April 28, 2015
The Counsellor of the Minister's Secretariat
Medical Device and Regenerative Medicine Product Evaluation
Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

Report on the Deliberation Results

Classification	Instrument & Apparatus 31 Medical Ablation Device
Term Name	1. PDT semiconductor laser 2. Single-use probe for PDT semiconductor laser
Brand Name	1. PD Laser 2. EC-PDT Probe
Applicant	Panasonic Healthcare Co., Ltd.
Date of Application	December 22, 2014 (1. Application for partial change approval; 2. Application for marketing approval)

Results of Deliberation
In its meeting held on April 28, 2015, 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 should be approved with a designation as a product subjected to a use-results survey and with the following condition. The product is not classified as a biological product or a specified biological product.

Approval Condition
The applicant is required to take necessary measures, in cooperation with relevant academic societies, to ensure that the product is used strictly for the intended purpose by physicians with adequate knowledge and experience in diagnosis and endoscopic treatment of esophageal carcinoma who have acquired photodynamic therapeutic techniques with the product and sufficient knowledge about therapy-associated complications through training sessions, etc.

The period for the use-results survey should be the same as the re-examination period (10 years) of talaporfin sodium (non-proprietary name; brand name is Laserphyrin 100 mg for Injection), the drug used in conjunction with the product.

Review Report

April 13, 2015
Pharmaceuticals and Medical Devices Agency

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

Classification	Instrument & Apparatus 31 Medical Ablation Device
Term Name	1. PDT semiconductor laser
	2. Single-use probe for PDT semiconductor laser (to be newly created)
Brand Name	1. PD Laser
	2. EC-PDT Probe
Applicant	Panasonic Healthcare Co., Ltd.
Date of Application	December 22, 2014
Items Warranting Special Mention	Orphan medical device
Reviewing Office	Office of Medical Devices II

Review Results

April 13, 2015

Classification	Instrument & Apparatus 31 Medical Ablation Device
Term Name	1. PDT semiconductor laser 2. Single-use probe for PDT semiconductor laser (to be newly created)
Brand Name	1. PD Laser 2. EC-PDT Probe
Applicant	Panasonic Healthcare Co., Ltd.
Date of Application	December 22, 2014

Results of Review

The PD laser is a laser oscillator used in photodynamic therapy (PDT). In use with an oncotropic photosensitizer, namely, talaporfin sodium (brand name, Laserphyrin® 100 mg for injection, approval No. 21500AMZ00509000; hereinafter Laserphyrin), PD Laser emits a continuous wave laser beam at a central excitation wavelength of 664 nm. PD Laser and Laserphyrin have already been approved for PDT for early-stage lung cancer. For PD Laser, the applicant has recently filed a partial change application with an additional indication of local residual/recurrent esophageal carcinoma after chemoradiotherapy or radiotherapy. EC-PDT Probe is a laser probe specially designed for the PDT of local residual/recurrent esophageal carcinoma after chemoradiotherapy or radiotherapy. Four to 6 hours after the administration of Laserphyrin, the treatment target lesion is irradiated with laser light using PD Laser/EC-PDT Probe (the product).

An investigator-initiated clinical trial (Study KUTR-015-2, Japanese phase II study) was conducted at 7 study centers in Japan to assess the efficacy and safety of PDT using the product with Laserphyrin on local residual/recurrent esophageal carcinoma after chemoradiotherapy or radiotherapy. The study was conducted without a control group, and all 26 enrolled subjects received PDT. The local complete response (L-CR) rate, the primary endpoint assessed by the central review committee, was 88.5% (23 of 26 subjects; 95% confidence interval [CI], 69.8-97.6). The probability that the L-CR rate would exceed the predefined threshold of 15% was estimated to be 100%. Secondary endpoints included confirmed L-CR, local progression-free survival, progression-free survival, time to local progression, overall survival, L-CR in each lesion, and confirmed L-CR in each lesion. All subjects experienced adverse events for which a causal relationship to Laserphyrin and/or PDT could not be ruled out. However, for all serious adverse events, a causal relationship to Laserphyrin, use of the product (laser irradiation), and PDT was ruled out. As evaluation data relating to non-clinical studies of PD Laser, the applicant submitted results from studies on electrical safety and electromagnetic compatibility. As evaluation data relating to non-clinical studies of EC-PDT Probe, the applicant submitted results from studies on stability and durability, biological safety, mechanical safety, and studies supporting the performance, efficacy, and method of use of the device, etc. Based on a comprehensive evaluation of the submitted data and the comments from the Expert Discussion, PMDA concluded that the efficacy and safety of the product had been demonstrated. Meanwhile, it is essential to take necessary measures such as providing physicians with learning opportunities such as a training program or workshop so that they become able to identify eligible patients for Laserphyrin-mediated PDT and have adequate knowledge in endoscopic treatment of esophageal carcinoma.

As a result of its regulatory review, PMDA has concluded that the product may be approved for the intended use shown below, with the following approval condition, and that this application should be subjected to deliberation by the Committee on Medical Devices and *In-vitro* Diagnostics.

Intended Use

PD Laser

PD Laser is a laser device to be used for photodynamic therapy in combination with a drug for the treatment of patients with the following conditions:

Drug to be used in combination:

Non-proprietary name: talaporfin sodium

Brand name: Laserphyrin 100 mg for Injection

Indications:

1) Early-stage lung cancer (Stage 0 or I) treatable with laser irradiation in patients ineligible for other radical interventions including surgical resection or in patients who require the preservation of pulmonary function but cannot receive other treatments. The entire tumor must be observable endoscopically.
2) Local residual/recurrent esophageal carcinoma after chemoradiotherapy or radiotherapy

EC-PDT probe

EC-PDT probe is used in the photodynamic therapy of local residual/recurrent esophageal carcinoma after chemoradiotherapy or radiotherapy.

Approval Condition

The applicant is required to take necessary measures, in cooperation with relevant academic societies, to ensure that the product is used strictly for the intended purpose by physicians with adequate knowledge and experience in diagnosis and endoscopic treatment of esophageal carcinoma who have acquired photodynamic therapeutic techniques with the product and sufficient knowledge about therapy-associated complications through training sessions, etc.

Review Report

April 13, 2015

I. Product for Review

Classification Instrument & Apparatus 31 Medical Ablation Device

Term Name 1. PDT semiconductor laser
2. Single-use probe for PDT semiconductor laser (to be newly created)

Brand Name 1. PD Laser
2. EC-PDT Probe

Applicant Panasonic Healthcare Co., Ltd.

Date of Application December 22, 2014 (Application for partial change approval for PD Laser)

Proposed Intended Use

1. 1. Intended use
   The product is a laser device intended for photodynamic therapy, in which an oncotropic photosensitizer is injected to be accumulated in tumors and is thereby activated via laser irradiation to kill the tumor cells. The product is used with the following drug:
   Marketing authorization holder: Meiji Seika Pharma Co., Ltd.
   Non-proprietary name: talaporfin sodium
   Brand name: Laserphyrin 100 mg for injection
   2. Indications
   1) Early-stage lung cancer (Stage 0 or I) with a lesion that is endoscopically fully observable and allows for laser irradiation, in patients ineligible for other radical interventions including surgical resection or in those who require the preservation of pulmonary function but are ineligible for other treatments.
   2) The product is used in the photodynamic therapy of local residual/recurrent esophageal carcinoma after chemoradiotherapy or radiotherapy.

   (Underline denotes additions.)

2. The product is used in the photodynamic therapy of local residual/recurrent esophageal carcinoma after chemoradiotherapy or radiotherapy.

Items Warranting Special Mention Orphan medical device

II. Product Overview

Photodynamic therapy (PDT) is a treatment involving a photochemical reaction of an oncotropic photosensitizer to light, which allows for the generation of excited-state singlet oxygen that is highly oxidative, thereby degenerating and necrotizing tumor cells. PD Laser (emits a continuous wave laser beam at a central wavelength of 664 nm. See Figure 1) was approved for marketing in January 2004 as a medical device to be used in combination with an oncotropic photosensitizer, talaporfin sodium (brand name, Laserphyrin® 100 mg for injection, approval No.

21500AMZ00509000) for the treatment of early-stage lung cancer. Recently, the applicant has submitted the partial change application for PD Laser for an additional indication of local residual/recurrent esophageal carcinoma after chemoradiotherapy (CRT) or radiotherapy (RT). In conjunction with the application for PD Laser, a marketing approval application for EC-PDT Probe (Figures 2 and 3), a laser probe specially designed for PDT of local residual/recurrent esophageal carcinoma, was filed.

Laser irradiation is performed using PD Laser/EC-PDT Probe (the product) 4 to 6 hours after intravenous administration of talaporfin sodium. EC-PDT Probe, connected to PD Laser, is passed through a flexible endoscope, which is then inserted into the esophagus. The target lesion is identified endoscopically and irradiated with laser light (Figure 4).

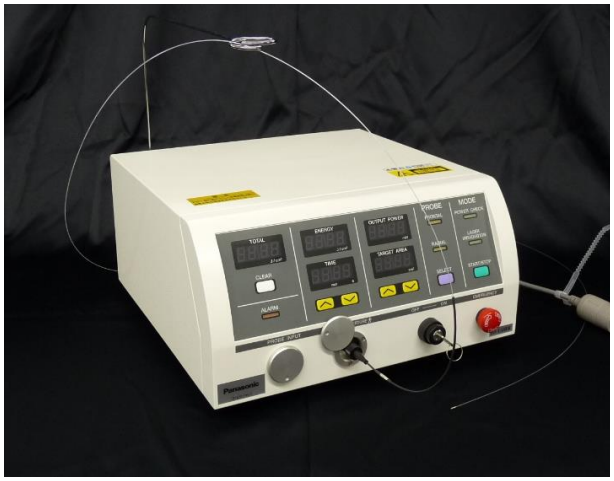


Figure 1. Appearance of PD Laser

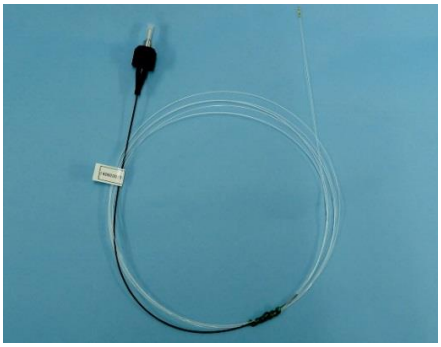


Figure 2. Appearance of EC-PDT Probe

Figure 3. Enlarged view of the tip of EC-PDT Probe

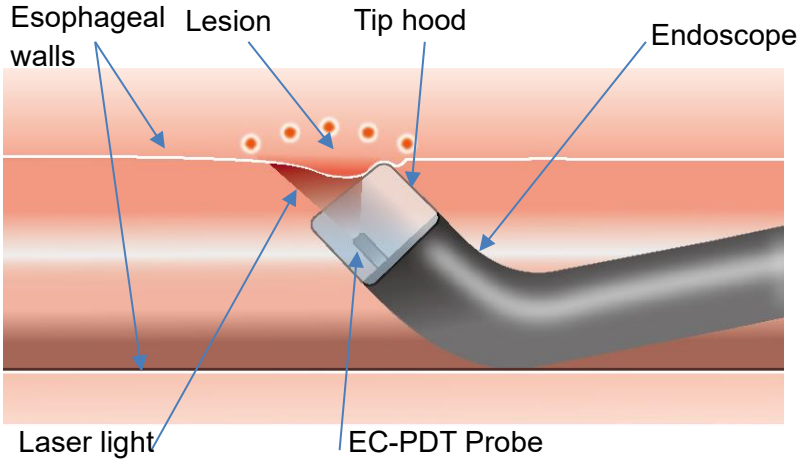


Figure 4. Schematic illustration of the treatment with PD Laser/EC-PDT Probe

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

The data submitted by the applicant and the applicant's responses to inquiries from the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined as follows. The review of the product focused primarily on the assessment on whether the product has quality, efficacy, and safety required in a laser irradiation system used for the photoexcitation of talaporfin sodium. As mentioned later, the review results of talaporfin sodium were cited in Section "8. Clinical data." Because the present application was filed for a partial change for PD Laser, the focus of review was efficacy and safety relating to the change. Because the present application was accepted after the enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices during the interim measure period (until March 31, 2015); the attached data were compiled in accordance with item 5, Article 40 of Regulation for Enforcement of the Pharmaceutical Affairs Act.

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

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

Origin or history of development

PDT is a treatment involving a photochemical reaction of an oncotropic photosensitizer to light, which allows for the generation of highly oxidative singlet oxygen, thereby degenerating and necrotizing tumor cells. Talaporfin sodium, the photosensitizer to be used with the product, has already been approved for the indications of early-stage lung cancer and primary malignant brain tumor. For early-stage lung cancer, PD Laser has been approved for use in combination with talaporfin sodium, while "PD Laser BT" has been approved for use with talaporfin sodium for primary malignant brain tumor (only in patients who undergo brain tumor resection) (Table 1).

Table 1. Approval status of talaporfin sodium-mediated PDT

Indications	Photosensitizer	Device
Early-stage lung cancer	Talaporfin sodium	Brand name: PD Laser Date of approval: January 7, 2004 Approval No.: 21600BZZ00026000 * The approval covers the light irradiation probe
Primary malignant brain tumor		Brand name: PD Laser BT Date of approval: September 20, 2013 Approval No.: 22500BZX00420000 * The approval covers the light irradiation unit
Local residual/recurrent esophageal carcinoma		**Brand name: PD Laser (the device)** **Brand name: EC-PDT Probe (the probe)**

The present application was filed for the indication of local residual/recurrent esophageal carcinoma after CRT or RT. Rapid growth of tumors may cause esophageal stenosis, dysphagia, and airway compression, etc., leading to significant deterioration of QOL. Therefore, local control of lesions is expected to improve QOL.[1] Currently, no standard treatment has been established for local residual/recurrent esophageal carcinoma after CRT or RT. Available salvage treatment includes surgical intervention, endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD).[2,3] However, salvage surgery is associated with frequent serious perioperative complications posed by radiation, which can cause adhesion of the esophagus to surrounding tissues and fragility of tissues in these areas due to decreased blood flow. Postoperative complication-associated hospital mortality is as high as 7% to 22%,[4,5,6,7,8] suggesting that salvage surgery is not a safe enough treatment. In addition, surgery is often impractical for being highly invasive. ESD and EMR also require skilled technique and can target only lesions with a wall invasion within the lamina propria.

