February 19, 2020

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

Report on the Deliberation Results

Classification	Instrument & Apparatus 9, Medical X-ray equipment and X-ray tube for medical X-ray equipment
Term Name	Neutron irradiation system for boron neutron capture therapy
Brand Name	NeuCure BNCT System
Applicant	Sumitomo Heavy Industries, Ltd.
Date of Application	October 11, 2019 (Application for marketing approval)

Results of Deliberation

In its meeting held on February 19, 2020, the Committee on Medical Devices and *In-vitro* Diagnostics reached the following conclusion, and decided that this conclusion should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

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

The use-results survey period should be 8 years.

This English translation of this Japanese review report is intended to serve as reference material made available for the convenience of users. In the event of any inconsistency between the Japanese original and this English translation, the Japanese original shall take precedence. PMDA will not be responsible for any consequence resulting from the use of this reference English translation.

Approval Conditions

1. The applicant is required to take necessary measures, such as disseminating the latest guidelines for proper use developed in cooperation with related academic societies, to ensure that physicians with adequate knowledge and experience in boron neutron capture therapy of unresectable, locally advanced or locally recurrent head and neck cancer, become fully familiar with the directions for use of NeuCure BNCT System, adverse events associated with neutron irradiation, and other relevant issues, and to ensure that the physicians use NeuCure BNCT System in accordance with the intended use and directions for use of NeuCure BNCT System at medical institutions capable of providing boron neutron capture therapy.

2. The applicant is required to take necessary measures, such as disseminating the latest guidelines for proper use developed in cooperation with related academic societies, to ensure that medical physics experts with adequate knowledge and experience in boron neutron capture therapy of unresectable, locally advanced or locally recurrent head and neck cancer, become fully familiar with the treatment plan for boron neutron capture therapy, quality control of NeuCure BNCT System, and other relevant issues, and to ensure that the experts use NeuCure BNCT System in accordance with the intended use and directions for use of NeuCure BNCT System at medical institutions capable of providing boron neutron capture therapy.

3. The applicant is required to conduct a use-results survey involving all patients treated with NeuCure BNCT System after the market launch until data from a certain number of patients have been gathered and take appropriate measures as necessary based on the survey results.

4. The applicant is required to take appropriate measures to minimize radiation exposure of healthcare professionals as much as practical during the use of NeuCure BNCT System.

Review Report

February 10, 2020

Pharmaceuticals and Medical Devices Agency

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

Classification	1. Medical X-ray equipment and X-ray tube for medical X-ray equipment 2. Disease treatment program
Term Name	1. Neutron irradiation system for boron neutron capture therapy 2. Treatment planning program for boron neutron capture therapy
Brand Name	1. NeuCure BNCT System 2. NeuCure BNCT Dose Engine
Applicant	Sumitomo Heavy Industries, Ltd.
Date of Application	October 11, 2019
Items Warranting Special Mention	SAKIGAKE designation device (SAKIGAKE Device Designation No. 2 of 2016 [*28 ki*]; PSEHB/MDED Notification No. 0228-6, dated February 28, 2017, by the Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare) SAKIGAKE comprehensive assessment consultation was conducted.
Reviewing Office	Office of Medical Devices I

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Review Results

February 10, 2020

Classification	1. Medical X-ray equipment and X-ray tube for medical X-ray equipment
	2. Disease treatment program
Term Name	1. Neutron irradiation system for boron neutron capture therapy
	2. Treatment planning program for boron neutron capture therapy
Brand Name	1. NeuCure BNCT System
	2. NeuCure BNCT Dose Engine
Applicant	Sumitomo Heavy Industries, Ltd.
Date of Application	October 11, 2019

Results of Review

NeuCure BNCT System (hereinafter referred to as "NeuCure System") is a neutron irradiation device intended to be used for boron neutron capture therapy (BNCT) to treat unresectable, locally advanced or locally recurrent head and neck cancer. NeuCure BNCT Dose Engine (hereinafter referred to as "NeuCure Dose Engine") is a medical device program intended to be used for calculation of dose distribution in BNCT using NeuCure System. NeuCure System is used in combination with L-4-boronophenylalanine-[^{10}B] (L-BPA) (brand name, Steboronine 9000 mg/300 mL for Infusion [Stella Pharma Corporation], hereinafter referred to as "Steboronine"). A marketing application for Steboronine was submitted simultaneously with the marketing application for NeuCure System and NeuCure Dose Engine. (NeuCure System and NeuCure Dose Engine are hereinafter collectively referred to as "NeuCure.")

The applicant submitted non-clinical data supporting the electrical safety, electromagnetic compatibility, biological safety, radiation safety, mechanical safety, and performance of NeuCure System. The submitted data indicated no particular problem. The applicant also submitted non-clinical data supporting the safety and performance of NeuCure Dose Engine. The submitted data indicated no particular problem.

Clinical data submitted were the results of a phase I clinical study (N = 9) and a phase II clinical study (N = 21) of NeuCure conducted in Japan. In the phase II clinical study, the response rate was determined by blinded independent central review (BICR) based on Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1. The response rate was 71.4% (90% confidence interval [CI], 51.3%, 86.8%). The lower limit of the 90% CI was above the predefined threshold response rate (20.0%). The safety of NeuCure was evaluated with a focus on serious adverse events and frequently reported Grade ≥3 adverse events as rated according to the Common Terminology Criteria for Adverse Events (CTCAE) in the

phase I and II studies. These adverse events did not lead to death or treatment discontinuation, but their causal relationship to BNCT with NeuCure and Steboronine could not be ruled out and they occurred with a certain incidence. These data should be communicated to healthcare professionals appropriately to raise cautions. Nevertheless, since the clinical studies demonstrated a certain level of response rate to BNCT with NeuCure and Steboronine in the treatment of unresectable, locally advanced or locally recurrent head and neck cancer, PMDA concluded that BNCT with NeuCure and Steboronine has an acceptable safety profile in view of its shown benefit.

As a result of overall evaluation of the submitted data based on the conclusion of the Expert Discussion, PMDA concluded that there was no particular problem with the performance, efficacy, and safety of NeuCure.

BNCT with NeuCure is a combination treatment with a boron drug and a neutron beam. This is a unique therapy because its effectiveness on tumors and the extent of unintended radiation exposure of normal tissues depend on the extent of boron accumulation in a tumor, unlike conventional radiotherapies such as X-ray and proton radiation. Special expertise is required for radiation safety management of NeuCure, including treatment planning, the quality control of devices, and the control of radioactivated devices. Considering these particularities of NeuCure, proper implementation of BNCT requires medical institutions equipped with a management system necessary for this therapy and healthcare professionals with sufficient relevant knowledge, techniques, and experience.

Because only limited safety information is available from Japanese and non-Japanese patients treated with BNCT, safety and efficacy information of NeuCure should be collected through a use-results survey involving all patients treated with NeuCure after the market launch until data from a certain number of patients have been gathered. In addition, additional risk mitigation measures should also be taken as necessary.

Since treatment with NeuCure System involves long-term neutron irradiation, which profoundly accelerates the radioactivation of devices, buildings, etc. compared with general radiotherapy equipment such as linear accelerators, necessary measures should be taken to reduce radiation exposure of medical professionals as much as practical.

As a result of its review, PMDA has concluded that NeuCure may be approved for the intended use shown below, with the following approval conditions, and that the results should be presented to the Committee on Medical Devices and *In-vitro* Diagnostics for further deliberation.

Intended Use

NeuCure BNCT System

NeuCure BNCT System is a neutron irradiation device intended to be used for boron neutron capture therapy to treat unresectable, locally advanced or locally recurrent head and neck cancer, and used in combination with the following drug:

Non-proprietary Name: Borofalan (^{10}B)

Brand Name: Steboronine 9000 mg/300 mL for Infusion

NeuCure BNCT Dose Engine

NeuCure BNCT Dose Engine is a program that calculates dose distribution achieved in boron neutron capture therapy based on contour information and irradiation conditions, to assist physicians in developing treatment plans with boron neutron capture therapy for patients with unresectable, locally advanced or locally recurrent head and neck cancer. NeuCure BNCT Dose Engine is used in combination with the following drug:

Non-proprietary Name: Borofalan (^{10}B)
Brand Name: Steboronine 9000 mg/300 mL for Infusion

Approval Conditions

NeuCure BNCT System

1. The applicant is required to take necessary measures, such as disseminating the latest guidelines for proper use developed in cooperation with related academic societies, to ensure that physicians with adequate knowledge and experience in boron neutron capture therapy of unresectable, locally advanced or locally recurrent head and neck cancer, become fully familiar with the directions for use of NeuCure BNCT System, adverse events associated with neutron irradiation, and other relevant issues, and to ensure that the physicians use NeuCure BNCT System in accordance with the intended use and directions for use of NeuCure BNCT System at medical institutions capable of providing boron neutron capture therapy.

2. The applicant is required to take necessary measures, such as disseminating the latest guidelines for proper use developed in cooperation with related academic societies, to ensure that medical physics experts with adequate knowledge and experience in boron neutron capture therapy of unresectable, locally advanced or locally recurrent head and neck cancer, become fully familiar with the treatment plan for boron neutron capture therapy, quality control of NeuCure BNCT System, and other relevant issues, and to ensure that the experts use NeuCure BNCT System in accordance with the intended use and directions for use of NeuCure BNCT System at medical institutions capable of providing boron neutron capture therapy.

3. The applicant is required to conduct a use-results survey involving all patients treated with NeuCure BNCT System after the market launch until data from a certain number of patients have been gathered and take appropriate measures as necessary based on the survey results.

4. The applicant is required to take appropriate measures to minimize radiation exposure of healthcare professionals as much as practical during the use of NeuCure BNCT System.

NeuCure BNCT Dose Engine

1. The applicant is required to take necessary measures, such as disseminating the latest guidelines for proper use developed in cooperation with related academic societies, to ensure that physicians with adequate knowledge and experience in boron neutron capture therapy of unresectable, locally advanced or locally recurrent head and neck cancer, become fully familiar with the directions for use

of NeuCure BNCT Dose Engine, adverse events associated with neutron irradiation, and other relevant issues, and to ensure that the physicians use NeuCure BNCT Dose Engine in accordance with the intended use and directions for use of NeuCure BNCT Dose Engine at medical institutions capable of providing boron neutron capture therapy.

2. The applicant is required to take necessary measures, such as disseminating the latest guidelines for proper use developed in cooperation with related academic societies, to ensure that medical physics experts with adequate knowledge and experience in boron neutron capture therapy of unresectable, locally advanced or locally recurrent head and neck cancer, become fully familiar with the treatment plan for boron neutron capture therapy, quality control of NeuCure BNCT Dose Engine, and other relevant issues, and to ensure that the experts use NeuCure BNCT Dose Engine in accordance with the intended use and directions for use of NeuCure BNCT Dose Engine at medical institutions capable of providing boron neutron capture therapy.

3. The applicant is required to conduct a use-results survey involving all patients treated with NeuCure BNCT Dose Engine after the market launch until data from a certain number of patients have been gathered and take appropriate measures as necessary based on the survey results.

Review Report

February 10, 2020

Product for Review

Classification	1. Medical X-ray equipment and X-ray tube for medical X-ray equipment 2. Disease treatment program
Term Name	1. Neutron irradiation system for boron neutron capture therapy 2. Treatment planning program for boron neutron capture therapy
Brand Name	1. NeuCure BNCT System 2. NeuCure BNCT Dose Engine
Applicant	Sumitomo Heavy Industries, Ltd.
Date of Application	October 11, 2019
Proposed Intended Use	1. Treatment of unresectable locally recurrent head and neck cancer Treatment of unresectable advanced head and neck non-squamous cell carcinoma 2. The product calculates dose distributions achieved in boron neutron capture therapy based on contour information (body contour, organ shape, bone region, shape/components of treatment area, and biological parameters) and irradiation conditions (irradiation equipment, number of irradiation ports, shape of collimator, isocenter, irradiation angle, and blood drug concentration) to assist physicians in developing treatment plans with boron neutron capture therapy.

Items Warranting Special Mention

SAKIGAKE designation device (SAKIGAKE Device Designation No. 2 of 2016 [*28 ki*]; PSEHB/MDED Notification No. 0228-6, dated February 28, 2017, by the Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)

SAKIGAKE comprehensive assessment consultation was conducted.

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List of Abbreviations

BICR	blinded independent central review
BNCT	boron neutron capture therapy
BNCT30	Investigational device code of NeuCure BNCT System
BPA	4-boronophenylalanine
CBE	Compound Biological Effectiveness
CheckMate 141 study	Study ONO-4538-11/CA209141
CHO cells	Chinese hamster ovary cells
CI	confidence interval
C_{max}	maximum concentration
CR	complete response
CRT	chemoradiotherapy
DCCT	Direct Current -Current Transformer
DICOM	Digital Imaging and Communications in Medicine
DICOM-RT	Digital Imaging and Communications in Medicine-Radiation Therapy
DLT	dose-limiting toxicity
DNA	Deoxyribonucleic acid
DVH	Dose Volume Histogram
EXTREME study	Study EMR62202-002
FBPA	4-borono-2-[18F]fluoro-L-phenylalanine
FBPA-PET	4-borono-2-[18F]fluoro-L-phenylalanine-positron emission tomography
GPSP	Good Post-marketing Study Practice
Gy-Eq	gray equivalent
IAEA-TECDOC-1223	International Atomic Energy Agency Technical Documents 1223
ICRP	International Commission on Radiological Protection
ICRU	International Commission on Radiation Units and Measurements
JENDL	Japanese Evaluated Nuclear Data Library
L-BPA	L-4-boronophenylalanine
LET	Linear energy transfer
MCNP	A General Monte Carlo N-Particle Transport Code
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MU	Monitor Unit
NCT	neutron capture therapy
NE	not evaluable
OECD	Organization for Economic Co-operation and Development
PC	Personal computer
PD	progressive disease
PET	Positron Emission Tomography
PHITS	Particle and Heavy Ion Transport code System
PK	pharmacokinetics
PMMA	Polymethylmethacrylate
PR	partial response
RADA	Radiation Application Development Association
RBE	Relative Biological Effectiveness
RECIST	Response Evaluation Criteria in Solid Tumors
ROI	Region of Interest
RT	radiotherapy
SD	stable disease
SERA	Simulation Environment for Radiotherapy Application
SOC	system organ class
Study 001	Study WW2P2040E001/SPM-011-JHN001
Study 002	Study WW2P2040E004/SPM-011-JHN002

T/B ratio	Tumor/Blood ratio
T/N ratio	Tumor/Normal Tissue ratio
$t_{1/2}$	elimination half-life
TLD	Thermoluminescent Dosimeter
X-CT	X-ray-Computed Tomography

I. Product Overview

I.(1) NeuCure BNCT System

NeuCure BNCT System (hereinafter referred to as "NeuCure System") is a neutron irradiation device intended to be used for boron neutron capture therapy (BNCT).

Figure 1 shows the principle of BNCT. First, a boron drug with high tumor accumulation is administered to a patient, followed by neutron[i] radiation. This causes a nuclear reaction between boron atoms (^{10}B) and thermal neutrons ([reaction formula, ^{10}B (n,α) ^{7}Li] [Figure 2]), yielding heavy charged particles (ionizing radiation), i.e., alpha particles[ii] (helium [^{4}He] atomic nucleus, kinetic energy 1.47 MeV, range 9 μm) and recoiling lithium (^{7}Li) nuclei[ii] (kinetic energy 0.84 MeV, range 4 μm). These heavy charged particles directly ionize[iii,iv,v,1,2,3] molecules (e.g., deoxyribonucleic acid [DNA]) constituting tumor cells that have incorporated boron. Ionization of the molecules causes DNA damage (single-strand break and double-strand break), inducing cell death (apoptosis and necrosis).

NeuCure System is intended to be used for the treatment of unresectable, locally advanced or locally recurrent head and neck cancer.

NeuCure System is used in combination with L-4-boronophenylalanine-[^{10}B] (L-BPA) (non-proprietary name, borofalan [^{10}B] [Figure 3]; brand name, Steboronine 9000 mg/300 mL for Infusion [Stella Pharma Corporation], hereinafter referred to as "Steboronine"). A marketing application for Steboronine was submitted simultaneously with the marketing application for NeuCure System.

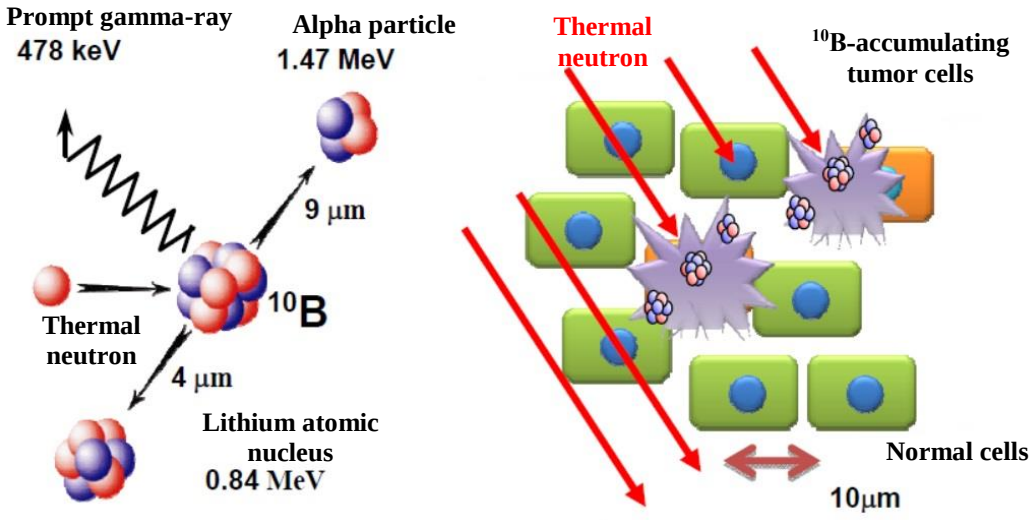

Figure 1. Principle of BNCT

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[i] Neutrons entering the body are scattered, etc. by atomic nuclei constituting the human body and then slow down to thermal neutrons.

[ii] High-linear energy transfer (LET) radiation

[iii] First ionization potential
Examples: H (13.6 eV), C (11.3 eV), N (14.5 eV), O (13.6 eV), Na (5.14 eV), Mg (7.65 eV), P (10.5 eV), S (10.4 eV), Cl (13.0 eV), K (4.34 eV), Ca (6.11 eV), Fe (7.9 eV), I (10.5 eV)

[iv] Ionization potential of nucleobase
Examples: Cytosine (8.90 eV), adenine (8.91 eV), thymine (9.43 eV), uracil (9.82 eV)

[v] Energy required to cause DNA damage (single-strand break, double-strand break): Single-strand break, 30 to 60 eV/strand; double-strand break, approximately 10 times the energy required to cause single-strand break

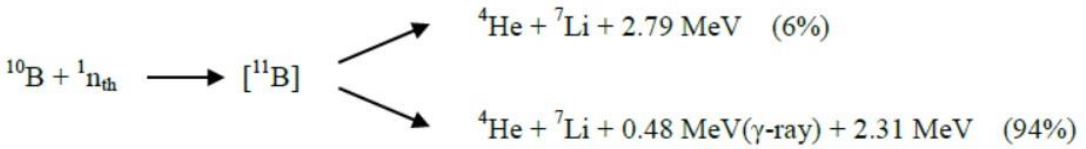

Figure 2. Reaction formula for ^{10}B (n,α) ^{7}Li reaction

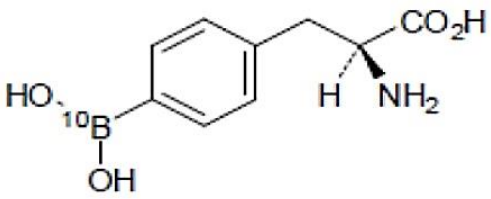

Figure 3. Chemical structure of borofalan (^{10}B)

NeuCure System consists of a proton accelerator, a proton beam transport system(s), a neutron irradiation device(s), and other relevant devices. Neutrons can be irradiated in multiple treatment rooms by installing multiple proton beam transport systems according to the facility layout, and by bending accelerated proton beams with electromagnets. However, neutron irradiation cannot be performed simultaneously in more than one room. Figure 4 illustrates a facility model having 2 treatment rooms. The proton accelerator, proton beam transport systems, and the neutron generator of the neutron irradiation device are installed in the cyclotron room. Figures 5, 6, and 7 show the appearance of the proton accelerator, proton beam transport system, and neutron irradiation device.[vi]

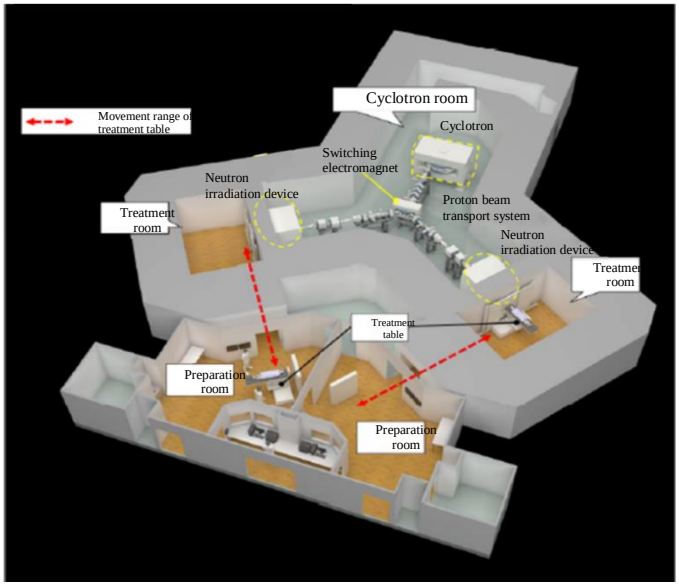

Figure 4. Bird's-eye view of a facility having 2 treatment rooms

[vi] In addition, NeuCure System requires a treatment room(s) where neutron is irradiated to a patient and a preparation room(s) where a patient is placed on a treatment table and all settings are made. NeuCure System is operated using a console installed in an operation room (not shown in Figure 4), separately from the treatment room(s) and the preparation room(s).

Figure 5. Appearance of proton accelerator (cyclotron)

Figure 6. Appearance of proton beam transport system

Cyclotron is used as a proton accelerator. A proton beam from the cyclotron (source particles, protons; proton energy, 30 MeV; rated proton beam current, 1.0 mA) is converged or deflected by the electromagnet in each proton beam transport system to strike the target placed on the neutron irradiation device (see Figure 8). The target is made of beryllium having a purity of ≥[redacted]%. The collision between protons and beryllium atomic nuclei induces a nuclear reaction (formula, ^{9}Be [p,n] ^{9}B), generating neutrons having energy up to 28 MeV with a peak around 1 MeV. International Atomic Energy Agency Technical Documents 1223 (IAEA-TECDOC-1223), Current States of Neutron capture Therapy, IAEA (2001)[4] recommends epithermal neutrons (defined as 0.5 eV-40 keV in the present application) for BNCT in order to obtain thermal neutron fluxes having a large boron neutron cross-section[vii] at a deeper level. Neutrons having higher energy than epithermal neutrons (mainly fast neutrons) need to be slowed down to epithermal neutrons. For this purpose, a moderator, which reduces neutron energy, is required between the target and the collimator. Lead and iron effectively slow down fast neutrons immediately after they are released. After neutrons lose energy to some extent, aluminum and calcium fluoride effectively moderate the neutrons.[viii,5] With these moderating materials placed effectively between the target and the collimator, NeuCure System delivers epithermal neutrons suitable for BNCT to a patient. NeuCure System also uses lead isotopes that scatter neutrons around the moderator in order to focus neutrons (mainly fast neutrons and epithermal neutrons) to the patient. To limit neutron irradiation to the desired area, the collimator other than its opening is covered by a shield. Gamma-rays from the nuclear reaction are shielded by lead, while neutrons are shielded by polyethylene. The collimator at the irradiation site uses lithium fluoride-loaded polyethylene to reduce neutron doses

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vii Represent the likelihood of neutrons in a substance to collide and react with atomic nuclei of the atoms that compose the substance.

viii Neutrons having an energy peak of 1 MeV released from the target are slowed down mainly to epithermal neutrons, which are then extracted from the collimator through the following process. Incident neutrons are slowed down by inelastic scattering and the (n, 2n) reaction in the lead layer (Pb-204, Pb-206, Pb-207, and Pb-208) and transported to the next layer. In the next iron layer (Fe-54, Fe-56, and Fe-57), neutrons themselves lose some energy mainly through inelastic scattering. These lead and iron layers substantially reduce the number of ≥1 MeV neutrons. Aluminum (AL-27) and fluorine (F-19) in calcium fluoride are a good combination for effective extraction of epithermal neutrons. In the aluminum and fluorine layers, ≥1 MeV and ≥100 keV neutrons, respectively, lose energy through inelastic scattering. Neutrons having energy lower than the above undergo only elastic scattering and capture reaction. While elastic scattering reduces neutron energy, some neutrons emit gamma-rays through the neutron capture reaction to annihilate themselves. This process is repeated by high-energy particles, which increases the number of neutrons in an energy range where capture reaction is less likely to occur, i.e., a region with a minimum neutron cross section. Neutrons whose energy is reduced by elastic scattering have an increased neutron capture cross-section; these low-energy neutrons are reduced in number by the capture reaction. As a result, neutrons with a small capture neutron cross-section are more likely to pass through the substance, which enables efficient extraction of 0. eV to 40 keV epithermal neutrons as defined for NeuCure System. This explains the existence of a region with a small capture neutron cross-section ($<10^{-3}$ barn) in the energy range of 1 eV to 10 keV in the neutron cross-section data of fluorine. The order of aluminum and calcium fluoride [redacted] (reference, Nuclear Data Library JENDL-4.0, https://wwwndc.jaea.go.jp/jendl/j40/j40.html; as of January 28, 2020).

outside the irradiation area so that the unnecessary exposure of patients to radiation can be minimized. The collimator opening diameter is changeable (i.e., 100, 120, or 150 mm).

The treatment table can be used in 2 ways (as a bed or chair) according to the irradiation position and direction. The treatment table is operated and moved using an operation pendant. Positioning of patients and confirmation of their position are performed using laser markers and an X-ray imaging device. The patient is set up on the treatment table in the preparation room adjacent to the treatment room and transferred to the irradiation position using the wagon without changing the patient's position on the table. The position of the patient is checked again in the treatment room using the laser markers. Once all settings for irradiation are completed according to a prescribed treatment plan, irradiation can be started. After the end of irradiation, the treatment table with the patient on it is moved back to the preparation room.

Figure 7. Appearance of neutron irradiation device

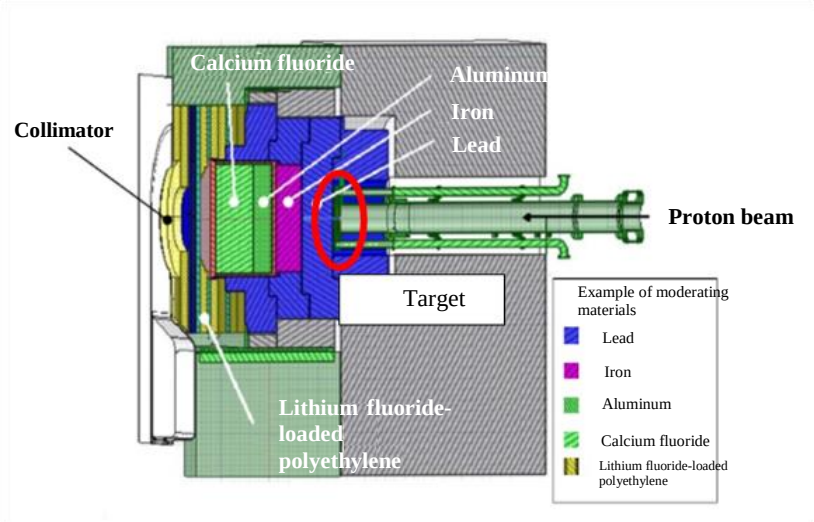

Figure 8. Structure of neutron irradiation device

I.(2) NeuCure BNCT Dose Engine

The NeuCure BNCT Dose Engine (hereinafter referred to as "NeuCure Dose Engine") is a medical device program intended to be used for calculation of dose distribution in BNCT using NeuCure System.

NeuCure Dose Engine is installed in a general-purpose personal computer (PC) and used in combination with a radiotherapy planning program “Radiotherapy Planning Software RayStation” (RaySearch Japan K.K., approval number 22900BZI00014000, hereinafter referred to as “RayStation”) installed in the same PC. Figure 9 presents the system configuration of NeuCure Dose Engine with RayStation. Figure 10 shows the actual process flow.

Contour information (body contour, organ shape, bone region, shape/components of treatment area, and biological parameters) and irradiation conditions (irradiation equipment, number of irradiation ports, shape of collimator, isocenter, irradiation angle, and blood drug concentration) are set on RayStation and recorded as treatment planning data (Digital Imaging and Communications in Medicine [DICOM] data, including Digital Imaging and Communications in Medicine-Radiation Therapy [DICOM-RT] data). The treatment planning data are used as input data in NeuCure Dose Engine. On the basis of the input data, NeuCure Dose Engine calculates dose distribution and monitor unit (MU) achieved in BNCT in a body region where the substance density is generally homogeneous. Calculated data are output on RayStation as DICOM data. RayStation displays the dose distribution and analyzes dose volume histogram (DVH) to assist users in developing treatment plans. One MU calculated for NeuCure System is equivalent to the charge of irradiated protons that are monitored during the therapy.

