October 3, 2022
Medical Device Evaluation Division
Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Report on the Deliberation Results

Classification	Instrument & Apparatus 7, Organ function replacement device
Term Name	Endobronchial valve (newly created)
Brand Name	Zephyr Endobronchial Valve System
Applicant	Pulmonx Corporation
Designated Marketing Authorization Holder	Prime Fine Co., Ltd.
Date of Application	December 16, 2021 (Application for marketing approval)

Results of Deliberation

In its meeting held on October 3, 2022, the Committee on Medical Devices and *In-vitro* Diagnostics reached the following conclusion, and decided that this conclusion should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

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

The use-results survey period should be 6 years. The product should be approved with the following conditions.

Approval Conditions

The applicant is required to:

1. Ensure that the product is used by physicians with adequate knowledge and experience in treating COPD who have competency to select eligible patients according to pathological condition, adequate procedural skills, and knowledge about complications, etc. associated with the procedure, and at medical institutions that have an established treatment system for the disease. For these purposes, the applicant is expected to disseminate the guidelines for proper use developed jointly with academic societies involved, provide learning opportunities, and take other necessary measures.
2. Ensure the proper use of the product by necessary measures such as the provision of the proper use guidelines developed by academic societies involved and learning opportunities for physicians.

3. Conduct a use-results survey in the post-marketing setting involving all Japanese patients treated with the product until obtaining data of a certain number of cases, report survey results to the Pharmaceuticals and Medical Devices Agency, and take appropriate measures as necessary.
4. Report the analysis results to the Pharmaceuticals and Medical Devices Agency on the long-term prognosis of the patients who participated in the clinical studies included in this submission, and take appropriate measures as necessary.

Review Report

September 7, 2022
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 7, Organ function replacement device
Term Name	Endobronchial valve (to be newly created)
Brand Name	Zephyr Endobronchial Valve System
Applicant	Pulmonx Corporation
Designated Marketing Authorization Holder	Prime Fine Co., Ltd.
Date of Application	December 16, 2021
Reviewing Office	Office of Medical Devices II

Review Results

September 7, 2022

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Applicant	Pulmonx Corporation
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Date of Application	December 16, 2021

Results of Review

Zephyr Endobronchial Valve System (hereinafter referred to as the Zephyr EBV System) is a bronchial valve intended for patients who are undergoing optimal non-invasive treatment for chronic obstructive pulmonary disease (COPD) accompanied by severe emphysema and hyperinflation in which there is little or no collateral ventilation from a neighboring lobe as determined by physiological measurement. The Zephyr EBV System is a one-way valve (hereinafter referred to as the "Valve") consisting of a self-expanding nitinol retainer and a silicon membrane. Multiple pieces of Valves are bronchoscopically placed in the bronchus feeding the target lobe of the lung using a special catheter (hereinafter referred to as the "Delivery Catheter"). The product occludes airflow into the hyperinflated lung lobe and removes the air trapped in it to reduce its volume.

The applicant submitted the non-clinical data including physiological and chemical properties, biological safety, stability and durability, performance, and the direction for use of the Zephyr EBV System. The submitted data showed no particular problem.

The applicant submitted clinical data from a multicenter, prospective, randomized, controlled study (the LIBERATE study) that was conducted in patients with heterogenous emphysema at 24 sites overseas to evaluate the safety and efficacy of bronchoscopic lung volume reduction (BLVR) with the Zephyr EBV System in comparison with the standard of care for COPD except for surgical therapy. The primary efficacy endpoint of the LIBERATE study was "the percentage of subjects with a ≥15% improvement in the forced expiratory volume in 1 second (FEV1) at 1 year after the procedure." The result was 47.7% (success, 57 subjects; failure, 58 subjects; data missing, 13 subjects) in the Zephyr EBV group and 16.8% (success, 10 subjects; failure, 49 subjects; data missing, 5 subjects) in the control group undergoing standard of care, showing the superiority of the Zephyr EBV System. The IMPACT study, a multicenter, prospective, randomized, controlled study in patients with severe COPD with homogenous emphysema, had yielded results that supplemented the outcome of the LIBERATE study.

In Japan, the treatment of COPD comprehensively involves antismoking education, drug therapy, respiratory rehabilitation, oxygen therapy, ventilatory support, and medical management of systemic complications. Lung volume reduction surgery (LVRS) is the option to be considered for inadequate responder to maximum medical therapies or patients with dyspnoea that significantly affects their daily living. LVRS is, however, a highly invasive surgery. The Zephyr EBV System enables endoscopic lung volume reduction and is a promising treatment option to be considered after non-surgical therapies and before LVRS for whom LVRS has been conventionally selected. Because LVRS is challenging in some patients, it is of clinical significance to introduce the Zephyr EBV System, whose efficacy and safety have been demonstrated in the LIBERATE and IMPACT studies, in Japan.

To ensure that the Zephyr EBV System is used properly, appropriate patient selection and management of adverse events occurring post-valve placement are essential, and the novelty of the procedure using the Zephyr EBV System and its suitability for the medical environment in Japan need to be fully taken into consideration. For these reasons, a use-results survey should be conducted after approval to evaluate the efficacy and safety of the Zephyr EBV System in clinical use.

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

Intended Use

The Zephyr EBV System is a one-way valve that is placed in the bronchus to occlude airflow into the target lung lobe. The Zephyr EBV System is intended for patients aged 18 years or older who are on optimal non-invasive treatment for COPD associated with severe emphysema and hyperinflation with little or no collateral ventilation from a neighboring lobe as determined by physiological measures and are eligible for bronchoscopic treatment.

Approval Conditions

The applicant is required to:

1. Ensure that the product is used by physicians with adequate knowledge and experience in treating COPD who have competency to select eligible patients according to pathological condition, adequate procedural skills, and knowledge about complications, etc. associated with the procedure, and at medical institutions that have an established treatment system for the disease. For these purposes, the applicant is expected to disseminate the guidelines for proper use developed jointly with academic societies involved, provide learning opportunities, and take other necessary measures.
2. Ensure the proper use of the product by necessary measures such as the provision of the proper use guidelines developed by academic societies involved and learning opportunities for physicians.
3. Conduct a use-results survey in the post-marketing setting involving all Japanese patients treated with the product until obtaining data of a certain number of cases, report survey results to the Pharmaceuticals and Medical Devices Agency, and take appropriate measures as necessary.
4. Report the analysis results to the Pharmaceuticals and Medical Devices Agency on the long-term prognosis of the patients who participated in the clinical studies included in this submission, and take appropriate measures as necessary.

Review Report

September 7, 2022

Product for Review

Classification	Instrument & Apparatus 7, Organ function replacement device
Term Name	Endobronchial valve (to be newly created)
Brand Name	Zephyr Endobronchial Valve System
Applicant	Pulmonx Corporation
Designated Marketing Authorization Holder	Prime Fine Co., Ltd.
Date of Application	December 16, 2021
Proposed Intended Use	The Zephyr EBV System is intended for bronchoscopic treatment of patients aged 18 years or older who have received optimal non-invasive treatment for hyperinflation associated with severe emphysema in a lung region that have little or no collateral ventilation as measured with a special device.

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List of Abbreviations

BLVR	Bronchoscopic Lung Volume Reduction
COPD	Chronic Obstructive Pulmonary Disease
FEV1	Forced Expiratory Volume in 1 second
GOLD	Global Initiative for Chronic Obstructive Lung Disease
LVRS	Lung Volume Reduction Surgery
mMRC	Modified Medical Research Council
RV	Residual Volume
SGRQ	St. George's Respiratory Questionnaire
TLC	Total Lung Capacity

I. Product Overview

The “Zephyr Endobronchial Valve System” (hereinafter referred to as the “Zephyr EBV System”) is a one-way valve (hereinafter referred to as the “Valve”) consisting of a self-expanding nitinol retainer and a silicon membrane. The Valves are placed bronchoscopically in the bronchus using a special catheter (hereinafter referred to as the “Delivery Catheter”) (Figure 1 to Figure 3). The Valve is stored inside the EL System (ELS), which is loaded in the Delivery Catheter prior to the bronchoscopic procedure. The following 4 different variations of the Valve are available: 2 different sizes according to the inner diameter of the target bronchus and 2 different lengths of the “retainer seal,” which adheres tightly to the bronchus (product numbers; “4.0,” “4.0 LP,” “5.5,” and “5.5 LP,” respectively) (Table 1).

The Zephyr EBV System is intended for patients with severe emphysema, a form of chronic obstructive pulmonary disease (COPD), accompanied by hyperinflation with little or no documented collateral ventilation from a neighboring lobe. This device occludes airflow into a target hyperinflated lung lobe and removes the air trapped to reduce the volume of the lobe, thereby allowing the neighboring ipsilateral lobe to expand.

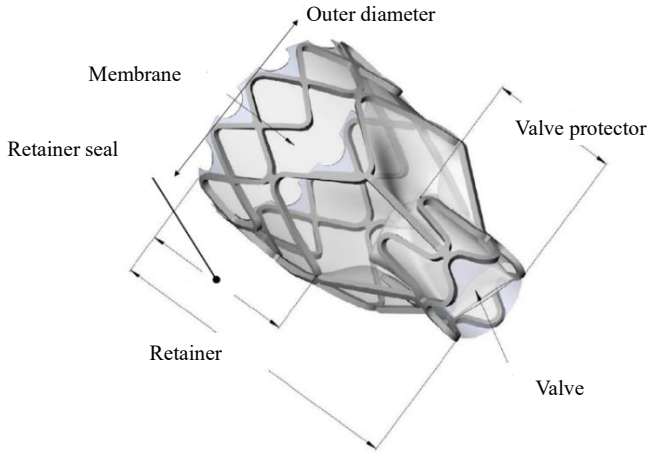

Figure 1. Implantable valve

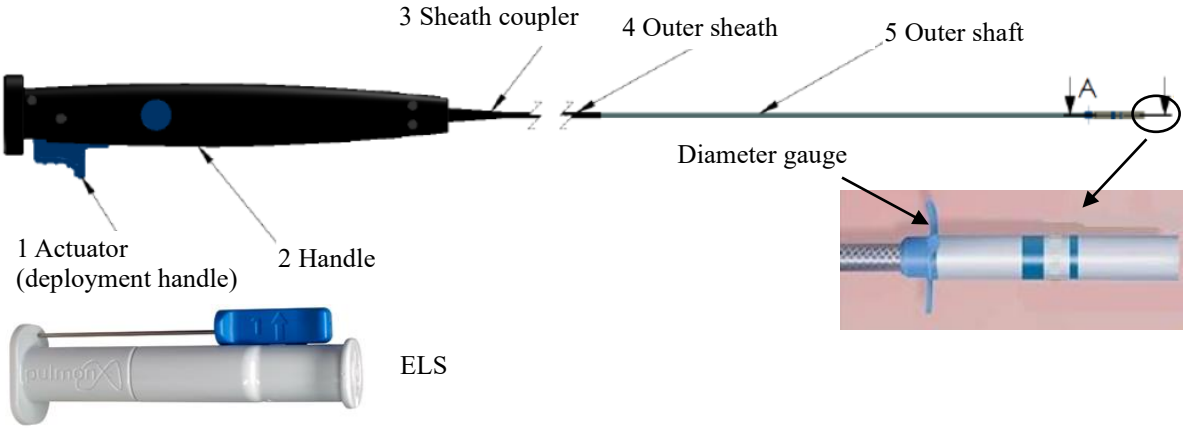

Figure 2. Magnified views of ELS, special Delivery Catheter, and its tip

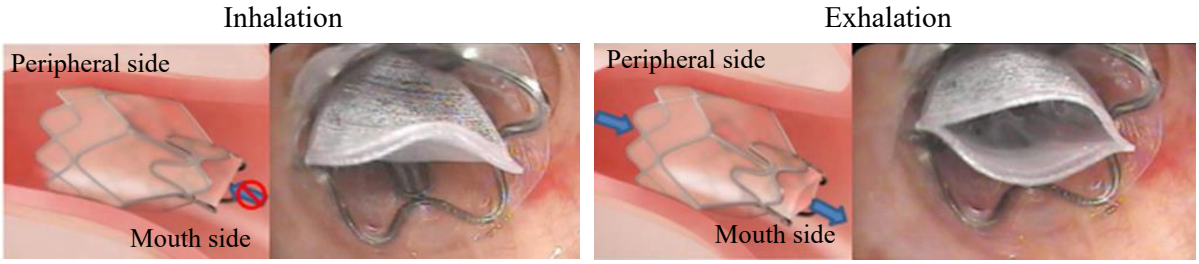

Figure 3. Valve appearance during inhalation and exhalation

Table 1. Product variation

Product number	Intended inner diameter of bronchus	Outer diameter	Length of retainer seal	Length of retainer
4.0	4.0-7.0 mm	8.05 [redacted] mm	6.85 [redacted] mm	11.60 [redacted] mm
4.0 LP		8.00 [redacted] mm	5.15 [redacted] mm	9.82 [redacted] mm
5.5	5.5-8.5 mm	9.67 [redacted] mm	8.02 [redacted] mm	13.25 [redacted] mm
5.5 LP		9.67 [redacted] mm	5.84 [redacted] mm	10.99 [redacted] mm

(Standard value ± tolerance)

The Zephyr EBV System is used on a lobe-by-lobe basis. The severity of emphysema is assessed based on CT images taken beforehand. The presence of collateral ventilation is checked using "Chartis Pulmonary Assessment System (catheter)" (submitted at the same timing as the Zephyr EBV System, Reception No. [redacted]) and "Chartis Pulmonary Assessment System (console) (submitted at the same timing as the Zephyr EBV System, Reception No. [redacted]) (the combination of the 2 products are referred to as "Chartis System"), which are intended to be used immediately before the valve placement, to determine the target lobe.

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

The data submitted in this application and the applicant's responses to the inquiries from the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined below.