In response to the growing demand for effective and safe new treatment options for patients with local residual/recurrent esophageal carcinoma, Study KUTR-015-2, a Japanese phase II study, was conducted in November 2012 in patients with local residual/recurrent esophageal carcinoma after CRT or RT to assess the efficacy and safety of talaporfin sodium-mediated PDT based on the results from clinical research which evaluated the efficacy and safety of PDT.[9,10,11]

The probe used in the clinical research and Study KUTR-015-2 was a direct irradiation probe which had been approved for the treatment of early-stage lung cancer (hereinafter Probe for lung cancer). However, PD Laser/EC- PDT Probe is intended for local residual/recurrent esophageal carcinoma after CRT or RT, which often causes bleeding from the lesion, unlike early-stage lung cancer. Blood can stain the lens on the probe tip and stick to the lens surface, which can decrease laser output, as observed occasionally. To solve the problem, the applicant made modification to the irradiation probe to reduce heat damage to it, and submitted a partial change application for PD Laser and an application for marketing approval of EC-PDT Probe.

An application for partial change for talaporfin sodium was filed by Meiji Seika Pharma Co., Ltd. for the indication of local residual/recurrent esophageal carcinoma. Talaporfin sodium was designated as an orphan drug in March 2014 (Orphan Drug Designation No. 330 of 2014 [*26 yaku*]) and PDT semiconductor laser (PD Laser/EC- PDT Probe) as an orphan medical device in

September 2014 (Orphan Device Designation No. 25 of 2014 [*26 ki*]), both for the indication of "local residual/recurrent esophageal carcinoma after chemoradiotherapy or radiotherapy."

Use in foreign countries
As of March 2015, no other countries or regions have filed applications for or obtained approval of PD Laser/EC-PDT Probe or Laserphyrin.

2. Specification (performance and safety specifications)

2.A Summary of the data submitted

In the partial change application for PD Laser, performance and safety specification were specified based on JIS T0601-1: 1999 (Medical electrical equipment—Part 1: General requirements for safety) for electrical safety and JIS T 0601-1-2: 2002 (Medical electrical equipment—Part 1: General requirements for safety, 2. Collateral standard: Electromagnetic compatibility—Requirements and tests) for electromagnetic compatibility. The performance and safety specification for a laser beam emitted from PD Laser in the present application remained unchanged from those of previously approved product.

The specification for the performance of EC-PDT Probe included beam divergence, transmittance, mean fluence rate, and beam profile. The following standards were applied for EC-PDT Probe: JIS T 0993-1: 2012 (Biological evaluation of medical devices—Part 1: Evaluation and testing within a risk management process), JIS T 0806-1: 2010 (Sterilization of health care products—Radiation—Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices), and JIS T 14971: 2012 (Medical devices—Application of risk management to medical devices). For EC-PDT Probe used in combination with PD Laser, applied standards include JIS T 0601-1: 1999 (Medical electrical equipment—Part 1: General requirements for safety) and JIS T 0601-1-2: 2002 (Medical electrical equipment—Part 1: General requirements for safety, 2. Collateral standard: Electromagnetic compatibility—Requirements and tests).

2.B Outline of the review conducted by PMDA

PMDA reviewed the submitted data primarily focusing on the following issues.

2.B.(1) Specifications of electrical safety and electromagnetic compatibility of PD Laser

The applicant's explanation:
At the filing of the present application for PD Laser, its conformance to an official standard was verified, which was not specified for the initial approval (in January 2004 for the treatment of early-stage lung cancer). Therefore, the standard was added to the present application as electrical safety and electromagnetic compatibility specifications.

PMDA concluded that there is no particular problem with the applicant's actions.

2.B.(2) Requirements for EC-PDT Probe as sterilized medical device

Regarding the requirements for a sterilized medical device, PMDA considered that in addition to applying the requirements of JIS T 0806-1: 2010 to EC-PDT Probe, a sterility assurance level (SAL) should also be specified according to the validation standards defined in JIS T 0806-1: 2010, and asked the applicant's view.

The applicant's response:
The SAL for the EC-PDT probe is 10^{-6}. The SAL and the sterility validation method will be added to the specification for performance and safety.

PMDA concluded that there is no particular problem with the SAL set in the specification for performance and safety by the applicant.

2.B.(3) Specification regarding the physical strength of EC-PDT Probe

Given the supposed situation in the clinical use of EC-PDT Probe, PMDA considered that the performance and safety specification should include the tensile strength of EC-PDT Probe against its insertion into or removal from the forceps channel of the endoscope as well as the bending resistance of the probe associated with the bending of the endoscope. PMDA asked the applicant's view on the matter.

The applicant stated that the performance and safety specification would include both tensile strength and bending resistance: the former would have a margin sufficient to secure the probe's durability against insertion into and removal from the forceps channel of the endoscope, and the latter would be a smaller value than the expected bending radius of EC-PDT Probe for clinical use.

PMDA concluded that there is no particular problem with the action taken by the applicant.

2.B.(4) Specification of the transmittance of EC-PDT Probe

While "a transmission efficiency of ≥80%" is specified for Probe for lung cancer, which was approved as a component of PD Laser, "a transmittance of ≥70%" was specified for EC-PDT Probe.

PMDA's view on the effect of the difference in transmittance on talaporfin sodium-mediated PDT:
For the purpose of the calibration of EC-PDT Probe prior to PDT with the product, the output of laser beam emitted from the tip is measured at the probe tip inserted into the power check insertion port on PD Laser. This ensures compatible laser output power (emitted from the probe tip) supplied for the treatment despite different transmittance levels of the fibers used in the probes. Therefore, the difference in transmittance of the probes will not affect PDT. The details of the calibration of laser output are described in the present application for marketing approval and in the package insert of the product.

Based on the above, PMDA concluded that there is no particular problem with the transmittance specification.

2.B.(5) Variation in mean fluence rate of laser emitted from EC-PDT Probe

The applicant proposed a ±20% variation for the mean fluence rate of EC-PDT Probe.

Based on the point in the review of the "PD Laser BT," which is used for PDT of malignant brain tumors, PMDA accepted the proposed specification for PD Laser/EC-PDT Probe as well (see "(3)

Rationale for the permissible variation range in output power" in "Review Report of PD Laser BT" dated August 15, 2013, p.10 [in Japanese]).

Based on the above, PMDA concluded that there is no particular problem with the rationale for the items and values of the specifications for performance and safety.

3. Stability and durability

3.A Summary of the data submitted

The applicant omitted stability data from the dataset submitted because stability was outside the scope of evaluation for PD Laser.

The following test data of EC-PDT Probe were submitted: high-temperature operation test ([redacted]°C) and low-temperature operation test ([redacted]°C) to evaluate the operation at temperatures in a normal use environment for EC-PDT Probe (10°C to 35°C). The results from a high-temperature storage test ([redacted]°C, stored for [redacted] hours), a low-temperature storage test ([redacted]°C, stored for [redacted] hours), and a humidity test ([redacted]°C, humidity [redacted]% RH, stored for [redacted] hours) demonstrated no performance deterioration under conditions more severe than the actual storage conditions. The temperature rise test (output, 150 mW; irradiated for 667 seconds) indicated that the temperature at the tip of EC-PDT Probe would be ≤60°C during laser irradiation in clinical use. The durability of EC-PDT Probe against laser irradiation was validated by an aging test evaluating the performance of the probe after [redacted] hours of continuous laser irradiation and stability tests including testing for material deterioration caused by gamma-ray irradiation (evaluated at 1 month after gamma-ray irradiation). The results showed no particular problems. The data submitted also included comparative data between EC-PDT Probe and Probe for lung cancer used in the clinical study on their durability against blood spots on the probe tips, the issue that motivated the development of EC-PDT Probe, i.e., how easily the probe tips can be contaminated with blood, time to output reduction during laser irradiation using a blood-spotted probe tip, and the ease of wiping off of blood spots. The study showed that EC-PDT Probe had less blood spots on its tip as compared to the Probe for lung cancer, presumably because of its different design. The ease of wiping off of blood spots was tested using each probe with tips contaminated with pig blood. After wiping off the blood, residual blood on the tip was qualitatively evaluated with photographs. The results indicated that blood had been wiped off more easily from EC-PDT Probe than from Probe for lung cancer. When the laser irradiation was performed without removing blood spots, there was no significant difference between the probes in time to laser output reduction (because of burnt and hardened blood spots). However, after the burned, hardened blood spots were removed, EC-PDT Probe was reusable while the Probe for lung cancer was not. The results indicated the superiority of EC-PDT Probe over Probe for lung cancer in terms of the ease of wiping off burnt and hardened blood spots on the probe.

3.B Outline of the review conducted by PMDA

PMDA asked the applicant's view on the rationale for the temperature specified in the temperature rise test (≤60°C):

The applicant explained that the temperature was determined based on the maximum temperature limit for "applied parts not intended to supply heat to patients" specified in JIS T 0601-1: 2012.

Although the maximum temperature limit was set based on the healthy skin of adults without the effect on esophageal mucosa taken into account, PMDA concluded that the specification of ≤60°C is acceptable based on the following standpoints:

- According to the method of use of the product, EC-PDT Probe does not intentionally come in contact with the esophageal mucosa.
- As discussed in Section "5.6.B Outline of the review conducted by PMDA," because of the tip hood attached to the endoscope, it is highly unlikely that the tip will come in contact with the esophageal mucosa. A rise of the tip temperature will have only an insignificant impact on the esophageal mucosa.

PMDA reviewed other submitted data and concluded that there was no particular problem.

During the review, the applicant further submitted documents for the stability study of EC-PDT Probe, including material deterioration caused by gamma-ray irradiation. The data comprised stability evaluation data at 9 months after gamma-ray irradiation and a plan for a stability evaluation at 24 months after gamma-ray irradiation.

PMDA reviewed the stability data at 9 months and the plan for evaluating stability at 24 months after gamma-ray irradiation, and concluded that there was no particular problem.

4. 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

4.A Summary of the data submitted

The applicant submitted a declaration of conformity declaring that the product meets the standards for medical devices as stipulated by the Minister of Health, Labour and Welfare in accordance with Paragraph 3 of Article 41 of the Pharmaceutical Affairs Act (hereinafter referred to as "the old Essential Principles") (MHLW Ministerial Announcement No. 122, 2005).

4.B Outline of the review conducted by PMDA

The application for PD Laser/EC-PDT Probe was submitted after the enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices, which was however still within the interim measure period that continued until November 24, 2015. Therefore, based on the submitted data, the conformity of PD Laser/EC-PDT Probe to the old Essential Principles was assessed.

PMDA's conclusion on the conformity of PD Laser/EC-PDT Probe to Article 1, which stipulates the preconditions for designing medical devices (particularly, the requirements for the users of the product, such as expected level of technical knowledge and experience, expected level of education and training to be provided to the users):
As discussed in Section "5.6.B Outline of the review conducted by PMDA," the applicant's initial proposals were considered insufficient in terms of the definitions of physicians qualified to operate the product, the method of irradiation, and the endoscopy systems to be used with the product. PMDA instructed the applicant to address these matters appropriately, and the applicant agreed.

5. Performance

5.1 Electrical safety and electromagnetic compatibility

5.1.A Summary of the data submitted

Data submitted included those indicating conformance with the new applicable standards for performance and safety specification in the present application for PD Laser, i.e., the standards for electrical safety and electromagnetic compatibility (JIS T 0601-1: 1999 and JIS T 0601-1-2: 2002). The data demonstrated conformance with all standards.

The evaluation of electrical safety and electromagnetic compatibility was not considered necessary for EC-PDT Probe, and therefore relevant data were omitted.

5.1.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.

5.2 Biological safety

5.2.A Summary of the data submitted

PD Laser is not designed to come in contact with patients, the evaluation was not considered necessary, and therefore relevant data were omitted.

EC-PDT Probe is inserted through a flexible endoscope into the esophagus. Because of the possibility that the probe may come in contact with the esophageal mucosa, the applicant submitted evaluation data on biological safety in accordance with the specification on biological safety stipulated as the performance and safety specifications. The probe will be classified as a medical device coming in short-term contact with human tissue based on the possible contact with the esophageal mucosa. Accordingly, the applicant conducted cytotoxicity, sensitization, and irritation tests, and submitted negative test results.

5.2.B Outline of the review conducted by PMDA

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

5.3 Mechanical safety

5.3.A Summary of the data submitted

The data on conformance with JIS T 0601-1 in Section “Electrical safety and electromagnetic compatibility” also included the results on mechanical safety of the product, which are thus omitted in this section.

Submitted testing data to verify the physical strength of the probe, in addition to the tensile strength test ([redacted]N) stipulated in the performance and safety specifications, included those of bending test (bending radius of [redacted] mm), torsion test (clockwise and counter-clockwise rotations, [redacted] times), drop test (JIS T 0601-1: 1999), and vibration test (amplitude [redacted] mm, wavelength [redacted] Hz). These data showed no particular problems.

5.3.B Outline of the review conducted by PMDA

Of the testing data submitted for the mechanical safety of the probe, the tensile strength test and bending test need to be included in the performance and safety specifications as mentioned in

Section “2.B.(3) Specification regarding the physical strength of EC-PDT Probe,” in light of expected clinical use. PMDA instructed the applicant to add these tests in the performance and safety specifications, to which the applicant agreed. PMDA reviewed the submitted data and concluded that there was no particular problem.

5.4 Performance

5.4.A Summary of the data submitted

Because of no changes in the performance of PD Laser in the present application, the evaluation of performance was considered unnecessary and thus omitted from the data submitted.

Performance data submitted comprised data on the basic performance of EC-PDT Probe and those demonstrating the equivalence between EC-PDT Probe and Probe for lung cancer in optical properties.

5.4.A.(1) Basic performance (Attached document 5-1.7)

The applicant submitted data which demonstrate that EC-PDT Probe meets the requirements for the performance and safety specifications including beam divergence, transmittance, mean fluence rate, and beam profile.

5.4.A.(2) Equivalence in optical properties with approved Probe for lung cancer (Attached document 5-1.8)

To extrapolate the results of Study KUTR-015-2 to the clinical data of the product, the applicant submitted data demonstrating the equivalence in optical properties between Probe for lung cancer used in the clinical trial and EC-PDT Probe. In the tests, laser beam profiles were measured on the irradiated surface (fluence rate distribution on the irradiated surface) that was [redacted] mm-distance from the tip of EC-PDT Probe or Probe for lung cancer. Although the beam profiles near the tip of the probe ([redacted] mm from the tip) varied between the two probes, the difference in beam diameter between the probes at measuring points [redacted] mm from the tip was within [redacted]%. The beam profiles on the irradiated surfaces which simulated the clinical situation indicated a similarity in beam profiles between the probes. The applicant therefore concluded that the results demonstrated the equivalence in optical properties between EC-PDT Probe and Probe for lung cancer.