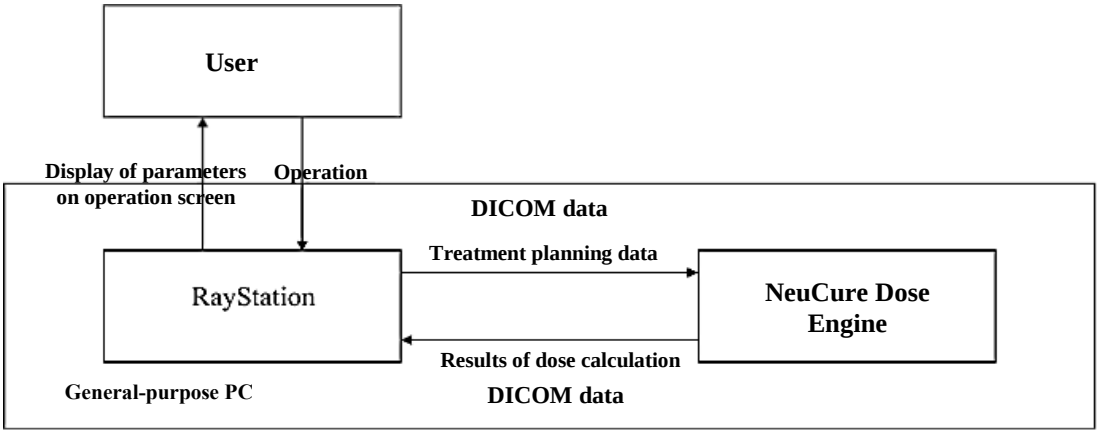

Figure 9. System configuration of NeuCure Dose Engine with RayStation

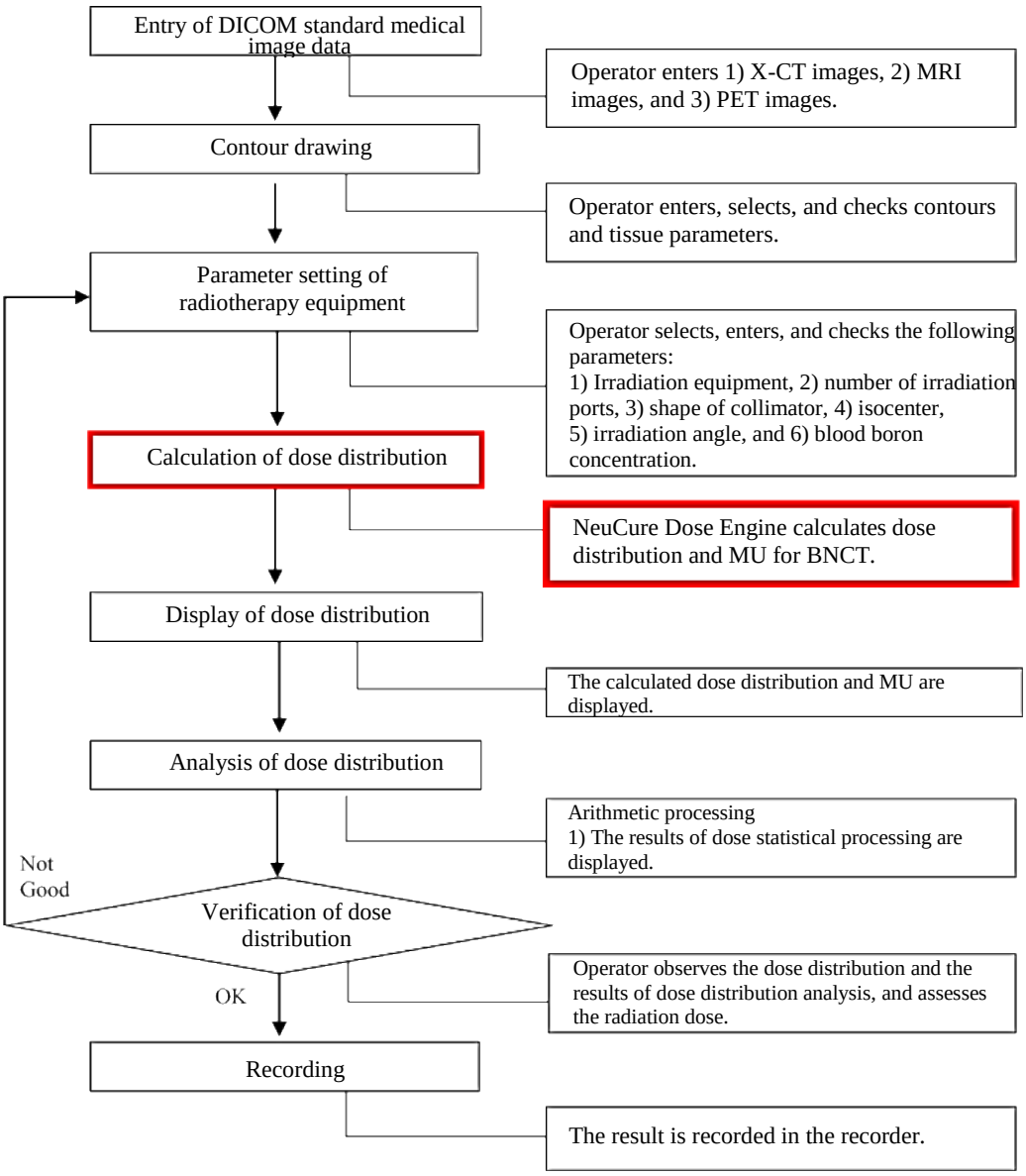

Figure 10. Process flow of NeuCure Dose Engine with RayStation
(NeuCure Dose Engine involved in the process in a red box)

Neutrons emitted from the collimator of NeuCure System are comprised mainly of epithermal neutrons (0.5 eV - 40 keV) and also include fast neutrons (≥40 keV) and thermal neutrons (≤0.5 eV). Incident epithermal neutrons entering the body are scattered by constituent elements of the human body to lose energy to become thermal neutrons. Thermal neutrons cause a nuclear reaction with nitrogen atoms in addition to boron atoms to generate protons[ii] and a neutron capture reaction by atoms constituting the human body to generate gamma-rays. Fast neutrons collide mainly with hydrogen atomic nuclei to generate recoil particles (protons). Contaminating gamma-rays that are produced when neutrons are slowing down in the neutron irradiation device are also delivered to the patient (Figure 11). To assess the total radiation dose delivered to the patient, therefore, the 4 doses, boron, hydrogen, nitrogen, and gamma-ray doses, need to be considered. Each dose component is defined as shown below.

- Boron dose

  The boron dose is defined as the dose derived from 1.47 MeV alpha particles (helium [^{4}He] atomic nuclei) and 0.84 MeV lithium (^{7}Li) atomic nuclei that are generated by the nuclear reaction between

thermal neutrons and ^{10}B (Figure 2). After administration of a boron drug, boron is taken up by cells all over the body. Because the uptake of boron is higher in tumor cells than normal cells, boron dose mainly contributes to the damage of tumor cells. The slower the speed of neutrons, the more likely this reaction is to occur. In most cases, therefore, the reaction occurs between boron and thermal neutrons.

- Hydrogen dose
  Some incident fast neutrons and epithermal neutrons entering the body undergo elastic scattering with the atomic nuclei of constituent elements of the body to pass kinetic energy over to the atomic nuclei of the elements to recoil the atomic nuclei. Resulting recoil nuclei produce a physical dose within their range. The hydrogen dose is defined as the dose induced by this reaction with hydrogen atomic nuclei.

- Nitrogen dose
  Incident fast neutrons and epithermal neutrons entering the body undergo elastic scattering mainly with hydrogen atomic nuclei to slow down to thermal neutrons. These thermal neutrons and nitrogen atomic nuclei (^{14}N) cause the (n,p) reaction (formula, ^{14}N [n,p]^{14}C) to generate 0.63 MeV protons. The nitrogen dose is defined as the dose given to the body by this nuclear reaction.

- Gamma-ray dose
  Gamma-rays are generated in the process where (a) neutrons slow down in the treatment system and (b) in a nuclear reaction between generated neutrons and constituent elements of the human body including boron and nitrogen. The gamma-ray dose is defined as the sum of the doses from these reactions.

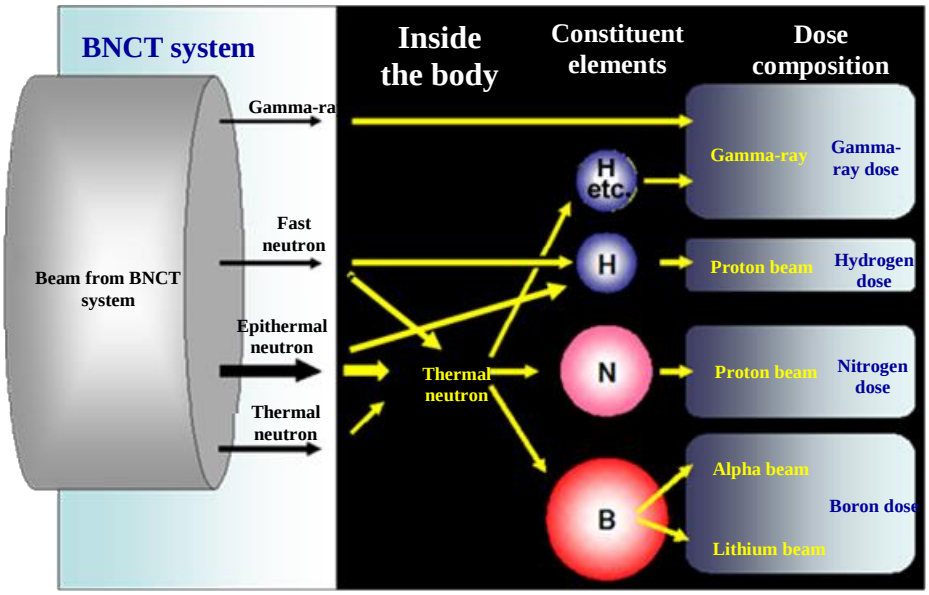

Figure 11. Dose composition for BNCT

As described above, the boron dose is derived from the reaction between ^{10}B accumulating in tumor cells and thermal neutrons. It is the boron dose that gives a therapeutic effect in BNCT. A boron drug injected into the body always exists in circulating blood, as well as normal tissues, such as blood vessels,

skin, and mucosa, at concentrations similar to those in blood. Boron in these normal tissues damages the tissues. On the other hand, neutron irradiation produces other unintended radiation doses derived from nitrogen, hydrogen, and gamma-rays similarly in both normal and tumor cells. The therapeutic effect of BNCT can, therefore, be evaluated by estimating a dose that can damage tumor cells without affecting normal cells based on the total of these doses (see Figure 12).

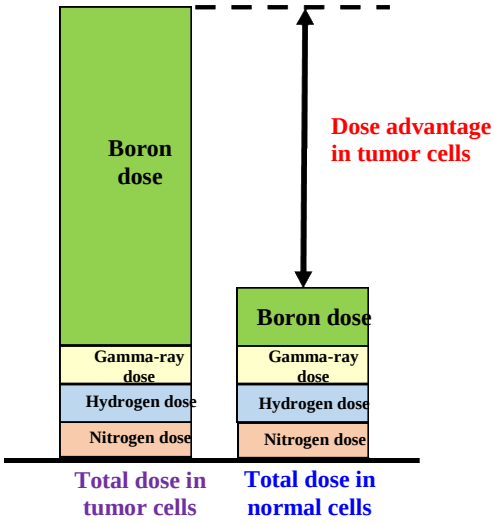

Figure 12. Overview of BNCT dose in tumor and normal cells

The doses of these 4 radiation components are expressed as an equivalent dose (gray equivalent [Gy-Eq]) calculated by multiplying each physical dose determined by Monte Carlo simulation by the coefficient of relative biological effectiveness (RBE) or compound biological effectiveness (CBE). The total equivalent dose of BNCT (E_{total}) is expressed as the following equation.

$$E_{total}\ [Gy-Eq] = E_B + E_N + E_H + E_\gamma$$
$$= CBE_B D_B + RBE_N D_N + RBE_H D_H + RBE_\gamma D_\gamma$$

E_B, boron dose; E_N, nitrogen dose; E_H, hydrogen dose; E_γ, gamma-ray dose
CBE_B, CBE for boron dose; RBE_N, RBE for nitrogen dose
RBE_H, BRE for hydrogen dose; RBE_γ, RBE for gamma-rays dose
D_B, physical absorbed boron dose
D_N, physical absorbed nitrogen dose
D_H, physical absorbed hydrogen dose
D_γ, physical absorbed gamma-ray dose

NeuCure Dose Engine uses Particle and Heavy Ion Transport code System (PHITS)[ix,6] developed by the Japan Atomic Energy Agency (JAEA) and others for dose calculation using Monte Carlo simulation. In Monte Carlo simulation using PHITS, the same method as A General Monte Carlo N-Particle Transport Code (MCNP), a Monte Carlo radiation transport calculation code developed by the US Los

[ix] PHITS is a general Monte Carlo simulation code that simulates various radiation behaviors in any object using a nuclear reaction model and nuclear data. It was developed by JAEA in collaboration with Research Organization for Information Science and Technology, High Energy Accelerator Research Organization, Kyushu University, etc.

Alamos National Laboratory, was used to calculate the transport of electrons and photons. For neutrons, nuclear data library (Japanese Evaluated Nuclear Data Library [JENDL]-4.0) and the same method as MCNP, Version 4C code were used.[7] Basically, in the Monte Carlo simulation using PHITS or MCNP, the transport and collision of incident particles are calculated by a random walk algorithm using a model built based on the Boltzmann equation and neutron cross-section data (JENDL-4.0). If secondary particles are produced at each step of the random walk, information of the produced secondary particles is recorded. The calculation for the secondary particles is performed after the end of the random walk of particles currently under the calculation. Neutron and gamma-ray fluxes are calculated by Monte Carlo simulation using PHITS based on a patient voxel model created from contour information and irradiation geometry conditions. The physical doses of boron, nitrogen, hydrogen, and gamma-rays are determined by multiplying the neutron flux by the kerma factor of each element and by multiplying the gamma-ray flux by the dose conversion factor. This calculation uses the reference data shown in Table. The kerma factor is the amount of energy that is produced per unit particle. It is calculated using the Monte Carlo simulation code based on the neutron cross-section and the amount of energy generated by the neutron reaction. As the boron dose, the dose per ppm of ^{10}B was calculated.

Table 1. Nuclear cross-section data and dose conversion factor used in NeuCure Dose Engine

Reference data	Source
Neutron cross-section data	JENDL-4.0[x]
Dose conversion factor	Effective dose based on the definition in ICRP publication 60 (recommendation in 1990)

The beam model used in the calculation is created based on the energy spectra and angle distribution of neutrons and gamma-rays considering the neutron-producing reaction and penetration into the moderator by a proton beam per unit irradiance determined for each device or facility at the target.

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

The data submitted for the present application and the applicant's responses to the inquiries from the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined below. PMDA reviewed NeuCure System and NeuCure Dose Engine (hereinafter collectively referred to as "NeuCure") with a focus on their performance, efficacy, and safety as a neutron irradiation device and a dose calculation program for BNCT, namely, whether NeuCure ensures safe and stable irradiation of neutron beams and appropriate pre-irradiation dosing simulation. The review results of Steboronine were used for the evaluation of the following efficacy and safety data of NeuCure in combination with Steboronine, including the dose advantage in tumor cells (Figure 12) and the safety in normal tissues: Section "2.(4).2) Studies to support the efficacy of the device," and Section "6. Clinical Data or Alternative Data Accepted by the Minister of Health, Labour and Welfare."

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

[x] Japanese Evaluated Nuclear Data Library: Japanese evaluated, universal, and standard nuclear data library created by the Nuclear Data Group, Nuclear Science and Engineering Center, JAEA in cooperation with nuclear data researchers in Japan. This library covers 406 nuclides in the incident neutron energy range from 10^{-5} eV to 20 MeV.

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

1.A Summary of the data submitted

1.A.(1) History of development

The efficacy of BNCT has been demonstrated mainly by clinical research using a nuclear reactor. It is, however, difficult to develop a nuclear reactor as a medical device. Popularization of BNCT requires a small special medical device for BNCT that can be installed at hospitals. For this reason, the applicant initiated the development of a neutron irradiation device for BNCT using an accelerator, not a nuclear reactor, in cooperation with Institute for Integrated Radiation and Nuclear Science, Kyoto University (former Kyoto University Research Reactor Institute).[xi] In addition, the applicant jointly developed a boron drug essential for BNCT with Stella Pharma Corporation.

The treatment planning program originally used for BNCT was Simulation Environment for Radiotherapy Application (SERA) jointly developed by the Idaho National Laboratory and the Montana State University in the United States. In the beginning of its development, the treatment planning program was not regulated as a medical device. The Pharmaceutical Affairs Act (Act No. 145 of 1960) was revised in 2014 to the "Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics." This revised act requires regulation of treatment planning programs as medical devices, and the treatment planning program for NeuCure needed a marketing approval accordingly. SERA has the following problems: (a) Necessity of a large voxel size because of memory usage limitation and low calculation speed, (b) complicated entry of region of interest (ROI) (patient's tissue information), (c) poor calculation precision because of the low calculation speed, and (d) poor input-output usability. Because these problems may affect treatment efficiency in future clinical use of NeuCure, the applicant decided to develop an original treatment planning program for BNCT[xii] and obtain a marketing approval for the program separately from NeuCure System.

BNCT is based on a new principle different from conventional treatments. On February 28, 2017, NeuCure was classified as a SAKIGAKE designation product by the Ministry of Health, Labour and Welfare, to be developed in Japan ahead of the rest of the world.

[xi] A part of the funds for following program and project were used in the development of NeuCure:
(a) The Program to Support Development of Medical Equipment and Devices to Solve Unmet Medical Needs 2013 (Kansai Bureau of Economy, Trade and Industry, Ministry of Economy, Trade and Industry) (Comprehensive Special Zone Coordination Fund).
(b) The Medicine-Engineering Collaboration Business Promotion Project 2014 (Kansai Bureau of Economy, Trade and Industry, Ministry of Economy, Trade and Industry) (Comprehensive Special Zone Coordination Fund).

[xii] To solve the problems of SERA, the following modifications were made to NeuCure Dose Engine:
(a) Limited voxel size due to memory usage limitation
SERA is a program that runs on a 32-bit operating system. Because of its limited memory usage, this program usually uses a voxel size of 10 mm for calculation. NeuCure Dose Engine runs on a 64-bit operating system to have an enough memory for calculation and uses the Monte Carlo code PHITS to allow for the use of a 1- to 5-mm voxel size in calculation.
(b) Complicated entry of ROI (patient's tissue information)
NeuCure Dose Engine is used with an approved treatment planning system having a contour drawing function commonly used in radiotherapy to provide a ROI entry function similar to that used for the current general radiotherapy.
(c) Poor calculation precision due to limited voxel size
SERA is expected to have a poor calculation precision in fine regions because of the limited voxel size due to the memory usage limitation. NeuCure Dose Engine uses a 1- to 5-mm voxel size that allows for dose calculation with a resolution close to the voxel size for patient's diagnostic images.
(d) Poor input-output usability
SERA requires patient's diagnostic images in bitmap format and does not use general-purpose format for outputting calculation results. NeuCure uses DICOM files for data input and output so that data can be input or output in the same file format as that used in current general radiotherapy systems.

1.A.(2) Use in foreign countries

Nuclear reactor-based neutron irradiation devices for BNCT already exist for research purposes. However, there is no accelerator-based neutron irradiation device for BNCT approved as a medical device either in Japan or foreign countries. NeuCure Dose Engine has not been used or marketed in foreign countries.

2. Design and Development

In order to ensure science-based, proper evaluation of the efficacy, safety, and quality of accelerator-based neutron irradiation devices for BNCT and concomitant treatment planning systems, evaluation indices ("Release of Evaluation Indices for Next-Generation Medical Devices" [PSEHB/MDED Notification No. 0523-2, dated May 23, 2019]) have been established by the Review Working Group for Projects of Preparing Evaluation Indices for Next-Generation Medical Devices and Regenerative Medicine Products. In this review, PMDA checked whether NeuCure was assessed mainly according to the above evaluation indices and whether NeuCure met endpoints.

2.(1) Performance and safety specifications

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

The proposed performance specifications for NeuCure System are designed to ensure the repeatability and stability of calibration of the dose monitoring system, the linearity of the dose monitoring system, depth-dose curve, peak dose, positioning reproducibility of the treatment bed, measurement precision of the charge monitors of charged particle beam, irradiation field size, and time of continuous proton beam irradiation. The proposed safety specifications for NeuCure System are designed to ensure its electrical safety, electromagnetic compatibility, mechanical safety, and radiation safety.

The proposed performance specifications for NeuCure Dose Engine are designed to evaluate the dose distribution calculation functions (data acquisition, BNCT dose calculation, and data output) and the dose calculation algorithm. The proposed safety specifications for NeuCure Dose Engine are designed to prevent the use by unauthorized personnel, establish data limits, protect data from tampering, and ensure accurate data transfer.

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

PMDA's review mainly focused on the following points for the performance and safety specifications for NeuCure.

2.(1).B.1) Appropriateness of the performance specification limits of NeuCure System

2.(1).B.1).(a) Repeatability and stability of calibration of dose monitoring system

The specifications are based on an "In-house standard: Standard for BNCT treatment system performance characteristics (ENC00002)." ENC00002 is basically the same as the official standard for functional performance characteristics of medical electron accelerators, JIS Z 4714:2001 (IEC 60976:1989, IEC 60976:1989/AMENDMENT 1 [62C/247/CDV:1998]), with some modifications to

requirements according to the characteristics of neutron beams and BNCT-specific performance characteristics.[xiii]

However, ENC00002 only defines the specification limit "performance display." PMDA asked the applicant to discuss the necessity of establishing a specification that enables quantitative evaluation of repeatability and stability of the monitoring system of NeuCure System.

The applicant's explanation:
The precision of a single measurement of thermal neutrons by the gold wire activation method[xiv] is approximately 5%.[8] In this test, [redacted]
For both repeatability and stability, therefore, the specification limit of "Not more than [redacted]% when measured using a gold wire or foil placed so that its center is located [redacted] mm from the surface of a water phantom[xv]" was proposed. When the maximum measured value is to be adopted as the specification limit, it must be the value measured on the phantom surface. However, the measured value on the surface is not suitable as the specification limit because the surface has more fast neutrons and a thermal neutron buildup region. For this reason, [redacted] mm, which is around the peak depth where stable measurements can be obtained, was selected as a reference point.

PMDA accepted the applicant's explanation.

2.(1).B.1).(b) Linearity of dose monitoring system

This specification is based on ENC00002. However, ENC00002 only defines the specification limit "performance display." PMDA asked the applicant to discuss the necessity of establishing a specification that enables quantitative evaluation of linearity of the monitoring system of NeuCure System.

The applicant's explanation:
The precision of a single measurement of thermal neutrons by the gold wire activation method is approximately 5%. In this test, [redacted], the following specification limit of linearity was used: "The deviation of ≤[redacted]% when measured using a gold wire or

[xiii] Requirements in JIS Z 4714:2001 were modified, adopted, or not adopted in ENC00002 according to the following principles:
(a) The requirements for items not included in the components of NeuCure System (e.g., gantry and wedge filter) were not adopted in ENC00002.
(b) Properties not incorporated in NeuCure System (e.g., definition of isocenter) were not adopted in ENC00002.
(c) The types of radiation were limited and changed in ENC00002 (neutrons and gamma-rays).
(d) Some terms were replaced and changed to corresponding NeuCure System-specific terms.
(e) The definitions of items identifying the performance of NeuCure System were adopted in ENC00002 without any change or with numerical changes as necessary.

[xiv] Gold is a widely used specimen for measurement of thermal neutron fluxes because gold has a relatively large absorption cross-section for thermal neutrons (98.5 barn) and gold with a purity high enough to tolerate radiation experiments is commercially easily available. For measurements, 412 keV gamma-rays are used. ^{198}Au decays 100% by β emission, 95.6% of which are accompanied by a gamma decay of 411.8 keV. Because no other gamma-rays are in proximity of this energy, which makes it hard for them to become background, this energy level is suitable for radioactivity assessment by the gold wire activation method.

[xv] The water phantom is made from polymethylmethacrylate (PMMA, acrylic) and filled with pure water because approximately 60% of the human body is water and approximately 70% of the constituent elements of the body are hydrogen and oxygen. It is cubical. Its horizontal size is large enough to accommodate target tumors. It is designed to ensure that [redacted]. Any phantom called "water phantom" on the following pages has the above specifications.

foil placed so that its center is located [redacted] mm from the surface of a water phantom." When the maximum measured value is to be adopted as the specification limit, it must be the value measured on the phantom surface. However, the measured value on the surface is not suitable as the specification limit because the surface has more fast neutrons and a thermal neutron buildup region. For this reason, [redacted] mm, which is around the peak depth where stable measurements can be obtained, was selected as a reference point.

PMDA accepted the applicant's explanation.

2.(1).B.1).(c) Depth-dose curve

This specification is based on ENC00002. However, ENC00002 only defines the specification limit "performance display." PMDA asked the applicant to discuss the necessity of establishing a specification that enables quantitative evaluation of the depth-dose curve of NeuCure System.

The applicant's explanation:

The points shown in Figure 13 were selected as reference points.

- P1: [redacted]
- P2: [redacted]
- P3: [redacted]

Figure 13. Reference points for quantitative evaluation of depth-dose curve

The precision of thermal neutron dosimetry by the activation foil method is approximately [redacted]%, and the doses at 2 points need to be measured to calculate a ratio. Because of this, and based on the evaluation of measures values, the applicant proposed the following specification limits (see Table 2), taking account of error propagation. The acceptable error from the product-specific specification limit is [redacted]%.

Table 2. Specifications for depth-dose curve

Diameter of collimator opening	Specification	
	P2/P1	P3/P1
100 mm	[redacted] ± [redacted] %	[redacted] ± [redacted] %
120 mm	[redacted] ± [redacted] %	[redacted] ± [redacted] %
150 mm	[redacted] ± [redacted] %	[redacted] ± [redacted] %

PMDA accepted the applicant's explanation.

2.(1).B.1).(d) Peak dose

The proposed specification limit of thermal neutron peak dose is $\geq 1.4 \times 10^9$ n/cm^2/s for the collimator with the 150-mm opening, $\geq 1.1 \times 10^9$ n/cm^2/s for the collimator with the 120-mm opening, and $\geq 1.0 \times 10^9$ n/cm^2/s for the collimator with the 100-mm opening.

The applicant's rationale for the specification limits:
Monte Carlo simulation based on the measured thermal neutron fluxes at the peak position when the collimator with the 100-mm opening was used, has demonstrated that the collimator can provide epithermal neutron fluxes with an intensity of approximately 1.0×10^9 n/cm^2/s on the surface of the water phantom, which is high enough for BNCT as recommended in IAEA-TECDOC-1223. Since the design of the collimator was thus justified, the applicant proposed the above specification limits determined from the measured value for each collimator.

PMDA's view:
A thermal neutron flux of 1.0×10^9 n/cm^2/s being maintained at the peak depth, where epithermal neutrons have slowed down and reacted to some extent, means that an epithermal neutron flux of approximately 1.0×10^9 n/cm^2/s is also maintained on the entrance surface. PMDA accepted the applicant's explanation that the measured values can be used as the specification limits of the peak dose of NeuCure System.

2.(1).B.1).(e) Positioning reproducibility of the treatment bed

The applicant proposed the specification limit of ±2 mm for the positioning reproducibility of the treatment bed with and without a load in the preparation room and the treatment room.

The applicant's rationale for the specification limit:
This specification limit is based on mechanical design limitations. The clinical acceptability of the specification limit is discussed as below.

The collimator controls neutrons released from the lead surface. The back of the collimator is tapered, and a deviation of the collimator from its original position alters the region where neutrons pass through. A deviation of the central axis is also expected to alter the peak dose. The impact of the alteration of the region where the neutron beam is controlled by the collimator due to such a deviation [redacted] 2.00 mm [redacted]. Figure 14 shows a graph of the distance from the beam axis versus epithermal neutron flux on the lead surface. This graph shows that the epithermal neutron flux around [redacted] mm is [redacted] lower than that around the center.

Figure 14. Distance from beam axis versus epithermal neutron flux on lead surface (calculated values)

Thus, even if the epithermal neutron flux increases or decreases because of a deviation of the beam axis, the impact is [redacted] smaller than the total neutron flux (integral value, [redacted] n/s) and is therefore negligible, as shown below.

[redacted]

As for the deviation of the central axis, [redacted] it results in only a [redacted]% deviation in peak dose, which is also negligibly small.

In summary, a deviation of the collimator of the treatment bed within the range of ±2.00 mm during its positioning on the moderating lead, where neutrons slow down, causes only a negligible effect on the epithermal neutron flux, with no clinically significant effects. Accordingly, the specification limit of ±2.00 mm was proposed.

PMDA accepted the applicant's explanation.

2.(1).B.1).(f) Measurement precision of the charge monitors of charged particle beam

The proposed specification limits of the measurement precision of the charge monitors of charged particle beam are ±[redacted]% for the primary dose monitor and ±[redacted]% for the secondary dose monitor.

These specification limits are based on the specification limits defined in the official standard for the safety of medical electron accelerators, JIS Z 4705:2006 (IEC 60601-2-1:1998, IEC 60601-2-1:1998/AMENDMENT 1:2002). PMDA concluded that the proposed specification limits were appropriate.

2.(1).B.1).(g) Irradiation field size

The proposed specification limit of the irradiation field size (opening diameter of each collimator, 100, 120, and 150 mm) is [redacted] mm.

The applicant's rationale for the specification limit:

The proposed specification is based on the user requirement specification describing product specification values determined after discussion with the user. The clinical acceptability of the specification limit was discussed based on calculations for the 100 mm collimator, which is most affected by a deviation of irradiation field size.

When the opening size of the collimator increases up to [redacted] mm, i.e., the diameter of [redacted] mm, due to a machining accuracy, the opening area increases by [redacted]% as shown below.

[redacted]

This will also increase the neutron flux passing through the collimator by [redacted]%. In view of [redacted], a change of approximately [redacted]% will not be a clinically significant problem in quality control of neutron measurements. On the basis of the above, the above specification limit was proposed.

PMDA accepted the applicant's explanation.

2.(1).B.1).(h) Time of continuous proton beam irradiation

The proposed specification limit of the time of continuous proton beam irradiation is "Stable operation for [redacted] hours at the beam current of 1 mA." In clinical practice, a proton beam of 1 mA is used for BNCT. In BNCT using dosage regimens selected based on previous clinical experience, etc., almost all patients were exposed to radiation for ≤1 hour. Accordingly, to be on the safe side, the operation of [redacted] hours was evaluated. In the clinical studies, irradiation was completed within 1 hour in all patients, except for 1 patient who underwent irradiation for 1 hour 5 minutes because of a device malfunction ([redacted]).

