** Freedom from documented symptomatic or asymptomatic atrial fibrillation, atrial tachycardia, or atrial flutter based on ECG data (≥30 seconds with arrhythmia monitoring device) during the efficacy assessment period (91 to 365 days postablation) Performance target: 50% **Primary safety endpoint** Incidence of primary adverse events (PAEs) within 7 days of the initial mapping and ablation procedure PAEs include the following adverse events: Atrio-oesophageal fistula,* phrenic nerve paralysis (permanent), cardiac

Item	Outline
	tamponade/perforation, pulmonary vein stenosis (≥70% reduction in pulmonary vein diameter),* device- or procedure-related death,* cerebrovascular accident/cerebrovascular disorder, major vascular access complication/bleeding, thromboembolism, myocardial infarction, transient ischaemic attack, pericarditis * Atrio-oesophageal fistula, pulmonary vein stenosis, and device- or procedure-related death occurring after 7 days post-procedure are considered PAEs and are subject to analysis. Performance target: 14%
Follow-up period	12 months

Long-term efficacy should be evaluated in pulmonary vein isolation for paroxysmal atrial fibrillation. The 2017 Heart Rhythm Society (HRS) Consensus Statement on catheter and surgical ablation of atrial fibrillation[10] (hereinafter referred to as "the 2017 Consensus Statement") recommends evaluation of freedom from atrial fibrillation at 12 months post-procedure. Accordingly, "freedom from documented symptomatic or asymptomatic atrial fibrillation, atrial tachycardia, or atrial flutter (≥30 seconds with arrhythmia monitoring device) based on ECG data during the efficacy assessment period (91-365 days postablation)" was selected as the primary efficacy endpoint. A performance target of 50% was selected based on the minimum success rates for ablation for paroxysmal atrial fibrillation at the 12-month post-procedure follow-up as recommended in the 2017 Consensus Statement, and also for the performance target set for the primary efficacy endpoint (long-term efficacy) in the SMART-AF study, which was conducted in patients with drug-refractory symptomatic paroxysmal atrial fibrillation, the data of which were included in the application documents for the currently approved "Thermocool Smarttouch SF" (Approved No. 22800BZX00244000). The primary safety endpoint was the incidence of early-onset PAEs within 7 days of the initial mapping and ablation procedure. On the basis of the definition in the 2017 Consensus Statement, PAEs were defined as follows:

Primary adverse events (PAE)s: Atrio-oesophageal fistula,* phrenic nerve paralysis (permanent), cardiac tamponade/perforation, pulmonary vein stenosis (≥70% reduction in pulmonary vein diameter),* device- or procedure-related death,* cerebrovascular accident/cerebrovascular disorder, transient ischaemic attack, major vascular access complication/bleeding, thromboembolism, myocardial infarction, pericarditis

* Atrio-oesophageal fistula, pulmonary vein stenosis, and device- or procedure-related death occurring at >7 days post-procedure are considered as PAEs and are subject to analysis.

In view of the criteria (14%) in the past applicant's clinical study data and a performance target (16.6%) of the primary safety evaluation in the SMART-AF study mentioned above, a performance target of 14% was selected. Other secondary endpoints and additional endpoints included acute procedural success, neurological assessment (Wave I only), and computed tomography (CT)/magnetic resonance angiography (MRA) (Wave I only).

Figure 7 shows the disposition of subjects in the analysis sets of Wave I. Of the 45 subjects enrolled in Wave I, a total of 5 subjects were excluded, with 3 subjects not meeting the selection criteria and 2 subjects excluded at the discretion of the physician (1 subject had another arrhythmia in addition to atrial fibrillation, and another subject had a low prothrombin time-international normalized ratio [PT-INR] within 3 weeks of pre-procedure). A total of 40 subjects who had a catheter inserted were included in the full analysis set (FAS). Since all subjects in the FAS were eligible, all 40 subjects were included in the modified intention-to-treat (mITT) population. The subjects underwent PFA, and none of them significantly deviated from the protocol. All 40 subjects were therefore included in the per protocol (PP) set. After PFA with the VARIPULSE Catheter during the blanking period (90 days postablation), 1 subject in the PP population set underwent pulmonary vein ablation using other device for the treatment of atrial flutter. This subject was excluded from the primary efficacy evaluation because it would not be possible to evaluate long-term efficacy.

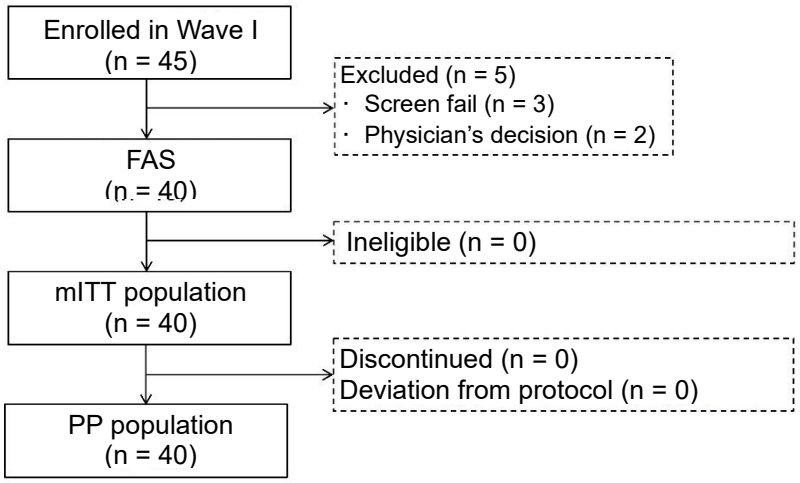

Figure 7. Disposition of Wave I analysis sets

Figure 8 shows the disposition of the Wave II analysis sets. Of the 227 subjects enrolled in Wave II, a total of 9 subjects were excluded i.e., 5 subjects not meeting the selection criteria, 2 subjects unable to use the device, 1 subject at the discretion of the physician (appropriate anticoagulation

therapy had not been performed), and 1 subject with difficulty visiting the study site due to foot injury. Thirty-two subjects in Wave II Roll-In and 186 subjects in Wave II Main had VARIPULSE Catheter inserted and were included in the respective FAS.

Of the 32 subjects in the FAS of Wave II Roll-In, 30 subjects underwent PFA, and were included in the Roll-In analysis set. Two subjects in Wave II Roll-In discontinued the study: there was a malfunction of the VARIPULSE Catheter in 1 patient, and the other subject was found to have an implantable loop recorder.

All 186 subjects in the FAS in Wave II Main met the eligibility criteria and were included in the mITT population. All 186 subjects underwent PFA and no significant protocol violation was reported; therefore, all 186 subjects were included in the PP population.

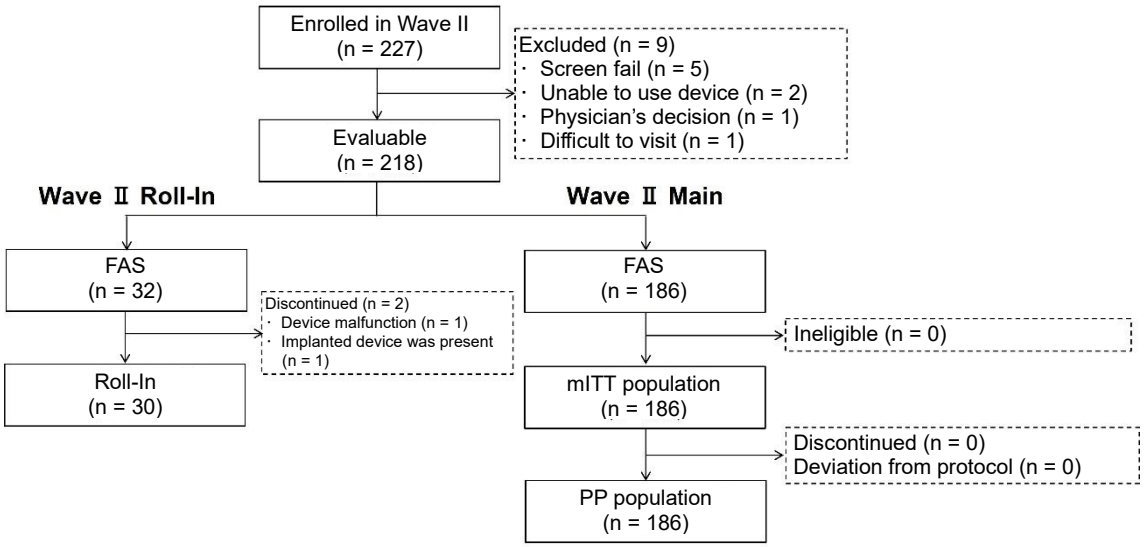

Figure 8. Disposition of Wave II analysis sets

6.A.(1) Patient characteristics

Table 7 shows the major baseline patient characteristics in the Wave I FAS (N = 40), Wave II Roll-In (N = 30), and Wave II Main FAS (N = 186).