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

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

1.A Summary of the data submitted

1.A.(1) History of development

Both in Japan and overseas, COPD is treated comprehensively involving antismoking education, drug therapy, respiratory rehabilitation, oxygen therapy, ventilatory support, and medical management of systemic complications. Lung volume reduction surgery (LVRS) is the option to be considered for patients with inadequate response to therapy or patients with dyspnoea that significantly affects their daily lives despite maximum medical therapies. LVRS is, however, a highly invasive surgery. The NETT study,[1] a large-scale, randomized, controlled study designed to evaluate the therapeutic effect of LVRS, was reported in 2003. The study demonstrated the clinical effect of LVRS in patients who had upper-lobe predominant emphysema with low exercise capacity, while revealing poorer prognosis after LVRS in patients who had non-upper-lobe predominant emphysema and high exercise capacity. The study

showed that a preoperative forced expiratory volume in 1 second[i] (FEV1) of ≤20% was associated with a high postoperative mortality, and the Japanese guidelines warn not to perform LVRS in those patients.[2] LVRS led to air leaks in 90% of the subjects within 30 days after surgery (median, 7 days), raising safety concerns, and resulted in a mortality of 5% and an incidence of non-fatal complications of 60% at 90 days after surgery.[3] For being highly invasive, LVRS has been rarely performed after the NETT study. The Japanese guidelines also restrict LVRS to extremely limited cases.

The Zephyr EBV System enables lung volume reduction endoscopically in patients with severe emphysema, thus is a promising treatment option to be performed following non-surgical therapies (before LVRS) for patients for whom LVRS is conventionally the only option. The Zephyr EBV System has been developed targeting patients with severe emphysema suffering from disabling symptoms despite maximum non-surgical therapies.

The product development began with Zephyr 4.0 and 5.5 ([redacted]), followed by Zephyr 4.0 LP and 5.5 LP ([redacted]) that increased design options. Furthermore, to improve the efficiency of the manufacturing process of the Valves, Zephyr 5.5 ([redacted]) and 5.5 LP ([redacted]) were designed with different [redacted]. The clinical studies of the Zephyr EBV System employed Zephyr 4.0 ([redacted]), Zephyr 4.0 LP ([redacted]), and Zephyr 5.5 ([redacted]).

Table 2 shows the major clinical studies of the Zephyr EBV System.

Table 2. Summary of the clinical studies of the Zephyr EBV System

	VENT study	LIBERATE study	IMPACT study
Study period	2004 to 2006	2013 to 2017	2014 to 2017
Sample size	321	190	93
Study population	Heterogenous emphysema	Heterogenous emphysema	Homogenous emphysema
Collateral ventilation	Not confirmed yet	No	No

The VENT study was conducted to evaluate the safety and efficacy of the procedure utilizing the Zephyr EBV System in subjects with heterogenous emphysema. Subjects with or without collateral ventilation were enrolled in the study. Based on the results of a post hoc analysis of the VENT study, the integrity of the interlobar fissure was visually assessed, and clinically significant improvement in the lung functions was shown in patients with emphysema who had achieved lobar occlusion with the Zephyr EBV System. The subsequent Chartis study showed that valve placement was highly likely to lead to a good prognosis in patients with little or no collateral ventilation as determined using the Chartis System.[4] On the basis of the findings from these studies, the IMPACT study and the LIBERATE study were conducted in patients with little or no collateral ventilation as determined using the Chartis System to evaluate the efficacy and safety of the Zephyr EBV System.

1.A.(2) Use in foreign countries

The Zephyr EBV System obtained the CE mark in Europe in September 2003 and PMA clearance in the US in June 2018. Table 3 shows the intended use and sales figures overseas.

[i] The volume of air exhaled in the first second during forced exhalation after deep inspiration

Table 3. Intended use and sales figures overseas (as of the end of September 2021)

	Intended use	Sales figures (number of valves)
Europe	The Zephyr EBV is an implantable bronchial valve intended to control airflow in order to improve lung function in patients with hyperinflation associated with severe emphysema with little to no collateral ventilation, and/or to reduce air leaks.	[redacted]
US	The Pulmonx Zephyr Endobronchial Valves (EBV) are implantable bronchial valves intended to occlude all airways feeding the target lobe of the lung and thereby decrease lung volume in that lobe. It is indicated for the treatment of patients with hyperinflation associated with severe emphysema in regions of the lung that have little or no collateral ventilation.	[redacted]

1.A.(3) Malfunctions and adverse events reported overseas

Table 4 shows malfunctions and adverse events of the Zephyr EBV System reported overseas as of September 2021.

Table 4. Malfunctions and adverse events reported overseas

Event	Number of cases reported	Incidence (%)*
Pneumothorax	[redacted]	0.64
Diameter gauge coming off from Delivery Catheter	[redacted]	0.07
Non-pneumothorax-related death after pneumothorax	[redacted]	0.05
Death	[redacted]	0.01
Valve removal	[redacted]	0.01
Damage of Delivery Catheter housing	[redacted]	0.01
Pleural effusion	[redacted]	0.005
Infection, COPD exacerbation	[redacted]	0.002
Hyperventilation, death	[redacted]	0.002
Hypoxia	[redacted]	0.002
Pneumonia	[redacted]	0.002
Pneumonia, valve removal	[redacted]	0.002
Abscess, pneumonia	[redacted]	0.002
Abscess, pneumothorax	[redacted]	0.002
Abscess, infection, death	[redacted]	0.002
Haemoptysis	[redacted]	0.002
Haemoptysis, granulation	[redacted]	0.002
Decreased cardiac output	[redacted]	0.002
Non-fatal respiratory failure	[redacted]	0.002
Valve migration	[redacted]	0.002
Valve clogging with mucus, endobronchoscopy, respiratory disorder	[redacted]	0.002

* Calculated using the sales figures of [redacted] as parameter.

1.B Outline of the review conducted by PMDA

The submitted data including the incidences of malfunctions/adverse events are reviewed later in Section 6.

2. Specifications

2.(1) Performance and safety specifications

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

The proposed performance and safety specifications for the Zephyr EBV System include flow rate, valve function, implantation stability, cracking pressure, durability, radial expansion force, EDC compatibility, ELS loading ability, corrosion resistance, drug compatibility, removal performance, joint strength, diameter gauge durability, biological safety, bacterial endotoxins, MRI compatibility, and residual ethylene oxide. The applicant submitted the data of the above tests.

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

PMDA reviewed the justification of the proposed performance and safety specifications, including the tests and their specification limits as well as the test data, and concluded that there were no particular problems.

2.(2) Safety specifications

2.(2).1) Physicochemical properties

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

The applicant submitted the results of corrosion resistance and drug compatibility as the data of the proposed physiochemical properties of the Zephyr EBV System. The results showed that the Zephyr EBV System met the acceptance criteria for both specifications, verifying the performance of the Zephyr EBV System.

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

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

2.(2).2) Biological safety

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

For the proposed biological safety of the Valve of the Zephyr EBV System, the applicant submitted the results of the tests required for implantable medical devices that come into prolonged contact with tissue (≥30 days), including cytotoxicity, sensitization, intracutaneous reactivity, systemic toxicity, implantation, genotoxicity, and pyrogenicity tests. None of these tests revealed findings of concern.

For the biological safety of the Delivery Catheter, the applicant submitted the results of the tests required for surface-contacting devices that come into contact with mucus transiently (≤24 hours), including cytotoxicity, sensitization, intracutaneous reactivity, and pyrogenicity. None of these tests revealed findings of concern.

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

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

2.(2).3) Stability and durability

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

The applicant submitted the test results of the cycle fatigue of the retainer as the data on the durability of the Valve. The applicant submitted the test results of the durability of the diameter gauge as data on the proposed durability of the Delivery Catheter. The results showed that the Valve and Delivery Catheter met the acceptance criteria, verifying the durability of the Zephyr EBV System.

The Zephyr EBV System requires no special storage condition. The product quality was retained over time in the stability studies, with ≥3-year long post-sterilization stability demonstrated. Therefore,

stability data pertaining to the determination of shelf life were omitted according to the "Handling of stability studies related to the determination of the shelf life in the application for marketing approval (certification) of medical devices" (PFSB/ELD/OMDE Notification No. 1227-5, dated December 27, 2012). The applicant submitted a self-declaration to the effect that the shelf life of the Zephyr EBV System had been determined based on the required stability evaluation.

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

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

2.(3) Performance

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

The applicant submitted the test results of flow rate, valve function, implantation stability, cracking pressure, radial expansion force, EDC compatibility, ELS loading ability, and removal performance as data on the proposed performance of the Valve of the Zephyr EBV System. The applicant submitted the test results of joint strength as data on the proposed performance of the Delivery Catheter. The results showed that the Valve and Delivery Catheter met the acceptance criteria, demonstrating the performance of the Zephyr EBV System.

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

PMDA reviewed the data on the performance of the Zephyr EBV System and concluded that there were no particular problems.

2.(4) Directions for use

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

The applicant submitted the test results of MRI compatibility under the condition of 1.5T and 3T as data on the proposed directions for use of the Valve. The applicant also submitted the results of a test in which the Valve was used in animals to evaluate the usability of [redacted] of the Zephyr EBV System.

Using the Delivery Catheter, [redacted] pieces of Valves ([redacted], [redacted] pieces; [redacted], [redacted] pieces) were placed in [redacted] for 30 days to evaluate [redacted] of the Zephyr EBV System. No particular problem was identified in [redacted]. The target bronchus was successfully occluded, showing the efficacy of the Zephyr EBV System. A total of [redacted] Valves migrated from the implantation sites and were lost.

The applicant submitted the results of a test in which the Valve was used in animals to evaluate the usability of [redacted] of the Zephyr EBV System. Using the Delivery Catheter, [redacted] pieces of Valves per [redacted] ([redacted], [redacted] pieces; [redacted], [redacted] pieces) were placed in [redacted] for 30 days to evaluate [redacted] associated with the use of the Zephyr EBV System. No particular problem was identified in [redacted]. The target bronchus was successfully occluded, showing

the efficacy of the Zephyr EBV System. A total of [redacted] Valves migrated from the implantation sites and were lost.

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

The applicant's explanation about the causes of valve migration in the animal studies:

In the animal study on [redacted], the bronchial diameters were re-measured at the sites where the Valves were placed and lost, and shown to be larger than the recommended sizes for the devices. The change in bronchial diameter was most likely because of the growth of [redacted] during the test period. It is, therefore, not a concern in clinical practice. In the animal study on [redacted], [redacted] was used so that the change in bronchial diameter during the test period as seen in the animal study on [redacted] would not cause valve migration. This, however, increased the distance to the target bronchus even more, which made it difficult to measure the bronchial diameter. In addition, the bronchoscope itself might have stimulated the bronchus, causing possible bronchial contractions during the measurement of the bronchial diameter. In clinical use, the administration of a bronchodilator before the procedure will help reduce bronchial contractions.

PMDA's view:

This animal study confirmed the possibility of bronchial occlusion by valve placement. Change in bronchial diameter, which is expected to occur in [redacted] used in the animal studies, and the valve placement procedure used in the animal studies, which is different from that in clinical use, was considered to have contributed to the valve migration in the animal studies. A non-clinical study confirmed the implantation stability, without valve migration, during simulated coughing and maximum inhalation. Nevertheless, potential valve migration should also be investigated based on the results of the clinical studies later described.

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

3.A Summary of the data submitted

The applicant submitted a declaration of conformity declaring that the Zephyr EBV 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 Ministerial Announcement No. 122, 2005).

3.B Outline of the review conducted by PMDA

PMDA reviewed the conformity of the Zephyr EBV System to the Essential Principles.

1) PMDA's view on the conformity to Article 1, which specifies preconditions, etc. for designing medical devices, (particularly the requirements for users including the levels of technical knowledge and experience expected and the levels of education and training to be provided):

   As described later in Section "6.B. Outline of the review conducted by PMDA" and Section "7.B. Outline of the review conducted by PMDA," the selection of eligible patients, users, and medical institutions, user training, and adherence to the guidelines for proper use are important to keep the

risk-benefit balance of the Zephyr EBV System. To this end, approval conditions 1 and 2 need to be attached to seek necessary measures.

2) PMDA's view on the conformity to Article 2, which specifies requirements for risk management throughout the product life cycle of medical devices:
As described later in Section "6.B. Outline of the review conducted by PMDA" and Section "7.B. Outline of the review conducted by PMDA," there are no clinical efficacy or safety data of the Zephyr EBV System in Japan. The efficacy and safety of the Zephyr EBV System need to be evaluated in clinical use in Japan. PMDA instructed the applicant to conduct a user-results survey.

3) PMDA's view on the conformity to Article 3, which specifies requirements for the performance and functions of medical devices, and Article 6, which specifies the efficacy of medical devices:
As described in Section 2.(3), PMDA verified the performance of the Zephyr EBV System. As described later in Section "6.B. Outline of the review conducted by PMDA" and Section "7.B. Outline of the review conducted by PMDA," the clinical studies showed a satisfactory outcome of the Zephyr EBV System and demonstrated that appropriate selection of eligible patients would ensure the efficacy and safety of the Zephyr EBV System. The Zephyr EBV System conforms to Articles 3 and 6.

4) PMDA's view on the conformity to Article 4, which specifies the shelf life or durable life of medical devices:
As described in Section 2.(2).3), the applicant submitted a self-declaration stating that the shelf life of the Zephyr EBV System was determined based on the results of necessary stability studies according to the "Handling of stability studies related to the determination of the shelf life in the application for marketing approval (certification) of medical devices" (PFSB/ELD/OMDE Notification No. 1227-5, dated December 27, 2012). The Zephyr EBV System conforms to Article 4.

5) PMDA's view on the conformity to Article 7, which specifies requirements for the chemical properties, biological safety, etc. of medical devices:
As described in Sections 2.(2).1) and 2.(2).2), the biological safety, etc. of the Zephyr EBV System was verified. The Zephyr EBV System conforms to Article 7.

6) PMDA's view on the conformity to Article 8, which specifies anti-microorganism contamination measures for medical devices:
As described later in Section "5.B Outline of the review conducted by PMDA," the anti-microorganism contamination measures for the Zephyr EBV System were verified. The Zephyr EBV System conforms to Article 8.

7) PMDA's view on the conformity to Article 17, which specifies requirements for information provision to users through publicized Information on Precautions, etc. or the instructions for use (Information on Precautions, etc.):
As described later in Section "6.B. Outline of the review conducted by PMDA" and Section "7.B.

