May 1, 2020

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

Report on the Deliberation Results

Classification	Medical product 4, Orthopedic products
Term Name	Prosthetic Material for Eustachian Tube
Brand Name	Eustachian Tube Plug
Applicant	Fuji Systems Corporation
Date of Application	June 18, 2019 (Application for marketing approval)

Results of Deliberation

In its meeting held on April 10, 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 not designated as a medical device subject to a use-results survey. The product should be approved with the following condition. The product is not classified as a biological product or a specified biological product.

Approval Conditions

1. The applicant is required to cooperate with the relevant academic societies and take necessary measures to ensure that physicians with adequate knowledge and experience in diagnosing and treating patulous eustachian tube acquire sufficient skills for using the product and knowledge about procedure-related complications, and use the product at medical institutions appropriately equipped to treat the disease in compliance with the intended use and directions for use of the product.

Review Report

April 1, 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	Medical product 4, Orthopedic products
Term Name	Prosthetic Material for Eustachian Tube
Brand Name	Eustachian Tube Plug
Applicant	Fuji Systems Corporation
Date of Application	June 18, 2019
Items Warranting Special Mention	None
Reviewing Office	Office of Medical Devices I

Review Results

April 1, 2020

Classification	Medical product 4, Orthopedic products
Term Name	Prosthetic Material for Eustachian Tube
Brand Name	Eustachian Tube Plug
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Date of Application	June 18, 2019

Results of Review

Eustachian Tube Plug is a device that narrows the excessively open eustachian tube lumen to improve symptoms in patients with refractory patulous eustachian tube, who do not respond to conservative treatments such as nasal instillation of physiological saline and treatment with traditional Chinese medicines.

Eustachian Tube Plug is made of silicon and consists of main body that is inserted into the eustachian tube and hooks that prevent the main body from falling off from the eustachian tube. Eustachian Tube Plug has a total length of 23.0 mm and comes in various effective lengths, widths, and thicknesses. The use of Eustachian Tube Plug that is excessively oversized for the patient's eustachian tube lumen increases the risk of otitis media, ear pain, etc., while the use of undersized Eustachian Tube Plug loses its efficacy. It is, therefore, important to measure the luminal diameter of patient's eustachian tube through imaging diagnosis with endoscopy, Computed Tomography (CT), or other diagnostic imaging equipment before surgery and select an appropriate size of Eustachian Tube Plug that fits the lumen of the patient's eustachian tube.

The applicant submitted non-clinical data supporting the biological safety, stability and durability, performance, and sterilization residuals. PMDA identified no particular problem.

The applicant submitted clinical data from an investigator-initiated Japanese clinical study of Eustachian Tube Plug (hereinafter referred to as the clinical study). This was a multicenter, prospective, open-label, uncontrolled study to evaluate the efficacy and safety of Eustachian Tube Plug in 30 ears of 30 patients with refractory patulous eustachian tube.

The primary endpoint of the clinical study was the level of improvement in abnormal auditory sensations such as autophony of voice or breathing sounds, which are symptoms of patulous eustachian tube. The efficacy was evaluated using Patulous Eustachian tube Handicap Inventory 10 (PHI10), which is a modified version of Tinnitus Handicap Inventory 12 (THI12), an international rating scale of tinnitus.

The clinical study showed improvement in total PHI10 score from 34.4 ± 4.2 points at baseline to 6.4 ± 9.0 points at 3 months after surgery ($P < 0.001$). The difference is clinically significant from the efficacy viewpoint in patients suffering from patulous eustachian tube, who do not respond to conservative

treatments. A total of 23 patients were responders, which were defined as patients with a PHI10 score of ≤16 points, with a percentage of responders of 82.1%, which exceeded the threshold percentage of responders of 40%, indicating the efficacy of Eustachian Tube Plug.

For the safety of Eustachian Tube Plug, adverse events were reported in 21 of 29 patients. Main adverse events were surgical procedure-related pain and serous otitis media. A serious adverse event leading to study discontinuation occurred in 1 patient. This patient experienced tinnitus with insomnia and dysphoria due to accompanying symptoms. The investigational device was removed upon request by the patient. Although the mechanism responsible for the occurrence of tinnitus is unknown, 1 of 29 patients (3.4%) removed the investigational device in the clinical study. The symptoms in this patient resolved after removal of the investigational device and closure of tympanic membrane perforation. The relevant information on the removal will be appropriately provided in the instructions for use, etc. As a result of the discussions at the Expert Discussion, PMDA concluded that there was no particular problem with the safety of Eustachian Tube Plug, including the surgical procedure.

The submitted data are relevant to evaluate the efficacy and safety of Eustachian Tube Plug. PMDA reviewed the data comprehensively based on the discussions at the Expert Discussion. Considering the lack of efficient therapeutic options for the treatment of refractory patulous eustachian tube in Japan, it is of significance to make Eustachian Tube Plug available in clinical practice.

To ensure the efficacy and safety of Eustachian Tube Plug, it is important to select appropriate patients and plug size for this treatment, as well as to comply with the precautions for its insertion. Treating physicians must have adequate knowledge and experience in diagnosing and treating patulous eustachian tube and use Eustachian Tube Plug in compliance with its intended use and directions for use. This should be mentioned as an approval condition of Eustachian Tube Plug.

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

Intended Use

Eustachian Tube Plug is intended to narrow the excessively open eustachian tube to improve symptoms of patients with refractory patulous eustachian tube, who do not respond to conservative treatments.

Approval Condition

The applicant is required to cooperate with the relevant academic societies and take necessary measures to ensure that physicians with adequate knowledge and experience in diagnosing and treating patulous eustachian tube acquire sufficient skills for using the product and knowledge about procedure-related complications, and use the product at medical institutions appropriately equipped to treat the disease in compliance with the intended use and directions for use of the product.

Review Report

April 1, 2020

Product for Review

Classification	Medical product 4, Orthopedic products
Term Name	Prosthetic Material for Eustachian Tube
Brand Name	Eustachian Tube Plug
Applicant	Fuji Systems Corporation
Date of Application	June 18, 2019
Proposed Intended Use	Eustachian Tube Plug is used to narrow the excessively open eustachian tube in patients with refractory patulous eustachian tube that cannot be improved by conservative treatments.

Items Warranting Special Mention

None

Table of Contents

List of Abbreviations

AMED	Japan Agency for Medical Research and Development
ATP	Adenosine Triphosphate Disodium Hydrate
CT	Computed Tomography
JIS	Japanese Industrial Standards
PET001	Development code of the product
PHI10	Patulous Eustachian tube Handicap Inventory 10
PS	Performance Status
QOL	Quality of life
THI12	Tinnitus Handicap Inventory 12
TTAG	Tubo Tympano Aerodynamic Graphy

I. Product Overview

Eustachian Tube Plug is a silicon plug intended to narrow the excessively open eustachian tube in patients with refractory patulous eustachian tube, who do not respond to conservative treatments. Eustachian Tube Plug has 2 different basic shapes, a taper type (sizes 3-5) that tapers toward the tip of the main body and a straight type (sizes 6-9). Eustachian Tube Plug consists of a main body and hooks, and has a total length of 23 mm (see Figure 1).

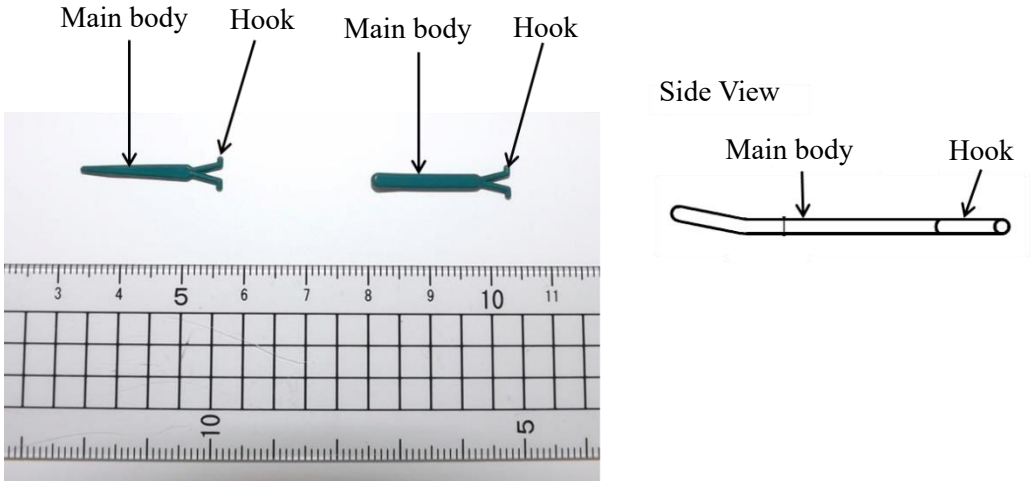

Figure 1. Appearance of Eustachian Tube Plug

The main body is the part that is inserted and implanted in the eustachian tube. The main body has a round tip and an end part that is slightly bent to facilitate insertion into the eustachian tube. The tail of the main body is designed with hooks to prevent descent into the eustachian tube. The hooks are formed integrally with the main body. Eustachian Tube Plug is used with either or both of the 2 types of coloring agents; a white coloring agent [redacted] or a green coloring agent [redacted]. Eustachian Tube Plug comes with excipients with or without a contrast medium ([redacted]) (see Table 1).

Table 1. Excipients of Eustachian Tube Plug

[redacted] (white coloring agent)	Used with either or both agents
[redacted] (green coloring agent)	
[redacted] (contrast medium)	With or without a contrast medium

The shape of Eustachian Tube Plug was designed with reference to the medical device used in previous clinical research. The eustachian tube has an overall length of approximately 35 mm: it is divided into the bony portion that is one third on the tympanic side and the cartilaginous portion that is two-thirds on the epipharyngeal side. The isthmus, i.e., the junction between the bony portion and the cartilaginous portion, is the narrowest point along the eustachian tube. By narrowing the isthmus with Eustachian Tube Plug, symptoms of patulous eustachian tube can be mitigated. The previous clinical research demonstrated that a device with a total length of 23 mm is long enough for its tip to reach the cartilaginous portion and narrows the isthmus. On the basis of this conclusion, the total length of Eustachian Tube Plug was determined to be 23 mm. A total of 7 sizes of Eustachian Tube Plug are available so that an appropriate size can be selected according to the lumen size of the patient's eustachian tube (see Table 2 and Figure 2).