Table 7. Baseline patient characteristics

Item	Wave I N = 40	Wave II Roll-In N = 30	Wave II Main N = 186
Age (years)			
Mean ± standard deviation (median)	58.4 ± 10.9 (58.5)	56.2 ± 11.7 (56.0)	59.4 ± 10.2 (61.0)
Min/Max	31/75	30/73	24/75

Item	Wave I N = 40	Wave II Roll-In N = 30	Wave II Main N = 186
Sex, n (%)			
Male	23 (57.5)	20 (66.7)	131 (70.4)
Female	17 (42.5)	10 (33.3)	55 (29.6)
Height (cm)			
Mean ± standard deviation (median)	174.4 ± 9.4 (172.0)	174.8 ± 9.9 (174.0)	176.4 ± 9.0 (177.0)
Min/Max	160/193	155/194	152/196
Body weight (kg)			
Mean ± standard deviation (median)	83.6 ± 17.0 (81.5)	86.0 ± 13.5 (86.7)	85.7 ± 14.7 (84.0)
Min/Max	57.0/127.0	60.6/118.0	52.0/125.0
BMI (kg/m^2)			
Mean ± standard deviation (median)	27.4 ± 4.3 (27.5)	28.1 ± 3.9 (27.7)	27.6 ± 4.3 (26.9)
Min/Max	19.0/37.9	22.7/37.6	18.2/41.3
Paroxysmal atrial fibrillation duration (months)			
Mean ± standard deviation (median)	76.9 ± 98.5 (36.15)	67.0 ± 89.9 (48.0)	60.1 ± 76.7 (28.8)
Min/Max	0.3/400.1	2.0/456.0	0.6/420.0
Symptomatic paroxysmal atrial fibrillation, n (%)	40 (100.0)	30 (100.0)	186 (100.0)
Failed AADs, n (%)	40 (100.0)	30 (100.0)	186 (100.0)
CHA_2DS_2-VASc score			
Mean ± standard deviation (median)	1.8 ± 1.5 (2.0)	1.2 ± 1.2 (1.0)	1.3 ± 1.2 (1.0)
Min/Max	0/5	0/4	0/5

6.A.(2) Procedural data

Table 8 shows the main procedural data used in the inspIRE study. The total procedural time was defined as the time between the initial femoral puncture and the final catheter removal. The mean total procedural time was 82.4 ± 20.0 minutes in Wave I, 114.0 ± 36.4 minutes in Wave II Roll-In, and 70.1 ± 27.7 minutes in Wave II Main. The total fluoroscopy time was 9.8 ± 6.8 minutes in Wave I, 12.2 ± 8.2 minutes in Wave II Roll-In, and 7.8 ± 7.0 minutes in Wave II Main.

Esophageal temperature was measured in 4 subjects in Wave II Main using an esophageal temperature probe. The changes between baseline and maximum temperature were within 0°C to 1°C in all subjects.

The proximity of the catheter to the phrenic nerve was evaluated by preablation phrenic nerve

pacing in all subjects.

Table 8. Procedural data

Item	Wave I N = 40	Wave II Roll-In N = 30	Wave II Main N = 186
Total procedural time (minutes)			
Mean ± standard deviation (median)	82.4 ± 20.0 (79.5)	114.0 ± 36.4 (106.5)	70.1 ± 27.7 (61.0)
Min/Max	52.0/144.0	58.0/240.0	27.0/168.0
Left atrial dwell time of VARIPULSE Catheter (minutes)			
Mean ± standard deviation (median)	46.2 ± 16.6 (45.0)	71.9 ± 24.8 (67.5)	44.7 ± 20.6 (38.5)
Min/Max	22.0/94.0	34.0/130.0	16.0/108.0
Total effective PFA energy delivery time[a] (seconds)			
Mean ± standard deviation (median)	11.2 ± 3.2 (11.9)	14.1 ± 3.0 (13.0)	12.1 ± 3.1 (11.9)
Min/Max	5.4/17.8	10.4/20.8	5.2/24.4
Total fluoroscopy time (minutes)			
Mean ± standard deviation (median)	9.8 ± 6.8 (8.3)	12.2 ± 8.2 (9.4)	7.8 ± 7.0 (5.1)
Min/Max	1.1/28.9	3.0/31.0	0.0/31.7
Esophagus monitoring, n (%)			
With esophageal temperature probe	0 (0.0)	0 (0.0)	4 (2.2)
Esophageal visualization with barium swallow or contrast medium	5 (12.5)	0 (0.0)	0 (0.0)
Phrenic nerve monitoring, n (%)			
Proximity of catheter to phrenic nerve evaluated by preablation phrenic nerve pacing	40 (100.0)	30 (100.0)	186 (100.0)

a, “Effective” indicates PFA application with 100% energy.

Table 9 shows the number of effective PFA energy deliveries in the inspIRE study. An energy delivery of PFA corresponds to an application by the IRE Generator. In the training session before the start of the inspIRE study, it was recommended to perform a total of 4 ablations per pulmonary vein (2 in the pulmonary vein ostium and 2 in the pulmonary vein antrum) while changing the direction of the VARIPULSE Catheter circumferentially. Taking account of the occurrence of asymptomatic cerebral embolism as discussed later in Section 6.B.(4).1), it was recommended that the number of applications per ablation should be manually set to 3 in the seventh subject and thereafter in Wave I. Therefore, the recommended PFA energy delivered per pulmonary vein was 12 in the inspIRE study.

Table 9. Number of effective PFA energy deliveries[a]

Item	Wave I N = 40	Wave II Roll-In N = 30	Wave II Main N = 186
Overall			
Mean ± standard deviation (median)	45.7 ± 12.9 (48.0)	57.2 ± 12.2 (52.5)	49.0 ± 12.5 (48.0)
Min/Max	22/72	42/84	21/99
Left superior pulmonary vein			
N	31	26	164
Mean ± standard deviation (median)	12.5 ± 4.5 (12.0)	15.4 ± 4.9 (12.5)	13.0 ± 3.4 (12.0)
Min/Max	6/24	12/27	6/35
Left inferior pulmonary vein			
N	31	26	164
Mean ± standard deviation (median)	11.3 ± 3.8 (12.0)	14.5 ± 3.6 (13.0)	12.3 ± 3.3 (12.0)
Min/Max	5/20	12/24	5/24
Left pulmonary vein (common)[b]			
N	9	4	22
Mean ± standard deviation (median)	15.4 ± 4.6 (15.0)	20.5 ± 6.9 (13.0)	22.4 ± 8.9 (24.0)
Min/Max	12/25	12/27	12/46
Right superior pulmonary vein			
N	40	30	185
Mean ± standard deviation (median)	13.0 ± 5.9 (12.0)	15.1 ± 4.0 (13.0)	12.5 ± 3.9 (12.0)
Min/Max	5/35	12/27	4/33
Right inferior pulmonary vein			
N	40	30	185
Mean ± standard deviation (median)	12.1 ± 4.9 (12.0)	14.8 ± 4.0 (13.0)	12.8 ± 4.5 (12.0)
Min/Max	6/27	12/28	2/33
Right pulmonary vein (common)[b]			
N	0	0	1
Mean ± standard deviation (median)	—	—	18.0 (18.0)
Min/Max	—	—	18/18
Right middle pulmonary vein[c]			
N	0	2	3
Mean ± standard deviation (median)	—	13.5 ± 10.6 (13.5)	12.7 ± 5.0 (12.0)
Min/Max	—	6/21	8/18

a, “Effective” indicates PFA application with 100% energy.

b, “Pulmonary vein (common)” refers to an anatomy where the inferior pulmonary vein merges the superior pulmonary vein and has 1 heart hilum of the venous part (opening).

c, “Right middle pulmonary vein” is located between the right superior pulmonary vein and right inferior pulmonary vein. Each of the right superior pulmonary vein, right middle pulmonary vein, and right inferior pulmonary vein has its own heart hilum.