5.4.B Outline of the review conducted by PMDA

PMDA’s conclusion:

EC-PDT Probe and Probe for lung cancer showed different beam profiles near their tips. However, as mentioned in Section “5.6.B. Outline of the review conducted by PMDA,” it is possible to keep an appropriate distance from the irradiation site as long as a hood is attached to the tip of the endoscope. Therefore, there is no particular problem with the applicant’s explanation about the tests for basic performance and equivalence in optical properties between the probes.

5.5 Efficacy

5.5.A Summary of the data submitted

In support of the efficacy of the product, the applicant submitted data on the *in vitro* cytocidal effects of talaporfin sodium-mediated PDT on esophageal carcinoma cells (Attached document 5-2.1). In the study, the antiproliferative effect of talaporfin sodium-mediated PDT against 2 types

of human esophageal carcinoma cell lines, TE-5 and TE-10, was assessed based on redox dye absorbance as an indicator. Each cell line was immersed in the culture medium containing talaporfin sodium 0, 3, 10, 30, or 100 μg/mL for 24 hours. Talaporfin sodium was then removed from the medium. The cell viability in the laser-irradiated group (with a fluence of 10 J/cm^2) and non-irradiated group was evaluated at 48 hours after laser irradiation (based on a viability of 100% of non-irradiated, non-talaporfin sodium-treated cells, absorbance percentage of each cell group was calculated. See Figure 5).

Both cell lines showed decreased cell viability in a talaporfin sodium concentration-dependent manner. The applicant explained that the results indicate the antiproliferative effect of talaporfin sodium-mediated PDT on esophageal carcinoma.

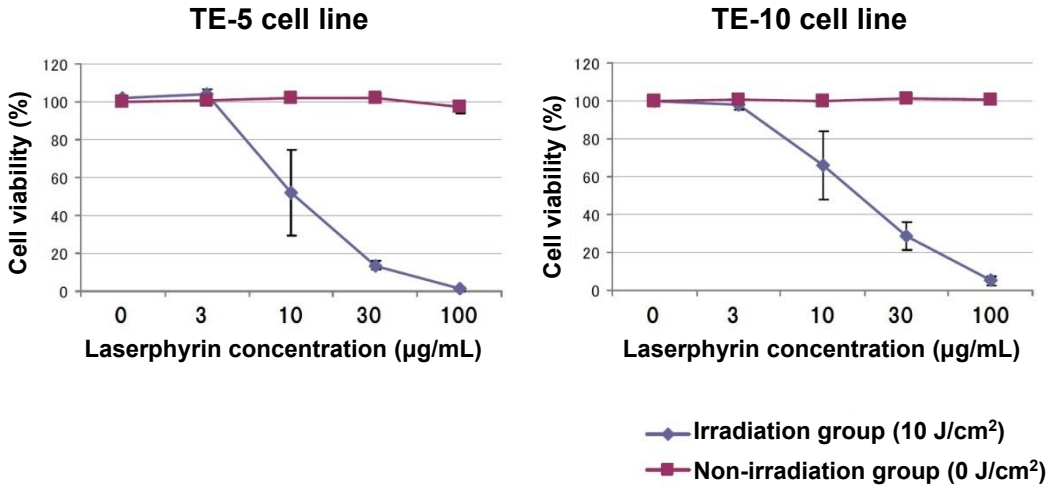


Figure 5. Antiproliferative effect of talaporfin sodium-mediated PDT against human esophageal carcinoma cell lines

(Mean ± standard deviation; n = 3)

5.5.B Outline of the review conducted by PMDA

PMDA's view:

The results showed that talaporfin sodium decreased cell viability in a concentration-dependent manner in the culture medium; therefore, talaporfin sodium-mediated PDT is expected to exert an antitumor effect against esophageal carcinoma. However, talaporfin sodium concentrations in the cells were not measured, and thus the clinical implications of the results remain unclear. Nevertheless, the data of this study is acceptable based on the discussion in Section "8.(i).B.(2) Efficacy" that indicates promising efficacy of talaporfin sodium-mediated PDT.

5.6 Method of use

In support of the method of use of PD Laser/EC-PDT Probe, the applicant submitted data from a mouse study which evaluated the antitumor effect of additional laser irradiation in talaporfin sodium-mediated PDT (study on the efficacy and safety of additional irradiation) (Attached document 5-3.1) at the time the application was filed. Subsequently, the applicant submitted data from a study on the irradiation method in PDT for esophageal carcinoma as a response to an inquiry from PMDA (Attached document 5-3.2).

5.6.A Summary of the data submitted

5.6.A.(1) A mouse study evaluating the antitumor effect of additional laser irradiation in talaporfin sodium-mediated PDT (Study on the efficacy and safety of additional irradiation) (Attached document 5-3.1)

According to the method of use of EC-PDT Probe, if any residual lesion[i] (non-irradiated lesion) is endoscopically observed on the day following PDT, an additional laser irradiation should be performed. In order to assess the efficacy and safety of additional irradiation, an *in vivo* study was conducted in mice subcutaneously transplanted with murine Meth-A fibrosarcoma tissue into the femoral region under the conditions shown in Table 2. In humans, plasma talaporfin concentration following additional irradiation is approximately half that following the initial irradiation (see "Review Report of Laserphyrin 100 mg for Injection" dated August 21, 2003), while in mice, the half-life of talaporfin sodium in plasma is shorter and its concentration following additional irradiation would lower than half that following the initial irradiation (see "Review Report of Laserphyrin 100 mg for Injection" dated August 21, 2003). Therefore, in this study, an additional dose of talaporfin sodium was administered before the additional irradiation so that the plasma talaporfin concentration following the additional irradiation would be approximately half that following the initial irradiation.

The applicant's explanation:
The laser beam was focused perpendicularly onto the skin surface with the transplanted tumor (7-11 mm in thickness at the time of PDT) (with a fluence of 100 J/cm^2 [same as that in clinical use]). Tumor tissue was then extracted at a prespecified time point for each group to measure the depth of necrotic foci. The measurements in Groups 2 and 4 were similar, suggesting that the treatment has an antitumor effect that is sufficient even when PDT is performed on Day 2, by which time plasma talaporfin concentration on Day 1 will be approximately halved. The results also showed that the depths of necrotic foci in Groups 3 and 5 were similar (i.e., the depths of necrotic foci following PDT performed on the same site for 2 consecutive days and following PDT performed on Day 1 only were similar), suggesting that PDT on 2 consecutive days will not cause significant safety problems, such as an increase in esophageal perforation.

[i] "Residual lesion" refers to any one of the following conditions: 1) residue of submucosal tumor-like protrusion components; 2) residue of neoplastic mucosa and ulcer; 3) lost edematous mucosa turning red or dark blue.

Table 2. The antiproliferative effect of additional laser irradiation in mice transplanted with murine fibrosarcoma tissue

Group	Day 1		Day 2		Day 3	Depth of necrotic foci (mm)
	Talaporfin sodium (5 mg/kg)	Laser irradiation (100 J/cm^2)	Talaporfin sodium (2.5 mg/kg)	Laser irradiation (100 J/cm^2)		
1	No	No	No	No	Necropsy	—
2	Yes	Yes	No (Necropsy 24 hours after PDT)		—	4.7 ± 0.8
3	Yes	Yes	No	No	Necropsy 48 hours after PDT	5.0 ± 0.8
4	Yes	No	Yes	Yes	Necropsy 24 hours after PDT	5.2 ± 0.7
5	Yes	Yes	Yes	Yes	Necropsy 24 hours after PDT	4.8 ± 1.0

(Mean ± standard error [n = 5; however, n = 4 in the Groups 4 and 5])

5.6.A.(2) Irradiation method in PDT for esophageal carcinoma (Attached document 5-3.2)
Based on the discussion in Section "5.6.B.(2) Area coverable by single spot irradiation and how to treat a lesion that is too large to be covered by single spot irradiation," the applicant submitted additional data, "Study on the irradiation method in PDT for esophageal carcinoma."

The applicant conducted an analysis using the PDT dosimetry model proposed by researchers including S. L. Jacques[12] to estimate the area to which the required level of laser energy for treatment is delivered by a single irradiation. Based on the model, the fluence required to reach the cytotoxicity threshold was calculated from the estimated talaporfin concentrations in tumor tissue. Then the area which achieves the cytotoxicity threshold was derived based on the laser light intensity distribution in the tissue (generated by Monte Carlo simulations) for an irradiation time of 11 minutes and 7 seconds per spot using optical properties that take into account physical conditions including the usual esophageal lumen diameter and endoscope diameter (elevation angle between the optical axis and the lesion surface, 30°; length between the probe tip to the intersection point of the optical axis and lesion surface, 17.1 mm). Based on the calculation, on the esophagus walls, the area to which the required level of laser energy can be delivered for the treatment (area that can be treated effectively) in a single irradiation session was estimated to be an oval area, 10.9 mm (axial direction) × 9.2 mm (circumferential direction) on the esophageal lumen.

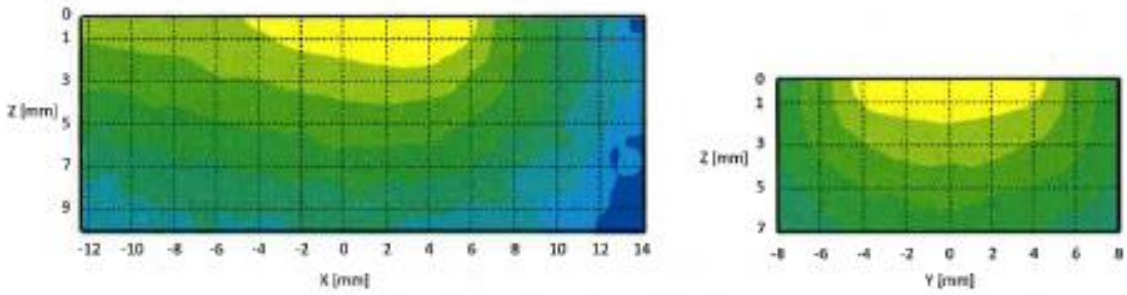


Figure 6. Light intensity distribution in the tissue
(Yellow indicates the area that can be expected to be treated effectively)

5.6.B Outline of the review conducted by PMDA

PMDA's review focused primarily on the following viewpoints.

5.6.B.(1) Method to keep EC-PDT probe in a fixed position in the esophagus

One of the difficulties in the PDT for esophageal carcinoma is to keep irradiating one desired spot steadily, due to breathing, heartbeat, peristalsis, etc. Therefore, PMDA instructed the applicant to propose a specific irradiation method.

The applicant's explanation about the standard method for PDT irradiation of esophageal carcinoma:
As shown in Figure 4, the endoscope should be placed in a way that allows the tip hood to touch the esophageal wall so that the endoscope and EC-PDT Probe are securely supported by the esophageal walls to perform irradiation. The method was employed in Study KUTR-015-2.

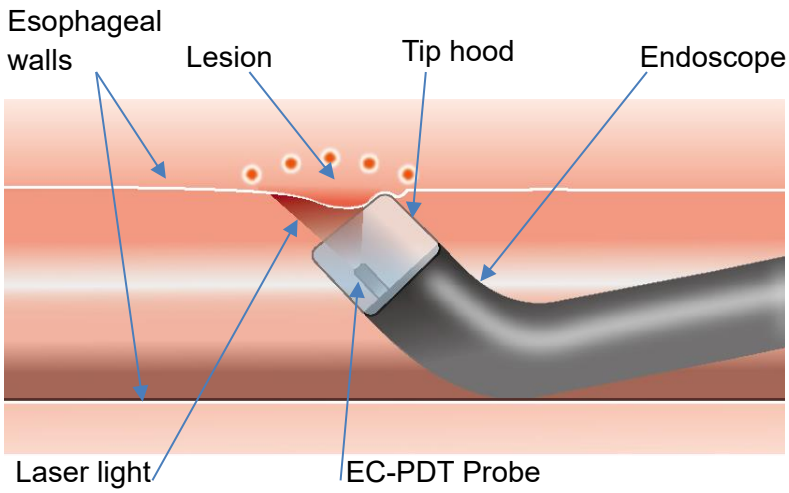


Figure 4. Schematic image of treatment with PD Laser/EC-PDT Probe (also shown in "II. Product Overview)

It is clear that the method proposed by the applicant allows for more spatially stable irradiation as compared to the method without securely supporting the endoscope. The method was employed

in Study KUTR-015-2, which demonstrated the efficacy of talaporfin sodium-mediated PDT. Therefore, PMDA concluded that the proposed method should be acknowledged as standard irradiation method with PD Laser/EC-PDT Probe, and given this, the method should be specified as the method of use of the product. PMDA instructed the applicant to add the proposed method in the method of use of the product, and the applicant agreed.

5.6.B.(2) Area coverable by single-spot irradiation and how to treat a lesion that is too large to be covered by single-spot irradiation

The method proposed by the applicant in Section 5.6.B.(1) has difficulty irradiating the esophageal wall surface perpendicularly, and thus may fail to deliver laser energy to the target tissue evenly. PMDA asked the applicant to explain about the range that can be treated effectively by the proposed irradiation method. In Study KUTR-015-2, some patients received irradiation onto the same lesion for multiple times, and PMDA asked the applicant to explain the situation.

The applicant submitted the data mentioned in Section "5.6.A.(2) Irradiation method in PDT for esophageal carcinoma" in response to the inquiry by PMDA.