Table 2. Size variation of Eustachian Tube Plug

Plug size	Effective length	Main body Maximum width/ shoulder width	Main body Minimum width/ tip width	Hook width
3	18.25 mm	2.5 mm	1.0 mm	5.5 mm
4			1.5 mm	
5			2.0 mm	
6			2.5 mm	
7	18.20 mm	3.0 mm	3.0 mm	
8		3.5 mm	3.5 mm	
9	18.15 mm	4.0 mm	4.0 mm	6.0 mm
Tolerance	[redacted] mm	[redacted] mm	[redacted] mm	[redacted] mm

* Total length, 23.0 mm; hook diameter, 1.0 mm; thickness, 1.0 to 1.5 mm; length of bent part, 3 to 8 mm

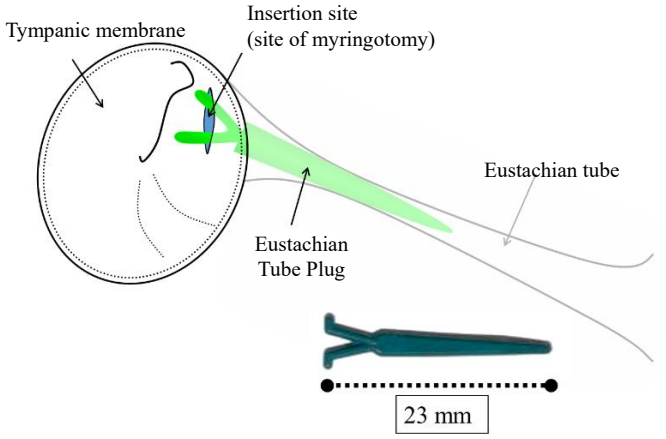

Figure 2. Inserted Eustachian Tube Plug (right ear)

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 by the applicant and the applicant's responses to the inquiries from the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined below.

The expert advisors for the Expert Discussion on Eustachian Tube Plug declared that it does 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).

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

1.(1) History of development

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

The human ear consists of three parts—the external ear, the middle ear, and the internal ear starting from the outside. The tympanic membrane serves as the boundary between the external ear and the middle ear. Behind the tympanic membrane, the tympanic cavity (middle ear cavity) is located, and this cavity is connected with the epipharynx through the eustachian tube. The eustachian tube is normally closed. It is open only for a very short period of <1 second during swallowing, etc. to adjust the middle ear pressure. Patulous eustachian tube is a disorder in which the eustachian tube is not closed and instead constantly remains open, causing symptoms including sensation of ear congestion (a sense of fullness in the ear) and an echoing sound of the person's own voice (autophony of voice) or hearing of the person's own breathing sounds (autophony of breathing sounds).

Various factors are involved in the occurrence of patulous eustachian tube, including acute body weight loss, pregnancy, use of oral contraceptives, otitis media, exercise, and cleft palate. Approximately 5% of the general population suffer from the symptoms of patulous eustachian tube, including mild cases, which are defined as the infrequent occurrence of symptoms.[1]

Patients with patulous eustachian tube are treated by conservative treatments such as nasal instillation of physiological saline and treatment with traditional Chinese medicines, and lifestyle guidance.[1] In past attempts to develop the treatment of refractory patulous eustachian tube that does not respond to conservative treatments, ligation of eustachian tube,[2] which is intended to treat the eustachian tube itself, and cartilage implantation in the eustachian tube,[3] which inserts a piece of cartilage collected from the patient's tragus in the open eustachian tube, were studied. However, there has been no established standard treatment (see Table 3).

Table 3. Insertion of Eustachian Tube Plug and other treatments for refractory patulous eustachian tube

	Insertion of Eustachian Tube Plug	Cartilage implantation in the eustachian tube	Eustachian tube ligation
Procedure	An incision is made on the tympanic membrane under local anaesthesia, followed by implantation of Eustachian Tube Plug in the eustachian tube. Finally, the site of myringotomy is closed.	The procedure is similar to the insertion of Eustachian Tube Plug, except for the use of a piece of cartilage collected from the patient's tragus.	The pharyngeal orifice of the eustachian tube is completely ligated with a suture by a transnasal approach under general anaesthesia.
Characteristics	Clinical research has been conducted in ≥252 patients since 2001.	Clinical research was conducted in 15 patients between 1995 and 1998. Removal of the implant is difficult during re-surgery because the cartilage adheres to the surrounding tissue.	The procedure involves an irreversible operation. The procedure is frequently associated with serous otitis media.

To address the problems with cartilage implantation in the eustachian tube, Dr. Toshimitsu Kobayashi, who was researching this technique, at Medical Corporation Hoju-Kai Sen-en Rifu Hospital designed a silicon "Eustachian Tube Plug" that could be inserted in the tube under local anaesthesia, had a longer total length than cartilage implants, and was unlikely to adhere to the surrounding tissues.

Upon request from Dr. Kobayashi, [redacted] developed a prototype of the Eustachian Tube Plug in 2001. The prototype was implanted in 115 patients. In 26 of them, the device was found to have fallen off in the throat. To solve this problem, a new model was created with the modified shape of the hooks. With this new model, the previous clinical research was conducted in 137 patients from 2008. After the modification of the hook shape, no patient was reported to have the device falling off in the throat.

The previous clinical research with the prototype and the new model demonstrated improvement of symptoms in 83.0% of the patients. Symptoms of traumatic tympanic membrane perforation were reported in 19.7% of the patients between 1 and 37 months after device insertion. Middle ear effusion was reported in 14.7% of the patients between 1 and 37 months after device insertion. Of these patients, 9.1% required the insertion of a tympanic membrane ventilation tube. In addition, 1.2% of the patients

experienced persistent otorrhoea for ≥2 weeks and required device removal. None of them, however, experienced any significant complication.

On the basis of these results, Dr. Kobayashi determined the specifications of the investigational device and proposed product, according to which Fuji Systems Corporation manufactured these devices. The hook width of the new model is 5 mm in its drawing. However, the actual measurement of the sample devices was 5.4 to 5.6 mm. The hook width of the investigational device of 5.5 mm was determined accordingly. In the previous clinical research, some patients required a plug having a larger tip width than 3.0 mm. On the basis of this experience, plugs with a wide tip were added to the product lineup. Table 4 presents the history of the specifications of the Eustachian Tube Plug.

To evaluate the Eustachian Tube Plug toward its practical use, Dr. Kobayashi applied for the conduct of an "Investigator-initiated confirmatory clinical study to evaluate the efficacy and safety of PET001 in patients with refractory patulous eustachian tube" in 2016 within the scope of "Research related to supporting and promoting implementation of investigator-initiated clinical trials" by the Japan Medical Association as part of the Project Promoting Clinical Trials for Development of New Drugs by the Japan Agency for Medical Research and Development (AMED). The conduct of the clinical study was approved by the Japan Medical Association on January 13, 2017.

Table 4. Differences between the models used in the clinical research and Eustachian Tube Plug

		Dimensions	Differences/similarities to Eustachian Tube Plug
Models used in clinical research	Prototype (2001-2007)	Total length, 23 mm Hook length, 3 mm Tip width, 1.0-3.0 mm	• The shape of the hooks is different from the current model. • The dimensions other than the total length are different from the current model. • The raw material of the device is silicone rubber. However, the details are unknown because this model used in the clinical research was developed by [redacted].
	New model (2008-)	Total length, 23 mm Hook length, 5 mm Tip width, 1.0-3.0 mm	• The shape is the same as the current model. • The dimensions other than the total length are different from the current model. • The raw material of the device is silicone rubber. However, the details are unknown because this model used in the clinical research was developed by [redacted].
Investigational device		Total length, 23 mm Hook length, 5.5 mm Tip width, 1.0-4.0 mm	• The shape and dimensions are the same as the current model. • The manufacturer of [redacted], a raw material of the device, is different from the current model.

1.(2) Use in foreign countries

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

Eustachian Tube Plug has not been approved/licensed or marketed in any foreign countries.

2. Design and Development

2.(1) Performance and safety specifications

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

The proposed performance specifications of Eustachian Tube Plug included appearance, tip shape, rupture strength, and radiopacity. The proposed safety specifications of Eustachian Tube Plug included biological safety, sterility assurance level, and ethylene oxide sterilization residuals.

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

PMDA reviewed the tests and justification of the data relating to the proposed performance and safety specifications, and concluded that there was no particular problem with these specifications.

2.(2) Physicochemical properties

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

The applicant did not submit data on the physicochemical properties of Eustachian Tube Plug because the data are included in the Sections "2.(4) Stability and durability" and "2.(5) Performance" (described later).

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

PMDA concluded that there was no particular problem with not submitting physicochemical data because the physicochemical properties of Eustachian Tube Plug can be confirmed in Section "2.(5) Performance" (described later).

2.(3) Biological safety

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

To support the biological safety of Eustachian Tube Plug, the applicant submitted the results of cytotoxicity, sensitization, intracutaneous reactivity, acute toxicity, subacute toxicity, genotoxicity (reverse mutation assay and chromosomal aberration assay), and implantation studies. The raw materials, other than [redacted] (coloring agent) used in Eustachian Tube Plug, are also used in contrast medium and CV Catheter (Approval number 22100BZX01081000) (hereinafter referred to as the company's approved product) that is classified in the same or higher contact risk category as Eustachian Tube Plug. Since no raw material-related malfunctions have been reported with the company's approved product, silicone rubber samples added with [redacted] were used in the biological safety studies. None of the above studies showed any problematic finding, assuring the biological safety of Eustachian Tube Plug.

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

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

2.(4) Stability and durability

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

Eustachian Tube Plug is produced with the same raw materials, other than [redacted], and by the same manufacturing process, and is subjected to the same sterilization method as the company's

approved product. The established expiration period of the company's approved product is >3 years. No problem related to the stability or durability of the raw materials has been reported since the approval.

For [redacted], a stability study was conducted under accelerated and real-time conditions using [redacted]-added silicone rubber samples. The study confirmed the stability of >3 years.

On the basis of this result, the expiration period of Eustachian Tube Plug of >3 years was proposed.

The applicant submitted a self-declaration regarding the stability and durability studies of Eustachian Tube Plug in accordance with the "Handling of stability studies related to the determination of the shelf life in the Application for Approvals (certifications) for Marketing Medical Devices" (PFSB/ELD/OMDE Notification No. 1227-5, dated February 8, 2013).

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

PMDA reviewed the data on the stability and durability of Eustachian Tube Plug and concluded that there was no particular problem.

2.(5) Performance

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

The applicant submitted performance data from appearance, tip shape, rupture strength, and radiopacity tests.

Eustachian Tube Plug was visually observed for its appearance to find no flaw, burr, or adhesion of foreign matter on the surface.

Eustachian Tube Plug was also visually observed for its tip shape to find that the tip was smooth and round.

The rupture strength of the main body and hooks was measured using samples of [redacted]. [redacted], the rupture strength of [redacted] was measured in a preliminary test of test samples. The results confirmed that [redacted] was the worst sample. The main body part was pulled at the tension rate of 500 mm/min, and the rupture strength was ≥[redacted]N. The hook part was pulled with the main body part secured, and the hook did not rupture at a strength of ≤[redacted]N.

The radiopacity test confirmed that the main body was visible under X-ray.

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

PMDA reviewed the data on the performance and concluded that there was no particular problem with the performance of Eustachian Tube Plug. PMDA also concluded that the proposed specification of rupture strength for the main body and hook parts were acceptable because Eustachian Tube Plug is a medical device that is inserted into the eustachian tube to narrow the excessively open eustachian tube

lumen and maintains the appropriate lumen size, and no excessive force is required to insert or remove it.