PMDA accepted the applicant's explanation.

2.(1).B.2) Appropriateness of the specification limits of the dose calculation algorithm of NeuCure Dose Engine

The proposed specification limit of the dose calculation precision of the dose calculation algorithm of NeuCure Dose Engine is "A gamma index of ≤1 using [redacted] as a reference for a comparison between the measured and calculated values of a thermal neutron flux and a gamma-ray dose rate on a water phantom at least 20 cm × 20 cm × 20 cm."

The applicant's rationale for the specification limit:

The proposed acceptance criterion for positioning error precision of [redacted] mm is based on the measurement of thermal neutrons using [redacted]- and [redacted]-mm long gold wires. In addition, the proposed acceptance criterion

for dose error precision of [redacted]% is derived from the approximately [redacted]% error in measurements by the gold wire activation method as aforementioned.

According to literature issued by the Radiation Application Development Association (RADA),[9] thermoluminescent dosimeter (TLD), which is used to measure gamma-rays, has a measurement error of approximately 7% and [redacted]% was selected for strict control. [redacted] was selected for strict control as with the error.

Thus, the applicant determined the acceptable value for the dose calculation precision of thermal neutrons and gamma-rays from the dosimeter size and the potential measurement error of the dosimetry. PMDA accepted this because of the absence of established precision or clear criterion for neutron dosimetry.

PMDA concluded that the performance and safety specifications, including the specification limits, for NeuCure were reasonable.

2.(2) Studies to support device safety

2.(2).1) Physicochemical properties

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

NeuCure System contains no component that needs to be tested for physicochemical properties. No study has been conducted to support the physicochemical properties of NeuCure System.

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

PMDA concluded that there is no particular problem with omitting studies for supporting the physicochemical properties of NeuCure System.

2.(2).2) Electrical safety and electromagnetic compatibility

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

To support the electrical safety and electromagnetic compatibility of NeuCure System, the applicant submitted data showing that NeuCure System meets the standard specifying general requirements for the basic safety and essential performance of medical electrical equipment (JIS T 0601-1:2017 [IEC 60601-1:2005, IEC 60601-1:2005/AMENDMENT 1:2012]), and the standard specifying the electromagnetic compatibility of medical electrical equipment (JIS T 0601-1-2:2012 [IEC 60601-1-2:2001, IEC 60601-2:2001/AMENDMENT 1:2004]).

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

PMDA reviewed the submitted data and concluded that there was no particular problem with the electrical safety and electromagnetic compatibility of NeuCure System.

2.(2).3) Biological safety

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

The treatment table is the only component of NeuCure System that comes in contact with patients. It temporarily comes in contact with the patient's skin surface. The raw materials of this component that may come in a direct contact with the patient's skin are stainless steel SUS304, which is specified in JIS G 4304:2005 (ISO 9444:2002) and aluminum A6063S, which is specified in JIS H 4100:2015 (ISO 209:2007, ISO 6362-1:2012, ISO 6362-2:2014, ISO 6362-4:2012, ISO 6362-7:2014). These materials have already been approved as the raw materials of many medical devices having comparable contact risk levels. Their biological safety thus has been confirmed. No new study to support the biological safety of the materials was, therefore, conducted.

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

PMDA concluded that there is no particular problem with omitting studies for supporting the biological safety of NeuCure.

2.(2).4) Radiation safety

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

To support the radiation safety of NeuCure System, the applicant submitted data on dose distribution measurements in and outside the radiation field.

In dose distribution measurements in the radiation field, thermal neutrons, fast neutrons, and gamma-rays in the radiation field were measured using gold wires, TLD, and indium foil, respectively, with a water phantom. The following were evaluated: the measured equivalent dose rate of thermal neutrons, dose distribution of thermal neutrons, gamma-rays during neutron irradiation, relative surface dose during neutron irradiation, and relative surface dose of fast neutrons. These parameters met the acceptance criteria defined in "In-house standard: Safety design index for BNCT treatment system (ENC00001)." ENC00001 defines the acceptance criteria using the reference points shown below (Figure 15).

- T1: [redacted]
- T2: [redacted]
- T3: [redacted]
- T4: [redacted]
- T5: [redacted]
- F1: [redacted]
- G1: [redacted]

Figure 15. Reference points for equivalent dose rate measurements

Table 3 shows the acceptance criteria.

Table 3. Acceptance criteria for dose distribution measurements in radiation field

Equivalent dose rate at T1	T2/T1	T3/T1	T4/T1	T5/T1	G1/T1	F1/T1
[redacted] (mGy-Eq/min)	>[redacted]	>[redacted]	>[redacted]	≤[redacted]	≤[redacted]	≤[redacted]

In dose distribution measurements outside the radiation field, thermal neutrons, epithermal neutrons, fast neutrons, and gamma-rays at the center and outside the radiation field [redacted] were measured using gold wires, gold wires + cadmium, TLD, and indium foils, respectively. The ratio of the total dose of thermal neutrons, epithermal neutrons, fast neutrons, and gamma-rays measured at each reference point to the dose at the center was determined. The ratio met the following acceptance criteria defined in ENC00001.

- [redacted]
- [redacted]

The applicant also submitted data for biodosimetry of the background dose outside the radiation field. Micronuclei were counted in [redacted] binucleated cells of the neck, chest, umbilicus, inguinal part, knee, and ankle of an irradiated human phantom[xvi] and a non-irradiated human phantom. The highest micronucleus count of [redacted] was observed in the neck. It is equivalent to an X-ray dose of 1.57 Gy-Eq. The estimated exposure doses at the other sites were approximately 0.35 to 0.78 Gy-Eq.

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

ENC00001 was created based on the standard that specifies particular requirements for the basic safety and essential performance of light ion beam medical electrical equipment, JIS T 0601-2-64:2016 (IEC

[xvi] The human phantom is made from PMMA (acrylic) and filled with distilled water. Unlike the aforementioned "water phantom," this phantom has a human body shape so that specimens can be placed in compartments corresponding to organs. This phantom was used in the test because approximately 60% of the human body is water and the position of each organ can be reproduced in this phantom. Any phantom called "human phantom" on the following pages has the above specifications.

60601-2-64:2014).[xvii] Requirements, etc. in this JIS standard that are not applicable for NeuCure System were replaced by IAEA-TECDOC-1223 or standards actually used in clinical practice by clinicians and medical physicists who have experience in treatment planning for nuclear reactor-based BNCT.

The following is the applicant's rationale for the acceptance criteria for the dose distribution test in and outside the radiation field:

(a) Dose distribution test in radiation field

- Thermal neutron equivalent dose rate at T1 > [redacted] mGy-Eq/min

T1 provides the peak dose rate. Assuming the epithermal neutron flux of 1×10^9 /cm^2/s as mentioned in Section 1.2 of IAEA-TECDOC-1223, the peak dose rate is [redacted] mGy-Eq/min when the mean blood boron concentration is 25 ppm with the Tumor/Normal Tissue (T/N) ratio of 3.5. This dose rate was selected as the lower limit of the peak dose rate of T1.

- T2/T1 > [redacted], T3/T1 > [redacted], and T4/T1 > [redacted]

T2, T3, and T4 represent the treatable region actually used in clinical practice. These positions were determined based on the opinions from clinicians and medical physicists who have experience in treatment planning for nuclear reactor-based BNCT.

The treatable region was determined so that an equivalent dose rate in tumor (calculated from a physical dose rate and biological effectiveness) is approximately [redacted] times that in normal cells. When the CBE factor in a tumor is 4.0, the CBE factor in normal tissue (brain) is 1.34, and the Tumor/Normal tissue ratio (T/N ratio) is 3.5, the equivalent dose rate derived solely from boron in tumor cells is approximately 10 times that in normal cells. To obtain a therapeutic dose at each reference point, the thermal neutron flux at each point should be at least [redacted] that at the peak position (T1). The thermal neutron flux at T2, T3, and T4 (i.e., reference points in the treatable region) needs to be approximately [redacted] that at T1. The above criteria were thus established.

- T5/T1 ≤ [redacted]

T5 provides the thermal neutron equivalent dose rate on the phantom surface at the central axis, which can be used as a dose rate index for the skin. When the CBE factor in normal skin (T5) is 2.5 and the CBE factor in normal tissue (brain) at the peak position (T1) is 1.34, the equivalent dose rate derived solely from boron is approximately doubled for the same thermal neutron flux. To ensure that the equivalent dose rate on the normal skin (T5) is comparable to that in normal cells at the peak position (T1), the thermal neutron flux at T5 must be not more than [redacted] that at the T1. Since the thermal neutron flux on the normal skin (T5) needs to be not more than [redacted] that at T1, the above criterion was established.

[xvii] Requirements in JIS T 0601-2-64:2016 were modified, adopted, or not adopted in ENC00001 according to the following principles:
(a) The requirements for items not included in the components of NeuCure System (e.g., horizontal magnification device, irradiation head, range modulator, range shifter, scanning mode, multileaf beam limiting device, radiation field limiting device prescribed for each patient, and particle-beam applicator) were not adopted in ENC00001.
(b) Properties not incorporated in NeuCure System (e.g., continuous neutron beam monitoring, the absence of real-time monitor, and definition of isocenter) were not adopted in ENC00001.
(c) The types of radiation were limited and changed in ENC00001 (neutrons and gamma-rays in NeuCure System).
(d) Some terms were replaced and changed to corresponding NeuCure System-specific terms.
(e) The definitions of items identifying the performance of NeuCure System were adopted in ENC00001 without any change or with numerical changes as necessary.

• G1/T1 ≤[redacted]

G1 provides the gamma-ray flux at the depth of [redacted] mm on the central axis, which can be used as the gamma background dose. At the depth of [redacted] mm on the central axis, the dose rates of both thermal neutron and gamma-ray fluxes almost reach their peaks. From a safety viewpoint, the maximum gamma-ray dose should not exceed the maximum boron dose in normal tissue. When the RBE factor of nitrogen dose is 2.9, the CBE factor in normal tissue is 1.34, and the blood boron concentration is 25 ppm, the boron dose rate is approximately [redacted] times the thermal neutron equivalent dose rate (nitrogen dose rate) for the same thermal neutron flux, as shown below (boron dose : nitrogen dose = [redacted]).

D (N) = [redacted]
= [redacted]
= [redacted]

D (N): Thermal neutron equivalent dose rate (nitrogen dose rate)
Nitrogen concentration: 0.02 (ratio by weight of nitrogen element in the human body)
ϕ (th): Thermal neutron flux

D (B) = [redacted]
= [redacted]
= [redacted]

D (B): Boron dose rate
Boron concentration: ppm = μg/g = 1.0E-6

For gamma -ray dose, as with nitrogen dose, “the maximum gamma-ray dose should not exceed the maximum boron dose in normal tissue.” Therefore G1/T1 should be ≤[redacted]. The applicant proposed the following acceptance criterion to be on the safe side: The gamma-ray flux should be ≤[redacted] times the peak thermal neutron flux.

• F1/T1≤[redacted]

F1 provides the fast neutron flux on the surface at the central axis, which can be used as the background dose derived from fast neutrons. In general, the dose rate of fast neutrons peaks at the surface of the central axis. From a safety viewpoint, the maximum fast neutron dose should not exceed the maximum boron dose in normal tissue. As with the rationale for G1/T1, the applicant proposed the following acceptance criterion to be on the safe side: The fast neutron flux should be ≤[redacted] times the peak thermal neutron flux.

(b) Dose distribution test outside radiation field

This test is based on the concepts in a) and b), “29.3.2 Leakage radiation outside the area M” in the official standard for the safety of medical electron accelerators (JIS Z 4705:2006 [IEC 60601-2-1:1998, IEC 60601-2-1:1998/AMENDMENT 1:2002]). Since NeuCure System uses a neutron beam for treatment, the leakage dose is assessed as the equivalent dose of neutron beam and gamma-rays.

PMDA's view on the applicant's explanation:
The dose distribution test outside radiation field is based on the concepts in the official standard for the safety of medical electron accelerators (JIS Z 4705:2006 [IEC 60601-2-1:1998, IEC 60601-2-1:1998/AMENDMENT 1:2002]). Requirements, etc. in this JIS standard that are not applicable for NeuCure System were replaced by requirements in IAEA-TECDOC-1223 or the treatable range (reference values) actually used in clinical practice based on opinions of clinicians and medical physicists who have experience in treatment planning for nuclear reactor-based BNCT. Since currently there is no public standard established for neutron irradiation devices, the applicant had no choice but to create the in-house standards based on the acceptance criteria used in clinical practice as well as on the relevant public standards.

PMDA thus accepted the applicant's explanation about the acceptance criteria in the radiation safety tests of NeuCure System.

The test regarding biodosimetry of background doses outside the radiation field was conducted assuming a malignant tumor in the right temporal lobe. PMDA asked the applicant to explain whether the results of this test can be applied to safety evaluation in head and neck cancer.

The applicant's explanation:
This test was conducted assuming treatment of a malignant tumor in the right temporal lobe, and the neck, which is closest to the head, had the highest dose outside the radiation field. On the other hand, when BNCT is performed on head and neck cancer, the neck is within the radiation field. The head, which is close to the irradiation opening, is likely to have the highest dose outside the radiation field. In treatment of head and neck cancer, the head will receive a comparable dose to that delivered to the neck in the above test. Since the tolerance dose is the same in both the head and neck, the results of the test can be used to assess the exposure dose outside the radiation field when BNCT is performed on head and neck cancer.

PMDA accepted the applicant's explanation.

PMDA also asked the applicant to explain how to treat the neutron-activated equipment, building, air, cooling water (accelerator and target), etc.

The applicant's explanation:
Those equipment, substances, etc. activated by the operation of NeuCure System will be disposed of, or managed, under the responsibility of each institution that installs NeuCure System, in accordance with the Act on Prevention of Radiation Hazards due to Radioisotopes, etc. (Act No. 167 of 1957) (Act on Prevention of Radiation Hazards), the Medical Care Act (Act No. 205 of 1948), and other relevant standards.

PMDA instructed the applicant to include appropriate information in the instructions for use to ensure that healthcare professionals can take necessary measures to handle activated equipment, substances, etc. The applicant responded as instructed.

PMDA reviewed the submitted data and concluded that the radiation safety of NeuCure System can be accepted.

2.(2).5) Mechanical safety

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

To support the mechanical safety of NeuCure System, the applicant submitted data showing that NeuCure System meets requirements in ENC00001 created based on JIS T 0601-1:2017 (IEC 60601-1:2005) and JIS T 0601-2-64:2016 (IEC 60601-2-64:2014). The applicant also provided data on a patient support test (static and dynamic) of the treatment table which may come into contact with patients.

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

PMDA reviewed the submitted data and concluded that there was no particular problem with the mechanical safety of NeuCure System.

2.(2).6) Stability and durability

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

NeuCure System is not a medical device that requires sterilization. NeuCure System requires no preservation, stockpiling, or other treatment while it is or is not in operation. NeuCure System has no components (excluding consumables) that have specified shelf lives. Periodic replacement of consumables, etc., and periodic maintenance and inspection can ensure the performance of NeuCure.

For these reasons, the applicant did not submit data supporting the stability and durability of NeuCure System and provided no information for this section.

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

PMDA asked the applicant to identify consumables and clarify the timing for their replacement.

The applicant's explanation:
Representative consumables of NeuCure System are the filament of the ion source, the stripper foil in the cyclotron, and the neutron producing target. The filament of the ion source is replaced when [redacted]. The stripper foil is replaced [redacted]. The neutron producing target is replaced before [redacted].
Replacement cycles of components made of organic materials, etc. that may deteriorate over time, were determined conservatively (so that they are replaced preventively) based on the use results during development, as described above. Users will be informed of this preventive replacement through the operating instructions, maintenance contracts, etc.

PMDA concluded that there was no particular problem with the applicant's explanation.

In line with the above review, PMDA concluded that there is no particular problem with omitting the submission of data supporting the stability and durability of NeuCure System.

2.(2).7) Studies to support the safety of NeuCure Dose Engine

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

To support the safety of NeuCure Dose Engine, the applicant submitted study data showing that the following points meet the standard (JIS Z 4715:2011 [IEC 62083:2000]) that specifies the requirements for the safety of radiotherapy treatment planning systems: prevention of the use by unauthorized personnel; data limits; protection of data from tampering; and the accuracy of data transfer.

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

PMDA reviewed the submitted study data and concluded that there was no particular problem with the safety of NeuCure Dose Engine.

In line with the above review, PMDA concluded that there is no particular problem with the studies to support the safety of NeuCure.

2.(3) Studies to support device performance

- **NeuCure BNCT System**

2.(3).1) Repeatability and stability of calibration of dose monitoring system

2.(3).1).A Summary of the submitted data

The applicant submitted data showing that the repeatability and calibration stability of the dose monitoring system of NeuCure System meet ENC00002 and the proposed specification [see Section "2.(1).B Outline of the review conducted by PMDA"].

The repeatability and calibration stability of the dose monitoring system of NeuCure System were assessed based on the measurements of a thermal neutron beam by the gold wire activation method. In BNCT, thermal neutrons are measured and assessed because of their large contribution to the dose. The thermal neutron dose was measured [redacted] at multiple points on the central axis of the phantom. These measurements were used to calculate the coefficient of variation and the maximum difference between the maximum and minimum coefficients of variation (maximum coefficient of variation difference). The repeatability was assessed based on the coefficient of variation, while the calibration stability was examined based on the maximum coefficient of variation difference. The maximum coefficient of variation was [redacted]% and the maximum value of the maximum coefficient of variation difference was [redacted]%. The coefficient of variation and maximum coefficient of variation difference at the reference point (the depth of [redacted] mm, which provided stable measurements) met the reference values.

2.(3).1).B Outline of the review conducted by PMDA

PMDA asked the applicant to explain the method to calculate the thermal neutron dose rate by the gold wire activation method.

The applicant's explanation:

The neutron flux can be calculated using reaction rates from the radioactivity of gold samples exposed to neutron irradiation. Since gold element (^{198}Au) has a high cross-section with neutrons (from thermal neutrons to epithermal neutrons of approximately 100 eV) (see Figure 16), the reaction rates of neutrons

having the above energy spectra can be determined by measuring the radioactivity of neutron-irradiated gold samples. On the other hand, since cadmium mainly absorbs thermal neutrons (see Figure 16), the same measurement using cadmium-covered gold samples allows the calculation of the reaction rate of epithermal neutrons (≥1 eV) alone in the same spectra. From these results, the thermal neutron flux is obtained using the cadmium ratio. From the thermal neutron flux, the equivalent dose rate is calculated using the dose conversion factor (kerma factor).

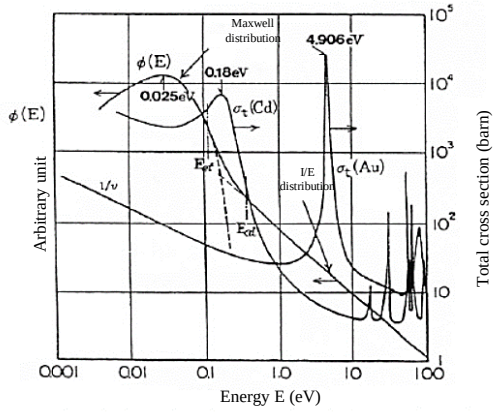

Figure 16. Neutron spectra of thermal neutron reactor and energy dependency of the total cross-section of cadmium and gold[10]

The conversion procedure is shown below:

1) The weight W (g) of the activated gold sample is measured.
2) Gamma-rays C (counts) of 412 keV generated from the activated gold sample are counted. During counting, the start time, end time, real time of counting system, and counting time excluding dead time are recorded.
3) Real count C_{real} is calculated from the real time, counting time, and C using the following equation.

$$C_{real} = \frac{real\_time}{live\_time} C$$

real_time: Real time(s) of gamma-ray counting
live_time: Counting time (s) excluding the dead time of the counting system at gamma-ray measurement

4) Adjustment factors A for cooling time and measurement time are calculated using the following equation.

$$A = e^{-\lambda T_c}(1 - e^{-\lambda T_m})$$
$$T_c = meas\_start\_time - ir\_end\_time$$

$$T_m = real\_time$$

meas_start_time: Start time of gamma-ray measurement
ir_end_time: End time of irradiation
λ: 2.997E-6/s (decay constant of ^{198}Au)

5) The corrected amount of charge Qcorr that takes into consideration the attenuation of product nuclei is calculated from temporal information of the irradiated charge, including trend data, using the following equation. Here, Δt is the number of seconds per data interval (based on settings of the data storage function), n is the number of trend data during irradiation, i is data number, and Qi is the amount of charge of data number i.

$$\mathrm{Qcorr} = \frac{1}{\lambda}\sum_{i=1}^{n}\frac{\mathrm{Q_i}}{\Delta \mathrm{t}}(1 - e^{-\lambda\Delta \mathrm{t}})e^{-\lambda(\mathrm{n-i})\Delta \mathrm{t}}$$

6) The number of atomic nuclei of gold N is determined using the following equation.

$$\mathrm{N} = \frac{W}{\mathrm{A_{Au}}} \times \mathrm{N_A}$$

A_{Au}: 196.97 (atomic weight of gold)
N_A: 6.02E + 23 atoms/mol (Avogadro constant)

7) Reaction rate R (/C) is determined using the following basic equation. Both R_{Au} (R with gold wires without a cadmium cover) and R_{Cd} (R with gold wires with a cadmium cover) are determined from the C_{real}, A, N, and Q_{corr} calculated as above.

$$\mathrm{R} = \frac{\mathrm{C_{real}}}{\varepsilon_{412}\gamma \mathrm{A Q_{corr} N}}$$

$$\mathrm{R_{Au}} = \frac{\mathrm{C_{real\_Au}}}{\varepsilon_{412}\gamma \mathrm{A_{Au} Q_{corr\_Au} N_{Au}}}$$

$$\mathrm{R_{cd}} = \frac{\mathrm{C_{real\_Cd}}}{\varepsilon_{412}\gamma \mathrm{A_{Cd} Q_{corr\_Cd} N_{Cd}}}$$

ε_{412}: Detection efficiency of 412-keV gamma-rays (separately measured using the standard radiation source)
γ: 0.9562 (412-keV gamma-ray emission ratio of ^{198}Au)

8) Cadmium ratio CR is determined using the following equation.

$$\mathrm{CR} = \frac{\mathrm{R_{Au}}}{\mathrm{R_{Cd}}}$$

9) The reaction rate of thermal neutrons $R_{thermal}$ (/s/mA) is determined using the following equation.

$$\mathrm{R_{thermal}} = \mathrm{R_{Au}}(1 - \frac{1}{\mathrm{CR}})/1000$$

10) Thermal neutron flux Φ (/s/cm^2/mA) is determined using the following equation.

$$\Phi = \frac{R_{thermal}}{f\sigma}$$

f: Self-shielding rate of gold

σ: Cross-section (cm^2) of ^{197}Au (n,γ) ^{198}Au

11) Thermal neutron dose rate $DR_{thermal}$ (Gy-Eq/h/mA) is determined using the following equation.

$$DR_{thermal} = \Phi \times 3600 \times K_n \times N \times RBE_{thermal}$$

K_n: 6.78E-12 Gy/cm^2 (kerma factor for conversion from neutron flux to equivalent dose)

N: 0.02 (weight ratio of nitrogen element in human body)

$RBE_{thermal}$: 2.9 Gy-Eq/Gy (biological effectiveness of thermal neutrons)

PMDA accepted the applicant's explanation.

PMDA's view on the test results:
This test showed a large coefficient of variation and a large maximum coefficient of variation difference only at the depth of 0 mm (surface). The surface has more fast neutrons and a thermal neutron buildup region, and is a low-dose region. Therefore, a positioning error of a gold sample profoundly affects the dose on the surface, which makes dose measurement near the surface susceptible to error. In addition, generally, the measurement precision of thermal neutrons by the gold wire activation method has been reported to be 1 σ or approximately 5%, which is assumed to be higher than the measurement precision of X-rays in general linear accelerators. This level of precision should be acceptable under the current scientific level. The dose per monitor unit is used in the calculation of coefficient of variation, and the relative error is larger for a lower dose. The absolute error was [redacted] Gy-Eq at the maximum on the phantom surface, which does not differ from the absolute errors of measurements at the other depths. This level of error is clinically acceptable. The results at the depth providing the maximum dose met the proposed specification limits and were considered acceptable.

PMDA reviewed the submitted data and concluded that there was no particular problem with the repeatability and calibration stability of the dose monitoring system.

2.(3).2) Linearity of dose monitoring system

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

The applicant submitted data showing that the linearity of the dose monitoring system of NeuCure System meets requirements in ENC00002 and the proposed specification [see Section "2.(1).B Outline of the review conducted by PMDA"].

The linearity of the dose monitoring system of NeuCure System was assessed based on gold wire activation measurements of a neutron beam. The response rate of neutrons was determined from measurements obtained by changing the amount of proton charge at multiple points on the central axis

of the phantom. The linearity was assessed based on the deviation of the thus obtained response rate from the response rate calculated by linear approximation. This test used no cadmium-covered gold sample unlike the test method in 2.(1).1) above, and the assessment was based on the response rate of neutrons including epithermal neutrons. The energy profile of neutrons is consistent even when the amount of proton charge is changed. The ratio of thermal neutrons and epithermal neutrons is also consistent. The proposed method can, therefore, assess the linearly of the monitoring system in measurement of thermal neutron dose. The maximum deviation was [redacted]%. The deviation at the depth of [redacted] mm, which provided the maximum dose, met the proposed reference value.

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

Although the test results were greater than those with general linear accelerators, the linearity of the dose monitoring system appeared to be acceptable because the results were within the specification limits, which were established during the review process as aforementioned [see Section "2.(1).B Outline of the review conducted by PMDA"].

PMDA reviewed the submitted data and concluded that there was no particular problem with the linearity of the dose monitoring system.

2.(3).3) Dose distribution measurement

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

The applicant submitted data showing that the dose distribution measurements by NeuCure System meet ENC00002 and the proposed specification [Section "2.(1).B Outline of the review conducted by PMDA"].

Figures 17, 18, and 19 show deep-dose curves and equivalent dose curves (opening diameter, 100 nm) determined from measurements of thermal neutrons using a water phantom by the gold wire method on the beam axis and 2 cross-sections perpendicular to the beam axis. All dose distribution measurements obtained met the reference values.

Figure 17. Deep-dose curve

Figure 18. Equivalent dose curve

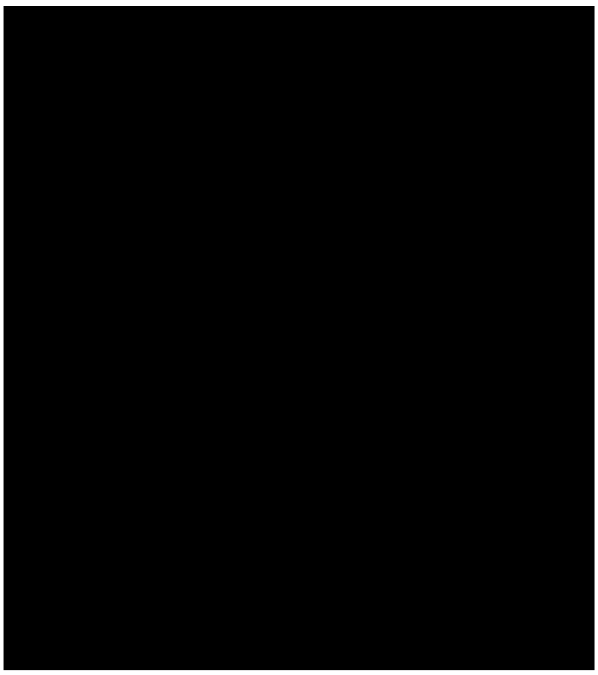

Figure 19. Equivalent dose curve at the depth of [redacted] mm

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

The results were within the range of the quantitative specification limits, which were established during the review process as aforementioned [see Section "2.(1).B Outline of the review conducted by PMDA"]. PMDA reviewed the submitted data and concluded that there was no particular problem with the dose distribution measurement.

2.(3).4) Peak dose measurement

2.(3).4).A Summary of the data submitted

The applicant submitted data showing that the peak dose measurements of thermal neutrons by NeuCure System meet ENC00002 [see Section "2.(1).B Outline of the review conducted by PMDA"].

2.(3).4).B Outline of the review conducted by PMDA

PMDA reviewed the submitted data and concluded that there was no particular problem with the peak dose measurement.

2.(3).5) Performance studies of irradiation system

2.(3).5).A Summary of the data submitted

The applicant submitted data showing that the performance of the irradiation system of NeuCure System (treatment table in the treatment room, treatment table in the simulation room, shielding block, movable shield, target exchange device, laser pointer, and target) and the dose at irradiation stoppage meet the acceptance criteria.

2.(3).5).B Outline of the review conducted by PMDA

PMDA asked the applicant to explain the risk of the exposure of healthcare professionals (including device maintenance service personnel), radiation workers engaging in system maintenance, etc., to residual radioactivity due to activated NeuCure System in the case of irradiation stoppage.

The applicant's explanation:
The residual radioactivity at 1 m downstream on the beam axis from the movable shield surface was measured at 15 minutes after completion of irradiation with the movable shield open. The reference value of ≤100 μSv/h was determined for the reason described below. The measured residual radioactivity was 14 μSv/h, showing that the exposure dose decreases to below the reference value in 15 minutes. In clinical practice, the actual exposure dose from the residual radioactivity is expected to be lower than this value because the movable shield closes automatically after the treatment table is withdrawn toward the direction of the beam axis following completion of irradiation.

The reference value of 100 μSv/h is based on the following assumptions:

- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

PMDA accepted the applicant's explanation.

PMDA asked the applicant for an additional explanation about the expected exposure dose in healthcare professionals in emergency cases.

The applicant's explanation:
In emergency cases, the safety of patients and healthcare professionals must be given priority in principle. If the patient's condition suddenly changes in the treatment room requiring interventions by healthcare professionals, they must immediately stop irradiation, open the shielding door, and take care of the patient. The physician responsible for the treatment decides whether the patient should be taken care of in the treatment room or in the preparation room. When the urgency is low, the patient should be treated after the treatment table is transferred from the treatment room to the preparation room. When the patient is treated in the treatment room, healthcare professionals are exposed to a higher dose. Assuming that healthcare professionals completed necessary interventions in the treatment room within 5 minutes, the cumulative exposure dose when the interventions were completed was 30 μSv (data submitted in Section "2.(4).1) Other safety studies"). If healthcare professionals have to provide emergency interventions to 600 patients per year, the healthcare professionals will be exposed to a dose of 18 mSv/year. This means that even if all 600 patients require emergency interventions, the level of exposure is not clinically significant because it is still below the effective dose limit for radiotherapy experts (50 mSv/year [100 mSv/5 years]).