Outline of the review conducted by PMDA," it is essential for users to fully understand the risk of the Zephyr EBV System, select patients eligible for the treatment with the Zephyr EBV System, and use the Zephyr EBV System properly so as to maintain its risk-benefit balance. To this end, the Information on Precautions, etc., the guidelines for proper use, and training, etc. should be utilized for information provision. PMDA instructed the applicant to provide cautionary advice in the instructions for use to the effect that the Zephyr EBV System must be used according to the guidelines for proper use that define criteria for eligible patients, users, medical institutions, training, etc.

PMDA reviewed the conformity of the Zephyr EBV System to the Essential Principles and concluded that there were no particular problems.

4. Risk Management

4.A Summary of the data submitted

The applicant submitted data summarizing the risk management system and risk management activities implemented for the Zephyr EBV System in accordance with ISO 14971:2019 "Medical devices – Application of risk management to medical devices."

4.B Outline of the review conducted by PMDA

PMDA reviewed the document on risk management taking into account the discussion presented 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 method (condition for sterility assurance level and ethylene oxide sterilization residuals) of the Zephyr EBV System.

5.B Outline of the review conducted by PMDA

PMDA reviewed the data on the manufacturing process of the Zephyr EBV System 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 of the LIBERATE study and the IMPACT study, which are multicenter, prospective, randomized, controlled studies to evaluate the efficacy and safety of the Zephyr EBV System as reference data.

6.A.(1) LIBERATE study (study period, June 6, 2013 to November 16, 2017)

6.A.(1).1) Methodology

Table 5 outlines the LIBERATE study, a multicenter, prospective, randomized, controlled clinical study conducted in patients with heterogenous emphysema at 18 sites in the US, 3 sites in the UK, 1 site in the Netherlands, and 2 sites in Brazil, to evaluate the safety and efficacy of bronchoscopic lung volume

reduction (BLVR) with the Zephyr EBV System in comparison with the standard of care (190 patients enrolled).

Table 5. Outline of the LIBERATE study

Item	Outline
Study type	Multicenter, prospective, randomized, controlled, one-way crossover study
Population	Patients with severe heterogenous emphysema (>50% destruction score of the target lobe and ≥15-point difference in destruction scores between the target and ipsilateral lobes)
Major inclusion criteria	Screening visit 1. Age, 40 to 75 years 2. BMI, <35 kg/m^2 3. Stable with prednisone <20 mg (or equivalent) daily 4. Nonsmoking for 4 months prior to screening interview Baseline visit 5. Completed pulmonary rehabilitation program within 6 months prior to baseline examination, or undergone the initial pulmonary rehabilitation program earlier than 6 months prior to baseline examination and receiving periodic respiratory rehabilitation as maintenance therapy 6. Baseline assessment within 120 days after screening examination 7. Continued non-smoking state since the first screening visit until baseline examination 8. FEV1 at baseline examination, 15% to 45% of predicted value 9. Post-rehabilitation 6MWD at baseline examination, 100 to 500 meters Eligibility for the procedure 10. Completed the procedure no later than 60 days after baseline examination 11. Little to no collateral ventilation as determined using the Chartis System
Major exclusion criteria	Screening visit 1. Clinically significant (>4 tablespoons per day) sputum production 2. ≥2 episodes of COPD exacerbation requiring hospitalization in 1 year before screening 3. ≥2 episodes of pneumonia in 1 year before screening 4. Unexpected weight loss of >10% of the standard weight within 90 days before enrollment 5. A history of exercise-related syncope 6. Myocardial infarction or congestive heart failure within 6 months before screening 7. Prior lung transplant, LVRS, bullectomy, or lobectomy 8. Clinically significant bronchiectasis 9. Unable to safely discontinue anti-coagulants or platelet activity inhibitors for 7 days 10. Uncontrolled pulmonary hypertension (systolic pulmonary arterial pressure, >45 mmHg) or evidence or a history of cor pulmonale as determined by recent echocardiogram (completed within the last 3 months before screening visit) 11. Pulmonary nodule requiring surgery as noted by chest X-ray or CT scan 12. Images of high-resolution computed tomography (HRCT) collected per CT scanning protocol within the last 3 months before screening date and evaluated by clinical site personnel using 510k-cleared CT software shows: a. Parenchymal destruction score, ≥75% in all 3 right lobes or 2 left lobes b. Difference in emphysema heterogeneity score, <15 points c. Large bullae encompassing >30% of either lung d. Insufficient landmarks to evaluate the CT study using the software as intended 13. Left ventricular ejection fraction (LVEF) as determined by recent echocardiogram, <45% (completed within the last 3 months before screening visit) 14. Resting bradycardia (<50 beats/min), frequent multifocal PVCs, complex ventricular arrhythmia, sustained SVT 15. Arrhythmia that may pose a risk during exercise or training 16. Post-bronchodilator FEV1 at screening, <15% or >45% of predicted value 17. TLC at screening, <100% of predicted value (determined by body plethysmography) 18. RV at screening, <175% of predicted value (determined by body plethysmography) 19. DLCO at screening, <20% of predicted value 20. 6MWD at screening, <100 meters or >450 meters 21. $PaCO_2$ on room air at screening, >50 mmHg 22. PaO_2 on room air at screening, <45 mmHg 23. Elevated white blood cell count at screening (>10,000 cells/μL) 24. Confirmed α1-antitrypsin deficiency as determined using the normal institutional range 25. Plasma cotinine level at screening, >13.7 ng/mL (or arterial carboxyhemoglobin, >2.5% if using nicotine products) Baseline visit 26. Myocardial infarction or congestive heart failure between screening examination and baseline examination 27. Other clinical evidence of pyrexia or active infection at baseline examination 28. ≥2 episodes of COPD exacerbation between screening examination and baseline examination

Item	Outline
	29. ≥2 episodes of pneumonia between screening examination and baseline examination Eligibility for the procedure 30. Evidence of collateral ventilation as determined using the Chartis System 31. Failure to determine collateral ventilation using the Chartis System 32. No assessment of collateral ventilation using the Chartis System
Enrolled sample size	190 patients (128 in the Zephyr EBV group, 62 in the control group)
Follow-up period	12 months (follow-up, 5 years)
Primary endpoint	Percentage of subjects meeting the threshold of ≥15% improvement in FEV1 at 1 year
Secondary endpoints	(1) Absolute change from baseline in FEV1 at 1 year (2) Absolute change from baseline in 6MWD at 1 year (3) Absolute change from baseline in St. George's Respiratory Questionnaire (SGRQ) score at 1 year

The primary endpoint was the "percentage of subjects who meet the threshold of ≥15% improvement in FEV1 at 1 year" as an outcome indicator to verify lung function improvement. The "threshold of ≥15% improvement in FEV1" was specified based on the minimally clinically important difference (MCID[5]) in FEV1 in clinical practice. The secondary endpoints were the "absolute change from baseline in FEV1 at 1 year," "absolute change from baseline in 6-minute walk distance at 1 year," and "absolute change from baseline in St. George's Respiratory Questionnaire (SGRQ) score at 1 year." The safety endpoint was the evaluation of adverse events during the treatment period (up to 45 days after the procedure) and long-term period (from 46 days after the procedure through follow-up visit at 1 year).

The sample size was determined based on the results of the preceding VENT study. The responder rate (percentage of subjects with ≥15% improvement in FEV1) at 1 year was estimated to be approximately 35% in the Zephyr EBV group and <10% in the control group. Assuming a two-sided significance level of 0.05, power of 90%, and a randomization ratio of 2:1, 147 subjects would be needed to verify the superiority of the Zephyr EBV to the control treatment. To allow for a dropout of 20%, the sample size would be 183. The enrollment sample size of 190 was determined.

The primary and secondary endpoints were analyzed in the Intent-to-Treat (ITT) population. The safety analysis was based on the ITT population and the As-Treated (AT) population consisting of all subjects who received either treatment (Figure 4). Following a 12-month follow-up, the subjects in the control group had an option to cross over to Zephyr EBV treatment, if eligible, to receive further follow-up for 5 more years.

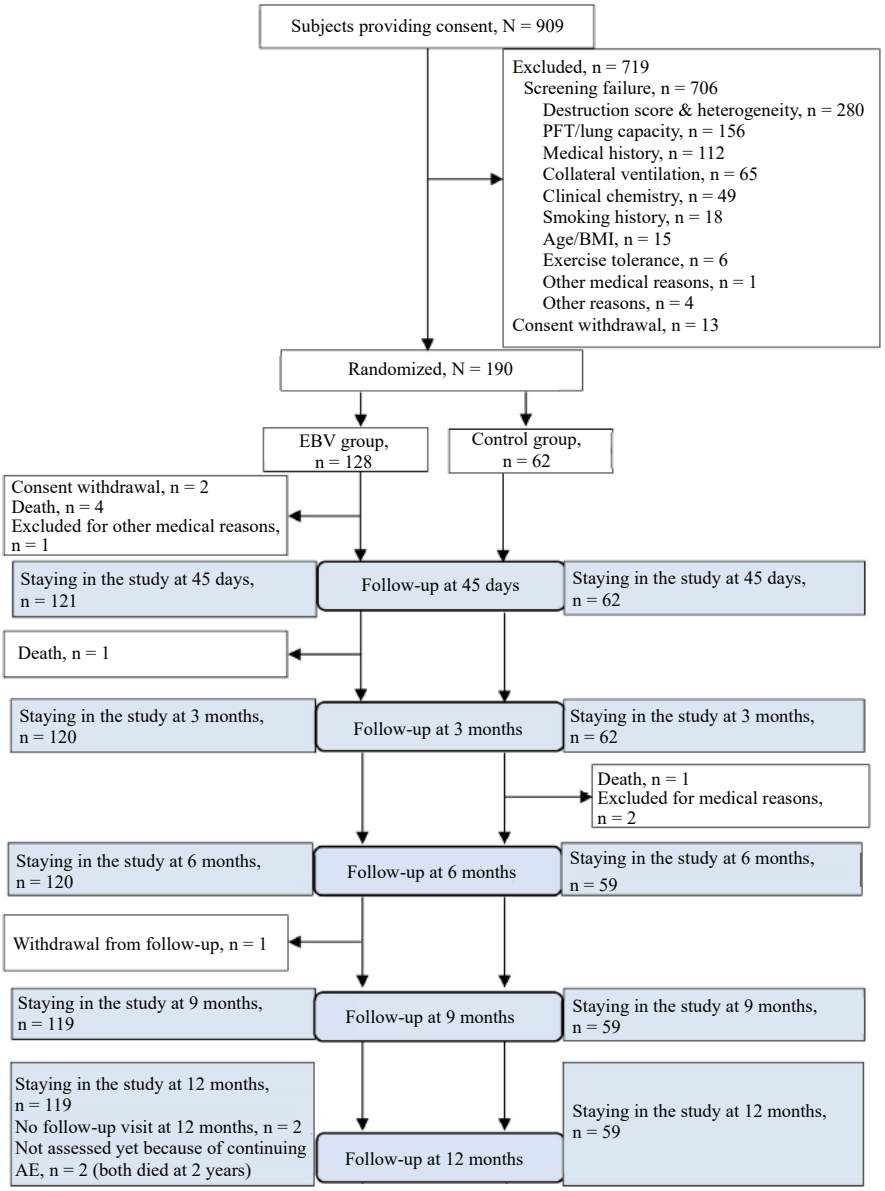

Figure 4. Flowchart of subject enrolment in the LIBERATE study

6.A.(1).2) Patient characteristics

Table 6 shows the patient characteristics in the LIBERATE study.

Table 6. Patient characteristics

	Zephyr EBV (n = 128)	Control (n = 62)
Age	64.0 ± 6.85	62.5 ± 7.12
Smoking history (pack/year)	50.78	48.59
Sex (male/female)	56 males, 72 females (44%/56%)	33 males, 29 females (53%/47%)
%FEV1 (%) (post-bronchodilator)	28.0 ± 7.45	26.2 ± 6.28
FEV1 (L)	0.763 ± 0.252	0.752 ± 0.217
FEV1/FVC	0.302 ± 0.063	0.294 ± 0.063
%TLC (%)	133.5 ± 21.17	130.2 ± 12.44
%RV (%)	224.5 ± 42.45	224.6 ± 38.86
GOLD stage	III: 54 (42.2%) IV: 74 (57.8%)	III: 16 (25.8%) IV: 46 (74.2%)
6MWD (m)	311.33 ± 81.33	301.91 ± 78.54

The data are expressed in mean ± standard deviation (SD). The same applies in the following tables.

Target lobes were selected at each study site from diseased lobes based on a >50% destruction score (voxel index, <-910 CT Hounsfield Unit) and a ≥15-point difference in destruction scores between the target and ipsilateral lobes. In subjects with >1 target lobe, the most diseased lobe with a highest destruction score was considered first for valve placement. Subjects in whom all target lobes had collateral ventilation were excluded from the study. Table 7 shows the details of the lobes treated in the study. The average number of the Valves placed per subject was 3.9 (median, 4).

Table 7. Lobes treated in the study

	Zephyr EBV (n = 128)
Left lower lobe (LLL)	15 (11.7%)
Left upper lobe (LUL)	85 (66.4%)
Right lower lobe (RLL)	6 (4.7%)
Right upper lobe (RUL)	14 (10.9%)
Right upper lobe + right middle lobe (RUL + RML)	8 (6.3%)

Table 8 shows the details of the therapeutic procedure. The time required for the procedure using the Chartis system was defined as the time from the insertion of the Chartis system into the body to its removal. It was 19.0 ± 16.52 minutes in the Zephyr EBV group and 19.5 ± 13.58 minutes in the control group.

The mean time required for valve placement was 34.8 ± 24.27 minutes (median, 28.5) in the Zephyr EBV group. The time required for valve placement was defined as the time from the insertion of the Delivery Catheter into the bronchoscope to its removal.

Table 8. Time required for therapeutic procedure

	Zephyr EBV (n = 128)	Control (n = 62)
Time required for the procedure using the Chartis system (min)	19.0 ± 16.52	19.5 ± 13.58
Time required for valve placement (min)	34.8 ± 24.27	NA

6.A.(1).3) Study results

6.A.(1).3).(a) Primary endpoint

Table 9 shows the results of the primary endpoint. The percentage of subjects achieving the threshold of ≥15% improvement in FEV1was 47.7% in the Zephyr EBV group and 16.8% in the control group, significantly higher in the Zephyr EBV group. The protocol-specified primary endpoint was met. Figure 5 shows a percent change in FEV1 for each subject.

