June 12, 2023
Medical Device Evaluation Division
Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Report on the Deliberation Results

Classification	Instrument & Apparatus 12, Apparatus for Physical Therapy
Term Name	Tremor brain electrical stimulator
Brand Name	Medtronic Percept PC
Applicant	Medtronic Japan Co., Ltd.
Date of Application	October 17, 2022

Results of Deliberation

In its meeting held on June 12, 2023, the Committee on Medical Devices and *In-vitro* Diagnostics reached the following conclusion, and decided that this conclusion should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The present application for partial change approval should be approved without imposing a use-results evaluation.

The approval condition for the present application should be the same as that for the preceding application.

Approval Condition

1. The applicant is required to take necessary actions to ensure that the product will be used, in compliance with the indication, by physicians with adequate knowledge and experience in the treatment of dystonia after acquiring sufficient knowledge about the product by attending relevant lectures or by other means.

Review Report

May 23, 2023
Pharmaceuticals and Medical Devices Agency

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

Classification	Instrument & Apparatus 12, Apparatus for Physical Therapy
Term Name	Tremor brain electrical stimulator
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Date of Application	October 17, 2022 (Application for partial change approval of a medical device)
Items Warranting Special Mention	Priority review
Reviewing Office	Office of Medical Devices II

Review Results

May 23, 2023

Classification	Instrument & Apparatus 12, Apparatus for Physical Therapy
Term Name	Tremor brain electrical stimulator
Brand Name	Medtronic Percept PC
Applicant	Medtronic Japan Co., Ltd.
Date of Application	October 17, 2022 (Application for partial change approval of a medical device)

Results of Review

"Medtronic Percept PC" (hereinafter referred to as "Percept PC") is an implantable electrical stimulation device intended for use in deep brain stimulation (DBS), which delivers electrical stimulation to deep brain structures to reduce various movement disorder symptoms. The present application for partial change approval for medical device was submitted to add the anterior nucleus of the thalamus (ANT) as a new placement site of the electrode leads in order to include "reduction in partial-onset seizures in patients with drug-resistant epilepsy" in the Intended Use of Percept PC.

The present partial change application is intended to add ANT as a new electrical stimulation site, but does not change the design, components, functions, and other features of Percept PC. For this reason, submission of non-clinical study results of Percept PC were omitted.

For the efficacy and safety clinical evaluation of Percept PC, the applicant submitted the results of a foreign clinical study of DBS in patients with drug-resistant epilepsy with partial-onset seizures (SANTE study) and a clinical evaluation report based on publications.

As for efficacy, the active group showed superior results than the control group in the primary efficacy endpoint of "reduction in the total seizure frequency" in the SANTE study. The study achieved the primary endpoint. DBS therapy resulted in a reduction in seizure frequency, which was sustained through 7 years after device implant. The results of other clinical studies in the literature reports were consistent with those of the SANTE study. There was no significant difference in therapeutic outcome between DBS and vagus nerve stimulation (VNS), which is a conventional therapy with the same clinical positioning as DBS with Percept PC.

As for safety, the SANTE study and the submitted literature reports revealed no unknown adverse events. Reported adverse events were consistent with those identified in patients who received treatment with Percept PC for the approved indications (e.g., tremor and dystonia). In the SANTE study, the incidence of depression and memory impairment was significantly higher in the active group than in the control group. These adverse events were considered related to ANT stimulation. All

of the events were mild or moderate in severity. Adjustment of stimulation resolved the events in some subjects. Since Percept PC is intended for the treatment of refractory drug-resistant epilepsy with partial-onset seizures, those risks are clinically acceptable provided that the applicant advises necessary caution and that eligible patients are selected.

Since Percept PC is intended for use in patients with refractory epilepsy with partial-onset seizures who do not respond to drug therapy, the benefits of DBS therapy with Percept PC outweigh its risks. Percept PC is a highly useful new treatment option.

The DBS system is an approved medical device available in Japan. It has been widely used for implantation and long-term placement. In addition, VNS therapy, which has the same clinical positioning as that of DBS with Percept PC, has been established for the treatment of drug-resistant epilepsy with partial-onset seizures in Japan. This means that the medical system required for the smooth introduction of Percept PC for epilepsy to Japan, including the patient selection criteria, has already been in place. Percept PC is the first medical device that delivers electrical stimulation to the ANT to be approved in Japan. However, no use-results survey is required for the proposed indication because there is no racial or ethnic difference in the brain structure or function, and because the efficacy and safety of Percept PC can be assessed based on the submitted clinical evaluation report and foreign use experience.

As a result of its review, PMDA has concluded that Percept PC may be approved for the intended use shown below with the same approval condition as that for the already approved indications, and decided that this conclusion should be presented to the Committee on Medical Devices and *In-vitro* Diagnostics for further deliberation. The intended use added in this submission is underlined.

Intended Use

- Medtronic Percept PC is used to deliver lateral or bilateral electrical stimulation to a deep brain structure (thalamus, subthalamic nucleus, or internal globus pallidus) in order to reduce the following symptoms that have an inadequate response to drug therapy:
  - Tremor
  - Movement disorder in Parkinson's disease
  - Dystonia
- <u>Medtronic Percept PC is used to deliver bilateral electrical stimulation to a deep brain structure (anterior nucleus of the thalamus) in order to reduce partial-onset epileptic seizures that have an inadequate response to drug therapy (except for patients who are expected to respond to craniotomy).</u>

Approval Condition

The applicant is required to take necessary actions to ensure that the product will be used, in compliance with the indication, by physicians with adequate knowledge and experience in the treatment of dystonia after acquiring sufficient knowledge about the product by attending relevant lectures or by other means.

Review Report

May 23, 2023

Product for Review

Classification	Instrument & Apparatus 12, Apparatus for Physical Therapy
Term Name	Tremor brain electrical stimulator
Brand Name	Medtronic Percept PC
Applicant	Medtronic Japan Co., Ltd.
Date of Application	October 17, 2022 (Application for partial change approval for medical device)
Proposed Intended Use (Underline denotes additions.)	Medtronic Percept PC is intended to be used to deliver lateral or bilateral electrical stimulation to a deep brain structure (thalamus, subthalamic nucleus, or internal globus pallidus) in order to reduce the following symptoms that have an inadequate response to drug therapy: • Tremor • Movement disorder in Parkinson's disease • Dystonia <u>Medtronic Percept PC is intended to be used to deliver bilateral electrical stimulation to a deep brain structure (anterior nucleus of the thalamus) in order to reduce partial-onset epileptic seizures that have an inadequate response to drug therapy (simple partial seizures, partial complex seizures, and secondary generalized seizures accompanied by movement symptoms that interrupt the activities of daily living).</u>

Items Warranting Special Mention

Priority review

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List of Abbreviations

ANT	Anterior nucleus of thalamus
CAP	Continued therapy access phase
DBS	Deep brain stimulation
DMC	Data monitoring committee
EOS	End of service
ERI	Elective replacement indicator
GEE	Generalized estimating equation
ILAE	International League Against Epilepsy
LTFU	Long term follow-up
NICE	National Institute for Health and Care Excellence
PMA	Premarket approval
SUDEP	Sudden unexpected death in epilepsy
VNS	Vagus nerve stimulation

I. Product Overview

"Medtronic Percept PC" (hereinafter referred to as "Percept PC") is an implantable electrical stimulation device intended for use in deep brain stimulation (DBS), which delivers electrical stimulation to deep brain structures to reduce various movement disorder symptoms. Percept PC consists of a stimulator, a patient programmer, a communicator, and accessories (a torque wrench and a connector plug) (Figure 1). Percept PC was approved for reducing the symptoms of tremor, Parkinson's disease, and dystonia that have an inadequate response to drug therapy on May 21, 2020 (Approval No. 30200BZX00163000). The present application for partial change approval for medical device (hereinafter referred to as "the present partial change application") was submitted to add the anterior nucleus of the thalamus (ANT) as a new placement site of the electrode leads in order to include "reduction in partial-onset epileptic seizures in patients with drug-resistant epilepsy" in Intended Use of Percept PC. The present partial change application is intended to add ANT as a new electrical stimulation site, but does not change the design, components, functions, and other features of Percept PC.

Stimulator　Patient programmer　Communicator

Torque wrench

Connector plug

Figure 1. External view of Percept PC

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

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

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

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

1.A Summary of the data submitted

1.A.(1) History of development

Epilepsy is a chronic disease of the brain and occurs in a wide range of age groups from infants to seniors. Its prevalence is approximately 1% of the population. Symptoms of epilepsy vary depending on the site of seizures in the brain and can include involuntary movements of the hands, legs, face, or other body parts, loss of consciousness followed by loss of movement or unnatural movements, and fall due to loss of consciousness followed by generalized muscle rigidity or convulsions.

In Japan, epilepsy is classified into 2 major categories (i.e., partial-onset seizure and generalized seizure) according to the International League Against Epilepsy (ILAE). A partial-onset seizure occurs when abnormal excitement starts in a localized area or one side of the brain. This abnormal excitement of cells in a part of the brain disables the cells from functioning, which results in various physical, motor, or sensory symptoms in a part of the body, including conscious disorder, based on the seizure onset site. A partial seizure may propagate throughout the entire brain and cause loss of consciousness, convulsions, and other symptoms (secondary generalized seizure). A generated seizure occurs when abnormal excitement starts over the entire brain simultaneously. Symptoms of a generalized seizure include generalized muscle rigidity (tonic seizure) and convulsions (clonus seizure). Typically, a seizure lasts for 2 to 3 minutes. A seizure may, however, occur multiple times and persist for a prolonged period of time (status epilepticus) or leave serious sequelae. Additionally, epilepsy is classified into the following 2 categories according to its etiology: Symptomatic epilepsy, which is triggered by some disorder or lesion in the brain; and idiopathic epilepsy, which has unknown causes. The treatment of epilepsy is determined according to these seizure categories and symptoms.

The first-line treatment of epilepsy is drug therapy for both partial-onset and generalized seizures. Patients who do not respond to monotherapy or have adverse drug reactions are treated with a combination of 2 to 3 drugs. Approximately 30% of patients with epilepsy, however, may have uncontrolled symptoms because of refractoriness to drugs, severe adverse drug reactions, etc. The Clinical Practice Guidelines for Epilepsy 2018 (edited by the Japanese Society of Neurology)[1] recommend that surgery be considered to treat “drug-resistant epilepsy,” which is defined as epilepsy that cannot be controlled for a certain period. The surgical treatment of epilepsy involves the surgical removal of a portion of the brain (onset site of a partial-onset seizure) (e.g., partial resective surgery) or vagus nerve stimulation (VNS), which electrically stimulates the vagus nerve. A partial resective surgery is considered as the first-line treatment because it may cure epilepsy. However, VNS is considered when the site of seizure origin in the brain cannot be located or there are risks associated with brain tissue resection, such as language disorder and memory impairment. VNS is an accommodative therapy to reduce epileptic seizures through electrical stimulation of the vagus nerve in the left side of the neck. This therapy is effective for not only partial-onset seizures but also generalized seizures.

DBS therapy for epilepsy was reported by Cooper *et al.* in the 1980’s. The reports showed that electrical stimulation of the thalamus, cerebellum, ANT, etc. in the deep brain alleviated epileptic seizures.[2,3,4] Subsequent studies investigated the effectiveness of this therapy in the cerebellum, head

of caudate nucleus, subthalamic nucleus, Centre median Luysi, ANT, etc. to optimize the therapy. Electrical stimulation of the ANT, among these tissues, reduced seizures in animal studies.[5,6] The efficacy of ANT stimulation in the treatment of human patients with epilepsy was also reported by multiple researchers.[7,8,9] Evidence of its therapeutic efficacy has been accumulating, although the mechanism of action is not fully understood. The applicant (the foreign manufacturer, Medtronic US) conducted a clinical study to evaluate the efficacy and safety of DBS of the ANT in the treatment of epilepsy in 2003 (SANTE study). The predecessor of Percept PC (Activa PC) acquired a CE mark in Europe in 2010 and a Premarket approval (PMA) in the US in 2018. Percept PC was approved as a successor of Activa PC in 2020.

The Japan Epilepsy Society requested the addition of epilepsy to the indications of Percept PC. In response to this, the "Study Group on the Early Introduction of Medical Devices, etc. with High Medical Need" selected Percept PC as a medical device with high medical need in November 2021.

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

Table 1 shows the approval status of Percept PC outside Japan. A total of [redacted] Percept PCs were shipped for the treatment of epilepsy as of March 2023 in the US and EU.

Table 1. Approval status outside Japan

Intended Use	Name of medical device	Region	Date of approval
Bilateral stimulation of the ANT to reduce the frequency of seizures in individuals ≥18 years of age diagnosed with epilepsy characterized by partial-onset seizures, with or without secondary generalization, who are refractory to at least 3 antiepileptic medications	Percept PC	US	June 24, 2020
		EU	January 2, 2020

In Japan, Percept PC has been approved as a DBS device for the treatment of tremor, etc. that have an inadequate response to drug therapy. A total of [redacted] Percept PCs were sold for these indications between the market launch in July 2020 and March 2023.

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

A total of [redacted] cases of malfunctions and adverse events have been reported in patients using Percept PC to treat epilepsy in Europe and the US as of March 2023. The number of malfunctions and adverse events by seriousness is as follows: [redacted] cases of death, [redacted] serious cases, [redacted] non-serious cases, and [redacted] cases of unknown seriousness. Table 2 shows the number and incidence (per shipping quantity) of each adverse event or malfunction.

Of the [redacted] cases of death, [redacted] unrelated to Percept PC. [redacted] of unknown cause but might have been sudden unexpected death in epilepsy (SUDEP). The incidence of epileptic seizures was 4.96%. Symptoms possibly related to ANT stimulation were cognitive changes (1.88%), depression (0.60%), loss of memory (0.60%), anxiety (0.50%), loss of consciousness (0.20%), and confusion/disorientation (0.20%). Events possibly caused by the effects of epileptic seizures on motor function were fall (1.09%) and fracture (0.20%).

Table 2. Deaths or serious adverse events/malfunctions outside Japan

Adverse event or malfunction	Number of events	%
Death		
Death	[redacted]	0.10%
Death, unrelated to the device	[redacted]	0.20%
Serious		
Epileptic seizure *	[redacted]	4.96%
Battery burnout or EOS	[redacted]	1.98%
Cognitive change *	[redacted]	1.88%
Therapeutic response decreased	[redacted]	1.09%
Fall *	[redacted]	1.09%
No therapeutic response	[redacted]	1.09%
Infection	[redacted]	0.99%
Stimulator migration	[redacted]	0.89%
Pain	[redacted]	0.89%
Depression *	[redacted]	0.60%
Loss of memory *	[redacted]	0.60%
Sleep disorder	[redacted]	0.60%
Low impedance or short circuit	[redacted]	0.50%
Anxiety *	[redacted]	0.50%
Hypersensitivity	[redacted]	0.30%
Sensation of irritation	[redacted]	0.30%
Vision disorder	[redacted]	0.30%
Output error	[redacted]	0.30%
Meningitis	[redacted]	0.30%
Fever	[redacted]	0.30%
ERI or low battery status	[redacted]	0.20%
Programing malfunction	[redacted]	0.20%
Loss of consciousness *	[redacted]	0.20%
Inflammation	[redacted]	0.20%
Excessive stimulation	[redacted]	0.20%
Non-regulation/setting failure	[redacted]	0.20%
Hematoma	[redacted]	0.20%
Malaise	[redacted]	0.20%
Fracture *	[redacted]	0.20%
Confusion/disorientation *	[redacted]	0.20%
Tremor	[redacted]	0.20%
Neurological deficit/dysfunction	[redacted]	0.20%
Early ERI	[redacted]	0.20%
Headache	[redacted]	0.20%
Dysphasia	[redacted]	0.20%
Ambulation difficulty	[redacted]	0.20%
Paralysis	[redacted]	0.20%
Unknown	[redacted]	1.59%
Others	[redacted]	3.97%
Seriousness, unknown		
Erosion	[redacted]	0.10%
Infection	[redacted]	0.10%
Malfunction of concomitant device	[redacted]	2.58%
Total	[redacted]	**31.45%**

* Serious adverse events possibly related to epilepsy

The following [redacted] malfunctions were reported in patients using Percept PC for the approved indications up to April 2023 in Japan: Abnormal resistance value ([redacted], 0.60%), early battery burnout ([redacted], 0.20%), unexpected end of service (EOS) ([redacted], 0.10%), poor communication ([redacted], 0.10%), and leads not adequately secured ([redacted], 0.10%).

