October 27, 2025
Medical Device Evaluation Division
Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

Report on the Deliberation Results

Classification	Instrument & Apparatus 12, Physical Therapy Apparatus
Term Name	Implantable phrenic nerve electrical stimulator (to be newly created)
Brand Name	remedē System
Applicant	ZOLL Respicardia, Inc.
Designated Marketing Authorization Holder	Cobridge Co., Ltd.
Date of Application	January 20, 2021 (Application for marketing approval of a medical device manufactured in a foreign country)

Results of Deliberation

In its meeting held on October 27, 2025, 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 Council.

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

The use-results survey period should be 9 years.

Approval Conditions

1. The applicant is required to take necessary measures, including dissemination of the proper-use guidelines developed in collaboration with relevant academic societies and provision of appropriate information. These measures are intended to ensure that the product is used in accordance with the approved indication by a physician with sufficient knowledge and experience in treating central sleep apnea, who has acquired the skills necessary to operate the product and has a thorough understanding of procedure-related complications. In addition, the product should be used at a medical institution capable of appropriately managing complications associated with treatment using the product.
2. The applicant is required to conduct post-marketing surveillance in all patients treated with the product until data from a certain number of patients have been accrued, to report the results of annual analyses of long-term outcomes to the Pharmaceutical and Medical Devices Agency, and to take any other appropriate measures as necessary.

Review Report

October 17, 2025

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, Physical Therapy Apparatus
Term Name	(to be newly created)
Brand Name	remedē System
Applicant	ZOLL Respicardia, Inc.
Designated Marketing Authorization Holder	Cobridge Co., Ltd.
Date of Application	January 20, 2021
Reviewing Office	Office of Medical Devices II

Review Results

October 17, 2025

Classification	Instrument & Apparatus 12, Physical Therapy Apparatus
Term Name	(to be newly created)
Brand Name	remedē System
Applicant	ZOLL Respicardia, Inc.
Designated Marketing Authorization Holder	Cobridge Co., Ltd.
Date of Application	January 20, 2021

Results of Review

The remedē System is an implantable stimulator designed to deliver transvenous phrenic nerve stimulation. It is intended for the treatment of patients with central sleep apnea (CSA) who are unsuitable for, or intolerant to, positive pressure ventilation (e.g., continuous positive airway pressure [CPAP] and adaptive servo-ventilation [ASV]) or oxygen therapy. The remedē System consists of a stimulator, respiratory-sensing and stimulation leads, a delivery system for lead implantation, and associated components.

The applicant submitted non-clinical data supporting the physicochemical properties, electrical safety, electromagnetic compatibility, biological safety, stability, durability, performance, and other properties. The data indicated no particular problems.

The applicant submitted clinical data from a foreign clinical study (hereinafter referred to as the "pivotal clinical study") conducted to evaluate the efficacy and safety of the remedē System in 151 patients with moderate to severe CSA, compared with a control group in which the remedē System was implanted but stimulation was withheld for 6 months.

The primary efficacy endpoint was the proportion of subjects achieving a ≥50% reduction in the apnea hypopnea index (AHI) from baseline to 6 months post-stimulation initiation. This proportion was 51.5% (95% confidence interval [CI], 39.0%-63.8%) in the treatment group and 11.0% (95% CI, 4.9%-20.5%) in the control group, demonstrating a significant difference (P <0.0001).

The primary safety endpoint was freedom from serious adverse events associated with the implant procedure, the remedē System, or delivered therapy from implantation through 12 months after stimulation initiation (for the control group, 6 months of non-stimulation followed by 6 months of stimulation). Related adverse events occurred in 13 subjects (8.6%), and all events resolved. A causal relationship between the remedē System and all deaths was ruled out.

Indices related to the following measures were established as secondary endpoints: breathing events during sleep (e.g., frequency of apnea and hypopnea, change in oxygen saturation), sleep

quality (arousal, percentage of rapid eye movement [REM] sleep), quality of life (QOL), and cardiac function (e.g., 6-minute walk distance, left ventricular ejection fraction [LVEF]). In the treatment group, improvements were observed in breathing-related measures, sleep quality indices, and QOL, while cardiac function-related indices were either maintained or showed trends toward improving.

In patients with CSA, the population enrolled in the pivotal clinical study, sympathetic nerve activity is known to be enhanced by persistent hypoxia associated with apnea, loss of pulmonary stretch reflex, arousal, and other factors. In particular, the clinical practice guidelines recommend that CSA with Cheyne-Stokes respiration in patients with heart failure should be treated after optimization of heart failure therapy. Therefore, improvement in AHI and sleep parameters is considered clinically meaningful. In contrast, for other types of CSA, the Japanese clinical practice guidelines do not specify the need for treatment or provide treatment strategies. Accordingly, the evaluation was performed separately for patients with CSA and comorbid heart failure (heart failure subgroup) and those with other types of CSA (non-heart failure subgroup).

Improvements in respiratory status, sleep quality, and QOL as well as reduction in AHI were observed in both subgroups. Based on the recommendation in the clinical practice guidelines, the remedē System can be expected to provide a clinical benefit through AHI reduction in the heart failure subgroup. For the non-heart failure subgroup, although the Japanese guidelines do not specify the need for treatment or provide treatment strategies, current clinical practice and the US clinical practice guidelines, which state that therapies such as positive pressure ventilation may be considered, suggest the existence of a certain degree of a need for reduction of AHI that may be addressed with the remedē System.

The remedē System, however, is highly invasive compared to conventional therapies such as positive pressure ventilation and oxygen therapy, and serious adverse events were reported in the pivotal clinical study. Therefore, patients who are likely to derive meaningful benefit from the remedē System through improvements in respiratory status and sleep quality that outweigh these risks must be carefully selected.

Based on the above clinical data, and to ensure the safe and effective introduction of the remedē System, the first implantable stimulator for CSA treatment in Japan, it is essential that physicians and medical institutions with sufficient knowledge and experience in sleep-related breathing disorders and the etiology of CSA acquire adequate knowledge of the remedē System and its use, and perform appropriate patient selection taking into account the characteristics of the remedē System. Additionally, the remedē System should be implanted and patients followed up at medical institutions capable of appropriately managing implant procedure- or device-related adverse events and providing appropriate follow-up care.

PMDA concluded that the applicant should continue to evaluate the incidence of adverse events, the appropriateness of patient selection, and the efficacy of the remedē System in clinical use through post-marketing surveillance, and that the applicant should implement additional risk minimization measures and revise the proper use guidelines as necessary.

Based on the results of review, PMDA has concluded that the remedē System may be approved

for the following intended use, with the approval conditions below, and that the results should be presented to the Committee on Medical Devices and *In-vitro* Diagnostics for further deliberation.

Intended Use

The remedē System is intended for the treatment of moderate to severe central sleep apnea in adult patients who are unsuitable for, or intolerant to, positive pressure ventilation or oxygen therapy. The device delivers transvenous phrenic nerve stimulation to induce diaphragmatic contraction and thereby assists respiration during sleep.

Approval Conditions

1. The applicant is required to take necessary measures, including dissemination of the proper-use guidelines developed in collaboration with relevant academic societies and provision of appropriate information. These measures are intended to ensure that the product is used in accordance with the approved indication by a physician with sufficient knowledge and experience in treating central sleep apnea, who has acquired the skills necessary to operate the product and has a thorough understanding of procedure-related complications. In addition, the product should be used at a medical institution capable of appropriately managing complications associated with treatment using the product.
2. The applicant is required to conduct post-marketing surveillance in all patients treated with the product until data from a certain number of patients have been accrued, to report the results of annual analyses of long-term outcomes to the Pharmaceutical and Medical Devices Agency, and to take any other appropriate measures as necessary.

Review Report

October 17, 2025

Product for Review	
Classification	Instrument & Apparatus 12, Physical Therapy Apparatus
Term Name	(to be newly created)
Brand Name	remedē System
Applicant	ZOLL Respicardia, Inc.
Designated Marketing Authorization Holder	Cobridge Co., Ltd.
Date of Application	January 20, 2021
Proposed Intended Use	The remedē System is an implantable phrenic nerve stimulator indicated for the treatment of moderate to severe central sleep apnea (CSA) in adult patients who are unsuitable for, or intolerant to, continuous positive airway pressure (CPAP) or adaptive servo-ventilation (ASV).

Table of Contents

List of Abbreviations

AED	Automated External Defibrillator
AHI	Apnea Hypopnea Index
ArI	Arousal Index
ASV	Adaptive Servo-Ventilation
CAI	Central Apnea Index
CEC	Clinical Events Committee
CPAP	Continuous Positive Airway Pressure
CRT-D	Cardiac Resynchronization Therapy Defibrillator
CSA	Central Sleep Apnea
CSA-CSB	Central Sleep Apnea with Cheyne-Stokes Breathing
EQ-5D	European Quality of Life-5 Dimensions
ESS	Epworth Sleepiness Scale
FSS	Fatigue Severity Scale
ICD	Implantable Cardioverter Defibrillator
IPG	Implantable Pulse Generator
ITT	Intent To Treat
LVEF	Left Ventricular Ejection Fraction
MLHFQ	Minnesota Living with Heart Failure Questionnaire
MRI	Magnetic Resonance Imaging
NYHA	New York Heart Association
ODI	Oxygen Desaturation Index
OSA	Obstructive Sleep Apnea
PGA	Patient Global Assessment
PP	Per Protocol
PSG	Polysomnography
QOL	Quality of Life
REM	Rapid Eye Movement
SF-12	12-Item Short-Form Health Survey

I. Product Overview

The remedē System is an implantable stimulator designed to deliver transvenous phrenic nerve stimulation to treat patients with central sleep apnea (CSA) who are unsuitable for (after attempting to use the therapies, it was found that the patient was unable to use them, or the therapies were found to be ineffective after they were used) or intolerant to positive pressure ventilation such as continuous positive airway pressure (CPAP) and adaptive servo-ventilation (ASV), or oxygen therapy.

The remedē System consists of stimulators, a respiratory sensing lead, stimulation leads, a delivery system for the lead, and additional supporting components (Figures 1 to 5). There are 2 types of stimulators: an implantable pulse generator (IPG; Figure 1), which is placed in the subclavicular area of the patient, and an external pulse generator (Figure 2), which is used for stimulation testing during implantation. Leads include left pericardiophrenic vein leads (2 or 4 electrodes; Figure 3) and right brachiocephalic vein leads (6 electrodes; Figure 4). The remedē System also includes a programmer for stimulation settings.

Figure 1. Implantable pulse generator (IPG)

Figure 2. External pulse generator

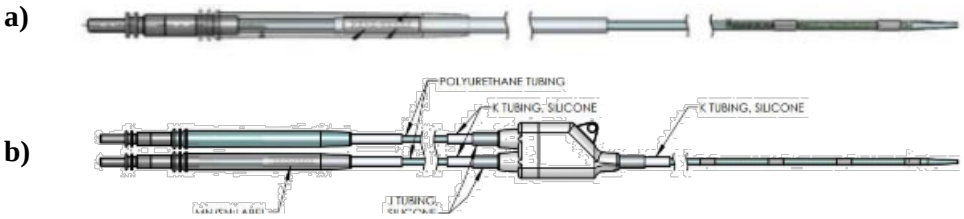

Figure 3. Left pericardiophrenic vein leads (a, 2-electrode type; b, 4-electrode type)

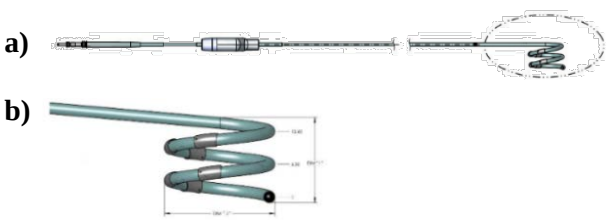

Figure 4. Right brachiocephalic vein lead (a, overall view; b, enlarged view of stimulation lead electrode)

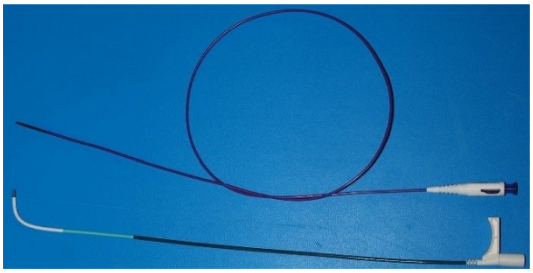

Figure 5. Delivery system

The remedē IPG measures the patient's body position and activity level using its built-in sensors

to determine whether the patient is asleep, and measures thoracic wall impedance via the implanted lead in the vein to determine whether the patient is breathing normally. Only one lead, either a left pericardiophrenic vein lead or a right brachiocephalic vein lead is implanted (see Figure 6 or Figure 7, respectively, for lead placement). During the physician-programmed therapy window, if the device detects respiratory abnormalities while the patient is asleep, the IPG delivers electrical stimulation to one side of the phrenic nerve via the implanted lead, causing the ipsilateral diaphragm to contract and expanding the lungs. The resulting activation of the respiratory tract receptors signals the respiratory center to stop inspiration and initiate expiration, thereby restoring a normal breathing pattern.[1] Stimulation parameters can be programmed in the following ranges: stimulation current, 0 to 10 mA; pulse width, 60 to 300 μs; and frequency, 1 to 40 Hz.

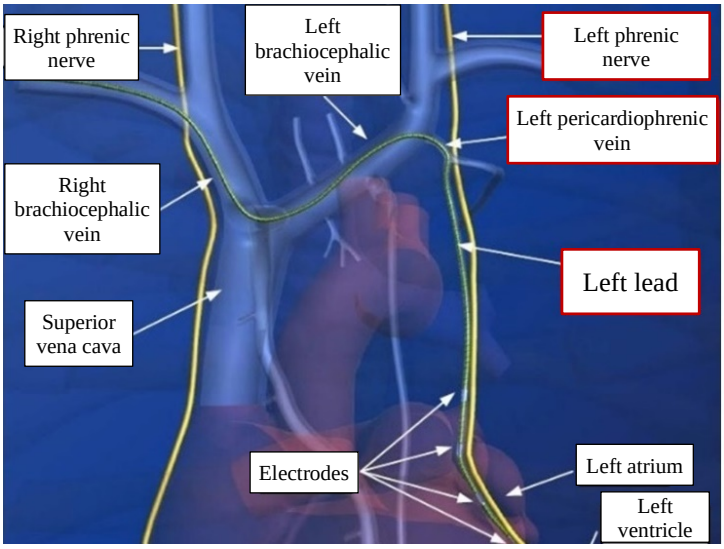

Figure 6. Image of placement in the left pericardiophrenic vein

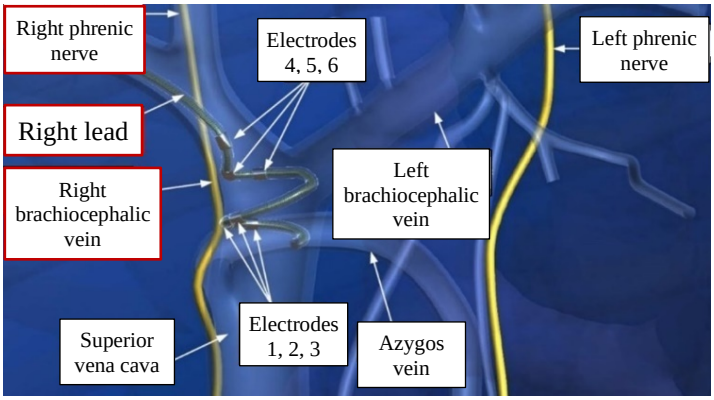

Figure 7. Image of placement in the right brachiocephalic vein

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

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

The expert advisors present during the Expert Discussion on the remedē System declared that they did not fall under the Item 5, Chapter 3 of the Rules for Convening Expert Discussions, etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

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

1.A Summary of the data submitted

1.A.(1) History of development

In the International Classification of Sleep Disorders. 3rd ed.[2] published by the American Academy of Sleep Medicine (AASM), sleep-related breathing disorders include obstructive sleep apnea (OSA) and central sleep apnea (CSA). Obstructive sleep apnea is characterized by cessation or reduction of airflow despite continued respiratory effort, typically due to airway narrowing, obstruction, or relaxation. CSA is characterized by cessation or reduction of airflow resulting from absence of respiratory effort due to abnormalities in the respiratory centers. In addition, CSA is classified into 8 subtypes, including CSA with Cheyne-Stokes breathing (CSA-CSB), CSA due to a medical disorder without Cheyne-Stokes breathing, and primary CSA.[2]

Polysomnography (PSG), which measures brain waves, airflow, thoracoabdominal movement, oxygen saturation (SpO_2), electrocardiograms, and other physiological parameters during sleep, is the standard test used to evaluate sleep-related breathing disorders such as OSA and CSA. Among the indices obtained from PSG, the Apnea Hypopnea Index (AHI), defined as the number of apneas[i] or hypopneas[ii] per hour of sleep, is widely used for diagnosis and assessment of disease severity. Based on AHI, patients are classified as having mild ($5 \leq$ AHI <15), moderate ($15 \leq$ AHI <30), or severe sleep apnea (AHI ≥ 30).

According to the "Sleep Apnea Syndrome (SAS) Clinical Practice Guidelines 2020" [in Japanese] (The Japanese Respiratory Society),[3] the prevalence of CSA among healthy individuals aged around 50 years is approximately 0.1% in females and approximately 1.0% in males. In contrast, the prevalence is reported to be 11.7% to 49% among patients with heart failure.

In patients with CSA, sympathetic nerve activity is known to increase as a result of hypoxia associated with apnea, loss of pulmonary stretch reflex, and arousal from sleep. Conventional treatments for CSA include pharmacotherapies such as acetazolamide, positive pressure ventilation, and oxygen therapy.[4] However, some patients are unable to continue treatment due to intolerance or poor adherence, or fail to achieve adequate efficacy. Therefore, treatment options are currently limited.[5]

Against this background, the remedē System was developed as an implantable phrenic nerve stimulator for the treatment of CSA in patients who are unable to continue treatment using positive pressure ventilation or oxygen therapy, or fail to achieve adequate efficacy with such therapies. The remedē System delivers electrical stimulation to the phrenic nerve via a transvenous lead,

[i] A condition characterized by a ≥90% reduction in airflow lasting ≥10 seconds.
[ii] A condition characterized by a ≥30% reduction in airflow lasting ≥10 seconds, accompanied by a ≥3% decrease in SpO_2 or an associated arousal response at the end of an event.

inducing diaphragmatic contraction and restoring a normal breathing pattern, thereby treating CSA.

1.A.(2) Use in foreign countries

Table 1 shows the approval status and number of units sold of the remedē System in foreign countries.

Table 1. Intended use and number of units sold of the remedē System in foreign countries (as of the end of June 2025)

	Intended use	Date approved	Quantity sold
Europe	Indicated for transvenous phrenic nerve stimulation to treat central sleep apnea	August 2010	123
US	Treatment of moderate to severe central sleep apnea in adult patients	October 2017	1,685

* Sales data between August 2010 and end of June 2025

1.A.(3) Malfunctions and adverse events in foreign countries

Table 2 and Table 3 show the number of cases of malfunctions and adverse events, respectively, reported in foreign countries.