6.A.(3) Study results

6.A.(3).1) Efficacy

Acute procedural success was achieved in 100.0% of all analysis sets in Wave I, Wave II Roll-In,

and Wave II Main. No catheters other than VARIPULSE Catheter were used to isolate the target pulmonary veins.

In Wave II Main, an interim analysis was planned to determine early success. All 186 subjects in Wave II Main completed the 3-month follow-up, and an early success interim analysis was performed when 83 subjects reached the 12-month follow-up. In the interim analysis, the mean posterior distribution of the freedom from atrial arrhythmia events, the primary efficacy endpoint, was 70.0% (two-sided 95% CI, 62.1%-77.4%). The posterior probability of the freedom from atrial arrhythmia events exceeding the performance target of 50% is >99.9%, which is greater than the threshold for early success (99.75%) for the primary efficacy endpoint. In Wave I, all 40 subjects reached the 12-month follow-up, with the efficacy endpoint result being 71.8% (28 of 39 subjects) (two-sided 95% CI, 55.1%-85.0%). In Wave II Roll-In, no interim analyses were planned for the primary efficacy endpoint.

While the recurrence of documented atrial arrhythmia (atrial fibrillation/atrial tachycardia/atrial flutter) based on electrocardiogram and failure in the acute phase procedure were the only unsuccessful criteria for the primary efficacy endpoint, factors that may affect the long-term efficacy were also evaluated, as shown below. The evaluation indicated that there were no subjects to whom these factors were applicable, and no effects were found on the results of the primary efficacy evaluation in Wave I and Wave II Main.

- New/increased dose of class I/III AADs for atrial fibrillation during the efficacy assessment period
- All repeat ablations for atrial arrhythmia during the efficacy assessment period
- ≥3 repeat ablations for atrial arrhythmia during the blanking period

The final report of the inspIRE study, submitted as a reference material, outlined the final study results for all subjects in Wave II Roll-In and Wave II Main who completed the 12-month follow-up. The results for the primary efficacy endpoint were 80.0% (24 of 30 subjects) in Wave II Roll-In and 75.5% (139 of 184 subjects) in Wave II Main. Results obtained for Wave II Main were similar to those of the interim analysis.

6.A.(3).2) Safety

The results for the primary safety endpoint were 0.0% in all of Wave I, Wave II Roll-In, and Wave II Main. There were no reports of PAEs up to the time of interim analysis.

The results of the interim analysis showed that the mean posterior probability of the incidence of

PAEs was 0.5% (two-sided 95% CI, 0.0%-2.0%). The posterior probability of the incidence of PAEs being lower than the performance target of 14% is >99.9%, which is greater than the threshold for early success (97.5%) for the primary safety endpoint.

There were no reports of PAEs in the final report of the inspIRE study, submitted as a reference material. The final results for the primary safety endpoint in Wave II Roll-In and Wave II Main were the same as the interim analysis results.

Neurological, esophageal, and pulmonary vein evaluations were performed in Wave I only. In the Wave I mITT population, 40 subjects underwent neurological evaluation by MRI, and asymptomatic cerebral embolism lesions were detected in 8 subjects at the time of hospital discharge. In the esophagus evaluation, no thermal esophageal lesions were detected endoscopically. In the pulmonary vein evaluation, no subjects presented with severe pulmonary stenosis in the imaging examination at 3-month follow-up.

In Wave I, the incidence of serious adverse events was 7.5% (3 of 40 subjects, 3 events) with 1 event each of acute coronary syndrome, coronary artery occlusion, and arthritis. A causal relationship to the study device or study procedure was denied for all events. In Wave II Roll-In, the incidence of serious adverse events was 6.7% (2 of 30 subjects, 3 events) with 1 event each of atrial flutter, respiratory tract infection, and nephrolithiasis. A causal relationship to the study device or study procedure was denied for all events. In Wave II Main, the incidence of serious adverse events was 2.7% (5 of 186 subjects, 5 events) with 1 event each of angina pectoris, ventricular tachycardia, intervertebral disc protrusion, invasive lobular breast carcinoma, and urinary retention. Urinary retention was determined to be related to the study procedure, while a causal relationship to the study device was denied. Urinary retention subsequently resolved. A causal relationship to the study device or study procedure was denied for all other serious adverse events. Table 10 summarizes nonserious adverse events.

Table 10. Nonserious adverse events for which a causal relationship to the study device or study procedure could not be ruled out

	Number of subjects with event (incidence, %) [number of events]		
	Wave I N = 40	Wave II Roll-In N = 30	Wave II Main N = 186
Overall	18 (45.0) [26]	7 (23.3) [9]	13 (7.0) [20]
Chest pain	0 (0.0) [0]	1 (3.3) [1]	2 (1.1) [2]
Headache	0 (0.0) [0]	1 (3.3) [1]	2 (1.1) [2]
Pericarditis	0 (0.0) [0]	1 (3.3) [1]	1 (0.5) [1]
Groin pain	1 (2.5) [1]	1 (3.3) [1]	1 (0.5) [1]
Groin haematoma	4 (10.0) [4]	0 (0.0) [0]	1 (0.5) [1]
Femoral artery pseudoaneurysm	1 (2.5) [1]	0 (0.0) [0]	1 (0.5) [1]
Atrial flutter	1 (2.5) [1]	0 (0.0) [0]	1 (0.5) [1]
Nausea	1 (2.5) [1]	0 (0.0) [0]	1 (0.5) [1]
Chest pressure sensation	0 (0.0) [0]	0 (0.0) [0]	1 (0.5) [1]
Dyspnoea	0 (0.0) [0]	0 (0.0) [0]	1 (0.5) [1]
Infection	0 (0.0) [0]	0 (0.0) [0]	1 (0.5) [1]
Urinary tract infection	0 (0.0) [0]	0 (0.0) [0]	1 (0.5) [1]
Urinary retention	0 (0.0) [0]	0 (0.0) [0]	1 (0.5) [1]
Oropharyngeal pain	0 (0.0) [0]	0 (0.0) [0]	1 (0.5) [1]
Constipation	0 (0.0) [0]	0 (0.0) [0]	1 (0.5) [1]
Flatulence	0 (0.0) [0]	0 (0.0) [0]	1 (0.5) [1]
Migraine	0 (0.0) [0]	0 (0.0) [0]	1 (0.5) [1]
Muscle tightness	0 (0.0) [0]	0 (0.0) [0]	1 (0.5) [1]
Vagal reaction	1 (2.5) [1]	1 (3.3) [1]	0 (0.0) [0]
Atrioventricular nodal reentrant tachycardia	0 (0.0) [0]	1 (3.3) [1]	0 (0.0) [0]
Haematuria	0 (0.0) [0]	1 (3.3) [1]	0 (0.0) [0]
Abdominal discomfort	0 (0.0) [0]	1 (3.3) [1]	0 (0.0) [0]
Vision blurred	0 (0.0) [0]	1 (3.3) [1]	0 (0.0) [0]
Asymptomatic cerebral embolism[a]	9 (22.5) [9]	0 (0.0) [0]	0 (0.0) [0]
Intubation complication (sore throat, cough, irritation)	5 (12.5) [6]	0 (0.0) [0]	0 (0.0) [0]
Back pain	1 (2.5) [1]	0 (0.0) [0]	0 (0.0) [0]
Pyrexia	1 (2.5) [1]	0 (0.0) [0]	0 (0.0) [0]

a The values are before assessment by a core laboratory. Of the 9 subjects in Wave I, 1 subject was determined to have no cerebral lesions based on the core laboratory assessment.