1.B Outline of the review conducted by PMDA

All of the events reported were known events that were possibly related to epilepsy or DBS. These events are later discussed in Section 6.

2. Design and Development

2.(1) Performance and safety specifications

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

The present partial change application included no change in the current performance and safety specifications of Percept PC. The applicant proposed to use the current performance and safety specifications.

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

PMDA concluded that the use of the current performance and safety specifications of Percept PC was acceptable because its design has not been changed and the directions for use for the additional indication will not be changed substantially.

2.(2) Physicochemical properties, electrical safety, electromagnetic compatibility, biological safety, etc.

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

No change was made to the design of Percept PC and no additional tests, etc. were conducted for the present partial change application. The applicant therefore did not submit data supporting the physicochemical properties, electrical safety, electromagnetic compatibility, biological safety, stability, durability, performance, and directions for use.

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

PMDA concluded that no data are required because its design has not been changed and the directions for use for the additional indication are the same as the current ones.

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

3.A Summary of the data submitted

The applicant submitted a declaration of conformity declaring that Percept PC meets the standards for medical devices as stipulated by the Minister of Health, Labour and Welfare in accordance with Paragraph 3 of Article 41 of Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (hereinafter referred to as "the Essential Principles") (MHLW Ministerial Announcement No. 122, 2005).

3.B Outline of the review conducted by PMDA

PMDA reviewed the conformity of Percept PC to the Essential Principles as shown below.

PMDA's view on the conformity of Percept PC to Article 17, which specifies requirements for publicizing information including precautions or provision of the information to users via instructions for use, etc. ("Information on Precautions, etc."):

As described later in Section "6.B Outline of the review conducted by PMDA," it is important for users to understand the risks for Percept PC and to appropriately select eligible patients. To this end, relevant information should be provided through the Information on Precautions, etc.

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

4. Risk Management

4.A Summary of the data submitted

The applicant submitted data summarizing the risk management system and risk management activities implemented for Percept PC in accordance with JIS T 14971 "Medical devices – Application of risk management to medical devices."

4.B Outline of the review conducted by PMDA

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

5. Manufacturing Process

5.A Summary of the data submitted

The applicant did not submit data on the manufacturing process because the present partial change application included no change in the manufacturing process of Percept PC.

5.B Outline of the review conducted by PMDA

PMDA concluded that no data on the manufacturing process of Percept PC are required.

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

6.A Summary of the data submitted

The applicant submitted the results of a clinical study that evaluated the efficacy and safety of DBS in the treatment of drug-resistant epilepsy with partial-onset seizures in the US (SANTE study) and a clinical evaluation report based on publications. They are the clinical evaluation data for the present partial change application.

6.A.(1) SANTE study (Study period, 2003 to 2018)

The SANTE study was a multicenter, prospective, randomized, double-blind, parallel-group study conducted at 17 study sites in the US to evaluate the efficacy and safety of bilateral stimulation of the ANT using the DBS system as an adjunctive therapy in adult patients diagnosed with drug-resistant epilepsy characterized by partial-onset seizures, with or without secondary generalized seizures. Table 3 shows the major inclusion and exclusion criteria of this clinical study.

Table 3. Major inclusion and exclusion criteria of the SANTE study

Major inclusion criteria	1) Partial-onset seizures with or without secondary generalized seizures. The final assessment by the investigator based on a clinical description(s) of epileptic seizures and a previous examination(s) that documented at least 1 event by a video or clinical-electroencephalogram (EEG). 2) An average of ≥6 partial-onset seizures (with or without secondary generalized seizures) per month during the baseline phase. 3) Refractory to antiepileptic drugs (not responding to at least 3 drugs). 4) Receiving 1 to 4 antiepileptic drugs. 5) Aged 18 to 65 years, inclusive (at the time of lead placement)
Major exclusion criteria	1) Multilobar (≥3 different lobes) anatomic areas of seizure onset. 2) Symptomatic generalized epilepsy. 3) Termination or start of an antiepileptic drug(s) within the 30 days prior to baseline assessment or change in an antiepileptic drug(s) (e.g., total daily dose or combination) within the 14 days prior to baseline assessment. Subjects receiving phenobarbital, primidone, or zonisamide are excluded if any change is made to these drugs within the 30 days prior to baseline assessment. 4) "Use of a rescue drug (e.g., acute benzodiazepine) within 48 hours" occurred at least 3 times within the 3 months prior to baseline assessment. 5) An average of ≥10 partial complex seizures per day over the 3-month period prior to baseline assessment. 6) Any episode of convulsive status epilepticus within the 12 months prior to baseline assessment. 7) Previous diagnosis of psychogenic/nonepileptic seizures. 8) Surgical candidate for, and willing to undergo, partial temporal lobectomy or lesionectomy. 9) MRI data showing a neurological condition that is likely to progress within the 5 years prior to baseline assessment (e.g., brain tumor, active encephalitis, active meningitis or abscess, arteriovenous malformations or cavernous angiomas that are likely to progress). 10) Diagnosis of progressive or degenerative neurological disorder affecting the brain. 11) Presence of an implanted electrical stimulation medical device anywhere in the body (e.g., cardiac pacemakers, spinal cord stimulator) or any metallic implants in the head (e.g., aneurysm clip and cochlear implant). Vagus nerve stimulation (VNS) devices are allowed if the device has been turned off for at least 30 days prior to baseline assessment and the subject agrees to have the generator explanted prior to or at the time of implantation of the study device.

In the clinical study, 157 patients were enrolled. A total of 110 subjects who met the implantation criteria after the 12-week baseline phase were implanted with the stimulation device and electrode leads (Table 4). The stimulation devices used in the clinical study were the following predecessors of Medtronic US: "Model 7426 Soletra" (Itrel II, approved in Japan [Approval No. 21100BZY00563000]), "Model 7428 Kinetra" (not approved in Japan), "Model 37601 Activa PC" (Activa PC, approved in Japan [Approval No. 22800BZX00343000]), or "Model 37612 Activa RC" (Activa RC, approved in Japan [Approval No., 22300BZX00412000]).

Table 4. Patient characteristics in each group

	Active		Control		*P*-value
	No. of subjects	%	No. of subjects	%	
Sex					
Male	25	46.3%	30	54.5%	0.389
Female	29	53.7%	25	45.5%	
Number of antiepileptic drugs					
1	6	11.1%	6	10.9%	0.287
2	25	46.3%	28	50.9%	
3	23	42.6%	18	32.7%	
4	0	0.0%	3	5.5%	
Prior therapy for epilepsy					
VNS device implantation	21	38.9%	28	50.9%	0.389
Partial resective surgery	11	20.4%	16	29.1%	0.292
Seizure type*					
Partial complex seizures	51	94.4%	50	92.6%	0.716
Partial seizures with secondary generalisation	38	70.4%	46	85.2%	0.115
Simple partial seizures	37	68.5%	36	66.7%	0.839
Generalisation	3	5.6%	2	3.7%	0.679
Others	0	0.0%	1	1.9%	1.000
Seizure onset location**					
Temporal lobe	35	64.8%	30	54.5%	0.331
Frontal lobe	15	27.8%	15	27.3%	1.000
Diffuse or multifocal	5	9.3%	5	9.1%	1.000
Parietal lobe	5	9.3%	5	9.1%	1.000
Occipital lobe	2	3.7%	3	5.5%	1.000

* A single patient may have experienced more than 1 seizure type.
** A single patient may have had seizures originating from more than 1 onset location.

At 4 weeks after implantation of the stimulation device and electrode leads, subjects were randomized to the active group (with stimulation[i]) or control group (without stimulation[ii]) in a 1:1 ratio. The efficacy and safety in the active and control groups during a 12-week blinded phase were evaluated (the end of blinded phase = Week 16 post-implant). During the subsequent 36-week unblinded phase, the subjects in both the active and control groups received stimulation; the efficacy and safety in this phase were evaluated (the end of unblinded phase = Week 52 post-implant). In addition, long-term efficacy and safety data were collected during a subsequent long-term follow-up (LTFU) and a continued therapy access phase (CAP). The LTFU was a follow-up phase until necessary data were gathered for the PMA application in the US, while the CAP was a follow-up phase after those data were accumulated. Figure 2 shows the number of subjects in each phase.

[i] Stimulation output 5 V, rate 145 Hz, pulse width 90 μs, cycling on interval 1 minute, cycling off interval 5 minutes

[ii] The stimulation output was set at 0 V.

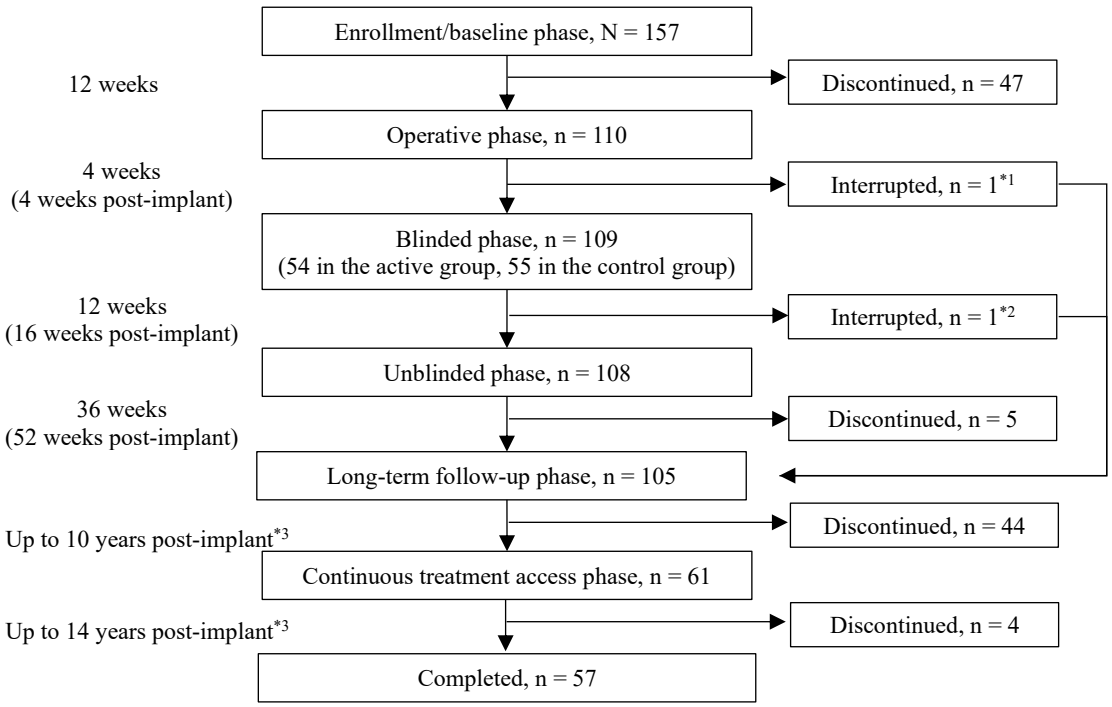


Figure 2. Number of subjects by study phase

*1 The device was removed because of postoperative infection. Stimulation was started during the long-term follow-up phase (13 months post-implant) after resolution of infection.
*2 The device was removed during the blinded phase because of the progression of infection. Observation was resumed during the long-term follow-up phase (13 months post-implant) after resolution of infection.
*3 The protocol specified that subjects should be followed up until the device was approved in the US or the study was completed. Therefore, the length of long-term follow-up phase and the continuous treatment access phase varied depending on subjects.

6.A.(1).1) Efficacy evaluation

The primary endpoint of the study was a reduction in the total seizure frequency from the baseline phase (the reduction in the active group should be greater than that in the control group). The secondary endpoints were the proportion of responders, number of seizure-free days, length of seizure-free interval, and proportion of treatment failures.

6.A.(1).1).(a) Primary endpoint: Reduction in total seizure frequency

The primary endpoint of the reduction in the total seizure frequency from the baseline phase was analyzed using a generalized estimating equations (GEE) model. The number of seizures per month was 17.5 in the active group and 21.1 in the control group. The active group had a 17.0% fewer total seizure frequency than that in the control group over the entire blinded phase, showing the superiority of the active treatment to the control (P = 0.045, Wald test). The median total seizure frequency compared with the baseline phase improved in both groups in the early period before blinding and, throughout the entire blinded phase, continued to improve in the active group but did not continue to improve in the control group. At the end of the blinded phase, the reduction in the median total seizure frequency was 14.5% in the control group and 40.4% in the active group (Figure 3).

Figure 4 and Figure 5 show the percent reduction in the median total seizure frequency at 1 and 7 years post-implant, respectively.