Table 2. Incidence of malfunctions in foreign countries (as of the end of June 2025)

Type	Case(s)	Incidence (%)*
Lead breakage	1	0.055%

*, Incidence (%) = number of cases / number of units sold (1,808 units) × 100.
Survey period: from August 2010 to end of June 2025

Table 3. Incidence of adverse events reported in foreign countries (as of the end of June 2025)

Type	Case	Incidence (%)*
Infections	11	0.608%
Implant site issues	3	0.166%
Deep vein thrombosis	2	0.111%
Haematoma	2	0.111%
Skin erosion caused by lead	1	0.055%
Skin erosion caused by IPG	1	0.055%
Interaction with concomitant device (implantable medical device)	1	0.055%
Haemothorax	1	0.055%

*1, Incidence (%) = number of cases / number of units sold (1,808 units) × 100.
Survey period: from August 2010 to end of June 2025

1.B Outline of the review conducted by PMDA

The applicant provided the following explanation regarding the causal analyses for the malfunction and adverse events reported in foreign countries.

Malfunction:

Lead breakage: The lead was accidentally cut when an incision was made to replace the IPG due to battery depletion.

Adverse events:

Deep vein thrombosis: In 1 patient, following implantation of the remedē System, an implantable cardioverter defibrillator (ICD) was implanted, and the patient was subsequently diagnosed with deep vein thrombosis; however, the patient recovered thereafter. In another patient with deep vein thrombosis, following implantation of the remedē System, deep vein thrombosis was observed in the right internal jugular vein, subclavian vein, axillary vein, and brachial vein, and superficial thrombosis was observed in the basilic vein. The patient was treated with an analgesic and an oral anticoagulant and recovered.

Infections and haematoma: Following the initial implantation or replacement of the remedē System, infections or haematoma occurred at the implant site. Additional interventions, including explantation and cleaning of the remedē System and administration of antibiotics, were performed, and the patients recovered.

Skin erosion by lead/IPG: Following explantation of the remedē System, the events resolved.

Implant site issues: The remedē System was explanted or replaced in 2 cases because of potential skin erosion or infection, and in another case, the implant site pocket was revised. None of the cases resulted in adverse health effects.

Concomitant device interaction: Testing for potential interactions between the remedē System and concomitant implantable cardiac therapy devices is required at the following times to ensure that stimulation from the remedē System does not cause malfunction of the concomitant device: at the time of remedē System implantation or its activation (1 month after implantation) in patients already using pacemakers or other implantable cardiac therapy devices, or at the time of implantation of a new device or when performing an additional procedure related to either the remedē System or a concomitant device in patients who have already been implanted with the remedē System. However, in 1 case reported outside Japan, the stimulation parameters used at the time of implant testing differed from those used after activation, and no additional interaction testing was performed. As a result, an interaction with a previously implanted cardiac resynchronization therapy defibrillator [iii] (CRT-D) occurred. The patient recovered after adjustment of the CRT-D parameters.

Haemothorax occurred as a result of dissection of the left pericardiophrenic vein during lead explantation, and the patient recovered after treatment.

Among adverse events reported overseas, infections, haematoma, and concomitant device interactions are discussed together in Section 6. In contrast, thrombosis, skin erosion by lead/IPG, and haemothorax are events that are expected to occur to some extent with implantable medical devices incorporating leads, such as pacemakers. PMDA concluded that there is no particular problem because the applicant explained that risk minimization measures, including provision of information to users through publication of Information on Precautions, etc. or inclusion of relevant precautionary information in the package insert (hereinafter referred to as “Information on Precautions, etc.”), together with training, would be implemented.

[iii] Corrected after the deliberation by the Committee on Medical Devices and In-vitro Diagnostics (Note: The text herein has been corrected in accordance with the errata sheet of the Japanese review report.)

2. Design and Development

2.(1) Performance and safety specifications

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

The proposed performance specifications for the remedē System include the following elements. IPG functions: body-position sensing, respiratory sensing, and stimulation delivery; telemetry functions: communication between the IPG and the programmer; battery performance: calculation of IPG battery life; stimulation leads: direct current resistance, dielectric strength, impedance, tensile strength, and repeated bending strength; and delivery system: bending strength, rupture strength, and liquid leakage and air leakage.

The proposed safety specifications include electrical safety, electromagnetic compatibility, biological safety, bacterial endotoxins, impact strength, adhered particles, magnetic resonance imaging (MRI) compatibility, and ethylene oxide sterilization residues.

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

PMDA reviewed the submitted data regarding the performance and safety specifications of the remedē System to verify the appropriateness of the specified items and acceptance criteria, and concluded that there were no particular problems.

2.(2) Physicochemical properties

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

The applicant submitted the data from particle tests of IPG and leads as materials related to the physicochemical properties of the remedē System. Compliance with the prespecified acceptance criteria was confirmed for both tests.

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

PMDA reviewed the data on the physicochemical properties and concluded that there were no particular problems.

2.(3) Electrical safety, electromagnetic compatibility

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

For the IPG and leads of the remedē System, the applicant submitted test results indicating that the devices conform to the standards that specify the requirements for implantable medical devices (ISO 14708-1:2014, ISO 14708-3:2008, and EN 45502-2-1:2003). For other items, namely, the remedē System programmer, patient programmer, and external pulse generator, the applicant submitted test results indicating that each of the devices conform to the standards that specify requirements concerning basic safety and essential performance that are generally applicable to medical electrical equipment (IEC 60601-1:2005 + Amd.1:2012), and those concerning electromagnetic compatibility (IEC 60601-1-2:2014).

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

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

2.(4) Conformity to IEC 62304

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

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

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

PMDA reviewed the data on conformity to IEC 62304 and concluded that there were no particular problems.

2.(5) Biological safety

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

For the biological safety evaluation of the IPG, tests appropriate for devices intended for long-term contact with tissue or bone were selected, and data from studies on cytotoxicity, sensitization, irritation/intracutaneous reactivity, pyrogenicity, acute systemic toxicity, implantation, genotoxicity, and chemical properties were submitted.

For leads, tests appropriate for devices intended for long-term contact with circulating blood were selected, and data from studies on cytotoxicity, sensitization, irritation/intracutaneous reactivity, pyrogenicity, acute systemic toxicity, subacute systemic toxicity, implantation, hemocompatibility, and genotoxicity were submitted.

For the delivery system, tests appropriate for devices intended for transient contact with circulating blood were selected, and data from studies on cytotoxicity, sensitization, irritation/intracutaneous reactivity, pyrogenicity, acute systemic toxicity, hemocompatibility, and genotoxicity were submitted.

These studies revealed no findings indicative of biological safety concerns.

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

PMDA reviewed the data on biological safety and concluded that there were no particular problems.

2.(6) Mechanical safety

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

To support the mechanical safety of the remedē System, the applicant submitted data on the impact strength of the IPG, lead strength (tensile strength and repeated bending strength), strength of the delivery system (bending strength, rupture strength, and liquid/air leakage), and strength of the programmer and external pulse generator. The test results confirmed that the devices met the prespecified acceptance criteria.

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

PMDA reviewed the data on mechanical safety and concluded that there were no particular problems.

2.(7) Stability and durability

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

In accordance with the notification, "Handling of stability studies related to the determination of the shelf life in Applications for Approvals (Certification) for Marketing Medical Devices" (PFSB/ELD/OMDE Notification No. 1227-5, dated December 27, 2012, issued by the Office of Medical Devices Evaluation, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare), submission of data from stability studies for the determination of shelf life was omitted, and the applicant submitted a self-declaration stating that the shelf-life had been established based on the required stability evaluations.

The applicant also submitted data demonstrating that the battery life exceeds 3 years within the proposed shelf life of 2 years for the IPG. Based on these data, the shelf life was established as 2 years for the IPG and 3 years for the leads and the delivery system.

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

PMDA reviewed the data on stability and durability and concluded that there were no particular problems.

2.(8) Usability study

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

The applicant submitted data demonstrating that the remedē System conforms to the international standard specifying the usability engineering process for medical devices (IEC 62366-1:2015).

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

PMDA reviewed the data on the conformity to IEC 62366-1 and concluded that there were no particular problems.

2.(9) Cybersecurity

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

The applicant submitted data demonstrating that the remedē System conforms to the standard specifying the cybersecurity requirements for medical devices (ISO 81001-5-1).

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

PMDA reviewed the data on the conformity to ISO 81001-5-1 and concluded that there were no particular problems.

2.(10) Studies supporting the device performance

The applicant submitted data from design verification studies and animal studies to support the performance of the remedē System.

2.(10).1) Design verification studies

2.(10).1).A Summary of the data submitted

The applicant submitted results of the following design verification studies: the IPG's body-position sensing, respiratory sensing, and stimulation functions; telemetry functions between the IPG and the programmer; verification of the programmer; assessment of the delivery system for

conformance to user needs using cadavers and glass vein models; and evaluation of interactions with concomitant devices (implantable cardiac therapy devices and automated external defibrillator). The results confirmed that the remedē System met the specifications. In addition, data from MRI verification testing (displacement, torque, image artifacts, heat generation, vibration, unintended stimulation, and device malfunction under MRI conditions) were submitted.

2.(10).1).B Outline of the review conducted by PMDA

Among the studies supporting the performance of the remedē System, PMDA reviewed data on design verification testing and concluded that there were no particular problems.

2.(10).2) Animal studies

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

Results from the following animal studies were submitted: (1) a 24-week implantation study in dogs and (2) a study evaluating interactions with concomitant devices using a swine model.

(1) A 24-week implantation study

This study was conducted in 12 dogs to evaluate histopathological changes at the stimulation site, pathology of organs, integrity of the conductive and insulation materials, and nerve responses to stimulation. In each dog, 2 stimulation leads (a left pericardiophrenic vein lead and a right brachiocephalic vein lead), a respiratory sensing lead, and an IPG were implanted and the animals were observed for up to 24 weeks. Stimulation was initiated 15 to 21 days post-implant, and delivered from the right brachiocephalic vein lead implanted in the inferior vena cava to the phrenic nerve. Stimulation was delivered using the remedē System at a stimulation amplitude of 1.5 to 9.5 mA depending on the animal and was applied for up to 12 hours a day. The left pericardiophrenic vein lead implanted in the intercostal vein delivered stimulation to the intercostal nerve every 2 weeks.

The results showed no morphological changes in local nerves, including the phrenic and intercostal nerves. The mean histological inflammation score was 2.33 at the IPG implant site (on a 5-point scale, where 1 indicates the lowest severity and 5 indicates the highest severity), which was considered minor. Infection occurred at the IPG implant site in 1 animal. No damage to the leads or IPG was observed after implantation.

The study confirmed diaphragmatic contraction following stimulation delivered at an amplitude of 2.0 to 4.0 mA from the right brachiocephalic vein lead, and intercostal muscle contraction following stimulation delivered at an amplitude of 0.2 to 2.7 mA from the left pericardiophrenic vein lead.

Intermittent stimulation occurred in 1 right brachiocephalic vein lead due to a malfunction in an electrical path of the lead. Since 5 more electrical paths were available for the right brachiocephalic vein lead, the IPG was reprogrammed to use alternative paths, restoring adequate function. The malfunction was attributed to insufficient connection strength between the lead and the connector. The manufacturing process for the connection of the connector and lead was improved to enhance the connection (welding) strength.

(2) Concomitant device interaction

The remedē System and an ICD were implanted in a pig to evaluate the operational behavior of both the remedē System and the ICD after inducing fibrillation. In another study, the remedē System was implanted in a pig, and following induction of fibrillation, an automated external defibrillator[iv] (AED) was used to evaluate the operational behavior of both the remedē System and the AED.

The tests revealed no interaction-associated effects on the detection of fibrillation, time required to confirm defibrillation, defibrillation energy, ICD and AED sensitivity, and behavior of the remedē System.

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

Among the studies supporting the performance of the remedē System, PMDA reviewed data from animal studies and concluded that there were no particular problems.

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 stating that the remedē System 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 Public Notice No. 122, 2005).

3.B Outline of the review conducted by PMDA

PMDA reviewed the conformity of the remedē System to the Essential Principles.

(1) Conformity to Article 1, which stipulates the preconditions for medical device design (particularly the assumptions regarding the level of technical knowledge and experience expected of users, as well as the level of education and training expected to be provided to users):

PMDA's view:

As described in Sections "6.B Outline of the review conducted by PMDA" and "7.B Outline of the review conducted by PMDA," ensuring an appropriate risk-benefit balance for the remedē System requires proper selection of eligible patients, users and implementing medical institutions, the implementation of user training programs, and compliance with the proper use guidelines. Therefore, PMDA decided to impose approval conditions to ensure that the necessary measures are implemented.

(2) Conformity to Article 2, which stipulates risk management throughout the life cycle of medical devices:

PMDA's view:

As described in Sections "6.B Outline of the review conducted by PMDA" and "7.B Outline of the review conducted by PMDA," no clinical data on the efficacy and safety of the remedē System are available in Japan. Therefore, its efficacy and safety in clinical use in Japan

[iv] Corrected after the deliberation by the Committee on Medical Devices and In-vitro Diagnostics (Note: The text herein has been corrected in accordance with the errata sheet of the Japanese review report.)

should be evaluated, and PMDA instructed the applicant to conduct post-marketing surveillance.

(3) Conformity to Article 3, which stipulates the performance and function of medical devices, and to Article 6, which stipulates the efficacy of medical devices:
PMDA's view:
As described in Sections "2.(10).1).B Outline of the review conducted by PMDA" and "2.(10).2).B Outline of the review conducted by PMDA," the performance of the remedē System was confirmed. As described in Sections "6.B Outline of the review conducted by PMDA," the results of foreign clinical studies on the remedē System were favorable. It was therefore considered that the device can be used effectively and safely through appropriate patient selection and other measures. There are no issues regarding conformity to Articles 3 and 6.

(4) Conformity to Article 4, which stipulates the term of validity or lifetime of medical devices:
PMDA's view:
As described in Section "2.(7).B Outline of the review conducted by PMDA," the stability and durability of the remedē System were confirmed, and therefore, there are no issues regarding conformity to Article 4.

(5) Conformity to Article 7, which stipulates the chemical properties, biological safety, and other characteristics of medical devices:
PMDA's view:
As described in Section "2.(5).B Outline of the review conducted by PMDA," the appropriateness of the biological safety and other related aspects of the remedē System was demonstrated. There are no issues regarding conformity to Article 7.

(6) Conformity to Article 8, which stipulates the prevention of microbial contamination of medical devices:
PMDA's view:
As described in Section "5.B Outline of the review conducted by PMDA," the appropriateness of the remedē System with respect to the prevention of microbial contamination and other related risks was demonstrated. There are no issues regarding conformity to Article 8.

(7) Conformity to Article 13, which stipulates considerations for active medical devices, Article 14, which stipulates considerations for protection from mechanical risks of medical devices, and Article 15, which stipulates considerations for medical devices that supply energy:
PMDA's view:
As described in Sections "2.(3).B Outline of the review conducted by PMDA," "2.(10).1).B Outline of the review conducted by PMDA," "2.(10).2).B Outline of the review conducted by PMDA," and "4.B Outline of the review conducted by PMDA," the appropriateness of the remedē System with respect to considerations for active medical devices, protection from mechanical risks, and medical devices that supply energy was demonstrated. There are no issues regarding conformity to Articles 13, 14, and 15.

(8) Conformity to Article 17, which stipulates the general requirements for information provision to users through publicizing precautions or including precautionary statements in the package insert (hereinafter referred to as the "Information on Precautions, etc."):
PMDA's view:
As described in Section "6.B Outline of the review conducted by PMDA," maintaining the risk-benefit balance of the product requires appropriate patient selection and proper use.

Therefore, the applicant is required to provide information through the proper use guidelines and training programs.

Based on the above, PMDA concluded that there are no particular issues regarding the conformity of the remedē System to the Essential Principles.

4. Risk Management

4.A Summary of the data submitted

The applicant submitted a summary of risk management performed for the remedē System, the risk management system, and its implementation status in accordance with the international standard specifying the risk management processes for medical devices (ISO 14971:2019).

4.B Outline of the review conducted by PMDA

PMDA reviewed the data on risk management, taking into account the matters discussed in Section "3.B Outline of the review conducted by PMDA," and concluded that there were no particular problems.

5. Manufacturing Process

5.A Summary of the data submitted

The applicant submitted data on the sterilization process for the remedē System (implementation status of sterilization validation, ethylene oxide gas sterilization residue test results, and data on bacterial endotoxins).

5.B Outline of the review conducted by PMDA

PMDA reviewed the data on the manufacturing process and concluded that there were no particular problems.

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 from a clinical study conducted outside Japan as evaluation data (hereinafter referred to as the "pivotal clinical study").

6.A.(1) Study design (April 2013 to December 2017)

As summarized in Table 4, the pivotal clinical study was conducted as a randomized open-label study in 151 patients with moderate to severe CSA at 31 study sites in the US and Europe. The study evaluated the efficacy and safety of the remedē System compared with the control group, in which the remedē System was implanted but stimulation was withheld for 6 months.