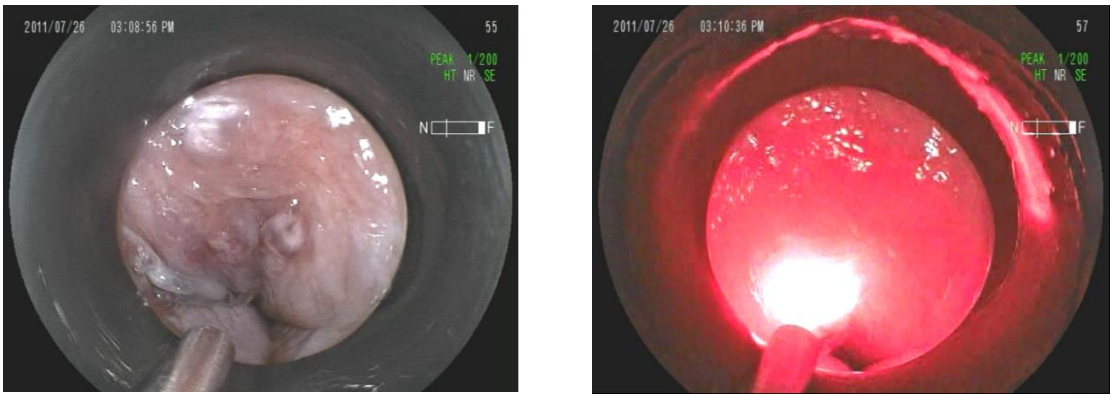
PMDA's conclusion concerning the submitted data:
The irradiation time in each irradiation session is consistent with that in clinical use and thus is appropriate. The angle between the optical axis and the lesion surface (30°) and the distance between the probe tip and the intersection point of the optical axis and lesion surface (17.1 mm) may not necessarily be suitable for all cases in the clinical setting. Nevertheless, these settings were determined based on the sizes of esophageal lumen and endoscope, taking into account the spatial requirements for the product in its clinical use, and are thus acceptable. In the Expert Discussion, the expert advisors concluded that there was no problem with the conditions specified in the data. Meanwhile, because of the red light illuminating the entire irradiation field during irradiation (Figure 7), the operator will have difficulty in distinguishing, through the endoscopic image, an area that appears to have been effectively treated from another area that appears to need further irradiation with the focus adjusted. Therefore, the users of the product should be advised of irradiation patterns that can cover the entire lesion. PMDA asked the applicant's view on information to be provided and how to provide such information to the users.

The applicant's explanation:
Physicians will be required to complete the training sessions for the use of the product. Irradiation patterns to deliver desired laser energy to the entire lesion will be elaborated for predictable lesion morphologies. These irradiation patterns will be communicated to users via training materials, etc. as a reference in treatment planning.

PMDA largely accepted the actions proposed by the applicant, but suggested the following additional actions:

- The procedure requires advanced skills for endoscope operation that allow for irradiation of a target lesion exactly according to the treatment plan developed based on the irradiation patterns informed. Therefore, for appropriate complete irradiation of the entire lesion, the product should be used only by physicians with adequate experience in the endoscopic treatment of esophageal carcinoma.

- Whether the requirement of attending training sessions will serve to achieve therapeutic effect in the post-marketing setting comparably with those achieved in Study KUTR-015-2, including the rationale for the irradiation method and the appropriateness of the information provided through training sessions, should be verified by a use-results evaluation.



Immediately before irradiation　　During irradiation

Figure 7. Endoscopic images before and during irradiation

5.6.B.(3) Limiting endoscopy systems that can be used with the product

Given that operators need to be able to recognize the area being irradiated with PD Laser/EC-PDT Probe in order to perform the procedure with suitable irradiation patterns described in Section 5.6.B.(2), PMDA asked the applicant whether all commercially available endoscopic systems in Japan can display laser light from PD laser/EC-PDT Probe at a wavelength of 664 nm (red) and allow operators to visually recognize the area being irradiated.

The applicant's explanation:

Endoscopy systems with no function to adjust the intensity of light obtained can cause halation during laser irradiation, which precludes viewing the irradiation site. In order to obtain a clear view of irradiation site, it is necessary to use an endoscopy system equipped with a light intensity control by a dimming filter, electronic shutter, etc. that helps attenuate halation. In Study KUTR-015-2, the endoscopy system was used after the confirmation of its compatibility with PD Laser/EC-PDT Probe (in particular, capability to attenuate halation so that the irradiation site is visible during the use with the product). The information on the endoscopy system used in Study KUTR-015-2 will be provided to users of the product to minimize risks.

The hindered view of the irradiation site during the procedure will impact the efficacy of the product immensely. PMDA instructed the applicant to limit endoscopy systems to be used with the product in the method of use, and to advise users in the package insert and training materials to check whether their endoscopy system is suitable to be used with the product before starting treatment. The applicant agreed.

5.6.B.(4) Rationale for additional irradiation

The method of use of EC-PDT Probe requires, in PDT using talaporfin sodium and the product in patients with local residual/recurrent esophageal carcinoma, that any residual lesion (non-

irradiated lesion) endoscopically observed on the day following PDT should undergo additional laser irradiation.

PMDA's view:
Based on the discussions in Section "5.6.A.(1) A mouse study evaluating the antitumor effect of additional laser irradiation in talaporfin sodium-mediated PDT" (the results of Group 4, in particular), even on the day following the administration of talaporfin sodium, laser irradiation is expected to be effective to a certain degree. It is thus meaningful to undergo additional irradiation onto a residual cancer lesion within the targeted irradiation area on the outermost layer of the esophageal wall that is endoscopically clearly observable on the day following PDT. Based on the results of this study, the efficacy and safety of additional irradiation may be predicted to some degree. However, the tumors treated in the study system were 7 to 11 mm in thickness before PDT, which is thicker than the human esophageal wall (approximately 4 mm) and thus not relevant to human esophageal carcinoma in terms of size. The human esophagus is not comparable with the subcutaneous tissue of murine femur in terms of surrounding organs. Lesions were irradiated perpendicularly to the skin surface in the study. Given these, the conditions of the study do not appropriately reflect the clinical use of the product and, therefore, preclude a precise evaluation of the efficacy and safety of additional irradiation based solely on the results of this study. As discussed in Section "8.(i).B.(3).4) Safety in patients who underwent additional laser irradiation," some adverse events occurred only in patients who underwent additional irradiation. Accordingly, caution should be advised against the occurrence of these events in the package insert. Furthermore, in patients undergoing an additional irradiation, the site of residual tumor should be accurately located and irradiated to obtain its optimum efficacy expected. An approach needs to be devised for appropriate endoscopy-based identification of residual tumor (decision on whether additional irradiation is necessary) on the day following PDT.

The applicant's explanation in response to PMDA's view:
In Study KUTR-015-2, if there was any residual lesion that meets any one of the following criteria, an additional irradiation was performed.

1) Residue of submucosal tumor-like protrusion components
2) Residue of neoplastic mucosa and ulcer
3) Lost edematous mucosa turning red or dark blue

These criteria will need to be communicated to the users of the product through training materials to help them make a decision about whether to perform additional irradiation. Information about the adverse events that occurred only in patients who had undergone additional irradiation in Study KUTR-015-2 will be provided via the package insert as done for talaporfin sodium.

PMDA's view:
As discussed in Section "8.(i).B.(2) Efficacy," in the study, the efficacy of talaporfin sodium-mediated PDT was demonstrated in patients including those who had underwent additional irradiation that was considered necessary according to the above 3 criteria. Based on the results, the applicant's decision to provide users with the 3 criteria is reasonable. At the same time, endoscopic findings of patients who did and did not need additional irradiation should be made available in training materials, etc. for users to refer to at decision making on the need for additional irradiation so that the experience in Study KUTR-015-2 will be made use of in the post-

marketing clinical practice. PMDA instructed the applicant to take these actions, and the applicant agreed. In addition, because only a limited number of patients were studied in KUTR-015-2, the applicant should continue to collect information on adverse events caused by additional irradiation (in particular, esophageal perforation) in the post-marketing setting.

6. Risk Management

The applicant submitted a summary of risk management measures that was specified in accordance with ISO 14971: 2007 "Medical devices—Application of risk management to medical devices" and implemented for the product. The summary also outlines the risk management system and its implementation status.

PMDA reviewed the risk management measures and concluded that there was no particular problem.

7. Manufacturing Process

The applicant submitted data relating to the manufacturing process of the product, which consist of data on the manufacturing process and facilities, quality control, and sterilization conditions.

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

8. Clinical Data

The applicant submitted clinical data from the Japanese phase II study (Attached document 8-1.1: Study KUTR-015-2 [November 2012 to May 2014]). The applicant also submitted a report on clinical research conducted in Japan (Attached document 8-1. Ref. 2 [September 2010 to [redacted] 20[redacted]]) as reference data. Study KUTR-015-2 was conducted as an investigator-initiated clinical trial at 7 study centers in Japan, and the results were also submitted for the partial change application for talaporfin sodium.

The following is the summary of Review Report (1) for Laserphyrin, which include citations from Review Report (1) and (2) for talaporfin sodium. In the cited portion of the sections, Laserphyrin is referred to as "talaporfin sodium," Meiji Seika Pharma Co., Ltd. as "the applicant."

8.(i) Summary of clinical efficacy and safety

8.(i).A Summary of the submitted data

The applicant submitted efficacy and safety evaluation data (a Japanese phase II clinical study) and reference data (a report of Japanese clinical research).

List of clinical studies for efficacy and safety evaluation

Data class	Location	Study identifier	Phase	Study population	Enrolled	Dosage regimen	Main endpoints
Evaluation	Japan	KUTR-015-2	II	Patients with local residual/recurrent oesophageal carcinoma after CRT or RT	26	Single intravenous injection of talaporfin sodium 40 mg/m^2 *1	Efficacy Safety
Reference	Japan	KUTR-015-1	I/II	Patients with local residual/recurrent oesophageal carcinoma after CRT or RT	19	Single intravenous injection of talaporfin sodium 40 mg/m^2 *2	Safety Efficacy

CRT, chemoradiotherapy; RT, radiotherapy

*1, The lesion was irradiated with laser light (with a fluence of 100 J/cm^2) using a semiconductor laser device (PNL6405EPG) 4 to 6 hours after administration of talaporfin sodium (and additionally, 22 to 32 hours after administration, if needed).

*2, The lesion was irradiated with laser light (with a fluence of 50, 75, or 100 J/cm^2) using a semiconductor laser device (PD laser) 4 to 6 hours after administration of talaporfin sodium (and additionally, the next day, if needed).

The clinical study and clinical research are outlined below.

Main adverse events, other than death, reported in the study or research are discussed in "8.(ii) Adverse events reported in clinical studies."

Evaluation data

Japanese phase II study (5.3.5.2-01, Study KUTR-015-2 [November 2012 to May 2014])

An open-label, uncontrolled study was conducted in patients with local residual/recurrent oesophageal carcinoma after CRT or RT[*1] (target sample size, 25 subjects) at 7 study centers in Japan to assess the efficacy and safety of talaporfin sodium-mediated PDT.

In this study, subjects received a single intravenous injection of 40 mg/m^2 talaporfin sodium. Four to 6 hours after administration of talaporfin sodium, the local residual/recurrent lesion was irradiated with 664-nm laser light (with a fluence of 100 J/cm^2, and a fluence rate of 150 mW/cm^2) using a semiconductor laser device. Lesions were endoscopically observed on the day following administration of talaporfin sodium and laser irradiation. If any residual lesion was detected, additional laser irradiation was performed between 22 and 32 hours after administration of talaporfin sodium.

All 26 subjects enrolled in the study were included in the efficacy analysis population, which was the full analysis set (FAS). All 26 subjects who received talaporfin sodium were included in the safety analysis population.

For efficacy, local complete response (L-CR)[*2] rate as assessed by central review, the primary endpoint, was 88.5% (95% confidence interval [CI]: 69.8%, 97.6%) (23 of 26 subjects). The probability of the L-CR rate exceeding 15%,[*3] the predefined threshold,[*4] was 100%.

Safety data showed that no adverse events resulted in death within 29 days of administration of talaporfin sodium.

*1 Patients with histologically confirmed oesophageal carcinoma unresectable by endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) who did not wish to, or cannot, undergo surgical resection.

*2 Patients meeting all of the following criteria were judged to have an L-CR:

(a) Endoscopy does not show evident residual tumor;

(b) Endoscopy shows scarring at the treated area; and
(c) Cancer cells have not been pathologically detected in tissue biopsy

*3 In this study, treatment was judged to be effective if the L-CR rate in patients undergoing talaporfin sodium-mediated PDT exceeded 15%, the predefined threshold, with a probability of >97.5%, based on the Bayesian statistical approach. The prior distribution was a beta distribution: Beta(1, 1), and the likelihood was a binomial distribution.

*4 This threshold was established based on the results from a clinical study of chemotherapy in patients with residual/recurrent oesophageal carcinoma after CRT (*Cancer Chemother Pharmacol*. 2011;67:1265-72).

Reference data

Japanese clinical research (5.3.5.2-02 and 5.3.5.2-03, Study KUTR-015-1 [September 2010 to [redacted]])

A clinical research was conducted in patients with local residual/recurrent oesophageal carcinoma after CRT or RT at 7 study centers in Japan to assess the recommended fluence (phase I part) and the efficacy and safety of talaporfin sodium-mediated PDT (phase II part).

In this research, subjects received a single intravenous injection of 40 mg/m^2 talaporfin sodium. Four to 6 hours after administration of talaporfin sodium, the local residual/recurrent lesion was irradiated with 664-nm laser light (with a fluence of 50, 75, or 100 J/cm^2, and a fluence rate of 150 mW/cm^2) using a semiconductor laser device. Lesions were endoscopically observed on the day following administration of talaporfin sodium and laser irradiation. If any residual lesion was detected, additional laser irradiation was performed.

All 19 subjects enrolled in the research (including 9 subjects enrolled in the phase I part) received talaporfin sodium (3 subjects in the 50 J/cm^2 cohort; 3 subjects in the 75 J/cm^2 cohort; and 13 subjects in the 100 J/cm^2 cohort), and were included in the safety analyses. All 19 subjects who received talaporfin sodium-mediated PDT were included in the FAS.

Dose limiting toxicity did not occur in any cohort (3 subjects per cohort) in the phase I part. Therefore, the recommended fluence was determined to be 100 J/cm^2.

No adverse events resulted in death.

8.(i).B Outline of the review conducted by PMDA

8.(i).B.(1) Clinical positioning

The Guidelines for the Diagnosis and Treatment of Carcinoma of the Esophagus, April 2012 version, edited by the Japan Esophageal Society [in Japanese] (Kanehara & Co., Ltd.; 2012) (the Japanese guideline for the treatment of oesophageal carcinoma), state that PDT and other endoscopic treatment procedures are performed in patients with local residual/recurrent oesophageal carcinoma after CRT.