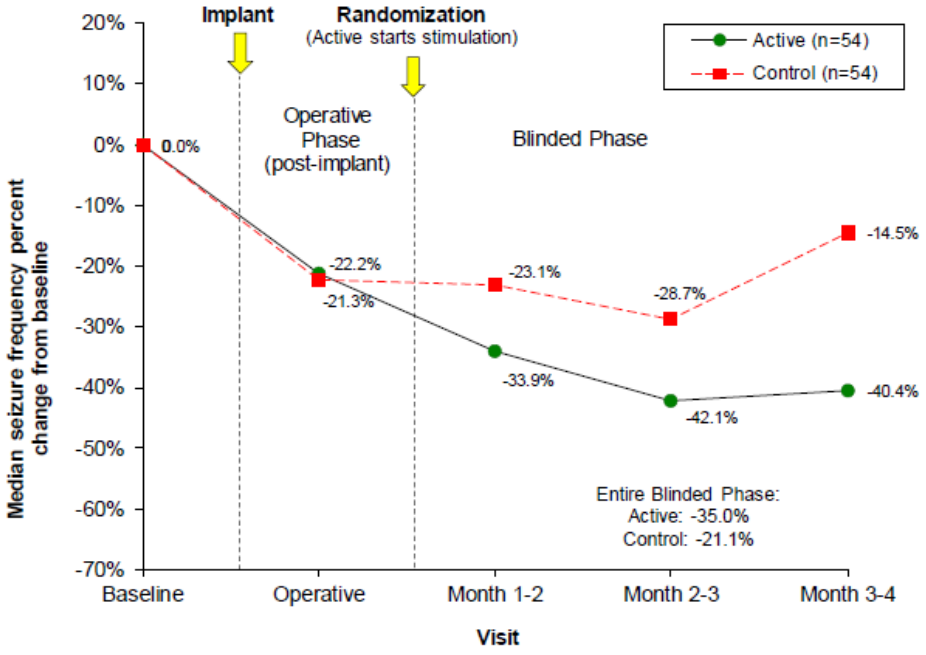
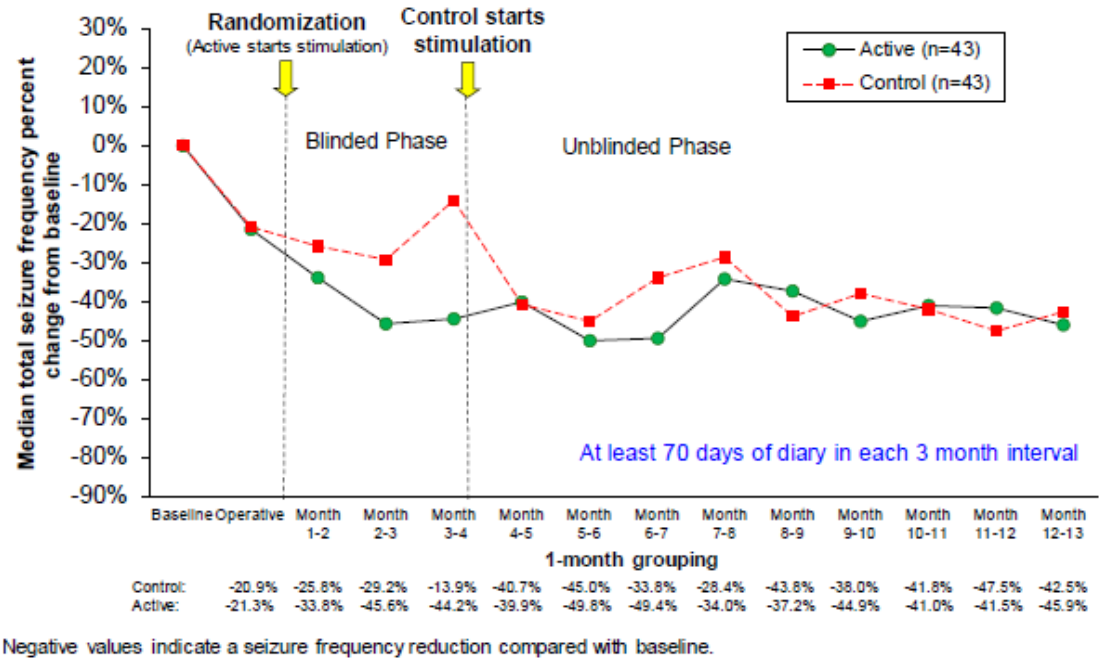


Figure 3. Change in total seizure frequency (median) from the baseline phase (blinded phase)



Negative values indicate a seizure frequency reduction compared with baseline.

Figure 4. Change in total seizure frequency (median) from the baseline phase (1 year post-implant)

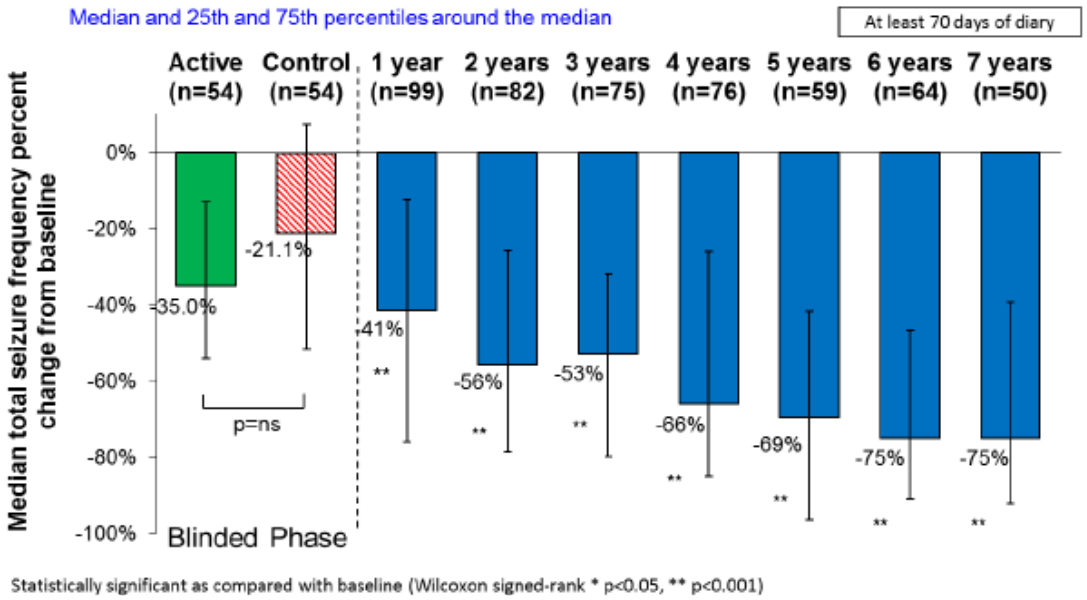


Figure 5. Change in total seizure frequency (median) from the baseline phase (7 years post-implant)

6.A.(1).1).(b) Secondary endpoint: Proportion of responders

In this study, responders were defined as subjects whose seizure frequency was reduced by ≥50% from the baseline phase. The proportion of responders was 29.6% in the active group and 25.9% in the control group during the blinded phase. The difference between the active and control groups was not statistically significant (P = 0.830, Fisher's exact test). The proportion of responders during the LTFU was 43% at 1 year post-implant and increased to 74% at 7 years post-implant (Figure 6).

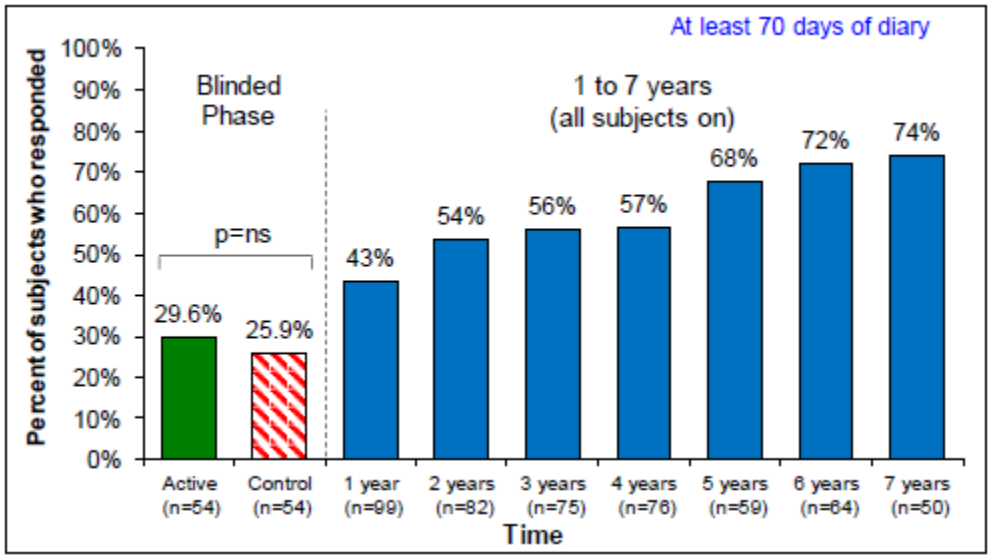


Figure 6. Proportion of responders

6.A.(1).1).(c) Secondary endpoint: Number of seizure-free days and length of seizure-free interval during the blinded phase

Table 5 shows the number of seizure-free days and length of seizure-free interval during the blinded phase. A comparison of the results between the active and control groups showed no statistically significant difference. In this study, 18% (20 of 110) of implanted subjects were seizure-free for at least 6 months. This included 9 subjects who were seizure-free for ≥2 years.

Table 5. Number of seizure-free days and length of seizure-free interval

Group	No. of subjects	Baseline	Blinded phase	Percent change	Percent change (median)	*P*-value*
Number of seizure-free days during the blinded phase						
Active	50	46.8 ± 20.9	57.2 ± 20.0	124.5% ± 446.1%	15.3%	0.112
Control	50	44.5 ± 23.5	51.7 ± 24.6	60.0% ± 208.5%	8.8%	
Length of seizure-free interval during the blinded phase						
Active	54	8.0 ± 4.5	11.8 ± 9.0	59.8% ± 98.2%	35.0%	0.768
Control	54	8.7 ± 6.2	13.4 ± 14.1	63.9% ± 121.7%	25.0%	

* Wilcoxon rank sum test

6.A.(1).1).(d) Secondary endpoint: Proportion of treatment failures

A treatment failure was defined as a subject who a) received ≥3 doses of rescue medication within the space of 48 hours during the blinded phase or b) had 3 episodes of epileptic convulsions during the blinded phase. There were no treatment failures in the active or control group.

6.A.(1).1).(e) Other evaluation: Efficacy in subjects with prior VNS therapy

The efficacy of DBS was evaluated in 49 subjects who had prior therapy with VNS, which is used to treat drug-resistant epilepsy. All subjects underwent removal of the VNS device, a procedure to insulate the VNS leads, etc. prior to DBS system implantation.

The results showed no statistical differences in seizure frequency between the active and control groups regardless of prior VNS therapy ($P = 0.158$ for subjects with prior VNS; $P = 0.516$ for subjects without prior VNS) probably because of the limited number of subjects. The seizure frequency decreased in both subject groups during the first 7 years after device implantation, with statistically significant differences from baseline (Figures 7 and 8).

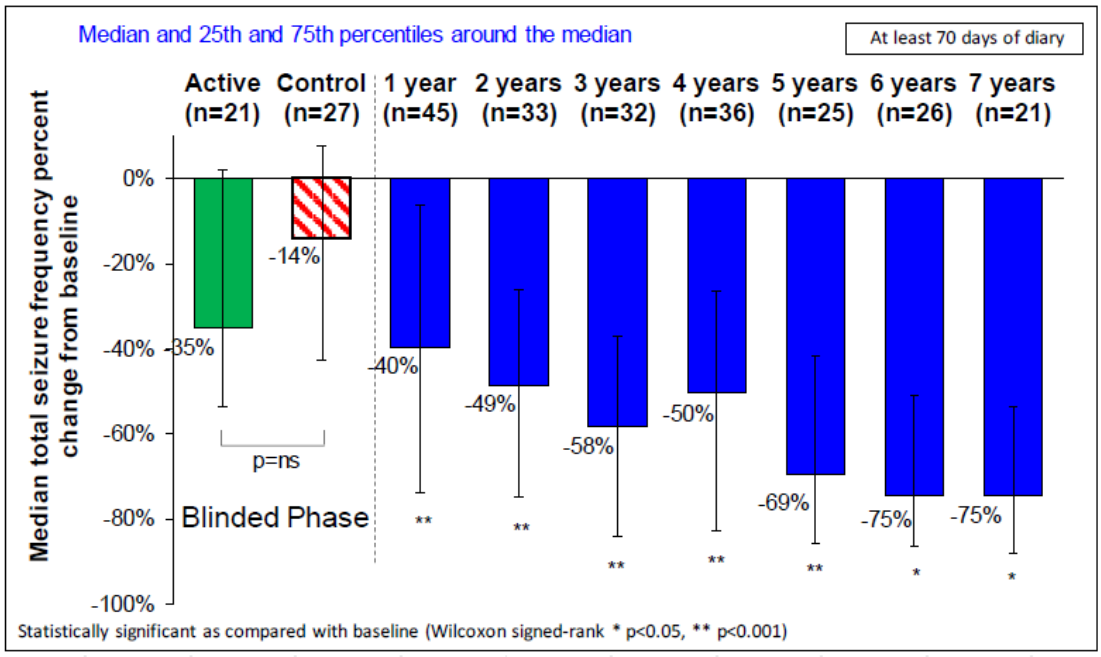


Figure 7. Change in seizure frequency (median) in subjects with prior VNS therapy

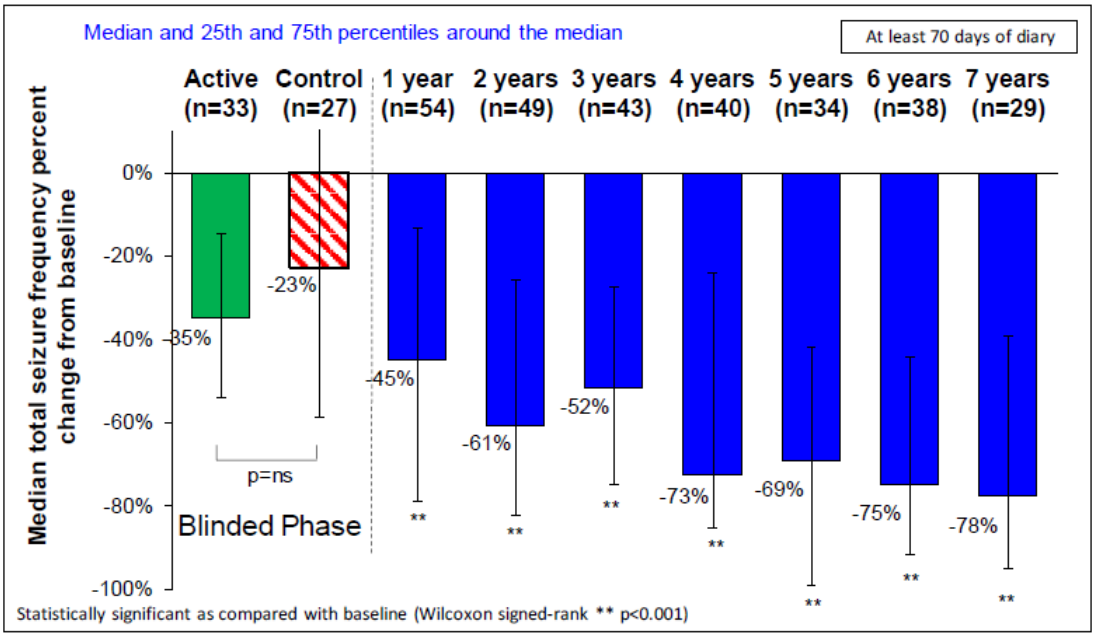


Figure 8. Change in seizure frequency (median) in subjects without prior VNS therapy

6.A.(1).2) Safety evaluation

6.A.(1).2).(a) Adverse events and serious adverse events during the blinded phase

Table 6 shows adverse events reported in ≥5% of subjects during the blinded phase. The incidence of depression and memory impairment differed statistically significantly between the active and control groups ($P < 0.05$, Fisher's exact test). These events are discussed in Sections 6.A.(1).2).(d) and 6.A.(1).2).(e).

Table 6. Adverse events during the blinded phase (incidence of ≥5%)

Event (MedDRA PT)	Active (n = 54)		Control (n = 55)		Difference*	*P*-value**
	No. of subjects	%	No. of subjects	%		
Depression	8	14.8%	1	1.8%	13.0%	0.016
Memory impairment	7	13.0%	1	1.8%	11.1%	0.032
Anxiety	5	9.3%	1	1.8%	7.4%	0.113
Confusional state	4	7.4%	0	0.0%	7.4%	0.057
Paraesthesia	5	9.3%	2	3.6%	5.6%	0.271
Influenza	3	5.6%	0	0.0%	5.6%	0.118
Partial seizures with secondary generalisation	5	9.3%	3	5.5%	3.8%	0.489
Simple partial seizures	3	5.6%	1	1.8%	3.7%	0.363
Partial complex seizures	5	9.3%	4	7.3%	2.0%	0.742
Implant site pain	3	5.6%	3	5.5%	0.1%	1.000
Anticonvulsant toxicity	3	5.6%	4	7.3%	−1.7%	1.000
Dizziness	3	5.6%	4	7.3%	−1.7%	1.000
Headache	2	3.7%	3	5.5%	−1.8%	1.000
Excoriation	1	1.9%	3	5.5%	−3.6%	0.618
Contusion	1	1.9%	4	7.3%	−5.4%	0.363
Nasopharyngitis	1	1.9%	5	9.1%	−7.2%	0.206
Upper respiratory tract infection	0	0.0%	4	7.3%	−7.3%	0.118
Injury	1	1.9%	7	12.7%	−10.9%	0.060

* Positive, more frequent in the active group; negative, more frequent in the control group.
** Fisher's exact test

Patients with epilepsy are known to be at a high risk of accidental injuries, including wound, excoriation, and contusion. Table 7 shows events that occurred as a direct result of an epileptic seizure

during the blinded phase. There was a statistically significant difference in the incidence of epilepsy-related events between the active group (7.4%, 4 of 54 subjects) and the control group (25.5%, 14 of 55 subjects) ($P < 0.019$, Fisher's exact test).