Table 4. Summary of pivotal clinical study

Objective	To evaluate the efficacy and safety of stimulation with the remedē System in patients with moderate to severe CSA who receive optimal medical management
Study design	Multi-center, prospective, open-label, randomized study
Randomized	151 patients Treatment group: successfully implanted in 71 of 73 patients. Control group: successfully implanted in 76 of 78 patients.
Key inclusion criteria	1. At least 18 years of age 2. CSA confirmed by core laboratory analysis of PSG:

	• AHI greater than or equal to 20 events/hour • Central apnea index (CAI) at least 50% of all apnea, with at least 30 central apnea events during PSG • Obstructive apnea index less than or equal to 20% of the total AHI 3. Medically stable (stable medications and therapies) at the time of enrollment: • No recent changes in medications. • For subjects with heart failure, enrollment should occur only after medications have been titrated to the maximum tolerated dose and implantation of any required cardiac therapy device, such as a pacemaker
Key exclusion criteria	1. Patients with treatment-resistant heart failure (American College of Cardiology [ACC]/American Heart Association Heart [AHA] Stage D) 2. Suspected inability to place the delivery system 3. Evidence of phrenic nerve palsy 4. CSA clearly attributable to analgesic uses 5. Cerebrovascular accident within 12 months of baseline testing 6. Limited pulmonary function and oxygenation 7. Patients scheduled for other surgery or invasive procedures that may interfere with assessments at the 6-month post-stimulation initiation visit
Primary efficacy endpoint	The proportion of subjects achieving a 50% or greater reduction in AHI from baseline to 6 months post-stimulation initiation
Primary safety endpoint	Freedom from serious adverse events associated with the implant procedure, the remedē System, or delivered therapy from implantation to 12 months post-stimulation initiation (including a 6-month non-stimulation period for the control group)
Secondary efficacy endpoints*1	1. Proportion of subjects achieving a 50% or greater reduction in AHI from baseline to 12 months post-stimulation initiation 2. Indices related to breathing events during sleep at 6 months and 12 months post-stimulation initiation: CAI, AHI, obstructive apnea index, hypopnea index, mixed apnea index 3. Arousal index (ArI)*2 at 6 months and 12 months post-stimulation initiation: 4. Percentage of REM sleep at 6 months and 12 months post-stimulation initiation: 5. Oxygen desaturation index 4% (4%ODI)*3 at 6 months and 12 months post-stimulation initiation: 6. QOL-related indices at 6 months and 12 months post-stimulation initiation: (1) Proportion of patients experiencing an improvement in global assessment of QOL*4 (patient global assessment [PGA]) (2) Epworth Sleepiness Scale (ESS) (3) QOL questionnaires: (a) 12-Item Short-Form Health Survey (SF-12) (b) European Quality of Life-5 Dimensions (EQ-5D) (c) Fatigue Severity Scale (FSS) (4) Minnesota Living with Heart Failure Questionnaire (MLHFQ) 7. Cardiac function-related indices at 6 months and 12 months post-stimulation initiation: 6-minute walk distance, echocardiography parameters including left ventricular ejection fraction (LVEF), heart rate variability, and abnormal electrocardiogram*5 8. Changes in stimulation lead threshold at 6 months and 12 months post-stimulation initiation
Exploratory endpoints	1. Patient questionnaire at 6 months and 12 months post-stimulation initiation: "Would you elect to have the remedē System implanted again?" 2. Percentage of sleep with SpO_2 <90% at 6 months post-stimulation initiation

*1, CAI, AHI, ArI, percentage of REM sleep, PGA, 4%ODI, and ESS at 6 months post-stimulation initiation were established as hierarchical secondary endpoints.
*2, Frequency of arousal responses (sudden change in brain wave frequency for ≥3 seconds after sleep lasting ≥10 seconds)
*3, Frequency of events in which SpO_2 dropped ≥4% from baseline and returned to the baseline level.
*4, Questionnaire on global assessment of health conditions compared to pre-implantation.
In this study, patients experiencing an improvement rated as the highest or second highest in the 7-point assessment system (corresponding to significant or moderate improvement) were classified as "patients experiencing an improvement"
*5, Mean number of ventricular ectopic beats (≥3 consecutive beats) per hour on Holter monitoring

The remedē System was implanted in 151 subjects, with 73 and 78 subjects in the treatment and control groups, respectively. In the treatment group, stimulation was initiated after the post-implant healing period (1 month). In the control group, stimulation was withheld for 6 months following completion of the post-implant healing period, and stimulation was initiated only after

the primary efficacy evaluation.

The primary efficacy endpoint for the pivotal clinical study was defined as “the proportion of subjects achieving a ≥50% reduction in AHI from baseline to 6 months post-stimulation initiation” and the primary safety endpoint was “freedom from serious adverse events associated with the implant procedure, the remedē System, or delivered therapy from implantation to 12 months post-stimulation initiation (the study period for the control group included a 6 month non-stimulation period). In the pivotal clinical study, PSG tests were performed every 6 months for up to 2 years. Thereafter, follow-up visits were performed every 3 months for up to 5 years.

Assuming that the proportion of subjects who achieved a ≥50% reduction in AHI would be 50% in the treatment group and 25% in the control group, the required sample size was calculated to be 132 patients, based on a one-sided significance level of 2.5% and 80% statistical power. Allowing for implant failure, dropouts, and other exclusions, a target sample size of 173 patients was set. The randomized, Intent-to-Treat (ITT) population was defined as the analysis population for the primary efficacy endpoint and the primary safety endpoint. The Per-Protocol (PP) population was defined as the analysis population for the secondary endpoints and exploratory endpoints.

Figure 8 shows the patient disposition through the 12-month follow-up period.

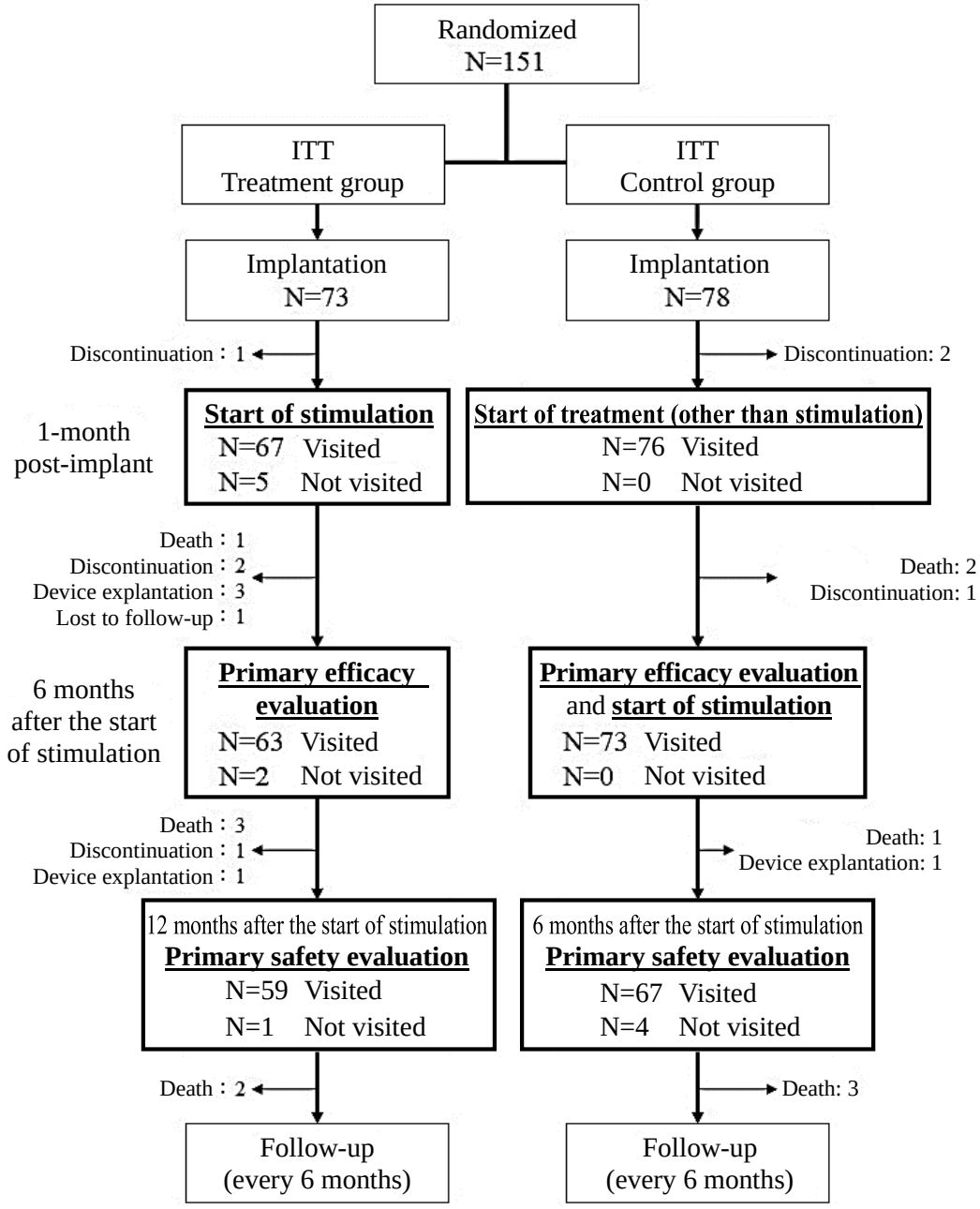

Figure 8. Patient disposition through 12-month follow-up

6.A.(2) Baseline patient characteristics

The baseline characteristics of patients enrolled in the pivotal clinical study and the treatment status of sleep-disordered breathing are presented in Table 5 and Table 6, respectively.

Table 5. Baseline patient characteristics

Item	Treatment (N = 73)	Control (N = 78)
Age (years)	65 ± 12	65 ± 13
Female	14% (10/73)	8% (6/78)
Male	86% (63/73)	92% (72/78)
Black or African American	4% (3/73)	4% (3/78)
Unknown	0% (0/73)	1% (1/78)
White	96% (70/73)	95% (74/78)
Height (cm)	175 ± 8	176 ± 10
Body weight (kg)	95 ± 18	97 ± 21
BMI (kg/m^2)	30.8 ± 5.3	31.3 ± 6.6
Neck (cm)	42 ± 5	43 ± 5
Heart rate (bpm)	75.4 ±12.6	72.9 ± 13.8
Systolic arterial pressure (mmHg)	125.3 ± 18.3	123.7 ± 17.7
Diastolic blood pressure (mmHg)	74.4 ± 10.5	75.3 ± 11.4
Respiratory rate (per minute)	17.5 ± 2.9	17.3 ± 2.6
LVEF (%)	39.7 ± 12.1	39.4 ± 12.2

Table 6. Proportion of subjects receiving treatment for sleep-disordered breathing at the time of obtaining consent

	Treatment (N = 73)	Control (N = 78)
Patients with prior treatment for sleep-related breathing disorders*	42.5% (31/73)	32.1% (25/78)

*, Patients receiving more than one treatment may be included

Table 7 through Table 9 show the medical history of cardiovascular diseases at the time of obtaining consent, medications used in ≥10% of subjects, and the status of concomitant device use at the time of obtaining consent.

Table 7. Medical history of cardiovascular diseases

Category	Treatment (N = 73)	Control (N = 78)
Hypertension	73% (53/73)	77% (60/78)
Hyperlipidemia	78% (57/73)	71% (55/78)
Heart failure	66% (48/73)	62% (48/78)
New York Heart Association (NYHA) Functional Class I	13% (6/48)	25% (12/48)
NYHA Functional Class II	44% (21/48)	42% (20/48)
NYHA Functional Class III	44% (21/48)	33% (16/48)
NYHA Functional Class IV	0% (0/48)	0% (0/48)
Coronary artery disease	56% (41/73)	56% (44/78)
History of cardiovascular surgery	52% (38/73)	47% (37/78)
Atrial fibrillation	44% (32/73)	41% (32/78)
Myocardial infarction	27% (20/73)	29% (23/78)
Stroke	8% (6/73)	8% (6/78)
Cardiac arrest	5% (4/73)	6% (5/78)
Hypotension	5% (4/73)	4% (3/78)

Congenital heart disease	0% (0/73)	1% (1/78)
Other general cardiovascular diseases	36% (26/73)	36% (28/78)

Table 8. Medications used in ≥10% of subjects at the time of obtaining consent

Medication category	Treatment (N = 73)	Control (N = 78)
β-blocker	67% (49/73)	65% (51/78)
Statin	64% (47/73)	60% (47/78)
Antiplatelet	53% (39/73)	62% (48/78)
Loop diuretic	52% (38/73)	37% (29/78)
Angiotensin-converting enzyme inhibitor	47% (34/73)	50% (39/78)
Aldosterone blocker	40% (29/73)	26% (20/78)
Anticoagulant	41% (30/73)	36% (28/78)
Vitamin/dietary supplements	48% (35/73)	47% (37/78)
H2 blocker	38% (28/73)	33% (26/78)
Digoxin	18% (13/73)	17% (13/78)
Thiazide diuretic	22% (16/73)	24% (19/78)
Angiotensin II receptor blocker	19% (14/73)	17% (13/78)
Diabetes medication	23% (17/73)	13% (10/78)
Nitrates	22% (16/73)	10% (8/78)
Insulin	16% (12/73)	10% (8/78)
Potassium	12% (9/73)	22% (17/78)
Antidepressant	30% (22/73)	18% (14/78)
Ca channel blocker	19% (14/73)	18% (14/78)
Gout medication	15% (11/73)	9% (7/78)
Pain medication (narcotic)	18% (13/73)	12% (9/78)
Pain medication (non-narcotic)	14% (10/73)	8% (6/78)
Antiarrhythmic	10% (7/73)	10% (8/78)
Hormone replacement	15% (11/73)	13% (10/78)
Lipid lowering drug (non-statin)	18% (13/73)	12% (9/78)
Steroid	10% (7/73)	17% (13/78)

Table 9. Status of concomitant device use at the time of obtaining consent

Concomitant device	Treatment (N = 73)	Control (N = 78)
Implantable cardiac therapy devices	42.4% (31/73)	42.3% (33/78)
ICD	61.3% (19/31)	42.4% (14/33)
Pacemaker	6.5% (2/31)	24.2% (8/33)
CRT-D	29.0% (9/31)	33.3% (11/33)
CRT pacemaker	3.2% (1/31)	0% (0/33)

6.A.(3) Results of pivotal clinical study

6.A.(3).1) Efficacy endpoints

The primary endpoint, the proportion of subjects achieving a ≥50% reduction in AHI from baseline to 6 months post-stimulation initiation, was 51.5% in the treatment group and 11.0% in the control group, indicating a significant difference (Table 10).

Table 10. Results for the primary efficacy endpoints (ITT population)

Treatment	Control	Between-group difference	*P*-value
51.5% (35/68) [39.0%, 63.8%]	11.0% (8/73) [4.9%, 20.5%]	40.5% [24.7%, 54.3%]	<0.0001

Table 11 shows the proportion of subjects who achieved a ≥50% reduction in AHI from baseline to 2 years post-stimulation initiation. In the control group, after the initiation of stimulation

following a 6-month non-stimulation period, the proportion of subjects who achieved a ≥50% reduction in AHI increased. This improvement was maintained through 2 years post-stimulation initiation in both groups.

Table 11. Proportion of patients who achieved a ≥50% reduction in AHI (long-term results) (PP population)

Period*	Treatment (N = 58)	Control (N = 73)
6 months	60.3% (35/58)	11.0% (8/73)
12 months	66.7% (36/54)	55.4% (36/65)
18 months	64.4% (29/45)	52.5% (32/61)
24 months	59.5% (25/42)	52.5% (31/59)

*, Time that elapsed from completion of the healing period after implantation (1 month post-implant) for both groups. The control group initiated stimulation at 6 months.

Table 12 shows the results for the main secondary endpoints. For indices related to breathing events, results for up to 2 years post-stimulation initiation are also presented.

Table 12. Results for main secondary endpoints (PP population)

Endpoint	Period*[1]	Treatment (N = 58)	Control (N = 73)
CAI (events/hour)	At implant	31.7 ± 18.6	26.2 ± 16.2
	6 months	6.0 ± 9.2	23.3 ± 17.4
	12 months	3.4 ± 6.9	3.7 ± 4.7
	18 months	5.0 ± 11.3	4.8 ± 9.0
	24 months	3.5 ± 10.4	4.4 ± 11.1
AHI (events/hour)	At implant	49.7 ± 18.9	43.9 ± 17.3
	6 months	25.9 ± 20.5	45.0 ± 20.3
	12 months	23.0 ± 21.9	23.2 ± 20.9
	18 months	23.7 ± 20.4	25.5 ± 19.8
	24 months	24.3 ± 22.1	22.6 ± 21.6
ArI (events/hour)	At implant	45.6 ± 18.9	44.0 ± 19.5
	6 months	25.4 ± 14.3	38.9 ± 19.5
	12 months	24.5 ± 14.5	22.8 ± 15.1
	18 months	23.8 ± 18.3	24.7 ± 15.6
	24 months	21.8 ± 17.0	23.1 ± 17.0
Percentage of REM sleep (%)	At implant	10.8 ± 6.6	11.8 ± 7.2
	6 months	12.6 ± 8.7	11.2 ± 7.4
	12 months	13.5 ± 8.8	15.8 ± 7.8
	18 months	14.6 ± 8.4	16.0 ± 9.0
	24 months	16.4 ± 9.2	15.6 ± 9.7
4%ODI (events/hour)	At implant	43.8 ± 21.5	37.3 ± 18.0
	6 months	24.7 ± 21.0	40.9 ± 21.3
	12 months	22.6 ± 23.5	22.1 ± 20.9
	18 months	22.0 ± 19.6	22.8 ± 17.7
	24 months	22.6 ± 23.0	19.5 ± 18.2
PGA*2 (%)	6 months	60.3	5.6
	12 months	60.0	58.2
ESS (points)	At implant	10.7 ± 5.3	9.3 ± 5.7
	6 months	7.1 ± 4.1	9.4 ± 6.1
	12 months	6.5 ± 3.5	6.7 ± 4.9
SF-12 (mental health) (points)	At implant	47.5 ± 9.5	49.5 ± 10.0
	6 months	50.9 ± 10.5	50.6 ± 8.5
	12 months	50.1 ± 10.1	50.2 ± 9.4
SF-12 (physical health) (points)	At implant	38.6 ± 10.1	41.7 ± 10.8
	6 months	39.4 ± 11.2	41.5 ± 9.5
	12 months	39.3 ± 10.1	42.0 ± 9.7
EQ-5D (points)	At implant	0.76 ± 0.14	0.79 ± 0.12
	6 months	0.76 ± 0.16	0.78 ± 0.16
	12 months	0.76 ± 0.17	0.80 ± 0.15

FSS	At implant	4.8 ± 1.5	4.3 ± 1.8
	6 months	4.2 ± 1.6	4.2 ± 1.8
	12 months	4.2 ± 1.6	3.7 ± 1.7
MLHFQ (points)	At implant	42.1 ± 23.6	40.0 ± 27.3
	6 months	38.1 ± 25.8	35.6 ± 24.4
	12 months	34.3 ± 22.3	30.9 ± 23.3
6-minute walk distance (m)	At implant	363.6 ± 111.4	372.8 ± 130.8
	6 months	361.4 ± 111.7	362.8 ± 136.2
	12 months	376.1 ± 129.7	385.0 ± 138.9
LVEF (%)	At implant	40.0 ± 12.3	39.9 ± 11.6
	6 months	41.7 ± 13.6	41.8 ± 12.0
	12 months	44.9 ± 12.9	42.0 ± 13.7
Abnormal change in electrocardiogram*3 (events)	At implant	0.14 ± 0.46	0.49 ± 3.04
	6 months	0.18 ± 1.01	0.63 ± 3.45

*1, Time that elapsed from completion of the healing period after implantation (1 month post-implant) for both groups. The control group initiated stimulation after the evaluation at 6 months (data at 6 months in the table are those measured before the initiation of stimulation).
*2, The proportion of patients who reported that they experienced "an improvement rated as the highest or second highest in the 7-point assessment system"
*3, Mean number of ventricular ectopic beats (≥3 consecutive beats) per hour on Holter monitoring

Among secondary endpoints, CAI, AHI, ArI, percentage of REM sleep, and 4%ODI at 6 months post-stimulation initiation improved in the treatment group compared with the control group. In the control group, similar improvements were observed once stimulation was initiated after the 6-month non-stimulation period. In both groups, the improvements were maintained through 2 years post-stimulation initiation.

Among QOL indices, ESS, a measure of daytime sleepiness, improved by ≥2 points in both groups, while PGA improved in approximately 60% of subjects. However, neither group showed changes in SF-12, EQ-5D, or FSS. Among cardiac function indices, there were no changes in 6-minute walk distance, LVEF, or abnormal electrocardiogram between pre- and post-stimulation initiation.

At the time of implantation, the percentage of sleep time with SpO_2 <90%, an exploratory endpoint, was 16.5 ± 17.9% and 11.2 ± 11.9% in the treatment and control groups, respectively. At 6 months post-stimulation initiation, the corresponding values were 11.5 ± 16.1% and 12.6 ± 13.1% in the treatment and control groups, respectively. An improvement was observed only in the treatment group.