6.A.(3).3) Malfunction

The number of device malfunctions for the VARIPULSE Catheter and IRE Generator was 5 events in Wave I, 9 events in Wave II Roll-In, and 31 events in Wave II Main. Table 11 shows the details of malfunctions. There were no adverse events reported to be attributable to device-related malfunctions.

Table 11. Malfunctions of VARIPULSE Catheter and IRE Generator

Device	Malfunction category	Number of subjects experiencing malfunction (incidence, %) [number of events]		
		Wave I N = 40	Wave II Roll-In N = 30	Wave II Main N = 186
VARIPULSE Catheter	Device malfunction	4 (10.0) [4]	1 (3.3) [1]	10 (5.4) [11]
	Damage to bending mechanism of device	0 (0.0) [0]	2 (6.7) [2]	10 (5.4) [10]
	Poor ECG signal	1 (2.5) [1]	1 (3.3) [1]	6 (3.2) [7]
	Unable to properly remove device from sheath	0 (0.0) [0]	0 (0.0) [0]	1 (0.5) [1]
	Structural failure of device	0 (0.0) [0]	1 (3.3) [1]	0 (0.0) [0]
	Difficulty in insertion of device	0 (0.0) [0]	1 (3.3) [1]	0 (0.0) [0]
IRE Generator	Device malfunction	0 (0.0) [0]	3 (10.0) [3]	2 (1.1) [2]

6.B Outline of the review conducted by PMDA

6.B.(1) Clinical positioning

The applicant's explanation of the clinical positioning of the VARIPULSE Platform:

The strength and total delivery time of a pulsed electric field sufficient to generate heat in tissue are higher than the intensity and duration sufficient to induce cell death. With a suitable intensity and duration of pulsed electric field output, PFA is suggested to cause cell death without being dependent on a thermal effect. Therefore, the VARIPULSE Platform can contribute to reduce events associated with excessive heating such as tissue carbonization and steam pops, leading to a reduction in embolism, cardiac perforation, and other adverse events. Basic research on between-tissue variation in the strength of a pulsed electric field required to induce cell death has revealed that myocardial tissue has a lower threshold than that of other tissues. These findings suggest that PFA using the VARIPULSE Platform can selectively target myocardial tissue while sparing surrounding tissue such as the esophagus, phrenic nerve, and vagal nerve. Therefore, the VARIPULSE Platform is expected to have safety equivalent to or better than that of the approved

ablation devices. In addition, even though the technologies and mechanisms of ablation differ, the VARIPULSE Platform and approved ablation devices both cause tissue degeneration; therefore, the VARIPULSE Platform is expected to be as effective as the approved ablation devices.

The VARIPULSE Platform is designed to deliver PFA in which rapid (<1 second) electrical fields are applied to the target tissue. A PFA effect can be achieved without holding the VARIPULSE Catheter electrode at the same position with the myocardial tissue for a prolonged period. With the simplicity of use and shorter procedure time, the VARIPULSE Platform can be an excellent option equivalent or superior to the approved ablation devices.

PMDA's view on the clinical positioning of the VARIPULSE Platform:
The limited number of subjects in the inspIRE study precludes a thorough evaluation of the advantages of the VARIPULSE Platform, namely, a reduction in adverse events associated with excessive heating and a reduction in damage to the surrounding tissues. However, given that no adverse events of particular concern were reported in the animal studies and the inspIRE study, the VARIPULSE Platform can be expected to exhibit its advantages based on the technology of PFA. The VARIPULSE Platform is intended to be used for pulmonary vein isolation, a conventional treatment in patients with drug-refractory symptomatic paroxysmal atrial fibrillation. If the results of the inspIRE study demonstrate efficacy not inferior to the approved devices, and if the VARIPULSE Platform is not considered to pose greater safety concerns than those of the approved devices, offering the device to clinical practice as a new option for atrial fibrillation has its significance. The positioning of the VARIPULSE Platform is similar to that of approved ablation device [for the efficacy and safety of the VARIPULSE Platform, see Section 6.B.(3) and Section 6.B.(4), respectively]. It is also important to continue assessing data in clinical practice and confirm the advantages of the VARIPULSE Platform.

6.B.(2) Extrapolation of foreign clinical study data to Japan and justification of evaluation in single-arm study

The applicant's explanation of the appropriateness of evaluating the VARIPULSE Platform based on study results from the inspIRE study conducted in Europe and Canada rather than conducting a trial in Japan:
The VARIPULSE Platform is a device for the treatment of atrial fibrillation and blocks the abnormal electrical conduction pathways. It is scientifically unlikely that the mechanism of PFA or the resulting size of ablation lesion would vary among the ethnic groups. Moreover, in relation to ablation treatment of symptomatic paroxysmal atrial fibrillation, conditions including vascular access and morphology or size of the left atrium and pulmonary vein ostia are also unlikely to vary among ethnic groups. Therefore, the impact of ethnic factors on the study results should be

insignificant.

In addition, the indication for ablation in atrial fibrillation recommended in the treatment guidelines in Japan does not substantially differ from that in other countries. The novelty of the VARIPULSE Platform compared with approved ablation devices is the use of PFA. The method of use of the VARIPULSE Platform and its procedure are based on general cardiac catheterization and percutaneous catheter ablation of myocardial tissue; therefore, the method of use of the VARIPULSE Platform, devices to be used in conjunction with it, environments in which the device is used, and other conditions in Japan are similar to those in other countries.

PMDA's view:
The applicant's explanation is generally acceptable. In terms of use, no substantial differences appear to exist in the efficacy and environment of usage for the VARIPULSE Platform between Japan and other countries. Given that balloon ablation catheters, a type of catheter similar to the VARIPULSE Platform, have been approved in Japan for circumferential ablation of the pulmonary vein ostia, PMDA concluded that it is acceptable to review the efficacy and safety of the VARIPULSE Platform in the Japanese medical environment using the data from the inspIRE study conducted outside Japan, without repeating the clinical trial in Japan.

The applicant's explanation of evaluating the VARIPULSE Platform based on a single-arm study:
The 2017 Consensus Statement mentions that, in the future, it would be possible to evaluate medical devices designed to treat patients with symptomatic paroxysmal atrial fibrillation in non-randomized trials comparing prespecified performance targets or objective performance criteria based on established standards. Pulmonary vein isolation using an ablation catheter has been established as the standard therapy for paroxysmal atrial fibrillation in Europe, the US, and in Japan. Published data on the efficacy and safety of ablation catheters investigated in recent clinical studies, evaluated using similar primary endpoints, are similar regardless of the catheter techniques used, demonstrating that pulmonary vein isolation is a reliable way to reduce the recurrence of paroxysmal atrial fibrillation over time.

In these circumstances where there are ablation catheters that use various techniques, the safety and efficacy of the VARIPULSE Platform can be evaluated in a single-arm study by selecting a suitable performance target.

PMDA's view:
A number of ablation catheters for pulmonary vein isolation have been approved in Japan, and data on their use have been accrued. Under such circumstance, it is acceptable to evaluate the

efficacy and safety of the VARIPULSE Platform in a single-arm study if a suitable primary endpoint and performance target can be selected.

The applicant explained that, as shown in Table 2 mentioned above, although the IRE Generator used in the inspIRE study differs from the TRUPULSE Generator, ablation procedures were performed under conditions practically identical to those with the TRUPULSE Generator, with the exception of some patients in Wave I; therefore, it is appropriate to evaluate the VARIPULSE Platform using data from the inspIRE study, which used the IRE Generator.

PMDA concluded that the applicant's explanation is acceptable and it is possible to evaluate the VARIPULSE Platform based on the data from the inspIRE study, which used the IRE Generator.