Table 7. Injuries and multiple injuries during the blinded phase

Event (MedDRA PT)	Active (%) (n = 54)	Control (%) (n = 55)	*P*-value*
Injury	1 (1.9%)	6 (10.9%)	
Contusion	1 (1.9%)	4 (7.3%)	
Excoriation	0.0%	2 (3.6%)	
Laceration	1 (1.9%)	0.0%	
Mouth injury	1 (1.9%)	0.0%	
Coccydynia	0.0%	1 (1.8%)	
Face injury	0.0%	1 (1.8%)	
Head injury	0.0%	1 (1.8%)	
Joint sprain	0.0%	1 (1.8%)	
Oedema	0.0%	1 (1.8%)	
Periorbital haematoma	0.0%	1 (1.8%)	
Total	**4 (7.4%)**	**14 (25.5%)**	**0.019**

* Fisher's exact test

Table 8 shows serious adverse events. Serious adverse events were reported in 8 subjects (8 events: 2 in the active group, 6 in the control group) during the blinded phase. These events were moderate to severe in severity. The subjects required inpatient hospitalization. Although the control group had a higher incidence of serious adverse events, these events showed no statistically significant difference between the active and control groups.

Table 8. Serious adverse events during the blinded phase

Event (MedDRA PT)	Active		Control	
	No. of subjects (%)	Severity	No. of subjects (%)	Severity
Implant site infection	-	-	2 (3.6%)	Severe or moderate
Partial complex seizures	-	-	1 (1.8%)	Severe
Depression	1 (1.9%)	Moderate	-	-
Partial seizures with secondary generalisation	-	-	1 (1.8%)	Severe
Anxiety	-	-	1 (1.8%)	Moderate
Muscle contractions involuntary	-	-	1 (1.8%)	Moderate
Status epilepticus	1 (1.9%)	Severe	-	-
Total	**2 (3.7%)**	**-**	**6 (10.9%)**	**-**

6.A.(1).2).(b) Adverse events in the entire population of the SANTE study

Table 9 shows adverse events (incidence of ≥5%) that occurred in subjects implanted with the stimulation device and electrode leads during the first 7 years after device implantation.

Table 9. Adverse events or malfunctions during the first 7 years post-implant (incidence of ≥5%)

Event (MedDRA PT) or malfunction	Operative phase (1 month) n = 110		1 year post-implant n = 110		7 years post-implant n = 110		Total* n = 110	
	No. of subjects	%	No. of subjects	%	No. of subjects	%	No. of subjects	%
Anticonvulsant toxicity	5	4.5%	20	18.2%	62	56.4%	66	60.0%
Nasopharyngitis	2	1.8%	22	20.0%	46	41.8%	49	44.5%
Injury	2	1.8%	20	18.2%	46	41.8%	48	43.6%
Depression	2	1.8%	22	20.0%	41	37.3%	43	39.1%
Headache	7	6.4%	23	20.9%	38	34.5%	39	35.5%
Partial complex seizures	1	0.9%	15	13.6%	37	33.6%	38	34.5%
Implant site pain	8	7.3%	21	19.1%	34	30.9%	35	31.8%
Upper respiratory tract infection	-	-	15	13.6%	34	30.9%	35	31.8%
Memory impairment	2	1.8%	23	20.9%	33	30.0%	34	30.9%
Partial seizures with secondary generalisation	1	0.9%	18	16.4%	32	29.1%	34	30.9%
Simple partial seizures	3	2.7%	14	12.7%	31	28.2%	31	28.2%
Skin laceration	1	0.9%	7	6.4%	30	27.3%	31	28.2%
Contusion	3	2.7%	15	13.6%	27	24.5%	31	28.2%
Paraesthesia	2	1.8%	21	19.1%	27	24.5%	27	24.5%
Back pain	-	-	7	6.4%	25	22.7%	27	24.5%
Sinusitis	1	0.9%	8	7.3%	23	20.9%	23	20.9%
Urinary tract infection	-	-	4	3.6%	21	19.1%	23	20.9%
Drug toxicity	3	2.7%	7	6.4%	17	15.5%	22	20.0%
Anxiety	1	0.9%	8	7.3%	20	18.2%	21	19.1%
Pain in extremity	2	1.8%	3	2.7%	16	14.5%	20	18.2%
Head injury	4	3.6%	9	8.2%	18	16.4%	19	17.3%
Excoriation	2	1.8%	8	7.3%	17	15.5%	18	16.4%
Laceration	1	0.9%	6	5.5%	16	14.5%	18	16.4%
Dizziness	1	0.9%	10	9.1%	17	15.5%	17	15.5%
Influenza	1	0.9%	7	6.4%	17	15.5%	17	15.5%
Insomnia	1	0.9%	5	4.5%	16	14.5%	17	15.5%
Implant site infection	5	4.5%	10	9.1%	15	13.6%	16	14.5%
Arthralgia	1	0.9%	4	3.6%	15	13.6%	16	14.5%
Pain	-	-	3	2.7%	14	12.7%	16	14.5%
Therapeutic product ineffective	-	-	-	-	14	12.7%	16	14.5%
Joint sprain	-	-	3	2.7%	13	11.8%	15	13.6%
Bronchitis	-	-	5	4.5%	12	10.9%	15	13.6%
Constipation	1	0.9%	2	1.8%	14	12.7%	14	12.7%
Diarrhoea	-	-	-	-	12	10.9%	14	12.7%
Sensory disturbance	1	0.9%	9	8.2%	13	11.8%	13	11.8%
Documented hypersensitivity to administered drug	2	1.8%	5	4.5%	12	10.9%	13	11.8%
Pharyngolaryngeal pain	1	0.9%	5	4.5%	12	10.9%	12	10.9%
Tremor	2	1.8%	4	3.6%	11	10.0%	12	10.9%
Hypertension	-	-	3	2.7%	11	10.0%	12	10.9%
Rash	-	-	-	-	11	10.0%	12	10.9%
Cellulitis	-	-	1	0.9%	10	9.1%	11	10.0%
Convulsion	-	-	2	1.8%	9	8.2%	11	10.0%
Shoulder pain	1	0.9%	5	4.5%	10	9.1%	10	9.1%
Gastrooesophageal reflux disease	-	-	2	1.8%	10	9.1%	10	9.1%
Limb injury	-	-	2	1.8%	10	9.1%	10	9.1%
Gastroenteritis viral	1	0.9%	1	0.9%	10	9.1%	10	9.1%
Hypoaesthesia	3	2.7%	6	5.5%	9	8.2%	10	9.1%
Haemorrhoids	-	-	1	0.9%	9	8.2%	10	9.1%
Ear infection	-	-	-	-	9	8.2%	10	9.1%
Fall	-	-	-	-	7	6.4%	10	9.1%
Lead(s) not within target	9	8.2%	9	8.2%	9	8.2%	9	8.2%
Implant site inflammation	2	1.8%	5	4.5%	8	7.3%	9	8.2%
Thermal burn	1	0.9%	5	4.5%	8	7.3%	8	7.3%
Vomiting	3	2.7%	4	3.6%	8	7.3%	8	7.3%
Nausea	1	0.9%	4	3.6%	8	7.3%	8	7.3%
Seasonal allergy	1	0.9%	3	2.7%	8	7.3%	8	7.3%
Hypersensitivity	-	-	3	2.7%	8	7.3%	8	7.3%

Event (MedDRA PT) or malfunction	Operative phase (1 month) n = 110		1 year post-implant n = 110		7 years post-implant n = 110		Total* n = 110	
	No. of subjects	%	No. of subjects	%	No. of subjects	%	No. of subjects	%
Dermatitis contact	2	1.8%	4	3.6%	7	6.4%	8	7.3%
Vaginal mycosis	-	-	2	1.8%	7	6.4%	8	7.3%
Migraine	-	-	-	-	7	6.4%	8	7.3%
Post-procedural pain	7	6.4%	7	6.4%	7	6.4%	7	6.4%
Status epilepticus	2	1.8%	4	3.6%	7	6.4%	7	6.4%
Hyponatraemia	1	0.9%	3	2.7%	7	6.4%	7	6.4%
Tooth infection	-	-	3	2.7%	7	6.4%	7	6.4%
Fatigue	1	0.9%	2	1.8%	7	6.4%	7	6.4%
Chest pain	-	-	2	1.8%	7	6.4%	7	6.4%
Mouth injury	-	-	3	2.7%	6	5.5%	7	6.4%
Gastroenteritis	-	-	2	1.8%	6	5.5%	7	6.4%
Suicidal ideation	-	-	1	0.9%	6	5.5%	7	6.4%
Epilepsy	-	-	-	-	6	5.5%	7	6.4%
Pharyngitis streptococcal	-	-	-	-	6	5.5%	7	6.4%
Confusional state	-	-	5	4.5%	6	5.5%	6	5.5%
Otitis media	-	-	4	3.6%	6	5.5%	6	5.5%
Acne	-	-	3	2.7%	6	5.5%	6	5.5%
Neurostimulator migration	-	-	3	2.7%	6	5.5%	6	5.5%
Skin papilloma	-	-	3	2.7%	6	5.5%	6	5.5%
Somnolence	-	-	3	2.7%	6	5.5%	6	5.5%
Abdominal pain	-	-	2	1.8%	6	5.5%	6	5.5%
Muscle twitching	-	-	1	0.9%	6	5.5%	6	5.5%
Sleep apnoea syndrome	-	-	1	0.9%	6	5.5%	6	5.5%
Hypokalaemia	-	-	-	-	6	5.5%	6	5.5%
Tooth fracture	-	-	-	-	6	5.5%	6	5.5%

* "Total" shows the total number of subjects (%) that experienced an adverse events or malfunction during the entire study period (i.e., until the end of follow-up).

During the operative phase (1 month post-implant), 83 subjects experienced 175 events. Commonly reported events were lead(s) not within target (8.2%, 9 of 110 subjects), implant site pain (7.3%, 8 of 110 subjects), headache (6.4%, 7 of 110 subjects), and post-procedural pain (6.4%, 7 of 110 subjects). During the first 1 year after device implantation, 109 subjects experienced 822 events (first-year events). Commonly reported events were headache (20.9%, 23 of 110 subjects), memory impairment (20.9%, 23 of 110 subjects), nasopharyngitis (20.0%, 22 of 110 subjects), and depression (20.0%, 22 of 110 subjects). During the first 7 years after device implantation, 110 subjects experienced 2,566 events (7-year events). Commonly reported events were anticonvulsant toxicity (56.4%, 62 of 110 subjects), nasopharyngitis (41.8%, 46 of 110 subjects), injury (41.8%, 46 of 110 subjects), and depression (37.3%, 41 of 110 subjects).

Serious adverse events accounted for 6.8% of all the first-year events (56 of 822 events) and 6.2% of all the 7-year events (158 of 2,566 events). Commonly reported serious events during the 7 years after device implantation were implant site infection (10.9%, 12 of 110 subjects), partial seizures with secondary generalisation (10.0%, 11 of 110 subjects), and lead(s) not within target (8.2%, 9 of 110 subjects). Implant site infection led to removal of a component(s) or the complete system in 7.3% (8 of 110) of subjects. Of them, 4.5% (5 subjects) had no system replacement and 2.7% (3 subjects) underwent system replacement.

The incidence of device-related adverse events was highest during the operative phase (1 month post-implant). The incidence of device-related adverse events during the first 1 year after device

implantation was 84.5% (93 of 110 subjects). Commonly reported device-related adverse events were implant site pain (19.1%, 21 of 110 subjects), paraesthesia (19.1%, 21 of 110 subjects), implant site infection (9.1%, 10 of 110 subjects), and lead(s) not within target (8.2%, 9 of 110 subjects). Serious adverse events accounted for 4.1% of all first-year device-related events (34 of 822 events). The incidence of device-related adverse events during the 7 years after device implantation was 90.9% (100 of 110 subjects). Commonly reported device-related events were implant site pain (30.9%, 34 of 110 subjects), paraesthesia (23.6%, 26 of 110 subjects), implant site infection (12.7%, 14 of 110 subjects), and therapeutic product ineffective (12.7%, 14 of 110 subjects). Serious adverse events accounted for 1.7% of all 7-year device-related events (44 of 2,566 events).

Table 10 shows device-related serious adverse events. Device-related serious adverse events were reported in 36 of 110 subjects (32.7%) during the 7 years after device implantation. Commonly reported device-related serious adverse events were implant site infection (10.0%, 11 of 110 subjects) and lead(s) not within target (8.2%, 9 of 110 subjects). The incidences of both events in DBS therapy were comparable to those for the approved indications of DBS.

The incidence of any device-related adverse event did not tend to increase during the follow-up phase (i.e., between the PMA application and the end of study).

Table 10. Device-related serious adverse events or malfunctions

Event (MedDRA PT) or malfunction	Operative phase (1 month) n = 110		1 year post-implant n = 110		7 years post-implant n = 110		Total* n = 110	
	No. of subjects	%	No. of subjects	%	No. of subjects	%	No. of subjects	%
Implant site infection	4	3.6%	8	7.3%	11	10.0%	12	10.9%
Lead(s) not within target	9	8.2%	9	8.2%	9	8.2%	9	8.2%
Post-procedural pain	2	1.8%	2	1.8%	2	1.8%	2	1.8%
Postoperative fever	2	1.8%	2	1.8%	2	1.8%	2	1.8%
Vomiting	2	1.8%	2	1.8%	2	1.8%	2	1.8%
Therapeutic product ineffective	-	-	-	-	2	1.8%	2	1.8%
Pyrexia	1	0.9%	1	0.9%	1	0.9%	1	0.9%
Set screws not adequately secured	1	0.9%	1	0.9%	1	0.9%	1	0.9%
Wound drainage	1	0.9%	1	0.9%	1	0.9%	1	0.9%
Muscle contractions involuntary	-	-	1	0.9%	1	0.9%	1	0.9%
Partial seizures with secondary generalisation	-	-	1	0.9%	1	0.9%	1	0.9%
Status epilepticus	-	-	1	0.9%	1	0.9%	1	0.9%
Tension	-	-	1	0.9%	1	0.9%	1	0.9%
Unresponsive to stimuli	-	-	1	0.9%	1	0.9%	1	0.9%
Convulsion	-	-	-	-	1	0.9%	1	0.9%
Device extension fracture	-	-	-	-	1	0.9%	1	0.9%
Implant site inflammation	-	-	-	-	1	0.9%	1	0.9%
Implant site pain	-	-	-	-	1	0.9%	1	0.9%
Implant site erosion	-	-	-	-	-	-	1	0.9%
Incision site complication	-	-	-	-	-	-	1	0.9%
Total	**22**	**20.0%**	**28**	**25.5%**	**36**	**32.7%**	**38**	**34.5%**

* "Total" shows the total number of subjects (%) that experienced an adverse events or malfunction during the entire study period (i.e., until the end of follow-up).