6.A.(3).2) Safety endpoints

Table 13 presents the results for the primary safety endpoint, defined as freedom from serious adverse events associated with the implant procedure, the remedē System, or delivered therapy from implantation through 1 year post-stimulation initiation (for the control group, 6 months of non-stimulation plus 6 months of stimulation).

Table 13. Results for primary safety endpoint (ITT population)

Overall	Treatment	Control
91.4% (138/151) [85.7%, 95.3%]	91.8% (67/73) [83.0, 96.9]	91.0% (71/78) [82.4, 96.3]

Table 14 shows deaths from implantation through 1 year post-stimulation initiation (for the control group, 6 months of non-stimulation plus 6 months of stimulation), and Table 15 shows

deaths up to 5 years post-implant. In all cases, the Clinical Events Committee[v] (CEC) ruled out any causal relationship to the remedē System.

Table 14. List of deaths from implantation through 1 year post-stimulation initiation (ITT population)

Cause of death	Treatment (N = 73)	Control (N = 78)
All deaths	4.1% (3/73)	3.8% (3/78)
Heart—pump failure	0% (0/73)	2.6% (2/78)
Heart failure	0% (0/73)	2.6% (2/78)
Heart—sudden death	2.7% (2/73)	0% (0/78)
Sudden death	1.4% (1/73)	0% (0/78)
Sustained ventricular tachyarrhythmia	1.4% (1/73)	0% (0/78)
Heart—other	1.4% (1/73)	0% (0/78)
Cardiac surgery complications	1.4% (1/73)	0% (0/78)
Non-cardiovascular	0% (0/73)	1.3% (1/78)
Lung cancer	0% (0/73)	1.3% (1/78)

Table 15. List of deaths from implantation up to 5 years post-implant (ITT population)

Cause of death	Treatment (N = 73)	Control (N = 78)
All deaths	20.5% (15/73)	17.9% (14/78)
Heart—pump failure	5.5% (4/73)	9.0% (7/78)
Acute exacerbation of chronic kidney disease	0% (0/73)	1.3% (1/78)
Heart failure	5.5% (4/73)	7.7% (6/78)
Heart—sudden death	5.5% (4/73)	1.3% (1/78)
Cardiac arrest	1.4% (1/73)	0% (0/78)
Sudden death	2.7% (2/73)	1.3% (1/78)
Sustained ventricular tachyarrhythmia	1.4% (1/73)	0% (0/78)
Heart—other	2.7% (2/73)	0% (0/78)
Cardiac surgery complications	1.4% (1/73)	0% (0/78)
Endocarditis infective	1.4% (1/73)	0% (0/78)
Non-cardiovascular	6.8% (5/73)	7.7% (6/78)
Adenocarcinoma	1.4% (1/73)	0% (0/78)
Lung cancer	0% (0/73)	1.3% (1/78)
Myelodysplastic syndrome	0% (0/73)	1.3% (1/78)
Osteomyelitis	0% (0/73)	1.3% (1/78)
Pneumonia	0% (0/73)	1.3% (1/78)
Renal failure	0% (0/73)	1.3% (1/78)
Respiratory failure	1.4% (1/73)	1.3% (1/78)
Sepsis	2.7% (2/73)	0% (0/78)
Fall injury	1.4% (1/73)	0% (0/78)

6.B Outline of the review conducted by PMDA

6.B.(1) Extrapolation of the pivotal clinical study data to Japan

The applicant provided an explanation regarding the extrapolation of the pivotal clinical study data to Japan:

The remedē System delivers electrical stimulation to the phrenic nerve, which transmits signals to the diaphragm (which controls respiration) to induce diaphragmatic contraction and restore a normal breathing pattern during sleep. Therefore, substantial ethnic differences in nerve

[v] Corrected after the deliberation by the Committee on Medical Devices and In-vitro Diagnostics (Note: The text herein has been corrected in accordance with the errata sheet of the Japanese review report.)

responsiveness to electrical stimulation or in muscular contractility are considered unlikely. Regarding venous diameter, an anatomic study[6] of 48 cadavers (23 males and 25 females) reported a pericardiophrenic vein diameter of 2 ± 1 mm and suggested that no correlation was observed between venous diameter and body size. In addition, no reports indicate ethnic differences in the diameter of the right brachiocephalic vein. Furthermore, in Japan, implantable cardiac therapy devices such as pacemakers are used in clinical practice, and their leads may pass through the right brachiocephalic vein. Based on the above, ethnic differences in venous diameter are not considered problematic.

PMDA's view:
Based on the currently available information, no marked differences are expected in terms of responsiveness to phrenic nerve stimulation or relevant anatomical characteristics. Therefore, the impact of ethnic differences on the evaluation of the remedē System is considered acceptable. In addition, the success rate of implant procedures for devices requiring techniques similar to those used for the remedē System does not differ substantially between Japan and other countries. Moreover, given that training will be provided to physicians who will perform implantation of the remedē System, the impact of differences in the medical environment on the evaluation of the remedē System is considered minimal.

6.B.(2) Efficacy and safety of the remedē System

6.B.(2).1) Evaluation strategy of the remedē System

PMDA asked the applicant to justify the appropriateness of applying the remedē System to all types of CSA, regardless of etiology when introducing the device in Japan.

The applicant's explanation:
The prevalence of CSA is highest among patients with heart failure. Approximately 75% of patients with CSA have CSA-CSB associated with heart failure, while the remaining 25% primarily comprise patients with CSA associated with atrial fibrillation or cerebrovascular disorder, as well as those with idiopathic CSA.[7]

For the treatment of CSA-CSB associated with heart failure, US and Japanese clinical practice guidelines recommend CPAP, bi-level positive airway pressure, ASV, and oxygen therapy, although the strength of recommendation varies.[3,8,9,10,11] Furthermore, the above-mentioned CPAP, etc. should be provided after optimization of pharmacotherapy and, where indicated, implantation of cardiac therapy devices such as pacemakers.[3,8,10,11] It is considered that the remedē System, as an implantable medical device, should be positioned for use in patients who are unsuitable for, or intolerant to, positive pressure ventilation (CPAP, ASV) and oxygen therapy. In addition, given the complexity of its settings, it was determined that it was unnecessary to consider bi-level positive airway pressure when introducing the remedē System in Japan.

Clinically, a certain number of cases of CSA other than CSA-CSB associated with heart failure are observed. Although the Japanese clinical practice guidelines do not specify treatment strategies for these etiologies, the US clinical practice guidelines[10] state that positive pressure ventilation and oxygen therapy may be considered.

In the pivotal clinical study, only information on prior treatment with positive pressure ventilation

and oxygen therapy was collected. However, based on the guideline recommendations described above, it was considered that patients who were considered unsuitable for these therapies had been enrolled.

In addition, subgroup analyses of the pivotal clinical study showed no marked differences in the results of the primary efficacy and primary safety endpoints among patients with CSA-CSB associated with heart failure, CSA associated with other diseases (atrial fibrillation or cerebrovascular disorder), and idiopathic CSA. Accordingly, the applicant considered that no restriction based on the type of CSA was necessary.

PMDA's view:
The applicant's explanation that the remedē System, given its invasive nature, should be used in patients who are unsuitable for, or intolerant to, positive pressure ventilation and oxygen therapy is reasonable, and the remedē System can be appropriately evaluated based on the pivotal clinical study, taking into account the applicant's considerations as well. Of the existing therapies described in the Japanese clinical practice guidelines, bi-level positive airway pressure is reportedly used less frequently in clinical practice due to the complexity of its settings and the lack of data demonstrating improved long-term outcomes.[12] Therefore, the applicant's approach of not requiring the use of bi-level positive airway pressure before the introduction of the remedē System is acceptable.

The treatment strategy for CSA-CSB associated with heart failure in Japan is similar to that in the clinical practice guidelines in the US[10] at the time the pivotal clinical study was conducted, and no substantial differences are considered to exist between Japan and other countries with respect to existing therapies or the treatment environment. In patients with CSA-CSB associated with heart failure, hypoxia and arousal caused by sleep-related breathing disorders, including CSA-CSB, are known to have adverse effects on cardiac function and prognosis.[3,11] This has been reported in several studies including the following: in a study in patients with heart failure with LVEF ≤40,[13] the risk of readmission due to a cardiac event within 6 months increased 1.5-fold in those with moderate to severe CSA; and in another study in patients with severe heart failure, there was a 3.8-fold increase in mortality in those exhibiting CSB during ≥10% of the daytime compared with those exhibiting CSB during <10% of the daytime.[14] The Japanese clinical practice guidelines also provide a treatment strategy for CSA-CSB associated with heart failure, which recommends treatment of heart failure before positive pressure ventilation and oxygen therapy is initiated.[3,8,9,11] Therefore, improving sleep status by reducing AHI for CSA-CSB associated with heart failure is considered clinically meaningful.

Conversely, although one report indicates that patients with non-CSB have a better prognosis than those with CSA-CSB with comorbid heart failure,[15] the number of studies evaluating prognostic factors remains limited,[4] and the prognostic impact of hypoxia and arousal remains unclear. While the US clinical practice guidelines[10] state that positive pressure ventilation and oxygen therapy may be considered for these patients, the Japanese clinical practice guidelines do not address the need for treatment or provide treatment strategies.

As discussed above, the clinical significance of reducing AHI differs depending on the underlying cause of CSA. Accordingly, in order to perform the analysis, the patient population for the pivotal clinical study was divided into 2 subgroups: the subgroup of patients with CSA-CSB, which is

CSA with comorbid heart failure (heart failure subgroup [HF subgroup]), and the subgroup of patients with other CSA (other than the heart failure subgroup [non-HF subgroup]). According to the NYHA[vi] Functional classification, which is used to assess the severity of heart failure,[8] patients with Class I or higher were included in the HF subgroup.

6.B.(2).2) Study results by subgroup

PMDA requested the applicant to submit additional data on the HF and non-HF subgroups from the pivotal clinical study, and the data were submitted.

In the HF subgroup (96 subjects total; 48 subjects each in the treatment and control groups), the remedē System was successfully implanted in 46 of 48 subjects in the treatment group and all 48 subjects in the control group.

In the non-HF subgroup (55 subjects total; 16 subjects had idiopathic CSA and 39 subjects had CSA with comorbidities other than heart failure), the remedē System was successfully implanted in all 25 subjects in the treatment group and 28 of 30 subjects in the control group.

6.B.(2).2).(a) Baseline patient characteristics

Table 16 shows the baseline characteristics of patients enrolled in the pivotal clinical study, and Table 17 shows the treatment status of sleep-disordered breathing. With the exception of blood pressure and LVEF, there were no differences between the groups.

Table 16. Baseline patient characteristics (by subgroup)

Item	HF subgroup		Non-HF subgroup		Overall population	
	Treatment (N = 48)	Control (N = 48)	Treatment (N = 25)	Control (N = 30)	Treatment (N = 73)	Control (N = 78)
Age (years)	66 ± 11	68 ± 12	62 ± 13	60 ± 14 (30)	65 ± 12	65 ± 13
Female	10% (5/48)	8% (4/48)	20% (5/25)	7% (2/30)	14% (10/73)	8% (6/78)
Male	90% (43/48)	92% (44/48)	80% (20/25)	93% (28/30)	86% (63/73)	92% (72/78)
Black or African American	6% (3/48)	6% (3/48)	0% (0/25)	0% (0/30)	4% (3/73)	4% (3/78)
Unknown	0% (0/48)	2% (1/48)	0% (0/25)	0% (0/30)	0% (0/73)	1% (1/78)
White	94% (45/48)	92% (44/48)	100% (25/25)	100% (30/30)	96% (70/73)	95% (74/78)
Height (cm)	175 ± 8	175 ± 10	176 ± 9	176 ± 9	175 ± 8	176 ± 10
Body weight (kg)	94 ± 18	95 ± 20	97 ± 18	100 ± 24	95 ± 18	97 ± 21
BMI (kg/m^2)	30.5 ± 5.4	30.9 ± 6.2	31.3 ± 5.2	32.0 ± 7.4	30.8 ± 5.3	31.3 ± 6.6
Neck (cm)	43 ± 4	43 ± 5	41 ± 5	43 ± 5	42 ± 5	43 ± 5
Heart rate (bpm)	72.8 ± 9.4	71.9 ± 13.7	80.4 ± 16.2	74.3 ± 14.2	75.4 ±12.6	72.9 ± 13.8
Systolic arterial pressure (mmHg)	121.9 ± 18.8	118.6 ± 17.6	131.8 ± 15.8	131.7 ± 14.7	125.3 ± 18.3	123.7 ± 17.7
Diastolic blood pressure (mmHg)	71.4 ± 10.8	72.3 ± 11.9	80.2 ± 7.0	80.2 ± 8.7	74.4 ± 10.5	75.3 ± 11.4
Respiratory rate (per minute)	17.6 ± 3.0	17.3 ± 2.6	17.5 ± 2.6	17.3 ± 2.6	17.5 ± 2.9	17.3 ± 2.6
LVEF (%)	35.6 ± 12.4	33.3 ± 11.9	47.4 ± 6.7	48.6 ± 4.6	39.7 ± 12.1	39.4 ± 12.2

[vi] Corrected after the deliberation by the Committee on Medical Devices and In-vitro Diagnostics (Note: The text herein has been corrected in accordance with the errata sheet of the Japanese review report.)

Table 17. Proportion of subjects receiving treatment for sleep-disordered breathing at the time of obtaining consent (by subgroup)

	HF subgroup		Non-HF subgroup		Overall population	
	Treatment (N = 48)	Control (N = 48)	Treatment (N = 25)	Control (N = 30)	Treatment (N = 73)	Control (N = 78)
Patients with prior treatment for sleep-related breathing disorders*	40.0% (19/48)	20.8% (10/48)	48.0% (12/25)	50.0% (15/30)	42.5% (31/73)	32.1% (25/78)

*, Patients receiving more than one treatment may be included

Table 18 through Table 20 summarize the medical history of cardiovascular diseases at the time of obtaining consent, medications used in ≥10% of subjects, and the status of concomitant device use at the time of obtaining consent. In the HF subgroup, the prevalence of cardiovascular disease was high and a larger proportion of subjects were receiving medications and using concomitant devices for the management of heart failure.

Table 18. Medical history of cardiovascular diseases (by subgroup)

Category	HF subgroup		Non-HF subgroup		Overall population	
	Treatment (N = 48)	Control (N = 48)	Treatment (N = 25)	Control (N = 30)	Treatment (N = 73)	Control (N = 78)
Hypertension	75% (36/48)	85% (41/48)	68% (17/25)	63% (19/30)	73% (53/73)	77% (60/78)
Hyperlipidemia	81% (39/48)	81% (39/48)	72% (18/25)	53% (16/30)	78% (57/73)	71% (55/78)
Heart failure	100% (48/48)	100% (48/48)	0% (0/25)	0% (0/30)	66% (48/73)	62% (48/78)
NYHA Functional Class I	13% (6/48)	25% (12/48)	0% (0/25)	0% (0/30)	13% (6/48)	25% (12/48)
NYHA Functional Class II	44% (21/48)	42% (20/48)	0% (0/25)	0% (0/30)	44% (21/48)	42% (20/48)
NYHA Functional Class III	44% (21/48)	33% (16/48)	0% (0/25)	0% (0/30)	44% (21/48)	33% (16/48)
NYHA Functional Class IV	0% (0/48)	0% (0/48)	0% (0/25)	0% (0/30)	0% (0/48)	0% (0/48)
Coronary artery disease	65% (31/48)	79% (38/48)	40% (10/25)	20% (6/30)	56% (41/73)	56% (44/78)
History of cardiovascular surgery	65% (31/48)	63% (30/48)	28% (7/25)	23% (7/30)	52% (38/73)	47% (37/78)
Atrial fibrillation	52% (25/48)	52% (25/48)	28% (7/25)	23% (7/30)	44% (32/73)	41% (32/78)
Myocardial infarction	40% (19/48)	46% (22/48)	4% (1/25)	3% (1/30)	27% (20/73)	29% (23/78)
Stroke	8% (4/48)	6% (3/48)	8% (2/25)	10% (3/30)	8% (6/73)	8% (6/78)
Cardiac arrest	8% (4/48)	10% (5/48)	0% (0/25)	0% (0/30)	5% (4/73)	6% (5/78)
Hypotension	6% (3/48)	4% (2/48)	4% (1/25)	3% (1/30)	5% (4/73)	4% (3/78)
Congenital heart disease	0% (0/48)	2% (1/48)	0% (0/25)	0% (0/30)	0% (0/73)	1% (1/78)
Other general cardiovascular diseases	35% (17/48)	42% (20/48)	36% (9/25)	27% (8/30)	36% (26/73)	36% (28/78)

Table 19. Medications used in ≥10% of subjects at the time of obtaining consent (by subgroup)

Medication category	HF subgroup		Non-HF subgroup		Overall population	
	Treatment (N = 48)	Control (N = 48)	Treatment (N = 25)	Control (N = 30)	Treatment (N = 73)	Control (N = 78)
β-blocker	92% (44/48)	85% (41/48)	20% (5/25)	33% (10/30)	67% (49/73)	65% (51/78)
Statin	67% (32/48)	73% (35/48)	60% (15/25)	40% (12/30)	64% (47/73)	60% (47/78)

Antiplatelet	60% (29/48)	71% (34/48)	40% (10/25)	47% (14/30)	53% (39/73)	62% (48/78)
Loop diuretic	71% (34/48)	58% (28/48)	16% (4/25)	3% (1/30)	52% (38/73)	37% (29/78)
Angiotensin-converting enzyme inhibitor	54% (26/48)	69% (33/48)	32% (8/25)	20% (6/30)	47% (34/73)	50% (39/78)
Aldosterone blocker	54% (26/48)	42% (20/48)	12% (3/25)	0% (0/30)	40% (29/73)	26% (20/78)
Anticoagulant	48% (23/48)	46% (22/48)	28% (7/25)	20% (6/30)	41% (30/73)	36% (28/78)
Vitamin/dietary supplements	44% (21/48)	44% (21/48)	56% (14/25)	53% (16/30)	48% (35/73)	47% (37/78)
H2 blocker	38% (18/48)	35% (17/48)	40% (10/25)	30% (9/30)	38% (28/73)	33% (26/78)
Digoxin	21% (10/48)	27% (13/48)	12% (3/25)	0% (0/30)	18% (13/73)	17% (13/78)
Thiazide diuretic	21% (10/48)	25% (12/48)	24% (6/25)	23% (7/30)	22% (16/73)	24% (19/78)
Angiotensin II receptor blocker	25% (12/48)	19% (9/48)	8% (2/25)	13% (4/30)	19% (14/73)	17% (13/78)
Diabetes medication	23% (11/48)	15% (7/48)	24% (6/25)	10% (3/30)	23% (17/73)	13% (10/78)
Nitrates	25% (12/48)	13% (6/48)	16% (4/25)	7% (2/30)	22% (16/73)	10% (8/78)
Insulin	19% (9/48)	17% (8/48)	12% (3/25)	0% (0/30)	16% (12/73)	10% (8/78)
Potassium	13% (6/48)	23% (11/48)	12% (3/25)	20% (6/30)	12% (9/73)	22% (17/78)
Antidepressant	23% (11/48)	10% (5/48)	44% (11/25)	30% (9/30)	30% (22/73)	18% (14/78)
Ca channel blocker	17% (8/48)	17% (8/48)	24% (6/25)	20% (6/30)	19% (14/73)	18% (14/78)
Gout medication	19% (9/48)	13% (6/48)	8% (2/25)	3% (1/30)	15% (11/73)	9% (7/78)
Pain medication (narcotic)	17% (8/48)	13% (6/48)	20% (5/25)	10% (3/30)	18% (13/73)	12% (9/78)
Pain medication (non-narcotic)	10% (5/48)	4% (2/48)	20% (5/25)	13% (4/30)	14% (10/73)	8% (6/78)
Antiarrhythmic	15% (7/48)	13% (6/48)	0% (0/25)	7% (2/30)	10% (7/73)	10% (8/78)
Hormone replacement	13% (6/48)	13% (6/48)	20% (5/25)	13% (4/30)	15% (11/73)	13% (10/78)
Lipid lowering drug (non-statin)	15% (7/48)	8% (4/48)	24% (6/25)	17% (5/30)	18% (13/73)	12% (9/78)
Steroid	6% (3/48)	15% (7/48)	16% (4/25)	20% (6/30)	10% (7/73)	17% (13/78)