Neutrons are produced only by the reaction between proton beams released during accelerator operation and the target. Once irradiation is completed, the generation of neutrons stops. Neutrons remaining in the treatment room are absorbed into constituent elements of the air and walls, and disappear in seconds. Neutrons, therefore, do not need to be monitored after completion of irradiation. The ambient dose can

be measured using area monitors in the room and the exhaust outlet, a survey meter, etc. In addition, there will not be residual radionuclides generating neutrons in the room. For these reasons, neutrons do not need to be treated as residual radiation. The individual exposure dose can be controlled using a pocket dosimeter, etc. for gamma-rays or neutrons. Users will be informed of the above emergency procedures through the operating instructions.

PMDA reviewed the submitted data and concluded that there was no particular problem with the performance of the irradiation system. PMDA also asked the applicant to explain specific measures to minimize the exposure of healthcare professionals to radiation as much as practical.

The applicant's explanation:
To minimize the radiation exposure of healthcare professionals as much as practical, the following measures will be taken:

- Data regarding residual radiation over time after neutron irradiation will be submitted to each institution.
- Data regarding estimated exposure dose in emergency cases will be submitted to the institutions.
- The applicant will give priority response to any abnormality, etc., reported from the institutions, regarding the amount of radiation leakage (which is controlled according to the Act on Prevention of Radiation Hazards, the Medical Care Act, and other regulations) and other matters.

PMDA accepted the applicant's explanation under the condition that Approval Condition 4 (for NeuCure System) would be added to ensure that necessary measures will be continuously taken to prevent the radiation exposure of healthcare professionals ("Individual dose limitation" in International Commission on Radiological Protection (ICRP) publication 60 [1990][11] and ICRP publication 73 [1996][12]).

2.(3).6) Measurement precision of the charge monitors of charged particle beam

2.(3).6).A Summary of the data submitted

The applicant submitted data showing that the measurement precision of the proton beam charge monitors for NeuCure System meets the specification limits defined in the official standard for the safety of medical electron accelerators (JIS Z 4705:2006 [IEC 60601-2-1:1998, IEC 60601-2-1:1998/AMENDMENT 1:2002]).

2.(3).6).B Outline of the review conducted by PMDA

NeuCure System is equipped with 2 dose monitoring systems that measure proton beam current (primary dose monitor, Direct-Current Current Transformer [DCCT] [Figure 20]; secondary dose monitor, charge conversion device [stripping foil] [Figure 21]) on each proton beam transport route. The DCCT is located upstream of the target, while the charge conversion device (foil stripper) is installed at the entrance to the cyclotron. Using these dose monitoring systems, NeuCure System constantly measures the charge of proton beams, thereby indirectly monitoring the neutron flux generated.

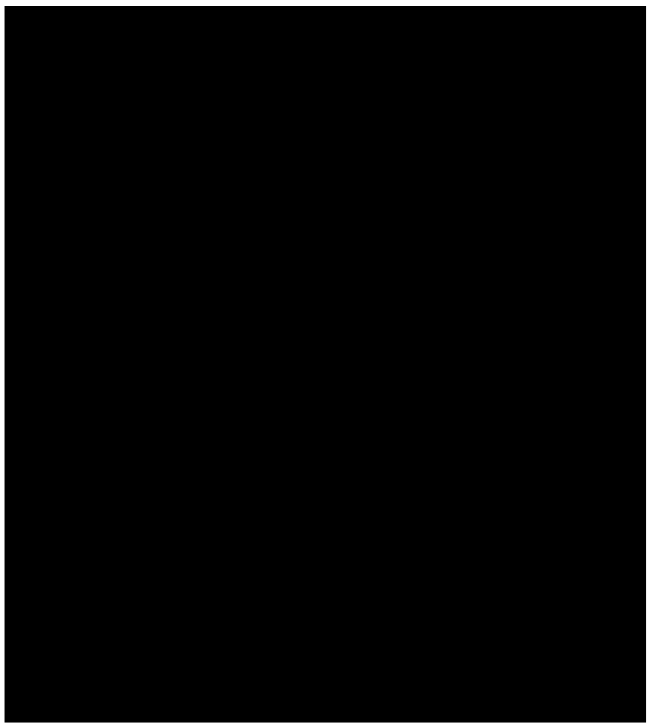

Figure 20. Primary dose monitoring system (DCCT) (red box)

Figure 21. Secondary dose monitoring system (stripping foil) (red box)

The applicant's explanation about the monitoring method of neutron flux produced from the neutron irradiation system:

Since neutrons have no charge, no high-precision/reproducible method has been established for real-time measurement of the neutron flux. It is difficult to directly monitor the neutron flux. On the other hand, the proton beam current before it is converted to neutrons can be measured in a real time manner. Neutrons are formed from protons through a nuclear reaction. There is a consistent relationship between the number of formed neutrons and the number of incident protons. This means that the neutron flux is proportional to the proton beam current. The neutron flux produced, therefore, can be monitored by monitoring the proton beam current.

The neutron irradiance is counted up to the preset monitor dose. Once the count by the primary or secondary dose monitoring system reaches the preset value, the system automatically stops irradiation. NeuCure System is also equipped with a timer, in case that the primary and secondary dose monitoring systems fail to stop irradiation, irradiation stops when the timer reaches the preset irradiation time. Even if the primary dose monitoring system becomes unable to count neutrons, the secondary dose monitoring system alone can stop irradiation once the irradiance reaches 110% of the preset value, as with general particle radiotherapy systems.

PMDA's view on the applicant's explanation:
General linear accelerators (Linac) have a monitor dosimeter (ionization chamber dosimeter) downstream of the target to directly monitor the irradiance of X-rays produced from the target in a real time manner. On the other hand, neutrons, which have no charge, cannot be measured by an ionization chamber dosimeter. Currently, the gold wire activation method is commonly used to measure thermal neutrons. The irradiated and activated gold wires are moved to another place where a spectrometer measures gamma-rays emitted from the wires, thereby measuring thermal neutrons indirectly. Thermal neutrons therefore cannot be measured in a real time manner. A technique using a fiber detector with a micro-scintillator has been proposed for real-time measurement of neutron fluence. However, it is still under development. Currently, therefore, it is considered reasonable to monitor neutrons through real-time monitoring of proton beams using a beryllium target that has not been deteriorated as confirmed by the gold wire activation method prior to the use of NeuCure System. The measurement precision of the 2 dose monitoring systems was assessed by this test. The test confirmed that the value of a simulated beam current supplied to the charge monitor was appropriately displayed on the monitor within the range of specification limits. In addition, the redundancy of the dose monitoring systems met the standard that specifies particular requirements for the basic safety and essential performance of light ion beam medical electrical equipment (JIS T 0601-2-64:2016). Thus the quality of neutrons produced by proton beams is consistent, and the 2 highly sound dose monitoring systems have been shown to measure proton beam current with high precision. This ensures adequate, although indirect, monitoring of the neutron flux released from the neutron irradiation system.

PMDA asked the applicant to explain how to provide users with information about quality control, including the method and frequency of calibration of the dose monitoring systems.

The applicant responded that they planned to communicate relevant information to users through the operating instructions (QA procedures for equipment).

PMDA reviewed the submitted data and concluded that there was no particular problem with the measurement precision of the charge monitors of charged particle beam.

2.(3).7) Irradiation field size

2.(3).7).A Summary of the data submitted

The applicant submitted data showing that the irradiation field size (opening diameter of each collimator, 100, 120, and 150 mm) of NeuCure System meets the proposed specification [see Section "2.(1).B Outline of the review conducted by PMDA"].

2.(3).7).B Outline of the review conducted by PMDA

PMDA reviewed the submitted data and concluded that there was no particular problem with the irradiation field size (opening diameter of the collimators).

2.(3).8) Time of continuous proton beam irradiation

2.(3).8).A Summary of the data submitted

The applicant submitted data on the time of continuous proton beam irradiation,[xviii] which show that NeuCure System irradiates proton beams for [redacted] hours in a stable manner.

2.(3).8).B Outline of the review conducted by PMDA

PMDA reviewed the submitted data and concluded that there was no particular problem with the time of continuous proton beam irradiation.

- **NeuCure BNCT Dose Engine**

2.(3).9) Dose distribution calculation functions (data acquisition, BNCT dose calculation, and data output)

2.(3).9).A Summary of the data submitted

The applicant submitted data regarding the dose distribution calculation functions (data acquisition, BNCT dose calculation, and data output) of NeuCure Dose Engine. The data show that NeuCure Dose Engine acquires treatment planning data, calculates the distribution of dose given by BNCT to the patient's body, and outputs calculation results in a DICOM file, the format accessible to concomitant radiotherapy planning software. The applicant also submitted data indicating that NeuCure Dose Engine in combination with RayStation appropriately performs the process flow shown in Figure 10.

2.(3).9).B Outline of the review conducted by PMDA

The applicant explained that NeuCure Dose Engine evaluates doses of boron, hydrogen, nitrogen, and gamma-rays to assess the equivalent dose delivered to the patient's organs. PMDA asked the applicant to provide the rationale for this.

The applicant's explanation:

As shown in Figure 22, the effects of neutrons on the human body differ depending on their energy (fast, epithermal, and thermal neutrons). Figure 22 shows that, when a neutron flux is the same, nitrogen dose is dominant on the low-energy side (below approx. 100 eV) and hydrogen dose on the high-energy side (above approx. 100 eV).

[xviii] When irradiation was performed using administration methods based on previous clinical experience, etc., almost all patients were exposed to radiation for ≤1 hour. Accordingly, the continuous irradiation time was set at [redacted] to be on the safety side. The operation for this duration was evaluated.

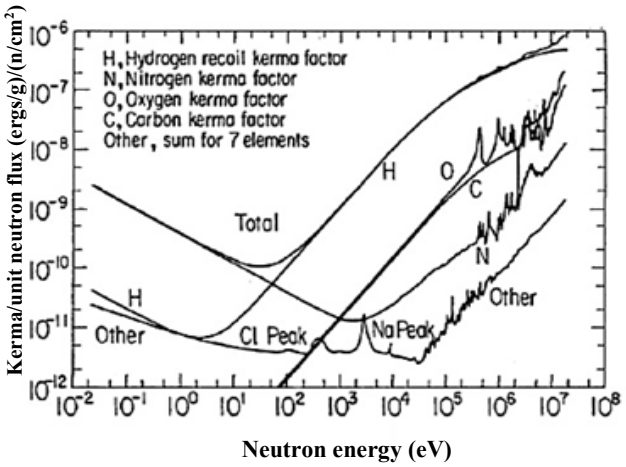

Figure 22. Kerma factor for living tissue[13]

Y axis, ratio of kerma coefficient to thermal neutron flux (related to absorbed dose); x axis, neutron energy

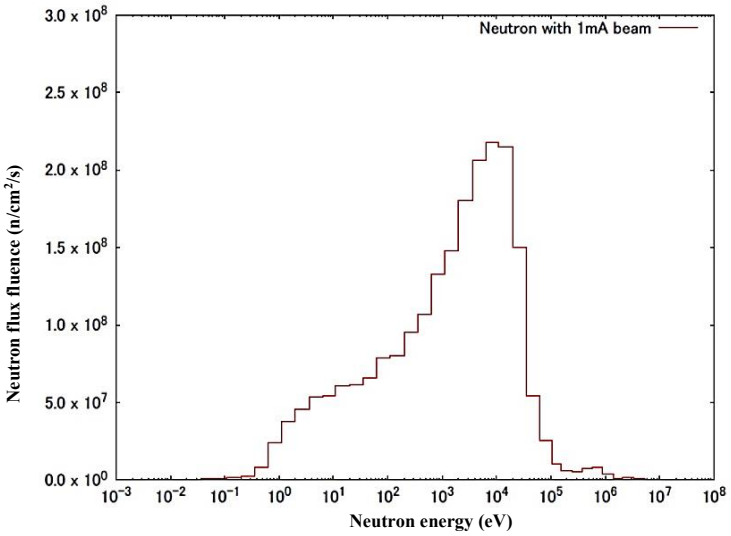

Figure 23. Neutron spectrum emitted from NeuCure System

Nuclear reactions of fast neutrons have the following features (the feature (b) does not depend on the speed of neutrons).

(a) Since NeuCure System has a modulator between the target and the collimator, there are almost no >1 MeV neutrons in the neutron spectrum, emitted from NeuCure System, at the collimator (Figure 23).

For this reason, the energy range of approximately ≤1 MeV should be taken into consideration in nuclear reactions of fast neutrons (in general, the neutron cross-section depends on nuclide, type of nuclear reaction, and energy level).

(b) The probability of nuclear reactions, including elastic scattering, is higher with the atomic nuclei having a higher number density, among the constituent elements of the body. (Hydrogen atomic nuclei have the highest number density among the constituent elements of the body.)

(c) Among the nuclear reactions, recoil reaction is more likely to occur with lighter atomic nuclei (nuclei having a mass close to that of neutrons, such as hydrogen atomic nucleus). Fast neutrons causing no recoil reaction repeatedly undergo elastic scattering and lose their energy to become epithermal neutrons and eventually thermal neutrons.

(d) As a result of the recoil reaction, in principle heavier atomic nuclei releases smaller physical dose circumferentially because of their shorter range.

(e) Among the nuclear reactions, absorption reaction has a smaller neutron cross-section than elastic scattering. (The probability of the nuclear reaction is small.)

In summary, most nuclear reactions of fast neutrons occur with the hydrogen atomic nuclei (protons), which have a mass almost equal to that of neutrons and have the highest number density among the constituent elements of the body. Only the hydrogen dose needs to be taken into consideration. (The reactions with atomic nuclei other than hydrogen atomic nuclei can be ignored.)

Nuclear reactions of epithermal neutrons are assessed together with nuclear reactions of thermal neutrons because epithermal neutrons, as with fast neutrons, repeatedly undergo elastic scattering with hydrogen atomic nuclei in the body to slow down to thermal energy. The hydrogen atomic nuclei receiving energy through elastic scattering contribute to the hydrogen dose as recoil protons although their kinetic energy is smaller than that derived from fast neutrons.

As shown in Figure 22, a nuclear reaction of thermal neutrons predominantly occurs with nitrogen. Other than this reaction, thermal neutrons are known to cause an absorption reaction (neutron capture reaction) with various types of nuclides. Table 4 shows nuclear reactions that occur in the body based on human body composition data in ICRP publication 23 “Report of the Task Group on Reference Man” (1975)[14] and International Commission on Radiation Units and Measurements (ICRU) report 44 “Tissue Substitutes in Radiation Dosimetry and Measurements” (1989).[15] In Monte Carlo simulation by NeuCure Dose Engine, the human body’s constituent elements for a registered patient’s contour information are determined based on ICRU report 46 “Photon, Electron, Proton and Neutron Interaction Data for Body Tissues” (1992).[16] ICRU report 46 is determined based on the body’s constituent elements in ICRU report 44. This means that the body’s constituent elements indicated in Table 4 cover those considered in NeuCure Dose Engine. Most of the product nuclides shown in Table 4 emit gamma-rays. Only nitrogen (^{14}N, ^{15}N) capture reactions produce protons. To discuss the dose from nuclear reactions by thermal neutrons, therefore, only the nitrogen dose and gamma-ray dose need to be considered.

In summary, the absorbed dose in the body can be determined from the doses of boron, hydrogen, nitrogen, and gamma-rays.

Table 4. Reaction between thermal neutrons and body's constituent elements

Element	Abundance ratio in the body [%]	Reaction formula	Product nucleus	Neutron cross-section (barns)*1	Mass (g) of product nucleus per g of body weight	Number of product nuclei per g of body weight
16O	6.13E+01	16O (n,γ) 17O	17O	1.80E-04		
17O	2.50E-02	17O (n,γ) 18O	18O	3.70E-03		
18O	1.40E-01	18O (n,γ) 19O	19O	1.60E-04		
12C	2.26E+01	12C (n,γ) 13C	13C	3.30E-03		
13C	2.70E-01	13C (n,γ) 14C	14C	1.40E-03		
1H	1.00E+01	1H (n,γ) 2H	2H	3.20E-01		
2H	3.00E-03	2H (n,γ) 3H	3H	5.30E-04		
14N	2.60E+00	14N (n,p) 14C	14C	1.80E+00		
15N	1.00E-02	15N (n,p) 15C	15C	0.00E+00		
40Ca	1.40E+00	40Ca(n,γ)41Ca	41Ca	3.90E-01		
42Ca	9.70E-03	42Ca(n,γ)43Ca	43Ca	6.60E-01		
43Ca	2.10E-03	43Ca(n,γ)44Ca	44Ca	6.00E+00		
44Ca	3.30E-02	44Ca(n,γ)45Ca	45Ca	8.60E-01		
46Ca	1.00E-04	46Ca(n,γ)47Ca	47Ca	7.20E-01		
48Ca	3.20E-03	48Ca(n,γ)49Ca	49Ca	1.10E+00		
31P	1.10E+00	31P(n,γ)32P	32P	1.60E-01		
32S	1.90E-01	32S(n,γ)33S	33S	5.10E-01		
33S	1.50E-03	33S(n,γ)34S	34S	3.40E-01		
34S	8.90E-03	34S(n,γ)35S	35S	2.20E-01		
36S	4.00E-05	36S(n,γ)37S	37S	1.40E-01		
39K	1.90E-01	39K(n,γ)40K	40K	2.00E+00		
40K	2.00E-05	40K(n,γ)41K	41K	2.90E+01		
41K	1.40E-02	40K(n,γ)42K	42K	1.40E+00		
23Na	1.40E-01	23Na (n,γ) 24Na	24Na	5.10E-01		
35Cl	1.00E-01	35Cl(n,γ)35Cl	36Cl	4.20E+01		
37Cl	3.40E-02	37Cl (n,γ) 38Cl	38Cl	4.20E-01		
24Mg	2.10E-02	24Mg(n,γ)25Mg	25Mg	5.10E-02		
25Mg	3.00E-03	25Mg(n,γ)26Mg	26Mg	1.90E-01		
26Mg	3.00E-03	26Mg(n,γ)27Mg	27Mg	3.82E-02		
54Fe	3.00E-03	54Fe(n,γ)55Fe	55Fe	2.25E+00		
56Fe	6.00E-03	56Fe(n,γ)57Fe	57Fe	2.59E+00		
57Fe	0.00E+00	57Fe(n,γ)58Fe	58Fe	2.48E+00		
58Fe	0.00E+00	58Fe(n,γ)59Fe	59Fe	1.28E+00		
127I	1.90E-05	127I(n,γ)128I	128I	6.20E+00		
10B *2	5.00E-04	10B(n,α)7Li	7Li	3.72E+03		
			α	3.72E+03		

*1 For neutrons at 36°C (equivalent to 0.0266 eV)
*2 Calculated with a blood ^{10}B concentration of 20 ppm assuming a blood weight of 5 kg in the human body.
Note) The human body composition is based on ICRU report 44 and Reference man weighing 70 kg in ICRP Pub. 23.

PMDA generally accepted the applicant's explanation.

However, the contribution of the doses from the body's constituent elements other than boron, nitrogen, and hydrogen, to the total absorbed dose should be shown to be negligible. According to the nucleus data library of the JAEA (JENDL-4.0), some constituent elements of the human body have nuclides that cause the (n,α) reaction. More specifically, ^{32}S (not listed in Table 4) causes this reaction. The neutron cross-section of the (n,α) reaction caused by ^{32}S is consistent within the energy region of ≤1.5 MeV. In

the region of fast neutrons (40 keV to 1 MeV [upper limit according to the specifications of NeuCure System, approximately 1 MeV), the difference between the neutron cross-section of ^{32}S and the neutron reaction-section of ^{10}B is small. Around the surface (normal tissue) where many fast neutrons exist, the (n,α) reaction of ^{32}S may not be negligible depending on its number density. PMDA asked the applicant to explain why the doses from the body's constituent elements other than boron, nitrogen, and hydrogen, are considered to be negligible by describing the nuclear reaction between ^{32}S and neutrons, which is expected to profoundly contribute to the absorbed dose.

The applicant's explanation:
Figures 24 and 25 show the neutron energy cross-sections of ^{10}B and ^{32}S according to the latest nuclear data library JENDL-4.0.

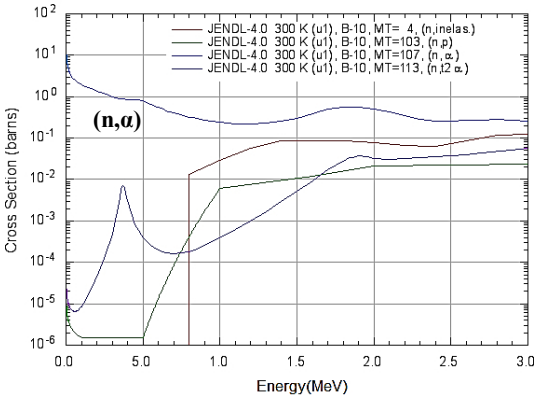

Figure 24. Neutron cross-section of ^{10}B

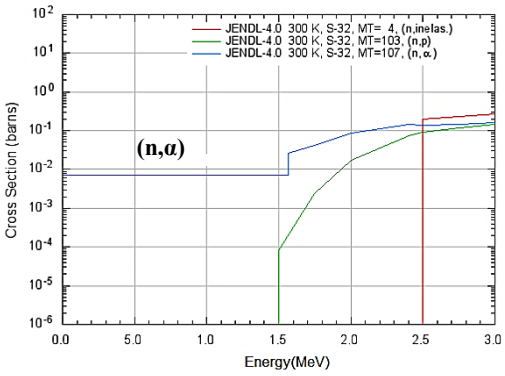

Figure 25. Neutron cross-section of ^{32}S

The neutron cross-section of ^{10}B decreases around 1 MeV (approximately 200 mb[xix]). In the same energy region, the cross-section of the (n,α) reaction of ^{32}S is consistent around 7 mb. The neutron energy spectrum in Figure 23 shows that most neutron fluxes are within the energy range from 1 eV to 100 keV. Assuming conservatively that all neutrons cause the (n,α) reaction with ^{32}S, the number of reactions per second on the skin is estimated as below.

Conditions for calculation:

The total neutron flux: 1.61 × 10^9/cm^2/s (the water phantom surface with a 120 mmΦ collimator, [redacted]).

The atomic weight of natural S: 32.075 (Chronological Scientific Tables 2015).

The cross-section of the (n,α) reaction with ^{32}S: 7.113 mb.

Alpha particle mass: 4.001506 u (https://physics.nist.gov, as of January 28, 2020).

Neutron mass: 1.00867 u (https://physics.nist.gov, as of January 28, 2020).

Skin density and the mass ratio of S atoms in the skin: 1.10 g/cm^3 and 0.159 wt%, respectively, as stated in ICRU pub. 44 (https://pml.nist.gov/cgi-bin/Star/compos.pl?matno=250, as of January 28, 2020).

Abundance ratio of ^{32}S: 94.99% (Chronological Scientific Tables 2015).

The kinetic energy of alpha particles: 2.56 MeV.

[xix] b (barn): 1 b = $10^{-24}$$cm^2$

With the above conditions, the number of ^{32}S atoms in a 1 cm^3 piece of skin is calculated as below:

$$\frac{1.10\ [g/cm^3]}{32.075\ [g/mol]} \times 0.00159 \times (6.022E+23)\ [/mol] \times 0.9499 = (3.12E+19))\ [/cm^3]$$

The number of the (n,α) reaction with ^{32}S per cm^3 of skin per second is calculated as follows:

$$(7.113E-27)\ [cm^2] \times (1.61E+9)\ [/cm^2/s]\ \times (3.12E+19)\ [/cm^3] = (3.57E+2)\ [/cm^3/s]$$

From the weight per cm^3 of skin and the kinetic energy of alpha particles, the physical dose rate per second is calculated as follows:

$$(3.57E+2)\ [/cm^3/s] \times \frac{2.56\ [MeV]}{0.00110\ [kg/cm^3]} \times (1.602E-13)\ [J/MeV] = (1.33E-7)\ [Gy/s]$$

This is equal to 7.97E-3 mGy/min. When the radiation weight coefficient of alpha-rays is 20 as recommended in ICRP 2007 although this can be excessive, a value corresponding to the equivalent dose rate is 0.159 mGy-Eq/min. When calculated similarly, this value with ^{33}S is 0.0595 mGy-Eq/min. The total of the 2 elements is 0.22 mGy-Eq/min.

In the dose distribution measurement test in radiation field, the total of the maximum dose rates of thermal neutrons and fast neutrons was [redacted] mGy-Eq/min (thermal neutrons [redacted] mGy-Eq/min, fast neutrons [redacted] mGy-Eq/min) on the water phantom surface with the 100-mmΦ collimator. The equivalent dose rate of alpha-rays produced from the reaction between neutrons and sulfur atoms is negligible because it is approximately [redacted]% compared with the total of the maximum dose rates of thermal neutrons and fast neutrons.

In summary, the dose from sulfur, which is considered to be the greatest contributor to the absorbed dose, was negligible, indicating that the doses from the body's constituent elements other than boron, nitrogen, and hydrogen, are most likely to be very low.

PMDA accepted the applicant's explanation.

PMDA also asked the applicant to explain how the effects of 0.48-MeV prompt gamma-rays (not listed in Table 4) indicated by reaction formula ^{10}B (n,α) ^{7}Li (Figure 2) are reflected in the results of dose calculation by NeuCure Dose Engine.

The applicant's explanation:
NeuCure Dose Engine does not calculate the transport of prompt gamma-rays using Monte Carlo transport simulation, and therefore the spread of prompt gamma-rays produced by the reaction between neutrons and boron is not considered in the calculation. The kerma factor is used in the calculation of

the boron dose from the reaction between neutrons and boron; this means that only the initial kinetic energy of charged particles generated from this reaction is considered.

To calculate the transport of boron-derived prompt gamma-rays, it is necessary to select an appropriate boron concentration for each voxel and calculate the dose of prompt gamma-rays produced by the reaction between neutrons incident on each voxel and boron, and transport the produced gamma-rays. As determined by the following equation (here, n is the calculated number of particles), [redacted] prompt gamma-rays are needed in each voxel to calculate the transport of prompt gamma-rays with a relative error of approximately [redacted]%.

$$\text{Relative error } [\text{redacted}]\% = 1/\sqrt{n} = 1/\sqrt{[\text{redacted}]}$$

To obtain [redacted] prompt gamma-rays in the voxel size of [redacted] mm with the boron concentration of [redacted] ppm (μg/g), when tissue density is [redacted] g/cm^3, N_A (Avogadro constant) is 6.02E+23/mol, and W_{10B} (mass number of boron atomic nucleus) is 10 g/mol, the number of boron atoms per cm^3 (N_{10B}) is calculated as follows:

$$[\text{redacted}]\ [\mu g/g] \times N_A\ [/\text{mol}] \times \frac{[\text{redacted}]\ [\frac{g}{cm}^3]}{W_{10B}\left[\frac{g}{mol}\right]} = ([\text{redacted}])\ [/\text{cm}^3]$$

Therefore, the following number of thermal neutrons incident on each voxel is required when the neutron cross-section of ^{10}B is [redacted] cm^2:

$$\frac{([\text{redacted}])}{[\text{redacted}]\ [\text{cm}^3] \times [\text{redacted}] \times ([\text{redacted}])[\text{cm}^2] \times ([\text{redacted}])[/\text{cm}^3]} = ([\text{redacted}])\ [/\text{cm}^2]$$

For the calculation in the region of [redacted] cm × [redacted] cm × [redacted] cm, the area of the incident surface of each voxel is [redacted] cm^2 ([redacted] voxels × [redacted] cm^2). [redacted] incident thermal neutrons are needed for the calculation in the entire region. In general, [redacted] initial incident particles are used to calculate the dose using a kerma factor, requiring a calculation time of approximately [redacted] hours. To calculate the distribution of the prompt gamma-ray dose from each voxel with a precision of [redacted]%, therefore, incident particles approximately [redacted] times the above number are required, which is not realistic.

On the other hand, the CBE factor is calculated from the test results under 3 conditions, namely, irradiation of X-rays, irradiation of neutron alone, and a boron compound + neutron irradiation. The cell-killing effect of a boron compound + neutron irradiation reflects all of the contributions from the prompt gamma-ray component. In other words, the CBE factor reflects all of the contributions from prompt gamma-rays. This means that the contribution of prompt gamma-rays is considered in the biological dose in the form of the CBE factor.

PMDA accepted the applicant's explanation.

In the dose distribution calculation, the following fixed values are used for the RBE, CBE, and the ratio of the boron concentration in tumor tissue to the boron concentration in whole blood (Tumor/Blood ratio [T/B ratio]) (Table 5).

Table 5. RBE, CBE, and T/B ratio

	Subject	Value
RBE	Nitrogen dose	2.9
	Hydrogen dose	2.4
	Gamma-ray dose	1.0
CBE	Tumor	4.0
	Brain	1.34
	Skin	2.5
	Normal mucosa	4.9
T/B ratio	Tumor/blood	3.5

The applicant's rationale for each fixed value:
The selective nuclear reaction between thermal neutrons and nitrogen atomic nuclei (formula, ^{14}N [n,p]^{14}C) generates protons. Since these protons have a constant energy, the biological effect resulting from this nuclear reaction is also constant. In theory, the RBE factor for nitrogen dose is constant not depending on the neutron beam source of reactors or accelerators. Table 6 shows the published RBE factors for nitrogen dose. The use of the maximum published RBE factor in calculation of the nitrogen dose results in the maximum nitrogen dose. To ensure the safety of patients, the maximum RBE factor of 2.9 was used in the calculation.