2.(6) Directions for use

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

The applicant did not submit data supporting the directions for use of Eustachian Tube Plug because the directions for use were verified in the clinical study.

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

An appropriate size of Eustachian Tube Plug needs to be selected according to the luminal diameter of patient's eustachian tube before insertion, and methods for size selection and precautions will be provided to users. The clinical study verified the directions for use and showed no malfunctions or plug rupture during insertion. For these reasons, PMDA concluded that there was no particular problem with the proposed directions for use.

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 Eustachian Tube Plug to the Essential Principles.

PMDA's conclusion on the conformity of Eustachian Tube Plug to Article 1, which defines preconditions, etc. for designing medical devices (particularly, the requirements for users, such as expected level of technical knowledge and experience, and expected level of education and training to be provided to users):

As explained later in Sections "6.B.(2) Efficacy," "6.B.(3) Safety," and "6.B.(4) Indication of Eustachian Tube Plug," selection of eligible patients and the size of Eustachian Tube Plug, and compliance with the precautions for the surgical procedure for the insertion of Eustachian Tube Plug are important. Treating physicians need to acquire knowledge to select an appropriate size of Eustachian Tube Plug for each patient so that the patient benefits from the treatment and experiences no adverse events, such as otitis media, attributable to eustachian tube obstruction, as well as skills to insert the device into the tube without affecting the ossicular chain, etc. The applicant explained that the relevant information would be provided to surgeons through training sessions. PMDA accepted the applicant's explanation.

PMDA's conclusion on the conformity of Eustachian Tube Plug to Article 17, which defines requirements for information provision to users using instructions for use, etc.:

As explained later in Section "6.B Outline of the review conducted by PMDA," because the treatment with Eustachian Tube Plug is predicted to cause serous otitis media due to its nature, patients need to be periodically followed up after the procedure and if uncontrollable otorrhoea occurs in association with infection, Eustachian Tube Plug must be removed immediately. In the clinical study, 1 patient required removal of the investigational device because of tinnitus. The relevant information on this subject needs to be appropriately provided to healthcare professionals. The applicant explained that the above 2 points would be provided in the instructions for use to raise cautions.

Since Eustachian Tube Plug is not the definitive therapy for patulous eustachian tube, patulous eustachian tube may recur after insertion of the device. When it recurs, the device may need to be replaced with a new one depending on the patient's condition, etc. The clinical study, however, did not verify the efficacy and safety of ≥2 replacements of the device. As such information needs to be provided to healthcare professionals to raise caution, PMDA instructed the applicant to provide the relevant information in the instructions for use, and the applicant agreed.

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

4. Risk Management

4.A. Summary of the data submitted

The applicant submitted a summary of risk management, the risk management system, and its implementation status in reference to ISO14971: 2007 "Medical devices—Application of risk management to medical devices."

4.B. Outline of the review conducted by PMDA

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

5. Manufacturing Process

5.A. Summary of the data submitted

The applicant submitted data on manufacturing process and site, quality control data, as well as sterilization method and sterility assurance for evaluation of the manufacturing process of Eustachian Tube Plug.

5.B. Outline of the review conducted by PMDA

PMDA reviewed the data on the manufacturing process of Eustachian Tube Plug and concluded that there was no particular problem.

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

6.A. Summary of the data submitted

This multicenter, open-label, uncontrolled study was conducted to assess the efficacy and safety of Eustachian Tube Plug in 30 patients with refractory patulous eustachian tube at 4 study sites in Japan

from June 2017 to January 2019. Table 5 presents a summary of the study protocol, and the primary inclusion and exclusion criteria.

Table 5. Summary of study protocol

Study objective	To confirm the efficacy and safety of PET001 (hereinafter referred to as the investigational device) in refractory patulous eustachian tube based on the level of improvement in patulous eustachian tube (primary endpoint).
Study type	Multicenter, open-label, uncontrolled study
Study population	Patients with refractory patulous eustachian tube
Inclusion criteria	Patients who meet all of the following criteria: (a) Patients with a definitive diagnosis of patulous eustachian tube at screening examination according to the draft diagnostic criteria for patulous eustachian tube 2016[4] (b) Patients who are not responding to conservative treatments such as lifestyle guidance and treatments for eustachian tube closure for ≥6 consecutive months (including treatment periods at other hospitals) at enrollment (c) Patients with a PHI10 score of ≥26 at screening examination (d) Patients with a mean air-conduction hearing ability of ≤40 dB at screening examination (e) Patient or the patient's legally acceptable representative (if necessary) is willing to provide written consent to participate in the study after a full explanation about the details of the study (f) Patients aged ≥12 years at the time of written informed consent (g) Patients being able to visit the study site according to the protocol-defined schedule
Exclusion criteria	Patients who meet any of the following criteria: (a) Patients with a history of infection of the external auditory canal or middle ear in ≤6 months before informed consent (b) Patients being pregnant or possibly pregnant at screening examination (c) Patients with allergy to lidocaine/Xylocaine (d) Patients with only hearing ear at screening examination (patients with a hearing ability of the non-test ear of ≥60 dB are excluded) (d) Patients with tympanic membrane perforation at screening examination (f) Patients with performance status (PS) of ≥2 at enrollment (g) Patients with any disease that interferes with accurate evaluation of the PHI10 questionnaire at screening examination (h) Patients who receive oral intake or periodic injection of any immunosuppressant or steroid at enrollment (i) Patients with presence of any foreign matter that interferes with the insertion of the investigational device as indicated by imaging findings at screening examination (j) Patients who participate in other clinical studies at enrollment (k) Patients who have been determined inappropriate by the investigator or subinvestigator
Sample size	30 patients
Method for use	An incision is made on the tympanic membrane, followed by implantation of the investigational device in the eustachian tube through the external auditory canal.
Efficacy endpoints	Primary endpoint: Level of improvement in subjective symptoms at Month 3 (percentage of patients with a PHI10 score of ≤16 points). In patients who have replaced the investigational device with a new one, the primary endpoint is the level of improvement in subjective symptoms 3 months from the date of device replacement. Secondary endpoints: • Level of improvement assessed by tubal function tests (sonotubometry, Tubo Tympano Aerodynamic Graphy [TTAG]) • Level of improvement assessed by visual inspection and auscultation (respiratory fluctuation of the tympanic membrane and otoscope findings)

Safety endpoints	(1) Adverse events (a) Serious postoperative pain (pain not responsive to various analgesics) (b) Severe infection (c) Haemorrhage (d) Deafness (≥40 dB) (e) Ear pain associated with pressure change (f) Other adverse events Planned hospitalization before and after the surgical procedure to insert the investigational device is within the scope of general medical care and is not reported as adverse events. (2) Malfunctions of investigational device
Criteria for replacement of investigational device	1. Not more than 2 months have passed since the implantation of the investigational device. 2. PHI10 score is ≥18 points before replacement of the investigational device. 3. Patulous eustachian tube is confirmed by the presence of respiratory fluctuation of the tympanic membrane, sonotubometry, or TTAG before replacement of the investigational device. 4. The patient requests replacement of the investigational device. 5. The investigational device has not been replaced since the first implantation. 6. No adverse event has occurred in the test ear. * The investigational device can be replaced when all of the above 6 criteria are met.
Duration of use	Long term
Follow-up period	6 months
Concomitant therapies	Concomitant use of conservative treatments for the treatment of patulous eustachian tube (e.g., nasal instillation of physiological saline, traditional Chinese medicines, and adenosine triphosphate disodium hydrate [ATP]) is permitted, provided that they have been administered to the patient before obtaining informed consent. The dosage and administration of conservative treatments should not be changed in principle. However, the dosage and administration may be adjusted according to the patient's condition at the discretion of the treating physician. If the patient strongly requests to receive new treatment for patulous eustachian tube of the non-test ear, the use of nasal instillation of physiological saline or treatment of the pharyngeal orifice of eustachian tube (e.g., application of gel or Lugol's solution) is permitted. Concomitant therapies other than those for patulous eustachian tube is permitted without restrictions. Possible concomitant therapies other than those for patulous eustachian tube • Antimicrobials to prevent infection • Insertion of an tympanic ventilation tube to treat serous otitis media • Use of an anesthetic or placement of chitin membrane sheet before insertion of the investigational device An oral antimicrobial will be started on the day of the surgery for prevention of perioperative infection. Postoperative infection, if it occurs, should be treated with oral or intravenous antibiotics, whichever is deemed appropriate according to the severity of infection and ear discharge culture, if necessary. Concomitant use of antimicrobial or anti-inflammatory analgesic eardrops is also permitted.

In this clinical study, 30 patients provided informed consent to participation. All of them were enrolled in the study (see Figure 3). One of the enrolled patients was hospitalized due to an accident after enrollment. The patient could not undergo any of the protocol-specified tests before the study treatment and was discontinued from the study before start of the study.

One of the remaining 29 patients who underwent the procedure to insert the investigational device was found with the bony part of the eustachian tube too narrow to insert even the smallest size of the investigational device during the surgical operation. The patient did not have the investigational device inserted. This patient was included in the safety analysis set because there might be patients with the same condition in the post-marketing setting.

Of the 28 patients who received the investigational device insertion, 27 patients completed the study, excluding 1 patient who was discontinued from the study due to a serious adverse event and had the investigational device removed.

Replacement of the investigational device was required in 4 of the 27 patients.