6.B.(3) Efficacy

The freedom from atrial arrhythmia events at 12 months post-procedure, the primary efficacy endpoint of the Wave II Main in the inspIRE study was 70.0% (two-sided 95% CI, 62.1%-77.4%). The posterior probability of the freedom from atrial arrhythmia events exceeding the performance target of 50% is >99.9%, which is greater than the threshold for early success (99.75%) for the primary efficacy endpoint.

The applicant's explanation of the efficacy of the VARIPULSE Platform compared with the approved devices:

The approved devices, namely "Arctic Front Advance Cryoablation Catheter" (Approval No. 22600BZX00062000), "SATAKE·HotBalloon Catheter" (Approval No. 22700BZX00355000), and "HeartLight Endoscopic Ablation System" (Approval No. 22900BZX00248000), are designed for the same indication and procedure as those of VARIPULSE Platform (pulmonary vein isolation for the treatment of drug-refractory symptomatic paroxysmal atrial fibrillation). At the time of filing applications, the results of long-term efficacy studies, in which the studies were conducted by using the same procedure as that of the inspIRE study, were 69.9% (114 of 163 subjects),[11] 59.0% (59 of 100 subjects),[12] and 61.1% (102 of 167 subjects),[13] respectively. The efficacy criteria used in these studies were not necessarily the same as those used in the inspIRE study. There were differences in the following aspects:

- The definition of the primary efficacy endpoint for "SATAKE·HotBalloon Catheter" and "HeartLight Endoscopic Ablation System" did not include acute procedural failure. In the inspIRE study, as mentioned earlier, no requirements regarding repeat ablation were included in the primary efficacy endpoint. However, an additional evaluation indicated no subjects to which the repeat ablation would apply. Repeat ablations during the blanking period were not allowed in the clinical studies of the approved products above, while repeat ablations were

allowed up to twice in the inspIRE study. Consequently, only 1 subject in Wave I underwent repeat ablation during the blanking period, and this subject was excluded from the primary efficacy evaluation.

- The number of pulmonary veins to be assessed for acute procedural success was different: in the inspIRE study, the proportion of subjects in whom all the target pulmonary veins isolated by the procedure were evaluated. In the clinical studies of approved devices, data used for evaluation were as follows: the proportion of subjects with ≥3 pulmonary veins being isolated in the clinical study of the "Arctic Front Advance Cryoablation Catheter"; the proportion of subjects in whom all 4 of the pulmonary veins (right superior, right inferior, left superior, and left inferior pulmonary veins) were isolated in the clinical study of the "SATAKE·HotBalloon Catheter"; and the proportion of subjects in whom all the target pulmonary veins treated by the procedure were isolated in the clinical study of the "HeartLight Endoscopic Ablation System."
- The number of AADs included in the inclusion criteria was the highest in the inspIRE study and the clinical study of the "SATAKE·HotBalloon Catheter" (failed AADs of classes I through IV).
- Differences concerning concomitant use of AADs during the efficacy assessment period: concomitant use of AADs was prohibited in the clinical studies of the "Arctic Front Advance Cryoablation Catheter" and "SATAKE·HotBalloon Catheter." Conversely, concomitant use of AADs was not prohibited in the inspIRE study and the clinical study of the "HeartLight Endoscopic Ablation System." However, in the clinical study of the "HeartLight Endoscopic Ablation System," administration of new or increased dose of AADs was determined as effectiveness failure in the primary efficacy evaluation. In the inspIRE study, as mentioned earlier, no requirements regarding AADs were included in the primary efficacy endpoint. An additional evaluation indicated no subjects to which the above would apply.

Taken together, there are no differences that could have favorably influenced the efficacy evaluation of the inspIRE study compared with the clinical studies of the approved devices. Therefore, within the range of available results, the long-term efficacy of 70.0% in the early success testing of Wave II Main in the inspIRE study is equivalent to or better than the results of the devices approved in Japan.

PMDA's view on the efficacy of the VARIPULSE Platform:

The applicant's strategy to evaluate the freedom from atrial arrhythmia events at 12 months post-procedure, the primary efficacy endpoint, is appropriate. The definition of effectiveness failure in the primary efficacy endpoint should have included administration of new or increased doses of AADs during the efficacy assessment period and repeat ablation during the blanking period or

efficacy assessment period, in addition to the documented recurrence of atrial arrhythmia and acute procedural failure. However, no effectiveness failure was identified up to the interim analysis of Wave I and Wave II Main; as a result, it was considered acceptable.

PMDA accepted that the applicant performs an interim analysis by Bayesian adaptive design to determine early success and evaluates trial success based on the interim analysis results because the assessment was performed based on the prespecified threshold of the posterior probability. The performance target had been selected according to the 2017 Consensus Statement and the applicant's other similar approved devices. Although this may be reasonable to some extent, the applicant is required to demonstrate that the long-term efficacy data of the VARIPULSE Platform are not inferior to those of the approved ablation devices because there are ablation devices with clinical positioning similar to that of the VARIPULSE Platform in Japan. There are limitations to comparing the VARIPULSE Platform with the approved devices in Japan due to the differences in the analysis method and efficacy evaluation criteria as mentioned by the applicant. However, the 70.0% freedom from atrial arrhythmia events at 12 months post-procedure is not inferior to the data for the approved ablation devices; therefore, the efficacy of the VARIPULSE Platform was determined to be acceptable. The applicant should assess whether the VARIPULSE Platform can achieve efficacy without any problems in clinical practice in Japan through the use-results survey.

6.B.(4) Safety

The incidence of PAEs within 7 days of procedure, the primary safety endpoint of Wave II Main in the inspIRE study, was 0.5% (two-sided 95% CI, 0.0%-2.0%). The posterior probability of the incidence of PAEs being lower than the performance target of 14% was >99.9%, which is greater than the threshold for early success (97.5%) of the primary safety endpoint.

The applicant's explanation of the safety of the VARIPULSE Platform compared with the approved devices:

The clinical study data submitted at the time of filing applications for the following currently approved devices, "Arctic Front Advance Cryoablation Catheter," "SATAKE·HotBalloon Catheter," and "HeartLight Endoscopic Ablation System" showed that the results for the primary safety endpoint were 3.1% (5 of 163 subjects),[11] 12.0% (12 of 100 subjects),[12] and 11.8% (20 of 170 subjects),[13] respectively. The PAEs and definition of events in the primary safety endpoint of the inspIRE study are different from those in the clinical studies of approved devices submitted at the time of filing applications in Japan. However, the PAEs and definition of events in the inspIRE study cover those specified in the clinical studies for the approved devices, and PAEs were not reported in the final results, suggesting that the safety of the VARIPULSE Platform is

superior to that of the approved devices.

PMDA's view:
No PAEs occurred in the inspIRE study, and only 1 event of device- or procedure-related serious adverse event occurred in Wave II Main. Thus, a certain level of safety was demonstrated. Given that PFA is a new ablation technique, PMDA focused on the following 4 major safety concerns associated with ablation:

6.B.(4).1) Cerebral embolism

In all of the Wave I, Wave II Roll-In, and Wave II Main, there were no serious or non-serious embolic or thrombotic PAEs reported, including cerebrovascular accident/cerebrovascular disorder, transient ischaemic attack, and thromboembolism. However, 40 subjects in the Wave I underwent neurological evaluation by MRI, and asymptomatic cerebral embolism lesions were detected in 8 subjects at a core laboratory.

The applicant's explanation about the risk of the asymptomatic cerebral embolism associated with the use of the VARIPULSE Platform:
Of the 40 subjects in the Wave I analysis set, 39 subjects underwent brain MRI examination at the time of hospital discharge, excluding 1 subject who was dismissed from the examination for physical reasons. The MRI examinations revealed cerebral embolism in 8 subjects. All lesions were asymptomatic in the 8 subjects and were not detected by MRI examination at 1 month after the procedure. A separate new asymptomatic lesion (in different part of the brain) was detected in 1 of the 8 subjects by the MRI examination at 1 month after the procedure; however, the lesion was not detected by MRI examination at 3 month after the procedure. No subjects reported significant deterioration in neurological status according to the assessments using the modified Rankin scale (mRS), National Institutes of Health stroke scale (NIHSS), and mini mental state examination (MMSE).