Table 20. Status of concomitant device use at the time of obtaining consent (by subgroup)

Concomitant device	HF subgroup		Non-HF subgroup		Overall population	
	Treatment (N = 48)	Control (N = 48)	Treatment (N = 25)	Control (N = 30)	Treatment (N = 73)	Control (N = 78)
Implantable cardiac therapy devices	60.4% (29/48)	64.6% (31/48)	8.0% (2/25)	6.7% (2/30)	42.4% (31/73)	42.3% (33/78)
ICD	65.5% (19/29)	45.2% (14/31)	0% (0/2)	0% (0/2)	61.3% (19/31)	42.4% (14/33)
Pacemaker	0% (0/29)	19.3% (6/31)	100% (2/2)	100% (2/2)	6.5% (2/31)	24.2% (8/33)
CRT-D	31.0% (9/29)	35.4% (11/31)	0% (0/2)	0% (0/2)	29.3% (9/31)	33.3% (11/33)
CRT pacemaker	3.4% (1/29)	0% (0/31)	0% (0/2)	0% (0/2)	3.2% (1/31)	0% (0/33)

6.B.(2).2).(b) Efficacy

Table 21 summarizes the results for the primary efficacy endpoint (proportion of subjects achieving a ≥50% reduction in AHI from baseline to 6 months post-stimulation initiation) by subgroup. In both subgroups, more than half of the subjects in the treatment group achieved a ≥50% reduction in AHI. In contrast, in the control group, the proportions were 4.4% in the HF subgroup and 21.4% in the non-HF subgroup, demonstrating a difference between groups.

Table 21. Results for the primary efficacy endpoint (ITT population; by subgroup)

	Treatment	Control	Between group difference	*P*-value
Overall population*	57.4% (35/61) [44.1%, 70.0%]	11.0% (8/73) [4.9%, 20.5%]	46.4% [30.0%, 60.1%]	<0.001
HF subgroup*	57.9% (22/38) [40.8%, 73.7%]	4.4% (2/45) [0.5%, 15.1%]	53.5% [35.2%, 69.7%]	<0.001
Non-HF subgroup*	56.5% (13/23) [34.5%, 76.8%]	21.4% (6/28) [8.3%, 41.0%]	35.1% [6.0%, 59.8%]	0.011

*, Calculated based on subjects with PSG test data at 6 months

Table 22 shows the long-term results for the proportion of subjects achieving a ≥50% reduction in AHI from baseline to 2 years post-stimulation initiation. In both subgroups, in the control group, after the initiation of stimulation following a 6-month non-stimulation period, the proportion of subjects achieving a ≥50% reduction in AHI increased. This improvement was maintained through 2 years post-stimulation initiation in both the control and treatment groups.

Table 22. Proportion of subjects achieving a ≥50% reduction in AHI (long-term results) (PP population; by subgroup)

Period*	HF subgroup		Non-HF subgroup		Overall population	
	Treatment (N = 35)	Control (N = 45)	Treatment (N = 23)	Control (N = 28)	Treatment (N = 58)	Control (N = 73)
6 months	62.9% (22/35)	4.4% (2/45)	56.5% (13/23)	21.4% (6/28)	60.3% (35/58)	11.0% (8/73)
12 months	71.0% (22/31)	48.7% (19/39)	60.9% (14/23)	65.4% (17/26)	66.7% (36/54)	55.4% (36/65)
18 months	62.5% (15/24)	48.6% (17/35)	66.7% (14/21)	57.7% (15/26)	64.4% (29/45)	52.5% (32/61)
24 months	57.1% (12/21)	51.5% (17/33)	61.9% (13/21)	53.8% (14/26)	59.5% (25/42)	52.5% (31/59)

*, Time that elapsed from completion of the healing period after implantation (1 month post-implant) for both groups. The control group initiated stimulation at 6 months.

Table 23 shows the results for the main secondary endpoints by subgroup.

Table 23. Results for main secondary endpoints (PP population; by subgroup)

Endpoint	Period*1	HF subgroup		Non-HF subgroup		Overall population	
		Treatment (N = 35)	Control (N = 45)	Treatment (N = 23)	Control (N = 28)	Treatment (N = 58)	Control (N = 73)
CAI (events/hour)	At implant	31.0 ± 18.4	25.3 ± 16.4	32.8 ± 19.3	27.7 ± 16.1	31.7 ± 18.6	26.2 ± 16.2
	6 months	4.4 ± 7.5	23.5 ± 17.9	8.4 ± 11.1	23.0 ± 16.9	6.0 ± 9.2	23.3 ± 17.4
	12 months	2.0 ± 3.4	3.7 ± 4.5	5.2 ± 9.6	3.7 ± 5.2	3.4 ± 6.9	3.7 ± 4.7
	18 months	2.3 ± 3.1	4.4 ± 8.0	8.1 ± 15.9	5.4 ± 10.2	5.0 ± 11.3	4.8 ± 9.0
	24 months	1.4 ± 2.5	4.0 ± 10.2	5.5 ± 14.3	4.9 ± 12.3	3.5 ± 10.4	4.4 ± 11.1
AHI (events/hour)	At implant	50.1 ± 19.2	43.6 ± 17.1	49.1 ± 18.9	44.4 ± 17.9	49.7 ± 18.9	43.9 ± 17.3
	6 months	25.8 ± 20.3	45.5 ± 17.1	25.9 ± 21.2	44.2 ± 24.8	25.9 ± 20.5	45.0 ± 20.3
	12 months	20.7 ± 18.7	24.4 ± 18.4	26.2 ± 25.7	21.5 ± 24.5	23.0 ± 21.9	23.2 ± 20.9
	18 months	23.5 ± 19.2	27.6 ± 18.1	23.9 ± 22.1	22.7 ± 21.9	23.7 ± 20.4	25.5 ± 19.8
	24 months	26.6 ± 22.0	22.5 ± 21.1	21.9 ± 22.5	22.8 ± 22.7	24.3 ± 22.1	22.6 ± 21.6
ArI (events/hour)	At implant	48.5 ± 19.0	43.0 ± 18.8	41.2 ± 18.3	45.5 ± 20.9	45.6 ± 18.9	44.0 ± 19.5
	6 months	27.8 ± 15.2	38.6 ± 19.1	21.8 ± 12.2	39.5 ± 20.6	25.4 ± 14.3	38.9 ± 19.5
	12 months	25.0 ± 13.2	22.5 ± 13.3	23.8 ± 16.3	23.2 ± 17.8	24.5 ± 14.5	22.8 ± 15.1
	18 months	25.6 ± 18.2	24.1 ± 15.2	21.8 ± 18.7	25.5 ± 16.4	23.8 ± 18.3	24.7 ± 15.6
	24 months	23.4 ± 13.4	22.9 ± 17.4	20.2 ± 20.1	23.3 ± 16.9	21.8 ± 17.0	23.1 ± 17.0
Percentage of REM sleep (%)	At implant	10.1±5.2	11.1 ± 7.0	11.9 ± 8.3	12.8 ± 7.5	10.8 ± 6.6	11.8 ± 7.2
	6 months	12.6 ± 8.0	10.9 ± 7.9	12.5 ± 9.7	11.8 ± 6.7	12.6 ± 8.7	11.2 ± 7.4
	12 months	12.9 ± 8.7	15.3 ± 8.4	14.3 ± 9.0	16.7 ± 6.9	13.5 ± 8.8	15.8 ± 7.8

	18 months	13.6 ± 8.4	16.4 ± 8.8	15.8 ± 8.5	15.4 ± 9.4	14.6 ± 8.4	16.0 ± 9.0
	24 months	15.7 ± 9.7	15.1 ± 9.5	17.1 ± 8.7	16.1 ± 10.1	16.4 ± 9.2	15.6 ± 9.7
4%ODI (events/hour)	At implant	45.3 ± 20.8	38.0 ± 17.8	41.5 ± 22.8	36.1 ± 18.7	43.8 ± 21.5	37.3 ± 18.0
	6 months	25.0 ± 21.4	42.2 ± 18.9	24.2 ± 20.8	38.8 ± 25.1	24.7 ± 21.0	40.9 ± 21.3
	12 months	20.8 ± 21.3	23.2 ± 19.3	25.1 ± 26.4	20.4 ± 23.5	22.6 ± 23.5	22.1 ± 20.9
	18 months	21.1 ± 17.2	26.3 ± 17.5	23.0 ± 22.4	18.1 ± 17.2	22.0 ± 19.6	22.8 ± 17.7
	24 months	25.2 ± 23.5	20.1 ± 19.1	19.9 ± 22.8	18.7 ± 17.3	22.6 ± 23.0	19.5 ± 18.2
PGA[*2] (%)	6 months	57.1	9.1	65.2	0	60.3	5.6
	12 months	56.3	58.5	65.2	57.7	60.0	58.2
ESS (points)	At implant	9.5 ± 4.9	8.6 ± 5.7	12.6 ± 5.5	10.5 ± 5.7	10.7 ± 5.3	9.3 ± 5.7
	6 months	6.1 ± 3.7	8.4 ± 5.6	8.7 ± 4.2	11.0 ± 6.6	7.1 ± 4.1	9.4 ± 6.1
	12 months	5.8 ± 3.5	6.0 ± 4.4	7.6 ± 3.2	7.7 ± 5.4	6.5 ± 3.5	6.7 ± 4.9
SF-12 (mental health) (points)	At implant	49.5 ± 9.9	50.6 ± 9.6	44.5 ± 8.4	47.7 ± 10.5	47.5 ± 9.5	49.5 ± 10.0
	6 months	51.7 ± 10.4	51.2 ± 9.3	49.8 ± 10.8	49.6 ± 7.1	50.9 ± 10.5	50.6 ± 8.5
	12 months	52.2 ± 10.3	49.2 ± 10.0	47.2 ± 9.3	51.9 ± 8.4	50.1 ± 10.1	50.2 ± 9.4
SF-12 (physical health) (points)	At implant	35.9 ± 9.3	38.6 ± 10.3	42.6 ± 10.2	46.6 ± 10.0	38.6 ± 10.1	41.7 ± 10.8
	6 months	36.8 ± 10.3	39.1 ± 9.1	43.4 ± 11.5	45.4 ± 9.0	39.4 ± 11.2	41.5 ± 9.5
	12 months	36.6 ± 10.1	38.8 ± 9.3	43.2 ± 9.1	47.0 ± 8.3	39.3 ± 10.1	42.0 ± 9.7
EQ-5D (points)	At implant	0.76 ± 0.15	0.76 ± 0.12	0.77 ± 0.12	0.83 ± 0.11	0.76 ± 0.14	0.79 ± 0.12
	6 months	0.75 ± 0.17	0.76 ± 0.18	0.77 ± 0.14	0.81 ± 0.11	0.76 ± 0.16	0.78 ± 0.16
	12 months	0.74 ± 0.19	0.75 ± 0.16	0.78 ± 0.12	0.87 ± 0.11	0.76 ± 0.17	0.80 ± 0.15
FSS	At implant	4.7 ± 1.7	4.4 ± 1.8	4.9 ± 1.3	4.2 ± 1.8	4.8 ± 1.5	4.3 ± 1.8
	6 months	4.2 ± 1.7	4.3 ± 1.8	4.2 ± 1.4	4.2 ± 1.8	4.2 ± 1.6	4.2 ± 1.8
	12 months	4.4 ± 1.6	3.7 ± 1.6	4.1 ± 1.4	3.6 ± 1.8	4.2 ± 1.6	3.7 ± 1.7
MLHFQ (points)	At implant	42.1 ± 23.6	40.0 ± 27.3	—	—	42.1 ± 23.6	40.0 ± 27.3
	6 months	38.1 ± 25.8	35.6 ± 24.4	—	—	38.1 ± 25.8	35.6 ± 24.4
	12 months	34.3 ± 22.3	30.9 ± 23.3	—	—	34.3 ± 22.3	30.9 ± 23.3
6-minute walk distance (m)	At implant	350.6 ± 122.4	337.1 ± 126.9	383.7 ± 90.9	430.0 ± 117.7	363.6 ± 111.4	372.8 ± 130.8
	6 months	349.0 ± 121.8	338.0 ± 144.7	381.5 ± 92.4	403.7 ± 111.6	361.4 ± 111.7	362.8 ± 136.2
	12 months	358.6 ± 144.5	356.4 ± 138.2	400.8 ± 104.4	423.6 ± 132.8	376.1 ± 129.7	385.0 ± 138.9
LVEF (%)	At implant	34.9 ± 12.5	34.2 ± 11.4	47.6 ± 6.9	48.6 ± 4.6	40.0 ± 12.3	39.9 ± 11.6
	6 months	35.3 ± 13.3	35.6 ± 11.3	50.7 ± 7.6	51.3 ± 4.6	41.7 ± 13.6	41.8 ± 12.0
	12 months	39.3 ± 14.2	35.0 ± 13.5	52.3 ± 5.3	52.2 ± 4.5	44.9 ± 12.9	42.0 ± 13.7
Abnormal change in electrocardiogram[*3] (events)	At implant	0.22 ± 0.58	0.77 ± 3.86	0.01 ± 0.04	0.03 ± 0.08	0.14 ± 0.46	0.49 ± 3.04
	6 months	0.30 ± 1.30	1.07 ± 4.47	0.01 ± 0.03	0.00 ± 0.02	0.18 ± 1.01	0.63 ± 3.45

*1, Time that elapsed from completion of the healing period after implantation (1 month post-implant) for both groups. The control group initiated stimulation after the evaluation at 6 months (data at 6 months in the table are those measured before the initiation of stimulation).

*2, The proportion of patients who reported that they experienced "an improvement rated as the highest or second highest in the 7-point assessment system"

*3, Mean number of ventricular ectopic beats (≥3 consecutive beats) per hour on Holter monitoring

Among the secondary endpoints, improvements in CAI, AHI, ArI, percentage of REM sleep, and 4%ODI, indices reflecting breathing events during sleep, sleep quality, and oxygenation, were observed after stimulation was initiated in both the treatment and control groups. These improvements were maintained through 2 years post-stimulation initiation, with a similar trend observed in both subgroups.

Among QOL indices, ESS and PGA showed improvements; however, neither group showed changes in SF-12, EQ-5D, or FSS, with a similar trend observed in both subgroups. Among cardiac function indices, the Minnesota Living with Heart Failure Questionnaire (MLHFQ)

improved by ≥8 points, while no improvements were observed in the 6-minute walk distance, LVEF, or abnormal electrocardiogram before and after stimulation initiation. These findings were consistent across both subgroups.

For the exploratory endpoint assessing the change in the percentage of sleep time with SpO_2 <90%, from baseline to 6 months post-stimulation initiation, the results were as follows: from 16.3 ± 17.6% to 10.6 ± 15.1% in the treatment group (HF subgroup) and from 13.4 ± 13.5% to 15.2 ± 14.6% in the control group (HF subgroup); from 16.9 ± 18.8% to 12.2 ± 17.8% in the treatment group (non-HF subgroup), and from 7.8 ± 7.8% to 8.4 ± 9.1% in the control group (non-HF subgroup). Improvements were observed only in the treatment groups.

6.B.(2).2).(c) Safety

Table 24 presents the results for the primary safety endpoint (freedom from serious adverse events associated with the implant procedure, the remedē System, or delivered therapy from implantation to 12 months post-stimulation initiation [for the control group, 6 months of non-stimulation plus 6 months of stimulation]) by subgroup. No clear differences were identified between the subgroups.

Table 24. Results for primary safety endpoint (ITT population; by subgroup)

	Overall	Treatment group	Control group
Overall population	91.4% (138/151) [85.7%, 95.3%]	91.8% (67/73) [83.0, 96.9]	91.0% (71/78) [82.4, 96.3]
HF subgroup	91.7% (88/96) [84.2, 96.3]	93.8% (45/48) [82.8, 98.7]	89.6% (43/48) [77.3, 96.5]
Non-HF subgroup	90.9% (50/55) [80.0%, 97.0%]	88.0% (22/25) [68.8%, 97.5%]	93.3% (28/30) [77.9%, 99.2%]

Table 25 summarizes the details of reported events. No events were unique to either subgroup. All events resolved after repositioning, replacement, or explantation of the IPG or leads of the remedē System, or with additional medication (Table 26).