6.A.(1).2).(c) Deaths and sudden unexpected death in epilepsy (SUDEP)

Seven subjects died during the 7 years after device implantation. One subject died prior to device implantation, 1 subject during the unblinded phase, and 5 subjects during the LTFU. Of these, 3 subjects died of SUDEP (including 1 subject who died before device implantation). The other deaths were attributed to completed suicide (1 subject), malignant neoplasm (liver cancer, 1 subject), cardio-respiratory arrest (1 subject), and drowning (possibly SUDEP, 1 subject) (Table 11). None of the deaths was related to the device or treatment.

Table 11. Deaths during the 7 years post-implant

No.	Timing of death (final evaluation)	Event (MedDRA PT)	Summary of death	Autopsy	Assessment of SUDEP by DMC	Stimulation ON at death
1	Baseline (Week -4)	Sudden unexpected deaths in epilepsy	The subject was found dead next to the bed.	No	Probably SUDEP	NA
2	Unblinded phase (Month 7)	Sudden unexpected deaths in epilepsy	The subject was unresponsive in the bed and did not respond to resuscitation.	Yes	Definitely SUDEP	Yes
3	LTFU (Month 20)	Drowning	The subject was found dead in the bathtub.	No	Possibly SUDEP	Yes
4	LTFU (Month 46)	Completed suicide	The subject committed suicide using a gun.	No	Not SUDEP	No
5	LTFU (Month 59)	Sudden unexpected deaths in epilepsy	The subject was found dead in the bed.	Yes	Definitely SUDEP	No
6	LTFU (Month 72)	Cardio-respiratory arrest	The subject was unresponsive. 3 episodes of cardio-respiratory arrest; removal of the life supporting device.	No	Not SUDEP	Yes
7	LTFU (Month 74)	Neoplasm malignant	Metastatic liver cancer was accidentally found after a fall due to seizures. The subject died 11 days after the fall.	No	Not SUDEP	Yes

Table 12 shows the number of SUDEP cases in the SANTE study and the pilot study. The SUDEP rate in the SANTE study (excluding the SUDEP case during the baseline phase) was 2.8 per 1,000 person-years (confidence interval, 0.34-10.13). When the data from the pilot study and 1 case of possible SUDEP are included, the SUDEP rate was 3.8 per 1,000 person-years (confidence interval, 0.78-11.11). These SUDEP rates are lower than that (9.3 per 1,000 person-years) in candidates for epilepsy surgery reported in a publication.[10] One subject died from status epilepticus after the PMA application, but the death was not SUDEP according to the investigator. The overall SUDEP rate throughout the entire study period, including the CAP, was 2.0 per 1,000 person-years. The rate did not tend to increase over time.

Table 12. SUDEP rate

Source of data	Number of SUDEP	Years of device use	SUDEP rate per 1,000 person-years	95% Poisson confidence interval
SANTE study	2	713 years	2.8 per 1,000 person-years	[0.34, 10.13]
(including a possible SUDEP case)	3	713 years	4.2 per 1,000 person-years	[0.87, 12.30]
Pilot Follow-up	0	76 years	0 per 1,000 person-years	[0, 48.54]
Total	**2**	**789 years**	**2.5** per **1,000 person-years**	**[0.31, 9.16]**
(including a possible SUDEP case)	**3**	**789 years**	**3.8** per **1,000 person-years**	**[0.78, 11.11]**

6.A.(1).2).(d) Details of depression cases

"Depression" occurred significantly more frequently in the active group than in the control group during the blinded phase. Table 13 shows the details of depression in 9 subjects (8 subjects in the active group, 1 subject in the control group). Of the 9 subjects with depression, 6 had a medical history of depression; the events in the 6 subjects were aggravation of depression during the blinded phase. The remaining 3 subjects had de novo depression after randomization. In 1 of the 3 subjects, de novo depression was reported to be related to stimulation and resolved by adjusting the stimulation settings. All of the events in 9 subjects were mild or moderate in severity. The event in 1 subject was moderate in severity and serious, requiring 2 hospitalizations for treatment. Of the 9 subjects with depression, 4 subjects recovered. The remaining 5 subjects did not recover by the day of the final outcome assessment (1-6 years post-implant). There was no study discontinuation due to depression.

In the SANTE study, the Profile of Mood States (POMS) was used for a neuropsychological test. The mean change in the depression score on the POMS (POMS-D) at 4 months after device implantation was 0.7 ± 9.3 in the active group and −0.5 ± 7.4 in the control group, showing no statistically significant difference (P = 0.396, Wilcoxon rank sum test). The mean change in the POMS-D score was 0.5 ± 10.9 at 1 year after device implantation and 0.1 ± 11.6 at 7 years after device implantation. The changes in the POMS-D score were not clinically relevant because the score did not tend to increase over time and the mean changes were smaller than 1 standard deviation.

Table 14 shows the incidence of depression during and after the unblinded phase. No substantial change was noted in the incidence of the event over time after device implantation.

Table 13. Details of depression cases

ID Group	Medical history of depression	Event category	Serious/ non-serious	Severity	Intervention	Time to onset	Outcome	Epileptic seizure frequency
0111 Active	No	De novo	Non-serious	Mild	Counselling and drug therapy	6 weeks post-implant	Not resolved	-84.3%
0202 Active	Yes	History of depression	Non-serious	Moderate	No	6 weeks post-implant	Resolved (15 days after onset)	8.5%
0302 Active	Yes	History of depression	Serious (2 hospitalizations)	Moderate	Drug therapy	2 months post-implant	Not resolved	-35.1%
0510 Active	Yes	History of depression	Non-serious	Mild	Drug therapy	6 weeks post-implant	Not resolved	-8.8%
0605 Active	Yes	History of depression	Non-serious	Mild	No	2 months post-implant	Resolved (128 days after onset)	-59.6%
0703 Active	Yes	History of depression	Non-serious	Moderate	No	6 weeks post-implant	Resolved (14 days after onset)	-53.9%
0707 Active	Yes	History of depression	Non-serious	Moderate	Drug therapy	2 months post-implant	Not resolved	-67.7%
1206 Active	No	Programing/ stimulation	Non-serious	Moderate	Counselling and stimulation adjustment	4 weeks post-implant	Resolved (145 days after onset)	-0.8%
1215 Control	No	De novo	Non-serious	Moderate	Referred to psychiatrist and drug therapy	2 months post-implant	Not resolved	13.6%

Table 14. Incidences of depression and memory impairment after the unblinded phase

Study period		Total number of subjects (n)	Event			
			Depression		Memory impairment	
			No. of subjects	%	No. of subjects	%
Unblinded phase		108	11	10.2	13	12.0
LTFU	1-2 years	105	7	6.7	3	2.9
	2-3 years	102	4	3.9	1	1.0
	3-4 years	98	3	3.1	3	3.1
	4-5 years	92	2	2.2	2	2.2
	5-6 years	83	4	4.8	3	3.6
	6-7 years	80	1	1.3	-	-
	7-8 years	73	-	-	1	1.4
	8-9 years	69	2	2.9	2	2.9
LTFU/CAP	9-10 years	66	2	3.0	-	-
	10-11 years	62	-	-	-	-
	11-12 years	53	-	-	-	-
	12-13 years	32	-	-	-	-
	13-14 years	24	-	-	-	-
	14-15 years	5	-	-	-	-
Total		**110**	**36**	**32.7**	**27**	**24.5**

6.A.(1).2).(e) Details of memory impairment cases

"Memory impairment" occurred significantly more frequently in the active group than in the control group during the blinded phase. Table 15 shows the details of memory impairment in 8 subjects (7 subjects in the active group, 1 subject in the control group). Of the 8 subjects with memory impairment, 2 had a medical history of memory impairment; the events in the 2 subjects were aggravation of memory impairment during the blinded phase. All of events in the 8 subjects were mild or moderate in severity. None was reported as serious. All of the subjects recovered without intervention or after adjustment of stimulation settings. There was no study discontinuation due to memory impairment.

In the SANTE study, verbal memory and visual memory were assessed by neuropsychological tests. Table 16 shows the mean changes in score at 4 months after device implantation. There was no statistically significant difference between the active and control groups at 4 months after device implantation (verbal memory, $P = 0.537$ in the active group, $P = 0.232$ in the control group; visual memory, $P = 0.317$ in the active group, $P = 0.156$ in the control group; Wilcoxon rank sum test). The results at 1 and 7 years after device implantation showed that the verbal and visual memory scores did not tend to worsen over time, and that all of the mean changes were smaller than 1 standard deviation. Therefore the changes in verbal and visual memory scores were not clinically relevant.

Table 14 shows the incidence of memory impairment during and after the unblinded phase. No substantial change was noted in the incidence of the event over time after device implantation.

Table 15. Details of memory impairment cases

ID Group	History of memory impairment (prior surgical therapy)	Event category	Serious/ non-serious	Severity	Intervention	Time to onset	Outcome
0202 Active	Yes (2 occipital lobe resections)	History of memory impairment	Non-serious	Mild	No	4 weeks post-implant	Resolved (15 days after onset)
0403 Active	No (Right parietal lobe resection)	Programing/ stimulation	Non-serious	Moderate	No	4 weeks post-implant	Resolved (12 days after onset)
0517 Active	No (no)	Programing/ stimulation	Non-serious	Mild	No	4 weeks post-implant	Resolved (61 days after onset)
0609 Active	No (no)	De novo	Non-serious	Mild	No	4 weeks post-implant	Resolved (126 days after onset)
0707 Active	Yes (no)	History of memory impairment	Non-serious	Moderate	Stimulation adjustment (2/6/06, 2/21/06)	4 weeks post-implant	Resolved (476 days after onset)
1209 Active	No (no)	De novo	Non-serious	Mild	No	6 weeks post-implant	Resolved (14 days after onset)
1302 Active	No (no)	Programing/ stimulation	Non-serious	Moderate	Stimulation adjustment (8/17/06)	4 weeks post-implant	Resolved (17 days after onset)
0604 Control	No (no)	De novo	Non-serious	Mild	No	2 months post-implant	Resolved (147 days after onset)

Table 16. Neuropsychological tests (verbal memory and visual memory)

	4 months post-implant		1 year post-implant (n = 105)	7 years post-implant (n = 66)
	Active (n = 54)	Control (n = 46)		
	Mean change ± SD	Mean change ± SD	Mean change ± SD	Mean change ± SD
Verbal memory (CVLT)				
Trial 1-5 Total (T)	−0.2 ± 8.6	−1.3 ± 9.2	0.8 ± 10.4	0.2 ± 10.9
Long Delay Free Recall (z)	−0.1 ± 0.9	0.1 ± 1.2	0.2 ± 1.1	0.2 ± 1.2
Visual memory (BVMT-R)				
Total Recall (T)	−0.2 ± 11.0	1.9 ± 11.4	1.7 ± 10.4	2.9 ± 10.1
Delayed Recall (T)	−1.3 ± 14.1	2.4 ± 13.7	0.7 ± 11.5	0.4 ± 12.3

SD: Standard deviation.

6.A.(1).2).(f) Safety in subjects with prior VNS therapy

During the first 7 years after device implantation, serious adverse events occurred in 49 subjects with prior VNS therapy (75 events) and 61 subjects without prior VNS therapy (83 events). Table 17 shows serious adverse events with an incidence of ≥2%. Commonly reported serious adverse events were implant site infection, partial seizures with secondary generalisation, and lead(s) not within target, showing no substantial difference between subjects with and without prior VNS therapy.

Table 17. Serious adverse events by prior VNS therapy (during the first 7 years post-implant, incidence of ≥2%).

Event (MedDRA PT) or malfunction	With prior VNS (n = 49)		Without prior VNS (n = 61)		Total (n = 110)	
	No. of subjects	%	No. of subjects	%	No. of subjects	%
Implant site infection	7	14.3%	5	8.2%	12	10.9%
Partial seizures with secondary generalisation	6	12.2%	5	8.2%	11	10.0%
Lead(s) not within target	3	6.1%	6	9.8%	9	8.2%
Status epilepticus	4	8.2%	2	3.3%	6	5.5%
Partial complex seizures	4	8.2%	2	3.3%	6	5.5%
Pyrexia	2	4.1%	1	1.6%	3	2.7%
Epilepsy	2	4.1%	1	1.6%	3	2.7%
Convulsion	1	2.0%	2	3.3%	3	2.7%
Conversion disorder	2	4.1%	1	1.6%	3	2.7%
Anticonvulsant toxicity	2	4.1%	1	1.6%	3	2.7%
Simple partial seizures	0	0.0%	3	4.9%	3	2.7%
Psychotic disorder	1	2.0%	2	3.3%	3	2.7%

6.A.(2) Literature review of efficacy and safety

The applicant conducted literature searches as summarized below. The database PubMed was searched with the keywords of “DBS” as therapy name, “Epilepsy” as disease name, and “ANT” as stimulation site over all publication years (Table 18).

Table 18. Methodology of literature searches

Database	PubMed
Keywords	([dbs] OR [deep brain stimulation]) AND (epilepsy) AND ([ant] OR [anterior nucleus of thalamus])
Refinement	● Refinement by filtering Condition 1: Clinical Study, Clinical Trial, and Randomized Controlled Trial Condition 2: Systematic Review ● Refinement based on contents • Overlapping Publications on the SANTE study were excluded. • Duration of follow-up Lead placement for DBS causes microfractures of cells, which may temporarily improve symptoms independent of stimulation early after implantation. Therefore, publications containing follow-up data for ≥3 months were extracted. • Off-label use Studies involving no ANT or reviews only in pediatric patients were excluded. • Reports from sources other than clinical studies/trials (Condition 1 alone) Reports from sources other than clinical studies/trials were excluded. ● Publication years All publication years were included. ● Follow-up publications Follow-up reports of publications after refinement were included, if any.