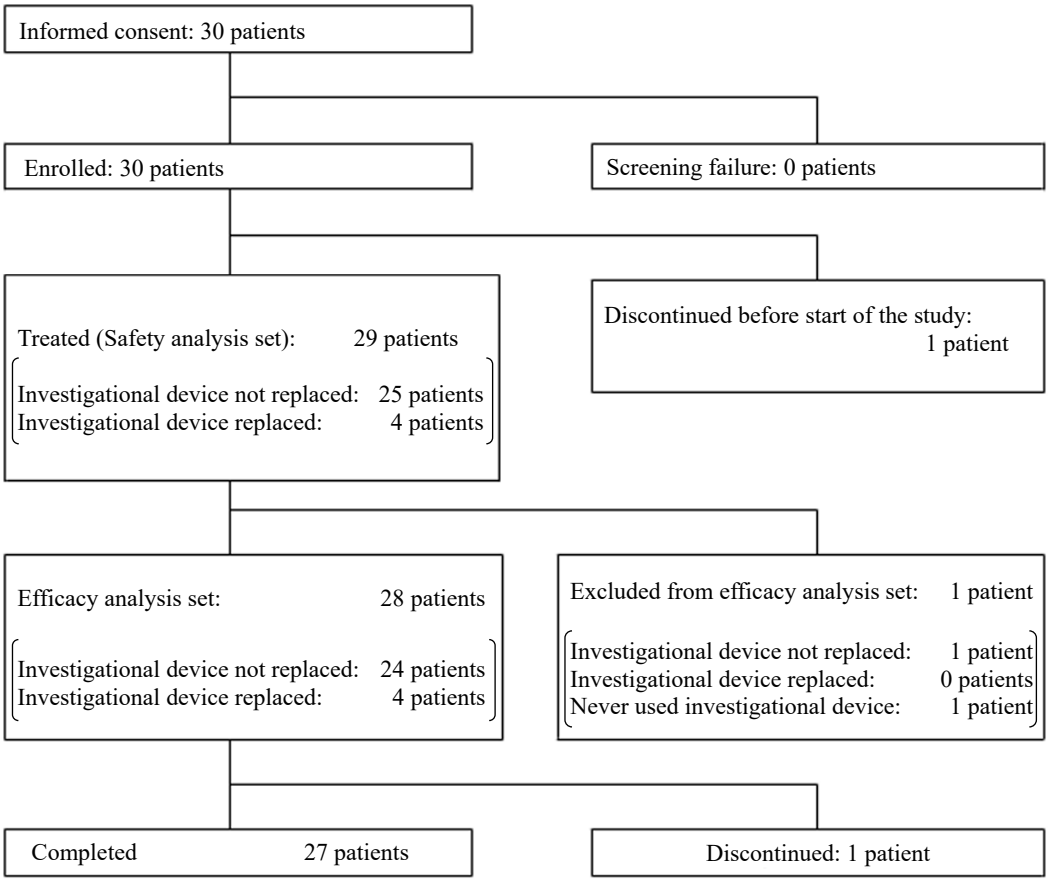

Figure 3. Disposition of patients

6.A.(1) Efficacy evaluation

6.A.(1).1) Primary endpoint

The primary efficacy endpoint of the clinical study was the level of improvement in subjective symptoms at 3 months after surgery (percentage of patients with a Patulous Eustachian tube Handicap Inventory 10 [PHI10] score of ≤16 points). In patients who replaced the investigational device with a new one, the primary endpoint was the level of improvement in subjective symptoms 3 months from the date of device replacement. PHI10 is a modified version of Tinnitus Handicap Inventory 12 (THI12),[5] an international rating scale of tinnitus (see Table 6).

Table 6. THI12 and PHI10 Questionnaire

Question			
No.	THI12	No.	PHI10
1	Because of your tinnitus is it difficult for you to concentrate?	1	Because of your symptom is it difficult for you to concentrate?
2	Does the loudness of your tinnitus make it difficult for you to hear people?	2	Does the loudness of your symptom make it difficult for you to hear people?
3	Does your tinnitus make you angry?	3	Does your symptom make you angry?
4	Do you feel as though you cannot escape your tinnitus?	4	Do you feel as though you cannot escape your symptom?
5	Does your tinnitus interfere with your ability to enjoy social activities?	5	Does your symptom interfere with your ability to enjoy social activities?
6	Because of your tinnitus do you feel frustrated?	6	Because of your symptom do you feel frustrated?
7	Does your tinnitus interfere with your job or household responsibilities?	7	Does your symptom interfere with your job or household responsibilities?
8	Because of your tinnitus is it difficult for you to read?	—	—
9	Do you feel that your tinnitus problem has placed stress on your relationship with members of your families and friends?	8	Do you feel that your symptom has placed stress on your relationships with members of your family and friends?
10	Do you find it difficult to focus your attention away from your tinnitus and on other things?	9	Do you find it difficult to focus your attention away from your symptom and on to other things?
11	Does your tinnitus make you feel anxious?	10	Does your symptom make you feel anxious?
12	Do you feel that you can no longer cope with your tinnitus?	—	—

*"Yes" = 4 points, "Sometimes" = 2 points, "No" = 0 points

Tinnitus also occurs in patients with most severe auditory disorders, indicating that the symptom can occur even when the patient is not speaking. On the other hand, patulous eustachian tube is characterized by autophony in which patients become aware of the symptom as they speak. For this reason, Question 8 of THI12, which is about the impact of the condition on reading, was removed from the PHI10 questionnaire. In addition to Question 8, statistical analysis of the usefulness and relevance of the 12 questions revealed that Question 12 was significantly less useful and relevant. Accordingly, Question 12 was also removed from the PHI10 questionnaire. The results of previous clinical research[6] that used THI12 showed no difference in the answer to Question 12 between patients treated with the Eustachian Tube Plug and patients treated with physiological saline.[7] This finding was also taken into account in the preparation of PHI10.

Before the development of PHI10, the scoring system by Poe et al.[8] was used when classifying treatment responses into (a) complete relief, (b) significant improvement (with occasional symptoms controlled by additional conservative treatments), (c) slight improvement (some improvement but definite residual symptoms requiring additional treatment), (d) unchanged, or (e) worse. Responders were defined as patients classified into (a) or (b). In the early stage of the previous clinical research, the efficacy of Eustachian Tube Plug was evaluated according to the above scoring system of Poe et al.[6] After PHI10 was developed, the efficacy of Eustachian Tube Plug was evaluated in 18 patients according to the scoring system by Poe et al. and PHI10 to assess the validity of PHI10. Patients with a PHI10 score of ≤16 points had consistent efficacy results with those obtained by the scoring system of Poe et al. The percentage of patients who demonstrated efficacy (response rate) was 77% in 18 patients using the cut-off score of 16 points, which was largely consistent with that in the previous clinical research in 252 patients. On the basis of this result, the applicant determined that PHI10 was a useful postoperative

rating scale. Accordingly, responders were defined as patients with a PHI10 score of ≤16 points for the clinical study. In the clinical study, patients indicated for the treatment with the Eustachian Tube Plug, in turn, had a PHI10 score of ≥26 points.

The mean total PHI10 score at 3 months after surgery, the primary endpoint, was 6.4 ± 9.0 points. A total of 23 patients were responders, which were defined as patients with a PHI10 score of ≤16 points, with the percentage of responders of 82.1% (95% confidence interval [CI], 63.1%-93.9%), which met the criterion for successful study (see Table 7).

Table 7. Level of improvement in subjective symptoms (PHI10 score)

Endpoint	Statistics or category	Efficacy analysis set
Level of improvement in subjective symptoms at Month 3 (PHI10 score)	Number of patients	28
	Mean ± SD	6.4 ± 9.0
	Median	2.0
	Minimum-Maximum	0-34
	Number of responders*1	23
	Percentage of responders*2	82.1
	95% CI of the percentage of responders*3	63.1%-93.9%

*1 Patients with a PHI10 score of ≤16 points after the surgery
*2 The successful study is defined as the percentage of responders of ≥70%.
*3 The threshold percentage of responders is assumed to be 40% because conventional therapies are unlikely to improve symptoms in patients with refractory patulous eustachian tube.

Table 8 and Figure 4 present PHI10 scores over time. The PHI10 score (mean ± standard deviation [SD]) decreased from 34.4 ± 4.2 points at baseline to 7.8 ± 9.8 points at Day 2, 6.4 ± 9.0 points at Month 3, and 5.7 ± 8.6 points at Month 6 ($P < 0.001$, paired t-test). Patients were followed up by telephone, etc. on the protocol-specified days in Months 1 and 2. Patients who had no abnormality and did not request replacement of the investigational device were allowed to skip Month 2 visit. PHI10 score was measured at Month 2, and 6 of 9 patients had a PHI10 score of ≥20 points. The PHI10 scores at Month 2 should be used for reference because 4 patients had an improved PHI10 score of ≤16 points at Month 3 (see Table 8 and Figure 4).

Table 8. Changes in PHI10 scores at each timepoint

	Baseline	Day 2	Month 1	Month 2	Month 3	Month 6	Discontinuation
Number of patients	28	28	28	9	28	27	1
Mean	34.4	7.8	8.6	20.7	6.4	5.7	0.0
SD	4.2	9.8	9.9	11.1	9.0	8.6	—
Minimum	26	0	0	0	0	0	0
Median	34	2.0	3.0	22.0	2.0	2.0	0.0
Maximum	40	34	32	34	34	34	0
P-value (paired t-test)	—	<0.001	<0.001	0.006	<0.001	<0.001	—

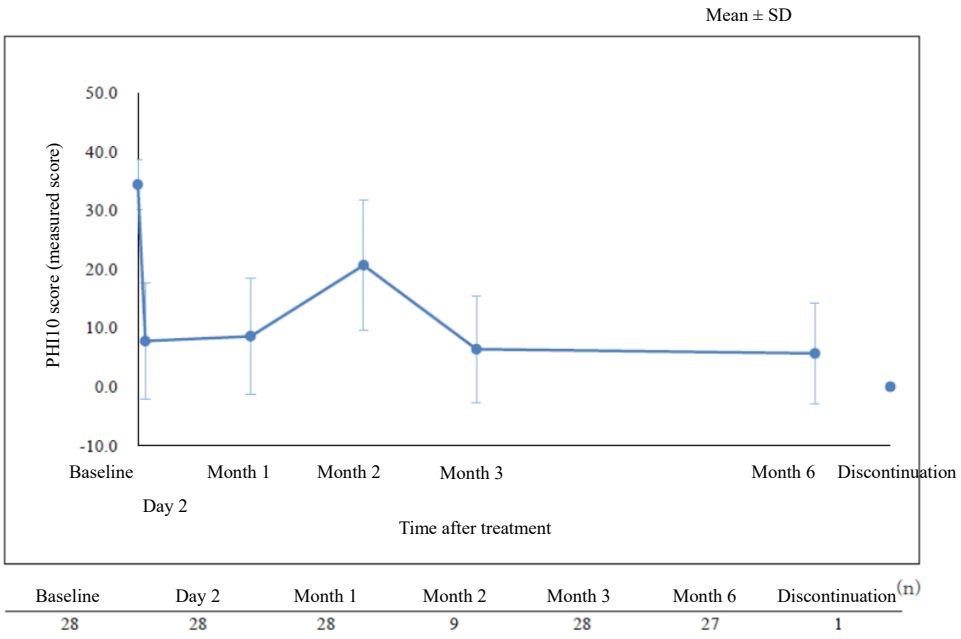

Figure 4. Changes in PHI10 scores at each timepoint

6.A.(1).2) Secondary endpoints

6.A.(1).2).i) Sonotubometry

Sonotubometry is a test to detect patulous eustachian tube. The test measures the sound pressure level of a probe sound applied in the nasopharyngeal cavity, using a microphone placed in the external auditory canal. The state of eustachian tube is evaluated based on the applied sound pressure and a patterned change during swallowing. Open eustachian tube is defined as the applied sound pressure is <100 dB or an open plateau pattern upon swallowing.[9]

Findings of sonotubometry were positive for patulous eustachian tube in 21 patients and negative in 7 patients at baseline. No positive finding was observed in 22 patients at Month 3, and 27 patients at Month 6 (see Table 9).

The applied sound pressure (mean ± SD) (dB) measured by sonotubometry was 96.61 ± 11.71 dB at baseline, 107.64 ± 11.33 dB at Month 1, 108.39 ± 11.06 dB at Month 3, and 109.89 ± 7.50 dB at Month 6 (see Table 10).