Table 6. Representative published RBE factors for nitrogen dose

RBE	Subject	Administration method	Endpoint
2.9[17]	Hamster, skin	*In vivo*	Desquamation
2.8[18]	9L Rat, tumor	*In vivo*	Survival rate of 10%

The hydrogen dose due to recoiling hydrogen atomic nuclei caused by neutrons changes depending on neutron energy, and the hydrogen dose depends on the neutron beam source of reactors and accelerators. In addition, the RBE factor for hydrogen dose profoundly changes in the energy range from fast neutrons to epithermal neutrons (0.5 eV to 40 keV). For this reason, the RBE factor for hydrogen dose was determined based on the experimental values in Section "2.(4).2) Studies to support the efficacy of the device."

Alpha particles and recoiling Li nuclei yielded by a selective nuclear reaction between thermal neutrons and ^{10}B nuclei (formula, ^{10}B [n,α]^{7}Li) have a constant energy.[xx] With the same distribution of boron in the body, the biological effect resulting from the aforementioned nuclear reaction is also constant. This means that in theory, the CBE factor for boron dose is constant for the same boron compound irrespective of the neutron beam source of reactors or accelerators. Tables 7 to 10 present the published CBE factors for boron dose in tumor, brain, skin, and normal mucosa used in calculation of BNCT doses. The CBE factors for boron dose are near identical for the same tissue irrespective of subjects and endpoints.

[xx] Alpha particles, 0.84 MeV (94%) and 1.01 MeV (6%); recoiling Li nuclei, 1.47 MeV (94%) and 1.78 MeV (6%)

Table 7. CBE factors for tumor

CBE	Subject	Administration method	Endpoint
4.0[18]	9L rat, tumor	*In vivo*	Survival rate of 10%
3.7[19]	Human HeLa cell	*In vitro*	D0 survival

Table 8. CBE factors for normal brain

CBE	Subject	Administration method	Endpoint
1.34[20]	Fischer344 rat, male	*In vivo*	50% incidence of myelosis
1.33[21]	Fischer344 rat, male	*In vivo*	50% incidence of myelosis

Table 9. CBE factors for skin

CBE	Subject	Administration method	Endpoint
2.5[22]	Human, skin	*In vivo*	Moist desquamation
2.4[17]	Hamster, skin	*In vitro*	Moist desquamation

Table 10. CBE factor for normal mucosa

CBE	Subject	Administration method	Endpoint
4.9[23]	Fischer344 rat, male	*In vivo*	Survival rate of 10%

The use of the maximum published CBE factor in calculation of the boron dose results in the maximum boron dose. To ensure the safety of patients, the maximum CBE factor for each tissue was adopted for the calculation. The maximum CBE factor for tumor, brain, skin, and normal mucosa was 4.0, 1.34, 2.5, and 4.9, respectively.

In a nonclinical study of Steboronine, the T/B ratio in mice was approximately 3 at the maximum.[xxi] There appears to be no clear difference in pharmacokinetics between Steboronine and the L-BPA formulation for clinical studies, and the published value in humans of 3.5[24] was adopted for T/B ratio.

PMDA's view on using the fixed values for RBE, CBE, and T/B ratio:
The RBE factor is a general measure showing the difference in radiation quality, namely, the effect of linear energy transfer (LET). It is reasonable to determine the RBE factors for nitrogen and hydrogen doses based on the published and experimental values of this applicable biological effectiveness measure. For the CBE factors for boron dose in tumor and normal mucosa, PMDA does not disagree with the applicant's rationale for using their published values, which have been verified under the same conditions as those used for assessment of the distribution of boron in the body. However, the T/B ratio, which indicates boron accumulation in a tumor, may vary according to the type and size of tumor, and the pharmacokinetics, health condition, etc. of individual patients. The use of the fixed value is therefore questionable.

One of the measures to determine the tumor uptake of boron during BNCT is 4-borono-2-[18F] fluoro-L-phenylalanine-positron emission tomography (F^{18}-BPA-PET) (FBPA-PET). FBPA-PET has not been popularized yet and is still under development because of limited clinical data and a poor synthetic yield of FBPA, which is used as a probe, by the current synthesis method. On the other hand, boron is estimated to be distributed equally to normal organs and blood,[25] and the boron concentrations in normal

[xxi] The tissue (including tumor)/whole blood ratio after a single subcutaneous dose of Steboronine to mice subcutaneously transplanted with tumor cells was 2.2 to 3.1 in the 500 mg/kg group and 1.9 to 3.0 in the 1000 mg/kg group.

organs can be estimated by measuring blood boron concentration in patients. The clinical studies of NeuCure used a normal organ (normal mucosa) as the reference tissue for dose prescription. Adverse effects on normal organs can be predicted even if the T/B ratio does not reflect the actual boron ratio and there is an individual difference in the boron dose in tumor, and the safety of patients can be ensured by measuring blood boron concentration prior to neutron irradiation. FBPA-PET having clinically acceptable performance needs to be developed in the future. Currently, it is reasonable to adopt the representative and published T/B ratio because the later-mentioned clinical studies demonstrated a certain therapeutic effect and safety of NeuCure in the treatment of unresectable, locally advanced or locally recurrent head and neck cancer.

PMDA also asked the applicant to explain the rationale for using the published CBE factor for brain tumor as the CBE factor for head and neck cancer.

The applicant's explanation:
L-BPA, the active ingredient of Steboronine, is taken up by tumor cells via LAT-1, an amino acid transporter. LAT-1 is highly expressed in many types of tumor, including laryngeal cancer and brain tumor.[26] Since LAT-1 is highly expressed in all types of tumor, the clinical studies of NeuCure in head and neck cancer used the CBE factor calculated using a brain tumor model as a fixed value, although no studies have directly compared the LAT-1 expression between head and neck cancer and brain tumor.

PMDA accepted the applicant's explanation.

On the basis of the above explanation, PMDA reviewed the submitted data and concluded that the applicant's explanations about the dose distribution calculation functions (data acquisition, BNCT dose calculation, and data output) are acceptable.

2.(3).10) Dose calculation algorithm

2.(3).10).A Summary of the data submitted

The applicant submitted data showing that the dose calculation algorithm of NeuCure Dose Engine meets the acceptance criterion for the dose calculation precision in the homogeneous area (the result of comparison between observed and calculated doses).

2.(3).10).B Outline of the review conducted by PMDA

The dose calculation precision of the dose calculation algorithm was assessed by comparing calculated doses and observed doses obtained by measuring thermal neutrons by the gold wire activation method and gamma-rays using TLD. NeuCure Dose Engine calculates boron, nitrogen, hydrogen, and gamma-ray doses. The hydrogen dose results from fast neutrons. However, this study did not measure fast neutrons to verify the calculation precision of the hydrogen dose. PMDA asked the applicant to explain this discrepancy.

The applicant's explanation:
In general, fast and epithermal neutrons are measured using radioactivation foils having a resonance absorption[xxii] of fast and epithermal neutrons. It is, therefore, difficult to measure all neutron fluxes having continuous energy spectra covering the energy range from epithermal to fast neutrons. For this reason, currently, there is no established method that can measure all fast and epithermal neutrons in the irradiation field for BNCT.

The dose calculation algorithm of NeuCure Dose Engine creates a beam model by Monte Carlo simulation of neutron beams and gamma-rays that are produced (by a proton beam irradiated on the target) and slowed down. Therefore fast and epithermal neutrons contained in radiation beams are also included in the dose calculation. Some of the fast and epithermal neutrons produced undergo elastic scattering with hydrogen atoms in the water phantom to slow down to thermal neutrons, contributing to the radiation dose for BNCT. This means that fast and epithermal neutron components before they slow down can be assessed by comparing observed results and the calculated flux of thermal neutrons resulting from the decreased energy of fast and epithermal neutrons. Because this assessment also evaluates the appropriateness of the beam model including fast neutrons, it can calculate the hydrogen dose indirectly.

PMDA's view on the applicant's explanation:
It is understandable that the hydrogen dose from fast neutrons cannot be measured directly because accurate measurement is challenging in the energy region of fast neutrons, where the resonance absorption occurs with gold. The calculation precision of doses from thermal neutrons resulting from slowing down of fast and epithermal neutrons was verified using the beam model created by Monte Carlo simulation. Thus, the calculation precision of the dose of fast neutrons, which are yielded in the upstream part of the beam, has also been verified. Since the cross-section between fast neutrons and hydrogen atoms is known, PMDA does not disagree with the assessment proposed by the applicant.

PMDA reviewed the submitted data and concluded that the evaluation of dose calculation algorithm was acceptable.

PMDA concluded that the data regarding the study to support the performance of NeuCure was acceptable.

2.(4) Other design verification studies

2.(4).1) Other safety studies

2.(4).1).A Summary of the data submitted

To support the other safety of NeuCure System (on-site tests of the dose monitoring systems, etc. and on-site control tests of device specifications), the applicant submitted data showing that NeuCure System meets requirements in ENC00001 created based on JIS T 0601-2-64:2016 (IEC 60601-2-64:2014). In addition, to support the design of the interlocks of the safety devices, the applicant submitted additional data that ensure the appropriate operations of electric power receipt, energization, water leak detection, cooling equipment, building interlock signals, beam interlock, high-speed radiation

[xxii] This means that the neutron cross-section abnormally increases at a particular energy level.

shut-off, emergency stop, etc. The applicant submitted additional data showing that the estimated exposure dose of healthcare professionals from residual radioactivity in the treatment room does not exceed the effective dose limit.

2.(4).1).B Outline of the review conducted by PMDA

The soundness of the beryllium target was assessed as part of the tests of the interlocks of the safety devices.

The applicant's explanation about the stability and soundness of the beryllium target in the submitted data:

The target of NeuCure System uses chemically stable beryllium characterized by a very high melting point of 1,278°C, specific heat of 1,925 J/kg/K at 20°C, melting heat of 311 kcal/m^2, and strength/weight ratio of 242 kN•m/kg. Thus, in principle, this beryllium target used in the neutron irradiation device does not change in its shape or fluctuate in the yield of neutrons relative to the irradiance of proton beam during the period of use.

To prevent heat concentration on the target, a scanner electromagnet is located upstream of the target to move the proton beam in a circle on the target. However, this cannot completely prevent the damage to the target. In fact, damage to the target occurred during neutron irradiation for dose measurement (not during the treatment of patients) in a clinical study [see Section "6.D NeuCure-specific matters in the clinical studies"]. In case of target damage, NeuCure System is equipped with double measures to detect the amount of cooling water of the target and the magnetic field of the scanner electromagnet so that irradiation stops immediately upon a drop in the flow rate or detection of any abnormality of scanner electromagnet. Target damage results in cooling water leakage in vacuum. Once a loss of vacuum is detected, the beam immediately stops and simultaneously each gate valve is closed. The target is designed to prevent the cooling water from leaking outside even in the case of target damage. The target has a thickness of 5.5 mm. Protons having an energy of 30 MeV have the range of 5.8 mm, which is greater than the target thickness, so that proton beams pass through the target and reach the cooling water. This structure prevents the occurrence of blistering (this is a phenomenon where a proton beam loses all of its energy in the target, which leads to production and accumulation of gas in the target, resulting in expansion and weakening of the target).

PMDA's view on the applicant's explanation:

Since beryllium has a high melting point and high thermal conductivity, exposure to high-energy proton beams appears to cause minimal deterioration of the shape of the target. The applicant's explanation that the yield of neutrons does not change during the period of use in principle [see Section "2.(2).6) Stability and durability"] is acceptable.

To ensure the soundness of its target, NeuCure System is equipped with structures and functions, including prevention of heat concentration on the target (scanner electromagnet for circular irradiation and cooling by cooling water), interlocks based on detection of a loss of vacuum, and prevention of blistering. As requested by PMDA, the applicant submitted additional data regarding the test of the interlocks of the safety devices to show that proton beam irradiation is stopped by the interlocks when

cooling or vacuum abnormality is detected. This data confirmed that the interlocks appropriately functioned. To support the design to prevent blistering, the range distribution of 30 MeV protons in a system with water circulating behind a 5.5-mm beryllium target was simulated and analyzed using Monte Carlo simulation software. The results of this analysis demonstrated that protons passed through the beryllium target and stopped in the cooling water, indicating that the structure is designed to prevent blisters. The cooling water activated by the proton beam is basically circulating inside the system because of its structure. Those equipment, substances, etc. activated as a result of operation of NeuCure System will be disposed of or managed in accordance with the Act on Prevention of Radiation Hazards due to Radioisotopes, etc., the Medical Care Act, and other relevant standards. On the basis of the above explanation, the target of the neutron irradiation device of NeuCure System was considered to ensure the stability and durability. PMDA accepted the applicant's explanation taking account of the additionally submitted data.

PMDA asked the applicant to explain interventions available when the target, etc. fails to operate appropriately during irradiation and the remaining irradiation becomes impossible, and the effects of such event on patients.

The applicant's explanation:
If the target, etc. malfunctions during irradiation and the remaining irradiation becomes impossible, first of all the defect must be repaired. After the defect is repaired, the remaining prescribed dose will be irradiated to the patient on later days based on the decision by the patient's attending physician. Divided irradiation is common in standard radiotherapy, and BNCT is radiotherapy in a broad term. Therefore irradiation of the remaining prescribed dose on later days is unlikely to impair the therapeutic effect of BNCT. As for the impact of repeated administration of boron drug, the results of a pharmacokinetic study show that the effects of the first dose can be ignored when the next dose is administered ≥3 days after the first dose. Additional administration of boron drug for re-irradiation is unlikely to compromise the safety of the patient provided that it occurs ≥3 days after the first irradiation. The rationale for the irradiation interval of ≥3 days is shown below.

The elimination half-life ($t_{1/2}$) of plasma borofalan (^{10}B) concentration in a non-compartment model was 9.470 ± 1.157 hours in the phase I study. In general, the concentration of a drug decreases to approximately 3% of its maximum concentration (C_{max}) after a period 4 to 5 times longer than $t_{1/2}$, indicating the clearance of the drug from the body. Five times the $t_{1/2}$ of borofalan is 47.35 hours. In the same study, the plasma borofalan (^{10}B) concentration at 72 hours post-dose decreased to approximately 1.29 μg/mL, which is approximately 0.2% of the C_{max} (812.0 ± 115.9 μg/mL). These results confirmed that there would be no effect of the remaining drug concentration in the body ≥3 days after a previous dose.

PMDA generally accepted the applicant's explanation. However, no clinical study evaluated re-irradiation and divided irradiation. When treatment is interrupted because of a device malfunction, etc., and divided irradiation must be performed, the treatment should be performed carefully under the decision by healthcare professionals. PMDA instructed the applicant to provide this information using the instructions for use to healthcare professionals, and the applicant accepted it.

PMDA reviewed the data on the studies to support the other safety (on-site tests of the dose monitoring systems, etc., on-site control tests of device specifications, and tests of the interlocks of the safety devices) and concluded that they were acceptable.

2.(4).2) Studies to support the efficacy of the device

To support the efficacy of BNCT using NeuCure System, the applicant submitted data regarding the RBE factor of fast neutrons and cell-killing effect, tumor-inhibitory effect (human tongue cancer cell SAS), and tumor-controlling effect (human brain tumor cell [redacted]) of BNCT using NeuCure System. The applicant also submitted data regarding the toxicity of single-dose BNCT in mice (acute phase toxicity, bone-marrow micronucleus assay, and long-term toxicity) to investigate the acute and long-term safety of BNCT. The above data were also included in the data submitted for marketing application for Steboronine, the boron drug to be used with NeuCure.

The summary of the PMDA's Review Report (1) of Steboronine, the boron drug to be used with NeuCure, is shown below.

In the excerpts from Review Report (1) of Steboronine in the following "Summary of the submitted data" and "Outline of the review conducted by PMDA," Steboronine is referred to as "borofalan" and Stella Pharma as "the applicant."

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

A colony forming assay was conducted to investigate the growth inhibitory effect of BNCT with borofalan (borofalan/BNCT; neutron beam irradiation dose of NeuCure System, 1.54×10^{11}, 3.08×10^{11}, 4.62×10^{11}, and 6.16×10^{11} n/cm^2) against human tongue cancer-derived SAS cell line, human glioblastoma-derived [redacted] cell line, mouse squamous cell carcinoma-derived SCCVII cell line, and human normal fibroblast-derived NB1RGB cell line. Borofalan/BNCT inhibited the growth of all cell lines tested.

The tumor growth-inhibitory effect of borofalan/BNCT was investigated using nude mice subcutaneously transplanted with SAS cell line (n = 8 or 10/group). The day when the tumor volume reached 1 to 2 mm^3 was defined as the study initiation day (Day 0). On Day 0, borofalan (500 mg/kg) was administered intravenously to mice, followed by irradiation of neutron beams (skin dose, 4 Gy-Eq.) and, on Day 22, tumor volume was calculated. A statistically significant inhibition of tumor growth was observed in the borofalan/BNCT group compared with the control groups (untreated group and neutron beam irradiation group) ($P < 0.0001$ against both control groups, Tukey test).

The tumor growth-inhibitory effect of borofalan/BNCT was investigated using nude mice subcutaneously transplanted with [redacted] cell line (n = 9 or 10/group). The day when tumor volume reached 1 to 2 mm^3 was defined as the study initiation date (Day 0). On Day 0, borofalan (500 mg/kg) was administered intravenously to mice, followed by irradiation of neutron beams (skin dose, 4 Gy-Eq.) and, on Days 21, 28, and 35, tumor volume was calculated. A statistically significant inhibition of tumor

growth was observed in the borofalan/BNCT group compared with the control groups (untreated group and neutron beam irradiation group) (Figure 26).

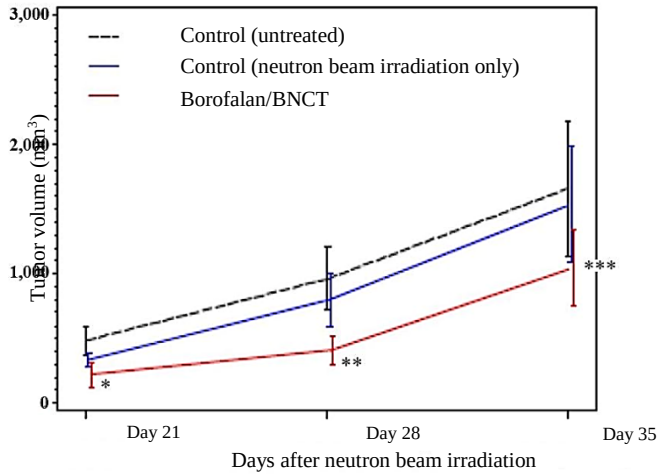

Figure 26. Tumor growth-inhibitory effect of borofalan/BNCT in nude mice subcutaneously transplanted with [redacted] cell line

n = 9 or 10;
* $P < 0.05$ against the untreated group
** $P < 0.0001$ and $P < 0.01$, respectively, against the untreated group and the neutron beam irradiation group
*** $P < 0.0001$ and $P < 0.001$, respectively, against the untreated group and the neutron beam irradiation group Repeated-measure analysis of variance

In single-dose toxicity studies of BNCT in mice (acute phase toxicity, bone-marrow micronucleus assay, and long-term toxicity), mice were given a subcutaneous administration[xxiii] of borofalan and then their heads were irradiated with a single dose of neutron beams for 30 or 40 minutes using NeuCure System, to evaluate acute phase toxicity (necropsied on Days 4, 8, 15, and 29 after irradiation) and long-term toxicity (necropsied on Days 90, 150, and 180 after irradiation). The approximate lethal dose of borofalan was 1,000 mg/kg in males and >1,000 mg/kg in females in the group receiving neutron beam irradiation for 30 minutes, and 500 mg/kg in males and 1,000 mg/kg in females in the group receiving neutron beam irradiation for 40 minutes (Table 11). Main toxicities observed included weight loss, decrease in food and water consumption, changes in hematopoietic and immunological organs, degeneration and necrosis of lingual mucosal epithelium, changes in male and female reproductive organs, and cataract. Deaths occurred during the early phase (Days 10-14 after irradiation) and during late phase (Days 51-94 after irradiation). The assumed causes of early-phase death were (a) eating disorder due to degeneration and necrosis of lingual mucosal epithelium and (b) the deterioration of systemic condition due to immune suppression. The assumed cause of late-phase death was deterioration of systemic condition due to immune suppression. In the preliminary study of this study, borofalan (1,000 mg/kg) was administered subcutaneously to mice, followed by neutron beam irradiation for 40 minutes using NeuCure System; the exposure dose in the skin and brain of the mice (corresponding to approximately 12 and 9 Gy-Eq., respectively) was approximately 1.3- and 4-times, respectively, the maximum estimated exposure dose in the skin (9 Gy-Eq.) and brain (2.25 Gy-Eq.) of humans receiving borofalan/BNCT.

[xxiii] Subcutaneous administration was used because this administration route results in PK similar to that in humans receiving a single intravenous administration of borofalan.

Table 11. Single-dose toxicity (borofalan/BNCT)

Test system	Route of administration	Dose (mg/kg)[a)]	Main findings	Approximate lethal dose (mg/kg)
Acute phase toxicity Male and female mice (BALB/c)	s.c.	0, 500, 1,000	Death[b)]: 500 (40-minute neutron beam irradiation: 2 of 18 males), 1,000 (30-minute neutron beam irradiation: 1 of 24 males), 1,000 (40-minute neutron beam irradiation: 7 of 24 males, 3 of 24 females), decreased activity, hunchback position, eye discharge, lid closure, decreases in body weight/food consumption/water consumption, decreased hematopoietic cells in sternal/femoral bone marrow, atrophy of thymus/spleen/submandibular lymph nodes, degeneration/necrosis of lingual mucosal epithelium, atrophy of ovarian/uterine/vaginal mucosal epithelia, etc. Changes observed at 0 (40-minute neutron beam irradiation): Decreases in body weight/food consumption/water consumption, decreases in platelet/white blood cell/lymphocyte/neutrophil/monocyte/eosinophil counts, increased bilirubin, decreases in thymic/splenic/testicular weights, decreases in hematopoietic cells in sternal/femoral bone marrow, atrophy of thymus/spleen/submandibular lymph node/mesenteric lymph node/Peyer's patch, regeneration of mucosal epithelium of small/large intestinal crypts, inhibition of spermatogenesis, etc. Changes observed at 500 or 1,000 (30- or 40-minute neutron beam irradiation): Decreases in body weight/food consumption/water consumption, effect on lymphatic/hematopoietic/gastrointestinal system, degeneration/necrosis of lingual mucosal epithelium, atrophy of ovarian/uterine/vaginal mucosal epithelia, inhibition of spermatogenesis, cataract, etc.	30-minute irradiation Males: 1,000 Females: >1,000 40-minute irradiation Males: 500 Females: 1,000
Long-term toxicity Male and female mice (BALB/c)	s.c.	0, 500, 1,000	Death[c)]: 500 (40-minute neutron beam irradiation: 9 of 18 males), 1,000 (30-minute neutron beam irradiation: 13 of 18 males, 1 of 18 females), 1,000 (40-minute neutron beam irradiation: 34 of 36 males, 28 of 36 females), eye discharge, lid closure, hunchback position, reduced body weight gain, decreases in food/water consumption, decreased hematopoietic cells in sternal/femoral bone marrow, atrophy of thymus/spleen/lymph nodes, degeneration/necrosis of lingual mucosal epithelium, atrophy of ovarian/uterine/vaginal mucosal epithelia, decreased pancreatic zymogen granules, etc. Changes observed at 0 (40-minute neutron beam irradiation): Increased total plasma cholesterol, decreased plasma amylase activity, decreased weight of submandibular gland/thymus/spleen/testis/ovary/uterus, cataract, atrophy of testicular seminiferous tubules, atrophy of ovarian/uterine/vaginal mucosal epithelia, decreased follicular count, mucus degeneration of vaginal mucous membrane, etc. Changes observed at 500 or 1,000 (30-or 40-minute neutron beam irradiation): Eye discharge, lid closure, hunchback position, reduced body weight gain, decreases in food/water consumption, increased total plasma cholesterol, decreases in plasma triglycerides/amylase activity, ocular white turbidity, small uterus, decreased weight of submandibular gland/thymus/spleen/testis/ovary/uterus/heart/kidney/liver, cataract, atrophy of testicular seminiferous tubules, atrophy of ovarian/uterine/vaginal mucosal epithelia, decreased follicular count, mucus degeneration of vaginal mucous membrane, etc.	30-minute irradiation Males: 1,000 Females: >1,000 40-minute irradiation Males: 500 Females: 1,000

a) Following a subcutaneous administration of borofalan or vehicle, the head of animals was irradiated with a single dose of neutron beams (30 or 40 minutes in the borofalan group, 0 or 40 minutes in the vehicle group). The day of administration of borofalan was counted as Day 1. Animals were necropsied on Days 4, 8, 15, and 29 for evaluation of acute phase toxicity and on Days 90, 150, and 180 for evaluation of long-term toxicity.
b) Death was observed 10 to 12 days after neutron beam irradiation.
c) Death was observed 10 to 14 and 51 to 94 days after neutron beam irradiation.

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

Stella Pharma's explanation about the mechanism of action of borofalan/BNCT and the efficacy for head and neck cancer:

Borofalan is a boron compound, namely phenylalanine labeled with ^{10}B (an isotope of boron). Phenylalanine is an amino acids essential for the growth of tumor cells (*J Am Chem Soc.* 1958;80:835-8). It has been suggested that the compound accumulates in tumor cells, mediated by L-type amino acid transporter-1 (LAT-1) (*Membrane.* 2008;33:108-17), an amino acid transporter highly expressed in multiple types of carcinomas including head and neck cancer (*Cancer Res.* 2009;69:2126-32).

Borofalan alone does not inhibit tumor growth, whereas upon irradiation of neutron beam from outside the body, ^{10}B atoms incorporated in tumor cells captures neutrons, resulting in the release of alpha rays and lithium nuclei generated by nuclear reaction, exhibiting a tumor growth-inhibitory effect (*Int J Radiat Biol.* 2006;82:21-9).

The efficacy of borofalan/BNCT is suggested by this mechanism of action and by the fact that borofalan/BNCT showed tumor growth-inhibitory effect in nude mice subcutaneously transplanted with a human head and neck carcinoma cell line.

PMDA accepted the applicant's explanation.

The applicant explained the changes in hematopoietic and immunological organs, degeneration and necrosis of lingual mucosal epithelium, changes in male and female reproductive organs, cataract etc., observed in the single-dose toxicity study of borofalan/BNCT in mice.

The applicant's explanation:
The above toxicity findings were not observed in the study of single-dose of borofalan alone, and all of them are known to be caused by exposure to radiation. In mice, toxicity findings were observed in regions other than those close to the neutron beam radiation field (e.g., tongue, eyes) because neutron beam irradiation to body parts other than the head and neck could not be avoided due to the small body size. In humans, in contrast, body parts other than the head and neck are outside the irradiation field, and the exposure dose in the clinical use of borofalan/BNCT is lower than that in mice. These facts suggest that serious adverse events are unlikely to occur in humans.

PMDA's view:
PMDA accepted the applicant's explanation from the toxicological point of view, regarding the systemic toxicity observed in the single-dose toxicity study of borofalan/BNCT in mice.

2.(4).3) Studies to support usage method of NeuCure System

2.(4).3).A Summary of the data submitted

To support the usage method of NeuCure System, the applicant (Sumitomo Heavy Industries, Ltd.) submitted data on bioequivalence and investigational device equivalence studies.

The bioequivalence study was conducted using NeuCure System installed in Innovation Research Laboratory, Kyoto University Research Reactor Institute (Kyoto University) and NeuCure System installed in Sothern Tohoku BNCT Research Center, Sothern Tohoku General Hospital, Sothern Tohoku Research Institute for Neuroscience (Sothern Tohoku BNCT Research Center). Cultured cells were

irradiated with neutron beams from NeuCure System at both institutions. The 2 NeuCure Systems were shown to be bioequivalent to each other based on the doses resulting in cell viability of 10% as determined by a colony counting method according to the rationale of the Organization for Economic Co-operation and Development (OECD) guidelines for phototoxicity testing.

The investigational device equivalence study was conducted using the devices installed at Kyoto University, Sothern Tohoku BNCT Research Center, and Kansai BNCT Medical Center, Osaka Medical College (Osaka Medical College) to compare the following: thermal neutron distribution measurement on the beam axis, fast neutron measurement, thermal neutron distribution measurement in the orthogonal direction to the beam axis, radiation dose rate measurement, collimator size measurement, gamma-ray dose measurement, and dose measurement outside the radiation field. The results showed the equivalence of neutron radiation quality.

2.(4).3).B Outline of the review conducted by PMDA

PMDA reviewed the data on the studies to support the usage method of NeuCure System and accepted the applicant's explanation.

2.(4).4) Other performance study

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

The applicant submitted data on another performance study of NeuCure Dose Engine that assessed the equivalence of SERA and NeuCure Dose Engine and compared their performance because the later-mentioned clinical studies used SERA instead of NeuCure Dose Engine.

For performance comparison, the dose distribution in a water phantom was calculated by SERA and NeuCure Dose Engine. Thermal neutron and gamma-ray doses were determined by γ analysis. The thermal neutron and gamma-ray doses met the acceptance criteria (i.e., position error ≤[redacted] mm and dose error ≤[redacted]%) at all points in the region from the entry point to the depth of [redacted] cm.

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

The gamma-ray dose did not meet the acceptance criteria at depths of >[redacted] cm from the surface of the water phantom. PMDA asked the applicant to explain whether the precision of dose calculation by NeuCure Dose Engine can be assured at depths of ≥[redacted] cm from the skin surface in clinical practice.

The applicant's explanation:

The doses calculated by NeuCure Dose Engine at depths of ≥[redacted] cm were consistent with the observed doses and met the acceptance criteria, showing that the precision of dose calculation by NeuCure Dose Engine was at least comparable to that by SERA. NeuCure Dose Engine thus assures a high calculation precision reflecting observed values for treatment in a region deeper than [redacted] cm.

PMDA's view on the applicant's explanation:

Treatment in the clinical studies was conducted according to radiation plans developed based on dose calculations by SERA. If the calculation results by NeuCure Dose Engine are not consistent with those by SERA, NeuCure Dose Engine may fail to provide a treatment outcome similar to that with SERA.