The precise cause of asymptomatic cerebral embolism in the 8 subjects could not be elucidated. However, the following measures were implemented when asymptomatic cerebral embolism was detected in 4 of the first 6 subjects in Wave I, and the incidence of asymptomatic cerebral embolism subsequently decreased to 12.1% (4 of 33 subjects).

- A ≥10 second-pause was implemented between PFA applications.
- Adherence to recommendations
  - Strict adherence to continued anticoagulant regimen initiated ≥3 weeks before ablation
  - An activated clotting time (ACT) should be ≥350 seconds preablation and throughout the ablation procedure.

- Catheter exchanges in the left atrium should be minimized.

Although the above measures do not completely resolve the onset of asymptomatic cerebral embolism, given that the incidence of asymptomatic cerebral embolism reported in the 2017 Consensus Statement is 2% to 15%, the risk of asymptomatic cerebral embolism is suggested to be reduced to the level comparable to the approved devices. Therefore, these measures are considered appropriate. In addition, the possibility of the VARIPULSE Platform causing embolism as a result of its morphology/structure, ablation technology, and ablation method is discussed below:

The "Lasso 2515 Navi" (Approval No. 22200BZX00740000) is a catheter-based electrode for the heart, which is morphologically similar to the VARIPULSE Catheter, in terms of tip morphology/structure. In the past 5 years (2018-2022), the percentage of reported malfunctions and adverse events of embolism associated with the "Lasso 2515 Navi" in Japan is 0.004% (4 events occurred among 95,866 catheters). Assuming that asymptomatic cerebral embolism is attributable to the tip morphology of the VARIPULSE Catheter, the incidence would be similar to that of the "Lasso 2515 Navi."

There are no approved PFA catheter devices. At present, whether asymptomatic cerebral embolism is attributable to the ablation technology of the VARIPULSE Platform is unknown. According to a study published recently,[14] asymptomatic cerebral embolism can occur in either radiofrequency ablation or cryoablation in nearly 25% of patients. Another study[15] has reported that 30%, 24%, 34%, and 39% of patients who received ablation procedure using the radiofrequency ablation catheter of "Arctic Front Advance Cryoablation Catheter," "SATAKE·HotBalloon Catheter," and "HeartLight Endoscopic Ablation System," respectively, developed asymptomatic cerebral embolism. Although it is unknown if embolism is attributable to ablation, a risk of embolism has been reported with other ablation catheters. Like other approved devices, the VARIPULSE Platform, which uses a new ablation technology, also involves a certain level of risk for developing embolism.

To investigate a causal relationship to the ablation method, a wide variety of available clinical data including the number of ablations, number of applications, the pause between applications and other parameters as well as the position of ablation for the first 6 subjects in Wave I were closely examined for any information indicating the cause of asymptomatic cerebral embolism. No relevant clinical data were identified. However, among the first 6 subjects in Wave I, 5 subjects had a shorter pause between applications with a mean of <10 seconds, and 4 of these subjects developed asymptomatic cerebral embolism. The event did not develop in 1 subject with

<10-second pause nor did it develop in 1 subject with ≥10-second pause; therefore, as mentioned above, ≥10-second pause between applications was implemented as one of the measures. Consequently, the incidence of asymptomatic cerebral embolism decreased, and therefore it was decided to continue implementing the measure after the market launch.

PMDA's view on the risk of asymptomatic cerebral embolism associated with the use of VARIPULSE Platform:
The measures implemented after 4 of the first 6 subjects developed asymptomatic cerebral embolism are considered to reduce a certain level of risks because the incidence of asymptomatic cerebral embolism in 33 subjects undergoing ablation after the measures were implemented decreased to 12.1% (4 of 33 subjects). However, the cause of asymptomatic cerebral embolism has not been identified. Moreover, the appropriateness of adopting each measure, especially the rationale for selecting a ≥10-second pause between applications, have not been properly explained. Conversely, according to the 2017 Consensus Statement and "Japanese Circulation Society/Japanese Heart Rhythm Society Guideline on Non-Pharmacotherapy of Cardiac Arrhythmias (2018)[16]" the incidence of asymptomatic cerebral embolism after atrial fibrillation ablation is reported to be range from 2% to 15%. In addition, some of the studies presented by the applicant reported an even higher incidence; all events of asymptomatic cerebral embolism in the inspIRE study resolved during the follow-up period; and no subjects presented significant deterioration in neurological status as assessed by mRS, NIHSS, or MMSE; therefore, it cannot be concluded that the incidence of asymptomatic cerebral embolism associated with the VARIPULSE Platform and the degree of seriousness are clearly higher than those of approved atrial fibrillation devices.

Although the influence of the ablation technology of the VARIPULSE Platform remains unclear, PFA is unlikely to generate heat based on its technology. Embolic events or thrombotic events other than asymptomatic cerebral embolism did not occur in Wave I or Wave II; a cardiac catheter morphologically similar to the VARIPULSE Platform is currently available on the market, and based on the results of clinical use, it is unlikely that asymptomatic cerebral embolism would occur due to the device's morphological structure. In the animal studies, thrombus at the VARIPULSE Catheter tip, mural thrombus in myocardial tissue, and thromboembolism in peripheral tissue were not reported. Therefore, the VARIPULSE Platform can be used clinically while implementing the risk minimization measures mentioned above. Since the causes of asymptomatic cerebral embolism have not been clearly identified, a detailed account of each instance of embolic events and thrombotic events in post-marketing settings should be included in the use-results survey, and if new knowledge becomes available, such information should be provided to healthcare professionals. On the basis of the foregoing, it cannot be concluded that

the risk of asymptomatic cerebral embolism associated with the VARIPULSE Platform is clearly higher than that of approved devices; in addition, brain MRI examination is not routinely performed in all patients after catheter ablation procedure in daily medical practice. Therefore, based on the comments from the Expert Discussion, brain MRI examination is not mandatory in post-marketing settings, and MRI should only be performed in patients who are more likely to have cerebral infarction or other lesions in accordance with the routine medical practice.

6.B.(4).2) Oesophageal injury and atrio-oesophageal fistula

The applicant's explanation about the risk of oesophageal injury and atrio-oesophageal fistula associated with the VARIPULSE Platform:

In Wave I, Wave II Roll-In, and Wave II Main, there were no reports of device- or procedure-related serious or non-serious esophageal adverse events, including PAE of left atrio-oesophageal fistula. The esophagus was endoscopically evaluated in 40 subjects of the Wave I analysis set only. Of these, 39 subjects underwent endoscopic examinations after the procedure, and the endoscopic images of 37 subjects were sent to the core laboratory. Of the 37 subjects, endoscopic images of 32 subjects were evaluated, and no esophageal thermal lesions were detected. Reasons for not conducting evaluation in 8 subjects were "refusal to endoscopic examination" (1 subject), "unable to obtain images that can be sent to the core laboratory" (2 subjects), and "poor quality of images sent to the core laboratory" (5 subjects), but all 8 subjects completed the study without developing device-related serious adverse events.

In the inspIRE study, esophageal monitoring was optional. In Wave I, radiographic visualization of the esophagus was performed in 5 of 40 subjects (12.5%) by either barium swallow examination or the use of contrast media. In Wave II Roll-In, no esophageal monitoring was performed. In Wave II Main, esophageal monitoring was performed using an esophageal temperature probe in 4 of 186 subjects (2.2%). Accordingly, esophageal monitoring will be optional in the post-marketing period, equivalent to the monitoring implemented in the inspIRE study.