In contrast, PDT for local residual/recurrent oesophageal carcinoma after CRT or RT is not mentioned in the foreign guidelines, such as *DeVita, Hellman, and Rosenberg's Cancer: Principles and Practice of Oncology, 10th edition* (PA, USA: Lippincott Williams & Wilkins; 2011), an internationally recognized textbook of oncology.

The applicant explained treatment modalities for local residual/recurrent oesophageal carcinoma after CRT or RT, and the clinical positioning of talaporfin sodium-mediated PDT among the treatment modalities.

The applicant's explanation:
While CRT and RT have been employed as treatment options for patients with oesophageal carcinoma who do not undergo surgical resection, the local residual tumor/recurrence rate in patients undergoing CRT or RT is as high as 34% to 40% (*N Engl J Med.* 1992;326:1593-8; *Int J Radiat Oncol Biol Phys*. 2003;57:425-33). Further, residual or recurrent lesions may cause dysphagia, malnutrition, airway stenosis, aspiration, chest pain, pneumonia due to fistula formation with adjacent organs, mediastinitis, pyothorax, major haemorrhage, and other conditions. Although no standard treatment has been established for patients with local residual/recurrent oesophageal carcinoma after CRT or RT, patients with tumor invasion limited to the muscularis propria have the following therapeutic options: surgical resection, endoscopic treatment (EMR or ESD), porfimer sodium-mediated PDT, and chemotherapy.

In patients with local residual/recurrent oesophageal carcinoma after CRT or RT who underwent porfimer sodium-mediated PDT, the rate of complete response (endoscopic or pathological disappearance of tumor) was 59.5% and the 5-year survival rate was 36.1% (*Endoscopy*. 2011;43:657-63) with no particular safety concerns. On the other hand, surgical resection in patients with local residual/recurrent oesophageal carcinoma after CRT or RT is reported to have a good prognosis if tumor removal is complete (*J Thorac Cardiovasc Surg.* 2009;137:49-54). Surgical resection, however, has safety problems, including a high incidence of postoperative complications and high treatment-related mortality. In patients with tumor invasion limited to the submucosa (among those with local residual/recurrent oesophageal carcinoma after CRT or RT) who underwent endoscopic treatment, the 5-year survival rate was 49%, with no particular safety concerns (*Gastrointest Endosc.* 2003;58:65-70; *Endoscopy*. 2008;40:717-21). In some patients, however, it is technically difficult to perform endoscopic treatment because of CRT- or RT-related ulcers or scars. [redacted].

The above findings suggest that, as with porfimer sodium-mediated PDT, talaporfin sodium-mediated PDT is a local treatment expected to alleviate or prevent symptoms accompanying the enlargement of local residual/recurrent lesions, and to improve the quality of life (QOL) in patients ineligible for surgical resection or endoscopic radical treatment.

PMDA accepted the applicant's explanation.

8.(i).B.(2) Efficacy
PMDA concluded that talaporfin sodium-mediated PDT is expected to be effective for the treatment of local residual/recurrent oesophageal carcinoma after CRT or RT, based on the following discussions.

Efficacy endpoint and evaluation results

The applicant explained the reason for selecting the efficacy endpoint and the evaluation results of Study KUTR-015-2, which was conducted in patients with local residual/recurrent oesophageal carcinoma after CRT or RT.

The applicant's explanation:
The purpose of talaporfin sodium-mediated PDT in patients with local residual/recurrent oesophageal carcinoma after CRT or RT is to control and eliminate local residual/recurrent lesions after CRT or RT, thereby alleviating and preventing symptoms including dysphagia, malnutrition, airway stenosis, aspiration, fistula formation, and chest pain, and improving QOL. An efficacy endpoint should therefore be a measure of tumor response (i.e., a measure representing the regression of local residual/recurrent lesion). Further, if complete response is not achieved and residual tumors are still present, these residual tumors may regrow, increasing the risk of developing the above symptoms; therefore, it was concluded that tumor complete response is of great importance, and the L-CR rate was selected as the primary endpoint.

According to the L-CR rate obtained in Study KUTR-015-2 [see Section "8.(i).A. Evaluation data. Japanese phase II study"] talaporfin sodium-mediated PDT is expected to be effective in patients with local residual/recurrent oesophageal carcinoma after CRT or RT.

PMDA's view:
Since Study KUTR-015-2 is an open-label, uncontrolled study, with no long-term treatment results, the study has limitations as a basis for assessing the efficacy of talaporfin sodium-mediated PDT in patients with local residual/recurrent oesophageal carcinoma after CRT or RT. However, PMDA concluded that talaporfin sodium-mediated PDT is expected to be effective in patients who fall within the target population of Study KUTR-015-2, based on the discussions in Section "8.(i).B.(1) Clinical positioning," taking into consideration the following points:

- Local residual/recurrent lesions after CRT or RT may cause conditions that could significantly deteriorate the patient's QOL. Such conditions include dysphagia, malnutrition, airway stenosis, aspiration, fistula formation, and chest pain. Therefore, local control of the lesions has a certain clinical significance.
- The results of Study KUTR-015-2 suggest that talaporfin sodium-mediated PDT is expected to achieve L-CR a certain level.

8.(i).B.(3) Safety [see Section "8.(ii) Adverse events reported in clinical studies" for the details of adverse events]

Close attention should be paid to oesophageal stenosis and oesophageal pain following the administration of talaporfin sodium to patients with local residual/recurrent oesophageal carcinoma after CRT or RT. Based on the discussion described in the following sections, PMDA concluded that talaporfin sodium-mediated PDT is tolerable, provided that these adverse events, as well as the adverse events observed in clinical studies of talaporfin sodium for the approved indications (i.e., early-stage lung cancer and primary malignant brain tumor) are carefully monitored in the same manner as in patients who receive treatment for the approved indications.

8.(i).B.(3).1) Safety profiles in patients with local residual/recurrent oesophageal carcinoma after CRT or RT

The applicant's explanation on the safety of talaporfin sodium:
In the safety analysis population (26 subjects) of Study KUTR-015-2, adverse events occurred in 26 subjects (100%), Grade ≥3 adverse events in 6 subjects (23.1%), and serious adverse events in 1 subject (3.8%).

PMDA asked the applicant to explain the difference in the safety profile between patients with local residual/recurrent oesophageal carcinoma after CRT or RT, and patients who receive treatment with talaporfin sodium for the approved indications, early-stage lung cancer or primary malignant brain tumor.

The applicant's response:
Data from the following studies were analyzed: Study KUTR-015-2 in patients with local residual/recurrent oesophageal carcinoma after CRT or RT; a Japanese phase II study (Study ME2906-BT-1) in patients with primary malignant brain tumor; and another Japanese phase II study (Study 2906-2-1) in patients with early-stage lung cancer.

The incidence of the following adverse events was ≥10% higher in subjects with local residual/recurrent oesophageal carcinoma than in subjects with early-stage lung cancer: oesophageal pain (53.8% and 0% in subjects with local residual/recurrent oesophageal carcinoma, and in subjects with early-stage lung cancer, respectively; the same applies hereinafter for the order of the subject groups), constipation (19.2% and 5.0%), aspartate aminotransferase (AST) increased (30.8% and 12.5%), blood albumin decreased (88.5% and 0%), blood potassium decreased (11.5% and 0%), blood potassium increased (30.8% and 0%), blood sodium decreased (26.9% and 2.5%), C-reactive protein increased (80.8% and 56.8%), neutrophil count increased (11.5% and 0%), lymphocyte count decreased (61.5% and 0%), and protein total decreased (15.4% and 0%). A Grade ≥3 adverse event occurring at an incidence ≥5% higher in subjects with local residual/recurrent oesophageal carcinoma than in subjects with early-stage lung cancer was lymphocyte count decreased (15.4% and 0%, in the former and latter subject groups, respectively). Furthermore, the incidence of the following adverse events was ≥10% higher in subjects with local residual/recurrent oesophageal carcinoma than in subjects with primary malignant brain tumor: oesophageal pain (53.8% and 0% in subjects with local residual/recurrent oesophageal carcinoma, and in subjects with primary malignant brain tumor, respectively; the same applies hereinafter for the order of the subject groups), blood potassium increased (30.8% and 11.1%), neutrophil count increased (11.5% and 0%), and protein urine present (11.5% and 0%). There were no Grade ≥3 adverse events occurring at an incidence ≥5% higher in subjects with local residual/recurrent oesophageal carcinoma than in subjects with primary malignant brain tumor.

The following adverse events occurred in ≥ 2 subjects with local residual/recurrent oesophageal carcinoma, but did not occur in any subjects with early-stage lung cancer or primary malignant brain tumor: oesophageal pain (14 subjects; 53.8%), neutrophil count increased (3 subjects; 11.5%), oesophageal stenosis (2 subjects; 7.7%), and lactescent serum (2 subjects; 7.7%). While a causal relationship to talaporfin sodium could not be ruled out for any of these events, all events were Grade 1 except for one event of Grade 2 oesophageal pain.

The majority of adverse events occurring at a higher incidence in subjects with local residual/recurrent oesophageal carcinoma than in subjects with early-stage lung cancer or primary

malignant brain tumor had already been identified as requiring special caution at the time of the review of the application for the approved indications. Among adverse events occurring only in subjects with local residual/recurrent oesophageal carcinoma (in ≥2 subjects), oesophageal pain and oesophageal stenosis are considered to be due to a local reaction to talaporfin sodium-mediated PDT, occurring typically in patients with local residual/recurrent oesophageal carcinoma. However, all of these events were either Grade 1 or Grade 2. Oesophageal pain and oesophageal stenosis are thus unlikely to cause clinical problems. Neutrophil count increased and lactescent serum occurred only in subjects with local residual/recurrent oesophageal carcinoma; the reason for this is unclear, but all of these events were Grade 1 and resolved without treatment. Neutrophil count increased and lactescent serum are thus unlikely to cause clinical problems.

PMDA's view:
Attention should be paid to adverse events occurring at a higher incidence in subjects with local residual/recurrent oesophageal carcinoma compared with subjects with early-stage lung cancer or primary malignant brain tumor. The information on the occurrence of the adverse events in subjects with local residual/recurrent oesophageal carcinoma should be provided in an appropriate manner. A serious adverse event (hypotension) occurred in a subject in Study KUTR-015-2. The event was judged to be unrelated to talaporfin sodium, but information on the event should also be provided because Study KUTR-015-2 was a single-arm study and therefore the relationship between the event and talaporfin sodium-mediated PDT has not been elucidated. Furthermore, when performing talaporfin sodium-mediated PDT in patients with local residual/recurrent oesophageal carcinoma after CRT or RT, extra attention should be paid to oesophageal pain and oesophageal stenosis, the adverse events occurring only in subjects with local residual/recurrent oesophageal carcinoma, but not in subjects with early-stage lung cancer or primary malignant brain tumor.

In addition to continuously being on the alert for adverse events for which it has already been advised that extra caution is required regarding patients who received treatment for the approved indications, the issues mentioned above need to be appropriately addressed. PMDA concluded that the tolerability of talaporfin sodium-mediated PDT is acceptable, provided that appropriate measures such as monitoring and management of adverse events are taken based on a full understanding of the safety profiles of talaporfin sodium.

8.(i).B.(3).2) Oesophageal stenosis and oesophageal pain
The applicant's explanation regarding oesophageal stenosis and oesophageal pain associated with talaporfin sodium-mediated PDT:
In Study KUTR-015-2, oesophageal stenosis occurred in 2 of 26 subjects (7.7%), oesophageal pain in 14 of 26 subjects (53.8%), dysphagia in 2 of 26 subjects (7.7%), and odynophagia in 1 of 26 subjects (3.8%).

These adverse events that occurred in Study KUTR-015-2 are summarized in the table below.

Adverse events associated with oesophageal stenosis and oesophageal pain

Event	Grade	Circumferential spread	Lesion site[*1]	Onset day[*2]	Seriousness	Treatment	Causal relationship to talaporfin sodium	Outcome	Outcome day[*2]
Oesophageal stenosis	1	1/4-1/2	L	28	Non-serious	None	Related	Recovered	58
Oesophageal stenosis	1	<1/4	M	17	Non-serious	None	Related	Recovered	18
Dysphagia	2	1/4-1/2	M	4	Non-serious	Endoscopic food residue removal	Related	Recovered	6
Dysphagia	1	1/4-1/2	L	5 24	Non-serious Non-serious	None None	Related Related	Recovered Recovered	16 88
Oesophageal pain	2	<1/4	L	1	Non-serious	Analgesic	Related	Recovered	5
Oesophageal pain	1	1/4-1/2	L	1	Non-serious	None	Related	Recovered	9
Oesophageal pain	1	1/4-1/2	M	1	Non-serious	None	Related	Recovered	2
Oesophageal pain	1	<1/4	M	2	Non-serious	Analgesic	Related	Recovered	26
Oesophageal pain	1	1/4-1/2	L	2	Non-serious	Analgesic	Related	Recovered	21
Oesophageal pain	1	<1/4	L	1	Non-serious	None	Related	Recovered	16
Oesophageal pain	1	<1/4	M	1	Non-serious	Analgesic	Related	Recovered	3
Oesophageal pain	1	1/4-1/2	M	1	Non-serious	Analgesic	Related	Recovered	4
Oesophageal pain	1	<1/4	M	7	Non-serious	Analgesic	Related	Recovered	15
Oesophageal pain	1	<1/4	L	2	Non-serious	Mucosal protectant	Related	Recovered	8
Oesophageal pain	1	<1/4	M	1	Non-serious	Analgesic Mucosal protectant	Related	Recovered	20
Oesophageal pain	1	<1/4	M	1	Non-serious	Analgesic	Related	Recovered	13
Oesophageal pain	1	<1/4	U	2	Non-serious	Mucosal protectant	Related	Recovered	23
Oesophageal pain	1	<1/4	M	1	Non-serious	Mucosal protectant	Related	Recovered	29
Odynophagia	1	1/4-1/2 1/4-1/2	U M	3	Non-serious	None	Related	Recovered	44

*1, L (lower intrathoracic esophagus; >32 cm and ≤43 cm from the incisors), M (middle intrathoracic esophagus; >24 cm and ≤32 cm from the incisors), and U (upper intrathoracic esophagus; >18 cm and ≤24 cm from the incisors)

*2, Day 1 is defined as the day talaporfin sodium-mediated PDT was performed.

PMDA asked the applicant to explain the risk factors for developing oesophageal stenosis associated with talaporfin sodium-mediated PDT, the preventive and treatment measures, and the necessity of providing a cautionary statement regarding the adverse event.