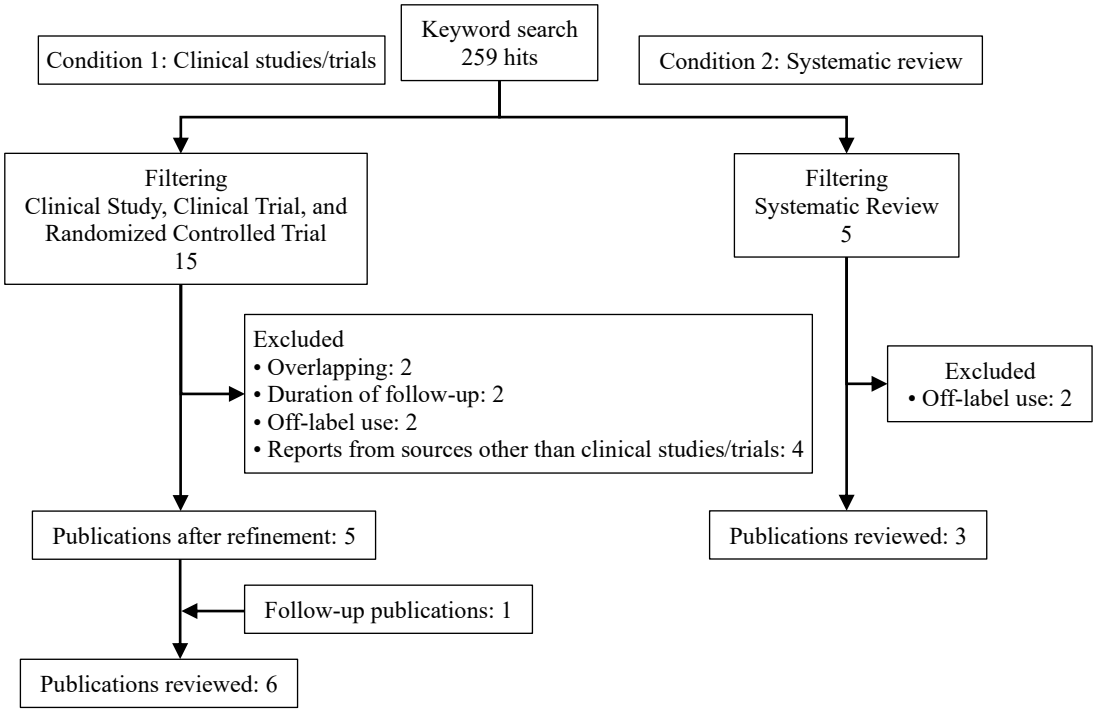


Figure 9. Flow chart of the process of literature extraction for review

Table 19. List of literature reports extracted for review (condition 1: clinical studies/trials)

No.	Author	Outline	Endpoints	No. of subjects	Follow-up period	Efficacy	Safety	Weighting
1	Herrman, H. *et al.*[11]	Efficacy and safety evaluation of DBS of the ANT in epileptic seizures **Design:** Prospective, randomized, double-blind study **Results:** The active group experienced 20% fewer seizures at Month 6 than baseline, while the control group experienced no change. Both groups had no change at Month 12. **Safety:** Central paresis of the left facial nerve in 1 subject (resolved in 2 to 3 days), no other serious adverse event or SUDEP	• Percent seizure reduction • Adverse events • SUDEP	18	12 months	✓	✓	A
2	Heminghyt, E. *et al.*[12]	Investigation of cognitive changes associated with DBS of the ANT **Design:** Prospective, randomized, double-blind study **Results:** There were changes in motor speed and sustained attention. Symptoms of higher brain dysfunction reduced at Month 12. Patients with a reduction in seizure frequency had better performance in verbal learning. DBS of the ANT has limited effects on cognitive function and may have a positive influence on executive function.	• Motor function • Cognitive function	18	12 months	✓	-	A
3	Lee, K. J. *et al.*[13]	Efficacy and safety evaluation of DBS of the ANT in epileptic seizures **Patients:** 15 patients with drug-resistant epilepsy with partial-onset seizures **Results:** The number of seizures reduced by 70.4% on average compared with baseline. **Safety:** Infection in 1 subject; no other serious adverse event or SUDEP	• Percent seizure reduction • Adverse events • SUDEP	15	27 months	✓	✓	B
4	Oh, Y. S. *et al.*[14]	Investigation of cognitive outcomes after DBS of the ANT **Results:** DBS resulted in a mean percent seizure reduction of 57.9%, improved verbal fluency and verbal memory, and no change in IQ, information processing, or executive function. A follow-up examination at Year 1 showed no cognitive decline.	• Percent seizure reduction • Cognitive function	9	12 months	✓	-	B
5	Lehtimäki, K. *et al.*[15]	Investigation of the correlation between the stimulation site and outcome **Results:** Analysis of the correlation between ANT anatomy and responders showed that stimulation in the anterior to posterior axis may result in an antiepileptic effect. Proportion of responders: 67% (10 of 15 patients)	• Stimulation site • Proportion of responders	15	18 months	✓	-	B

No.	Author	Outline	Endpoints	No. of subjects	Follow-up period	Efficacy	Safety	Weighting
9	Kim, S. H. *et al.*[16]	11-year follow-up of the study by Lee, K. J. *et al.* Efficacy and safety evaluation of DBS of the ANT in epileptic seizures **Patients:** 29 patients with drug-resistant epilepsy with partial-onset seizures **Results:** The overall median percent seizure reduction throughout the entire study was ≥70%. **Safety:** Haemorrhage intracranial in 1 subject, infection in 1 subject, and SUDEP in 1 subject	• Percent seizure reduction • Adverse events	29	11 years	✓	✓	B

Table 20. List of literature reports extracted for review (condition 2: systematic review)

No.	Author	Outline	Endpoints	No. of literature	Efficacy	Safety	Weighting
6	Chang, B. *et al.*[17]	Meta-analysis to identify possible predictors of DBS outcomes Percent seizure reduction: 59% DBS is effective in patients with lateralized electroencephalogram abnormalities and patients treated on the ictal side. This meta-analysis was conducted on the pooled results of DBS of the ANT and hippocampus.	• Percent seizure reduction • Safety	8	✓	✓	-
7	Zhou, J. J. *et al.*[18]	Systematic review of the efficacy of DBS in epilepsy Percent seizure reduction: 44% to 100% Level I evidence supported the efficacy of DBS of the ANT and the hippocampus.	• Percent seizure reduction • Safety	19	✓	✓	-
8	Vetkas, A. *et al.*[19]	Systematic review of the efficacy of DBS in epilepsy Percent seizure reduction: 60.8% The results of RCTs and large clinical studies/trials serve as better evidence for DBS of the ANT.	• Percent seizure reduction • Safety	23	✓	✓	-

6.A.(2).1) Results of literature search 1: Clinical studies/trials

Herrman, H. *et al.* reported the results, including follow-up results at 12 months after device implantation, of a controlled study in 18 patients with drug-resistant partial epilepsy (having most serious epileptic symptoms, 2-3 prior antiepileptic drugs used, age of ≥18 years, and mean duration of illness of 24 years) (Literature report 1). The blinded period was 6 months, during which the level of stimulation was kept unchanged. The active group achieved a 20% reduction in seizure frequency compared with the control group at the end of the blinded period (at 6 months), which was consistent with the result of the SANTE study. However, there was no change in percent seizure reduction at 12 months. Since this outcome was not as good as expected, the study was terminated after 18 patients were enrolled (the planned sample size, 40 subjects). This study enrolled patients with severe symptoms, which might explain the poor outcome of the study according to the authors. The authors also explained that the follow-up period might have been too short to demonstrate a therapeutic effect. As for safety, 1 subject had central paresis of the left facial nerve, which resolved in 2 to 3 days. There were no other serious adverse events or SUDEP.

Heminghyt, E. *et al.* reported the effects on cognitive function in 18 subjects enrolled in the clinical study that had been reported by Herrman, H. *et al.* (Literature report 2). A follow-up examination at 12

months showed fewer symptoms of higher brain dysfunction. Patients with a reduction in seizure frequency had better performance in verbal learning. These results led to the conclusion that DBS of the ANT has limited effects on cognitive functioning and may have a positive influence on the executive function.

Lee, K. J. *et al.* reported the efficacy and safety results of DBS of the ANT for 27 months on average in 15 patients with drug-resistant partial epilepsy who had previously used multiple antiepileptic drugs (age of 14-54 years, and mean duration of illness of 17 years) (Literature report 3). The seizure frequency was reduced by 70.5% on average compared with baseline. Patients who had seizure reduction at 3 months achieved similar results at subsequent follow-up visits, indicating that the short-term outcome reflects the long-term outcome. One subject had infection during the follow-up period. No other serious adverse event or SUDEP was reported.

Oh, Y. S., *et al.*, who were in the same research group as Lee, K. J. *et al.*, reported the long-term effects of DBS of the ANT on cognitive function in 9 patients with drug-resistant partial epilepsy who had previously used multiple antiepileptic drugs (age of 14-50 years) (Literature report 4). The cognitive outcomes were evaluated at 12 months. DBS improved verbal fluency and verbal memory but did not change IQ, information processing, or executive function. The seizure frequency was reduced by 57.9% on average compared with baseline.

Kim, S. H. *et al.*, who were in the same research group as Lee, K. J. *et al.*, reported the results of 11-year follow-up of 29 subjects. The overall median percent seizure reduction was ≥70% throughout the entire study period (Literature report 9). Regarding safety information, haemorrhage intracranial in 1 subject (3.4%) and early infection in 1 subject (3.3%) were reported as treatment-related serious adverse events. Other adverse events reported were pain (34.4%, 10 subjects), uncomfortable sensory change (27.6%, 8 subjects), infection during the follow-up period (3.4%, 1 subject). Malfunctions were correction of lead position (5.2%, 3 of 58 leads) and high impedance (6.9%, 2 subjects). Cognitive adverse events and other events were depression (17.2%, 5 subjects, including 3 having medical history of depression), suicide attempt (6.9%, 2 subjects), suicide (3.4%, 1 subject, 7.5 years post-implantation, not related to the device), memory impairment (24.1%, 7 subjects, non-serious for all), and death (4 subjects; SUDEP, suicide, cardio-respiratory arrest due to septic shock, and road traffic accident). The authors reported that the efficacy and safety of DBS of the ANT were demonstrated by the long-term follow-up results, which were consistent with the results of the SANTE study.

Lehtimäki, K. *et al.* conducted DBS of the ANT in 15 patients with drug-resistant partial epilepsy (age of 23-50 years) and reported the correlation between stimulation sites and antiepileptic effects (Literature report 5). Different stimulation sites of 62 contacts were assessed. The follow-up results of 18.3 months on average showed that stimulation in the anterior to posterior axis might produce antiepileptic effects. For the efficacy for seizure, 10 of 15 subjects (67%) were responders.

The safety information in each literature report is summarized below. Safety data were obtained from a total of 75 subjects in the 5 references, approximately 223 person-years throughout the entire

follow-up period. Literature reports Nos. 1, 3, and 9 include safety data from 47 subjects, approximately 192 person-years throughout the entire follow-up period. There were 3 adverse events (6%) and 1 SUDEP. The adverse events and their incidences reported in these reports were consistent with those in the SANTE study.

Table 21. Safety information reported in literature reports

No.	Author	N0. of subjects	Duration of follow-up	Total duration of follow-up*	Event	No. of events
1	Herrman, H.	18	12 months	18 person-years	Central paresis	1
3, 9	Lee, K. J. Kim, S. H.	29	11 years (6 years on average)	174 person-years	Infection Haemorrhage intracranial SUDEP	1 1 1
4	Oh, Y. S.	9	12 months	9 person-years	Not reported	-
5	Lehtimäki, K.	15	18 months	22.5 person-years	Not reported	-
Total		**71 (47)****		**223.5 person-years (192 person-years)****	**Serious adverse event SUDEP**	**2 1**

* Total duration of follow-up was calculated by multiplying the number of patients by duration of follow-up.
** The data in parenthesis are the sum of the figures in the literature reports that included safety data.

6.A.(2).2) Results of literature search 2: Systematic review

Chang, B. *et al.* conducted meta-analysis of data from 61 subjects in 8 literature reports that reported DBS of the hippocampus and ANT in order to identify possible predictors of antiepileptic effects (Literature report 6). The meta-analysis demonstrated that the percent seizure reduction was 59%, and that stimulation of the hippocampal and ANT resulted in a similar percent seizure reduction. The authors concluded that DBS was effective in patients with lateralized electroencephalogram abnormalities and in patients who had previously received treatment for the ictal side.

Zhou, J. J. *et al.* conducted a systematic review of the efficacy of DBS in epilepsy (Literature report 7). Publications on PubMed between 2008 and 2018 were searched. As a result of literature search, 41 reports met the conditions, including 19 reporting DBS of the ANT. DBS of the ANT resulted in a percent seizure reduction of 44% to 100%. Level I evidence (the SANTE study) showed a response rate of 53% at 2 years after the start of stimulation. Complications in the SANTE study were consistent with those in other reports on DBS. The systematic review reported long-term follow-up results, which supported the long-term safety of DBS of the ANT. The authors concluded that Level I evidence supported the efficacy of DBS of the ANT and the hippocampus.

Vetkas, A. *et al.* conducted a systematic review of the efficacy of DBS in epilepsy (Literature report 8). Publications on PubMed between 2000 and 2021 were searched. As a result of literature search, 44 publications met the search conditions, including 23 reporting DBS of the ANT (330 patients). DBS of the ANT resulted in a percent seizure reduction of 60.8%. The systematic review included a funnel plot of the percent seizure reductions after DBS of the ANT in the publications to assess the bias of each publication. The funnel plot showed a symmetric distribution relative to the median, suggesting low publication bias. The authors discussed that the low percent seizure reduction in the publication by Herrman, H. *et al.* (presented above) was because stimulation was not optimized. The authors also mentioned the programming for stimulation based on the results from the publications and proposed the following standard settings based on the protocol of the SANTE study: 5 V, 145 Hz, 90 μs, cycling on interval 1 minute, and cycling off interval 5 minutes. As for safety, the authors only mentioned adverse events reported in the SANTE study and stated that the risk of the procedure for DBS of the

ANT was comparable to the general DBS procedure. The authors concluded that DBS was an effective and safe treatment for patients with drug-resistant partial epilepsy and that the results of the systematic publication review demonstrated a potent effect of DBS of the ANT in reducing seizures.

6.B Outline of the review conducted by PMDA

Taking account of comments raised in the Expert Discussion, PMDA focused on the following issues:

(1) Clinical positioning
(2) The appropriateness of conducting clinical evaluation of Percept PC based on literature reports
(3) Extrapolation of the foreign clinical data and the study results of the predecessors of Percept PC
(4) Efficacy and safety of Percept PC
(5) Intended use or indication
(6) Post-marketing safety measures

6.B.(1) Clinical positioning

In Japan, VNS is already approved for the treatment of patients with drug-resistant partial epilepsy who are not eligible for surgery. PMDA asked the applicant to explain how physicians will choose VNS or DBS for the treatment of this patient population.

The applicant's explanation:
Both VNS and DBS are indicated for patients with drug-resistant partial epilepsy who do not respond to surgical therapy or are not eligible for surgery; thus the target populations of VNS and DBS are the same. However, potential adverse reactions etc., of DBS and VNS may differ because of the differences in the implantation procedure and stimulation site. In selection of treatment, therefore, medical history and living environment of each patient must be considered. More specifically, DBS is associated with risks of intracranial events, such as haemorrhage intracranial, as well as depression and memory impairment. On the other hand, VNS may cause cervical events, such as dysphagia and dyspnoea. In selection of treatment, therefore, the medical history and living environment must be considered for each patient.

PMDA asked the applicant to explain what clinical benefits can be expected from the introduction of DBS when VNS is already available for treatment.

The applicant's explanation:
The target disease and therapeutic efficacy of Percept PC are similar to those of VNS. As mentioned above, however, VNS and DBS use different implantation procedures and stimulation sites. DBS may be used in patients with prior cervical vagotomy, which is a contraindication to VNS, or in patients who are not eligible for VNS because of its risks, such as dysphagia and dyspnoea. The SANTE study demonstrated the efficacy of DBS in subjects with and without prior VNS therapy, suggesting that switching from VNS to DBS may reduce seizures in patients who have an inadequate response to VNS. This is because DBS and VNS have a different mechanism of therapeutic efficacy. Reversely, VNS may be effective in patients who have an inadequate response to DBS. In summary, DBS can be used to complement VNS and is expected to expand eligible patients for accommodative treatment of drug-resistant partial epilepsy.

PMDA's view, considering the comments from the Expert Discussion:
The "Clinical Practice Guidelines for Epilepsy 2018" currently recommend that surgical resection (partial resective surgery), which is expected to cure the disease, be considered for patients with epilepsy who have an inadequate response to drug therapy and have an identified seizure onset location in the brain. For patients who have no identified onset location and therefore are not eligible for surgery, VNS is considered to be a treatment option. VNS requires placement of the device in the chest and electrode leads in the vagus nerve. Percept PC, a DBS system, requires placement of the electrode leads in the brain. This is a highly invasive accommodative treatment as with VNS. DBS, whose mechanism of action is different from that of VNS, is expected to be a highly useful treatment option because patients with epilepsy have a variety of different characteristics. The clinical positioning of Percept PC should be the same as that of VNS.

It is difficult to decide which procedure, DBS or VNS, should be the first-line treatment based on the clinical study results submitted. The percent seizure reductions reported in the SANTE study and the other literature reports are comparable to the treatment outcomes of VNS (percent seizure reduction, 38.4% at 1 year, 48.9% at 3 years, and 68.5% at 5 years[20]). As explained by the applicant, therefore, treatment should be selected for each patient based on their potential risks, pathological condition, characteristics, etc.