Table 9. Changes in sonotubometry findings

Timepoint		Baseline					
		Positive (n = 21)		Negative (n = 7)		Total (n = 28)	
Day 2	Positive	0	(0.0%)	0	(0.0%)	0	(0.0%)
	Negative	6	(75.0%)	2	(25.0%)	8	(100.0%)
	Total	6	(75.0%)	2	(25.0%)	8	(100.0%)
Month 1	Positive	5	(17.9%)	1	(3.6%)	6	(21.4%)
	Negative	16	(57.1%)	6	(21.4%)	22	(78.6%)
	Total	21	(75.0%)	7	(25.0%)	28	(100.0%)
Month 2	Positive	0	(0.0%)	1	(33.3%)	1	(33.3%)
	Negative	1	(33.3%)	1	(33.3%)	2	(66.7%)
	Total	1	(33.3%)	2	(66.7%)	3	(100.0%)
Month 3	Positive	5	(17.9%)	1	(3.6%)	6	(21.4%)
	Negative	16	(57.1%)	6	(21.4%)	22	(78.6%)
	Total	21	(75.0%)	7	(25.0%)	28	(100.0%)
Month 6	Positive	0	(0.0%)	0	(0.0%)	0	(0.0%)
	Negative	20	(74.1%)	7	(25.9%)	27	(100.0%)
	Total	20	(74.1%)	7	(25.9%)	27	(100.0%)
Discontinuation	Positive	0	(0.0%)	0	(0.0%)	0	(0.0%)
	Negative	1	(100.0%)	0	(0.0%)	1	(100.0%)
	Total	1	(100.0%)	0	(0.0%)	1	(100.0%)

* Findings were positive in 21 patients and negative in 7 patients at baseline (total number of patients, 28).
* The percentage (%) was calculated using the total number of patients at each timepoint as the parameter.

Table 10. Sonotubometry results, change in altered sound pressure (dB) at each timepoint

	Baseline	Day 2	Month 1	Month 2	Month 3	Month 6	Discontinuation
Number of patients	28	8	28	3	28	27	1
Mean (dB)	96.61	117.00	107.64	101.33	108.39	109.89	113.00
SD (dB)	11.71	4.50	11.33	11.93	11.06	7.50	—
Minimum (dB)	76.0	109.0	81.0	88.0	78.0	101.0	113.0
Median (dB)	96.50	117.50	109.00	105.00	109.00	108.00	113.00
Maximum (dB)	121.0	123.0	123.0	111.0	123.0	123.0	113.0
P-value (paired t-test)	—	0.002	<0.001	0.816	<0.001	<0.001	—

6.A.(1).2).ii) Tubo Tympano Aerodynamic Graphy (TTAG)

TTAG is a test to detect patulous eustachian tube by measuring changes in the pressure of the nasopharyngeal cavity transmitted to the middle ear with a pressure transducer inserted in the external auditory canal. In patients with patulous eustachian tube, a synchronous change with a pressure change in the nasopharynx upon sniffing or deep breathing is observed as a fluctuation in the pressure of the external auditory canal.[9, 10]

Findings of TTAG were positive for patulous eustachian tube in 25 of 28 patients and negative in 3 patients at baseline. No positive finding was observed in 26 patients at Month 3, and 22 of 25 patients at Month 6 (see Table 11).

Table 11. Changes in TTAG findings

Timepoint		Baseline					
		Positive (n = 25)		Negative (n = 3)		Total (n = 28)	
Day 2	Positive	0	(0.0%)	0	(0.0%)	0	(0.0%)
	Negative	2	(100.0%)	0	(0.0%)	2	(100.0%)
	Total	2	(100.0%)	0	(0.0%)	2	(100.0%)
Month 1	Positive	4	(23.5%)	0	(0.0%)	4	(23.5%)
	Negative	12	(70.6%)	1	(5.9%)	13	(76.5%)
	Total	16	(94.1%)	1	(5.9%)	17	(100.0%)
Month 2	Positive	0	(0.0%)	0	(0.0%)	0	(0.0%)
	Negative	2	(66.7%)	1	(33.3%)	3	(100.0%)
	Total	2	(66.7%)	1	(33.3%)	3	(100.0%)
Month 3	Positive	2	(7.1%)	0	(0.0%)	2	(7.1%)
	Negative	23	(82.1%)	3	(10.7%)	26	(92.9%)
	Total	25	(89.3%)	3	(10.7%)	28	(100.0%)
Month 6	Positive	3	(12.0%)	0	(0.0%)	3	(12.0%)
	Negative	20	(80.0%)	2	(8.0%)	22	(88.0%)
	Total	23	(92.0%)	2	(8.0%)	25	(100.0%)
Discontinuation	Positive	0	(0.0%)	0	(0.0%)	0	(0.0%)
	Negative	0	(0.0%)	1	(100.0%)	1	(100.0%)
	Total	0	(0.0%)	1	(100.0%)	1	(100.0%)

* Findings were positive in 25 patients and negative in 3 patients at baseline (total number of patients, 28).
* The percentage (%) was calculated using the total number of patients at each timepoint as the parameter.

6.A.(1).2).iii) Respiratory fluctuation of the tympanic membrane

The tympanic membrane of the patient is monitored with a microscope or endoscopy during forced deep breathing via the ipsilateral nostril. Synchronous fluctuation of the tympanic membrane with breathing is defined as positive for patulous eustachian tube.

Respiratory fluctuation of the tympanic membrane was observed in 19 of 28 patients and no fluctuation was observed in 9 patients at baseline. Respiratory fluctuation was observed in 1 patient at Month 1. From Months 1 to 6, no patient with a new respiratory fluctuation was identified (see Table 12).

Table 12. Changes in respiratory fluctuation of the tympanic membrane

Timepoint		Baseline					
		Positive (n = 19)		Negative (n = 9)		Total (n = 28)	
Day 2	Positive	0	(0.0%)	0	(0.0%)	0	(0.0%)
	Negative	11	(84.6%)	2	(15.4%)	13	(100.0%)
	Total	11	(84.6%)	2	(15.4%)	13	(100.0%)
Month 1	Positive	1	(3.6%)	0	(0.0%)	1	(3.6%)
	Negative	18	(64.3%)	9	(32.1%)	27	(96.4%)
	Total	19	(67.9%)	9	(32.1%)	28	(100.0%)
Month 2	Positive	1	(8.3%)	0	(0.0%)	1	(8.3%)
	Negative	4	(33.3%)	7	(58.3%)	11	(91.7%)
	Total	5	(41.7%)	7	(58.3%)	12	(100.0%)
Month 3	Positive	1	(3.6%)	0	(0.0%)	1	(3.6%)
	Negative	18	(64.3%)	9	(32.1%)	27	(96.4%)
	Total	19	(67.9%)	9	(32.1%)	28	(100.0%)
Month 6	Positive	1	(3.7%)	0	(0.0%)	1	(3.7%)
	Negative	17	(63.0%)	9	(33.3%)	26	(96.3%)
	Total	18	(66.7%)	9	(33.3%)	27	(100.0%)
Discontinuation	Positive	0	(0.0%)	0	(0.0%)	0	(0.0%)
	Negative	1	(100.0%)	0	(0.0%)	1	(100.0%)
	Total	1	(100.0%)	0	(0.0%)	1	(100.0%)

* Findings were positive in 19 patients and negative in 9 patients at baseline (total number of patients, 28).
* The percentage (%) was calculated using the total number of patients at each timepoint as the parameter.

6.A.(1).2).iv) Sound leakage from the external auditory canal based on otoscopic findings

Otoscopy is performed to detect sound leakage from the external auditory canal. After an otoscope is inserted into the patient's external auditory canal, the patient is asked to speak. Using an auscultation tube connecting the patient's test ear to the examiner's ear, the examiner checks sound leakage from the external auditory canal. Positive sound leakage is defined as the hearing of abnormally loud sounds.[11]

Otoscopic findings were positive for sound leakage from the external auditory canal in 20 of 28 patients and negative in 8 patients at baseline. Negative finding was observed in all patients on Day 2 and at Month 1. Positive finding was observed in 1 patient at Months 3 and 6 (see Table 13).

Table 13. Sound leakage from the external auditory canal based on otoscopic finding

Timepoint		Baseline					
		Positive (n = 20)		Negative (n = 8)		Total (n = 28)	
Day 2	Positive	0	(0.0%)	0	(0.0%)	0	(0.0%)
	Negative	20	(71.4%)	8	(28.6%)	28	(100.0%)
	Total	20	(71.4%)	8	(28.6%)	28	(100.0%)
Month 1	Positive	0	(0.0%)	0	(0.0%)	0	(0.0%)
	Negative	20	(71.4%)	8	(28.6%)	28	(100.0%)
	Total	20	(71.4%)	8	(28.6%)	28	(100.0%)
Month 2	Positive	1	(10.0%)	0	(0.0%)	1	(10.0%)
	Negative	6	(60.0%)	3	(30.0%)	9	(90.0%)
	Total	7	(70.0%)	3	(30.0%)	10	(100.0%)
Month 3	Positive	1	(3.6%)	0	(0.0%)	1	(3.6%)
	Negative	19	(67.9%)	8	(28.6%)	27	(96.4%)
	Total	20	(71.4%)	8	(28.6%)	28	(100.0%)
Month 6	Positive	1	(3.7%)	0	(0.0%)	1	(3.7%)
	Negative	18	(66.7%)	8	(29.6%)	26	(96.3%)
	Total	19	(70.4%)	8	(29.6%)	27	(100.0%)
Discontinuation	Positive	0	(0.0%)	0	(0.0%)	0	(0.0%)
	Negative	1	(100.0%)	0	(0.0%)	1	(100.0%)
	Total	1	(100.0%)	0	(0.0%)	1	(100.0%)

* Finding was positive in 20 patients and negative in 8 patients at baseline (total number of patients, 28).
* The percentage (%) was calculated using the total number of patients at each timepoint as the parameter.

6.A.(2) Safety evaluation

For adverse events, 29 patients who underwent the surgical procedure to insert the investigational device were included in analysis. A total of 49 adverse events were reported in 21 of the 29 patients included in the safety analysis (see Table 14).

Main adverse events were procedural pain, otitis media, and tympanic membrane perforation. All of these events were Grade ≤2 in severity and resolved or were resolving during the study period. Adverse events that may occur in relation to standard middle ear operation included serious postoperative pain, severe infection, haemorrhage, deafness, and ear pain associated with a change in air pressure. In the clinical study, haemorrhage (1 event) and ear pain associated with a change in air pressure (1 event) were reported.

Serious adverse events were reported in 3 patients (4 events). Of these, serious adverse event for which a causal relationship to Eustachian Tube Plug was related or could not be ruled out was reported in 1 patient (1 event). The patient experienced serious tinnitus with insomnia and dysphoria due to accompanying symptoms. The investigational device was removed upon request by the patient. The insertion of the investigational device was unlikely to have caused this severe inner ear disorder because it did not occur immediately after the insertion of the investigational device. However, conductive deafness induced by a large tympanic membrane perforation might have contributed to refractory tinnitus. For the serious adverse event, therefore, a causal relationship to Eustachian Tube Plug could not be ruled out by the investigator. The serious adverse event was resolving after the removal of the investigational device and tympanic membrane perforation closure. Other than this serious adverse event, 3 serious adverse events were reported, for which a causal relationship to the investigational device was denied because they did not occur in the ears. Neither deaths nor malfunctions were reported in the clinical study.