The applicant's response:
Following talaporfin sodium-mediated PDT, ulcers formed at the laser irradiated site or adjacent areas become scarred, resulting in oesophageal stenosis. Given this, a large circumferential spread is a risk factor for oesophageal stenosis. Endoscopy should therefore be performed to determine the presence or absence of oesophageal stenosis on a regular basis; further, patients with large circumferential spread should receive oral steroid or local steroid injection to prevent oesophageal stenosis following talaporfin sodium-mediated PDT. In the event of oesophageal stenosis, endoscopic balloon dilation is recommended. In Study KUTR-015-2, endoscopic balloon dilation was performed in 1 of 26 subjects (3.8%). However, if ulcers caused by talaporfin sodium-mediated PDT extend beyond the muscularis propria, endoscopic balloon dilation should be avoided because it may cause oesophageal perforation, and other appropriate measures (e.g., short-term fasting) should be taken. In Study KUTR-015-2, patients were carefully monitored after PDT to determine the presence or absence of oesophageal stenosis and to regularly examine the condition of ulcers caused by PDT, and received appropriate treatments as necessary. In the study, adverse events such as oesophageal stenosis could be managed through these measures; accordingly, the information on these measures should be provided to healthcare professionals.

PMDA's view:
Oesophageal stenosis and oesophageal pain that occurred in Study KUTR-015-2 were able to be managed by the following measures: regular endoscopy; endoscopic balloon dilation and other measures for oesophageal stenosis or dysphagia; and administration of an analgesic for oesophageal pain. Therefore, oesophageal stenosis and oesophageal pain associated with talaporfin sodium-mediated PDT are generally manageable, provided that endoscopy is performed on a regular basis after talaporfin sodium-mediated PDT, and appropriate measures are taken if these adverse events occur, in the same manner as they were performed in the clinical study.

In addition to the paucity of patient data to assess the safety of talaporfin sodium-mediated PDT, the applicant explained that (a) patients with lesions in which the circumferential spread is more than half of the luminal circumference were excluded from Study KUTR-015-2; (b) 1 subject underwent endoscopic balloon dilation to treat oesophageal stenosis,* which was not reported as an adverse event; (c) benefits of preventive measures for oesophageal stenosis have not been clearly demonstrated; and (d) if performed in patients with deep ulcers, endoscopic balloon dilation may cause oesophageal perforation, which could have fatal consequences. Based on the above, PMDA considers that the package insert should provide information on (1) patients enrolled in the clinical study, (2) the details of regular endoscopic monitoring methods used in the clinical study, (3) the preventive measures actually taken against oesophageal stenosis, and (4) the incidence of oesophageal stenosis and oesophageal pain. PMDA also considers that the applicant should appropriately advise healthcare professionals to take appropriate measures in the event of oesophageal stenosis or oesophageal pain.

* Endoscopic balloon dilation and local steroid injection were performed 84 days and 97 days after talaporfin sodium-mediated PDT; and endoscopic balloon dilation was performed 119 days and 36 weeks after talaporfin sodium-mediated PDT.

8.(i).B.(3).3) Photosensitivity

The applicant's explanation on the light protection methods used in Study KUTR-015-2 for managing or preventing photosensitivity reactions in patients:
Since talaporfin sodium has been known to induce photosensitivity, the protocol of Study KUTR-015-2 specified that subjects should wear sunglasses for 3 days following administration of talaporfin sodium, stay in a room in which illuminance was controlled at ≤500 lux using blackout curtains or other light shading measures for 2 weeks following administration of talaporfin sodium, and preferably avoid direct sunlight for 4 weeks following administration of talaporfin sodium.

The results of KUTR-015-2 showed that 1 adverse event (purpura) classified as skin and subcutaneous tissue disorders (MedDRA System Organ Class [SOC]) occurred in 1 of 26 subjects (3.8%) 1 day after administration; however, the possibility of a photosensitivity reaction was ruled out for this event.

In the initial approval of talaporfin sodium, the timing of conducting a skin photosensitivity test for determining whether light protection measures can be discontinued, was defined as "2 weeks after administration of talaporfin sodium." In the current partial change application, however, the applicant proposed to change the timing to "1 week after administration of talaporfin sodium." PMDA asked the applicant to explain the appropriateness of the change.

The applicant's response:
Currently, the package insert for the approved indications (early-stage lung cancer and primary malignant brain tumor) specifies that patients should be protected from light (≤500 lux) for 2 weeks after administration of talaporfin sodium. This measure was based on the following findings: (1) In Study 2906-2-1, 28 of 33 subjects (84.8%) showed no photosensitivity reactions in skin photosensitivity tests conducted by 2 weeks post-dose. (2) In Study ME2906-BT-1, 21 of 27 subjects (77.8%) showed the absence or disappearance of photosensitivity reactions in skin photosensitivity tests conducted by 8 days post-dose, and 27 of 27 subjects (100%) by 15 days post-dose. (3) In Study ME2906-BT-1, however, after discontinuing the light protection measures, adverse events classified as skin and subcutaneous tissue disorders (SOC) occurred in 13 of 27 subjects (48.1%), and a causal relationship to talaporfin sodium could not be ruled out in 1 patient with rash.

Skin photosensitivity tests* conducted in Study KUTR-015-2 showed that 69.2% (18 of 26) of subjects had a score of 0 at 7 days after administration of talaporfin sodium and 100% (26 of 26) of subjects at 15 days after administration of talaporfin sodium. No adverse events classified as skin and subcutaneous tissue disorders (SOC) occurred after the light protection measures were discontinued.

* Photosensitivity reactions such as erythema were evaluated according to the criteria shown in the table below by exposing the dorsum of the hand or other area of skin of patients to direct sunlight for 5 minutes between 11 a.m. and 2 p.m., prior to administration of talaporfin sodium, 5 to 9 days, 12 to 16 days, 19 to 23 days, and 26 to 30 days after administration of talaporfin sodium, and on the day of study discontinuation.

Score	Criteria
0	No change
1	Slightly noticeable erythema
2	Clear erythema
3	Strong erythema or oedema

Based on the above discussion, the applicant considered it appropriate to change the timing of skin photosensitivity testing to 1 week after administration of talaporfin sodium.

PMDA's view:
No patients experienced skin disorders after the light protection measures were discontinued in Study KUTR-015-2. However, in view of the issues listed below, patients receiving talaporfin sodium for the treatment of local residual/recurrent oesophageal carcinoma should be protected from light, and these patients and healthcare professionals should be appropriately cautioned regarding the risk of skin disorders, as with patients receiving the treatment for the approved indications. The period of light protection in patients with local residual/recurrent oesophageal carcinoma should be the same as that in patients receiving treatment for the approved indications, in order to ensure a careful light protection.

- Talaporfin sodium is a photosensitizer, and the proposed dosage and route of administration for the current partial change application are the same as those for the approved indications.
- In Study ME2906-BT-1, 1 subject experienced rash after discontinuing the light protection measures, and a causal relationship to talaporfin sodium could not be ruled out for this event.

8.(i).B.(3).4) Safety in patients who underwent additional laser irradiation

The applicant's explanation on the safety in patients who received additional laser irradiation:
In Study KUTR-015-2, additional laser irradiation was performed in 16 of 26 subjects (61.5%). Adverse events occurred in all 26 subjects, regardless of additional laser irradiation. Grade ≥3 adverse events occurred in 18.8% (3 of 16) of subjects receiving additional laser irradiation, and in 30.0% (3 of 10) of subjects not receiving additional laser irradiation.

The incidence of the following adverse events was ≥10% higher in subjects who underwent additional laser irradiation than in those who did not: AST increased (37.5% and 20.0% in subjects with additional laser irradiation, and in subjects with no additional laser irradiation, respectively; the same applies hereinafter in this paragraph for the order of subject groups), blood potassium increased (37.5% and 20.0%), and haemoglobin decreased (31.3% and 10.0%). The following adverse events occurred in ≥ 2 subjects who underwent additional laser irradiation, but did not occur in any of the subjects who did not undergo additional laser irradiation: blood alkaline phosphatase increased (3 subjects; 18.8%), dysphagia, nausea, and neutrophil count decreased (2 subjects each; 12.5%).

All events of dysphagia and nausea were Grade ≤2. All laboratory test abnormalities were Grade 1 and resolved without any treatment, except for Grade 3 neutrophil count decreased in 1 patient. These events are thus unlikely to pose any clinical problems. Accordingly, there are no adverse events requiring particular attention in patients receiving additional laser irradiation.

PMDA's view:
There were adverse events that occurred at a higher incidence in subjects who underwent additional laser irradiation than in subjects who did not, or that occurred only in subjects who underwent additional laser irradiation, but not in subjects who did not. Therefore, it is necessary to pay close attention to these adverse events in patients undergoing additional laser irradiation, and to provide a caution on the status of occurrence of these adverse events in an appropriate manner.

8.(i).B.(3).5) Safety in patients with aortic invasion (T4) diagnosed by computed tomography (CT) prior to CRT or RT

The applicant's explanation on the safety in patients with a diagnosis of aortic invasion (T4):
There was a report that a patient who had been diagnosed with aortic invasion (T4) by CT prior to CRT or RT experienced an aorto-oesophageal fistula following porfimer sodium-mediated PDT, resulting in death. Therefore, patients with aortic invasion (T4) were excluded from Study KUTR-015-2 under the eligibility criteria. Talaporfin sodium-mediated PDT may pose a risk of serious adverse events (e.g., aorto-oesophageal fistula and oesophageal perforation) in patients with aortic invasion (T4). As there are no effective measures to reduce the risk, talaporfin sodium-mediated PDT should be contraindicated in patients with aortic invasion (T4).

PMDA accepted the applicant's explanation.

8.(i).B.(4) Indications

The proposed indication for talaporfin sodium was "local residual/recurrent oesophageal carcinoma after chemoradiotherapy or radiotherapy."

Based on the discussions in the above sections [see Sections "8.(i).B.(1) Clinical positioning," "8.(i).B.(2) Efficacy," "8.(i).B.(3) Safety"] and in the following sections, PMDA concluded that the proposed indication, "local residual/recurrent oesophageal carcinoma after chemoradiotherapy or radiotherapy," is acceptable, provided that the "Precautions Concerning Indications" section includes statements to the following effect:

- Radical treatment (e.g., surgical resection, endoscopic treatment [EMR or ESD]) should be prioritized over talaporfin sodium-mediated PDT in patients with local residual/recurrent oesophageal carcinoma who are eligible for such radical treatment.
- The eligibility of a patient with local residual/recurrent oesophageal carcinoma for talaporfin sodium-mediated PDT should be determined only after thoroughly reviewing the "Clinical studies" section for the disease stages and other information on patients enrolled in the study, and becoming fully acquainted with the efficacy and safety of talaporfin sodium.
- The efficacy and safety of talaporfin sodium-mediated PDT have not been established in patients with local residual/recurrent oesophageal carcinoma meeting any of the following criteria:
  (a) Lesions classified as T3 or T4, in terms of depth of invasion
  (b) Lesions with a major axis of >3 cm
  (c) Lesions in which the circumferential spread is more than half of the luminal circumference
  (d) Lesions extending to the cervical esophagus

Discussion on eligible patients for talaporfin sodium-mediated PDT

In the current partial change application for talaporfin sodium, the following cautionary statements are proposed in the "Precautions Concerning Indications" section:

- Efficacy and safety have not been established in patients with local residual/recurrent oesophageal carcinoma meeting any of the criteria (a) to (d) (see below). Therefore, in order to determine whether a patient is eligible for treatment with talaporfin sodium, testing such as endoscopic ultrasonography should be conducted to determine the depth of invasion, size, and other conditions of the tumor. Talaporfin sodium-mediated PDT should be performed only after evaluating the risks and benefits of the treatment based on these results.
  (a) Lesions classified as T3 or T4, in terms of depth of invasion
  (b) Lesions with a major axis of >3 cm
  (c) Lesions in which the circumferential spread is more than half of the luminal circumference
  (d) Lesions extending to the cervical esophagus

Patients eligible for surgical resection or endoscopic treatment (EMR or ESD) were excluded from Study KUTR-015-2. PMDA asked the applicant to discuss the appropriateness of talaporfin sodium-mediated PDT in such patients.

The applicant's response:

There are no study results showing the efficacy and safety of talaporfin sodium-mediated PDT in such patients. Surgical resection and endoscopic treatment (EMR or ESD) should therefore be prioritized over talaporfin sodium-mediated PDT in such patients. This information should be provided as a cautionary statement in the "Precautions Concerning Indications" section of the package insert.

PMDA's view:

The applicant's explanation is generally acceptable. Since Study KUTR-015-2 excluded patients with distant metastasis or metastases to lymph nodes, for which systemic chemotherapy is indicated, the applicant should provide information on the disease stages of patients enrolled in Study KUTR-015-2 (in the "Clinical Studies" section of the package insert) and add the following cautionary statement to the "Precautions for indications" section of the package insert:

- The eligibility of a patient for talaporfin sodium-mediated PDT should be determined only after thoroughly reviewing the "Clinical studies" section for the disease stages and other information on patients enrolled in the study, and becoming fully acquainted with the efficacy and safety of talaporfin sodium.

8.(i).B.(5) Dosage and administration

The proposed dosage and administration for talaporfin sodium was as follows: "The dosage is 40 mg/m^2 of talaporfin sodium administered as an intravenous injection. The lesion is irradiated with laser light between 4 and 6 hours after intravenous injection."

Based on the discussions in the following sections, PMDA concluded that the proposed dosage and administration for talaporfin sodium were acceptable, and that a statement to the following effect should be included in the "Precautions Concerning Dosage and Administration" section:

- In patients with local residual/recurrent oesophageal carcinoma, the irradiated site must be examined endoscopically for residual lesion and ulcers on the day following laser irradiation. If any residual lesion is detected, additional laser irradiation should be performed between 22 and 32 hours after intravenous administration of talaporfin sodium.

8.(i).B.(5).1) Dosage of talaporfin sodium

The applicant's explanation on the dosage of talaporfin sodium:

In Study KUTR-015-2, talaporfin sodium was administered at the same dosage recommended for the approved indications (early-stage lung cancer and primary malignant brain tumor), and the efficacy and safety of the dosage were demonstrated. Therefore, 40 mg/m^2 (the same dosage recommended for the approved indications) was selected for patients with local residual/recurrent oesophageal carcinoma after chemoradiotherapy or radiotherapy. No other dose levels have been studied.