PMDA's view on the risk of oesophageal injury and atrio-oesophageal fistula associated with the VARIPULSE Platform:

In Wave I, endoscopic images of the esophagus were evaluated in 32 of 40 subjects with and without symptoms, and no esophageal thermal lesions were detected. Throughout the inspIRE study, esophageal monitoring was performed as an option, and no oesophageal injury or atrio-oesophageal fistula was reported. Accordingly, the VARIPULSE Platform does not necessarily have a higher risk of oesophageal injury and atrio-oesophageal fistula compared with the approved devices. As was done in the inspIRE study, it is acceptable to perform esophageal

monitoring as an option, but the applicant should collect information on the occurrence of esophageal adverse events in the use-results survey, and new information should be appropriately communicated to healthcare professionals when it becomes available.

6.B.(4).3) Phrenic nerve paralysis

The applicant's explanation about the risk of phrenic nerve paralysis associated with the VARIPULSE Platform:

In the inspIRE study, there were no reports of permanent phrenic nerve paralysis, a PAE, nor serious or non-serious adverse events including transient phrenic nerve paralysis. In the study, preablation phrenic nerve pacing was required in the right pulmonary vein for all subjects, and diaphragmatic capture was monitored to assess the proximity of the right pulmonary vein to the phrenic nerve. Diaphragmatic capture was achieved in 23 of 40 subjects (57.5%) in Wave I, 22 of 30 subjects (73.3%) in Wave II Roll-In, and 168 of 186 subjects (90.3%) in Wave II Main. Only the number of subjects who received the postablation phrenic nerve pacing was collected as follows: 40 of 40 subjects (100.0%) in Wave I, 24 of 30 subjects (80.0%) in Wave II Roll-In, and 177 of 186 subjects (95.2%) in Wave II Main.

In the inspIRE study, ablation was allowed even when preablation phrenic nerve pacing indicated that the pulmonary vein was in close proximity to the phrenic nerve. Consequently, some subjects underwent ablation close to the phrenic nerve, but no phrenic nerve paralysis occurred throughout the study. The need to avoid the phrenic nerve during ablation with the VARIPULSE Platform was not suggested from a clinical viewpoint. In the swine workflow study [see Section "2.(6) Performance"], ablation was performed intentionally in the areas adjacent to the phrenic nerve rather than avoiding these areas in 6 of 9 animals in the PFA group, but postablation phrenic nerve pacing confirmed a response, indicating no phrenic nerve injury. Accordingly, phrenic nerve monitoring before and during ablation will be optional in post-marketing settings.

PMDA's view on the risk of phrenic nerve paralysis associated with the VARIPULSE Platform:

In the inspIRE study, preablation phrenic nerve pacing was required for all subjects to assess the proximity to the phrenic nerve. However, even when preablation phrenic nerve pacing indicated that the pulmonary vein was in close proximity to the phrenic nerve, ablation at such a site was allowed. As a result, no phrenic nerve paralysis occurred throughout the inspIRE study, and it was therefore determined that the VARIPULSE Platform does not necessarily have a higher risk of phrenic nerve paralysis compared with the approved devices. Phrenic nerve pacing during ablation causes diaphragm to move, possibly dislocating the VARIPULSE catheter. Furthermore, each PFA energy delivery time is extremely short, with a duration of 239 ± 5 ms. According to the information provided, placement of other metal object in the same atrium during ablation with

the VARIPULSE Catheter may affect the pulsed electric field, causing thermal burns, and thus should be avoided. Therefore, there are no compelling medical reasons to perform phrenic nerve pacing during ablation. Taking account of the comments from the Expert Discussion, PMDA concluded that the risk of phrenic nerve paralysis is acceptable and that the applicant's plan to implement phrenic nerve monitoring as an option in the post-marketing settings is acceptable. Data on phrenic nerve paralysis should be collected in the use-results survey to confirm that the risk is maintained at an acceptable level in clinical practice, and if new knowledge becomes available, such information should be provided to healthcare professionals.

6.B.(4).4) Pulmonary vein stenosis

The applicant's explanation about the risk of pulmonary vein stenosis associated with the VARIPULSE Platform:

In Wave I, Wave II Roll-In, and Wave II Main of the inspIRE study, the protocol required CT/MRA to be performed in subjects who presented with symptoms of pulmonary vein stenosis, such as chest pain, dyspnoea, and cough. The following adverse events occurred: chest pain in 1 subject (precordial pain and interscapular pain) in Wave I; chest pain in 2 subjects (transient chest pain [1 subject] and retrosternal pain [1 subject]) in Wave II Roll-In; and chest pain in 2 subjects (aggravated chest pressure sensation and chest pain exertional aggravated [1 subject], and thoracic pain [1 subject]), and dyspnoea in 4 subjects (dyspnoea [2 subjects], sporadic dyspnoea [1 subject], and dyspnoea exertional [1 subject]) in Wave II Main. All of these events were classified as non-serious and did not require CT/MRA examinations at the discretion of the investigator. On the basis of the above, no pulmonary vein stenosis as classified as PAE were reported. As an additional safety endpoint, imaging examinations by CT/MRA were performed at 3 months postablation only in the 40 subjects in the analysis set of Wave I. After excluding 2 subjects for "unanalyzable CT images at 3 month after the procedure (Month 3) as assessed by the core laboratory" (1 subject) and "refusal of examination" (1 subject), the images at baseline and Month 3 were analyzed at the core laboratory for the remaining 38 subjects. The results showed absence of pulmonary vein stenosis in 11 of 38 subjects (28.9%) and minor stenosis (0%-25% narrowing of pulmonary vein diameter) in 27 of 38 subjects (71.1%). There were no reports of mild stenosis (25%-50%), moderate stenosis (50%-70%), or severe stenosis (≥70%).

PMDA's view on the risk of pulmonary vein stenosis associated with the VARIPULSE Platform:

Pulmonary vein stenosis after pulmonary vein isolation is a complication which is also reported with approved ablation devices. With the VARIPULSE Platform, however, ablation is performed on a wide area at once using multiple electrodes; and the technology of ablation differs from that of the conventional methods; therefore, it is important to note that the risk of pulmonary vein stenosis associated with the VARIPULSE Platform may be higher than the risk associated with

approved ablation devices. To accurately evaluate the risk of pulmonary vein stenosis associated with the VARIPULSE Platform, image evaluation should have been performed for all subjects in the latter part of the post-procedure period regardless of symptoms in the inspIRE study. However, taking into account the 2017 Consensus Statement, in which image evaluation at several months post-procedure is proposed for screening of pulmonary vein stenosis, it was considered that a certain level of risk was evaluated. Throughout the inspIRE study, no subjects presented with symptoms of pulmonary vein stenosis that are deemed to require CT/MRA examinations, no PAE of pulmonary vein stenosis occurred, and none of the CT/MRA images evaluated in Wave I indicated >25% stenosis. These findings suggest that the risk of pulmonary vein stenosis associated with the VARIPULSE Platform is not necessarily higher than that associated with the approved devices. Therefore, PMDA concluded that the VARIPULSE Platform can be made available to clinical practice. The incidence of pulmonary vein stenosis-related adverse events should be collected in the use-results survey, and if new knowledge becomes available, such information should be appropriately communicated to healthcare professionals.

6.B.(5) Post-marketing safety measures

The applicant plans to provide a training program as shown below for physicians who will be using the VARIPULSE Platform for the first time, based on the training program provided in the inspIRE study. The applicant explained that details would be prepared in cooperation with the Japanese Heart Rhythm Society.

- Lecture: Overview of VARIPULSE Platform, explanation of technology, directions for use, etc. data from the inspIRE study, precautions for proper use and safety
- Hands-on training: Operation of catheter using the simulator and heart model

The applicant's explanation of physicians and medical institutions that intend to use the VARIPULSE Platform:

The applicant plans to develop requirements tailored for the VARIPULSE Platform in cooperation with Japanese Heart Rhythm Society based on the "Facility requirements and qualification required to implement percutaneous cardiac catheter cryoablation" (dated June 25, 2014) published by the Ablation Committee of the Japanese Heart Rhythm Society.