Table 25. List of serious adverse events related to the implant procedure, the remedē System, or delivered therapy from implantation through 12 months post-stimulation initiation (ITT population; by subgroup)

Item	HF subgroup		Non-HF subgroup		Overall population	
	Treatment (N = 48)	Control (N = 48)	Treatment (N = 25)	Control (N = 30)	Treatment (N = 73)	Control (N = 78)
All adverse events	6.3% (3/48)	10.4% (5/48)	12.0% (3/25)	6.7% (2/30)	8.2% (6/73)	9.0% (7/78)
Device system	4.2% (2/48)	4.2% (2/48)	4.0% (1/25)	3.3% (1/30)	4.1% (3/73)	3.8% (3/78)
Concomitant device interaction	2.1% (1/48)	0% (0/48)	0% (0/25)	0% (0/30)	1.4% (1/73)	0% (0/78)
Extra-respiratory stimulation*[1]	2.1% (1/48)	0% (0/48)	0% (0/25)	0% (0/30)	1.4% (1/73)	0% (0/78)
Lead failure	0% (0/48)	0% (0/48)	0% (0/25)	3.3% (1/30)	0% (0/73)	1.3% (1/78)
Lead dislodgement*[2]	0% (0/48)	4.2% (2/48)	0% (0/25)	0% (0/30)	0% (0/73)	2.6% (2/78)
Lead displacement*[3]	0% (0/48)	0% (0/48)	4.0% (1/25)	0% (0/30)	1.4% (1/73)	0% (0/78)
Device implant procedure	2.1% (1/48)	4.2% (2/48)	8.0% (2/25)	0% (0/30)	4.1% (3/73)	2.6% (2/78)

Impending pocket erosion	0% (0/48)	2.1% (1/48)	4.0% (1/25)	0% (0/30)	1.4% (1/73)	1.3% (1/78)
Implant site haematoma	0% (0/48)	2.1% (1/48)	0% (0/25)	0% (0/30)	0% (0/73)	1.3% (1/78)
Implant site infection	2.1% (1/48)	0% (0/48)	4.0% (1/25)	0% (0/30)	2.7% (2/73)	0% (0/78)
General disorders	0% (0/48)	0% (0/48)	0% (0/25)	3.3% (1/30)	0% (0/73)	1.3% (1/78)
Non-cardiac chest pain	0% (0/48)	0% (0/48)	0% (0/25)	3.3% (1/30)	0% (0/73)	1.3% (1/78)
Investigations	0% (0/48)	2.1% (1/48)	0% (0/25)	0% (0/30)	0% (0/73)	1.3% (1/78)
Elevated transaminase	0% (0/48)	2.1% (1/48)	0% (0/25)	0% (0/30)	0% (0/73)	1.3% (1/78)

*****1, Discomfort associated with stimulation perceived at sites distant from the diaphragm

*****2, To enable treatment, the stimulation lead had to be withdrawn from the target vessel, and repositioning or replacement of the lead was required.

*****3, Although a stimulation lead was implanted in the target vessel, effective treatment could not be delivered from the implanted electrode position.

Table 26. Treatment for and outcomes of serious adverse events related to the implant procedure, the remedē System, or delivered therapy from implantation through 12 months after stimulation initiation (ITT population)

Group	Event	Days post-implant	Additional treatment and outcome
Treatment group*	Concomitant device (ICD) interaction	49	Resolved following reprogramming of the remedē System
Treatment group*	Extra respiratory stimulation	34	Resolved following repositioning of the stimulation lead
Treatment group	Lead displacement	50	Resolved following repositioning of the stimulation lead
Treatment group	Impending pocket erosion	134	Resolved following repositioning of the IPG
Treatment group*	Implant site infection	33	Resolved following explantation of the remedē System and administration of antibiotics
Treatment group	Implant site infection	30	Resolved following explantation of the remedē System and administration of antibiotics
Control group	Lead failure	217	Resolved following explantation of the remedē System
Control group*	Lead dislodgement	28	Resolved following stimulation lead replacement
Control group*	Lead dislodgement	50	Resolved following stimulation lead replacement
Control group*	Impending pocket erosion	342	Resolved following repositioning of the IPG
Control group*	Implant site haematoma	2	Resolved following hospitalization for monitoring and administration of antibiotics
Control group*	Non-cardiac chest pain	3	Resolved following analgesic administration
Control group*	Elevated transaminase	17	Resolved following diuretic administration

*, Subject in the HF subgroup

Table 27 lists the patients by group who died from the time of implantation through 1 year post-stimulation initiation (for the control group, 6 months of non-stimulation followed by 6 months of stimulation). Table 28 shows the number of days from implantation of the remedē System to death, the causes of death, and summaries of each case. All deaths occurred in the HF subgroup;

however, a causal relationship to the remedē System was ruled out for all these cases, as adjudicated by the Clinical Events Committee (CEC). There was no difference in mortality between the treatment and control groups.

Table 27. List of subjects who died from implantation through 1 year after stimulation initiation (ITT population; by subgroup)

Cause of death	HF subgroup		Non-HF subgroup		Overall population	
	Treatment (N = 48)	Control (N = 48)	Treatment (N = 25)	Control (N = 30)	Treatment (N = 73)	Control (N = 78)
All deaths	6.3% (3/48)	6.3% (3/48)	0% (0/25)	0% (0/30)	4.1% (3/73)	3.8% (3/78)
Heart—pump failure	0% (0/48)	4.2% (2/48)	0% (0/25)	0% (0/30)	0% (0/73)	2.6% (2/78)
Heart failure	0% (0/48)	4.2% (2/48)	0% (0/25)	0% (0/30)	0% (0/73)	2.6% (2/78)
Heart—sudden death	4.2% (2/48)	0% (0/48)	0% (0/25)	0% (0/30)	2.7% (2/73)	0% (0/78)
Sudden death	2.1% (1/48)	0% (0/48)	0% (0/25)	0% (0/30)	1.4% (1/73)	0% (0/78)
Sustained ventricular tachyarrhythmia	2.1% (1/48)	0% (0/48)	0% (0/25)	0% (0/30)	1.4% (1/73)	0% (0/78)
Heart—other	2.1% (1/48)	0% (0/48)	0% (0/25)	0% (0/30)	1.4% (1/73)	0% (0/78)
Cardiac surgery complications	2.1% (1/48)	0% (0/48)	0% (0/25)	0% (0/30)	1.4% (1/73)	0% (0/78)
Non-cardiovascular	0% (0/48)	2.1% (1/48)	0% (0/25)	0% (0/30)	0% (0/73)	1.3% (1/78)
Lung cancer	0% (0/48)	2.1% (1/48)	0% (0/25)	0% (0/30)	0% (0/73)	1.3% (1/78)

Table 28. Details of the deaths that occurred from implantation through 1 year after stimulation initiation (ITT population)

Group	Days after implantation	Comorbidities	Cause	Summary
Treatment	216	e.g., systolic heart failure, ischaemic cardiomyopathy, myocardial infarction, left bundle branch block, atrial fibrillation, coronary artery disease, hypertension, diabetes mellitus, renal disease	Sustained ventricular tachyarrhythmia	The patient died following ventricular tachycardia/ventricular fibrillation. An ICD analysis confirmed that stimulation had been delivered multiple times during daytime.
Treatment	116	e.g., systolic heart failure, ischaemic cardiomyopathy, myocardial infarction, atrial fibrillation, coronary artery disease, hypertension, diabetes mellitus, carotid artery disease	Sudden death	The patient was found dead at home during daytime. The causes of death were determined to be intracranial haemorrhage, atrial fibrillation, and coronary artery disease. The pacemaker analysis revealed no recorded arrhythmia at the time of death.
Treatment	287	e.g., heart failure, coronary artery disease, hypertension, diabetes mellitus, hyperlipidaemia, renal disease	Cardiac surgery complications	The patient developed acute renal failure following aortic valve replacement. During insertion of a dialysis catheter, the right brachiocephalic vein was damaged, leading to haemorrhage, shock, and cardiac arrest. Subsequently, the patient developed respiratory failure and acute cerebral infarction, and later died.
Control	331	e.g., heart failure, ischaemic cardiomyopathy, coronary artery disease, atrial fibrillation, mitral	Lung cancer	Metastases were noted in a wide area, and the patient died.

		regurgitation, hypertension, hyperlipidemia, smoking history		
Control	112	e.g., heart failure, coronary artery disease, ventricular tachycardia, prior mitral valve replacement, hypertension, diabetes mellitus	Heart failure	The patient was hospitalized because of cardiovascular deterioration. The patient developed respiratory infection and septic shock and died before initiation of stimulation with the remedē System.
Control	97	e.g., heart failure, myocardial infarction, ischaemic cardiomyopathy, coronary artery disease, prior valve repair/replacement	Heart failure	The patient was hospitalized for stroke and myocardial infarction and subsequently developed deteriorated cardiac function and renal failure. Despite implantation of a left ventricular assist device, the patient's condition worsened, and the patient died before initiation of stimulation with the remedē System.

Table 29 summarizes the deaths reported up to 5 years post-implant. A causal relationship to the remedē System was ruled out for all these events, as adjudicated by the CEC.

Table 29. Details of deaths that occurred up to 5 year post-implant (ITT population; by subgroup)

Cause of death	HF subgroup		Non-HF subgroup		Overall population	
	Treatment (N = 48)	Control (N = 48)	Treatment (N = 25)	Control (N = 30)	Treatment (N = 73)	Control (N = 78)
All deaths	29.2% (14/48)	25.0% (12/48)	4.0% (1/25)	6.7% (2/30)	20.5% (15/73)	17.9% (14/78)
Heart—pump failure	8.3% (4/48)	14.6% (7/48)	0% (0/25)	0% (0/30)	5.5% (4/73)	9.0% (7/78)
Acute exacerbation of chronic kidney disease	0% (0/48)	2.1% (1/48)	0% (0/25)	0% (0/30)	0% (0/73)	1.3% (1/78)
Heart failure	8.3% (4/48)	12.5% (6/48)	0% (0/25)	0% (0/30)	5.5% (4/73)	7.7% (6/78)
Heart—sudden death	6.3% (3/48)	2.1% (1/48)	4.0% (1/25)	0% (0/30)	5.5% (4/73)	1.3% (1/78)
Cardiac arrest	0% (0/48)	0% (0/48)	4.0% (1/25)	0% (0/30)	1.4% (1/73)	0% (0/78)
Sudden death	4.2% (2/48)	2.1% (1/48)	0% (0/25)	0% (0/30)	2.7% (2/73)	1.3% (1/78)
Sustained ventricular tachyarrhythmia	2.1% (1/48)	0% (0/48)	0% (0/25)	0% (0/30)	1.4% (1/73)	0% (0/78)
Heart—other	4.2% (2/48)	0% (0/48)	0% (0/25)	0% (0/30)	2.7% (2/73)	0% (0/78)
Cardiac surgery complications	2.1% (1/48)	0% (0/48)	0% (0/25)	0% (0/30)	1.4% (1/73)	0% (0/78)
Endocarditis infective	2.1% (1/48)	0% (0/48)	0% (0/25)	0% (0/30)	1.4% (1/73)	0% (0/78)
Non-cardiovascular	10.4% (5/48)	8.3% (4/48)	0% (0/25)	6.7% (2/30)	6.8% (5/73)	7.7% (6/78)
Adenocarcinoma	2.1% (1/48)	0% (0/48)	0% (0/25)	0% (0/30)	1.4% (1/73)	0% (0/78)
Lung cancer	0% (0/48)	2.1% (1/48)	0% (0/25)	0% (0/30)	0% (0/73)	1.3% (1/78)
Myelodysplastic syndrome	0% (0/48)	0% (0/48)	0% (0/25)	3.3% (1/30)	0% (0/73)	1.3% (1/78)
Osteomyelitis	0% (0/48)	2.1% (1/48)	0% (0/25)	0% (0/30)	0% (0/73)	1.3% (1/78)
Pneumonia	0% (0/48)	0% (0/48)	0% (0/25)	3.3% (1/30)	0% (0/73)	1.3% (1/78)
Renal failure	0% (0/48)	2.1% (1/48)	0% (0/25)	0% (0/30)	0% (0/73)	1.3% (1/78)
Respiratory failure	2.1% (1/48)	2.1% (1/48)	0% (0/25)	0% (0/30)	1.4% (1/73)	1.3% (1/78)
Sepsis	4.2% (2/48)	0% (0/48)	0% (0/25)	0% (0/30)	2.7% (2/73)	0% (0/78)
Fall injury	2.1% (1/48)	0% (0/48)	0% (0/25)	0% (0/30)	1.4% (1/73)	0% (0/78)

6.B.(2).3) Efficacy

6.B.(2).3).(a) Appropriateness of primary efficacy endpoint

PMDA asked the applicant to justify the use of AHI as the measure for the primary efficacy endpoint.

The applicant's explanation:
Because the remedē System was developed for the treatment of CSA, an endpoint that directly reflects improvement in sleep was selected as the primary efficacy endpoint. The Apnea Hypopnea Index is an established gold standard for diagnosing and assessing treatment effectiveness in OSA and CSA. In a US Food and Drug Administration panel discussion,[16] AHI was recognized as an important endpoint. A 50% reduction in AHI was used as an indicator of clinical improvement in the clinical study[17] of the implantable hypoglossal nerve stimulation device "Inspire UAS System" (Approval No. 23000BZI00019000), which aims to improve airway patency in patients with OSA. In addition, in the CANPAP study,[18] a clinical study of CPAP, which is the most commonly used treatment for CSA, the reduction in AHI from baseline was also 50%.

PMDA's view:
Regarding the HF subgroup, given that the remedē System is a highly invasive, long-term implantable medical device, and that its efficacy and safety must be evaluated in patients with CSA-CSB associated with heart failure, the ideal approach would be to assess the suppression of cardiac events or improvement in prognosis rather than reduction in AHI. On the other hand, evaluation of the long-term suppression of cardiac events and improvement in prognosis in patients with CSA-CSB and comorbid heart failure would require a clinical study with a long-term follow-up period. It is therefore accepted that conducting such a long-term study with an untreated control group would not be feasible. Taking into account that the mechanism of action of the remedē System is to stimulate the phrenic nerve to induce respiration, and that, as described in Section "6.B.(2).1) Evaluation strategy of the remedē System," multiple reports have shown that moderate to severe CSA-CSB (AHI ≥15) adversely affects the prognosis of patients with heart failure, the applicant's approach to evaluating the efficacy of the remedē System based on achievement of at least a 50% reduction in AHI, rather than improvement in prognosis, is considered acceptable. In the non-HF subgroup, as described in Section "6.B.(2).1) Evaluation strategy of the remedē System," although the US clinical practice guidelines[10] state that positive pressure ventilation and oxygen therapy may be considered, the Japanese clinical practice guidelines do not specify the need for treatment or provide a treatment strategy. In addition, given the diverse etiologies of CSA, evaluation of AHI reduction, which reflects the clinical performance of the remedē System, is necessary to assess the risk-benefit balance for each patient.

6.B.(2).3).(b) Study outcomes
PMDA asked the applicant to explain the efficacy of the remedē System in the intended patient population taking into account the changes observed in the primary and secondary endpoints.

The applicant's explanation:
Reduction in CAI and AHI indicate reduction in apnea and restoration of regular breathing patterns. Improvements in ArI and the percentage of REM sleep confirmed enhanced sleep quality. In addition to the improvement in 4%ODI, the percentage of sleep time spent with SpO_2 <90%, an exploratory endpoint, showed statistically significant improvements in the treatment group compared to the control group. These results suggest that reduction in hypoxia is associated with improved clinical outcomes in patients with cardiovascular diseases, and may have a positive impact on inflammation and cellular damage.

Beyond improvements in breathing/sleeping events, in the treatment group, at 6 months, the Epworth Sleepiness Scale (ESS), an indicator of daytime sleepiness, improved by at least 2 points in both subgroups. PGA improved in 74.3% of subjects in the HF subgroup and 87.0% of subjects in the non-HF subgroup. In the MLHFQ, the total score improved over time, with a mean improvement of 6.6 points (pooled data from the treatment and control groups) at 12 months. The non-disease specific, general questionnaires SF-12, EQ-5D, and FSS were used to evaluate the broader impact of treatment with the remedē System on patients.

The endpoints adopted in the pivotal clinical study, AHI and 4%ODI, are associated not only with sleep, but also with other clinical outcomes. It has been suggested that reduction in AHI is associated with improvement in LVEF, brain natriuretic peptide levels, and reduction in heart-failure-related hospitalization.[19,20,21,22,23,24] Meanwhile, the 4%ODI correlates with the duration of sleep time spent with SpO_2 <90%, which is reported to be an independent predictor of all-cause mortality in patients with heart failure.[25] In patients in the HF subgroup of the pivotal clinical study, an analysis was performed to evaluate the effects on heart failure-related hospitalization by comparing the treatment group and control group (no stimulation with the remedē System) at 6 months. The rate of heart failure-related hospitalization was 4.7% in the treatment group and 17.0% in the control group, representing a reduction of 12.3% with stimulation using the remedē System (P = 0.0654).[26] These findings suggest that treatment with the remedē System has the potential to delay the time to first heart failure-related hospitalization.

The above results suggest that treatment with the remedē System has the potential to improve sleep/breathing event indices, daytime sleepiness, and QOL in patients with CSA, and delay the time to first heart failure-related hospitalization in patients with CSA and comorbid heart failure.

PMDA concluded that assessing the clinical meaningfulness of the remedē System requires evaluation of not only effectiveness in reducing AHI, the primary efficacy endpoint, but also the improvements in breathing events, QOL, and heart failure-related indices included as secondary endpoints, as these collectively demonstrate improvement in clinical outcomes. The following sections present the PMDA's evaluation of each of these aspects.

6.B.(2).3).(b).i) Apnea and hypopnea during sleep and sleep quality

In both subgroups, AHI was reduced by half at 6 months post-stimulation initiation, decreasing to approximately 25 events per hour on average, indicating improvement from severe to moderate AHI. In addition, CAI decreased significantly and these improvements were sustained over time. Therefore, it was concluded that stimulation with the remedē System restored a normal breathing pattern, thereby demonstrating the device's clinical performance in reducing apnea. In addition, reductions in 4%ODI and the percentage of sleep time spent with SpO_2 <90% indicate that improvement in oxygenation during sleep may be expected. Furthermore, because ArI decreased by 15 to 20 events per hour in both the treatment and control groups, and the percentage of REM sleep increased from the time of implantation by approximately 25% to 50% in the HF subgroup and by approximately 20% to 40% in the non-HF subgroup, it is considered that improvement in sleep quality can also be expected.

6.B.(2).3).(b).ii) Daytime sleepiness, QOL

In patients with OSA, an improvement of 2 to 3 points in ESS is considered to represent a

clinically meaningful change.[27] However, CSA is known to present without noticeable symptoms such as insomnia,[11] and the ESS, a questionnaire developed for patients with OSA to assess daytime sleepiness, has been reported in some studies not to change in patients with CSA.[28] On the other hand, because the ESS is the most commonly used questionnaire for assessing sleep-related symptoms in clinical studies on CSA,[29] its use as an index to evaluate improvement in daytime sleepiness associated with stimulation using the remedē System is considered acceptable.

In the pivotal clinical study, in both subgroups, both the treatment and control groups demonstrated an improvement in ESS of ≥2 points, which is considered clinically meaningful, at 6 months post-stimulation initiation, and this improvement was confirmed to be sustained thereafter.

No worsening was observed in the indices of the general QOL questionnaires (SF-12, EQ-5D, and FSS). Because a study[30] has shown that a ≥5 point improvement in MLHFQ, which is a heart failure-specific questionnaire, is clinically meaningful, it is considered that stimulation with the remedē System may provide a clinically meaningful improvement in QOL.

6.B.(2).3).(b).iii) Cardiac function

Among cardiac function-related indices, it is assumed that 6-minute walk distance and LVEF will deteriorate over time in patients with heart failure; however, baseline levels tended to be maintained. Data presented by the applicant from the HF subgroup in the pivotal clinical study showed that rates of heart failure-related hospitalization decreased following 6 months of stimulation with the remedē System.[26] Based on this report, it was considered that the remedē System can suppress cardiac events to some extent in patients with heart failure.

Taken together, although the pivotal study did not have statistical power to evaluate the results of each subgroup, improvements were observed in respiratory status, sleep quality, and QOL. In addition, the results suggested a certain degree of improvement in cardiac function and suppression of cardiac events in the HF subgroup could be expected following stimulation with the remedē System. Therefore, PMDA concluded that the remedē System has demonstrated efficacy.