Patients with prior VNS therapy may receive DBS. The SANTE study enrolled 49 patients with prior VNS therapy (44.5% of the 110 subjects enrolled). A stratified analysis showed no substantial difference in efficacy and safety between subjects with and without prior VNS therapy (Figures 7 and 8, and Table 17). Since prior VNS therapy is unlikely to affect the efficacy and safety of DBS, DBS appears to cause no particular problem in patients with prior VNS therapy.

PMDA concluded that the clinical positioning of Percent PC should be the same as that of VNS in treatment of drug-resistant partial epilepsy.

6.B.(2) The appropriateness of conducting clinical evaluation of Percept PC based on literature reports

PMDA's view:
DBS is a medical device that is already approved in Japan. The present partial change application includes no change in the design of Percept PC or its accessories including the electrode leads. There are numerous safety data regarding the basic procedure and device implantation for DBS. For this reason, the review for the present partial change application should be focused on the efficacy and safety of Percept PC when the ANT is used as the stimulation site in patients with drug-resistant partial epilepsy. DBS of the ANT has been evaluated in the SANTE study, which is the grounds for approval in the US, as well as in other clinical studies and systematic reviews. Long-term outcomes are also available; up to 14-year data from the SANTE study and 11-year data from the publication by Kim, S. H. *et al* (Literature report 9 in Table 19).

In addition, the National Institute for Health and Care Excellence (NICE) Guidelines in the UK recommend that DBS for drug-resistant partial epilepsy be offered as "Special arrangement."[iii] It can be said that the efficacy and safety of DBS in the treatment of drug-resistant partial epilepsy are publicly known to some extent. Percept PC has been designated as a medical device with high medical needs and there have been requests for its early introduction to Japan. Taking account of comments raised in the Expert Discussion, PMDA concluded that the efficacy and safety of Percept PC could be evaluated based on the currently available results of the SANTE study and the clinical evaluation report summarizing the data in the literature reports.

6.B.(3) Extrapolation of the foreign clinical data and the study results of the predecessors of Percept PC

The applicant's explanation about the extrapolation of the foreign clinical data:

Table 22 shows a comparison of the medical environment between Japan and Europe/the US. Japan and other countries have the same definition of drug-resistant epilepsy, and similar treatment strategies and therapeutic drugs for partial epilepsy. DBS is widely used in Japan. While the DBS procedure at the ANT slightly differs from the conventional procedure, the implantation path can be designed by using the conventional method. The directions for use and specifications of the DBS system including a stimulator are common throughout the world. There is no racial or ethnic difference in the function of the brain tissue. For the above reasons, it is possible to extrapolate the foreign data to Japan.

[iii] Among the 4 recommendation levels, "special arrangement" is classified as the second highest level. This means that DBS for drug-resistant partial epilepsy has uncertain safety and efficacy and may cause serious harm, and that patients should be carefully informed about DBS before receiving the treatment.

Table 22. Differences in medical environment between Japan and Europe/the US

	Japan	Europe/the US	Discussion
Definition of drug-resistant epilepsy	The epilepsy that cannot be controlled for a certain period by using ≥2 appropriately selected antiepileptic drugs (whether as monotherapy or combination therapy). (The Clinical Practice Guidelines for Epilepsy 2018)	The epilepsy that cannot be controlled for a certain period by using ≥2 appropriately selected antiepileptic drugs (whether as monotherapy or combination therapy). (International League Against Epilepsy [ILAE])	The definition of drug-resistant epilepsy in the Japanese guidelines matches that in the ILAE.
Treatment strategy	First, radical treatment should be considered. DBS or VNS should be considered as an accommodative therapy for patients who have not responded to radical treatment.	First, radical treatment should be considered. DBS, VNS, or RNS should be considered accommodative therapies for patients who have not responded to radical treatment.	The treatment ladder and the clinical positioning of DBS are the same in Japan and Europe/the US. In Europe and the US, RNS is listed as a treatment option but none of the accommodative therapies take precedence over the others.
Drugs for partial epilepsy	First-line drugs: Carbamazepine, lamotrigine, levetiracetam, zonisamide, topiramate Second-line drugs: Phenytoin, valproate, clobazam, clonazepam, phenobarbital, gabapentin, lacosamide, and perampanel (The Clinical Practice Guidelines for Epilepsy 2018 CQ3-2)	First-line drugs: Carbamazepine, oxcarbazepine, and zonisamide Adjunctive drugs: Carbamazepine, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, topiramate, and zonisamide (The NICE Guidelines 2022, Epilepsies in children, young people and adults 5.2 Focal seizures with or without evolution to bilateral tonic-clonic seizures)	The antiepileptic drugs recommended by the Japanese guidelines are similar to those recommended by the NICE guidelines. Oxcarbazepine is indicated for use in pediatric patients in Japan, but is not listed in the Japanese guidelines because the guidelines are intended for adult patients.
Medical environment	DBS system was first introduced in 1999. Lead placement procedure: ANT was added, in addition to subthalamic nucleus, ventrointermedius, internal globus pallidus Surgeons: Epilepsy surgeons were allowed to perform DBS procedure, in addition to neurosurgeons	The DBS system was first introduced in Europe in 2010 and the US in 2018.	The DBS system is widely used in Japan. While the DBS procedure at the ANT slightly differs from the conventional procedure, the implantation path can be designed by using the conventional method. Since the DBS procedure in epilepsy surgery is relatively low invasive, procedural skills of surgeons matter little.

The applicant's explanation about the extrapolation of the study results of the predecessors of Percept PC:

The clinical studies including the SANTE study used predecessor stimulators of Percept PC. Table 23 shows stimulators reported in each literature report. The stimulators differ in stimulator size and the number of electrode leads (number of channels) because of the battery specifications. These differences cause the differences in some settings but are unlikely to affect the clinical effects of the devices. The voltage unit and current unit for output programming differ between Percept PC and its predecessors. Since they follow Ohm's law, an electric current of 2.5 to 20 mA will pass through the tissue at a stimulation voltage of 5 V with a patient's tissue impedance of approximately 250 to 2,500 Ω. This is within the output range of Percept PC.

The unique functions "sensing function"[iv] and "aDBS function"[v] are incorporated only in Percept PC. The "sensing function" does not affect the therapeutic performance or safety in the treatment of epilepsy and therefore can be used in patients with epilepsy. On the other hand, the efficacy of the "aDBS function" in epilepsy has not been confirmed yet. The use of this function is, therefore, restricted in the treatment of epilepsy, as in tremors and dystonia, so that the aDBS function cannot be set on the physician's programmer.

Table 23. Stimulators and programmed stimulation parameters used in each clinical study

Product name or brand name (Approval No.)	Kinetra (not approved in Japan)	Itrel II (21100BZY00563 000)	Activa PC (22800BZX00343 000)	Activa RC (22300BZX00412 000)	Percept PC (30200BZX00163 000)
Output	0-10.5 V	0-10.5 V	0-10.5 V 0-25.5 mA	0-10.5 V 0-25.5 mA	0-25.5 mA
Rate	2-250 Hz	2-185 Hz	2-250 Hz	2-250 Hz	2-250 Hz
Pulse width	60-450 µA	60-450 µA	60-450 µA	60-450 µA	20-450 µA
Number of channels	Dual	Single	Dual	Dual	Dual
Battery	Non-rechargeable	Non-rechargeable	Non-rechargeable	Rechargeable	Non-rechargeable
Others	-	-	-	-	• Sensing • aDBS
Indication of epilepsy (the US)	-	-	✓	-	✓

PMDA's view, considering the comments from the Expert Discussion:
There appear to be no substantial regional difference in the medical environment, including the definition or treatment strategy and treatment options for epilepsy (extrinsic factors), and no racial or ethnic difference in the directions for use or efficacy of DBS (intrinsic factors). The differences, if any, will be too little to affect the evaluation of Percept PC. Although Percept PC uses a stimulator that is different from those of the predecessors, Percept PC will provide similar clinical outcomes as its predecessors since the programmable range of stimulation parameters of Percept PC includes that of its predecessors. It is reasonable to restrict the use of the "aDBS function," whose efficacy and safety have not been demonstrated yet. The use of the "sensing function" alone is unlikely to affect the efficacy and safety of the treatment. PMDA agreed with the applicant's discussions on each function. PMDA concluded that it was possible to evaluate the efficacy and safety of Percept PC in Japan based on the results of the foreign clinical study and those reported in the literature reports.

6.B.(4) Efficacy and safety of Percept PC

6.B.(4).1) Efficacy

PMDA asked the applicant to explain the reasons that (a) the proportion of responders, a secondary endpoint, did not statistically significantly differ between the active and control groups during the blinded phase and (b) the proportion of responders increased after 1 year post-implant.

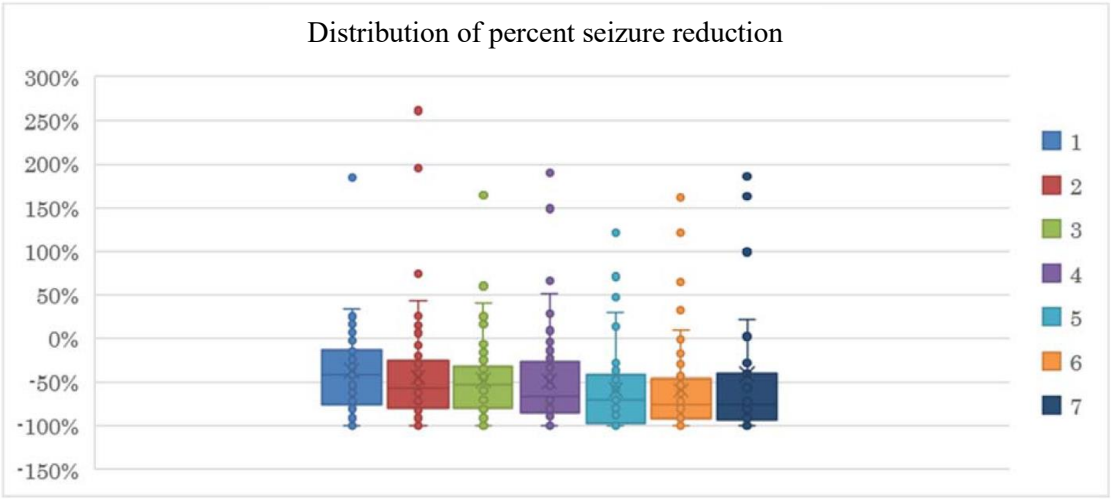
The applicant's explanation:
The subjects received stimulation using the same programmed parameters throughout the blinded phase. Since the parameters were not adjusted for each subject during this period, stimulation may

[iv] Sensing function measures the local field potential (LFP) in the brain via the leads.

[v] aDBS function automatically adjusts the stimulation output according to a change in measured LFP to treat movement disorder of Parkinson's disease.

have not been necessarily optimal for each subject. In general, DBS is associated with a microlesion effect after placement of the electrode leads, which may lead to a temporal therapeutic effect. There might not have been an enough washout period to eliminate this effect. These factors probably contributed to the lack of difference in the proportion of responders between the active and control groups during the early blinded phase. In fact, the percent seizure reduction showed no substantial difference between the active and control groups up to 3 months after device implantation, but the seizure frequency in the control group increased from 3 to 4 months, suggesting the disappearance of the microlesion effect.

The proportion of responders at ≥1 year is discussed here. Figure 10 shows the distribution of the percent seizure reduction at each follow-up visit from 1 to 7 years after device implantation. There is no substantial difference in the distribution among the follow-up visits, with the percent seizure reduction tending to increase gradually. At each follow-up visit, the number of responders was constant (approximately 40 subjects [37-46 subjects]) while the number of non-responders decreased year by year from 56 at 1 year to 13 at 7 years. Subjects withdrawn from the study included both responders and non-responders. It is, therefore, reasonable to conclude that the proportion of responders, reported in the study, tended to increase.



Statistic	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7
Number of subjects	99	82	75	76	59	64	50
Mean	-37.24%	-44.46%	-47.64%	-49.01%	-58.86%	-59.34%	-40.72%
Standard deviation	56.86%	57.36%	44.24%	53.15%	45.42%	50.09%	127.21%
Max	328.00%	261.00%	165.00%	190.00%	121.00%	162.00%	735.00%
Min	-100.00%	-100.00%	-100.00%	-100.00%	-100.00%	-100.00%	-100.00%

Figure 10. Distribution of percent seizure reduction* from 1 to 7 years after device implantation

* Percent seizure reduction means the percentage of a change relative to baseline (negative = decrease).

PMDA's view. considering the comments from the Expert Discussion:

In the SANTE study, the active group showed superior results than the control group in the primary efficacy endpoint of "reduction in the total seizure frequency" during the blinded phase. The study achieved the primary endpoint and the therapeutic efficacy was still observed at 7 years after device implantation; this shows the efficacy of Percept PC. The applicant's discussions on the results of the secondary endpoints are also reasonable and do not deny the efficacy of Percept PC.

The therapeutic outcomes of DBS and VNS are as follows:

VNS:

Percent reduction in seizure frequency: approximately 40% to 50% at 1 year after the start of stimulation and approximately 50% to 70% at 3 years.[20,21]

Proportion of responders (i.e., a percent seizure reduction of ≥50%): 42.7% at 3 months and 58.0% at 3 years.[21]

DBS:

Percent reduction in seizure frequency: 41% at 1 year after the start of stimulation, 53% at 3 years, and 75% at 7 years (Figure 5)

Proportion of responders: 43% at 1 year, 56% at 3 years, and 74% at 7 years (Figure 6)

In summary, the therapeutic outcomes of DBS were comparable to those of the conventional treatment. The results of the clinical studies of DBS in the literature reports were also consistent with those of the SANTE study. PMDA therefore concluded that the efficacy of Percept PC has been demonstrated.

6.B.(4).2) Safety

Depression and memory impairment occurred significantly frequently in the active group during the blinded phase. PMDA asked the applicant to explain (a) the differences in the medical history of depression and memory impairment between the active and control groups and (b) the risk of aggravation of these events in patients with a medical history of depression or memory impairment.

The applicant's explanation:

There was no statistically significant difference in the proportion of subjects with a history of depression between the active group (53.7%, 29 of 54 subjects) and the control group (40.0%, 22 of 55 subjects) (P = 0.181). The incidence of depression reported as an adverse event was 5.5% (3 of 55 subjects) in the control group during the 3 months from the start of stimulation after the end of blinded phase (4-7 months after device implantation during the unblinded phase). None of the events were serious. Of the 3 subjects, 2 subjects (with a medical history of depression) had mild depression: the event in one resolved with drug therapy and the event in the other resolved after the stimulation potency was decreased to 3.5 V. The remaining 1 subject (without a history of depression) had moderate depression and was treated with drug therapy, with the outcome of "not resolved."

There was no statistically significant difference in the proportion of subjects with a history of memory impairment between the active group (35.2%, 19 of 54 subjects) and the control group (32.7%, 18 of 55 subjects) (P = 0.841). The incidence of memory impairment reported as an adverse event was 10.9% (6 of 55 subjects) in the control group during the 3 months from the start of stimulation after the end of the blinded phase (4-7 months after device implantation during the unblinded phase). This was slightly lower than the incidence in the active group (13.0%, 7 of 54 subjects). Of the 6 subjects, 2 subjects (with a medical history of memory impairment) had moderate memory impairment. The dose of the antiepileptic drug was reduced in 1 subject. In the other subject, the stimulation parameter was changed from 185 Hz to 145 Hz. However, the outcome was "not resolved" in both subjects. The

remaining 4 subjects had no medical history of memory impairment. Of the 4 subjects, 2 received no intervention because their events were mild; the event in 1 subject resolved but the event in the other did not. The events in the remaining 2 subjects were moderate. The event in 1 subject resolved after the stimulation rate was changed from 185 Hz to 145 Hz. The symptoms in the other subject improved and the event resolved after stimulation was turned off by programming the device.