Table 9. Primary endpoint
(percentage of subjects who met the threshold of ≥15% improvement in FEV1 at 1 year)

Zephyr EBV (n = 128)	Control (n = 62)	Between-group difference	*P*-value
47.7% (success 57, failure 58, missing 13)	16.8% (success 10, failure 49, missing 5)	31.0 points (95% CI, 18.0-43.9)	<0.001

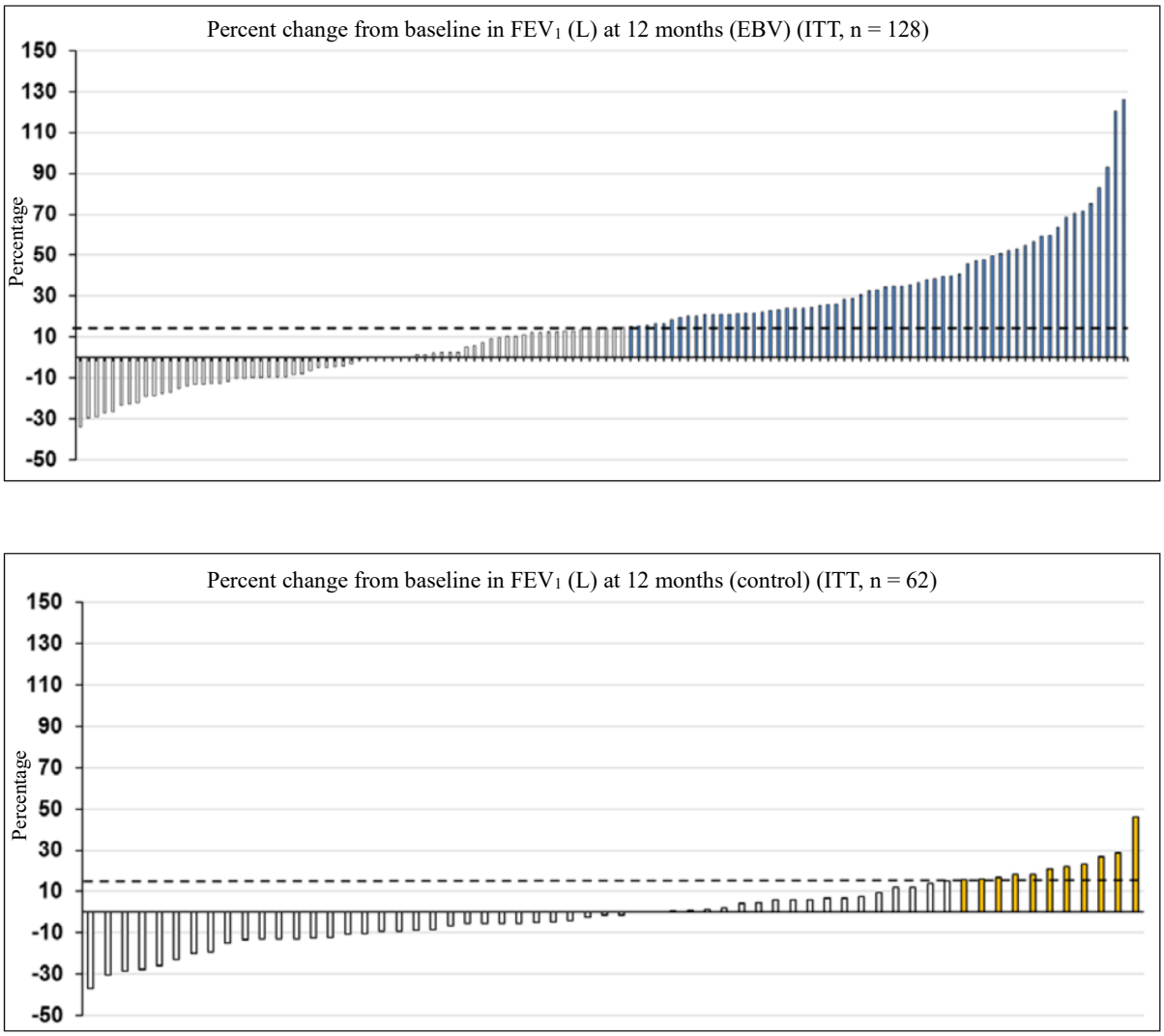

Figure 5. Percent change in FEV1 for each subject (upper, Zephyr EBV; lower, control)

6.A.(1).3).(b) Secondary endpoints

Table 10 to Table 12 show the analysis results of the secondary endpoints.

Table 10. Absolute change from baseline in FEV1 at 1 year

Zephyr EBV (n = 128)	Control (n = 62)	Between-group difference	*P*-value
0.104 ± 0.200 L	-0.003 ± 0.194 L	0.106 L	<0.001

(Least squares mean ± SD)

Table 11. Absolute change from baseline in 6-minute walk distance at 1 year

Zephyr EBV (n = 128)	Control (n = 62)	Between-group difference	*P*-value
12.98 ± 81.54 m	-26.33 ± 81.50 m	39.31 m	0.002

(Least squares mean ± SD)

Table 12. Absolute change from baseline in SGRQ score at 1 year

Zephyr EBV (n = 128)	Control (n = 62)	Between-group difference	*P*-value
-7.55 ± 15.71 points	-0.50 ± 15.50 points	-7.05 points	0.004

(Least squares mean ± SD)

6.A.(1).3).(c) Safety endpoint

Malfunctions and adverse events

Malfunctions and adverse events in the study were collected in the safety analysis population for a short-term period, as, the treatment period (day of procedure/randomization to 45 days) and a long-term period (46 days after the study procedure/randomization until the 1-year follow-up visit). Serious adverse events, device-related adverse events, and adverse events of special interest were assessed by the Clinical Event Committee, a third party independent of each study site.

Adverse events throughout the study period

During the treatment period (day of procedure/randomization to 45 days), 352 cases of adverse events were reported from 106 subjects (82.8%) in the Zephyr EBV group while 35 cases of adverse events were reported from 25 subjects (40.3%) in the control group. The Zephyr EBV group revealed a high percentage of adverse events in each severity as compared with the control group; severe, 23.4% vs. 6.5%; moderate, 35.2% vs. 16.1%; mild, 24.2% vs. 17.7%. A “relationship to the device” assessed by the investigator was “definitely related” for 30.5%, “probably related” for 18.8%, “possibly related” for 14.1%, and “unrelated” for 19.5% of the events. A “relationship to the procedure” assessed by the investigator was “definitely related” for 22.7%, “probably related” for 14.1%, “possibly related” for 26.6%, and “unrelated” for 19.5% of the events.

During the long-term period (46 days after the study procedure/randomization until the 1-year follow-up visit), 326 cases of adverse events were reported from 110 subjects (90.2%) in the Zephyr EBV group, while 144 cases of adverse events were reported from 51 subjects (82.3%) in the control group. Serious adverse events included 86 cases reported from 48 subjects (39.3%) in the Zephyr EBV group and 47 cases reported from 21 subjects (33.9%) in the control group. The results of comparison of the percentage of adverse events between the Zephyr EBV group and the control group by severity were; severe, 23% vs. 24.2%; moderate, 48.4% vs. 37.1%; mild, 18.9% vs. 21.0%. A “relationship to the investigational device” assessed by the investigator was “definitely related” for 4.9%, “probably related” for 11.5%, “possibly related” for 24.6%, and “unrelated” for 48.4% of the events. A “relationship to the procedure” assessed by the investigator was “definitely related” for 2.5%, “probably related” for 5.7%, “possibly related” for 13.9%, and “unrelated” for 68.0% of the events.

Table 13 shows adverse events occurring at an incidence, of ≥3.0% based on the number of subjects with the events in either the Zephyr EBV or control group during the treatment or long-term period.

Table 13. Adverse events reported by ≥3.0% of subjects

Event	Treatment period (day of procedure/randomization to 45 days)		Long-term period (46 days after the study procedure/randomization until the 12-month follow-up visit)	
	Zephyr EBV (N = 128)	Control (N = 62)	Zephyr EBV (N = 122)	Control (N = 62)
Respiratory adverse events				
Pneumothorax	38 (29.7%)*	0 (0.0%)	8 (6.6%)	0 (0.0%)
Chest pain	33 (25.8%)*	1 (1.6%)	8 (6.6%)	0 (0.0%)
COPD	25 (19.5%)	7 (11.3%)	69 (56.6%)	35 (56.5%)
Cough	23 (18.0%)*	3 (4.8%)	6 (4.9%)	2 (3.2%)
Dyspnoea	21 (16.4%)*	2 (3.2%)	16 (13.1%)*	1 (1.6%)
Haemoptysis	11 (8.6%)	1 (1.6%)	12 (9.8%)*	0 (0.0%)
Oropharyngeal pain	10 (7.8%)	3 (4.8%)	0 (0.0%)	0 (0.0%)
Pleural effusion	9 (7.0%)*	0 (0.0%)	0 (0.0%)	0 (0.0%)
Chest discomfort	8 (6.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hypoxia	7 (5.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pneumonia	6 (4.7%)	0 (0.0%)	11 (9.0%)	6 (9.7%)
Sputum increased	4 (3.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pulmonary mass	0 (0.0%)	0 (0.0%)	7 (5.7%)	3 (4.8%)
Upper respiratory tract infection	0 (0.0%)	0 (0.0%)	7 (5.7%)	0 (0.0%)
Bronchitis	0 (0.0%)	0 (0.0%)	6 (4.9%)	3 (4.8%)
Lower respiratory tract congestion	0 (0.0%)	0 (0.0%)	5 (4.1%)	0 (0.0%)
Sinusitis	0 (0.0%)	0 (0.0%)	3 (2.5%)	3 (4.8%)
Respiratory failure	0 (0.0%)	0 (0.0%)	1 (0.8%)	2 (3.2%)
Pharyngitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (3.2%)
Non-respiratory adverse events				
Headache	10 (7.8%)	1 (1.6%)	4 (3.3%)	0 (0.0%)
Nausea	10 (7.8%)*	0 (0.0%)	0 (0.0%)	0 (0.0%)
Constipation	8 (6.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Functional gastrointestinal disorder	6 (4.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Arrhythmia	5 (3.9%)	0 (0.0%)	2 (1.6%)	2 (3.2%)
Dizziness	4 (3.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pyrexia	4 (3.1%)	1 (1.6%)	0 (0.0%)	0 (0.0%)
Infection	0 (0.0%)	0 (0.0%)	10 (8.2%)	4 (6.5%)
Urinary tract infection	0 (0.0%)	0 (0.0%)	2 (1.6%)	4 (6.5%)
Diverticulitis	0 (0.0%)	0 (0.0%)	1 (0.8%)	2 (3.2%)
Nephrolithiasis	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (3.2%)

* $P < 0.05$ (significant difference between the Zephyr EBV and control groups as determined by Fisher's exact test)

Respiratory adverse events during the treatment period (day of procedure/randomization to 45 days)
Table 14 shows respiratory adverse events during the treatment period. Respiratory adverse events during the treatment period included 238 cases in 102 subjects (79.7%) in the Zephyr EBV group and 22 cases in 19 subjects (30.6%) in the control group. Table 15 shows serious respiratory adverse events during the treatment period. Serious respiratory adverse events during the treatment period included 55 cases reported from 45 subjects (35.2%) in the Zephyr EBV group and 3 cases reported from 3 subjects (4.8%) in the control group.

A common serious adverse event was pneumothorax in 34 subjects (26.6%) in the Zephyr EBV group. No subject in the control group experienced pneumothorax. COPD exacerbation occurred in 10 subjects (7.8%) in the Zephyr EBV group and 3 subjects (4.8%) in the control group.

Table 14. Respiratory adverse events during the treatment period

Event	Zephyr EBV (n = 128)		Control (n = 62)	
	Number of subjects (%)	Number of events	Number of subjects (%)	Number of events
Respiratory adverse events	102 (79.7%)	238	19 (30.6%)	22
Anaesthetic complication pulmonary	1 (0.8%)	1	0 (0.0%)	0
Anosmia	1 (0.8%)	1	0 (0.0%)	0
Bronchitis	1 (0.8%)	1	1 (1.6%)	1
Bronchitis chronic	1 (0.8%)	1	1 (1.6%)	1
Bronchospasm	1 (0.8%)	1	1 (1.6%)	1
Chest discomfort	8 (6.3%)	8	0 (0.0%)	0
Chest pain	33 (25.8%)	38	1 (1.6%)	1
Choking sensation	0 (0.0%)	0	1 (1.6%)	1
Chronic obstructive pulmonary disease	25 (19.5%)	25	7 (11.3%)	7
Cough	23 (18.0%)	24	3 (4.8%)	3
Dyspnoea	21 (16.4%)	23	2 (3.2%)	2
Dyspnoea exertional	1 (0.8%)	1	0 (0.0%)	0
Epistaxis	1 (0.8%)	1	0 (0.0%)	0
Haemoptysis	11 (8.6%)	14	1 (1.6%)	1
Hiccups	1 (0.8%)	1	0 (0.0%)	0
Hypoxia	7 (5.5%)	7	0 (0.0%)	0
Lower respiratory tract congestion	3 (2.3%)	3	0 (0.0%)	0
Musculoskeletal chest pain	1 (0.8%)	1	0 (0.0%)	0
Nasopharyngitis	0 (0.0%)	0	1 (1.6%)	1
Non-cardiac chest pain	2 (1.6%)	2	0 (0.0%)	0
Oropharyngeal pain	10 (7.8%)	10	3 (4.8%)	3
Painful respiration	1 (0.8%)	1	0 (0.0%)	0
Pleural effusion	9 (7.0%)	9	0 (0.0%)	0
Pleurisy	2 (1.6%)	2	0 (0.0%)	0
Pleuritic pain	1 (0.8%)	1	0 (0.0%)	0
Pneumonia	6 (4.7%)	6	0 (0.0%)	0
Pneumothorax	38 (29.7%)	38	0 (0.0%)	0
Productive cough	1 (0.8%)	1	0 (0.0%)	0
Respiratory failure	2 (1.6%)	2	0 (0.0%)	0
Rhinitis allergic	1 (0.8%)	1	0 (0.0%)	0
Sinus congestion	1 (0.8%)	1	0 (0.0%)	0
Sneezing	1 (0.8%)	1	0 (0.0%)	0
Sputum increased	4 (3.1%)	4	0 (0.0%)	0
Tracheitis	1 (0.8%)	1	0 (0.0%)	0
Tracheobronchitis	2 (1.6%)	2	0 (0.0%)	0
Upper respiratory tract infection	1 (0.8%)	1	0 (0.0%)	0
Upper-airway cough syndrome	1 (0.8%)	1	0 (0.0%)	0
Wheezing	3 (2.3%)	3	0 (0.0%)	0