Table 14. Adverse events reported in the clinical study

Event term	Safety analysis set (n = 29)					
	Grade 1		Grade 2		Grade 3	
	No. of events	No. of patients with event (%)	No. of events	No. of patients with event (%)	No. of events	No. of patients with event (%)
Infections and infestations	3	1 (3.4%)	16	12 (41.9%)	0	0 (0.0%)
Gastroenteritis	0	0 (0.0%)	1	1 (3.4%)	0	0 (0.0%)
Influenza	0	0 (0.0%)	2	2 (6.9%)	0	0 (0.0%)
Mastitis	0	0 (0.0%)	1	1 (3.4%)	0	0 (0.0%)
Nasopharyngitis	3	1 (3.4%)	5	4 (13.8%)	0	0 (0.0%)
Otitis media	0	0 (0.0%)	5	5 (17.2%)	0	0 (0.0%)
Otitis media acute	0	0 (0.0%)	1	1 (3.4%)	0	0 (0.0%)
Pharyngitis	0	0 (0.0%)	1	1 (3.4%)	0	0 (0.0%)
Blood and lymphatic system disorders	0	0 (0.0%)	0	0 (0.0%)	1	1 (3.4%)
Haemorrhagic anaemia	0	0 (0.0%)	0	0 (0.0%)	1	1 (3.4%)
Nervous system disorders	0	0 (0.0%)	2	2 (6.9%)	0	0 (0.0%)
Dizziness	0	0 (0.0%)	1	1 (3.4%)	0	0 (0.0%)
Headache	0	0 (0.0%)	1	1 (3.4%)	0	0 (0.0%)
Eye disorders	0	0 (0.0%)	1	1 (3.4%)	0	0 (0.0%)
Retinal haemorrhage	0	0 (0.0%)	1	1 (3.4%)	0	0 (0.0%)
Ear and labyrinth disorders	2	2 (6.9%)	5	4 (13.8%)	1	1 (3.4%)
Ear pain	0	0 (0.0%)	1	1 (3.4%)	0	0 (0.0%)
Eustachian tube patulous	0	0 (0.0%)	1	1 (3.4%)	0	0 (0.0%)
Tinnitus	0	0 (0.0%)	1	1 (3.4%)	1	1 (3.4%)
Tympanic membrane perforation	2	2 (6.9%)	2	2 (6.9%)	0	0 (0.0%)
Respiratory, thoracic and mediastinal disorders	1	1 (3.4%)	1	1 (3.4%)	0	0 (0.0%)
Upper respiratory tract inflammation	0	0 (0.0%)	1	1 (3.4%)	0	0 (0.0%)
Oropharyngeal discomfort	1	1 (3.4%)	0	0 (0.0%)	0	0 (0.0%)
Gastrointestinal disorders	0	0 (0.0%)	0	0 (0.0%)	1	1 (3.4%)
Gastric polyps	0	0 (0.0%)	0	0 (0.0%)	1	1 (3.4%)
Hepatobiliary disorders	0	0 (0.0%)	0	0 (0.0%)	1	1 (3.4%)
Hyperplastic cholecystopathy	0	0 (0.0%)	0	0 (0.0%)	1	1 (3.4%)
Skin and subcutaneous tissue disorders	1	1 (3.4%)	1	1 (3.4%)	0	0 (0.0%)
Scab	1	1 (3.4%)	1	1 (3.4%)	0	0 (0.0%)
General disorders and administration site conditions	1	1 (3.4%)	1	1 (3.4%)	0	0 (0.0%)
Pyrexia	1	1 (3.4%)	0	0 (0.0%)	0	0 (0.0%)
Medical device pain	0	0 (0.0%)	1	1 (3.4%)	0	0 (0.0%)
Injury, poisoning and procedural complications	1	1 (3.4%)	9	7 (24.1%)	0	0 (0.0%)
Post procedural haemorrhage	0	0 (0.0%)	1	1 (3.4%)	0	0 (0.0%)
Procedural pain	1	1 (3.4%)	8	7 (24.1%)	0	0 (0.0%)

* No Grade 4 or 5 adverse event was reported.

Table 15. Grading criteria for adverse events

Grade	Severity
1	Mild; Asymptomatic or mild symptoms; clinical or diagnostic observations only; no intervention indicated.
2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.*1
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.*2
4	Life-threatening consequences; urgent intervention indicated.
5	Death related to adverse event.

*1 Instrumental activities of daily living include meal preparation, shopping for personal items and clothes, using the telephone, and managing personal finances.

*2 Activities of daily living include bathing, dressing, eating, toileting, taking medicines, and ambulating.

6.B. Outline of the review conducted by PMDA

Taking account of the comments from the Expert Discussion, PMDA conducted reviews focusing on the following issues:

(1) Appropriateness of the clinical study design

1) Efficacy evaluation using PHI10
2) Definition of responders (patients with a PHI10 score of ≤16 points)
3) Sample size
4) Duration of follow-up

(2) Efficacy
1) Patients with subjective symptoms improved but some objective findings not improved
2) Patients found to be pregnant after surgery

(3) Safety
1) Adverse events
2) Replacement of Eustachian Tube Plug

(4) Indication of Eustachian Tube Plug

(5) Clinical significance

(6) Necessity of use-results survey

6.B.(1) Appropriateness of the clinical study

6.B.(1).1) Efficacy evaluation using PHI10

The applicant's explanation on the primary efficacy endpoint for the clinical study:

Tinnitus is abnormal ear noise the patient hears in the absence of a sound source. In severe cases, the abnormal auditory perception substantially interferes with activities of the patient's daily living. The main symptoms of patulous eustachian tube are autophony, sensation of ear congestion, and autophony of breathing sounds. Because patulous eustachian tube is similar to tinnitus in that the patient's quality of life (QOL) is impaired by abnormal auditory perception that cannot be controlled by patients themselves, the PHI10 questions were developed for patulous eustachian tube with reference to THI12.

PMDA's view:

Currently, there is no established rating scale to assess the effect of abnormal auditory perception caused by patulous eustachian tube on activities of daily living. Developing PHI10 based on THI12, an international rating scale of tinnitus whose reliability and validity have been established, is acceptable. Removing the 2 questions in THI12 that were found to be not correlated to symptoms of patulous eustachian tube to develop PHI10 based on the results of the previous clinical research is also appropriate. The 3 major symptoms of patulous eustachian tube are autophony, sensation of ear congestion, and autophony of breathing sounds. Although PHI10 is not intended to identify which of the 3 major symptoms is improved by the treatment, comprehensively assessing the effect of the 3 symptoms on the activities of daily living using PHI10 is reasonable because symptoms of patulous eustachian tube vary and their severity depend on individual patients.

6.B.(1).2) Definition of responders (patients with a PHI10 score of ≤16 points)

The applicant's explanation on the appropriateness of defining responders as patients with a PHI10 score of ≤16 points:

Before the development of PHI10, the developer of Eustachian Tube Plug evaluated the efficacy of treatment of patulous eustachian tube using the evaluation method by Poe et al.[8] The treatment responses were classified into (a) complete relief, (b) significant improvement, (c) slight improvement, (d) unchanged, and (e) worse. Responders were defined as patients classified into (a) or (b).

After PHI10 was developed, the efficacy of Eustachian Tube Plug was evaluated in 18 patients according to the aforementioned efficacy endpoint in the previous clinical research. Patients with a PHI10 score of ≤16 points had consistent efficacy results with those obtained by the scoring system of Poe et al. The efficacy of Eustachian Tube Plug was evaluated in 18 patients using the cut-off score of 16 points and the response rate was 77%, which was largely consistent with that in the previous clinical research in 252 patients. The result indicated the usefulness of PHI10 as postoperative evaluation criteria.

PMDA's view:
The development of PHI10 to quantitatively assess the severity of patulous eustachian tube by modifying the qualitative assessment of Poe et al. is of significance in providing a useful assessment tool for clinical studies in the field of sensory organs, such as otorhinolaryngology. Evaluating the efficacy of Eustachian Tube Plug using the cut-off score of PHI10 determined based on the scoring system of Poe et al. is, therefore, acceptable. Because improvement in the PHI10 score from ≥26 to ≤16 points appears to correspond to a change in the frequency of interference by symptoms from "Often" to "Sometimes" in ≥5 question items or to "Never" in ≥2 question items, setting 16 points as the cut-off score is of clinical significance. This clinical study showed that the mean PHI10 score improved from 34.4 ± 4.2 to 6.4 ± 9.0, indicating a greater level of improvement than the above frequency of interference by symptoms. In conclusion, a decreased frequency of interference with activities of daily living is of clinical significance in patients suffering from refractory patulous eustachian tube.

6.B.(1).3) Sample size

The applicant's explanation on the appropriateness of the sample size:
The expected percentage of patients experiencing improvement in subjective symptoms of patulous eustachian tube, the primary endpoint, was estimated to be 70% with reference to the results of research on treatment methods of refractory patulous eustachian tube.[1] The threshold percentage of responders was assumed to be 40% because conventional therapies are unlikely to improve refractory patulous eustachian tube. Assuming a two-sided significance level of 2.5% and a power of 80%, the clinical study required 24 patients. Allowing for dropouts, etc., the target sample size of 30 was determined.

PMDA's view:
Estimating the threshold percentage of responders to determine the sample size for the clinical study is appropriate taking into account that conventional therapies are unlikely to improve refractory patulous eustachian tube and there is no established standard therapy for refractory patulous eustachian tube in Japan. It is of clinical significance that ≥40% of patients who do not respond to conservative treatments for ≥6 months and suffer from symptoms of patulous eustachian tube responded to the treatment.

6.B.(1).4) Duration of follow-up

The applicant's explanation on the appropriateness of the follow-up period:
In the previous clinical research, 18 of 137 patients (13.1%) underwent device replacement with the new model due to poor response or discomfort. Of these patients, 14 patients (77.8%) underwent device replacement within 6 months after the insertion of the device. Accordingly, follow-up of approximately 6 months after the final insertion of the Eustachian Tube Plug was considered sufficient to evaluate the long-term safety. Thus, the follow-up duration of 6 months was determined.

The mechanism of action of Eustachian Tube Plug and the results of the previous clinical research, etc. indicate improvement in autophony due to patulous eustachian tube 1 or 2 months after device insertion. Thus, efficacy was evaluated at Month 3, by which time the concept of Eustachian Tube Plug was expected to be achieved. For patients with patulous eustachian tube, having no symptoms for 3 months will profoundly improve the QOL. If symptoms recur, Eustachian Tube Plug needs to be replaced. Patients who responded once to this treatment are most likely to respond to the treatment again after device replacement. This also supports the efficacy evaluation at Month 3.

PMDA's view:
Factors involved in the occurrence of patulous eustachian tube include acute body weight loss, pregnancy, the use of oral contraceptives, otitis media, exercise, and cleft palate. Considering that Eustachian Tube Plug is a medical device that narrows the excessively open eustachian tube lumen and maintains the appropriate lumen size, the device may need to be replaced with a new one if symptoms recur after the insertion of Eustachian Tube Plug. Nevertheless, the maintenance of efficacy and long-term safety of Eustachian Tube Plug need to be evaluated since it would be placed in the eustachian tube for a long time.