However, because the effects on cardiac event suppression and long-term prognosis were not sufficiently evaluated in the pivotal clinical study, and the efficacy with respect to the original objective of treatment remains unclear, PMDA concluded that, after the market launch, patient selection should be carefully considered based on a thorough understanding of the results of the pivotal clinical study.

6.B.(2).4) Safety

6.B.(2).4).(a) Adverse events related to the remedē System implant procedure

Because a certain number of serious adverse events related to the implant procedure, such as implant site infection, were observed, and because the lead of the remedē System is implanted in veins different from those used for conventional implantable cardiac therapy devices, PMDA asked the applicant to further explain the risk mitigation measures for such events.

The applicant’s explanation:

The incidence of serious infections related to the remedē System within 1 year post-stimulation initiation in the pivotal clinical study was 1.3% (2 of 151 subjects) for the overall population, 1.0% (1 of 96 subjects) in the HF subgroup, and 1.8% (1 of 55 subjects) in the non-HF subgroup. Based on a systematic review of implantable cardiac therapy devices,[31] the incidence of implant-procedure-related infections within 1 year is approximately 1% for existing implantable cardiac therapy devices.

In the pivotal clinical study, the incidence of serious haematoma related to the remedē System within 1 year after implantation was 0.7% (1 of 151 subjects) for the overall population, 1.0% (1 of 96 subjects) in the HF subgroup. Based on a systematic review of implantable cardiac therapy devices,[32] the mean incidence of pocket haematoma is reported as 2.2% for the ICDs and 2.4% for CRT-D and CRT pacemakers.

Based on the above, the incidence of infection and haematoma in the pivotal clinical study was not considered to be substantially different from that reported for the implantable cardiac therapy devices described above.

In the pivotal clinical study, 2 cases of impending pocket erosion were reported. In both cases, pocket erosion was not actually observed, but the cases were reported as adverse events because precautionary measures (IPG repositioning) were implemented to prevent subsequent worsening. Implantable pulse generator-related events have also been reported in published data on implantable medical devices. The incidence of reported events including IPG migration and pocket erosion was 2.7%, and that of IPG site pain was 0.4%.[33,34] Furthermore, to minimize the incidence of adverse events, the applicant plans to implement a hands-on training program for all physicians who will perform implantation of the remedē System. If any infection is detected at the implant site of the remedē System, the device is typically explanted, and the patient is treated appropriately with medication. It is possible to re-implant a new remedē System device subsequently.

Lead displacement, a situation in which a stimulation lead is implanted within the target vessel, but fails to deliver effective treatment, can usually be resolved by repositioning the lead. In the pivotal clinical study, 1 case was reported as a serious adverse event; however, the lead could not be positioned appropriately because implantation in the vessel proved to be technically difficult. Accordingly, it was determined that the training program should include instruction on appropriate implantation techniques using contrast media and fluoroscopy to enhance anatomical visualization.

In a case of non-cardiac chest pain, 3 days after implantation of the remedē System, the patient presented to the emergency department with a complaint of chest pain and was hospitalized. The test results indicated no cardiovascular findings, and the chest pain subsided after administration of ibuprofen. Because no other attributable causes were identified, the event was assessed as related to the implant procedure.

Elevated transaminase levels were noted 17 days after implantation of the remedē System, resulting in hospitalization. The event resolved within 4 days without sequelae. Because no other attributable causes were identified, the event was assessed as related to the implant procedure.

Events such as implant site pain, haematoma, and elevation of transaminase can be managed using treatment approaches similar to those used for other implantable medical devices.

Based on the above, the occurrence of serious adverse events related to the implant procedure, the remedē System, or delivered therapy was considered clinically acceptable.

PMDA concluded that the remedē System implant-procedure-related risks are clinically acceptable taking into account the following factors:

- Incidence of adverse events related to the remedē System implant procedure in the pivotal clinical study
- The applicant's explanation regarding the comparability of the incidence of adverse events (e.g., haematoma, infections, interaction with concomitant devices) described in Section "1.A.(3) Malfunctions and adverse events in foreign countries" with that for implantable cardiac therapy devices
- The details of the training program planned by the applicant
- As described in Section "6.B.(2).5) Summary of efficacy and safety," eligible patients for the remedē System are those who are unsuitable for, or intolerant to, existing positive pressure ventilation, who have no other treatment options, and who are likely to derive benefits from the remedē System that outweigh the implant procedure- or device-related risks.[vii]

6.B.(2).4).(b) Concomitant device interactions, stimulation-related adverse events, or malfunction of the remedē System

Because concomitant device interactions, serious adverse events related to remedē System stimulation, and remedē System malfunctions occurred at certain frequencies, PMDA asked the applicant to provide an additional explanation regarding risk mitigation measures for these events.

The applicant's explanation:
As described in Section "1.B Outline of the review conducted by PMDA," interaction testing between the remedē System and concomitant implantable cardiac devices is required in patients already using such devices, or those newly implanted with a concomitant device. A single case of interaction with a concomitant device (ICD) occurred within 1 year post-implant in the pivotal clinical study. In this patient, although an interaction test was performed, an ICD shock occurred. The patient was hospitalized for monitoring; however, the event resolved following reprogramming of the remedē System (Table 26). Based on this event, the interaction testing procedure was revised. Two additional cases of concomitant device interactions were identified before completion of the pivotal clinical study. In one case, no interaction test was performed because the procedure for the concomitant device had been conducted at another medical institution. In the other case, the patient was hospitalized because non-sustained ventricular tachycardia associated with oversensing of remedē System stimulation was identified during a routine ICD test. A device interaction test was performed; however, oversensing could not be reproduced. The remedē System was reprogrammed to minimize the possibility of similar events, and no further such events were reported. Thereafter, enrolled subjects using a concomitant device

[vii] Corrected after the deliberation by the Committee on Medical Devices and In-vitro Diagnostics (Note: The text herein has been corrected in accordance with the errata sheet of the Japanese review report.)

and newly enrolled subjects underwent the revised interaction test. At all study sites, retraining of physicians was implemented, and if any change was made to the remedē System or the concomitant devices, an interaction test was carried out again. As a result, no serious adverse events related to device interactions occurred during the 5-year follow-up surveillance after implantation.

Two cases of non-serious, extra-respiratory stimulation reported in the pivotal clinical study resolved by changing parameters. One case, reported as a serious adverse event, was stimulation felt by the subject in the shoulder, instead of the diaphragm. Because this event did not resolve with reprogramming, the lead was repositioned.

Lead failure typically occurs long after implantation. However, in the case reported in the pivotal clinical study, it was considered that excessive bending of the lead during implantation and excessive movement of the patient's upper body and arms after implantation, including swimming, resulted in lead failure. Although no adverse health effects occurred, the remedē System was explanted. Based on the result, it was decided that the physician training program would include instructions to advise patients to limit ipsilateral arm movement for several weeks after implantation. The causes could not be identified for the 2 cases of lead dislodgement. In one case, however, it was likely that excessive upper limb movement after implantation was involved.

The applicant explained that, as described in Section "2.(10).2) Animal studies," non-clinical studies confirmed that concomitant devices expected to be used in clinical practice, such as implantable cardiac therapy devices (e.g., pacemakers), continue to function as intended under stimulation from the remedē System. Based on these findings, procedures for interaction testing were established and specified in the instructions for use. In addition, the applicant stated that the risks of these events can be reduced by ensuring adequate mastery of the implantation techniques through training, strict implementation of interaction testing, and appropriate patient counselling regarding precautions after implantation. PMDA concluded that the applicant's explanation above is acceptable.

6.B.(2).4).(c) Effects on cardiovascular system (heart failure and arrhythmia)

From implantation through 1 year after stimulation initiation (for the control group, 6 months of non-stimulation followed by 6 months of stimulation), the following adverse events occurred in the treatment group and control group: heart failure (12%; 18 of 151 subjects), sustained ventricular tachyarrhythmia (7%; 11 of 151 subjects), and atrial fibrillation (5%; 8 of 151 subjects). PMDA asked the applicant to explain the effects of stimulation with the remedē System on heart failure and arrhythmia.

The applicant's explanation:

In the pivotal clinical study, for all cases of heart failure that occurred after implantation, the CEC determined that none were causally related to the implant procedure, the remedē System, or stimulation with the remedē System. In the HF subgroup, it has been reported that stimulation with the remedē System has the potential to delay the time to first heart failure-related hospitalization.[26]

All patients who experienced sustained ventricular tachyarrhythmia had been using an ICD or

CRT-D prior to the initiation of remedē System stimulation. Six of these patients had a history of sustained ventricular arrhythmia. The remaining 5 patients, although without a history of ventricular tachyarrhythmia, were considered at increased risk for ventricular arrhythmia due to underlying conditions such as heart failure, coronary artery disease, or hypertension, and therefore an ICD had been implanted as a precautionary measure. Six patients experienced their first event only after initiation of remedē System stimulation, and only 1 patient developed an event at night during stimulation. In a study of patients with CSA who had an ICD implanted, the incidence of ventricular arrhythmia was ≥30% at 1 year.[35] Based on a review of the patient records including log data from the concomitant cardiac therapy devices, the CEC determined that none of the sustained ventricular arrhythmia events were related to remedē System stimulation, and that none occurred during remedē System stimulation.

Of the 8 patients who developed atrial fibrillation, 5 patients experienced their first event only after initiation of remedē System stimulation. Two of the 8 patients did not have a history of atrial arrhythmia, while one developed atrial fibrillation only after initiation of remedē System stimulation. This patient had history of systolic heart failure, which increases the risk of atrial arrhythmia. In patients with heart failure who had sinus rhythm at baseline, the annual incidence of atrial fibrillation is approximately 5%,[36] which is comparable to the incidence in the pivotal clinical study. The CEC ruled out any relationship between atrial fibrillation and remedē System stimulation.

The remedē System stimulation lead is implanted in a vein running along the outer surface of the pericardium and stimulates the phrenic nerve, which is surrounded by thick fibrous connective tissue. Because of the high impedance of connective tissue, the stimulation parameters of the remedē System (0-10 mA, 60-300 μs) are not expected to allow conduction to the heart, and therefore are not considered to have direct cardiovascular effects.

No trend was observed in the pivotal clinical study to suggest that stimulation with the remedē System affected the incidence of heart failure or arrhythmia events; therefore, PMDA concluded that the incidence of these events was clinically acceptable.

6.B.(2).4).(d) Deaths

The applicant's explanation regarding deaths in the pivotal clinical study:

In the pivotal clinical study, the mortality at 1 year post-stimulation initiation in the overall population was 4.1% (3 of 73 subjects) in the treatment group and 3.8% (3 of 78 subjects) in the control group. All deaths occurred in the HF subgroup, with an incidence of 6.3% (3 of 48 subjects) in both the treatment and control groups.

Compared with existing treatments, clinical studies that evaluated ASV in patients with heart failure (LVEF ≤45%) and comorbid CSA with AHI ≥15, reported mortality at 1 year of 9.1% in the ASV group and 7.6% in the control group, both of which received pharmacotherapy conforming to the guidelines (SERVE-HF study[37]). The mortality at 1 year was ≥10% in both the ASV group and control group, which received pharmacotherapy conforming to the guidelines (ADVENT-HF study[38]). In the clinical study on CPAP,[18] 16.0% of patients in the CPAP group and 6.0% of patients in the control group (receiving optimum pharmacotherapy for heart failure) had undergone heart transplantation or had died at 1 year. Therefore, the mortality rate for the remedē

System in the HF subgroup at 1 year in the pivotal clinical study was lower than that reported for ASV or CPAP treatment groups, and comparable to the control groups (pharmacotherapy) in these clinical studies.

Furthermore, for all 29 subjects who died during the 5-year follow-up period, the CEC ruled out any causal relationship to the implant procedure, the remedē System, or delivered therapy. These findings indicate that implantation of or stimulation with the remedē System are not likely to increase the risk of death.

PMDA's view:
Although a certain number of deaths occurred, patients enrolled in the pivotal clinical study, including those with cardiovascular comorbidities, were known to be at high risk (Table 28). In addition, patients with CSA-CSB with comorbid heart failure are known to have a poor prognosis compared with those with other types of CSA.[15] The mortality at 1 year in this study was comparable to that in patients with CSA with comorbid heart failure receiving pharmacotherapy, and there was no evidence over the 5-year follow-up period that implantation of or stimulation with the remedē System contributed to mortality. Therefore, mortality findings are clinically acceptable.

Based on the above, PMDA concluded that there are no particular concerns regarding the safety of the remedē System, taking into account the following factors:

- Although remedē System procedure- or device-related serious adverse events occurred in the pivotal clinical study, these events resolved with additional treatments and did not result in long-term health impairment.
- Regarding deaths up to 1 year after initiating stimulation, there were no marked differences between the groups in terms of the number of days from implantation to death; therefore, it is unlikely that stimulation with the remedē System increases mortality.
- The high mortality in the HF subgroup is assumed to be associated with heart failure or other comorbidities. No remedē System-related deaths occurred over the long term. In addition, sleep-related breathing disorders are recognized as one of the factors contributing to worsening heart failure .

6.B.(2).5) Summary of efficacy and safety[viii]

The pivotal clinical study demonstrated that the remedē System reduces AHI in patients with CSA, which reflects the clinical performance of the device.

The results by subgroup indicated not only a reduction in AHI, but also improvements in respiratory status, sleep quality, and QOL.

In the HF subgroup, based on the recommendations of the guidelines described in Section 6.B.(2).1) Evaluation strategy of the remedē System," the efficacy of the device in reducing AHI in patients with CSA-CSB and comorbid heart failure can be expected.

[viii] Corrected after the deliberation by the Committee on Medical Devices and In-vitro Diagnostics (Note: The text herein has been corrected in accordance with the errata sheet of the Japanese review report.)

Regarding the non-HF subgroup, although the Japanese clinical practice guidelines do not specify the need for treatment or provide a treatment strategy, currently, there have been reports that positive pressure ventilation and oxygen therapy are implemented in clinical practice in Japan.[39,40] The US clinical practice guidelines state that therapies such as positive pressure ventilation and oxygen therapy may be considered, suggesting the existence of a need for reduction of AHI that may be addressed with the remedē System.

The remedē System, however, is highly invasive compared to conventional therapies such as positive pressure ventilation (e.g., CPAP and ASV) and oxygen therapy, and in the pivotal clinical study, implant procedure-related serious adverse events occurred at an incidence comparable to that for implantable cardiac therapy devices.

Therefore, in patients who are unsuitable for, or intolerant to, existing positive pressure ventilation and have no other treatment options, if the benefits of improved respiratory status and sleep quality are expected to outweigh the risks associated with the implant procedure or the remedē System, it is considered meaningful to introduce the remedē System into clinical practice as a treatment option. Therefore, it is important to select patients for whom a favorable benefit-risk balance can be achieved, in accordance with the risk minimization measures described in Section "6.B.(4) Post-marketing safety measures" so that the clinical utility of the remedē System can be maximized.

In addition, long-term safety and efficacy related to prognostic improvement, including the incidence of cardiovascular events, in the Japanese medical setting, which were not clarified in the pivotal clinical study, should continue to be evaluated through post-marketing surveillance as discussed in Section 7.

6.B.(3) Intended use and eligible patients

As described in Section "6.B.(2).1) Evaluation strategy of the remedē System," eligible patients for the remedē System are those who are unsuitable for, or intolerant to, existing therapies (e.g., positive pressure ventilation and oxygen therapy). PMDA considers that the proposed "Intended use or indication" is appropriate and concluded that the "Intended use or indication" of the product should be as follows.

Intended use or indication (Underlined denotes changes from the proposed text)

The remedē System is intended for the treatment of moderate to severe central sleep apnea in adult patients who are unsuitable for, or intolerant to, <u>positive pressure ventilation</u> or oxygen therapy. <u>The device delivers transvenous phrenic nerve stimulation to induce diaphragmatic contraction and thereby assists respiration during sleep.</u>

6.B.(4) Post-marketing safety measures

PMDA's view:

The remedē System, a long-term implantable medical device intended for use in patients with CSA, is the first such product to be introduced into Japan. Because a certain number of serious adverse events occurred in the pivotal clinical study, it is important for physicians to gain a thorough understanding of these adverse events through the Information on Precautions, etc., educational materials, and training program. In addition, it is important to determine whether a

patient is eligible for the treatment by carefully considering the patient's characteristics and the benefit-risk balance.

Therefore, the following are required to ensure effective and safe introduction of the remedē System into Japan:

(a) Physicians with sufficient knowledge and experience in sleep-related breathing disorders and the etiologies of CSA should appropriately select patients who are likely to have a favorable benefit-risk balance.
(b) Because effective and safe use of the remedē System requires procedure-related knowledge, skills, and experience, physicians and/or medical institutions should have the knowledge and skills to manage adverse events associated with use of the remedē System (especially, implant-procedure-related adverse events) and to provide postoperative care (e.g., infection management), and should be capable of responding promptly, including surgical intervention, when necessary.
(c) Based on the treatment outcomes after the product launch, the proper use guidelines should be reviewed and additional safety measures should be implemented as necessary.

Regarding item (a) above, eligible patients should be selected by physicians who meet the requirements specified in the proper use guidelines developed by the relevant academic societies (the Japanese Respiratory Society, the Japanese Circulation Society, the Japanese Society of Sleep Research) (Table 30). Regarding patient eligibility, it is important to establish criteria related to CSA etiologies and sleep-related breathing disorders (including severity of CSA and patient symptoms) in collaboration with the relevant academic societies.

In the SERVE-HF study conducted in patients with CSA-CSB and comorbid heart failure, the mortality rate was higher in the ASV group. The study used ASV, which involves forced ventilation similar to the remedē System. Based on the study results, statements[41] were issued by the Japanese Circulation Society advising careful consideration of ASV use in patients with CSA-CSB with LVEF ≤45%. Because eligible patients for the remedē System should be selected taking into account the precautions described in the statements, PMDA determined that appropriate cautionary information should be included.

Regarding item (b), given that eligible patients should be carefully selected, and the remedē System lead is implanted in a vein different from that used for existing implantable cardiac therapy devices, it was considered necessary to implement a training program, including hands-on training, for physicians and medical institutions that meet the requirements specified in the proper use guidelines. The outline of training (draft) proposed by the applicant (Table 31) indicates that the training will provide information on patient selection, implant procedure, adverse events, and their management. Therefore, PMDA concluded that the proposed training program was appropriate.

Regarding item (c), based on the results of post-marketing surveillance and other data, the proper use guidelines are to be reviewed as necessary by the relevant academic societies, and additional safety measures are to be implemented by the applicant. Therefore, PMDA concluded that item (c) is appropriate.

The requirements in items (a), (b), and (c) are important to ensure the efficacy and safety of the remedē System in Japan; therefore, PMDA concluded that these requirements should be imposed as Approval Condition 1.