Table 15. Serious respiratory adverse events during the treatment period

Event	Zephyr EBV (n = 128)		Control (n = 62)	
	Number of subjects (%)	Number of events	Number of subjects (%)	Number of events
Respiratory adverse events	45 (35.2%)	55	3 (4.8%)	3
Anaesthetic complication pulmonary	1 (0.8%)	1	0 (0.0%)	0
Chest pain	1 (0.8%)	1	0 (0.0%)	0
Chronic obstructive pulmonary disease	10 (7.8%)	10	3 (4.8%)	3
Dyspnoea	2 (1.6%)	4	0 (0.0%)	0
Pleural effusion	2 (1.6%)	2	0 (0.0%)	0
Pneumonia	1 (0.8%)	1	0 (0.0%)	0
Pneumothorax	34 (26.6%)	34	0 (0.0%)	0
Respiratory failure	2 (1.6%)	2	0 (0.0%)	0

Respiratory adverse events during the long-term period (46 days after the study procedure/randomization until the 1-year follow-up visit)

Table 16 shows respiratory adverse events during the long-term period. A total of 228 cases were reported from 102 subjects (83.6%) in the Zephyr EBV group during the long-term period, while 98

cases were reported from 41 subjects (66.1%) in the control group. Table 17 shows serious respiratory adverse events during the long-term period, including 64 cases in 33.6% of the subjects in the Zephyr EBV group and 39 cases in 30.6% of the subjects in the control group. A common serious adverse event was pneumothorax in 8 subjects (6.6%) in the Zephyr EBV group. No subject in the control group experienced pneumothorax. COPD exacerbation occurred in 28 subjects (23%) in the Zephyr EBV group and 19 subjects (30.6%) in the control group. Pneumonia occurred in 7 subjects (5.7%) in the Zephyr EBV group and 5 subjects (8.1%) in the control group. Respiratory failure occurred in 1 subject (0.8%) in the Zephyr EBV group and 2 subjects (3.2%) in the control group.

Table 16. Respiratory adverse events during the long-term period

Event	Zephyr EBV (n = 122)		Control (n = 62)	
	Number of subjects (%)	Number of events	Number of subjects (%)	Number of events
Respiratory adverse events	102 (83.6%)	228	41 (66.1%)	98
Acute sinusitis	2 (1.6%)	2	0 (0.0%)	0
Asthma	0 (0.0%)	0	1 (1.6%)	1
Bronchitis	6 (4.9%)	7	3 (4.8%)	3
Chest pain	8 (6.6%)	9	0 (0.0%)	0
Chronic obstructive pulmonary disease	69 (56.6%)	118	35 (56.5%)	70
Cough	6 (4.9%)	7	2 (3.2%)	2
Dyspnoea	16 (13.1%)	16	1 (1.6%)	1
Haemoptysis	12 (9.8%)	12	0 (0.0%)	0
Influenza	2 (1.6%)	2	1 (1.6%)	1
Lower respiratory tract congestion	5 (4.1%)	5	0 (0.0%)	0
Musculoskeletal chest pain	1 (0.8%)	1	0 (0.0%)	0
Nasal congestion	1 (0.8%)	1	0 (0.0%)	0
Nasopharyngitis	1 (0.8%)	1	0 (0.0%)	0
Non-cardiac chest pain	1 (0.8%)	1	0 (0.0%)	0
Pharyngitis	0 (0.0%)	0	2 (3.2%)	2
Pleural effusion	1 (0.8%)	1	0 (0.0%)	0
Pleurisy	1 (0.8%)	1	0 (0.0%)	0
Pneumonia	11 (9.0%)	12	6 (9.7%)	7
Pneumothorax	8 (6.6%)	8	0 (0.0%)	0
Post-thoracotomy pain syndrome	1 (0.8%)	1	0 (0.0%)	0
Pulmonary cavitation	0 (0.0%)	0	1 (1.6%)	1
Pulmonary embolism	0 (0.0%)	0	1 (1.6%)	1
Pulmonary mass	7 (5.7%)	8	3 (4.8%)	3
Respiratory failure	1 (0.8%)	1	2 (3.2%)	2
Respiratory tract infection	1 (0.8%)	1	0 (0.0%)	0
Respiratory tract infection viral	1 (0.8%)	1	0 (0.0%)	0
Rhinitis allergic	1 (0.8%)	1	0 (0.0%)	0
Rhinorrhoea	1 (0.8%)	1	0 (0.0%)	0
Sinusitis	3 (2.5%)	3	3 (4.8%)	3
Upper respiratory tract infection	7 (5.7%)	7	0 (0.0%)	0

Table 17. Serious respiratory adverse events during the long-term period

Event	Zephyr EBV (n = 122)		Control (n = 62)	
	Number of subjects (%)	Number of events	Number of subjects (%)	Number of events
Respiratory adverse events	41 (33.6%)	64	19 (30.6%)	39
Chronic obstructive pulmonary disease	28 (23.0%)	40	19 (30.6%)	29
Dyspnoea	3 (2.5%)	3	0 (0.0%)	0
Haemoptysis	2 (1.6%)	2	0 (0.0%)	0
Pleural effusion	1 (0.8%)	1	0 (0.0%)	0
Pneumonia	7 (5.7%)	7	5 (8.1%)	6
Pneumothorax	8 (6.6%)	8	0 (0.0%)	0
Pulmonary embolism	0 (0.0%)	0	1 (1.6%)	1
Pulmonary mass	1 (0.8%)	1	0 (0.0%)	0
Respiratory failure	1 (0.8%)	1	2 (3.2%)	3
Respiratory tract infection	1 (0.8%)	1	0 (0.0%)	0

Deaths

In this study, 17 deaths were reported up to 3 years. Table 18 details the death cases. A total of 6 deaths occurred up to 1 year. During the treatment period, deaths of 4 subjects (3.3%) occurred in the Zephyr EBV group while no death occurred in the control group. During the long-term period, 1 subject (0.8%) in the Zephyr EBV group and 1 subject (1.6%) in the control group died. Death occurred in 9 subjects in the Zephyr EBV group and 1 subject in the control group up to 2 years. Death occurred in 1 subject in the Zephyr EBV group up to 3 years.

Table 18. Deaths in the LIBERATE study

Group	Age	Sex	Time to death (days)	Cause of death	Summary	Relationship to investigational device
Zephyr EBV	5[redacted]	Male	3	Pneumothorax	After the treatment with the Zephyr EBV System, the subject had a favorable clinical course and was discharged from the study site without complications 2 days after the procedure. On the same day, he visited an emergency room and stopped responding in approximately 1 minute after arrival. Immediately, cardiopulmonary resuscitation was started but he died. Autopsy showed bilateral pneumothorax with total collapse on the left side.	Definitely related
Zephyr EBV	7[redacted]	Female	3	Pneumothorax	A postoperative chest X-ray after the treatment with the Zephyr EBV System revealed the progression of atelectasis without pneumothorax. The subject complained of pain in the neck and shoulders around 5 o'clock at 2 days after the procedure. The oxygen saturation decreased to the 70 level. The oxygen saturation improved with a reservoir mask. However, the doctor felt no pulse and started sternum compression. A chest tube was placed within several minutes, which disclosed air leaks. The heart started beating again. Chest X-rays showed large pneumothorax, and air leak persisted. Her pulse was lost again. Sternum compression and lifesaving measures were started. Her heart beats were restored and lost repeatedly. She was transferred to the MICU. Her daughter did not want to continue aggressive care. She had cardiac arrest and died.	Definitely related

Group	Age	Sex	Time to death (days)	Cause of death	Summary	Relationship to investigational device
Zephyr EBV	7[redacted]	Female	11	Respiratory failure	After the treatment with the Zephyr EBV System, the subject did not develop pneumothorax but had mild wheezing on exhalation all over the chest associated with COPD exacerbation. Intravenous treatment started. On the next day, she had dyspnoea and tachypnoea, which were treated with BiPAP, steroids, and antibiotics. She was transferred to MICU. Although BiPAP normalized ABG, she could not tolerate the facemask of BiPAP. CT revealed a small pneumothorax anterior to the apical portion of the left lung. A chest tube was placed under CT guidance. The maximum treatment failed to bring clinical improvement. All Valves were removed at 5 days after the procedure. At 7 days after the procedure, the doctor suggested endotracheal intubation and bronchoscopy to treat new atelectasis of the left lower lobe. Her family did not consent to aggressive treatment based on her will. She was transferred from the ICU to the hospital ward and received morphine for pain management. On the same day, she died.	Definitely related
Zephyr EBV	6[redacted]	Male	13	Pneumothorax	The subject was discharged from the study site without complications at 5 days after the treatment with the Zephyr EBV System. After discharge, he complained of dyspnoea with minimal exertion, which resolved immediately after rest. At 13 days after the procedure, the study coordinator tried to call the subject as scheduled but could not reach him. Later, his daughter said that the subject died on that morning. Autopsy revealed tension pneumothorax.	Probably related
Control	6[redacted]	Female	141	Cardiac arrhythmia	The subject was admitted to a hospital with COPD exacerbation at 4 months after the procedure. She was intubated and put on a respirator. She was once extubated but intubated again because of respiratory failure, and put on a respirator again. She had atrial fibrillation, which led to tachycardia and then cardiac arrest. She received lifesaving measures but died.	-
Zephyr EBV	7[redacted]	Female	147	COPD exacerbation	The subject had left pneumothorax requiring a chest tube after the treatment with the Zephyr EBV System. The chest tube did not help recovery from pneumothorax, and 2 Valves were removed. She was discharged from the study site at 13 days after the procedure. She was admitted to ICU with COPD exacerbation at 4 months after the procedure. CT revealed no pneumothorax. After the hospitalization, her family signed the DNR order. She died of respiratory failure resulting from acute COPD exacerbation at 147 days after the procedure.	Unrelated
Zephyr EBV	5[redacted]	Female	378	Pneumonia	The subject was admitted to a hospital with pneumonia at 1 year after the treatment with the Zephyr EBV System. As her condition required intubation, she was intubated. She died of refractory shock.	Unrelated
Control	6[redacted]	Male	385	COPD exacerbation	The subject died of COPD exacerbation while waiting to cross over to the valve treatment after the 12-month follow-up.	-

Group	Age	Sex	Time to death (days)	Cause of death	Summary	Relationship to investigational device
Zephyr EBV	7[redacted]	Male	416	Pneumonia	The subject was admitted to a hospital with COPD exacerbation, small intestinal obstruction, acute renal injury, and oesophageal stenosis at 1 year after the treatment with the Zephyr EBV System. He went back home for a short period but was admitted to the hospital again with COPD exacerbation and pneumonia. Eventually, all Valves were removed for treatment, which did not improve his condition. The subject and his family decided not to continue aggressive treatment. Later, he died.	Probably related
Zephyr EBV	7[redacted]	Female	419	COPD exacerbation	The subject was admitted to a hospital multiple times with COPD exacerbation at 1 year after the treatment with the Zephyr EBV System. After hospitalization, she was admitted to hospice care. Later, her death was notified.	Unrelated
Zephyr EBV	6[redacted]	Female	563	Unknown	The subject was found dead by her husband when he came back home from shopping.	Unknown
Zephyr EBV	6[redacted]	Female	604	Pneumonia	The subject was admitted to a hospital with acute COPD exacerbation and pneumonia at 1 year and 8 months after the treatment with the Zephyr EBV System. Next day, she had severe vomiting and then cardiac arrest. She was intubated but did not regain consciousness. Her family did not want autopsy.	Unrelated
Zephyr EBV	6[redacted]	Female	607	Respiratory failure	The subject had persistent dyspnoea and atrial fibrillation at 1 year after the treatment with the Zephyr EBV System. The symptoms were likely because of pulmonary hypertension caused by the lung volume reduction treatment. All of the Valves were removed at 1 year and 2 months after the procedure. He was diagnosed with terminal COPD at 1 year and 4 months after the treatment with the Valves and died of terminal COPD at 1 year and 8 months after the procedure.	Unrelated
Zephyr EBV	5[redacted]	Male	631	Blunt force trauma injury	The subject died of blunt trauma injury caused by a car accident on a highway.	Unrelated
Zephyr EBV	7[redacted]	Male	709	Terminal COPD	The subject died of terminal COPD at 1 year and 11 months after the treatment with Zephyr EBV System.	Unrelated
Zephyr EBV	5[redacted]	Female	720	Haemoptysis	The subject had haemoptysis from erosive ulcers on the opposite wall of the main left lower lobe bronchus close to the proximal end of the Valve at approximately 2 years after the treatment with the Zephyr EBV System. This was likely because of compression by the pulmonary artery that expanded because of exacerbated pulmonary hypertension. Multiple interventions including bronchial artery embolisation, and thoracotomy and transthoracic excision of the left lower lobe resolved haemoptysis. However, the subject required re-intubation because of hospital-acquired pneumonia, atrial fibrillation, clostridium difficile infection, and recurrent respiratory failure. The subject and her family wanted to discontinue the aggressive treatment taking into consideration generalized weakness, the respiratory condition due to severe lung diseases, and pulmonary hypertension. The subject died.	Definitely related
Zephyr EBV	7[redacted]	Female	939	Terminal COPD	The subject died of terminal COPD at 2 years and 7 months after the treatment with Zephyr EBV System.	Unrelated

Malfunctions

A total of 10 cases of device malfunctions were reported in the study, including 3 cases that led to adverse events. Table 19 shows the device malfunctions.