PMDA's view:

It is unknown whether the dosage selected in Study KUTR-015-2 is optimal for patients with local residual/recurrent oesophageal carcinoma, because no other dose levels have been studied. However, given that Study KUTR-015-2 demonstrated a certain degree of efficacy and safety of talaporfin sodium, the proposed dosage and administration is acceptable.

8.(i).B.(5).2) Interval between talaporfin sodium administration and laser irradiation, additional laser irradiation, and fluence

In the current partial change application for talaporfin sodium, the proposed timing of laser irradiation was "between 4 and 6 hours after intravenous injection," namely, a 4- to 6-hour interval between administration of talaporfin sodium and laser irradiation (as presented in the proposed "Dosage and administration" section). A cautionary statement regarding additional laser irradiation (see below) was included in the proposed "Precautions for dosage and administration" section. The proposed fluence of laser light was 100 J/cm^2 (as presented in the proposed package insert).

Precautions for dosage and administration

- In patients with local residual/recurrent oesophageal carcinoma, the irradiated site must be examined endoscopically for residual lesion and ulcers on the day following laser irradiation. If any residual lesion is detected, additional laser irradiation should be performed between 22 and 32 hours after intravenous administration of talaporfin sodium.

The applicant explained the grounds for setting the time of laser irradiation, additional laser irradiation, and fluence in Study KUTR-015-2, and the appropriateness of the above-mentioned cautionary statement regarding these matters.

The applicant's explanation:

The interval between administration of talaporfin sodium and laser irradiation in Study KUTR-015-2 was determined based on the results of a foreign phase I study conducted in patients with

superficial malignant tumors for the assessment of the safety, tolerability, and other aspects of talaporfin sodium-mediated PDT. The interval used in Study KUTR-015-2 was identical to that used in a Japanese phase I study (in patients with early-stage lung cancer) and Study 2906-2-1.

The movement of the irradiation site caused by respiratory movement, heartbeat, peristalsis, spasm, and other reasons may result in insufficient laser light irradiation. Lesions were therefore examined endoscopically on the day following laser irradiation, and if any residual lesion was detected, additional laser irradiation was performed [see Section "8.(i).A. Evaluation data. Japanese phase II study"].

The fluence was selected based on the occurrence of DLT in the clinical research [see Section "8.(i).A. Reference data. Japanese clinical research"].

Study KUTR-015-2, conducted under the conditions described above, demonstrated that talaporfin sodium-mediated PDT has a certain degree of efficacy and safety in patients with local residual/recurrent oesophageal carcinoma after CRT or RT [see Sections "8.(i).B.(2) Efficacy" and "8.(i).B.(3).4) Safety in patients who underwent additional laser irradiation"]; therefore, it is appropriate to provide a cautionary statement regarding the interval between administration of talaporfin sodium and laser irradiation, additional laser irradiation, and fluence in the "Dosage and administration" and "Precautions for dosage and administration" sections.

PMDA's view:
It is unknown whether the benefit-risk balance of talaporfin sodium-mediated PDT can be optimized by "the interval between administration of talaporfin sodium and laser irradiation," "the conditions for additional laser irradiation," and "the fluence" used in Study KUTR-015-2. However, given that Study KUTR-015-2 demonstrated a certain degree of efficacy and safety of talaporfin sodium-mediated PDT, PMDA accepted the applicant's explanation on the provision of a cautionary statement regarding the interval between administration of talaporfin sodium and laser irradiation, conditions for additional laser irradiation, and fluence.

8.(i).B.(6) Post-marketing investigations

8.(i).B.(6).1) Post-marketing surveillance of talaporfin sodium

The applicant's explanation on the post-marketing surveillance plan:
A post-marketing surveillance will be conducted using a central registration method in patients with local residual/recurrent oesophageal carcinoma who receive talaporfin sodium, mainly to assess the safety of talaporfin sodium-mediated PDT in postmarketing clinical settings.

Among important identified risks for talaporfin sodium, photosensitivity and hepatic dysfunction will be excluded from the priority survey items for the post-marketing surveillance because of the absence of serious cases in Study KUTR-015-2. Dyspnoea, another important identified risk, will also be excluded from the priority survey items because it is a typical event in early-stage lung cancer.

The target sample size was determined to be 100 patients based on the incidence of each adverse reaction reported in Study KUTR-015-2.

The follow-up period was set at 30 days because in Study KUTR-015-2, all adverse events had developed by 30 days after PDT.

PMDA's view:
The use-results survey in Japanese patients with early-stage lung cancer (the approved indication) who underwent talaporfin sodium-mediated PDT has already been completed. A certain amount of safety data on Japanese patients have thus already been collected. However, another use-results survey should be conducted to assess the safety and other aspects of talaporfin sodium-mediated PDT in Japanese clinical settings, because Study KUTR-015-2 enrolled only 26 patients and reported some adverse events that had not been reported in clinical studies supporting the approved indications, early-stage lung cancer or primary malignant brain tumor [see Section "8.(i).B.(3) Safety"].

The post-marketing surveillance should include oesophageal stenosis and oesophageal perforation as the priority survey items: Oesophageal stenosis was first reported in Study KUTR-015-2. Oesophageal perforation was not reported in Study KUTR-015-2, but has been reported in a patient undergoing PDT with a similar drug; vigilance is therefore necessary regarding the risk of oesophageal perforation in patients undergoing talaporfin sodium-mediated PDT.

The follow-up period should be at least 3 months after PDT, because (1) in Study KUTR-015-2, a patient underwent endoscopic dilation of the esophagus and local steroid injection to treat oesophageal stenosis at 84 days after talaporfin sodium-mediated PDT, and (2) there is a report of oesophageal perforation that occurred approximately 2 months after PDT with a similar drug. The target sample size proposed by the applicant is acceptable.

8.(i).B.(6).2) Proper treatment with talaporfin sodium-mediated PDT
The applicant's explanation on the measures for proper treatment with talaporfin sodium-mediated PDT in patients with local residual/recurrent oesophageal carcinoma in post-marketing settings:
In cooperation with the relevant academic societies, the applicant will prepare guidelines on treatment with talaporfin sodium-mediated PDT, develop training programs, and host training sessions. The guidelines, training programs, and training sessions will be provided to physicians who perform talaporfin sodium-mediated PDT to ensure that they are familiar with (a) the eligibility for talaporfin sodium-mediated PDT; (b) the appropriate environment and conditions for treatment; and (c) how to use the semiconductor laser device for PDT.

PMDA accepted the applicant's explanation.

8.(ii) Adverse events reported in clinical studies
The data on deaths in the submitted clinical studies are presented in the "8.(i) Summary of clinical efficacy and safety." The following sections summarize other main adverse events observed in the studies.

8.(ii).(1) Clinical research (Study KUTR-015-1)
Adverse events occurred in 3 of 3 subjects (100%) irradiated with a fluence of 50 J/cm^2 (level 1), 2 of 3 subjects (66.7%) irradiated with 75 J/cm^2 (level 2), and 9 of 13 subjects (69.2%) irradiated

with 100 J/cm^2 (level 3). Adverse events for which a causal relationship to talaporfin sodium could not be ruled out occurred in 1 of 3 subjects (33.3%) in the 50 J/cm^2 (level 1) group, 2 of 3 subjects (66.7%) in the 75 J/cm^2 (level 2) group, and 8 of 13 subjects (61.5%) in the 100 J/cm^2 (level 3) group.

The table below shows adverse events occurring in ≥10% of subjects in at least 1 group.

Adverse events occurring with an incidence of ≥10% in at least 1 group

System Organ Class	Number of subjects (%)					
Preferred Term	50 J/cm^2 (N = 3)		75 J/cm^2 (N = 3)		100 J/cm^2 (N = 13)	
(MedDRA/J ver 17.0)	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Adverse events total	3 (100%)	0	2 (66.7%)	0	9 (69.2%)	0
Gastrointestinal disorders						
Oesophageal pain	1 (33.3%)	0	2 (66.7%)	0	6 (46.2%)	0
Dysphagia	1 (33.3%)	0	0	0	4 (30.8%)	0
General disorders and administration site conditions						
Pyrexia	0	0	1 (33.3%)	0	0	0
Investigations						
White blood cell count decreased	1 (33.3%)	0	0	0	0	0
Blood sodium decreased	1 (33.3%)	0	0	0	0	0
Aspartate aminotransferase increased	0	0	0	0	2 (15.4%)	0
Skin and subcutaneous tissue disorders						
Dry skin	1 (33.3%)	0	0	0	0	0
Blood and lymphatic system disorders						
Anaemia	0	0	0	0	2 (15.4%)	0

There were no serious adverse events, or adverse events that led to treatment discontinuation of talaporfin sodium in any of the groups.

8.(ii).(2) Japanese phase II study (Study KUTR-015-2)

Adverse events occurred in 26 of 26 subjects (100%). All 26 subjects (100%) experienced an adverse event for which a causal relationship to talaporfin sodium could not be ruled out.

The table below shows adverse events with an incidence of ≥10%.

Adverse events with an incidence of ≥10%

System Organ Class Preferred Term (MedDRA/J ver 17.0)	Number of subjects (%) N = 26	
	All Grades	Grade ≥3
Adverse events total	26 (100%)	6 (23.1%)
Investigations		
Blood albumin decreased	23 (88.5%)	0
C-reactive protein increased	21 (80.8%)	0
Lymphocyte count decreased	16 (61.5%)	4 (15.4%)
Aspartate aminotransferase increased	8 (30.8%)	0
Blood potassium increased	8 (30.8%)	0
Blood sodium decreased	7 (26.9%)	1 (3.8%)
Alanine aminotransferase increased	6 (23.1%)	0
Haemoglobin decreased	6 (23.1%)	0
Protein total decreased	4 (15.4%)	0
White blood cell count decreased	4 (15.4%)	0
Blood potassium decreased	3 (11.5%)	0
Gamma-glutamyltransferase increased	3 (11.5%)	0
Neutrophil count increased	3 (11.5%)	0
Protein urine present	3 (11.5%)	0
Blood alkaline phosphatase increased	3 (11.5%)	0
Gastrointestinal disorders		
Oesophageal pain	14 (53.8%)	0
Constipation	5 (19.2%)	0
General disorders and administration site conditions		
Pyrexia	8 (30.8%)	0

A serious adverse event (hypotension) occurred in 1 of 26 subjects (3.8%). A causal relationship to the study drug was ruled out for the event.

There were no adverse events that led to treatment discontinuation of talaporfin sodium.

The following sections outlines the discussions by the Expert Discussion and subsequent review by PMDA (outline of the Review Report (2) of talaporfin sodium).

(1) Clinical positioning and efficacy

PMDA's conclusion:

Study KUTR-015-2 (a Japanese phase II study in patients with local residual/recurrent oesophageal carcinoma after CRT or RT) has limitations as a basis for evaluating the efficacy of talaporfin sodium-mediated PDT, because it was an open-label, uncontrolled study and no long-term results have been obtained from the study. However, the discussions in Section "8.(i).B.(1) Clinical positioning" have shown that talaporfin sodium-mediated PDT is a new local treatment option for patients with local residual/recurrent oesophageal carcinoma after CRT or RT. Further, the local complete response rate in Study KUTR-015-2 was 88.5% [95% confidence interval: 69.8%, 97.6%]. PMDA has thus concluded that talaporfin sodium-mediated PDT is expected to be effective in the treatment of local residual/recurrent oesophageal carcinoma after CRT or RT.

This conclusion was supported by the expert advisors at the Expert Discussion.

(2) Safety

PMDA's conclusion:

According to the discussion in Section "8.(i).B.(3) Safety," oesophageal stenosis and oesophageal pain were identified as adverse events requiring extra caution when talaporfin sodium-mediated PDT is performed in patients with local residual/recurrent oesophageal carcinoma after CRT or RT. Nevertheless, PMDA has concluded that talaporfin sodium-mediated PDT is tolerable, provided that these patients are carefully monitored for these adverse events, as well as for adverse events observed in clinical studies for the approved indications (early-stage lung cancer or primary malignant brain tumor), in the same manner as patients receiving treatment for the approved indications.

Talaporfin sodium-mediated PDT may cause serious adverse events (e.g., aorto-oesophageal fistula) in patients with aortic invasion (T4) diagnosed by CT prior to CRT or RT. PMDA therefore concluded that talaporfin sodium-mediated PDT should be contraindicated in such patients.

This conclusion was supported by the expert advisors at the Expert Discussion. The following comments were made by an expert advisor:

- Patients with tracheal or bronchial invasion diagnosed by CT prior to CRT or RT have an increased risk of oesophageal perforation associated with talaporfin sodium-mediated PDT. The applicant should issue a cautionary statement regarding the risk.

PMDA asked the applicant to explain the safety of talaporfin sodium-mediated PDT in patients with tumor invasion to the adjacent organs as diagnosed by CT prior to CRT or RT.

The applicant's response:

The safety of talaporfin sodium-mediated PDT has not been established in patients with tumor invasion to the adjacent organs as diagnosed by CT prior to CRT or RT, because such patients were not enrolled in Study KUTR-015-2. In such patients, since tissues around the esophagus become fragile after CRT or RT, talaporfin sodium-mediated PDT may cause tissue damage extending beyond the oesophageal wall, possibly resulting in oesophageal perforation.

PMDA's view:

Patients with tracheal or bronchial invasion diagnosed by CT prior to CRT or RT may have an increased risk of oesophageal perforation associated with talaporfin sodium-mediated PDT. Therefore, using the package insert or other relevant materials, the applicant should appropriately advise healthcare professionals to determine whether a patient is eligible for talaporfin sodium-mediated PDT according to the condition of the tumor on CT performed prior to CRT or RT. It is also necessary to collect information on the status of tumors on CT performed prior to CRT or RT in patients who presented with oesophageal perforation, an adverse event that should be selected as a priority survey item for the post-marketing surveillance [see Section "8.(i).B.(6) Post-marketing investigations"]. New findings obtained from the surveillance should be provided to healthcare professionals in an appropriate manner.

PMDA instructed the applicant to take appropriate measures on the above issues. The applicant agreed.