Table 30. Proper use guidelines (draft)

Category	Outline
Requirements for physicians	(1) Decision on eligibility Decision should be made by a team consisting of the healthcare professionals specified in 1) and 2) below 1) Board Certified Member of the Japanese Circulation Society (physicians with sufficient knowledge and experience*1 in heart failure and who are familiar with pacemaker implantation/management), who completed the specified manufacturer's training program. 2) Board Certified Fellow of the Japanese Society of Sleep Research or Board Certified Member of the Japanese Respiratory Society (physicians with sufficient knowledge and experience in treating sleep-disordered breathing and PSG) (2) Implantation 1) Same as (1).1) (3) Follow-up The following 2 requirements must be met: 1) Board Certified Member of the Japanese Circulation Society, Board Certified Fellow of the Japanese Society of Sleep Research, or Board Certified Member of the Japanese Respiratory Society 2) Physicians who completed the specified follow-up training program
Requirements for medical institutions	(1) Medical institutions in which implantation is performed A single medical institution meeting the following requirements, or 2 medical institutions, each meeting one of the following requirements should collaborate with each other 1) Facilities for implantation: the Japanese Circulation Society training facilities with proven record of implantation of new transvenous pacemakers, ≥10 cases annually 2) PSG facilities: at least 10 cases of Type 1 or 2*2 PSG are performed annually, and Board Certified Fellow of the Japanese Society of Sleep Research or Board Certified Member of the Japanese Respiratory Society are always available (2) Follow-up The Japanese Circulation Society training facilities, facilities certified by the Japanese Society of Sleep Research, or facilities certified by the Japanese Respiratory Society

*1, For cases of CSA and comorbid heart failure
*2, PSG including electroencephalogram, electrooculogram, mentalis electromyogram, electrocardiogram or pulse rate, airflow, respiratory effort, and SpO_2.
Trained testers constantly monitor the recordings for Type 1, and no monitoring is performed for Type 2.

Table 31. Outline of training proposed by the applicant (draft)

Lecture, Hands-on training	• Acquiring knowledge of the venous system and neuroanatomy required for implantation of the remedē System • Acquiring knowledge of anatomical displacement of veins • Acquiring knowledge of equipment (including stimulation leads) used for implantation of the remedē System ➢ Venographic technique for small vessels by slowly and cautiously injecting a small amount of contrast media • Understanding and practicing the implant procedure for the remedē System, including right and left leads and IPG ➢ Learning the implant procedure for the remedē System, including right and left leads and IPG ➢ Importance of implanting the lead at an appropriate position in the vein to minimize the potential for lead migration ➢ Prevention of excessive lead bending and prevention of component failure ➢ Formation of the subcutaneous pocket for the IPG, and recognition that subpectoral placement may be necessary in patients with very little subcutaneous fat

	➢ The importance of limiting mobility of the ipsilateral arm and avoiding lifting the arm above shoulder level for several weeks after remedē System implantation to allow the IPG and leads to be securely fixed ➢ Importance of confirming procedural duration to prevent complications such as elevated transaminase ➢ Importance of conducting follow-up visits at the hospital at appropriate times • Explanation of the procedure to prevent infection and reduce pocket erosion ➢ Measures to minimize infection and pocket erosion ➢ Confirmation of the sterile field to prevent infection ➢ Importance of cauterization and suturing to prevent bleeding and haematoma formation ➢ Hygiene management of the incision site during healing
Requirements for completion	In the presence of a proctor, at least 5 cases of implantation

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

7.A Summary of the data submitted

Table 32 shows the outline of the planned post-marketing surveillance to assess the safety and efficacy of the remedē System in the post-marketing setting.

Table 32. Post-marketing surveillance plan (draft)

Period	Overall survey period	9 years from approval day
	Preparation period	1.5 years
	Registration period	5 years
	Observation period	2 years
	Analysis period	0.5 years
Target sample size		100 patients (all case survey)
Survey item		• Demographic characteristics: Sex, age, height, body weight, medical history (heart failure, atrial fibrillation, cerebrovascular disorder, prior treatment for CSA), concomitant implantable cardiac therapy device • Use status of the remedē System: Procedure date, successful/unsuccessful, procedure duration, IPG and lead model numbers, lead implantation site • PSG testing: AHI, CAI, 4%ODI • Patient subjective questionnaire (PGA)* • Cardiac function assessment (NYHA classification, LVEF) • Incidence of cardiovascular events • Malfunctions and adverse events

*, The same questionnaire on global assessment of health conditions implemented in the pivotal clinical study

The applicant provided the following explanation regarding the rationale for the sample size for the planned post-marketing surveillance:

Because no accumulated data exist for transvenous implantable phrenic nerve stimulators, including the remedē System, the applicant set the performance target based on the device-related adverse event-free rate of 70% used at the time of submission of an application for the CRT-D in the US, taking into account the similarity of the implant procedure and lead-related events.[42] In the pivotal clinical study, the serious adverse event-free rate in the overall population was 91.4%; however, because this will be the first survey of the remedē System conducted in Japan, the

estimated event-free rate was set at 85%. Using a one-sample exact binomial test, if the *P*-value is ≤0.025, it can be concluded that the rate would not be lower than the performance target of 70%. Under an estimated event-free rate of 85% and a statistical power of 90%, 86 patients are required. Taking into account dropouts, the target sample size was set at 100 patients, with all cases being included in the survey.

7.B Outline of the review conducted by PMDA

PMDA's view:

Although the efficacy and safety of the remedē System for the treatment of CSA can be evaluated by extrapolating the results of the pivotal clinical study, because there is no experience with the use of the remedē System in Japan, in addition to the need to evaluate its long-term safety and prognostic improvement, it is necessary to collect information through post-marketing surveillance and confirm whether risk management and responses to adverse events can be appropriately implemented in the Japanese medical setting. Furthermore, it is also important to confirm the efficacy and proper use of the remedē System, including patient selection, in the Japanese medical setting.

The sample size was set at 100 patients, which is sufficient to confirm the 8.6% incidence of device- or implant-procedure-related serious adverse events observed in the pivotal clinical study. Because the number of patients expected to use the remedē System at each medical institution is as low as approximately 3 to 4 patients, PMDA concluded that the applicant's plan to include all cases is reasonable.

Regarding the follow-up period, although the incidence of adverse events in the pivotal clinical study was high within 1 year of implantation, many patients requiring reoperation for lead explantation were reported within 2 years in both the pivotal clinical study and post-marketing settings. Therefore, PMDA judged that a 2-year follow-up period is appropriate.

Among the items established in the pivotal clinical study, in addition to the parameters used to assess the improvement in CSA symptoms (e.g., AHI, CAI, and 4%ODI), items related to cardiac function and cardiac events have also been included as the survey items. Therefore, PMDA concluded that the survey items are acceptable.

Based on the above, PMDA concluded that the applicant's post-marketing surveillance plan, including the survey items, is appropriate, and decided to impose it as Approval Condition 2.

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 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 appropriate precautionary information is included.

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

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

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

IV. Overall Evaluation

The review of the remedē System focused primarily on (1) product efficacy and safety and (2) post-marketing safety measures. Taking the issues raised at the Expert Discussion into account, PMDA reached the following conclusions:

(1) Efficacy and safety of the remedē System

The primary efficacy endpoint was the proportion of subjects achieving a ≥50% reduction in the AHI from baseline through 6 months after stimulation initiation. This proportion was 51.5% in the treatment group and 11.0% in the control group, demonstrating that stimulation with the remedē System has the clinical performance to reduce AHI in patients with CSA. In the secondary endpoints, improvements were observed in breathing-related measures, sleep quality indices, and QOL, while cardiac-function-related indices were either maintained or showed trends toward improvement.

The primary safety endpoint was freedom from serious adverse events associated with the implant procedure, the remedē System, or delivered therapy from implantation through 12 months after stimulation initiation (for the control group, 6 months of non-stimulation followed by 6 months of stimulation). Related adverse events occurred in 13 subjects (8.6%). In 7 of these subjects, explantation of the remedē System, or lead replacement/repositioning was required, and all subjects recovered. A causal relationship between the remedē System and all deaths was ruled out.

In both the HF subgroup and non-HF subgroup, similar results were obtained. Views on the significance of reducing AHI differ between the subgroups, including the status of recommendation in the Japanese clinical practice guidelines; however, based on the recommendation in overseas clinical practice guidelines and actual clinical practice in Japan, there is a need for reduction of AHI that may be addressed with the remedē System to some extent. However, the remedē System is highly invasive compared to conventional therapies. If infection or malfunction occurs, there is a risk that device explantation or retrieval will be required. Therefore, PMDA concluded that it is clinically meaningful to introduce the remedē System into Japan as a new treatment option for patients with CSA, provided that eligible patients are selected

by a physician with sufficient knowledge and experience after implementing risk minimization measures such as training.

(2) Post-marketing safety measures

In Japan, no implantable phrenic nerve stimulators intended for the treatment of CSA have been approved. When introducing the product in Japan, patients with CSA and impaired QOL who are eligible for the remedē System must be appropriately selected and safely treated by physicians and medical teams with sufficient knowledge and experience in CSA. Such physicians and medical teams should acquire the necessary knowledge and skills related to the device and implant procedure through appropriate training. To this end, compliance with the proper use guidelines developed by the relevant academic societies is essential. PMDA therefore concluded that such compliance should be imposed as Approval Condition 1.

In the post-marketing surveillance, the incidence of adverse events, appropriateness of patient selection, and the efficacy of the remedē System in clinical practice should be evaluated. It is considered important that additional risk minimization measures and the proper use guidelines are revised if necessary. The use-results survey period for the remedē System should be 9 years (marketing preparation, 1.5 years; registration, 5 years; follow-up, 2 years; analysis, 0.5 years), and PMDA concluded that this should be imposed as Approval Condition 2.

Based on the above, PMDA concluded that the remedē System may be approved for the intended use, modified as shown below, with the following approval conditions.

Intended Use

The remedē System is intended for the treatment of moderate to severe central sleep apnea in adult patients who are unsuitable for, or intolerant to, positive pressure ventilation or oxygen therapy. The device delivers transvenous phrenic nerve stimulation to induce diaphragmatic contraction and thereby assists respiration during sleep.

Approval Conditions

1. The applicant is required to take necessary measures, including dissemination of the proper-use guidelines developed in collaboration with relevant academic societies and provision of appropriate information. These measures are intended to ensure that the product is used in accordance with the approved indication by a physician with sufficient knowledge and experience in treating central sleep apnea, who has acquired the skills necessary to operate the product and has a thorough understanding of procedure-related complications. In addition, the product should be used at a medical institution capable of appropriately managing complications associated with treatment using the product.
2. The applicant is required to conduct post-marketing surveillance in all patients treated with the product until data from a certain number of patients have been accrued, to report the results of annual analyses on long-term outcomes to the Pharmaceutical and Medical Devices Agency, and to take any other appropriate measures as necessary.

The product is not classified as a biological product or a specified biological product. The product is designated as a medical device subject to a use-results survey. The use-results survey period should be 9 years.

PMDA has concluded that the present application should undergo deliberation by the Committee on Medical Devices and *In-vitro* Diagnostics.

Reference

[1] Schwartz AR, *et al.* Novel phrenic nerve stimulator treats Cheyne-Stokes respiration: polysomnographic insights. *J Clin Sleep Med.* 2020;16(5):817-820.

[2] American Academy of Sleep Medicine. *International Classification of Sleep Disorders.* 3rd ed. Darien, IL: American Academy of Sleep Medicine; 2014.

[3] The Japanese Respiratory Society. *Sleep Apnea Syndrome (SAS) Clinical Practice Guidelines 2020*. [in Japanese]. Nankodo. 2020.

[4] Regn DD, *et al*. Central Sleep Apnea in Adults: Diagnosis and Treatment. *Fed Pract.* 2023 Mar;40(3):78-86.

[5] Fudim, *et al*. Evaluation and Treatment of Central Sleep Apnea in Patients with Heart Failure. *Current Problems in Cardiology.* 2022;47:101364.

[6] Bramante CT, *et al*. Suitability of the pericardiophrenic veins for phrenic nerve stimulation: an anatomic study. *Neuromodulation.* 2011;14(4):337-341.

[7] Javaheri S. Central sleep apnea. *Clin Chest Med.* 2010;31(2):235-248.

[8] The Japanese Circulation Society, *et al*. *Guidelines for Diagnosis and Treatment of Acute and Chronic Heart Failure* (revised in 2017/updated in 2022) [in Japanese]. 2022.

[9] The Japanese Respiratory Society. *NPPV (Non-invasive positive pressure ventilation) Guidelines* (revised second ed.) [in Japanese]. Nankodo.2015.

[10] Aurora RN, *et al*. The treatment of central sleep apnea syndromes in adults: practice parameters with an evidence-based literature review and meta-analyses. *Sleep.* 2012;35(1):17-40.

[11] The Japanese Circulation Society, *et al*. *Guideline on Diagnosis and Treatment of Sleep Disordered Breathing in Cardiovascular Disease*. [in Japanese]. 2023.

[12] Takeishi R, Yoshihisa A, Hotsuki Y, *et al*. Temporal Trends in the Practice Pattern for Sleep-Disordered Breathing in Patients With Cardiovascular Diseases in Japan ― Insights From the Japanese Registry of All Cardiac and Vascular Diseases – Diagnosis Procedure Combination. *Circ J.* 2022; 86: 1428-1436.

[13] Khayat R, *et al*. Central sleep apnea is a predictor of cardiac readmission in hospitalized patients with systolic heart failure. *J Card Fail.* 2012;18(7):534-540.

[14] Brack T, *et al*. Daytime Cheyne-Stokes respiration in ambulatory patients with severe congestive heart failure is associated with increased mortality. *Chest.* 2007;132(5):1463-1471.

[15] Agrawal R, *et al*. Mortality Patterns Associated with Central Sleep Apnea among Veterans: A Large, Retrospective, Longitudinal Report. *Ann Am Thorac Soc.* 2023;20(3):450-455.

[16] Mann EA, *et al*. Study design considerations for sleep-disordered breathing devices. *J Clin Sleep Med.* 2020;16(3):441-449.

[17] Strollo PJ Jr, *et al*. Upper-airway stimulation for obstructive apnea. *N Engl J Med*. 2014;370:139-149.

[18] Bradley TD, *et al*. CANPAP Investigators. Continuous positive airway pressure for central sleep apnea and heart failure. *N Engl J Med.* 2005;353(19):2025-2033.

[19] Hastings PC, *et al*. Adaptive servo-ventilation in heart failure patients with sleep apnea: a real world study. *Int J Cardiol.* 2010;139(1):17-24.

[20] Kasai T, *et al*. Effect of flow-triggered adaptive servo-ventilation compared with continuous positive airway pressure in patients with chronic heart failure with coexisting obstructive sleep apnea and Cheyne-Stokes respiration. *Circ Heart Fail.* 2010;3(1):140-148.

[21] Arzt M, *et al*. Suppression of central sleep apnea by continuous positive airway pressure and transplant-free survival in heart failure: a post hoc analysis of the CANPAP trial. *Circulation.* 2007;115(25):3173-3180.

[22] Philippe C, *et al*. Compliance with and effectiveness of adaptive servo ventilation versus continuous positive airway pressure in the treatment of Cheyne-Stokes respiration in heart failure over a six month period. *Heart.* 2006;92(3):337-342.

[23] Arzt M, *et al*. Auto-servo ventilation in heart failure with sleep apnoea: a randomised controlled trial. *Eur Respir J.* 2013;42(5):1244-1254.

[24] Yoshihisa A, *et al*. Short-term use of adaptive servo ventilation improves renal function in heart failure patients with sleep-disordered breathing. *Heart Vessels.* 2013;28(6):728-734.

[25] Oldenburg O, *et al*. Nocturnal hypoxaemia is associated with increased mortality in stable heart failure patients. *Eur Heart J.* 2016;37(21):1695-1703.

[26] Costanzo MR, *et al*. Phrenic nerve stimulation to treat patients with central sleep apnoea and heart failure. *Eur J Heart Fail.* 2018;20(12):1746-1754.

[27] Patel S, *et al*. The Epworth Sleepiness Scale: Minimum Clinically Important Difference in Obstructive

Sleep Apnea. *Am J Respir Crit Care Med.* 2018;197(7):961-963.

[28] Hastings PC, *et al*. Symptom burden of sleep-disordered breathing in mild-to-moderate congestive heart failure patients. *Eur Respir J.* 2006;27(4):748-755.

[29] Voigt J, *et al*. Meta-Analysis Comparing Outcomes of Therapies for Patients With Central Sleep Apnea and Heart Failure With Reduced Ejection Fraction. *Am J Cardiol.* 2020;127:73-83.

[30] Rector TS, *et al*. Use of the living with heart failure questionnaire to ascertain patients' perspectives on improvement in quality of life versus risk of drug-induced death. *J Card Fail.* 1995;1(3):201–206.

[31] Han HC, *et al*. Epidemiology of cardiac implantable electronic device infections: incidence and risk factors. *Europace.* 2021 Jun 23;23(23 Suppl 4):iv3-iv10.

[32] van Rees JB, *et al*. Implantation-related complications of implantable cardioverter-defibrillators and cardiac resynchronization therapy devices: a systematic review of randomized clinical trials. *J Am Coll Cardiol.* 2011. Aug 30;58(10):995-1000.

[33] Kirkfeldt RE, *et al*. Complications after cardiac implantable electronic device implantations: an analysis of a complete, nationwide cohort in Denmark. *Eur Heart J.* 2014;35(18):1186-1194.

[34] Ezzat VA, *et al*. A systematic review of ICD complications in randomised controlled trials versus registries: is our 'real-world' data an underestimation? *Open Heart.* 2015;2(1):e000198.

[35] Bitter T, *et al*. Cheyne-Stokes respiration and obstructive sleep apnoea are independent risk factors for malignant ventricular arrhythmias requiring appropriate cardioverter-defibrillator therapies in patients with congestive heart failure. *Eur Heart J.* 2011;32(1):61-74.

[36] Efremidis M, Pappas L. Atrial fibrillation in heart failure patients. *Eur Cardiol* 2009;5:41-5.

[37] Cowie MR, *et al*. Adaptive Servo-Ventilation for Central Sleep Apnea in Systolic Heart Failure. *N Engl J Med.* 2015;373:1095-1105.

[38] Lyons OD, *et al*. Design of the effect of adaptive servo-ventilation on survival and cardiovascular hospital admissions in patients with heart failure and sleep apnoea: the ADVENT-HF trial. *Eur J Heart Fail.* 2017;19(5):579-587.

[39] Hamada S, *et al*. Good clinical response achieved by changing servo-ventilation devices in a patient with central sleep apnea: a case report. *J Clin Sleep Med.* 2023;19(8):1557-1561.

[40] Murashima R, *et al*. A case of middle-aged central sleep apnea due to Joubert syndrome with different treatment effects of oxygen and acetazolamide. *J Clin Sleep Med.* 2024 Oct 1;20(10):1705-1710.

[41] The Japanese Circulation Society, the Japanese Heart Failure Society. *Statement on appropriate use of ASV for heart failure* (second report) [in Japanese]. 2016.

[42] U.S. Food and Drug Administration (FDA). *Premarket Approval (PMA): Boston Scientific Cardiac Resynchronization Therapy Defibrillators (CRT-Ds)*. 2010. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P010012S230