PMDA's view on post-marketing safety measures:

The VARIPULSE Platform differs from conventional radiofrequency ablation devices or balloon ablation devices in terms of the configuration and technology of ablation. In addition, there is not enough evidence supporting the advantages expected from the PFA technology (e.g., reduction in thermal adverse events and injury of surrounding tissue). Therefore, to ensure safety, the VARIPULSE Platform should be used carefully after clearly understanding the risks associated

with the VARIPULSE Platform. The VARIPULSE Platform should be used at medical institutions capable of responding to various complications by physicians with sufficient experience in percutaneous ablation for the treatment of arrhythmia after participating in appropriate training workshops on the VARIPULSE Platform. The applicant plans to establish the requirements for performing physicians and facilities, as well as the details of training workshops in cooperation with relevant academic societies, and PMDA concluded that the applicant's strategy is appropriate, and decided to set these conditions for approval.

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

7.A Summary of the data submitted

Table 12 shows the summary of the use-results survey (draft) submitted by the applicant. To implement the use-results survey, the applicant plans to use the Japanese Catheter Ablation Registry (J-AB Registry), an all-patient registration project which has been implemented jointly by the National Cerebral and Cardiovascular Center and Japanese Heart Rhythm Society. The preparation for the survey is currently in progress in cooperation with the Japanese Heart Rhythm Society.

Table 12. Outline of use-results survey (draft)

Objective	To investigate the safety and efficacy of ablation procedures with the VARIPULSE Platform in patients with drug-refractory symptomatic paroxysmal atrial fibrillation
Planned sample size	300 patients
Number of planned study centers	Maximum of 25 study centers
Survey period	4 years (survey preparation period, 12 months; registration period, 18 months; follow-up period, 12 months; evaluation/analysis period, 6 months)
Key survey items	Acute procedural success, recurrence at 1 year, primary adverse events (atrio-oesophageal fistula, phrenic nerve paralysis, cardiac tamponade/perforation, pulmonary vein stenosis, death, cerebrovascular accident/cerebrovascular disorder/transient ischaemic attack, complications/haemorrhage associated with main vascular access, myocardial infarction), malfunctions

The applicant's explanation about the sample size for the use-results survey:
Since no PAEs occurred in the inspIRE study, the sample size was determined based on the

incidence of main adverse events (phrenic nerve paralysis, pericardial effusion, cardiac tamponade, haematoma at the puncture site, pleural effusion, pulmonary vein stenosis, death, and left atrio-oesophageal fistula) in the use-results survey of "Arctic Front Advance Cryoablation Catheter," an approved device used in Japanese clinical practice for the same indication and procedure (i.e., pulmonary vein isolation in patients with drug-refractory symptomatic paroxysmal atrial fibrillation) as those for the VARIPULSE Platform. The incidences of these events during a follow-up period of 6 months were 3.7% (23 of 616 subjects) for device-related adverse events and 3.9% (24 of 616 subjects) for procedure-related adverse events.[17] Given that no PAEs were reported in the inspIRE study, and a lower incidence of above-mentioned adverse events is assumed for the use-results survey of the VARIPULSE Platform, a sample size of 300 patients is calculated to allow detection of ≥1 such event occurring at an incidence of 1% with a probability of 95%.

7.B Outline of the review conducted by PMDA

The VARIPULSE Platform is a device with a novel technology of ablation, and available clinical data are limited; therefore, it is important to investigate efficacy and safety in clinical use in Japan through the post-marketing use-results survey and take additional risk minimization measures as necessary. On the basis of the data from the use-results survey of an approved device, the applicant plans to select a sample size of 300 patients so as to detect adverse events occurring at an incidence of 1%, lower than the incidence reported with the approved device. PMDA concluded that the applicant's plan regarding the sample size is acceptable. Taking into consideration the type of disease to be treated, a follow-up period of 12 months was proposed for each patient, and based on the follow-up period, a survey period of 4 years for the use-results survey was proposed. PMDA considers that there is no particular problem with the proposed follow-up and survey period at present. In addition, the proposed key survey items, which include commonly reported events associated with atrial fibrillation ablation, are also acceptable.

On the basis of the above, PMDA concluded that the proposed use-results survey (draft) is acceptable.

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

8.A Summary of the data submitted

The applicant submitted Information on Precautions, etc. (draft) for the VARIPULSE Catheter as an attachment in accordance with the Notification titled "Application for Marketing Approval of

Medical Devices" (PFSB Notification No. 1120-5, dated November 20, 2014).

8.B Outline of the review conducted by PMDA

On the basis of the conclusion of the Expert Discussion, PMDA concluded that there was no particular problem with the proposed Information on Precautions etc., provided that the applicant advises necessary caution.

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 inspections and data integrity assessment

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

PMDA's conclusion concerning the results of the on-site GCP inspection

The medical device application data 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.

IV. Overall Evaluation

The review of the VARIPULSE Platform focused primarily on (1) the efficacy and safety of the VARIPULSE Platform; and (2) post-marketing safety measures. PMDA reached the following conclusions, taking account of comments from the Expert Discussion:

(1) Efficacy and safety of the VARIPULSE Platform

The inspIRE study investigated the efficacy and safety of the VARIPULSE Platform when used for pulmonary vein isolation in patients with drug-refractory symptomatic paroxysmal atrial fibrillation. In the inspIRE study, the results achieved both the prespecified performance targets of "freedom from atrial fibrillation at 12 months post-procedure" (primary efficacy endpoint) and "incidence of PAEs within 7 days of procedure" (primary safety endpoint). A comparison with the clinical study data for the approved devices indicated that the performance of the VARIPULSE Platform was not inferior to that of the approved devices. The advantages of the VARIPULSE Platform, a reduction in adverse events associated with excessive heating and a

reduction in damage of the surrounding tissues, can be expected in clinical practice, in principle. Therefore, it is important to make the VARIPULSE Platform available in clinical practice as a new device option to be used in pulmonary vein isolation, while evaluating data related to these advantages in actual clinical practice.

(2) Post-marketing safety measures

The VARIPULSE Platform differs from conventional radiofrequency ablation devices or balloon ablation devices with respect to configuration and technology of ablation. Therefore, the VARIPULSE Platform should be used carefully to ensure safety after the risks associated with the procedure are clearly understood. The VARIPULSE Platform should be used at medical institutions capable of responding to various complications by physicians with sufficient experience in percutaneous ablation for the treatment of arrhythmia after participating in appropriate training workshops on the VARIPULSE Platform. PMDA decided to impose the approval condition.

The VARIPULSE Platform, a device with novel ablation technology, has not previously been used in Japan, and available clinical data are limited at present; therefore, PMDA considers that efficacy and safety in actual clinical use in Japan should be confirmed through the post-marketing safety measures discussed above, and additional risk minimization measures should be taken as necessary. PMDA concluded that the duration of the use-results survey should be 4 years (12 months survey preparation, 18 months registration, 12 months follow-up, and 6 months evaluation/analysis).

As a result of the above review, PMDA has concluded that the VARIPULSE Platform may be approved with the following intended use and approval conditions.

Intended Use of VARIPULSE Catheter

The VARIPULSE Catheter is a multielectrode catheter intended to be used for pulsed field ablation and cardiac electrophysiologic examination for the treatment of drug-refractory symptomatic paroxysmal atrial fibrillation.

Intended Use of TRUPULSE Generator

The TRUPULSE Generator is a device that delivers pulsed field ablation energy for percutaneous myocardial catheter ablation in the treatment of tachyarrhythmia.

Approval Conditions

The applicant is required to take necessary actions such as; (i) disseminating information on the

eligibility requirements for physicians who perform ablation and eligibility criteria for medical institutions prepared in cooperation with relevant academic societies; (ii) providing training workshops for physicians who have sufficient knowledge and experience in percutaneous catheter ablation for the treatment of arrhythmia including atrial fibrillation, so that the physicians would sufficiently acquire the required skills and adequate knowledge including procedural complications, etc. before using the product at medical institutions capable of providing appropriate medical care.

The product is not classified as a biological product or a specified biological product. The product should be designated as a medical device subject to a use-results survey. The use-results survey period should be 4 years.

PMDA has concluded that this application should be deliberated at the Committee on Medical Devices and *In-vitro* Diagnostics.

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