Because of this concern, the applicant's explanation cannot be accepted without further explanations. In the clinical studies, however, BNCT was administered to the head and neck. In all patients, the normal mucosa (in the oral cavity, pharynx, or larynx) defined as reference tissue for dose prescription was located not deeper than [redacted] cm from the body surface. In this region, NeuCure Dose Engine can calculate the doses appropriately. SERA tends to estimate lower doses than NeuCure Dose Engine. This means that NeuCure Dose Engine estimates unnecessary doses at depths of >[redacted] cm on the safe side compared with SERA. On the other hand, NeuCure Dose Engine may estimate higher doses in the treatment target region. However, it was the calculated value of gamma-ray dose that differed between SERA and NeuCure Dose Engine; this difference is unlikely to affect the treatment profoundly. Since the thermal neutron doses calculated by NeuCure Dose Engine and SERA were consistent, the efficacy and safety of the thermal neutron dose can be assured in treatment using NeuCure Dose Engine.

PMDA reviewed the data on another performance study to support the usage method of NeuCure Dose Engine and accepted the applicant's explanation.

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

3.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 Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics (hereinafter referred to as "the Essential Principles") (MHLW Ministerial Announcement No. 122, 2005).

3.B Outline of the review conducted by PMDA

PMDA reviewed the conformity of NeuCure to the Essential Principles.

(a) PMDA's view on the conformity of NeuCure to Article 1, which defines preconditions, etc. for designing medical devices (particularly conditions for users, such as technical knowledge, experience, education, and training for intended user):

As described later in Section 6.D.(6), to ensure the safe implementation of BNCT with NeuCure, physicians and medical physics experts with adequate knowledge and experience in boron neutron capture therapy should conduct the treatment at medical institutions where NeuCure is installed, treatment plans are developed, and quality control is performed. In line with this, PMDA instructed the applicant to take necessary measures.

(b) PMDA's view on the conformity of NeuCure to Article 2, which defines risk management throughout the product life-cycle of medical devices:

As described later in Section "7.B Outline of the review conducted by PMDA," clinical results in Japan should be collected through use-results surveys and appropriate risk mitigation measures should be taken as necessary. Accordingly, PMDA instructed the applicant to conduct a use-results survey.

(c) PMDA's view on the conformity of NeuCure to Article 3, which defines the performance and function of medical devices:

As described earlier in the "Outline of the review conducted by PMDA" sections under Sections "2.(1) Performance and safety specifications" and "2.(3) Studies to support device performance," all of the specifications for performance, function, etc. of NeuCure have been shown to be appropriate.

(d) PMDA's view on the conformity of NeuCure to Article 6, which defines the efficacy of medical devices:

As described later in Section 6.B.(4), making NeuCure available for clinical use as a local treatment option will benefit patients with unresectable, locally advanced or locally recurrent head and neck cancer who are not eligible for standard treatments, such as chemoradiotherapy.

(e) PMDA's view on the conformity of NeuCure to Article 7, which defines the chemical characteristics of medical devices:

As described earlier in Section "2.(4).1).B Outline of the review conducted by PMDA," the stability and soundness of the beryllium (^{9}Be) target of NeuCure have been shown to be appropriate.

(f) PMDA's view on the conformity of NeuCure to Article 9, which defines the environment in which medical devices are intended to be used:

As described earlier in Section "2.(2).2).B Outline of the review conducted by PMDA," the electrical safety and electromagnetic compatibility of NeuCure System have been shown to be appropriate.

(g) PMDA's view on the conformity of NeuCure to Article 10, which defines requirements to ensure the accuracy, precision, etc. of medical devices with a measuring function:

As described earlier in the "Outline of the review conducted by PMDA" sections under Section "2.(3) Studies to support device performance," the accuracy, precision, etc. of the measuring functions of NeuCure have been shown to be appropriate.

(h) PMDA's view on the conformity of NeuCure to Article 11, which defines protection against radiation:

As described earlier in Section "2.(2).4).B Outline of the review conducted by PMDA," the dose distribution tests both in and outside radiation field were conducted to reflect the clinical use of NeuCure System. The tests were therefore appropriate.

On the other hand, as described earlier in Section "2.(3).5).B Outline of the review conducted by PMDA," the exposure dose of medical professionals is shown not to exceed the expected reference level, but, treatment with NeuCure System involves long-term neutron irradiation, which profoundly accelerates the activation of devices, buildings, etc. compared with general radiotherapy equipment such as linear accelerators. Accordingly, PMDA instructed the applicant to take necessary measures to minimize the exposure of medical professionals to neutron irradiation as much as practical.

(i) PMDA's view on the conformity of NeuCure to Article 12, which defines the requirements for development life cycle of medical devices that incorporate software:
As described earlier in Section "2.(2).7).B Outline of the review conducted by PMDA," the safety of radiotherapy treatment planning system has been evaluated. The results provided justification.

(j) PMDA's view on the conformity of NeuCure to Article 13, which defines requirements for elimination, etc. of consequent risks in the event of a single fault condition for active medical devices:
As described earlier in Section "2.(2).2).B Outline of the review conducted by PMDA," NeuCure System has been assessed for the general requirements for the basic safety and essential performance of medical electrical equipment. The results confirmed the safety of NeuCure System in the event of single fault condition.

(k) PMDA's view on the conformity of NeuCure to Article 14, which defines the protection against mechanical risks of medical devices:
As described earlier in Sections "2.(2).2).B Outline of the review conducted by PMDA" and "2.(2).5).B Outline of the review conducted by PMDA," NeuCure System has been assessed for the general requirements, etc. for the basic safety and essential performance of medical electrical equipment. The results confirmed the mechanical safety of NeuCure System.

(l) PMDA's view on the conformity of NeuCure to Article 14, which defines the requirements for medical devices that supply the patient with energy:
As described earlier in Section "2.(4).1).B Outline of the review conducted by PMDA," on-site tests of the dose monitoring systems, etc., on-site control tests of device specifications, and tests of the interlocks of the safety devices have been conducted. The results provided justification.

(m) PMDA's view on the conformity of NeuCure to Article 17, which defines the general requirements for information provision to users through instructions for use, etc.:
As described later in Section 6.D.(6), since NeuCure should be used by medical professionals with adequate knowledge, techniques, and experience in BNCT at medical institutions appropriately equipped for managing and implementing BNCT, PMDA instructed the applicant to include a caution statement to the following effect in the instructions for use: "NeuCure should be used in accordance with the guidelines for proper use developed in cooperation with related academic societies."

As described later in Section 6.D.(4), PMDA also instructed the applicant to include the following information in the instructions for use: (i) a statement to the effect that NeuCure should be used with care in patients who have difficulty in keeping the same body posture for a long period of time; and (ii) appropriate caution statements regarding intended use.

In addition, as described later in Section "6. Clinical Data or Alternative Data Accepted by the Minister of Health, Labour and Welfare," PMDA instructed the applicant to add the NeuCure-related information included in the package insert of Steboronine, a concomitant boron drug, to the instructions for use of NeuCure to provide caution to healthcare professionals.

PMDA comprehensively reviewed the conformity of NeuCure to the Essential Principles and concluded that there was no particular problem.

4. Risk Management

4.A Summary of the data submitted

The applicant submitted data summarizing the risk management system and risk management activities implemented for NeuCure System based on JIS T 14971:2012 (ISO 14971:2007).

The applicant submitted data summarizing the risk management system and risk management activities implemented for NeuCure Dose Engine based on JIS T 14971:2012 (ISO 14971:2007).

4.B Outline of the review conducted by PMDA

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

5. Manufacturing Process

5.A Summary of the data submitted

The applicant submitted data on the manufacturing process and manufacturing site of NeuCure System.

Since NeuCure Dose Engine is a medical device software, the applicant did not submit data on the manufacturing process of NeuCure Dose Engine, in accordance with the "Handling of Medical Device Software" (PFSB/MDRMPE Notification No. 1121-33, PFSB/SD Notification No. 1121-1, and PFSB/CND Notification No. 1121-29, dated November 21, 2014).

5.B Outline of the review conducted by PMDA

PMDA reviewed the data on the manufacturing process of NeuCure System and concluded that there was no particular problem. PMDA also concluded that there is no particular problem with omitting the submission of data on the manufacturing process of NeuCure Dose Engine.

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

The applicant submitted the results of a phase I clinical study, another phase I clinical study (Post Study Follow-up), and a phase II clinical study, all conducted in Japan (Appendix 6-1-1, phase I clinical study, March 2014 to [redacted]); Appendix 6-1-2, phase I clinical study [Post Study Follow-up], December 2014 to [redacted]; Appendix 6-1-3, phase II clinical study, June 2016 to [redacted]). These clinical study results were also included in the data submitted for marketing application for Steboronine.

The above clinical studies of NeuCure used SERA as a treatment planning program instead of NeuCure Dose Engine. As aforementioned, the process flow and dose calculation precision of NeuCure Dose Engine in combination with RayStation were compared with those of SERA in combination with the same treatment planning system, and NeuCure Dose Engine was shown to be equivalent to SERA [see Section 2.(4).4)].

PMDA concluded that the efficacy and safety of NeuCure Dose Engine were evaluable based on the submitted clinical study data.

The summary of the PMDA's Review Report (1) of Steboronine, the boron drug to be used with NeuCure, is shown below.

In the following excerpts from Review Report (1) of Steboronine, NeuCure System is referred to as "BNCT30," Steboronine as "borofalan," and Stella Pharma as "the applicant."

Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

6.A Summary of the data submitted

The applicant submitted efficacy and safety evaluation data, in the form of results from 2 studies: 1 Japanese phase I study and 1 Japanese phase II study (Table 12).

Table 12. List of clinical studies on efficacy and safety

Dara category	Region	Study ID	Phase	Study population	No. of enrolled subjects	Outline of dosage regimen	Major endpoints
Evaluation	Japan	001	I	Patients with unresectable locally recurrent head and neck squamous cell carcinoma or with unresectable, locally advanced or locally recurrent head and neck non-squamous cell carcinoma	9 (a) 6 (b) 3	(a) A single dose of borofalan (500 mg/kg) was administered intravenously at the rate of 200 mg/kg/h during the first 2 hours, then at 100 mg/kg/h. A single-dose neutron beam irradiation (10 Gy-Eq.)[*1] was started at 2 hours after the start of administration of borofalan.[*2] (b) A single dose of borofalan (500 mg/kg) was administered intravenously at the rate of 200 mg/kg/h during the first 2 hours, then at 100 mg/kg/h. A single-dose neutron beam irradiation (12 Gy-Eq.)[*1] was started at 2 hours after the start of administration of borofalan.[*2]	Safety Tolerability
		002	II	(a) Patients with post-CRT or -RT unresectable locally recurrent head and neck squamous cell carcinoma and (b) patients with unresectable, locally advanced or locally recurrent head and neck non-squamous cell carcinoma	21	A single dose of borofalan was administered intravenously at the rate of 200 mg/kg/h during the first 2 hours, then at 100 mg/kg/h during neutron beam irradiation. A single-dose neutron beam irradiation (12 Gy-Eq.)[*1] was started at 2 hours after the start of administration of borofalan.[*2]	Efficacy Safety

[*1] Dose given to mucosa of the oral cavity, pharynx, or larynx; [*2] BNCT30 was used.

The outline of each clinical study is shown below. Main adverse events other than death observed in each clinical study are described in Section "6.C Adverse events, etc. observed in clinical studies."

6.A.(1) Japanese phase I study (CTD 5.3.3.2-1 and 5.3.3.2-2, Study WW2P2040E001/SPM-011-JHN001 [Study 001] [March 2014 to [redacted]])

An open-label, uncontrolled study was conducted to investigate the safety and tolerability of borofalan/BNCT in patients with unresectable locally recurrent head and neck squamous cell carcinoma or patients with unresectable, locally advanced or locally recurrent head and neck non-squamous cell carcinoma[xxiv] (target sample size, 12 subjects at the maximum) in 2 study sites in Japan.

A single dose of borofalan (500 mg/kg) was administered intravenously at the rate of 200 mg/kg/h during the first 2 hours, then at 100 mg/kg/h. Starting at 2 hours after the start of administration of borofalan, a single-dose neutron beam irradiation was given using BNCT30 for a maximum of 60 minutes at 10 Gy-Eq. (low dose) or 12 Gy-Eq. (high dose) as mucosal dose in the oral cavity, pharynx, or larynx.

All of the 9 patients enrolled in the study (6 in the low-dose group, 3 in the high-dose group) received borofalan/BNCT, and were included in the safety analysis population.

The dose-limiting toxicities (DLTs)[xxv] evaluation period was up to Day 90 after administration of borofalan/BNCT. DLT (Grade 3 dysphagia) was observed in 1 of 6 patients in the low dose group, whereas no DLT was observed in the high dose group. Therefore, the recommended dose of borofalan/BNCT was determined to be 12 Gy-Eq.

No death occurred during treatment with borofalan/BNCT or during 90 days after the treatment.

6.A.(2) Japanese phase II study (CTD 5.3.5.2-1, Study WW2P2040E004/SPM-011-JHN002 [Study 002] [June 2016 to [redacted]])

An open-label, uncontrolled study was conducted to investigate the efficacy and safety of borofalan/BNCT in (a) patients with post-chemoradiotherapy (CRT) or post-radiotherapy (RT) unresectable locally recurrent[xxvi] head and neck squamous cell carcinoma[xxvii] and (b) patients with unresectable, locally advanced or locally recurrent head and neck non-squamous cell carcinoma[xxviii] (target sample size, 21 subjects) in 2 study sites in Japan.

A single dose of borofalan was administered intravenously at the rate of 200 mg/kg/h during the first 2 hours, and at 100 mg/kg/h during the neutron beam irradiation. Starting at 2 hours after the start of

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[xxiv] The study enrolled patients who met both of the following criteria:
(a) Head and neck squamous cell carcinoma with prior RT at ≥40 and ≤75 Gy to the target lesion, or head and neck non-squamous cell carcinoma with prior RT at ≤75 Gy to the target lesion.
(b) The last irradiation to the target lesion was performed 180 or more days before the enrollment.

[xxv] DLT was defined as Grade ≥3 nonhematological toxicity and Grade ≥4 hematological toxicity for which a causal relationship to BNCT could not be ruled out. Among these events, those meeting both of the following criteria were not considered as DLT: (i) Adverse events common to existing RT ([a] Grade 3 mucositis oral, pharyngeal mucosa inflammation, laryngeal mucosa inflammation, dry mouth, and salivary gland inflammation; [b] Grade ≥3 fatigue, anorexia, headache, ear pain. vertigo, nausea, vomiting, and serum amylase increased (salivary gland type), and [c] Grade ≥4 anaemia, white blood cell decreased, platelets decreased, lymphopenia, and neutropenia), and (ii) serious adverse events that resolved without surgical intervention.

[xxvi] The study also enrolled patients who showed partial response (PR) or stable disease (SD) after CRT or RT but required additional treatment for residual tumor.

[xxvii] The following patients were enrolled: (a) Patients who received [i] platinum-based CRT or [ii] platinum-based induction chemotherapy + RT. (b) Patients showing local recurrence within 6 months after completing [i] RT alone, [ii] non-platinum-based CRT, or [iii] CRT including cetuximab who were intolerant to, or refused, platinum-based chemotherapy. The study also enrolled patients who showed local recurrence at >6 months after completing multimodality therapy including RT if they had disease progression or recurrence during or after platinum-based chemotherapy or if they were intolerant to, or refused, platinum-based chemotherapy.

[xxviii] These patients were enrolled regardless of prior RT or chemotherapy.

administration of borofalan, a single-dose neutron beam irradiation was given using BNCT30 for a maximum of 60 minutes at 12 Gy-Eq. as mucosal dose in the oral cavity, pharynx, or larynx.

All of the 21 patients enrolled in the study received borofalan/BNCT, and were included in the efficacy analysis population and the safety analysis population.

The primary endpoint of the study was response rate assessed by blinded independent central review (BICR) based on Response Evaluation Criteria in Solid Tumors (RECIST) ver.1.1.

Table 13 shows the results of response rate assessed by BICR based on RECIST ver.1.1, the primary efficacy endpoint of the study. The lower limit of 90% confidence interval (CI) of the response rate exceeded the prespecified threshold response rate (20.0%).[xxix]

Table 13. Best overall response and response rate
(RECIST Ver. 1.1, efficacy analysis population, BICR assessment, data cut off on [redacted])

Best overall response	n (%)
	N = 21
CR	5 (23.8)
PR	10 (47.6)
SD	5 (23.8)
PD	0
NE	1 (4.8)
Response (CR + PR) (response rate [90% CI*] %)	15 (71.4 [51.3, 86.8])

* Clopper-Pearson method

No death occurred during, or within 90 days after, treatment with borofalan/BNCT.

6.B Outline of the review conducted by PMDA

6.B.(1) Data for review

PMDA concluded that, among the evaluation data submitted, the most important clinical study for evaluating the efficacy and safety of borofalan/BNCT was the Japanese phase II study (Study 002) conducted to investigate the efficacy and safety of borofalan/BNCT in (a) patients with post-CRT or -RT unresectable locally recurrent head and neck squamous cell carcinoma and (b) patients with unresectable, locally advanced or locally recurrent head and neck non-squamous cell carcinoma. PMDA therefore decided to evaluate the submitted data focusing on Study 002.

6.B.(2) Clinical positioning and efficacy

On the basis of the following review, PMDA has concluded that a certain level of efficacy of borofalan/BNCT has been demonstrated in patients with unresectable, locally advanced or locally recurrent head and neck cancer.

[xxix] The threshold response rate was set at 20% based on the clinical data in patients receiving 5-FU and a platinum antineoplastic drug in a foreign phase III study (Study EMR62202-002 [EXTREME study]), which was conducted to compare the efficacy and safety of cetuximab/5-FU/platinum antineoplastic drug and 5-FU/platinum antineoplastic drug in patients with recurrent or metastatic head and neck squamous cell carcinoma without a prior chemotherapy (*N Engl J Med*. 2008;359:1116-27).

6.B.(2).1) Clinical positioning

The description on borofalan/BNCT was not found in Japanese or foreign clinical practice guidelines or representative textbooks on clinical oncology.

The applicant's explanation about the treatment algorithm for patients with unresectable, locally advanced or locally recurrent head and neck cancer and about the clinical positioning of borofalan/BNCT in the treatment algorithm:
Among patients with unresectable, locally advanced or locally recurrent head and neck cancer, those with squamous cell carcinoma are treated, as the standard treatment, (i) with nivolumab if local recurrence is observed within 6 months after CRT or RT and (ii) with cetuximab, nivolumab, etc., if local recurrence is observed at >6 months after CRT or RT.

In patients with non-squamous cell carcinoma, which accounts for only approximately 10% of head and neck cancer, it is practically impossible to obtain evidence for establishing the standard treatment. For this reason, these patients are treated in a similar manner as in patients with squamous cell carcinoma in clinical practice (*Shin Rinsho Shuyo Gaku*, 5th revised edition [Nankodo, 2018]).

Patients with head and neck cancer may experience dysfunctions in vocalization, swallowing, mastication, respiration, etc. because of locally advanced or locally recurrent lesion. In Study ONO-4538-11/CA209141 (CheckMate 141 study),[xxx] the response rate [95% CI] assessed by the investigator based on RECIST ver.1.1 was 13.3% [9.3%, 18.3%] (*N Engl J Med*. 2016;375:1856-67); this suggests that nivolumab has only a limited therapeutic effect on head and neck cancer. In addition, re-irradiation after CRT or RT is not established as a standard treatment because it may exceed the tolerance dose in the normal tissues around the tumor, posing an increased risk of serious adverse reactions (*Int J Radiat Oncol Biol Phys*. 2011;81:1211-9).

In contrast, borofalan/BNCT is a local treatment in which ^{10}B, a nuclide species highly reactive with neutron, is incorporated into tumor cells which are then disrupted by the reaction between ^{10}B atoms and neutrons. This treatment has little effect on normal cells surrounding the tumor and is expected to preserve functions such as vocalization, swallowing, mastication, and respiration by controlling local lesions. The treatment is therefore considered to be positioned as one of the local treatments for patients with unresectable, locally advanced or locally recurrent head and neck cancer.

PMDA accepted the explanation of the applicant.

6.B.(2).2) Efficacy endpoints and evaluation results

The applicant's explanation about efficacy endpoints and evaluation results of Study 002:
Patients with unresectable, locally advanced or locally recurrent head and neck cancer who respond to treatment with borofalan/BNCT can preserve the functions of vocalization, swallowing, mastication,

[xxx] A global phase III study conducted to compare the efficacy and safety of nivolumab and an investigator-selected drug (cetuximab, methotrexate, or docetaxel hydrate) in patients with recurrent or metastatic head and neck squamous cell carcinoma of oral, oropharyngeal, hypopharyngeal, or laryngeal origin who showed disease progression or recurrence within 6 months after the completion of platinum-based chemotherapy (including radical or postoperative chemoradiotherapy).

respiration etc. The treatment is thus expected to increase QOL of patients, which is of clinical significance. Therefore, the response rate was selected as the primary endpoint in Study 002.

In Study 002, the response rate [90% CI] was 71.4% [51.3%, 86.8%], with the lower limit exceeding the prespecified threshold response rate [see Section 6.A.(2)]. Table 14 shows the results classified by tissue type ([a] squamous cell carcinoma, [b] non-squamous cell carcinoma). No clear difference was observed in the response rate between these tissue types. Based on the above, borofalan/BNCT is expected to be effective in the patient population in Study 002, regardless of tissue type ([a] squamous cell carcinoma, [b] non-squamous cell carcinoma).

Table 14. Best overall response and response rate by tissue type ([a] squamous cell carcinoma, [b] non-squamous cell carcinoma) (RECIST Ver.1.1, efficacy analysis population, BICR assessment, data cut off on [redacted])

Best overall response	n (%)	
	(a) Patients with squamous cell carcinoma (N = 8)	(b) Patients with non-squamous cell carcinoma (N = 13)
CR	4 (50.0)	1 (7.7)
PR	2 (25.0)	8 (61.5)
SD	1 (12.5)	4 (30.8)
PD	0	0
NE	1 (12.5)	0
Response (CR + PR) (response rate [90% CI*] (%))	6 (75.0 [40.0, 95.4])	9 (69.2 [42.7, 88.7])

* Clopper-Pearson method

PMDA's view:

Since Study 002 was an open-label, uncontrolled study without long-term data, there are limitations to evaluating, based on the results of the study, the efficacy of borofalan/BNCT in patients with unresectable, locally advanced or locally recurrent head and neck cancer. However, taking account of the review in Section "6.B.(2).1) Clinical positioning" and of the following points, PMDA considers that borofalan/BNCT has showed a certain level of efficacy in these patients:

- Localized lesions in patients with unresectable, locally advanced or locally recurrent head and neck cancer may severely impair QOL of patients by causing dysphagia, malnutrition, airway stenosis, aspiration, fistulization, etc. Localized control of the lesions is considered to have a certain level of clinical significance.

- In Study 002, patients showed a certain level of response to borofalan/BNCT.

6.B.(3) Safety [for adverse events, see Section "6.C Adverse events, etc. observed in clinical studies"]

Based on the review described in the sections below, PMDA considers that particular attention should be paid to the following adverse events when administering borofalan/BNCT to patients with unresectable, locally advanced or locally recurrent head and neck cancer: dysphagia, brain abscess, skin disorder, crystal urine, cataract, and carotid haemorrhage.

Attention should be paid to the above adverse events in using borofalan/BNCT. However, PMDA has concluded that borofalan/BNCT is tolerable provided that appropriate actions, such as monitoring and

controlling of adverse events, are taken by physicians with adequate knowledge and experience in cancer chemotherapy.

6.B.(3).1) Safety profile

The applicant's explanation about the safety profile of borofalan/BNCT, based on the safety information obtained from Studies 002 and 001:

Table 15 shows the outline of safety in Studies 002 and 001.

Table 15. Outline of safety (Studies 002 and 001)

	n (%)	
	Study 002	Study 001
	N = 21	N = 9
All adverse events	21 (100)	9 (100)
Grade ≥3 adverse events	18 (85.7)	3 (33.3)
Adverse events leading to death	0	0
Serious adverse events	1 (4.8)	1 (11.1)
Adverse events leading to discontinuation of borofalan/BNCT	0	0

In Study 002, all-grade adverse events with an incidence of ≥20% were alopecia in 19 patients (90.5%), amylase increased in 18 patients (85.7%), nausea in 17 patients (81.0%), dysgeusia in 15 patients (71.4%), parotitis and decreased appetite in 14 patients (66.7%) each, stomatitis in 13 patients (61.9%), vomiting in 10 patients (47.6%), malaise, thirst, and radiation skin injury in 9 patients (42.9%) each, conjunctivitis and sialoadenitis in 7 patients (33.3%) each, blood prolactin abnormal and blood prolactin increased in 6 patients (28.6%) each, and constipation in 5 patients (23.8%). Grade ≥3 adverse events were amylase increased in 16 patients (76.2%), lymphopenia, lymphocyte count decreased, stomatitis, brain abscess,[xxxi] and radiation skin injury in 1 patient (4.8%) each. Brain abscess[xxxi] in 1 patient (incidence 4.8%) was the only serious adverse event observed, and its causal relationship to borofalan/BNCT could not be ruled out. No adverse events led to death or discontinuation of borofalan/BNCT.

In Study 001, all-grade adverse events reported by ≥3 patients were haematuria in 9 patients (100%), malaise and alopecia in 8 patients (88.9%) each, blood prolactin abnormal in 7 patients (77.8%), face oedema, amylase increased, C-reactive protein increased, hypoalbuminaemia, and decreased appetite in 6 patients (66.7%) each, nausea, stomatitis, and lymphopenia in 5 patients (55.6%) each, conjunctivitis, hyperglycaemia, proteinuria, laryngeal inflammation, and hypertension in 4 patients (44.4%) each, anaemia, lacrimation increased, constipation, application site erythema, influenza like illness, pain, pyrexia, radiation skin injury, hypertriglyceridaemia, hyponatraemia, headache, urine abnormality, and pharyngeal inflammation in 3 patients (33.3%) each. Grade ≥3 adverse events were lymphocyte count decreased in 3 patients (33.3%), anaemia, dysphagia,[xxxii] upper gastrointestinal haemorrhage,

[xxxi] A 50-year-old woman. On Day 54 after borofalan/BNCT, she had disturbances in consciousness and visited another hospital, where she was diagnosed with cerebral edema. On Day 55, external decompression was performed on the cerebral edema, which resulted in discharge of pus from inside the cranium. This confirmed that the disturbed consciousness had been caused by cerebral abscess. Cerebral abscess drainage was performed and treatment with antibiotics was started. On Day 265, findings associated with cerebral abscess disappeared, and cerebral abscess was considered as "resolved."

[xxxii] A 68-year-old woman. From 26 days before the enrollment in the study, she had dysphagia (Grade 2) as a concurrent illness. On Day 6 after borofalan/BNCT, dysphagia worsened (Grade 3). Contrast CT on Day 32 showed a shrinkage of the irradiated lesion (left posterior oropharyngeal wall). However, dysphagia worsened due to a new lesion which developed from outside the irradiated area and, on Day 95, the patient died of disease progression.

hypercalcaemia, hypoalbuminaemia, pharyngeal haemorrhage, pharyngeal inflammation, laryngeal inflammation, and hypertension in 1 patient (11.1%) each. Dysphagia[xxxii] in 1 patient (incidence 11.1%) was the only serious adverse event observed and its causal relationship to borofalan/BNCT could not be ruled out. No adverse events led to death or discontinuation of borofalan/BNCT.

PMDA asked the applicant to explain the mechanism of increase in amylase by borofalan/BNCT and actions that should be taken in response to this event.

The applicant's response:
(a) Both in Studies 002 and 001, the observed increase in amylase was due to an increase in salivary gland-type amylase, and (b) salivary gland injury with radiation leads to an increase in salivary gland-type amylase (*Strahlenther Onkol*. 1990;166:688-95); this suggests that the observed increase in amylase was due to borofalan/BNCT. However, an increase in amylase is considered to be well tolerated because, in both studies, (a) the increase in salivary gland-type amylase was transient, and no objective findings associated with the increase in amylase were observed, and (b) the increased amylase resolved during follow-up without any additional treatment.

PMDA's view:
In treatment with borofalan/BNCT, attention should be paid to the serious adverse events and Grade ≥3 adverse events that occurred in Studies 002 and 001 as well as adverse events that occurred frequently in the studies. Information on the incidence of these events should be provided appropriately to healthcare professionals. Because of the extremely limited safety information available on borofalan/BNCT in patients with head and neck cancer, relevant information should be collected continuously after the market launch and new information should be provided to healthcare professionals promptly when it becomes available.

In the following sections, PMDA reviewed the safety of borofalan/BNCT, based on the safety results in Studies 002 and 001, focusing on serious adverse events for which a causal relationship to borofalan/BNCT could not be ruled out and on Grade ≥3 adverse events occurring frequently in the studies.

6.B.(3).2) Dysphagia

The applicant's explanation about dysphagia caused by borofalan/BNCT:
As for dysphagia, the applicant collected events[xxxiii] classified as the following Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs): "endoscopic swallowing evaluation," "endoscopic swallowing evaluation abnormal," "swallow study," "swallow study abnormal," "odynophagia," "dysphagia," "dysphagia lusoria," "malignant dysphagia," "radiation dysphagia," "aerophagia," or "sideropenic dysphagia."

In Study 002, all-grade dysphagia was reported in 1 of 21 patients (4.8%, Grade 1 odynophagia). There were no cases of serious dysphagia or dysphagia leading to death or discontinuation of borofalan/BNCT.

[xxxiii] MedDRA ver. 19.0 was used in Study 002 and ver. 18.1 in Study 001.

In Study 001, all-grade dysphagia was observed in 1 of 9 patients (11.1%, Grade 3 dysphagia). Serious dysphagia was observed in 1 of 9 patients (11.1%, dysphagia[xxxii]). Its causal relationship to borofalan/BNCT could not be ruled out. There were no cases of dysphagia leading to death or discontinuation of borofalan/BNCT.

The time to the first onset of dysphagia was 5 days in Study 002 and 7 days in Study 001.

PMDA's view:
Serious dysphagia for which a causal relationship to borofalan/BNCT could not be ruled out was observed in a submitted clinical study, warranting caution against dysphagia in treatment with borofalan/BNCT. Information on the incidences of dysphagia in clinical studies should be provided appropriately to healthcare professionals using the package insert, to raise cautions.