(3) Indications

Based on the discussions in Sections "8.(i).B.(1) Clinical positioning" and "8.(i).B.(4) Indications," PMDA concluded that the proposed indication for talaporfin sodium, "local residual/recurrent oesophageal carcinoma after chemoradiotherapy or radiotherapy," is appropriate provided that the following cautionary statements are included in the "Precautions for indications" section:

Precautions for indications

- Radical treatment (e.g., surgical resection, endoscopic treatment [EMR or ESD]) should be prioritized over talaporfin sodium-mediated PDT in patients with local residual/recurrent oesophageal carcinoma who are eligible for such radical treatment.
- The eligibility of a patient for talaporfin sodium-mediated PDT should be determined only after thoroughly reviewing the "Clinical studies" section for the histological types of cancers and other information on patients enrolled in the clinical study, and becoming fully acquainted with the efficacy and safety of talaporfin sodium.
- The efficacy and safety of talaporfin sodium-mediated PDT have not been established in patients with local residual/recurrent oesophageal carcinoma meeting any of the following criteria:
  (a) Lesions classified as T3 or T4, in terms of depth of invasion
  (b) Lesions with a major axis of >3 cm
  (c) Lesions in which the circumferential spread is more than half of the luminal circumference
  (d) Lesions extending to the cervical esophagus

This conclusion was supported by the expert advisors at the Expert Discussion.

(4) Dosage and administration

After the discussion in Section "8.(i).B.(5) Dosage and administration," PMDA concluded that the "Dosage and Administration" and "Precautions Concerning Dosage and Administration" sections should be as follows:

Dosage and administration

The usual adult dosage is 40 mg/m^2 of talaporfin sodium administered as an intravenous injection. The lesion is irradiated with laser light between 4 and 6 hours after intravenous injection.

Precautions for dosage and administration

- The irradiated site must be examined endoscopically for residual lesion and ulcers on the day following laser irradiation. If any residual lesion is detected, additional laser irradiation should be performed between 22 and 32 hours after intravenous administration of talaporfin sodium.

This conclusion was supported by the expert advisors at the Expert Discussion.

(5) Post-marketing investigations and risk management plan (draft)

After the discussion presented in Section "8.(i).B.(6) Post-marketing investigations," PMDA concluded that a post-marketing surveillance should be conducted to assess the safety and other aspects of talaporfin sodium-mediated PDT in clinical settings, and the safety information

collected should be provided to healthcare professionals in an appropriate manner, because Study KUTR-015-2 enrolled only a limited number of patients and reported some adverse events that had not been reported by the clinical studies conducted for the approved indications.

PMDA's conclusion regarding the plan for the post-marketing surveillance:

(a) Oesophageal stenosis and oesophageal perforation should be included in the priority survey items: Oesophageal stenosis was first reported in Study KUTR-015-2. Oesophageal perforation requires caution because it was reported in a patient undergoing PDT with a similar drug, although it was not reported by Study KUTR-015-2.
(b) The proposed target sample size for the surveillance (100 patients) is acceptable.
(c) The follow-up period should be 3 months after PDT, because (1) in Study KUTR-015-2, a patient underwent endoscopic dilation of the esophagus and local steroid injection to treat oesophageal stenosis at 84 days after talaporfin sodium-mediated PDT, and (2) the reported case of oesophageal perforation occurred approximately 2 months after PDT with a similar drug.

Further, in order to perform talaporfin sodium-mediated PDT properly, it is essential for a physician to gain the necessary knowledge and skills required for the procedure. Therefore, after the market launch, appropriate measures should be taken to ensure that talaporfin sodium will be administered only under the supervision of a physician who has undergone training sessions on talaporfin sodium-mediated PDT, and has sufficient knowledge and experience in PDT.

This conclusion was supported by the expert advisors at the Expert Discussion.

PMDA instructed the applicant to take appropriate measures on the above issues. The applicant agreed.

Based on the above discussion, PMDA concluded that the applicant should establish the safety and efficacy specification in the risk management plan (draft), and implement additional pharmacovigilance actions and risk minimization actions, as shown in the table below.

Safety and efficacy specification for the risk management plan (draft)

<table>
<tr><td colspan="3">Safety specification</td></tr>
<tr><td>Important identified risks</td><td>Important potential risks</td><td>Important missing information</td></tr>
<tr><td>• Photosensitivity
• Hepatic dysfunction
• Dyspnoea (early-stage lung cancer)
• Oesophageal stenosis (local residual/recurrent oesophageal carcinoma after CRT or RT)</td><td>• Oesophageal perforation (local residual/recurrent oesophageal carcinoma after CRT or RT)</td><td>None</td></tr>
<tr><td colspan="3">Efficacy specification</td></tr>
<tr><td colspan="3">• Efficacy in patients with primary malignant brain tumor in clinical settings (use-results survey)
• Efficacy in patients with local residual/recurrent oesophageal carcinoma after CRT or RT in clinical settings (use-results survey)</td></tr>
</table>

Summary of additional pharmacovigilance and risk minimization actions for the risk management plan (draft)

Additional pharmacovigilance actions	Additional risk minimization actions
• Early post-marketing phase vigilance (local residual/recurrent oesophageal carcinoma after CRT or RT) • Use-results survey for primary malignant brain tumor • Use-results survey for local residual/recurrent oesophageal carcinoma after CRT or RT (see the table below for the outline of use-results survey plan [draft])	• Information provision by implementing early post-marketing phase vigilance (local residual/recurrent oesophageal carcinoma after CRT or RT) • Specifying use conditions

Items underlined are activities planned for the new indication.

Outline of use-results survey plan (draft)

Objective	To assess the safety and other aspects of talaporfin sodium under actual use conditions
Survey method	Central registration method
Target patients	Patients with local residual/recurrent oesophageal carcinoma after CRT or RT, who received talaporfin sodium
Follow-up period	For 3 months after PDT
Planned sample size	100 patients
Main survey items	Priority survey items: oesophageal stenosis and oesophageal perforation Main survey items other than the above include patient characteristics, status of treatment with talaporfin sodium, concomitant medications and therapies, adverse events (including changes in laboratory values)

Based on the Review Report of talaporfin sodium cited above, PMDA asked the applicant (Panasonic Healthcare Co., Ltd.) if there are any necessary actions relevant to PD Laser/EC-PDT Probe.

The applicant's explanation about actions to be taken for the use-results evaluation and the package insert descriptions:

(1) Use-results evaluation

The applicant submitted a post-marketing surveillance plan. For the purposes to elucidate the occurrence of adverse events or malfunctions associated with the clinical use of talaporfin sodium-mediated PDT in patients with local residual/recurrent esophageal carcinoma after CRT or RT, identify potential contributory factors that affect the efficacy and safety of the therapy, and investigate long-term outcome, a post-marketing use-results survey should be conducted and the efficacy and safety of the therapy should be verified at a certain time point after the survey. The applicant's post-marketing surveillance plan submitted with the approval application describes as follows: The lowest incidence of an adverse event in Study KUTR-015-2 was 3.8%. In order to detect at least 1 patient experiencing an adverse event occurring at an incidence of 3.0%, which is lower than 3.8%, with a CI of 95%, 99 patients would need to be involved in the survey. Thus, the proposed sample size was 100 patients. A safety observation period of 30 days was proposed because, in Study KUTR-015-2, the latest onset of adverse event was reported at 29 days post-PDT. Furthermore, the last patient who had achieved L-CR was confirmed at 20 weeks post-PDT in the study, and thus the maximum evaluation period for antitumor effect was determined to be 24 weeks post-PDT. The registration period was expected to be 3 years. Including a 5-year observation period to confirm the survival of patients, a planned survey period of 8 years was proposed.

PMDA's view:
Talaporfin sodium-mediated PDT with PD Laser/EC-PDT Probe is a combination therapy of talaporfin sodium with the product. Therefore, the post-marketing surveillance of the product should be conducted in conjunction with that of talaporfin sodium. Considering the rationality of conducting the surveillance of the product in coordination with the talaporfin sodium post-marketing surveillance, PMDA instructed the applicant to implement the surveillance of the product in accordance with the surveillance plan for talaporfin sodium in terms of survey components [see "Outline of use-results survey plan (draft)" on the previous page] and period. The applicant agreed.

(2) Cautionary advice to be given on the use of the product
The package insert of talaporfin sodium contains information relevant to the use and after the use of PD Laser/EC-PDT Probe. Such information should also be provided in the package insert of the product. PMDA instructed the applicant to discuss information to be covered in the package insert of the product based on the contents of the package insert of talaporfin sodium.

The applicant mentioned that the following action would be taken for the package insert of the product.
- PDT-related information in the "Precautions" in the package insert of talaporfin sodium will also be presented in the package insert of PD Laser/EC-PDT Probe.

PMDA concluded that there is no particular problem with the applicant's action.

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

The medical device application data (8-1.1) were subjected to GCP on-site inspection in accordance with the provisions of the Pharmaceutical Affairs Act.[ii] The results showed satisfactory overall compliance with GCP in the conduct of clinical studies, and PMDA therefore concluded that there were no obstacles to conducting its review based on the application documents submitted. Meanwhile, the inspection revealed findings at some study centers. Although no substantial impact on the evaluation of the entire study, the matters were notified to the head of the study centers to seek corrective actions.

Findings requiring corrective actions
Study centers
- A clinical study-related task (upper gastrointestinal endoscopy) was performed by a physician who was not listed in the responsibility chart that was prepared by the principal investigator.
- A clinical study-related test (skin photosensitivity test) was proceeded before obtaining consent.

[ii] The present application for approval of PD Laser/EC-PDT Probe was originally filed under the Pharmaceutical Affairs Act, and subsequently reclassified as an application under the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (PMD Act), to ensure that the product is subjected to a quality management system (QMS) inspection under the PMD Act. While the document-based compliance inspection and on-site GCP inspection were implemented in accordance with the Pharmaceutical Affairs Act, these inspections were regarded as equivalent to those under the PMD Act.

V. Overall Evaluation

The product is a laser device with a special probe to be used in talaporfin sodium-mediated PDT in patients with local residual/recurrent esophageal carcinoma after CRT or RT.

The main issues in the review of the product were (1) the rationale for the use of the result from Study KUTR-015-2 as evaluation data, (2) the method of laser light irradiation and how to acquaint users with the method, and (3) necessity of use-results evaluation. Taking into account the comments from the Expert Discussion, PMDA has reached the conclusions below.

(1) Rationale for the use of the results from Study KUTR-015-2 as evaluation data

In Study KUTR-015-2, Probe for lung cancer was used. After that, in response to a request from users, the applicant newly developed a special probe for esophageal carcinoma, for which the marketing approval application was filed. Surfaces exposed to irradiation with EC-PDT Probe in a simulation of its clinical use demonstrated optical equivalence of the probe and Probe for lung cancer. Accordingly, in use for esophageal carcinoma, EC-PDT Probe has ability to excite talaporfin sodium equally to Probe for lung cancer. Therefore, the results from Study KUTR-015-2 are valid as the grounds for the current application.

(2) Method of laser light irradiation and how to acquaint users with the method

PDT can exert its therapeutic effect in the presence of talaporfin sodium on the target tumor tissue when sufficient laser energy is delivered from the product to the target tissue. In light of such characteristics of PDT, PMDA concluded that the following points are particularly important in the use of the product.

1) Only patients who are highly likely to respond to PDT and in whom PDT can be performed safely are eligible for PDT. Such patients should be selected based on the understanding of the characteristics of the therapy.
2) The following information should be provided based on the laser irradiation method employed in Study KUTR-015-2:
   (a) How to place EC-PDT Probe securely for steady laser irradiation of the target tissue
   (b) Useful information for treatment planning, such as multiple-spot irradiation patterns for a lesion that cannot be covered by single-spot irradiation
3) The product should be operated by physicians who are able to make an appropriate judgment on the need for an additional irradiation.
4) The product should be operated by physicians who are able to take appropriate measures in case of serious adverse events such as esophageal perforation and esophageal stenosis.

The proper use of the product presupposes physicians' technical knowledge in PDT, knowledge and experience in dealing with the target illness of the therapy, and advanced endoscopic techniques. Accordingly, and based on comments from the Expert Discussion, etc., it is essential for the applicant to take appropriate measures to ensure that the product be used by physicians with adequate experience in endoscopic treatment of esophageal carcinoma who have been trained for its operation and lectured about PDT, and therefore the product should be approved with these conditions.

(3) Necessity of use-results evaluation

Talaporfin sodium-mediated PDT employs PD Laser/EC-PDT Probe in combination with talaporfin sodium. The method of use of the product can affect the efficacy and safety of the therapy significantly. To assess the appropriateness of the irradiation method and the safety of additional irradiation specified in the method of use for EC-PDT Probe, post-marketing information on the product should be collected. The post-marketing surveillance for talaporfin sodium needs to be implemented also as a part of the surveillance for PD Laser/EC-PDT Probe, and it is thus rational to conduct the post-marketing surveillance for PD Laser/EC-PDT Probe and for talaporfin sodium in a coordinated manner. The period and survey components of the post-marketing surveillance for PD Laser/EC-PDT Probe should be the same as those for talaporfin sodium.

Based on the above discussions, the provision of the product to the clinical setting is beneficial because it offers a new treatment option for local residual/recurrent esophageal carcinoma after CRT or RT, for which no standard treatment has been available until now. PMDA concluded that the product may be approved for the intended use refined as follows, with the following approval conditions.

Intended Use

PD Laser

PD Laser is a laser device to be used for photodynamic therapy in combination with a drug for the treatment of patients with the following conditions:

Drug to be used in combination:

Non-proprietary name: talaporfin sodium

Brand name: Laserphyrin 100 mg for Injection

Indications:

1) Early-stage lung cancer (Stage 0 or I) treatable with laser irradiation in patients ineligible for other radical interventions including surgical resection, or in patients who require the preservation of pulmonary function but cannot receive other treatments. The entire tumor must be observable endoscopically.
2) Local residual/recurrent esophageal carcinoma after chemoradiotherapy or radiotherapy

EC-PDT Probe

EC-PDT Probe is used in the photodynamic therapy of local residual/recurrent esophageal carcinoma after chemoradiotherapy or radiotherapy.

Approval Condition

The applicant is required to take necessary measures, in cooperation with relevant academic societies, to ensure that the product is used strictly for the intended purpose by physicians with adequate knowledge and experience in diagnosis and endoscopic treatment of esophageal carcinoma who have acquired photodynamic therapeutic techniques with the product and sufficient knowledge about therapy-associated complications through training sessions, etc.

The product should be subjected to a use-results evaluation, and the evaluation period should be the same as that of the re-examination period of talaporfin sodium. The product is not classified as a biological product or specified biological product.

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

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