The efficacy should be evaluated at an appropriate timepoint after symptoms stabilizes with insertion of the Eustachian Tube Plug and before patulous eustachian tube recurs. Considering that Eustachian Tube Plug is a medical device to be inserted into the eustachian tube to narrow the excessively open eustachian tube lumen, the efficacy is expected to appear immediately after the surgery. In fact, the previous clinical research, etc. demonstrated improvement in symptoms 1 or 2 months after insertion. However, Eustachian Tube Plug would be placed in the eustachian tube for a long time. Evaluating its efficacy 3 months after insertion is acceptable to evaluate the maintenance of efficacy. For patients suffering from symptoms of patulous eustachian tube for ≥6 months for which no effective treatment is available, having no symptoms for ≥3 months will improve their QOL. Having the maintained efficacy for ≥3 months is of clinical significance.

The safety of Eustachian Tube Plug can be evaluated based on findings at 6 months after surgery because patients who participated in the previous clinical research have experienced no significant adverse event to date and patients who participated in the clinical study did not experience new adverse event up to this submission since the completion of the study. Patients in the clinical study underwent the insertion of investigational device between August 2017 and January 2018, including the winter when serous otitis media is likely to occur in association with cold symptoms. This follow-up period was appropriate for safety evaluation.

6.B.(2) Efficacy

6.B.(2).1) Patients with subjective symptoms improved but some objective findings not improved

In the clinical study, 4 patients shown in Table 16 had improved subjective symptoms as confirmed by their PHI10 scores, but some objective findings of sonotubometry, TTAG, respiratory fluctuation of tympanic membrane, and otoscopy did not improve.

The applicant's explanation on patients with subjective symptoms improved but some objective findings not improved:
These patients had a PHI10 score of ≤16 points, which resulted in a decreased number of positive objective findings. In addition, they noticed improved symptoms of patulous eustachian tube. For these reasons, it is reasonable to include them in responders.

PMDA's view:
The objective tests are poorly reproducible, and subjective symptoms and objective findings in patients with patulous eustachian tube do not always correlate with each other, thus, individual objective findings do not necessarily reflect the patient's pathological condition. These patients had a decreased number of positive objective findings. Besides, the main goal of treatment of patulous eustachian tube is improvement in patient's subjective symptoms. It can be concluded that the efficacy of Eustachian Tube Plug was confirmed in patients with an improved PHI10 score in the clinical study. In addition, even when the 4 patients in Table 16 were excluded, 19 of 28 patients responded to the treatment, with the percentage of responders of 67.9% (95% CI, 47.6%-84.1%), which exceeded the threshold percentage of responders of 40%, indicating the efficacy of Eustachian Tube Plug.

Table 16. Patients with subjective symptoms improved but some objective findings not improved

Patient code	Endpoint		Baseline	Month 3
NU-002 (302)	Primary endpoint	PHI10 score	34	6
	Secondary endpoints	Sonotubometry	Positive	Positive
		TTAG	Positive	Positive
		Respiratory fluctuation of the tympanic membrane	Positive	Negative
		Otoscopic finding	Positive	Positive
NU-003 (304)	Primary endpoint	PHI10 score	34	10
	Secondary endpoints	Sonotubometry	Positive	Positive
		TTAG	Positive	Negative
		Respiratory fluctuation of the tympanic membrane	Positive	Negative
		Otoscopic finding	Positive	Negative
NU-008 (308)	Primary endpoint	PHI10 score	40	6
	Secondary endpoints	Sonotubometry	Positive	Positive
		TTAG	Positive	Negative
		Respiratory fluctuation of the tympanic membrane	Positive	Negative
		Otoscopic finding	None	Negative
NU-011 (311)	Primary endpoint	PHI10 score	26	6
	Secondary endpoints	Sonotubometry	Positive	Positive
		TTAG	Positive	Negative
		Respiratory fluctuation of the tympanic membrane	Positive	Negative
		Otoscopic finding	Positive	Negative

6.B.(2).2) Patients found to be pregnant after surgery

The applicant's explanation:
Patient numbers 105 and 402 shown in Table 17 were found pregnant after the surgery in the clinical study. Patient number 105 was pregnant at the screening examination (September 26, 2017), but was not aware of her pregnancy at that timepoint. On a postoperative day (October 10, 2017), she was found to be at 6 weeks of pregnancy. Patient number 402 was at 5 months of pregnancy on June 8, 2018 when

the outcome of an adverse event in the non-test ear (right eustachian tube patulous, onset on March 2, 2018) was confirmed.

Since pregnancy is expected to facilitate eustachian tube opening, data from pregnant patients may lead to underestimation of the efficacy of Eustachian Tube Plug. Still, there would be no problem with including the results from these patients in efficacy analysis. On the other hand, patients being pregnant or possibly pregnant at the screening examination must be excluded from the clinical study according to exclusion criterion (b) of the clinical study. This exclusion criterion was described in the justification section of the study protocol that symptoms of patulous eustachian tube may regress after delivery.

PMDA's view:
Patient number 402 had symptoms of patulous eustachian tube before her pregnancy. Since her pregnancy did not cause the disease, inclusion of the patient in efficacy and safety analyses is acceptable.

Patient number 105 was pregnant at the screening examination. However, the patient was not responding to conservative treatments for ≥6 consecutive months at enrollment as described in the inclusion criterion (b) of the clinical study. It is evident that the patient developed patulous eustachian tube of the test ear before her pregnancy. In addition, new adverse event has not been reported between the completion of the clinical study and the submission of application on June 18, 2019. These suggest that no causal relationship is found between pregnancy and patulous eustachian tube in this patient. Inclusion of patient number 105 in efficacy and safety analyses is also acceptable.

Table 17. Changes in PHI10 scores in patients found to be pregnant after surgery

Patient number	Test ear	Visit	Conducted/ not conducted	Date	Total PHI10 score
105	Right	Screening	Conducted	09/26/2017	40
		Date of surgery (before treatment)	Not conducted	—	—
		Day 2	Conducted	09/27/2017	0
		Month 1	Conducted	10/24/2017	0
		Month 2	Not conducted	—	—
		Month 3	Conducted	12/19/2017	0
		Month 6	Conducted	02/20/2018	0
402	Left	Screening	Conducted	09/14/2017	40
		Date of surgery (before treatment)	Not conducted	—	—
		Day 2	Conducted	09/21/2017	0
		Month 1	Conducted	10/12/2017	0
		Month 2	Not conducted	—	—
		Month 3	Conducted	11/30/2017	0
		Month 6	Conducted	03/02/2018	0

6.B.(3) Safety

6.B.(3).1) Adverse events

Of adverse events for which a causal relationship to Eustachian Tube Plug was assessed as causally related or could not be ruled out, an event in 1 patient led to study discontinuation, and the incidence was 3.4%. The patient experienced Grade 3 tinnitus with insomnia and dysphoria due to accompanying symptoms. The investigational device was removed upon request by the patient. Tinnitus was considered clinically manageable since the event resolved after the removal of the investigational device and closure

of tympanic membrane perforation, and occurred in 1 of 29 patients. Relevant information on this event needs to be provided in the instructions for use, etc.

Ear and labyrinth disorders causally related to Eustachian Tube Plug were ear pain in 1 patient, tinnitus in 2 patients, and tympanic membrane perforation in 4 patients. The severity of these events was Grade 2 for ear pain, and Grades 1 and 2 for tympanic membrane perforation. These events were resolving or resolved with concomitant medication. The events were considered clinically acceptable.

In this clinical study, 5 of 29 patients experienced serous otitis media.

The applicant explained that the incidence of these adverse events was clinically acceptable because all of them commonly occur with any surgical procedure on the eustachian tube.

PMDA's view:
The events of serous otitis media were clinically manageable because they were Grade 2 and were resolving or resolved with concomitant medication. New case of serous otitis media has not been reported up to the submission since the completion of the clinical study. In view of the above, serous otitis media is considered clinically acceptable. Nevertheless, because serous otitis media is anticipated to occur in the treatment with Eustachian Tube Plug, by its nature, patients need to be periodically followed up after the surgery and if uncontrollable otorrhoea occurs in association with infection, Eustachian Tube Plug must be removed immediately. PMDA concluded that such information should be provided to healthcare professionals using the instructions for use. In addition, as described later in the approval condition, treating physicians must be required to take training sessions, etc. to acquire adequate knowledge and relevant skills on patulous eustachian tube and insertion of the Eustachian Tube Plug.

On the basis of the above, PMDA concluded that there was no particular problem with the safety of Eustachian Tube Plug, including the surgical procedure. As described later in Section "(2) Post-marketing safety measures" of "IV. Overall Evaluation," relevant information on precautions for surgical procedure and expected adverse events should be appropriately provided to healthcare professionals.

Table 18. Information on patients with otitis media

Patient number	Date of surgery	Adverse event	Date of onset	Date of outcome confirmed	Outcome	Action taken with investigational device
107	10/17/2017	Postoperative pain	10/17/2017	10/18/2017	Resolved	None
		Serous otitis media	11/14/2017	04/24/2018	Resolved	None
112	12/19/2017	Postoperative pain	01/09/2018	02/14/2018	Resolved	None
		Serous otitis media	03/30/2018	Ongoing	Resolving	None
		Influenza A	03/26/2018	03/31/2018	Resolved	None
113	01/09/2018	Upper respiratory tract inflammation acute	06/25/2018	07/02/2018	Resolved	None
		Serous otitis media	06/28/2018	Ongoing	Resolving	None
304	10/17/2017	Serous otitis media	01/23/2018	04/10/2018	Resolved	None
		Scab (in ear cavity)	12/08/2017	12/11/2017	Resolved	None
401	09/07/2017	Serous otitis media	10/05/2017	Ongoing	Resolving	None

6.B.(3).2) Replacement of Eustachian Tube Plug

In the clinical study, 4 patients received replacement of the investigational device. These patients had persistent subjective symptoms and objective findings after the first insertion of the investigational device or recurrence of symptoms within 2 months after the first insertion. They met the protocol-specified criteria for replacement of the investigational device and received only one new unit of the investigational device. All of the 4 patients received a larger size at replacement. Response was confirmed in 2 of the 4 patients 3 months after device replacement.

The applicant explained that ≥2 replacements of the device was clinically acceptable because some patients underwent ≥2 replacements in the previous clinical research and experienced no adverse event, etc. other than those reported in the current clinical study.

PMDA's view:

Replacement of Eustachian Tube Plug is associated with risks including persisting tympanic membrane perforation. The risks depend on the patient's conditions, such as complications and concomitant medication. In the clinical study, the efficacy and safety of device replacement were evaluated in patients who received 1 replacement, and ≥2 replacements were not adequately evaluated. In light of this point, setting the upper limit on the frequency of replacement is difficult. However, the previous clinical research suggested no safety problem with ≥2 device replacements depending on patients. It is, therefore, acceptable to replace Eustachian Tube Plug as needed after healthcare professionals fully understand the risks of device replacement and discuss risks and benefits. PMDA considers that it is necessary to advise in the instructions for use and training sessions, etc. that the efficacy and safety of ≥2 device replacements are not confirmed in the clinical study.