Table 19. Malfunctions in the LIBERATE study

Malfunctions	Cause	Valve removal	Adverse event
Loading difficulty	The Valve was loaded in a wrong catheter.	-	None
Loading difficulty	The Valve was stuck in the loading catheter.	-	None
Loading difficulty	The Valve was stuck in the loader.	-	None
Loading difficulty	Valve loading problem	-	None
Loading difficulty	Valve loading problem	-	None
Valve migration	The subject's excessive coughing	Yes	Valve migration
Valve migration	The Valve was migrated.	Yes	Valve migration
The Valve was coughed up.	Cough	Yes	The Valve was coughed up.
The Valve did not function.	The Valve did not function.	Yes	None
The wing of the catheter came off.	Catheter	-	None

6.A.(2) IMPACT study (study period, August 12, 2014 to March 15, 2017)

6.A.(2).1) Methodology

The IMPACT study was a multicenter, prospective, randomized, controlled clinical study conducted in patients with severe homogenous emphysema (<15-point difference in destruction scores between the target and ipsilateral lobes) as shown in Table 20 at 1 site in Austria, 6 sites in Germany, and 2 sites in the Netherlands to evaluate the safety and efficacy of BLVR with the Zephyr EBV System in comparison with the standard of care.

Table 20. Outline of the IMPACT study

Item	Outline
Study type	Multicenter, prospective, randomized, controlled, one-way crossover study
Population	Patients with severe homogenous emphysema (<15-point difference in destruction scores between the target and ipsilateral lobes)
Major inclusion criteria	1. Diagnosis of homogenous emphysema with a <15-point heterogeneity index between the target and ipsilateral lobes 2. Men and women at the age of ≥40 years 3. Understood the contents of the consent form for study participation and voluntarily signed it. 4. Diagnosis of COPD with %FEV1 of ≥15% and ≤45% despite optimal medical treatment 5. TLC, >100%; and RV, ≥200% 6. 6MWD, ≥150 meters 7. >8-week nonsmoking period before signing the consent form for study participation 8. No collateral ventilation in the target lobe
Major exclusion criteria	1. Active lung infection 2. ≥4 COPD exacerbation episodes requiring hospitalization in the last 12 months 3. Pulmonary hypertension (sPAP >45 mmHg) 4. Myocardial infarction or other related cardiovascular event in the last 6 month 5. α1-antitrypsin deficiency 6. Bronchiectasis with >2 tablespoons of sputum production per day 7. Surgical history of LVR or LVRS 8. Pulmonary nodule requiring follow-up for the inside of the target lobe 9. >20% difference in perfusion rate between the left and right lungs 10. Hypercapnia ($PaCO_2$ >55 mmHg) 11. Asthma 12. Use of >25 mg prednisolone (or equivalent) daily 13. Systemic disease or malignant disease likely resulting in death within 12 months 14. Severe bullous emphysema (>1/3 of the hemithorax)
Enrolled sample size	93 patients (43 in the Zephyr EBV group, 50 in the control group)

Item	Outline
Follow-up period	Zephyr EBV: 30 days, 3, 6, and 12 months after the procedure Control: 3 and 6 months after bronchoscopy (randomization)
Primary endpoint	The mean percent change in FEV1 from baseline to 3 months
Secondary endpoints	(1) Change in FEV1 from baseline to 3 months in the Zephyr EBV group as compared to the control group (2) Percent change and change in FEV1 from baseline to 6 months in the Zephyr EBV group as compared to the control group (3) Percent change and change in FEV1 from baseline to 12 months in the Zephyr EBV group (4) Percentages of subjects achieving MCIDs in FEV1, 6MWD, SGRQ, and mMRC at 3 and 6 months in the Zephyr EBV group as compared to the control group (5) Percentages of subjects achieving MCIDs in FEV1, 6MWD, SGRQ, and mMRC at 12 months in the Zephyr EBV group (6) Percent change and change in the target lobe volume (target lobe volume reduction [TLVR]) as assessed by quantitative HRCT from baseline to 3 months in the Zephyr EBV group (7) Percentage of subjects achieving ≥350 mL TLVR at 3 months in the Zephyr EBV group (8) Percent change and absolute change in the following parameters from baseline to 3 and 6 months in the Zephyr EBV group as compared to the control group (a) RV (b) Health-related quality of life as assessed using SGRQ (c) Exercise capacity as assessed based on 6MWD (d) Shortness of breath as assessed by mMRC (e) COPD assessment test (CAT) score (f) EQ-5D Summary Index (g) Percent change and absolute change in the following parameters from baseline to 12 months in the Zephyr EBV group

The primary endpoint was a "mean percent change in FEV1 from baseline to 3 months." The safety endpoint was adverse events during the treatment period (day of procedure to 30 days) and long-term period (31 days after the procedure to 6 months).

The sample size was determined based on the results of the preceding studies, estimating the mean percent change as 17% in the Zephyr EBV group and 1.3% in the control group. Assuming a two-sided significance level of 0.05 and power of 80%, 44 subjects were needed to verify the superiority of the Zephyr EBV to the control treatment. Allowing for a dropout of 20%, the sample size was determined as 56. During the preparation for an interim analysis, the percentage of subjects in whom the upper lobe was targeted and those in whom the lower lobe was targeted were found to be imbalanced both in both the Zephyr EBV and control groups. To correct the imbalance, additional 24 subjects were decided to be stratified and randomized to the study. As a result, the planned sample size of 80 was determined.

The primary and secondary endpoints were analyzed in the Intent-to-Treat (ITT) population, which included all randomized subjects in each group, who were subjected to group-by-group-analyses (either in the Zephyr EBV or control group) (Figure 6).

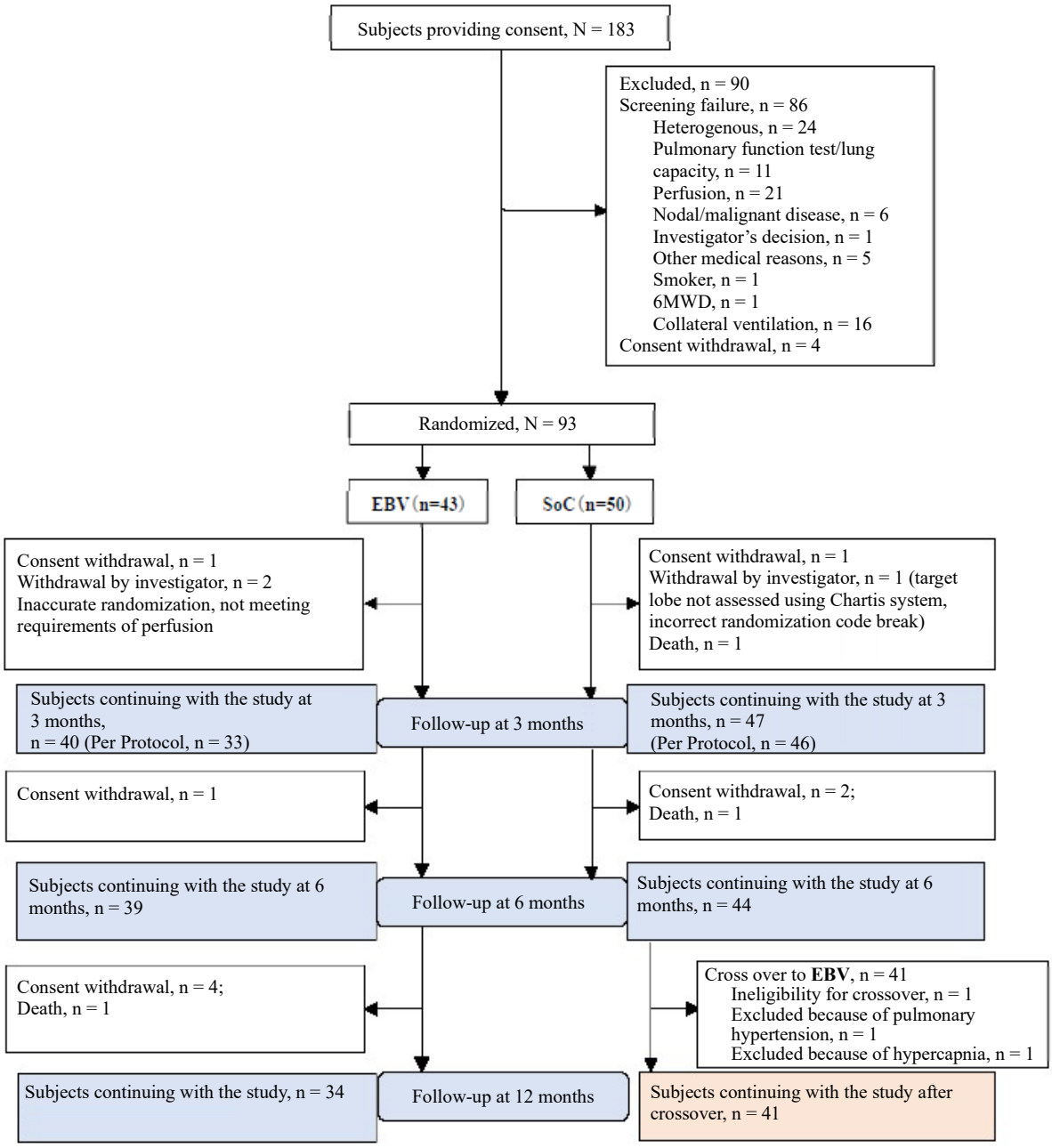

Figure 6. Flowchart of subject enrolment in the IMPACT study

6.A.(2).2) Patient characteristics

Table 21 shows the patient characteristics in the IMPACT study.

Table 21. Patient characteristics in the IMPACT study

	Zephyr EBV (N = 43)	Control (N = 50)
Age	64.3 ± 6.3	63.2 ± 6.0
Smoking history (pack/year)	41.5 ± 19.6	42.5 ± 22.0
Sex (male/female)	20 males, 23 females (47%/53%)	16 males, 34 females (32%/68%)
%FEV1 (post-bronchodilator)	28.4 ± 6.3	30.0 ± 6.6
FEV1 (L)	0.76 ± 0.17	0.75 ± 0.19
FEV1/FVC	36.3 ± 7.2	35.8 ± 8.6
%TLC (% of predicted)	145 ± 21	144 ± 18
%RV (% of predicted)	277 ± 55	274 ± 63
GOLD stage	Stage III, 18 subjects Stage IV, 25 subjects	Stage III, 23 subjects Stage IV, 27 subjects
6MWD (m)	308 ± 91	328 ± 93

The diseased lobe was determined as the target lobe if there is neither ≥15-point difference in destruction scores as compared with ipsilateral lobes nor collateral ventilation between it and ipsilateral lobes. Table 22 shows the details of lobes treated in the study. The average number of Valves per subject was 4.2 (median, 4).

Table 22. Lobes treated in the study

	Zephyr EBV (N = 43)
Left lower lobe (LLL)	18 (41.9%)
Left upper lobe (LUL)	12 (27.9%)
Right lower lobe (RLL)	9 (20.9%)
Right upper lobe (RUL)	4 (9.3%)

6.A.(2).3) Study results

6.A.(2).3).(a) Primary endpoint

The primary endpoint of "the mean percent change in FEV1 from baseline to 3 months" was a 15.3% increase in the Zephyr EBV group and a 3.4% decrease in the control group. The mean between-group difference (Zephyr EBV group - Control group) in FEV1 from baseline to 3 months was 18.8 ± 22.1 points. The mean percent change in FEV1 was significantly higher in the Zephyr EBV group than in the control group, meeting the protocol-specified primary endpoint (Table 23).

Table 23. Primary efficacy endpoint (mean percent change in FEV1 [L] from baseline to 3 months)

Zephyr EBV (n = 43)	Control (n = 50)	Between-group difference	*P*-value
15.3%	-3.4%	18.8 points (95% CI, 9.2-28.4)	<0.001

6.A.(2).3).(b) Secondary endpoints

The Zephyr EBV group had statistically and clinically significant improvements in FEV1, residual volume (RV), 6MWD, SGRQ score, and BODE Index as compared with the control group at 3 and 6 months after the treatment. The Zephyr EBV group also had statistically significant improvements in modified medical research council (mMRC) and the European version of EQ-5D Summary Index as

compared with the control group at 3 months (Table 24). The Zephyr EBV group had statistically significant improvements in mMRC and the European and Japanese versions of EQ-5D Summary Index as compared with the control group at 6 months.

Table 24. Secondary endpoints in the IMPACT study (3 months after the treatment)

	Zephyr EBV	Control	Between-group difference	*P*-value
Absolute change in FEV1 (L)	0.10 ± 0.18	-0.02 ± 0.10	0.12 ± 0.15	<0.001
Change in RV (L)	-0.42 ± 0.90	0.05 ± 0.87	-0.48 ± 0.89	0.011
6MWD (m)	22.63 ± 66.63	-17.34 ± 52.80	39.97 ± 59.32	0.002
SGRQ score	-8.63 ± 11.25	1.01 ± 9.36	-9.64 ± 10.22	<0.001
BODE Index	-0.74 ± 1.53	0.42 ± 1.13	-1.16 ± 1.32	<0.001

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

Malfunctions and adverse events

Malfunctions and adverse events in the study were collected in the safety analysis population for a short-term period (day of valve placement to 30 days), and a long-term period (31 days after the procedure to the 6 months).

Adverse events throughout the study period

The adverse event profiles of the Zephyr EBV and control groups were compared for the short-term period (day of valve placement to 30 days) and a long-term period (31 days after the procedure to the 6 months). Table 25 shows adverse events reported in the Zephyr EBV and control groups during the 6-month safety evaluation period. Respiratory adverse events were reported from 36 subjects (83.7%, 111 cases) in the Zephyr EBV group and 32 subjects (64.0%, 54 cases) in the control group. The total number of non-respiratory adverse events was 36 in 22 subjects (51.2%) in Zephyr EBV group, which was greater than 14 cases in 10 subjects (20.0%) in the control group.