6.B.(3).3 Brain abscess

The applicant's explanation about brain abscess caused by borofalan/BNCT:
As for brain abscess, the applicant collected events[xxxiii] classified as MedDRA PT "amoebic brain abscess" or "brain abscess." No brain abscess was observed in Study 001.

In Study 002, all-grade brain abscess was observed in 1 of 21 patients (4.8%, Grade 3 brain abscess). Serious brain abscess was observed in 1 of 21 patients (4.8%, brain abscess in 1 patient[xxxi]), and its causal relationship to borofalan/BNCT could not be ruled out. There were no cases of brain abscess leading to death or discontinuation of borofalan/BNCT.

PMDA's view
Serious brain abscess for which a causal relationship to borofalan/BNCT could not be ruled out was observed in a submitted clinical study, warranting caution against brain abscess in treatment with borofalan/BNCT. Information on the incidences of brain abscess in clinical studies should be provided appropriately to healthcare professionals using the package insert, to raise cautions.

6.B.(3).4 Radiation skin injury

The applicant's explanation about radiation skin injury caused by borofalan/BNCT:
As for radiation skin injury, the applicant collected events[xxxiii] classified as MedDRA PT "radiation skin injury" or "recall phenomenon."

In Study 002, all-grade radiation skin injury was observed in 9 of 21 patients (42.9%, radiation skin injury in 9 patients). Grade ≥3 radiation skin injury was observed in 1 of 21 patients (4.8%, radiation skin injury in 1 patient). There were no cases of serious radiation skin injury or radiation skin injury leading to death or discontinuation of borofalan/BNCT.

In Study 001, all-grade radiation skin injury was observed in 3 of 9 patients (33.3%, radiation skin injury in 3 patients). There were no cases of Grade ≥3 radiation skin injury, serious radiation skin injury, or radiation skin injury leading to death or discontinuation of borofalan/BNCT.

The median time (range) to the first onset of radiation skin injury was 8 days (2-30 days) in Study 002 and 3 days (2-8 days) in Study 001.

PMDA's view
In the submitted clinical studies, skin disorder was observed at a certain incidence following administration of borofalan/BNCT. Also, skin disorder is a known risk of irradiation, warranting caution against skin disorder in treatment with borofalan/BNCT. Therefore, information on the incidence of skin disorder in clinical studies should be provided appropriately to healthcare professionals using the package insert, to raise cautions.

6.B.(3).5) Renal dysfunction

The applicant's explanation about renal dysfunction caused by borofalan/BNCT:
As for renal dysfunction, the applicant collected events classified as MedDRA system organ class (SOC) "renal and urinary disorders" or MedDRA high level group term (HLGT) "renal and urinary tract investigations and urinalyses."

Table 16 shows the incidence of renal dysfunction in Studies 002 and 001.

Table 16. Incidence of renal dysfunction (Studies 002 and 001)

PT*	n (%)			
	Study 002 (N = 21)		Study 001 (N = 9)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Renal dysfunction	2 (9.5)	0	9 (100)	0
Haematuria	2 (9.5)	0	9 (100)	0
Dysuria	2 (9.5)	0	0	0
Proteinuria	0	0	4 (44.4)	0
Urine abnormality	0	0	3 (33.3)	0
Crystal urine	0	0	2 (22.2)	0
Urinary tract pain	0	0	2 (22.2)	0
Cystitis noninfective	0	0	2 (22.2)	0
Urine output decreased	0	0	1 (11.1)	0
Neurogenic bladder	0	0	1 (11.1)	0

* The MedDRA version19.0 was used in Study 002 and version 18.1 in Study 001.

In Studies 002 and 001, there were no cases of serious renal dysfunction or renal dysfunction leading to death or discontinuation of borofalan/BNCT.

The median time (range) to the first onset of renal dysfunction was 1 day (1-1 day) in Study 002 and 1 day (1-50 days) in Study 001.

PMDA asked the applicant to explain the mechanism of borofalan/BNCT-induced renal dysfunction and how to prevent it.

The applicant's response:
In toxicity studies, rats showed colored urine and dogs showed precipitates supposedly consisting of borofalan in urinary crystalline sediment. These crystals are likely to induce renal dysfunction such as hematuria.

In Study 001, water intake before borofalan/BNCT was prohibited for the purpose of accurate pharmacokinetics (PK) measurement. In Study 002, in contrast, water intake after borofalan/BNCT was recommended as necessary in order to prevent renal dysfunction induced by borofalan crystals in urine. The percentage of patients who experienced renal dysfunction was lower in Study 002 than in Study 001, presumably as a result of water intake. These results suggest that renal dysfunction is preventable by drinking water after borofalan/BNCT, as appropriate.

PMDA's view:
In the submitted clinical studies, all events of borofalan/BNCT-induced renal dysfunction was Grade ≤2. However, attention should be paid to adverse events associated with urinary crystals in treatment with borofalan/BNCT, because (1) borofalan/BNCT caused renal dysfunction supposedly associated with urinary crystals, at a certain incidence, and (2) in Study 002, taking a preventive action against urinary crystals was recommended. Therefore, the package insert should state that urinary crystals may occur in patients treated with borofalan/BNCT, and healthcare professionals should be appropriately informed, via the package insert, about the preventive action recommended in Study 002.

6.B.(3).6) Cataract

The applicant's explanation about borofalan/BNCT-induced cataract:
As for cataract, the applicant collected events[xxxiii] classified as MedDRA PT "cataract" or "radiation cataract." Cataract was not observed in Study 001.

In Study 002, all-grade cataract was observed in 2 of 21 patients (9.5%, cataract in 2 patients). There were no cases of Grade ≥3 cataract, serious cataract, or cataract leading to death or discontinuation of borofalan/BNCT.

The median time (range) to the first onset of cataract in Study 002 was 67 days (34-100 days).

PMDA's view:
In a submitted clinical study, cataract was observed at a certain incidence following administration of borofalan/BNCT, and cataract is a known risk of radiation exposure. Therefore, attention should be paid to borofalan/BNCT-induced cataract. Information on the incidence of cataract in clinical studies should be provided appropriately to healthcare professionals using the package insert, to raise cautions.

6.B.(3).7) Safety in patients with tumor infiltration into carotid artery

The applicant's explanation about the safety in patients with tumor infiltration into carotid artery:
Bleeding from carotid artery occurred after borofalan/BNCT in patients who had tumor infiltration into carotid artery or to a wide area of skin after radiotherapy (*Appl Radiat Isot*. 2015;106:202-6). Therefore, the package insert will include a statement that borofalan/BNCT may cause carotid haemorrhage in patients with tumor infiltration into carotid artery, to raise cautions.

Since the carotid artery becomes fragile after radiotherapy, patients with circumferential tumor infiltration to the carotid artery are extremely likely to experience carotid haemorrhage after receiving borofalan/BNCT. Therefore, borofalan/BNCT will be contraindicated in this patient group.

PMDA's view:
PMDA generally accepted the applicant's explanation. Given the mechanism of action of borofalan/BNCT, carotid haemorrhage is likely to occur and, once it occurs, it may become serious. Therefore, attention should be paid to carotid haemorrhage. To raise cautions, healthcare professionals should be appropriately informed, via the package insert, that carotid haemorrhage may occur in patients treated with borofalan/BNCT.

6.B.(3).8) Safety in patients within 90 days after receiving the last RT at the site of lesion

The applicant's explanation about the safety in patients within <90 days after receiving the last RT at the site of lesion:
Patients within <90 days after receiving the last RT at the site of lesion were excluded from Study 002 for the following reasons: (a) The efficacy evaluation of RT may have not been established, and (b) cumulative dose of RT may affect the safety of borofalan/BNCT. Thus, clinical safety data on borofalan/BNCT in this patient group are unavailable. However, because the cumulative dose in the normal tissue after RT cannot be accurately measured, whether to repeat radiotherapy is determined based on the clinical symptoms of organs in the radiation field as well as on the cumulative dose and the tolerance dose of organs in the radiation field; this suggests that it is acceptable to administer borofalan/BNCT to (a) patients who did not respond to RT and (b) patients without Grade ≥3 adverse events in the radiation field.

PMDA's view:
PMDA generally accepted the explanation of the applicant. However, since no clinical study data are available on the efficacy and safety of borofalan/BNCT in patients who received the last RT on the lesion site less than 90 days before, healthcare professionals should be appropriately informed, via the package insert, that this patient group was excluded from Study 002.

6.B.(3).9) Safety in patients who received radiotherapy in a total dose of ≥75 Gy at the lesion site

The applicant's explanation about the safety in patients who received radiotherapy in a total dose of ≥75 Gy at the lesion site:
Since radiotherapy in a total dose of ≥75 Gy at a lesion site exceeds the standard radiation dose, patients who had received such a treatment were excluded from Study 002. Therefore, no efficacy or safety data of borofalan/BNCT in this patient group are available. However, because whether to repeat radiotherapy is determined based on the cumulative dose, tolerance dose, and clinical symptoms of the organs within the radiation field, borofalan/BNCT in these patients is considered to be acceptable although clinical symptoms of organs within the radiation field should be carefully monitored.

PMDA's view:
PMDA generally accepted the explanation of the applicant. However, since no clinical study data are available on the efficacy and safety of borofalan/BNCT in patients who had received radiotherapy in a

total dose of ≥75 Gy at the lesion site, healthcare professionals should be appropriately informed, via the package insert, that this patient group was excluded from Study 002.

6.B.(3).10) Safety in patients without mucous membrane on the irradiation axis within the range of 1.0 to 5.0 cm from the skin surface

The applicant's explanation about the safety in patients without mucous membrane on the irradiation axis within the range of 1.0 to 5.0 cm from the skin surface:

The incidence of mucositis in patients receiving RT for head and neck cancer was 80% and the incidence of Grade 3 or 4 mucositis was 39% (*Radiother Oncol.* 2003;66:253-62). In Study 001, the recommended radiation dose of borofalan/BNCT was 12 Gy-Eq., based on the tolerance dose of the mucous membrane [see Section 6.A.(1)]. Based on the above, in Study 002, patients without mucous membrane on the irradiation axis within the range of 1.0 to 5.0 cm from the skin surface were excluded in order to accurately evaluate the occurrence of adverse events in mucous membrane. As a result, efficacy and safety data of borofalan/BNCT in this patient group are unavailable. However, since the radiation dose applied to the mucous membrane of these patients will be less than 12 Gy-Eq., whether to administer borofalan/BNCT to these patients can be determined based on the cumulative dose and the tolerance dose in the normal tissue other than mucous membrane within the radiation field.

PMDA's view:

PMDA generally accepted the explanation of the applicant. However, since no clinical data are available on the efficacy and safety of borofalan/BNCT in patients without mucous membrane on the irradiation axis within the range of 1.0 to 5.0 cm from the skin surface, healthcare professionals should be appropriately informed, via the package insert, that this patient group was excluded from Study 002.

6.B.(4) Indications

The proposed indications for borofalan/BNCT were "Unresectable locally recurrent head and neck cancer" and "Unresectable advanced head and neck non-squamous cell carcinoma." The Precautions Concerning Indication section included the following statement:

Eligible patients must be selected by physicians with a full understanding of the information presented in the Clinical Studies section and of the efficacy and safety of borofalan.

In view of the reviews in Sections "6.B.(2) Clinical positioning and efficacy" and "6.B.(3) Safety" and the discussion described in the following section, PMDA concluded that the indication should be "Unresectable, locally advanced or locally recurrent head and neck cancer," and that Precautions Concerning Indication section should include the following precautionary statements:

- The standard therapy such as chemoradiotherapy, if feasible, should be performed in preference to borofalan/BNCT.

- The efficacy and safety of borofalan as adjuvant therapy have not been established.

- Eligible patients must be selected by physicians with a full understanding of the information presented in the "Clinical Studies" section and of the efficacy and safety of borofalan.

6.B.(4).1) Target patient population for borofalan/BNCT and indications

The applicant's explanation about target patients for borofalan/BNCT and indications:
On the basis of the results of Study 002 [see Sections 6.A.(2) and 6.B.(2)], the applicant considers that borofalan/BNCT is positioned as a treatment option for patients with unresectable, locally advanced or locally recurrent head and neck cancer.

Study 002 did not include patients with unresectable locally advanced head and neck squamous cell carcinoma, and therefore clinical data of borofalan/BNCT in these patients have not been obtained. However, borofalan/BNCT is a treatment option for them as well because current treatment for them is similar to that for patients with unresectable locally recurrent head and neck squamous cell carcinoma.

Based on the above, the applicant has proposed the following indications for borofalan/BNCT: "Unresectable locally recurrent head and neck cancer" and "Unresectable advanced head and neck non-squamous cell carcinoma." Details of patients treated in Study 002 will be described in the Clinical Studies section of the package insert and the following precautionary statement will be included in the Precautions Concerning Indication section.

- Eligible patients must be selected by physicians with a full understanding of the information presented in the Clinical Studies section and of the efficacy and safety of borofalan.

In addition, Clinical data of borofalan/BNCT have not been obtained from patients with metastatic head and neck cancer or patients with head and neck cancer eligible for adjuvant therapy after surgery. Borofalan/BNCT is not recommended for these patients.

PMDA's view:
PMDA generally accepted the applicant's explanation. However, the efficacy of borofalan/BNCT was evaluated mainly based on the response rate in Study 002, and no information on the survival benefit is available. Therefore, patients eligible for the standard therapy (including local treatments such as CRT) should be treated with the standard therapy in preference to borofalan/BNCT; this should be communicated to physicians to urge caution.

Also, since clinical data on the efficacy and safety of borofalan/BNCT as an adjuvant therapy are unavailable, borofalan/BNCT is not recommended for patients requiring adjuvant therapy. This caution should be included in the Precautions Concerning Indication section.

On the basis of the above review, the indication should be "unresectable, locally advanced or locally recurrent head and neck cancer." Details of patients treated in Study 002 should be described in the "Clinical Studies" section of the package insert, and the following precautionary statements should be included in the Precautions Concerning Indication section.

- The standard therapy such as chemoradiotherapy, if feasible, should be performed in preference to borofalan/BNCT.

- The efficacy and safety of borofalan as adjuvant therapy have not been established.

- Eligible patients must be selected by physicians with a full understanding of the information presented in the "Clinical Studies" section and of the efficacy and safety of borofalan.

6.B.(5) Dosage and administration

The proposed dosage regimen for borofalan was "Usually, for adults, a single dose of 500 mg/kg of borofalan (^{10}B) is administered as an intravenous infusion over 3 hours, at the rate of 200 mg/kg/h during the first 2 hours, then at 100 mg/kg/h during the last 1 hour. Irradiation of neutron beams to the cancer area is started at 2 hours after the start of intravenous infusion. The intravenous infusion is terminated at the end of irradiation. (In a patient weighing 60 kg, 800 mL of Steboronine solution is intravenously infused over 2 hours, followed by intravenous infusion of 200 mL over 1 hour.)" The following statements were included in the Precautions Concerning Dosage and Administration section of the proposed package insert:

- The efficacy and safety of borofalan in combination with other antineoplastic agents have not been established.

- Neutron beam irradiation should be performed using a neutron beam-irradiating device manufactured by Sumitomo Heavy Industries, Ltd. Read the instructions for use and the instruction manual of the device before using the neutron beam-irradiating device.

In view of the reviews in Sections "6.B.(2) Clinical positioning and efficacy" and "6.B.(3) Safety" and the discussion described in the following section, PMDA concluded that the dosage and administration for borofalan should be "Usually, for adults, borofalan (^{10}B) is administered as an intravenous infusion over 2 hours at the rate of 200 mg/kg/h, followed by irradiation of neutron beams to the cancer area. During the irradiation, borofalan (^{10}B) is intravenously infused at the rate of 100 mg/kg/h." The following precautionary statements should be included in the Precautions Concerning Dosage and Administration section:

- The efficacy and safety of borofalan in combination with other antineoplastic agents have not been established.

- Neutron beam irradiation should be performed using a neutron beam-irradiating device manufactured by Sumitomo Heavy Industries, Ltd.

6.B.(5).1) Dosage regimen for borofalan

The applicant's rationale for the dosage regimen of borofalan:

Study 002 was conducted using the dosage regimen chosen based on the study results listed below, and results of Study 002 suggested the efficacy and safety of borofalan/BNCT in patients treated in this study. Therefore, the applicant has proposed the following dosage and administration for borofalan based on the dosage regimen used in Study 002: "Usually, for adults, a single dose of 500 mg/kg of borofalan (^{10}B) is administered as an intravenous infusion over 3 hours, at the rate of 200 mg/kg/h during the first 2 hours, then at 100 mg/kg/h during the last 1 hour. Irradiation of neutron beams to the cancer area is started at 2 hours after the start of intravenous infusion. The intravenous infusion is terminated at the end of irradiation. (In a patient weighing 60 kg, 800 mL of Steboronine solution is intravenously infused over 2 hours, followed by intravenous infusion of 200 mL over 1 hour.)" The device to be used for

neutron beam irradiation will be specified in the Precautions Concerning Dosage and Administration section.

- PK data of boron obtained from single-dose studies in rats, etc., were used to estimate boron concentration in whole blood[xxxiv] in humans receiving a single intravenous administration of borofalan at the rate of 200 mg/kg/h during the first 2 hours then at 100 mg/kg/h. Based on the results, it was estimated that boron concentration in whole blood from 2 to 3 hours after the start of administration was maintained roughly at 20 ppm, a concentration necessary for obtaining the therapeutic effect of borofalan/BNCT.

- In Study 001, boron concentration in whole blood was >20 ppm when a single dose of borofalan (500 mg/kg) was administered intravenously at the rate of 200 mg/kg/h during the first 2 hours and then at 100 mg/kg/h

.

- Borofalan/BNCT was well tolerated in Study 001.

No clinical data are available on the efficacy and safety of borofalan in combination with other antineoplastic agents. This will be mentioned in the Precautions Concerning Dosage and Administration section.

PMDA's view:
No dosage regimens other than that used in Study 002 were investigated in clinical studies, leaving room for further investigations. This being said, PMDA largely accepted the rationale presented by the applicant, because Study 002 demonstrated the clinical usefulness of borofalan at the following dosage regimen: (a) Borofalan was administered intravenously at the rate of 200 mg/kg/h during the first 2 hours and then at 100 mg/mg/h, and (b) the tumor was irradiated with a single dose of neutron beam using BNCT30 for a maximum of 60 minutes starting at 2 hours after the start of administration of borofalan. The Precautions Concerning Dosage and Administration section of the proposed package insert includes a statement that the instructions for use and the instruction manual for the neutron beam-irradiating device must be read before administering borofalan. This statement is unnecessary because this is a common caution not requiring special mention in the treatment with borofalan.

Based on the above, the dosage and administration of borofalan/BNCT should be "Usually, for adults, borofalan (^{10}B) is administered as an intravenous infusion over 2 hours at the rate of 200 mg/kg/h, followed by irradiation of neutron beams to the cancer area. During the irradiation, borofalan (^{10}B) is intravenously infused at the rate of 100 mg/kg/h." Also, the following precautionary statements should be included in the Precautions Concerning Dosage and Administration section:

- The efficacy and safety of borofalan in combination with other antineoplastic agents have not been established.

- Neutron beam irradiation should be performed using a neutron beam-irradiating device manufactured by Sumitomo Heavy Industries, Ltd.

[xxxiv] The boron concentration in whole blood thus estimated was roughly the same as that estimated from PK parameters of boron in humans receiving borofalan (*Appl Radiat Isot*. 2004;61:1095-100, etc.)

6.B.(6) Post-marketing investigations

The applicant's explanation about the plan of post-marketing investigations:
In order to evaluate the safety, etc., of borofalan in post-marketing clinical use, the applicant plans to conduct post-marketing surveillance covering all patients treated with borofalan.

The safety specification of the surveillance includes events requiring caution in treatment with borofalan/BNCT (dysphagia, brain abscess, radiation skin injury, cataract, crystal urine, arterial haemorrhage [carotid haemorrhage associated with tumor shrinkage/necrosis], osteoradionecrosis/osteomyelitis, eye disorder, and central nervous system injuries), as well as the safety in patients with renal impairment and patients with cardiac impairment.

The target sample size was set at 100 patients treated with borofalan/BNCT based on the incidence, in Studies 002 and 001, of events included in the safety specification of the surveillance.

The observation period was set at 3 years from the start of administration of borofalan, based on the time to onset, in Studies 002 and 001, of events included in the safety specification of the surveillance, and based on published reports (*Appl Rad Isot.* 2015;106:202-6 and *Int J Rad Oncol Biol Phys.* 2012;82:e67-75, etc.).

PMDA's view:
Because of the extremely limited safety information available for Japanese patients treated with borofalan, the applicant should conduct post-marketing surveillance covering all borofalan-treated patients for a certain period after the market launch, to collect safety information promptly without bias, and to provide safety information thus obtained to healthcare professionals without delay.

Based on the review in Section "6.B.(3) Safety," safety specification of the surveillance should include dysphagia, brain abscess, severe skin disorder, crystalluria, cataract, and carotid haemorrhage.

The planned sample size and the observation period should be reconsidered based on the incidence of events to be included in safety specification of the surveillance.

6.C Adverse events etc. observed in clinical studies

Death reported in the safety evaluation data were detailed in Section "6.A Summary of the submitted data." The major non-fatal adverse events are summarized below.

6.C.(1) Japanese phase I study (Study 001)

Adverse events were reported in 6 of 6 patients (100%) in the 10 Gy-Eq group and 3 of 3 patients (100%) in the 12 Gy-Eq group. Adverse events for which a causal relationship to borofalan/BNCT could not be ruled out were observed in 6 of 6 patients (100%) in the 10 Gy-Eq group and in 3 of 3 patients (100%) in the 12 Gy-Eq group. The following adverse events occurred with an incidence of ≥50% in either group:

The 10 Gy-Eq group:

Malaise, haematuria, and alopecia in 6 patients (100%) each, blood prolactin abnormal in 5 patients (83.3%), face oedema, amylase increased, C-reactive protein increased, hyperglycaemia, decreased appetite, and hypertension in 4 patients (66.7%) each, constipation, nausea, stomatitis, pyrexia, radiation skin injury, lymphocytes decreased, hypoalbuminaemia, and proteinuria in 3 patients (50.0%) each.

The 12 Gy-Eq group:
Hyponatraemia and haematuria in 3 patients (100%) each, nausea, stomatitis, application site erythema, face oedema, malaise, conjunctivitis, amylase increased, blood prolactin abnormal, C-reactive protein increased, lymphocyte count decreased, hyponatraemia, decreased appetite, pharyngeal inflammation, laryngeal inflammation, and alopecia in 2 patients (66.7%) each.

A serious adverse event was observed in 1 of 6 patients (16.7%) in the 10 Gy-Eq group, with no serious adverse events in the 12 Gy-Eq group. The serious adverse event was dysphagia in 1 patient (16.7%). Its causal relationship to borofalan/BNCT could not be ruled out.

There were no adverse events leading to discontinuation borofalan/BNCT.

6.C.(2) Japanese phase II study (Study 002)

Adverse events were observed in 21 of 21 patients (100%). Adverse events for which a causal relation to borofalan/BNCT could not be ruled out were observed in 21 of 21 patients (100%). Adverse events with an incidence of ≥30% were alopecia in 19 patients (90.5%), amylase increased in 18 patients (85.7%), nausea in 17 patients (81.0%), dysgeusia in 15 patients (71.4%), parotitis and decreased appetite in 14 patients (66.7%) each, stomatitis in 13 patients (61.9%), vomiting in 10 patients (47.6%), malaise, thirst, and radiation skin injury in 9 patients (42.9%) each, and conjunctivitis and sialoadenitis in 7 patients (33.3%) each.

A serious adverse event was observed in 1 of 21 patients (4.8%). The serious adverse event was brain abscess in 1 patient (4.8%), and its causal relationship to borofalan/BNCT could not be ruled out.

There were no adverse events leading to discontinuation of borofalan/BNCT.

The summary of the PMDA's **Review Report (2) of Steboronine**, the boron drug to be used with NeuCure (summary of comments made during the Expert Discussion and subsequent review by PMDA) are described below.

[1] Clinical positioning and efficacy

In the Japanese phase II study (Study 002) in (a) post-CRT or -RT patients with unresectable locally recurrent head and neck squamous cell carcinoma and (b) patients with unresectable, locally advanced or locally recurrent head and neck non-squamous cell carcinoma, the response rate [90% CI] was 71.4% [51.3%, 86.8%] (15 of 21 of patients).

As a result of its review on Section "6.B.(2) Clinical positioning and efficacy" of the Review Report (1), PMDA concluded that borofalan has shown a certain level of efficacy in patients with unresectable, locally advanced or locally recurrent head and neck cancer and that borofalan/BNCT is positioned as a treatment option for these patients, taking account of the above response rate and the following:

- Localized lesions in patients with unresectable, locally advanced or locally recurrent head and neck cancer may cause various pathologies such as dysphagia, malnutrition, airway constriction, aspiration, and fistulation, thereby severely reducing their quality of life (QOL). Locally controlling the lesions is clinically meaningful.

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion.

[2] Safety

As a result of the review on Section "6.B.(3) Safety" of the Review Report (1), PMDA concluded that special attention should be paid to the following adverse events when administering borofalan/BNCT to patients with unresectable, locally advanced or locally recurrent head and neck cancer: dysphagia, brain abscess, skin disorder, crystal urine, cataract, and carotid haemorrhage.

PMDA also concluded that although attention should be paid to the above-mentioned adverse events during treatment with borofalan/BNCT, the treatment is tolerable if adverse events are monitored and controlled and other appropriate actions are taken by physicians with adequate knowledge and experience in cancer chemotherapy.

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion.

[3] Indication

As a result of the review on Section "6.B.(4) Indications" of the Review Report (1), PMDA concluded that the indication should be "unresectable, locally advanced or locally recurrent head and neck cancer," that details of patients treated in Study 002 should be described in the Clinical Studies section of the package insert, and that the following precautionary statements should be included in the Precautions Concerning Indication section:

Precautions Concerning Indication

- The standard therapy such as chemoradiotherapy, if feasible, should be performed in preference to borofalan/BNCT.

- The efficacy and safety of borofalan as adjuvant therapy have not been established.

- Eligible patients must be selected by physicians with a full understanding of the information presented in the Clinical Studies section and of the efficacy and safety of borofalan.

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion.

Based on the above, PMDA instructed the applicant to use the above wording for Indication and include the above precautionary statements in the Indication and Precautions Concerning Indication section. The applicant agreed.

[4] Dosage and administration

As a result of the review on Section "6.B.(5) Dosage and administration" of the Review Report (1), PMDA concluded that the dosage and administration for borofalan should be "Usually, for adults, borofalan (^{10}B) is administered as an intravenous infusion over 2 hours at the rate of 200 mg/kg/h, followed by irradiation of neutron beams to the cancer area. During the irradiation, borofalan (^{10}B) is intravenously infused at the rate of 100 mg/kg/h," and that the following precautionary statements should be included in the Precautions Concerning Dosage and Administration section:

Precautions Concerning Dosage and Administration

- The efficacy and safety of borofalan in combination with other antineoplastic agents have not been established.

- Neutron beam irradiation should be performed using a neutron beam-irradiating device manufactured by Sumitomo Heavy Industries, Ltd.

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion.

Based on the above, PMDA instructed the applicant to use the above wording for Dosage and Administration and include the above precautionary statements in the Precautions Concerning Dosage and Administration section. The applicant agreed.

[5] Risk management plan (draft)

In order to evaluate the safety, etc., of borofalan in post-marketing clinical use, the applicant plans to conduct post-marketing surveillance covering all patients treated with borofalan, with the planned sample size of 100 patients receiving borofalan/BNCT and the observation period of 3 years.

As a result of the review on Section "6.B.(6) Post-marketing investigations" of the Review Report (1), PMDA concluded that the applicant should conduct post-marketing surveillance covering all borofalan-treated patients for a certain period after the market launch, to collect safety information promptly without bias, and to provide safety information thus obtained to healthcare professionals without delay. Also, PMDA concluded that the surveillance plan should be designed as follows:

- Safety specification of the surveillance should include dysphagia, brain abscess, severe skin disorder, crystalluria, cataract, and carotid haemorrhage.

- The planned sample size and the observation period should be reconsidered based on the incidence of events to be included in safety specification of the surveillance.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion. At the same time, the following comment was raised by the expert advisors:

- The clinical studies have provided only limited information on the safety after a certain period of time following the administration of borofalan/BNCT, and late toxicity is a known risk of existing RT. Therefore, information on late toxicity should also be collected in the surveillance.

Based on the above discussion, PMDA instructed the applicant to revise the surveillance plan.

The applicant's response:
- Safety specification will include dysphagia, brain abscess, severe skin disorder, crystalluria, cataract, carotid haemorrhage, and late toxicities.

- The planned sample size and the observation period will be 150 patients and 3 years, respectively, based on the feasibility and the incidence of events included in the safety specification.

PMDA accepted the explanation of the applicant.

In view of the discussion above, PMDA has concluded that the risk management plan (draft) should include the safety specification presented in Table 17, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Tables 18 and 19.

Table 17. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Dysphagia • Brain abscess • Severe skin disorder • Crystalluria • Cataract • Carotid haemorrhage	None	• Later toxicity
Efficacy specification		
None		

Table 18. Summary of additional pharmacovigilance activities, efficacy surveillance and study, and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Efficacy surveillance and study	Additional risk minimization activities
• Early post-marketing phase vigilance • General use-results survey (all-case surveillance)	None	• Disseminate data gathered through early post-marketing phase vigilance

Table 19. Outline of post-marketing surveillance plan (draft)

Objective	To investigate the safety, etc. of borofalan in clinical use after the market launch
Survey method	All-case surveillance
Population	All patients treated with borofalan
Observation period	3 years
Planned sample size	150 (safety analysis population consisting of patients receiving borofalan/BNCT)
Main survey items	Safety specification: Dysphagia, brain abscess, severe skin disorder, crystalluria, cataract, carotid haemorrhage, and late toxicities Other main survey items: Patient characteristics (age, sex, disease stage, past illness, concurrent illness, etc.), use of borofalan, neutron beam irradiation, adverse events, etc.