No aggravation of symptoms in patients with a history of depression or memory impairment has been reported. The risk of onset/aggravation of depression or memory impairment due to a surgery to implant the device for DBS therapy or stimulation during DBS therapy appears to be similar regardless of a medical history of depression or memory impairment. As shown in Table 14, the incidence of depression and memory impairment decreased over time. Attention must be paid to their occurrence especially in the early stage of device implantation.

PMDA's view, considering the comments from the Expert Discussion:
The serious adverse events documented in the SANTE study have been also reported in patients using Percept PC for the approved indications, with no substantial difference in incidence. In addition, there was no statistically significant difference in the incidence of these adverse events between the active and control groups during the blinded phase. Thus these adverse events are not new risks associated with the proposed indication. The incidence of SUDEP in the SANTE study was lower than that in surgical candidates reported in a publication (9.3 per 1,000 person-years[10]) and comparable to that in patients treated with VNS (2.10 per 1,000 person-years over 3-10 years[22]). The mortality in the SANTE study is thus acceptable.

The active and control groups had a similar number of subjects with a medical history of depression or memory impairment, but the active had a higher incidence of depression and memory impairment during the blinded phase. These events may have been caused by stimulation of the ANT. However, the risks of depression and memory impairment appear to be clinically acceptable because the symptoms were mild or moderate and did not lead to study discontinuation in any subject, and some subjects recovered after adjustment of stimulation. When considering using Percept PC in a patient, however, their medical history of depression and memory impairment should be taken into account. Patients, healthcare professionals, etc. should be informed about the risks of depression and memory impairment. The applicant has included necessary precautions about the risks in the Precautions section in the Information on Precautions, etc. (draft) submitted. PMDA agrees with this applicant's measure.

In summary, Percept PC is expected to have similar therapeutic benefits in efficacy and safety to VNS, a conventional therapy, in patients with drug-resistant partial epilepsy. The adverse events reported in the SANTE study and the publications did not substantially differ from those in patients who used DBS for the approved indications. PMDA concluded that the foreseeable risks would be clinically acceptable when weighed against the expected benefits provided that eligible patients were selected for the treatment. Patients eligible for Percept PC have limited therapeutic options because they do not respond to drug therapy. Percept PC is therefore a highly useful new treatment option because it uses a principle that is different from the conventional treatment.

6.B.(5) Intended use or indication

Only patients aged ≥18 years are allowed to use Percept PC in Europe and the US, but this minimum age requirement is not specified in the proposed intended use of the present partial change application. PMDA asked the applicant to explain the reason that the age requirement was omitted.

The applicant's explanation:

The minimum age requirement is unnecessary because DBS is expected to have a comparable effect in children and adolescents whose brain has developed at a comparable level to adults. For DBS, there has been no age requirement. The efficacy and safety of DBS do not particularly depend on age. and this has been shown by historical data. Use experience and systematic reviews published, although their numbers are limited, demonstrate no worrisome difference in efficacy or safety between children/ adolescents and adults. Literature report 9[16] included in the clinical evaluation report presents the results of DBS in 29 patients including those aged <18 years (age breakdown unknown), showing no efficacy or safety concern due to age. A systematic review[23] of 21 publications reported use experience of DBS of the ANT or centromedian nucleus of thalamus in patients aged 4 to 18 years who had drug-resistant epilepsy. DBS resolved epileptic seizures in 12.5% of the patients and reduced seizure frequency in 85% of the patients. Of the 40 patients, 8 patients received DBS of the ANT, including 6 patients who had a 37% to 90% seizure reduction. No death occurred. Adverse events reported were infection in 1 patient, skin erosion in 2 patients, and lead breakage in 1 patient. The authors concluded that DBS of the ANT or centromedian nucleus of thalamus was effective and was a useful accommodative treatment option for children and adolescents with drug-resistant partial epilepsy who are not eligible for surgery. The directions for use of Percept PC in foreign countries specify the minimum age requirement. This is not because the clinical effect of DBS with Percept PC may differ depending on age, but because only patients aged ≥18 years were enrolled in the SANTE study. The applicant considers that the efficacy and safety of DBS with Percept PC in patients with epilepsy aged <18 years are comparable to those in adult patients and therefore the age requirement of ≥18 years old is unnecessary.

The use of Percept PC in children/adolescents might be associated with a risk of lead dislodgement, discomfort (stretched feeling), etc. because the leads in a children/adolescent may be pulled as they grow due to the growing distance between the implantation site and the brain. However, the use experience in a small number of children/adolescents has shown the efficacy of the treatment, suggesting that some children/adolescents may benefit substantially from the treatment with Percept PC. It is therefore unnecessary to ban its use in children/adolescents. Prior to the use of Percept PC in children/adolescents, the following should be assessed: (a) whether their brain has developed to a level comparable to adults and (b) the risk of lead dislodgement. The current package insert for Percept PC already includes these precautions for the indication of pediatric dystonia. The applicant considers that the precautions can also be applied to pediatric epilepsy and therefore will include them in the Information on Precautions, etc.

PMDA's view, considering the comments from the Expert Discussion:

The applicant explained that the effect of DBS in patients aged <18 years would be similar to that in adult patients if their brains have developed to a level comparable to adults. This explanation is acceptable for the following reasons:

(a) The literature reports submitted by the applicant demonstrated the efficacy of DBS in children/adolescents, although the number of those patients was limited.

(b) The results of the re-examination for the approved indication of dystonia including patients aged <18 years[24] revealed no particular problem.

The concerns in using Percept PC in patients aged <18 years are lead dislodgement and malfunctions that might occur as they grow. The patient eligibility for treatment with Percept PC should be assessed not based on their age but based on the growth and size of the brain, and the maturity of the skull (i.e., whether the skull is manure enough to fit in the head fixation frame used during surgery). The applicant plans to apply the same precautions already established for pediatric dystonia (an approved indication of Percept PC) to pediatric epilepsy (i.e., patients <18 years, especially children). This applicant's plan is reasonable. PMDA concluded that Percept PC could be used in patients with epilepsy aged <18 years.

PMDA concluded that the intended use or indication of Percept PC proposed by the applicant required the following modifications. The modified intended use of Percept PC is shown below.

- To clarify the clinical positioning of Percept PC, the phrase "except for patients who are expected to respond to craniotomy" should be added as with the approved stimulators for VNS.
- The phrase "simple partial seizures, partial complex seizures, and secondary generalized seizures accompanied by movement symptoms that interrupt the activities of daily living" should be removed because those symptoms are too obvious in the target patient population of Percept PC (i.e., patients with partial-onset epileptic seizures who have an inadequate response to drug therapy).

Intended use or indication (the underlined part is added by the present partial change application)

- Medtronic Percept PC is used to deliver lateral or bilateral electrical stimulation to a deep brain structure (thalamus, subthalamic nucleus, or internal globus pallidus) in order to reduce the following symptoms that have an inadequate response to drug therapy:
  - Tremor
  - Movement disorder in Parkinson's disease
  - Dystonia
- <u>Medtronic Percept PC is used to deliver bilateral electrical stimulation to a deep brain structure (anterior nucleus of the thalamus) in order to reduce partial-onset epileptic seizures that have an inadequate response to drug therapy (except for patients who are expected to respond to craniotomy).</u>

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

PMDA asked the applicant to explain whether any training, lecture, etc. were required prior to the introduction of Percept PC to Japan.

The applicant's explanation:
No new training or lecture for the placement procedure for DBS for epilepsy is planned because the procedure is almost the same as that for the approved indications. Documents that include precautions (e.g., eligible patients with epilepsy) will be prepared and distributed to users for information provision. In Japan, the Clinical Practice Guidelines for Epilepsy will be revised, or a new guideline will be prepared by the Japan Epilepsy Society or Epilepsy Surgery Society of Japan.

PMDA's view, considering the comments from the Expert Discussion:
DBS has been used in Japan for ≥20 years. The safety of DBS has been confirmed by the completed use-results survey of a reduction in tremors associated with Parkinson's disease, essential tremor, etc. and the completed use-results survey of a reduction in symptoms of dystonia. There are many accumulating data on the use of DBS. The requirements for physicians who perform DBS, and requirements and structures of medical institutions that perform DBS have already been established in Japan. The implantation sites of the electrode leads in the treatment of epilepsy differ from those for the approved indications. However, the ANT, where stimulation is delivered to treat epilepsy, is anatomically close to the stimulation sites for the approved indications. Prior to placement of the electrode leads, the positions of blood vessels and brain tissues are checked using X-ray, etc. to plan out an insertion route for each patient; there is thus no substantial difference in the directions for use regarding the placement of the electrode leads between the treatment of epilepsy and the treatment of the approved indications. Accordingly, no change has been made to the design, structure, function, etc. of Percept PC or the electrode leads. The requirements for physicians and medical institutions that use Percept PC to treat epilepsy are the same as those for the approved indications. Considering the above, PMDA concluded that training in the implantation procedure of Percept PC specific to epilepsy was not essential.

As described in the Clinical Practice Guidelines for Epilepsy 2018, VNS is an established accommodative therapy for the treatment of drug-resistant epilepsy. This means that the medical system, including the protocols for diagnosis, treatment, and long-term follow-up, for this patient population has also been established. Both DBS with Percept PC and VNS are electrical stimulation therapies with the same clinical positioning. The target patient population and the medical system, including treating physicians, of DBS and VNS are also the same. The only difference is the implantation sites of the electrode leads. PMDA concluded that the efficacy and safety of Percept PC under the current medical environment in Japan can be ensured by disseminating the following information: the treatment outcomes with Percept PC and precautions in selecting eligible patients described in Section "6.B.(4) Efficacy and safety of Percept PC."

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

7.A Summary of the data submitted

The present partial change application of Percept PC is intended for a new indication using conventional technology. Percept PC has the same structure, directions for use, and performance as those of the similar medical devices. Percept PC delivers performance by sending electric stimulation to the deep brain. This mechanism of action is also fundamentally the same as conventional therapy.

As discussed in the clinical evaluation report, Percept PC has been used in foreign countries and the efficacy and safety data of DBS in foreign countries can be extrapolated to Japan. Since the report shows a low possibility of significant malfunctions etc., no use-result survey is required for Percept PC for epilepsy. Accordingly, no plan for post-marketing surveillance, etc. was submitted.

7.B Outline of the review conducted by PMDA

Activa PC, the processor of Percept PC, has been used in Europe for 12 years after its approval and in the US for 4 years with accumulating data. No unknown serious adverse event etc. have been reported. In Asia, treatment outcomes similar to those in the SANTE study have been reported.[13,14,16] There is no racial or ethnic difference in the function or structure of the brain, or in the pathology or treatment outcomes of epilepsy. There is also no substantial concern about the experience and treatment outcomes of Percept PC in foreign countries, the implantation procedure for Percept PC, or the medical system for the epilepsy treatment in Japan as mentioned earlier. PMDA agreed with the applicant's decision of omitting a use-results survey of Percept PC for epilepsy.

The Japan Epilepsy Society plans to collect data regarding treatment outcomes of DBS with Percept PC in Japan.

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

8.A Summary of the data submitted

The applicant submitted Information on Precautions, etc. (draft) as an attachment in accordance with the Notification titled "Application for Marketing Approval of Medical Devices" (PFSB Notification No. 1120-5, dated November 20, 2014).

8.B Outline of the review conducted by PMDA

On the basis of the conclusion of the Expert Discussion, as described earlier in Section "6.B. Outline of the review conducted by PMDA," PMDA concluded that there were no particular problems with the proposed Information on Precautions etc., provided that the applicant advises necessary caution.

III. Overall Evaluation

Percept PC is an implantable electrical stimulation device intended for use in DBS therapy to reduce partial-onset seizures in drug-resistant epilepsy. The key issues in the review of Percept PC were (1) the clinical positioning and (2) the efficacy and safety of Percept PC. PMDA's view based on the comments from the Expert Discussion are described in the section below.

(1) Clinical positioning

The Clinical Practice Guidelines for Epilepsy 2018 currently recommend that surgical resection (partial resective surgery), which is a radical cure for the disease, be considered for patients with epilepsy who have an inadequate response to drug therapy if the seizure onset location can be identified in the brain. For patients not eligible for surgery (e.g., the onset location cannot be

identified), VNS should be considered as a treatment option. VNS requires placement of the device in the chest and electrode leads in the vagus nerve. DBS with Percept PC differs from VNS in the location of leads (i.e., the brain) but is a highly invasive accommodative treatment similarly as VNS. DBS is expected to be a highly useful treatment option because patients with epilepsy have a variety of different characteristics, and DBS and VNS have a different mechanism of action. The clinical positioning of Percept PC should be the same as that of conventional VNS.

(2) Efficacy and safety of Percept PC

In the SANTE study, the active group showed superior results than the control group in the primary efficacy endpoint of "reduction in the total seizure frequency" during the blinded phase. The study achieved the primary endpoint and the therapeutic efficacy was still observed at 7 years after device implantation. The proportion of responders, a secondary endpoint of the study, was 43% at 1 year post-implant and 74% at 7 years post-implant, showing an increasing trend year by year. The results of the clinical studies of DBS in the literature reports were consistent with those of the SANTE study. The therapeutic outcomes of DBS were also comparable to those of VNS, a conventional therapy. PMDA concluded that the efficacy of Percept PC has been demonstrated.

As for safety, the serious adverse events documented in the SANTE study have been also reported in patients using Percept PC for the approved indications, with no substantial difference in incidence. In addition, there was no statistically significant difference in the incidence of these adverse events between the active and control groups during the blinded phase. Thus these adverse events are not new risks associated with the proposed indication. The incidence of SUDEP in the SANTE study was lower than that in surgical candidates reported in a publication and comparable to that in patients treated with VNS. The mortality in the SANTE study is thus acceptable. Depression and memory impairment, which were likely related to ANT stimulation, occurred more frequently in the active group than in the control group during the blinded phase. The events were mild or moderate in severity and did not lead to study discontinuation in any subject. Some subjects recovered after adjustment of stimulation. Since Percept PC is intended for the treatment of refractory drug-resistant epilepsy with partial-onset seizures, those risks are clinically acceptable provided that the relevant information about these risks is provided to patients and healthcare professionals.

PMDA concluded that the benefits of DBS therapy with Percept PC would outweigh its risks and that Percept PC would be a highly useful new treatment option for patients with refractory epilepsy with partial-onset seizures who do not respond to drug therapy.

As a result of the above review, PMDA has concluded that Percept PC may be approved for the intended use shown below with the same conditions as those for the approved indications. The underlined words are the intended use added by the present partial change application.

Intended Use

- Medtronic Percept PC is used to deliver lateral or bilateral electrical stimulation to a deep brain structure (thalamus, subthalamic nucleus, or internal globus pallidus) in order to reduce the following symptoms that have an inadequate response to drug therapy:
  - Tremor

- Movement disorder in Parkinson's disease
- Dystonia

● Medtronic Percept PC is used to deliver bilateral electrical stimulation to a deep brain structure (anterior nucleus of the thalamus) in order to reduce partial-onset epileptic seizures that have an inadequate response to drug therapy (except for patients who are expected to respond to craniotomy).

Approval Condition

The applicant is required to take necessary actions to ensure that the product will be used, in compliance with the indication, by physicians with adequate knowledge and experience in the treatment of dystonia after acquiring sufficient knowledge about the product by attending relevant lectures or by other means.

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

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

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