Table 25. Adverse events in the Zephyr EBV and control groups during the 6-month safety evaluation period

Event	Zephyr EBV (n = 43)		Control (n = 50)	
	Number of subjects with event (%)	Number of events	Number. of subjects with event (%)	Number of events
Total number of respiratory adverse events	36 (83.7)	111	32 (64.0)	54
COPD exacerbation	20 (46.5)	42	20 (40.0)	25
Pneumothorax	11 (25.6)	12	0 (0.0)	0
Common cold	6 (14.0)	9	6 (12.0)	8
Cough	6 (14.0)	6	1 (2.0)	1
Pulmonary infection	3 (7.0)	4	1 (2.0)	1
Thoracalgia	4 (9.3)	4	1 (2.0)	1
Dyspnoea	3 (7.0)	3	2 (4.0)	4
Pleural effusion	3 (7.0)	3	0 (0.0)	0
Diagnostic bronchoscopy	2 (4.7)	2	0 (0.0)	0
Mucus production	2 (4.7)	2	0 (0.0)	0
Lung granulation	2 (4.7)	2	0 (0.0)	0
Pulmonary shunt	2 (4.7)	2	0 (0.0)	0
Purulent bronchitis	2 (4.7)	2	1 (2.0)	1
The Valve was coughed up.	1 (2.3)	2	0 (0.0)	0
Valve migration	1 (2.3)	2	0 (0.0)	0
Bronchitis	1 (2.3)	1	0 (0.0)	0
Chest pain	1 (2.3)	1	0 (0.0)	0
Haemoptysis	1 (2.3)	1	0 (0.0)	0
Hypoxemia	1 (2.3)	1	0 (0.0)	0
Pharyngitis	1 (2.3)	1	0 (0.0)	0

Event	Zephyr EBV (n = 43)		Control (n = 50)	
	Number of subjects with event (%)	Number of events	Number. of subjects with event (%)	Number of events
Pneumonia	1 (2.3)	1	3 (6.0)	4
Productive cough	1 (2.3)	1	0 (0.0)	0
Intra-alveolar bulla	1 (2.3)	1	0 (0.0)	0
Pulmonary nodule	1 (2.3)	1	0 (0.0)	0
Purulent sputum	1 (2.3)	1	0 (0.0)	0
Sinusitis	1 (2.3)	1	0 (0.0)	0
Valve dislocation	1 (2.3)	1	0 (0.0)	0
Valve replacement	1 (2.3)	1	0 (0.0)	0
Wheezing sound	1 (2.3)	1	0 (0.0)	0
Cardiac pulmonary oedema	0 (0.0)	0	1 (2.0)	1
Hypercapnia	0 (0.0)	0	3 (6.0)	3
Lung lesion	0 (0.0)	0	3 (6.0)	3
Respiratory failure	0 (0.0)	0	1 (2.0)	1
Rhinorrhoea	0 (0.0)	0	1 (2.0)	1
Total number of non-respiratory adverse events	22 (51.2)	36	10 (20.0)	14
Urinary tract infection	3 (7.0)	3	0 (0.0)	0
Back pain	2 (4.7)	2	1 (2.0)	1
Depression	2 (4.7)	2	0 (0.0)	0
Diarrhoea	2 (4.7)	2	0 (0.0)	0
Insomnia	2 (4.7)	2	0 (0.0)	0
Tachycardia	2 (4.7)	2	1 (2.0)	1
Abdominal pain	1 (2.3)	1	0 (0.0)	0
Antibiotic allergy	1 (2.3)	1	0 (0.0)	0
Clostridium difficile infection	1 (2.3)	1	0 (0.0)	0
Epistaxis	1 (2.3)	1	0 (0.0)	0
Fatigue	1 (2.3)	1	0 (0.0)	0
Leg torsion	1 (2.3)	1	0 (0.0)	0
Gastroesophageal reflux	1 (2.3)	1	0 (0.0)	0
Herpes infection	1 (2.3)	1	0 (0.0)	0
Hoarseness	1 (2.3)	1	0 (0.0)	0
Infection	1 (2.3)	1	1 (2.0)	1
Leukocytosis	1 (2.3)	1	0 (0.0)	0
Local allergic reaction	1 (2.3)	1	0 (0.0)	0
Nausea	1 (2.3)	1	0 (0.0)	0
Neuritis	1 (2.3)	1	0 (0.0)	0
Oral candidiasis	1 (2.3)	1	0 (0.0)	0
Otitis media	1 (2.3)	1	0 (0.0)	0
Palpitations	1 (2.3)	1	0 (0.0)	0
Recurrent paralysis	1 (2.3)	1	0 (0.0)	0
Tendonitis	1 (2.3)	1	0 (0.0)	0
Vaginal mycosis	1 (2.3)	1	0 (0.0)	0
Influenza	1 (2.3)	1	0 (0.0)	0
Weight decreased	1 (2.3)	1	0 (0.0)	0
Impaired wound healing	1 (2.3)	1	0 (0.0)	0
Ankle oedema	0 (0.0)	0	1 (2.0)	1
Cardiac failure	0 (0.0)	0	1 (2.0)	1
Dry oropharyngeal mucosa	0 (0.0)	0	1 (2.0)	1
Ear pain	0 (0.0)	0	1 (2.0)	1
Hernia surgery	0 (0.0)	0	1 (2.0)	1
Nephrolithiasis	0 (0.0)	0	1 (2.0)	1
Rib fracture	0 (0.0)	0	1 (2.0)	1
Costal fracture	0 (0.0)	0	1 (2.0)	1
Tonsillitis	0 (0.0)	0	1 (2.0)	1
Loss of consciousness	0 (0.0)	0	1 (2.0)	1
Spinal fracture	0 (0.0)	0	1 (2.0)	1

Respiratory adverse events in the first 30 days after procedure (randomization)

The Zephyr EBV group reported greater numbers of respiratory adverse events and subjects affected than in the control group during the first 30 days after the procedure (Table 26). Respiratory adverse

events that occurred more frequently in the Zephyr EBV group than the control group were COPD exacerbation (12 cases in the Zephyr EBV group, 2 cases in the control group), pneumothorax (10 cases in the Zephyr EBV group, 0 case in the control group), and cough (4 cases in the Zephyr EBV group, 0 case in the control group).

The percentages of mild, moderate, and severe respiratory adverse events occurring in the 30 days after valve placement were 26.5%, 44.9%, and 28.6%, respectively. All 5 adverse events in the control group were moderate. In the Zephyr EBV group, a relationship of each respiratory adverse event to the procedure was "unlikely" for 41%, "possibly" for 24.5%, and "likely" for 34.7% of the events. In the control group, all of the respiratory adverse events were unlikely to be related to the procedure. In the Zephyr EBV group, a relationship of each respiratory adverse event to the investigational device was "unlikely" for 77%, "possibly" for 19%, and "likely" for 4% of the events. In the control group, all of the respiratory adverse events were not related to the investigational device.

Table 26. Respiratory adverse events for the first 30 days after procedure

Event	Zephyr EBV (n = 43)		Control (n = 50)	
	Number of subjects (%)	Number of events	Number of subjects (%)	Number of events
Total number of respiratory adverse events	28 (65.1)	50	4 (8.0)	5
COPD exacerbation	12 (27.9)	12	2 (4.0)	2
Pneumothorax	10 (23.3)	10	0 (0.0)	0
Cough	4 (9.3)	4	0 (0.0)	0
Common cold	3 (7.0)	3	2 (4.0)	2
Thoracalgia	3 (7.0)	3	0 (0.0)	0
Pulmonary infection	2 (4.7)	2	0 (0.0)	0
Pulmonary shunt	2 (4.7)	2	0 (0.0)	0
Valve migration	1 (2.3)	2	0 (0.0)	0
Bronchitis	1 (2.3)	1	0 (0.0)	0
Chest pain	1 (2.3)	1	0 (0.0)	0
Dyspnoea	1 (2.3)	1	0 (0.0)	0
Haemoptysis	1 (2.3)	1	0 (0.0)	0
Mucus production	1 (2.3)	1	0 (0.0)	0
Pharyngitis	1 (2.3)	1	0 (0.0)	0
Pleural effusion	1 (2.3)	1	0 (0.0)	0
Productive cough	1 (2.3)	1	0 (0.0)	0
Lung granulation	1 (2.3)	1	0 (0.0)	0
Purulent bronchitis	1 (2.3)	1	0 (0.0)	0
Sinusitis	1 (2.3)	1	0 (0.0)	0
Wheezing sound	1 (2.3)	1	0 (0.0)	0
Pneumonia	0 (0.0)	0	1 (2.0)	1

Table 27 shows serious respiratory adverse events during the first 30 days after the procedure (randomization). The Zephyr EBV group reported greater numbers of serious respiratory adverse events and subjects affected than in the control group during the first 30 days after the procedure. Pneumothorax occurred in 10 subjects (23.3%, 10 cases) in the Zephyr EBV group, while no pneumothorax occurred in the control group. COPD exacerbation was the only serious adverse event other than pneumothorax occurring during the 30-day period at statistically significant different incidences between the groups, i.e., 6 cases in 6 subjects (14.0%) in the Zephyr EBV group and 1 case in 1 subject (2.0%) in the control group.

Table 27. Serious respiratory adverse events for the first 30 days after procedure

Event	Zephyr EBV (n = 43)		Control (n = 50)	
	Number of subjects (%)	Number of events	Number of subjects (%)	Number of events
Total number of serious respiratory adverse events	19 (44.2)	20	1 (2.0)	1
Pneumothorax	10 (23.3)	10	0 (0.0)	0
COPD exacerbation	6 (14.0)	6	1 (2.0)	1
Valve migration	1 (2.3)	2	0 (0.0)	0
Dyspnoea	1 (2.3)	1	0 (0.0)	0
Purulent bronchitis	1 (2.3)	1	0 (0.0)	0

* Including adverse events occurring within 30 days after re-treatment according to the protocol

Respiratory adverse events from 31 days after procedure (randomization) to 6 months

During the period from 31 days after the procedure to 6 months, the Zephyr EBV group reported a higher incidence of respiratory adverse events, i.e., 61 cases in 31 subjects (72.1%), than the control group, which reported 49 cases of 32 subjects (64.0%). Table 28 shows adverse events.

Table 28. Respiratory adverse events from 31 days after procedure to 6 months

Event	Zephyr EBV (n = 43)		Control (n = 50)	
	Number of subjects (%)	Number of events	Number of subjects (%)	Number of events
Total number of respiratory adverse events	31 (72.1)	61	32 (64.0)	49
COPD exacerbation	17 (39.5)	30	19 (38.0)	23
Common cold	4 (9.3)	6	5 (10.0)	6
Cough	2 (4.7)	2	1 (2.0)	1
Diagnostic bronchoscopy	2 (4.7)	2	0 (0.0)	0
Dyspnoea	2 (4.7)	2	2 (4.0)	4
Pleural effusion	2 (4.7)	2	0 (0.0)	0
Pneumothorax	2 (4.7)	2	0 (0.0)	0
Pulmonary infection	2 (4.7)	2	1 (2.0)	1
Valve expectoration	1 (2.3)	2	0 (0.0)	0
Hypoxemia	1 (2.3)	1	0 (0.0)	0
Mucus production	1 (2.3)	1	0 (0.0)	0
Pneumonia	1 (2.3)	1	3 (6.0)	3
Intra-alveolar bulla	1 (2.3)	1	0 (0.0)	0
Lung granulation	1 (2.3)	1	0 (0.0)	0
Pulmonary nodule	1 (2.3)	1	0 (0.0)	0
Purulent bronchitis	1 (2.3)	1	1 (2.0)	1
Purulent sputum	1 (2.3)	1	0 (0.0)	0
Thoracalgia	1 (2.3)	1	1 (2.0)	1
Valve dislocation	1 (2.3)	1	0 (0.0)	0
Valve replacement	1 (2.3)	1	0 (0.0)	0
Cardiac pulmonary oedema	0 (0.0)	0	1 (2.0)	1
Hypercapnia	0 (0.0)	0	3 (6.0)	3
Lung lesion	0 (0.0)	0	3 (6.0)	3
Respiratory failure	0 (0.0)	0	1 (2.0)	1
Rhinorrhoea	0 (0.0)	0	1 (2.0)	1

Table 29 shows serious respiratory adverse events occurred during the period from 31 days after the procedure to 6 months. There was no difference in serious respiratory adverse events between the Zephyr EBV and control groups.

Table 29. Serious respiratory adverse events from 31 days after procedure to 6 months

Event	Zephyr EBV (n = 43)		Control (n = 50)	
	Number of subjects (%)	Number of events	Number of subjects (%)	Number of events
Total number of respiratory adverse events	15 (34.9)	20	13 (26.0)	17
COPD exacerbation	8 (18.6)	12	10 (20.0)	10
Diagnostic bronchoscopy	2 (4.7)	2	0 (0.0)	0
Dyspnoea	2 (4.7)	2	0 (0.0)	0
Pneumothorax	2 (4.7)	2	0 (0.0)	0
Pneumonia	1 (2.3)	1	2 (4.0)	2
Valve dislocation	1 (2.3)	1	0 (0.0)	0
Cardiac pulmonary oedema	0 (0.0)	0	1 (2.0)	1
Hypercapnia	0 (0.0)	0	3 (6.0)	3
Purulent bronchitis	0 (0.0)	0	1 (2.0)	1

Death

There were 2 deaths in the control group and 1 death in the Zephyr EBV group during the 12-month study period. Table 30 shows the outline of the death cases.

Table 30. Deaths in the IMPACT study

Group	Age	Sex	Time of death	Cause of death	Outline	Relationship to investigational device
Zephyr EBV	7[redacted]	Male	12 months	COPD exacerbation	At 12 months after valve placement and resulted in death, the subject presented with severe COPD exacerbation and the obstruction of the left bronchus due to viscus mucous hypersecretion after an abdominal operation.	Unrelated
Control	6[redacted]	Male	5 months	COPD exacerbation	At 5 months after randomization, the subject presented with COPD exacerbation and died of respiratory failure after removal from non-invasive ventilation.	Unlikely
Control	6[redacted]	Female	2 months	Respiratory failure	At 2 months after randomization, the subject presented with hospital-acquired pneumonia, refused non-invasive ventilation and surgical treatment, and died of respiratory failure.	Unrelated

Malfunctions

Two device malfunctions were reported during the study treatment. Table 31 outlines the device malfunctions. All of the device malfunctions were related to the failure of the Valves to close.

Table 31. Malfunctions in the IMPACT study

Malfunctions	Cause	Valve removal	Valve replacement
The valve did not close.	Device failure	Removed	Replaced
The valve did not close.	Device failure	Removed	Not replaced because of granulation found in the affected area

6.B Outline of the review conducted by PMDA

6.B.(1) Justification of evaluating efficacy and safety based on the results of the foreign clinical studies only using some of the proposed models

PMDA's view:

The following observations indicate that the evaluation of the Zephyr EBV System is feasible based on the results of the foreign clinical studies.