In view of the Review Reports of Steboronine, the boron drug to be used with NeuCure, PMDA asked the applicant (Sumitomo Heavy Industries, Ltd.) to clarify Steboronine-related matters to be dealt with by the applicant as the manufacturer of NeuCure.

The applicant's response:

- The NeuCure-related information included in the package insert of Steboronine will be added to the instructions for use of NeuCure.

PMDA concluded that there was no particular problem with the applicant's response.

6.D NeuCure-specific matters in the clinical studies

6.D.(1) Malfunctions observed in clinical studies

The applicant's explanation about malfunctions of NeuCure observed in the clinical studies (Tables 20 and 21):

Table 20. Malfunction in the Phase I study

	Malfunction	Intervention	Malfunction-related injury	Safety measure to prevent the malfunction
1	The investigational device could not be started appropriately [redacted] at start-up of the device.	[redacted]	None	A procedure to confirm the soundness [redacted] prior to start-up was added.

Table 21. Malfunctions in the Phase II study

	Malfunction	Intervention	Malfunction-related injury	Safety measure to prevent the malfunction
1	The target was broken [redacted].	[redacted]	None	To prevent the recurrence of the malfunction, the risk analysis was reviewed and the following improvements were made. [redacted]
2	The proton beam current could not be [redacted] during irradiation.	[redacted]	None	A procedure to confirm [redacted] was added.
3	[redacted]	[redacted]	None	[redacted]

PMDA's view:

Malfunction 1 in the phase I study, and 1 and 3 in the phase II study are not clinically significant provided that the quality control of device is performed appropriately, because these malfunctions occurred during

inspection of the device and caused no injury in the patients. Malfunction 2 in the phase II study occurred during treatment, which resulted in a prolonged irradiation time in the patient. No noteworthy adverse event was reported after the completion of irradiation, and the malfunction appeared not to be clinically significant. For a safety measure to prevent the malfunction, a procedure to confirm [redacted] was added. By checking the output of the proton beam prior to treatment, the readiness of device for use in treatment can be ensured to prevent unstable irradiation to patients. There is no disagreement with the safety measure taken by the applicant.

PMDA concluded that there was no particular problem with the measures taken by the applicant to prevent the malfunctions observed in the clinical studies.

6.D.(2) Dose determination in clinical practice

PMDA asked the applicant to explain the appropriateness of the radiation dose in clinical use of NeuCure.

The applicant's explanation:

The dose of BNCT is determined as an equivalence dose. The CBE factor in L-BPA-mediated BNCT is 2.5 for skin tissue, 1.34 for brain tissue, and 4.0 for tumor tissue. Normal mucosal tissue has a high CBE factor of 4.9, indicating a higher sensitivity to radiation than tumor tissue. Almost all patients treated with conventional radiotherapy for head and neck cancer experienced mucositis. Approximately half the cases of mucositis were reported as Grade 3 or 4 adverse reactions. In particular, oral mucositis is a significant issue in radiotherapy for head and neck cancer. For the following reasons, therefore, the upper dose limit in clinical use of NeuCure for head and neck cancer was determined based on the dose in the oral, pharyngeal, or laryngeal mucosa:

- The primary sites of head and neck cancer are largely divided into the lips/oral cavity, nasal cavities/nasal sinuses, nasopharynx, oropharynx, hypopharynx, larynx, and salivary glands. Mucosa lines the lips/oral cavity, nasal cavities/nasal sinuses, nasopharynx, oropharynx, hypopharynx, and larynx.

- Normal mucosal cells have a shorter life than the cutaneous epithelium, acutely respond to radiation, and have a higher sensitivity to L-BPA-mediated BNCT.

- Conventional radiotherapy almost always causes mucositis in the oral cavity, pharynx, or larynx. As approximately half the cases of mucositis are severe, it is a significant problem.

- Mucositis in the oral cavity, pharynx, or larynx is a representative acute phase reaction to radiotherapy and is suitable for safety evaluation in clinical studies in patients with head and neck cancer.

The tolerance dose of the normal mucosal tissue of the oral cavity, pharynx, or larynx in the clinical studies of BNCT in patients with head and neck cancer was determined based on a dose that would cause "ulceration accompanied by severe pain that might affect food intake and swallowing."

For X-ray-related ulceration, Coderre JA et al., reported that ulcers developed in the sublingual mucosa of rats by 9 to 10 days after a single irradiation of X-ray at >12 Gy to the mucosa, with a peak at 10 to 13 days after irradiation.[23] The CBE factor of 4.9 in normal mucosal tissue is derived from this report (by Coderre JA et al.) that used the rat sublingual mucosa model.

In the single-dose toxicity study of BNCT in mice, mice died at the oral mucosal dose of 13.01 Gy-Eq. The clinical dose should not exceed this dose. Further, based on the report by Coderre JA et al., the threshold dose that would cause "ulceration accompanied by severe pain that might affect food intake and swallowing" was determined to be 12 Gy. This dose was defined as the tolerance dose in the normal mucosal tissue in the oral cavity, pharynx, or larynx in clinical use of NeuCure. The threshold dose does not apply to the mucosa of the nasal cavities/nasal sinuses, because the mucosa of the nasal cavities/nasal sinuses is unlikely to affect food intake or swallowing and no report has shown the tolerance dose in this mucosa in standard radiotherapy.

The applicant's explanation about the relevance of nonclinical data to humans:
The doses used in the single-dose toxicity study of BNCT in mice and the estimated *in vitro* exposure doses outside the irradiation field were evaluated. The result showed that the systemic exposure dose differed between humans and mice, with a higher systemic exposure dose in mice than in humans due to the difference in body size between mice and humans and technical limitations of BNCT in mice. This means that the systemic changes observed in mice are unlikely to occur in humans.

PMDA's view on the applicant's explanation:
The following applicant's explanations are reasonable: The upper dose limit was based on the dose in normal mucosa; the dose in normal mucosa was based on the results of a nonclinical study and published data; and the systemic changes observed in mice are unlikely to occur in humans because systemic irradiation in mice is greater than that in humans. To be on the safe side based on this rationale, the starting dose of 10 Gy was used in the phase I study. After the tolerability and safety of this dose were confirmed in humans, the mucosal dose of 12 Gy was finally selected. The applicant's explanations about dose determination in clinical use of NeuCure were acceptable.

6.D.(3) Rationale for the necessity of maintaining blood boron concentration at ≥20 ppm

PMDA asked the applicant to explain the rationale for the necessity of maintaining blood boron concentration at ≥20 ppm in clinical practice.

The applicant's explanation:
To ensure the antitumor effect of BNCT, boron needs to be distributed to all targeted cancer cells in theory. To kill cancer cells, at least 10^9 boron atoms/cell are required. This condition will be achieved when the tissue boron concentration is >20 ppm.[27,28] To obtain the antitumor effect of BNCT, therefore, the boron concentration in tumor tissue needs to exceed 20 ppm. As an alternative indicator, the whole blood boron concentration of 20 ppm was selected.

PMDA's view on the applicant's explanation:
No simple method that directly measures the boron concentration in tumor tissue has been established yet. On the other hand, blood boron concentration can be easily measured by collecting blood. The blood boron concentration can be used as an alternative measure of the boron concentration in tumor tissue. In that case, when the tumor boron concentration reaches the therapeutic level, boron is distributed to blood (normal tissue) at 20 ppm, which is a relatively high concentration.

Since the cell-killing effect of BNCT is derived from the nuclear reaction between epithermal neutrons and boron, the existence of boron itself does not result in cell deaths. To kill cells, irradiation of a sufficient epithermal flux is required. In planning the treatment with BNCT, an appropriate irradiation angle and body position should be selected so that the target lesion receives a sufficient epithermal flux while the normal tissue avoids receiving the epithermal flux as much as possible. Even if the boron concentration in blood (normal cells) exceeds 20 ppm, BNCT is unlikely to damage normal cells compared with tumor cells.

It is impossible to reduce the radiation doses in normal tissues to zero in general radiotherapy or BNCT. After careful assessment of patient eligibility for radiotherapy, the radiation doses in each normal organ are determined so that they do not exceed the tolerance doses. ("Justification of practices" and "Optimization in radiological protection" in ICRP publication 60 [1990][11] and ICRP publication 73 [1996][12]). In making a treatment plan, NeuCure Dose Engine calculates the dose distribution and simulates the equivalent dose to be delivered to each target organ. This simulation shows the doses delivered to normal organs so that BNCT is conducted within the tolerance dose of each organ.

PMDA accepted the applicant's explanation about the use of the blood boron concentration as an alternative indicator of the boron concentration in tumor tissue for the following reasons: "No simple method that directly measures the tumor boron concentration has been established yet" and "a treatment plan is prepared so that the doses in normal tissues do not exceed their tolerance doses."

6.D.(4) Measures for long irradiation

The irradiation time was 1 hour at the maximum in the clinical studies. To ensure that patients can tolerate long irradiation, the applicant explained that "the body posture that ensures that the patient remains in a fixed position for long periods is determined (simulated) prior to the day of irradiation" and that "the patient's position is constantly monitored using the patient's monitoring system during irradiation." However, since the target organs are the head or neck, some patients may have difficulty in maintaining the same posture. Remaining in a fixed position for a long period may be difficult depending on the patient's condition. PMDA instructed the applicant to inform healthcare professionals, through the instructions for use, that NeuCure should be used with care in patients who have difficulty in maintaining the same posture for a long period. The applicant agreed.

6.D.(5) Intended use or indication of NeuCure

The proposed intended use or indication of NeuCure System is "treatment of unresectable locally recurrent head and neck cancer and treatment of unresectable advanced head and neck non-squamous cell carcinoma." The proposed intended use or indication of NeuCure Dose Engine is as follows: "The

product calculates dose distributions achieved in boron neutron capture therapy based on contour information (body contour, organ shape, bone region, shape/components of treatment area, and biological parameters) and irradiation conditions (irradiation equipment, number of irradiation ports, shape of collimator, isocenter, irradiation angle, and blood drug concentration) to assist physicians in developing treatment plans with boron neutron capture therapy." BNCT using NeuCure is implemented in combination with Steboronine and was evaluated in the clinical studies with Steboronine. Therefore, the intended use or indication of NeuCure should be "unresectable, locally advanced or locally recurrent head and neck cancer," (the same as the indication of Steboronine), with a statement that NeuCure should be used in combination of Steboronine [see Section [3] in Review Report (2) of Steboronine]. In addition, the details of patients participating in Study 002 should be included in the "Clinical Studies" section of the instructions for use. In relation to the information in the Precautions Concerning Indication section of the package insert of Steboronine, the following information should also be included in the "Precautions Concerning Intended Use or Indication" section of the instructions for use of NeuCure ("Justification of practices" in ICRP publication 60 [1990][11] and ICRP publication 73 [1996][12]).

- The standard therapy such as chemoradiotherapy, if feasible, should be performed in preference to treatment with Steboronine in combination with NeuCure System and NeuCure Dose Engine.

- The efficacy and safety of NeuCure System and NeuCure Dose Engine as adjuvant therapy have not been established.

- Eligible patients must be selected by physicians with a full understanding of the information presented in the "Clinical Studies" section and of the efficacy and safety of NeuCure System and NeuCure Dose Engine.

6.D.(6) Points to consider, including requirements for healthcare professionals and facilities for BNCT

BNCT is a combination treatment with a boron drug and a neutron beam. This is a unique therapy in that its effectiveness on tumors and the extent of unintended exposure of normal tissues to a neutron beam depend on the extent of boron accumulation in a tumor, unlike other existing radiotherapies. Special expertise is required for radiation safety management of NeuCure, including treatment planning, the quality control of devices, and the control of radioactivated devices. For its appropriate and safe implementation, BNCT should be implemented by healthcare professionals with sufficient knowledge, techniques, and experience in BNCT ("Justification of practices" and "Optimization in radiological protection" in ICRP publication 60 [1990][11] and ICRP publication 73 [1996][12]). PMDA asked the applicant to explain the points to consider, including requirements for healthcare professionals and facilities for BNCT.

The applicant's explanation:

The requirements for facilities and healthcare professionals for BNCT will be defined as below in the "Treatment Guidebook for Accelerator-based BPA-BNCT (Point to Considers for Safe Boron Neutron Capture Therapy using a borofalan [^{10}B] drug and a BNCT treatment system) [in Japanese]" created by the Japanese Society of Neutron Capture Therapy:

(a) Requirements for physicians

- Physicians must be certified to perform neutron capture therapy (NCT) by the Japanese Society of Neutron Capture Therapy.
- Physicians must attend a lectures(s) on the directions for use of the BNCT treatment system.

(b) Requirements for facilities or medical institutions

- Facilities or medical institutions must have a medical physicist(s) who can make treatment plans.
- Facilities or medical institutions must be capable of diagnostic imaging for lesion assessment.
- Facilities or medical institutions must be able to promptly communicate with medical institutions having relevant departments such as otorhinolaryngology and neurosurgery in case of adverse events.

PMDA's view:

PMDA largely accepted the applicant's explanation. These requirements, etc. have been established by the relevant academic societies. The applicant also needs to take necessary measures, such as providing relevant medical institutions with the latest guidelines for proper use of the BNCT treatment system in cooperation with related academic societies. In line with this, PMDA considers Approval Conditions 1 and 2 are necessary.

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

7.A Summary of the data submitted

The applicant submitted the outline of the post-marketing surveillance plan shown in Table 22.

Table 22. Outline of use-results survey

Objective	An all-case surveillance will be conducted under the specified approval conditions in compliance with the Good Post-marketing Study Practice (GPSP), to collect the following safety and efficacy information of Steboronine and NeuCure in post-marketing clinical practice. Steboronine and NeuCure are used for BNCT. BNCT in this plan refers to administration of Steboronine and neutron beam irradiation by NeuCure. • Unknown adverse reactions • Incidence of adverse reactions in clinical use of Steboronine • Understanding of incidence of malfunctions of NeuCure • Factors that may affect the safety of BNCT • Factors that may affect the efficacy of BNCT
Population	All patients treated with Steboronine on and after the day of launch
Sample size	Unresectable locally recurrent head and neck cancer and unresectable advanced head and neck non-squamous cell carcinoma: 100 patients The necessity of additional safety measures will be discussed according to the occurrence of significant risks or unknown adverse reactions in the post-marketing setting. The sample size will be reviewed so that the survey includes at least 50 cases of 3-year survivors.
Rationale	• Number of patients required for safety evaluation Listed below are the incidences of the adverse reactions defined as important identified risks in the following Japanese clinical studies in patients with head and neck cancer: ➢ A phase I study "Phase I clinical study of SPM-011 BNCT treatment system (BNCT30) in patients with unresectable locally recurrent head and neck cancer or unresectable locally advanced head and neck non-squamous cell carcinoma" ➢ A phase II study "Phase II clinical study of SPM-011 BNCT treatment system (BNCT30) in patients with unresectable locally recurrent head and neck squamous cell carcinoma or unresectable head and neck non-squamous cell carcinoma" Dysphagia, 3.3% (1 of 30 patients) Brain abscess, 3.3% (1 of 30 patients) Radiation skin injury, 40.0% (12 of 30 patients) Cataract, 6.7% (2 of 30 patients) Crystal urine present, 6.7% (2 of 30 patients) The survey needs 99 patients to detect at least 1 adverse reaction with an incidence of 3.0%, which is lower than the lowest incidence (3.3%) shown above, with a 95% confidence level. Accordingly, the target sample size of 100 was determined. • Number of patients required for efficacy evaluation According to the survival statistics (April 2019) by the Japanese Association of Clinical Cancer Centers, the 3-year relative survival rate was 0.516 (hypopharynx) to 0.68 (nasopharynx). The sample size of 100 appears to be large enough to obtain at least 50 cases of 3-year survivors.
Survey period	3 years of observation period
Safety specification	Important identified risks: Dysphagia, brain abscess, radiation skin injury, cataract, and crystal urine present Important potential risks: Arterial haemorrhage (haemorrhage in the carotid artery associated with tumor shrinkage/necrosis), osteoradionecrosis/osteomyelitis, eye disorder, central nervous system injury, and radiation pneumonia Important missing information: Safety in patients with serious renal impairment

7.B Outline of the review conducted by PMDA

Since BNCT using Steboronine and NeuCure is a combination therapy of Steboronine and NeuCure, the post-marketing surveillance of Steboronine and the post-marketing surveillance of NeuCure should be conducted together. It is reasonable to conduct the post-marketing surveillance of NeuCure in coordination with the post-marketing surveillance of Steboronine. PMDA instructed the applicant to conduct the post-marketing surveillance of NeuCure according to the same protocol and during the same period as those of the post-marketing surveillance of Steboronine. The applicant agreed.

The applicant should collect information from all patients treated with NeuCure in clinical practice in Japan until data from a certain number of patients are accumulated, to evaluate the safety and efficacy of NeuCure and to take appropriate measures as necessary. In line with this, PMDA considers that Approval Condition 3 is necessary.

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

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

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

IV. Overall Evaluation

1. Major issues in reviews

The main issues in the reviews of NeuCure System were (1) the stability and soundness of the target used in the neutron irradiation device, (2) the quality and repeatability of neutrons produced from the neutron irradiation device, (3) monitoring of neutron fluxes produced from the neutron irradiation device, and (4) the appropriateness of the assessment results of the repeatability, stability, and linearity of the dose monitoring system. PMDA's view based on the comments from the Expert Discussion are described in the following sections.

(1) Stability and soundness of the target used in the neutron irradiation device

Since the beryllium target used in the neutron i
rradiation device of NeuCure System has a high melting point and high thermal conductivity, exposure to a high-energy proton beam appears to cause a minimal deterioration of the shape of the target. In theory, the yield of neutrons is unlikely to change during the period of use.

To ensure the soundness of its target, NeuCure System is equipped with structures and functions, including [redacted] and prevention of blistering. The submitted data showed that the interlocks appropriately functioned to stop proton beam irradiation once

[redacted] was detected. In addition, the target was shown to have a structure that prevents blistering. The stability and soundness of the target used in the neutron irradiation device of NeuCure System is thus secured.

(2) Quality and repeatability of neutrons produced from the neutron irradiation device

The spectrum calculated by Monte Carlo simulation was specified in the shape, structure, and principle section of the application document, to show the quality of neutron beams produced from the neutron irradiation device of NeuCure System. The deep dose distribution of epithermal neutrons in the water phantom (a deep dose curve and an equivalence dose curve) is presented in Section "2.(3).3) Dose distribution measurement." Section "2.(4).3) Studies to support usage method of NeuCure System" shows that NeuCure Systems installed at different sites are equivalent in terms of the quality of neutrons. PMDA thus considers that NeuCure Systems located in different facilities produce the same quality of radiations (thermal neutrons, fast neutrons, and gamma-rays) as long as they have the same acceleration energy of protons and the same mechanical structure, dimensions, and materials.

(3) Monitoring of neutron fluxes produced from the neutron irradiation device

NeuCure System is equipped with 2 dose monitoring systems that measure proton beam current (primary dose monitor and secondary dose monitor). Using these dose monitoring systems, NeuCure System indirectly monitors neutron fluxes generated by constantly measuring the charge of proton beams.

A technique that measures neutron fluxes real-time is still under development. Currently, it is considered reasonable to monitor neutrons through real-time monitoring of proton beams using a beryllium target that has been confirmed to have no deterioration in advance.

In Section "2.(3).6) Measurement precision of the charge monitors of charged particle beam," the measurement precision of the 2 dose monitoring systems is shown to be within the range of specification limits. In addition, the redundancy of the primary and secondary dose monitoring systems met the official standard. PMDA considers that neutron fluxes released from the neutron irradiation device can be appropriately monitored, because (1) the quality of neutrons produced by proton beams is consistent, (2) the 2 dose monitoring systems can measure proton beam current with high precision, and (3) NeuCure System is equipped with an appropriate safety function.

(4) Appropriateness of the assessment results of the repeatability, stability, and linearity of the dose monitoring system

In determination of the specification limits of the repeatability and stability of the dose monitoring system, the depths from the body surface with stable measurements were used as reference points. The specification limits were determined to ensure that the precision at these points is not higher than the general measurement precision of the gold wire activation method. The test results met the specification limits. Because the body surface has more fast neutrons and a thermal neutron buildup region, and is a low-dose region, a positioning error of a gold sample profoundly affects the dose on the surface, which makes dose measurement itself susceptible to error. Measurements on the body surface do not represent the performance of NeuCure. It is therefore reasonable to perform dose assessment at the points that provide stable measurements. In addition, since the dose per monitor unit is used in the calculation of

coefficient of variation, lower doses are associated with large relative errors. The absolute error of measurement on the body surface was [redacted] Gy-Eq at the maximum, which does not differ from the absolute errors of measurements at the other depths. The measurements on the body surface are also clinically acceptable.

The specification limit of the linearity of the dose monitoring system was determined as with its repeatability and stability. The test results met the specification limit.

On the basis of the above explanation, PMDA considers the assessment results of the repeatability, stability, and linearity of the dose monitoring system are appropriate.

The main issues in the reviews of NeuCure Dose Engine were (5) the appropriateness of the precision assessment criteria for dose calculation algorithm, (6) dose components for assessment of dose calculation precision, (7) the region where the calculation precision can be ensured, and (8) the use of the fixed values of CBE, RBE, and T/B ratio.

PMDA's view based on the comments from the Expert Discussion:

(5) Appropriateness of the precision assessment criteria for dose calculation algorithm

The acceptance criteria for gamma-ray analysis used in the test on the precision of dose calculation algorithm allow a larger error than that of general radiotherapy systems. Detectors of X-rays produced during general radiotherapy are well-established with high precision. However, there is no established method that measures neutron fluxes with high precision. The gold wire activation method, which uses micro gold wires to be attached to a phantom, is assumed to result in a certain level of error between calculated and measured values because attaching the gold wires to a phantom is difficult. In view of (a) the principle of the measurement and (b) the fact that the level of the error in the test on the precision of dose calculation algorithm is clinically acceptable, PMDA considers that the acceptance criteria used in this test are reasonable from the viewpoint of the current scientific level.

(6) Dose components for assessment of dose calculation precision

Currently, there is no established method that correctly measures fast neutron fluxes in the BNCT irradiation field. In dose calculation by NeuCure Dose Engine, the dose distribution of fast neutrons contained in a radiation beam are also calculated based on a beam model of NeuCure System simulated by Monte Carlo simulation. Fast neutrons undergo elastic scattering with hydrogen atoms in the water phantom to slow down to thermal neutrons, which are then distributed in the water phantom. If fast neutrons from the established beam model are not calculated correctly, thermal neutrons resulting from the decreased energy of fast neutrons are not calculated correctly. The fast neutron flux before they slow down can be assessed by comparing the calculated flux of thermal neutrons and the observed results. For this reason, dose calculation precision is not affected even if the calculated and observed doses of fast neutrons are not compared directly.

(7) Region where the calculation precision can be ensured

In comparison between the calculated gamma-ray doses by NeuCure Dose Engine and SERA, the gamma-ray dose did not meet the acceptance criteria at depths of >[redacted] cm from the surface of the water

phantom. In the clinical studies, however, BNCT was administered to the head and neck, and the normal mucosa of the oral cavity, pharynx, or larynx was defined as reference tissue for dose prescription in radiotherapy planning. In all patients in the clinical studies, the reference tissue was located not deeper than [redacted] cm from the body surface. In this region, NeuCure Dose Engine is expected to yield comparable calculation results to those in the studies using SERA. SERA tends to estimate lower doses than NeuCure Dose Engine; this means that NeuCure Dose Engine estimates unnecessary doses deeper than [redacted] cm from the surface on the safe side compared with SERA and therefore will not raise any safety concerns. Further, the thermal neutron doses calculated by NeuCure Dose Engine and SERA were consistent. PMDA thus considers that the efficacy and safety of the thermal neutron dose can be assured in treatment using NeuCure Dose Engine.

(8) Use of the fixed values of CBE, RBE, and T/B ratio

The RBE factor is a general measure showing the difference in radiation quality. It is reasonable to determine the RBE factors for nitrogen and hydrogen doses based on the published and experimental values of this applicable biological effectiveness measure. For the CBE factors for boron dose in tumor and normal mucosa, the applicant's rationale for using their published values, which have been verified under the same conditions as those used for assessment of the distribution of boron in the body, is reasonable. The T/B ratio, which indicates the boron accumulation in a tumor, may vary according to the type and size of tumor and the pharmacokinetics, etc. of individual patients. The boron concentration in a normal organ can be estimated by measuring blood boron concentration in individual patients because the boron concentration in a normal organ is similar to that in blood.[25] The clinical studies used a normal organ (normal mucosa) as reference tissue for dose prescription. Adverse effects on a normal organ can be predicted even if there is an individual difference in the boron dose in tumor, and the safety of patients can be ensured. PMDA thus considers that the use of the representative published value for the T/B ratio is reasonable from the viewpoint of the current scientific level.

2. Post-marketing safety measures

BNCT with NeuCure is a combination treatment with a boron drug and a neutron beam. This is a unique therapy because its effectiveness on tumors and the extent of unintended exposure of normal tissues to a neutron beam depend on the extent of born accumulation in a tumor, unlike conventional radiotherapies such as X-ray and proton radiation. Special expertise is required for radiation safety management of NeuCure, including treatment planning, the quality control of devices, and the control of radioactivated devices. Considering these particularities of NeuCure, proper implementation of BNCT requires medical institutions equipped with a management system necessary for this therapy and healthcare professionals with sufficient relevant knowledge, techniques, and experience (Approval Conditions 1 and 2).

Because only very limited safety information is available from Japanese and non-Japanese patients treated with BNCT, the applicant should conduct a use-results survey after the market launch to collect safety and efficacy information of NeuCure from all patients treated with NeuCure until data from a certain number of patients have been gathered, and should take additional risk mitigation measures as necessary (Approval Condition 3). It is reasonable to conduct the post-marketing surveillance of NeuCure in coordination with the post-marketing surveillance of Steboronine. The post-marketing

surveillance of NeuCure should be conducted according to the same protocol and during the same period as those of the post-marketing surveillance of Steboronine.

Since treatment with NeuCure System involves long-term neutron irradiation, which profoundly accelerates the radioactivation of devices, buildings, etc. compared with general radiotherapy equipment such as linear accelerators, necessary measures should be taken to reduce the exposure of medical professionals to neutron irradiation as much as practical (Approval Condition 4 only for NeuCure System).

As a result of the above review, PMDA concludes that making NeuCure available for clinical use as a local treatment option will benefit patients with unresectable, locally advanced or locally recurrent head and neck cancer who are not eligible for standard cancer treatments, such as chemoradiotherapy, and that NeuCure may be approved for the following intended use (modified from the proposed wording), with the approval conditions shown below.

Intended Use

NeuCure BNCT System

NeuCure BNCT System is a neutron irradiation device intended to be used for boron neutron capture therapy to treat unresectable, locally advanced or locally recurrent head and neck cancer, and used in combination with the following drug:

Non-proprietary Name: Borofalan (^{10}B)
Brand Name: Steboronine 9000 mg/300 mL for Infusion

NeuCure BNCT Dose Engine

NeuCure BNCT Dose Engine is a program that calculates dose distribution achieved in boron neutron capture therapy based on contour information and irradiation conditions, to assist physicians in developing treatment plans with boron neutron capture therapy for patients with unresectable, locally advanced or locally recurrent head and neck cancer. NeuCure BNCT Dose Engine is used in combination with the following drug:

Non-proprietary Name: Borofalan (^{10}B)
Brand Name: Steboronine 9000 mg/300 mL for Infusion

Approval Conditions

NeuCure BNCT System

1. The applicant is required to take necessary measures, such as disseminating the latest guidelines for proper use developed in cooperation with related academic societies, to ensure that physicians with adequate knowledge and experience in boron neutron capture therapy of unresectable, locally advanced or locally recurrent head and neck cancer, become fully familiar with the directions for use of NeuCure BNCT System, adverse events associated with neutron irradiation, and other relevant issues, and to ensure that the physicians use NeuCure BNCT System in accordance with the intended

use and directions for use of NeuCure BNCT System at medical institutions capable of providing boron neutron capture therapy.

2. The applicant is required to take necessary measures, such as disseminating the latest guidelines for proper use developed in cooperation with related academic societies, to ensure that medical physics experts with adequate knowledge and experience in boron neutron capture therapy of unresectable, locally advanced or locally recurrent head and neck cancer, become fully familiar with the treatment plan for boron neutron capture therapy, quality control of NeuCure BNCT System, and other relevant issues, and to ensure that the experts use NeuCure BNCT System in accordance with the intended use and directions for use of NeuCure BNCT System at medical institutions capable of providing boron neutron capture therapy.

3. The applicant is required to conduct a use-results survey involving all patients treated with NeuCure BNCT System after the market launch until data from a certain number of patients have been gathered and take appropriate measures as necessary based on the survey results.

4. The applicant is required to take appropriate measures to minimize radiation exposure of healthcare professionals as much as practical during the use of NeuCure BNCT System.

NeuCure BNCT Dose Engine

1. The applicant is required to take necessary measures, such as disseminating the latest guidelines for proper use developed in cooperation with related academic societies, to ensure that physicians with adequate knowledge and experience in boron neutron capture therapy of unresectable, locally advanced or locally recurrent head and neck cancer, become fully familiar with the directions for use of NeuCure BNCT Dose Engine, adverse events associated with neutron irradiation, and other relevant issues, and to ensure that the physicians use NeuCure BNCT Dose Engine in accordance with the intended use and directions for use of NeuCure BNCT Dose Engine at medical institutions capable of providing boron neutron capture therapy.

2. The applicant is required to take necessary measures, such as disseminating the latest guidelines for proper use developed in cooperation with related academic societies, to ensure that medical physics experts with adequate knowledge and experience in boron neutron capture therapy of unresectable, locally advanced or locally recurrent head and neck cancer, become fully familiar with the treatment plan for boron neutron capture therapy, quality control of NeuCure BNCT Dose Engine, and other relevant issues, and to ensure that the experts use NeuCure BNCT Dose Engine in accordance with the intended use and directions for use of NeuCure BNCT Dose Engine at medical institutions capable of providing boron neutron capture therapy.

3. The applicant is required to conduct a use-results survey involving all patients treated with NeuCure BNCT Dose Engine after the market launch until data from a certain number of patients have been gathered and take appropriate measures as necessary based on the survey results.

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