6.B.(4) Indication of Eustachian Tube Plug

The applicant's explanation:

The proposed indication of Eustachian Tube Plug is confirmed patulous eustachian tube that meets the draft diagnostic criteria for patulous eustachian tube (2016) presented by Japan Otological Society and is not responding to conservative treatments such as nasal instillation of physiological saline and traditional Chinese medicines. Patients aged ≥12 years are eligible for the treatment with Eustachian Tube Plug because symptoms may improve as the shape of the eustachian tube changes with growth.

PMDA's view:

The insertion of the Eustachian Tube Plug is more invasive than conservative treatments such as nasal instillation of physiological saline and traditional Chinese medicines. Considering the risk-benefit balance, patients who may respond to conservative treatments should be excluded from the indication of the Eustachian Tube Plug. PMDA concluded that refractory patulous eustachian tube is an appropriate indication of Eustachian Tube Plug because the Japanese clinical study in patients with refractory patulous eustachian tube demonstrated the efficacy and safety of Eustachian Tube Plug as described in Sections "6.B.(2) Efficacy" and "6.B.(3) Safety."

In young pediatric patients, symptoms may improve as the shape of the eustachian tube changes with growth. When the shape of the eustachian tube changes after the insertion of Eustachian Tube Plug, the device will not fit anymore. In addition, serous otitis media commonly occurs in young pediatric patients

regardless of the use of Eustachian Tube Plug, and the insertion of Eustachian Tube Plug may induce serous otitis media. Considering the characteristics of this disease and diagnostic methods, the reliability of the diagnosis is questionable in young pediatric patients. However, there is no difference between adverse events caused by unsuitable plug size due to a change in the shape of the eustachian tube and those caused by unsuitable plug size in the first insertion. In addition, as described later in Section "(2) Post-marketing safety measures" of "IV. Overall Evaluation," healthcare professionals will be advised on the need to follow-up patients periodically because the treatment with Eustachian Tube Plug, by its nature, may cause serous otitis media. For these reasons, the safety of Eustachian Tube Plug in young pediatric patients is clinically acceptable. The clinical study and previous clinical research were conducted in patients aged ≥12 years. Patients who actually received Eustachian Tube Plug in the clinical study were ≥24 years old, while 5 of 252 patients who participated in the previous clinical research were in their 10s, suggesting that limited number of young pediatric patients will require Eustachian Tube Plug.

The age in which the eustachian tube completes its development has not been clinically elucidated. The device was inserted in patients aged ≥24 years in the clinical study and ≥16 years in the previous clinical research. Therefore, it is difficult to provide information on the recommended age for insertion. On the basis of the above discussion, it is acceptable to assess the eligibility of patients for the insertion of Eustachian Tube Plug according to the patient's condition, etc. in the clinical practice after marketing. To support healthcare professionals assess the eligibility of patients for the insertion of Eustachian Tube Plug, relevant information about the age of patients and results of the clinical study and previous clinical research, etc. should be appropriately provided to healthcare professionals.

In pregnant women, symptoms of patulous eustachian tube may improve after delivery as the eustachian tube lumen returns to normal. In pregnant women who received the Eustachian Tube Plug, a change in the shape of eustachian tube due to delivery may cause serous otitis media. As described later in Section "(2) Post-marketing safety measures" of "IV. Overall Evaluation," this condition in pregnant women is clinically manageable by periodical follow-up as in young pediatric patients. Pregnant women may be allowed to use Eustachian Tube Plug if healthcare professionals find this treatment beneficial considering the risk-benefit balance.

6.B.(5) Clinical significance

Patulous eustachian tube interferes with the "patient's hearing ability" because of sensation of ear congestion, autophony, autophony of breathing sounds. In addition to impaired hearing, refractory patulous eustachian tube may cause communication disorder. In particular, in patients whose occupation involves speaking, patulous eustachian tube may interfere with their jobs, resulting in resignation or loss of job. Such patients, however, do not respond to conservative treatments such as nasal instillation of physiological saline and traditional Chinese medicines. In the past, research was conducted on ligation of the eustachian tube and cartilage implantation in the eustachian tube for the treatment of refractory patulous eustachian tube. However, there has been no established standard treatment.

The insertion of the Eustachian Tube Plug involves invasive procedures including myringotomy. As described in Sections "6.B.(2) Efficacy" and "6.B.(3) Safety," the efficacy and safety of Eustachian Tube Plug for ≥3 months in refractory patulous eustachian tube have been verified. The PHI10 score (mean ±

SD) decreased from 34.4 ± 4.2 points at baseline to 6.4 ± 9.0 points at Month 3. The level of improvement was clinically significant. In patients who do not respond to conservative treatments and suffered from symptoms of patulous eustachian tube for ≥6 months, having no symptoms for ≥3 months will profoundly improve the QOL. The Eustachian Tube Plug can be chosen from sizes 3 to 9 according to the lumen size of the patient's eustachian tube. In addition, patients can undergo the insertion of the Eustachian Tube Plug on an outpatient basis or on an inpatient basis (overnight). This surgical treatment is expected to impose no great burden on treating physicians with a certain level of experience in ear surgery or patients.

On the basis of the above, PMDA concluded that it was of significance to make Eustachian Tube Plug available in clinical practice provided that relevant information on the clinical efficacy and safety of insertion of the Eustachian Tube Plug is provided to healthcare professionals.

6.B.(6) Necessity of use-results survey

The clinical study demonstrated a profound improvement in the PHI10 score on Day 2 and the clinical significance of Eustachian Tube Plug at Month 3, when the primary efficacy evaluation was conducted.

As described in Sections "6.B.(1).4) Appropriateness of duration of follow-up" and "6.B.(3) Safety," the safety evaluation was sufficient.

For the following reasons, PMDA considers that the necessary safety evaluation has been conducted before marketing and new safety concern will not arise after the launch. After discussing at the Expert Discussion, PMDA concluded that Eustachian Tube Plug does not need to be further investigated through a use-results survey.

- The clinical study included a sufficient follow-up period. During this period, no particularly significant adverse event occurred.
- New adverse event has not been reported between the completion of the clinical study and submission of the present application.
- Patients who participated in the previous clinical research in 2001 have experienced no significant adverse event to date.
- Since treating physicians are required to have experience in clinical practice and surgery in the field of otorhinolaryngology, and received necessary education through training sessions, etc., physicians who perform the insertion of Eustachian Tube Plug after marketing are expected to have comparable skills to those investigators who participated in the previous clinical research or clinical study.

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

As described in Section 6, PMDA concluded that Eustachian Tube Plug does not need to be further investigated through a use-results survey.

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 in conducting its review based on the application documents submitted.

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

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

IV. Overall Evaluation

Eustachian Tube Plug is a medical device that narrows the constantly open eustachian tube lumen and maintains the appropriate lumen size in order to improve uncomfortable conditions in patients with refractory patulous eustachian tube, including sensation of ear congestion, autophony of voice or breathing sounds. The main points in the regulatory review of the Eustachian Tube Plug were as follows: (1) efficacy and safety of Eustachian Tube Plug, (2) post-marketing safety measures. The PMDA's conclusions, taking account of discussions with the expert advisors, are as follows:

(1) Efficacy and safety of Eustachian Tube Plug

The clinical study was conducted to confirm the efficacy and safety of Eustachian Tube Plug in patients with refractory patulous eustachian tube. The results demonstrated the total PHI10 score at Month 3, the primary endpoint, of 6.4 ± 9.0 points. A total of 23 patients were responders, which were defined as patients with a PHI10 score of ≤16 points, with the percentage of responders of 82.1% (95% CI, 63.1%-93.9%), which exceeded the pre-specified threshold of 40%.

The main adverse events reported in 21 of 29 patients included surgical procedure-related pain and serous otitis media. A serious adverse event leading to study discontinuation occurred in 1 patient. This patient experienced tinnitus with insomnia and dysphoria due to accompanying symptoms. The investigational device was removed upon request by the patient. Although the mechanism responsible for the occurrence of tinnitus is unknown, 1 of 29 patients (3.4%) removed the investigational device in the clinical study. The symptoms in this patient resolved after removal of the investigational device and closure of tympanic membrane perforation. The relevant information on the removal will be appropriately provided in the instructions for use, etc. As a result of the discussions at the Expert Discussion, PMDA concluded that there was no particular problem with the safety of Eustachian Tube Plug, including the surgical procedure.

On the basis of the above, PMDA concluded that the results of the clinical study demonstrated the efficacy and safety of Eustachian Tube Plug in refractory patulous eustachian tube.

(2) Post-marketing safety measures

Since mild or moderate patulous eustachian tube can be treated with conservative treatments such as nasal instillation of physiological saline, traditional Chinese medicines, and lifestyle guidance, the indication of Eustachian Tube Plug, the insertion of which involves invasive procedures including myringotomy, should be refractory patulous eustachian tube. Symptoms in young pediatric patients may improve as the shape of the eustachian tube changes with growth, while those in pregnant women may improve after delivery. Treating physicians must have sufficient knowledge to appropriately select eligible patients for Eustachian Tube Plug.

In executing the insertion of Eustachian Tube Plug, the following precautions must be followed to ensure the efficacy and safety of the device:

- The use of Eustachian Tube Plug that is oversized for the patient's eustachian tube lumen may cause otitis media, ear pain, etc., while the use of undersized Eustachian Tube Plug decreases its efficacy. An appropriate size of Eustachian Tube Plug must be chosen according to the lumen size of the patient's eustachian tube.
- Postoperative periodic follow-up is required to examine patients for serous otitis media associated with persisting tympanic membrane perforation or eustachian tube obstruction.
- If uncontrollable otorrhoea associated with infection occurs, Eustachian Tube Plug must be removed immediately.
- The efficacy and safety of ≥2 replacements of Eustachian Tube Plug have not been fully verified.

PMDA concluded that this information should be provided in the instructions for use, etc. and that the necessity of training sessions for treating physicians to ensure the proper use of Eustachian Tube Plug should be mentioned as an approval condition. It is expected that the efficacy and safety results from the previous clinical research will be provided to physicians through training sessions, etc.

As a result of its review, PMDA has concluded that Eustachian Tube Plug may be approved for the following intended use with the approval conditions below.

Intended Use

Eustachian Tube Plug is intended to narrow the excessively open eustachian tube to improve symptoms of patients with refractory patulous eustachian tube, who do not respond to conservative treatments.

Approval Condition

The applicant is required to cooperate with the relevant academic societies and take necessary measures to ensure that physicians with adequate knowledge and experience in diagnosing and treating patulous eustachian tube acquire sufficient skills for using the product and knowledge about procedure-related complications, and use the product at medical institutions appropriately equipped to treat the disease in compliance with the intended use and directions for use of the product.

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

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

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