1) The foreign Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines and the Japanese guidelines suggest no differences in the medical environment (in terms of the diagnosis and treatment of COPD) in and outside Japan that may affect the evaluation of the Zephyr EBV System.

2) The Zephyr EBV System is available in 4 sizes with different lengths and diameters. Although racial anatomical differences, including smaller body and bronchi of Japanese patients, needs to be taken into consideration in the evaluation, the 4 size options will allow for appropriate selection according to the length and diameter of the bronchus.

3) The patient characteristics and treatment backgrounds of the patient population may not differ substantially among the countries because the Zephyr EBV System is intended for patients with severe emphysema with lung hyperinflation who have dyspnoea despite drug therapy and non-surgical therapies.

4) The placement of the Zephyr EBV System involves a bronchoscopic procedure. The procedure is not particularly difficult for doctors who regularly perform bronchoscopy, and there should be no particular concerns about the procedure with the Zephyr EBV System as long as it is performed by doctors regularly performing bronchoscopic procedures who have been trained for the use of the Zephyr EBV System.

For the evaluation of the Zephyr EBV System, some of the proposed models were used. The LIBERATE and IMPACT studies used 4.0, 4.0 LP, and 5.5 ([redacted]) among the available sizes, but did not use 5.5 LP, which was under development at that time. The non-clinical studies tested [redacted] and 5.5 LP (flow rate and valve function tests) in simulated clinical conditions. The studies showed similar results with [redacted] and [redacted], leading to the conclusion that the removal of air from the hyperinflated lung lobe is practically feasible in their clinical use. Because 5.5 LP is smaller in size (contact area) and has lower expansion force than 5.5, 5.5 LP is considered less risky in terms of the impact of direct contact with the bronchus. In contrast, the non-clinical results showed lower valve expansion force of 5.5 LP than the 5.5, indicating a higher risk of valve migration. Nevertheless, valve migration is unlikely to cause serious adverse events, and thus no additional clinical study with 5.5 LP is necessary. The incidence of valve migration will be investigated for all sizes including 5.5 LP in the use-results surveys later described. It is, therefore, reasonable to add 5.5 LP to the size lineup of the Zephyr EBV System.

6.B.(2) Primary endpoint for the LIBERATE study

The applicant's explanation about the reasons for specifying the primary endpoint of the "threshold of ≥15% improvement in FEV1:"

- When FEV1 changes by approximately 100 mL, patients can notice a change in their condition.[5]
- Clinical studies of bronchodilators[6] employed 15% improvement as the appropriate threshold for the change in FEV1 measurements. The improvement rate changed by 10% to 14% with FEV1 changing from 1 to 0.7 L.
- The COPD guidelines (European Respiratory Society [ERS], American Thoracic Society [ATS], Global Initiative for Chronic Obstructive Lung Disease [GOLD], and American College of Clinical

Pharmacy [ACCP]) also support the threshold of ≥15% improvement in FEV1. The threshold is thus applicable to Japanese patients.

PMDA's view:
The treatment with the Zephyr EBV System is expected to reduce the volume of the target lung lobe and dilate the alveoli in the other area of the ipsilateral lung. FEV1 is used in severity assessment of COPD. Many clinical studies of therapeutic drugs for COPD used the primary endpoint of FEV1. For these reasons, there is no particular problem in specifying a percent improvement in FEV1 as the primary endpoint. The Zephyr EBV System is intended for patients with severe emphysema who have already received maximum non-surgical therapies. The applicant's explanation is justifiable that the effect of a ≥15% improvement in FEV1 is noticeable by patients themselves. As described in "Efficacy evaluation" below, however, the efficacy of the Zephyr EBV System should also be evaluated using additional endpoints other than FEV1.

6.B.(3) Efficacy evaluation

PMDA's view:
The Zephyr EBV System reduces the volume of the target lung lobe and dilate the untreated alveoli of the ipsilateral lung. On the basis of this principle, the Zephyr EBV System is expected to improve respiratory function and, consequently, clinical symptoms. The LIBERATE study used the primary endpoint of the percent improvement in FEV1 at 1 year after valve placement. It is understandable to use a percent improvement in FEV1 as the primary endpoint because FEV1 is used for severity assessment of COPD. However, respiratory function should be evaluated based not only on FEV1 but also on other parameters of lung function. "The JRS Guidelines for the Management of Chronic Obstructive Pulmonary Disease 2022" (sixth Edition, the Japanese Respiratory Society) in Japan recommend "Improvements and maintenance of symptoms, QOL, exercise tolerance, and physical activities" and "Prevention of exacerbation, delaying disease progression, and prolongation of healthy life expectancy" as COPD management goals. In the evaluation of the Zephyr EBV System, QOL (SGRQ), exercise tolerance, etc., should also be taken into consideration in addition to respiratory function, including long-term outcomes of these elements.

The LIBERATE study demonstrated a significantly greater percentage of subjects who had a ≥15% improvement in FEV1 at 1 year after valve placement in the Zephyr EBV group than the control group that received the conventional treatment. The protocol-defined primary endpoint for the study was met. The secondary endpoints of improvements in FEV1, SGRQ score (disease-specific QOL questionnaire), and 6MWD were also significantly higher in the Zephyr EBV group. The changes in the other respiratory function parameters also tended to improve in the Zephyr EBV group. The indices quantified by HRCT showed the reduction of target lobe volume from baseline at 45 days and 1 year after valve placement. PMDA concluded that the efficacy at 1 year after valve placement is assessable based on the results of the LIBERATE study.

The IMPACT study was conducted in patients with homogeneous emphysema using the primary endpoint of a percent change from baseline in FEV1 at 3 months after valve placement, which was significantly higher in the Zephyr EBV group than the control group. The secondary endpoints included

other respiratory parameters, QOL score (SGRQ), and exercise tolerance, which showed significant improvements. These results of the IMPACT study complemented the outcome of the LIBERATE study that employed different pathological condition-related inclusion criteria.

The Valves are placed for a long term. Its long-term efficacy should also be evaluated based on data from the LIBERATE study at and after 1 year. From the LIBERATE study, the long-term results up to 4 years after valve placement were submitted. The mean FEV1 up to 4 years was still higher than that at baseline, indicating the long-lasting efficacy of the treatment with the Zephyr EBV System. Because the follow-up of the subjects in the LIBERATE study is still underway at the time of the submission, data should be analyzed over years continuously to confirm the long-term efficacy (approval condition 4, later described).

6.B.(4) Safety evaluation

PMDA's view:

Because the Zephyr EBV System is intended for patients with severe COPD, serious adverse events including pneumothorax, COPD exacerbation, respiratory failure, and pneumonia and haemoptysis resulting in death, which commonly occurred in multiple subjects in the early period after the treatment with the Zephyr EBV System in the LIBERATE and IMPACT studies, warrant particular attention in the safety evaluation.

Pneumothorax

The applicant's explanation about the risk of pneumothorax:

Pneumothorax is likely to be caused by the following mechanism: Placed Zephyr EBV System reduces the volume of the target lung lobe, causing a space to be formed in the chest cavity. The ipsilateral lobe then rapidly inflates so that the space is filled until beyond the elastic limit of the lobe tissue, and causes the formation of bronchoalveolar fistulas, resulting in pneumothorax.

In the LIBERATE study, 46 cases of pneumothorax were reported from 44 of 128 subjects (34.4%) during the 12-month follow-up period, including 2 subjects who had 2 episodes. Table 32 shows the subjects with pneumothorax and the details of each case. A total of 34 cases (74%) occurred within 3 days after the procedure. A total of 26 cases (57%) were severe pneumothorax, including 3 cases (2.3%) that resulted in death. Table 33 shows the incidence of pneumothorax in each treated lobe. Pneumothorax occurred in all treated lobes, although its incidences differed among the lobes.

In the IMPACT study, a total of 26 cases of pneumothorax were reported from 22 of 84 subjects (26.2%) during the 6-month follow-up period (Table 34). Of these, 13 cases occurred in 11 of 43 subjects (25.6%) in the first Zephyr EBV group. The remaining 13 cases occurred in 11 of 41 subjects (26.8%) in the crossover Zephyr EBV group. A total of 4 subjects had 2 episodes of pneumothorax. Of 26 pneumothorax cases, 22 (84.6%) were managed by chest tube placement. The remaining 4 cases (15.4%) were managed by close follow-up. No deaths occurred.

In light of the high probability of pneumothorax, patients must be carefully monitored for the occurrence of this adverse event after the procedure. Because most pneumothorax occurred within 3 days after the

procedure, patients must be admitted to a hospital for ≥3 days after the procedure and undergo vital sign measurements at least once daily during hospitalization. Patients must also be instructed to notify their doctors or nurses immediately of chest pain or dyspnoea if any. In addition, patients should undergo chest X-ray multiple times during hospitalization. The directions for use should specify that the first chest X-ray, etc. be performed within several hours after the procedure. Prior to discharge from hospital, patients and their families or caregivers should be advised to seek immediate emergency care in case of the onset of any acute pneumothorax symptoms, provide emergency contact numbers and other information to healthcare providers, and avoid certain activities for a certain duration, etc.

Before the introduction of the Zephyr EBV System in clinical practice in Japan, later-described educational training will be organized jointly with Japanese academic societies on adverse events including pneumothorax management. Japan has a system called the Bronchoscopy Specialist Qualification System established by the Japan Society for Respiratory Endoscopy, and pulmonologists and paramedics with adequate knowledge and experience in pneumothorax management. Therefore, pneumothorax can be safely managed in Japan as in Europe and the US.

Table 32. Pneumothorax in the LIBERATE study

	Number of days after procedure	Severity	Hospitalization	Treatment	Valve removal	Outcome	Duration
1	2 days	Severe	No	Chest tube (1 day)	No	Death	1 day
2	2 days	Severe	No	Chest tube (1 day)	No	Death	1 day
3	12 days	Severe	No	No intervention	No	Death	1 day
4	13 days	Severe	Yes	Chest tube (5 days)	Yes	With sequela	6 days
5	1 day	Moderate	Yes	Chest tube (18 days)	No	With sequela	18 days
6	0 days	Severe	Yes	Chest tube (1 day)	Yes	Resolved	2 days
7	125 days	Severe	Yes	Chest tube (2 days)	No	Resolved	13 days
8	3 days	Severe	No	Chest tube (3 days)	No	Resolved	4 days
9	253 days	Severe	Yes	Chest tube (3 days)	No	Resolved	5 days
10	1 day	Severe	Yes	Chest tube (4 days)	No	Resolved	6 days
11	2 days	Severe	Yes	Chest tube (4 days)	No	Resolved	6 days
12	2 days	Severe	Yes	Chest tube (6 days)	No	Resolved	7 days
13	1 day	Severe	Yes	Chest tube (9 days)	Yes	Resolved	13 days
14	0 days	Severe	Yes	Chest tube (10 days)	Yes	Resolved	11 days
15	2 days	Severe	Yes	Chest tube (10 days)	Yes	Resolved	12 days
16	4 days	Severe	Yes	Chest tube (10 days)	Yes	Resolved	12 days
17	2 days	Severe	No	Chest tube (11 days)	No	Resolved	14 days
18	4 days	Severe	Yes	Chest tube (12 days)	No	Resolved	23 days
19	0 days	Severe	Yes	Chest tube (13 days)	Yes	Resolved	13 days
20	0 days	Severe	No	Chest tube (14 days)	No	Resolved	16 days
21	0 days	Severe	Yes	Chest tube (14 days)	Yes	Resolved	16 days
22	5 days	Severe	Yes	Chest tube (14 days)	Yes	Resolved	30 days
23	1 day	Severe	Yes	Chest tube (15 days)	No	Resolved	16 days
24	0 days	Severe	Yes	Chest tube (18 days)	No	Resolved	20 days
25	3 days	Severe	Yes	Chest tube (19 days)	No	Resolved	20 days
26	0 days	Severe	Yes	Chest tube (22 days)	No	Resolved	16 days
27	6 days	Severe	Yes	Chest tube (22 days)	No	Resolved	23 days
28	1 day	Moderate	Yes	Chest tube (3 days)	No	Resolved	6 days
29	1 day	Moderate	Yes	Chest tube (4 days)	No	Resolved	5 days
30	3 days	Moderate	Yes	Chest tube (4 days)	No	Resolved	15 days
31	1 day	Moderate	Yes	Chest tube (5 days)	No	Resolved	6 days
32	5 days	Moderate	Yes	Chest tube (5 days)	No	Resolved	5 days
33	0 days	Moderate	Yes	Chest tube (7 days)	No	Resolved	8 days
34	10 days	Moderate	Yes	Chest tube (11 days)	No	Resolved	12 days
35	0 days	Moderate	No	Chest tube (12 days)	Yes	Resolved	12 days
36	1 day	Moderate	Yes	Chest tube (15 days)	Yes	Resolved	41 days
37	0 days	Moderate	No	Chest tube (21 days)	No	Resolved	46 days
38	0 days	Moderate	Yes	Chest tube (43 days)	No	Resolved	63 days

	Number of days after procedure	Severity	Hospitalization	Treatment	Valve removal	Outcome	Duration
39	1 day	Moderate	No	No intervention	No	Resolved	5 days
40	159 days	Moderate	Yes	No intervention	No	Resolved	12 days
41	1 day	Mild	No	Chest tube (2 days)	Yes	Resolved	3 days
42	0 days	Mild	No	No intervention	No	Resolved	3 days
43	1 day	Mild	No	No intervention	No	Resolved	13 days
44	1 day	Mild	Yes	No intervention	No	Resolved	6 days
45	2 days	Mild	Yes	No intervention	No	Resolved	17 days
46	4 days	Mild	No	No intervention	No	Resolved	29 days

Table 33. Incidence of pneumothorax for each treated lobe in the LIBERATE study

	Left lower lobe (N = 15)		Left upper lobe (N = 85)		Right lower lobe (N = 6)		Right upper lobe (N = 14)		Right upper + middle lobes (N = 8)	
	Number of subjects with event (%)	Number of events	Number of subjects with event (%)	Number of events	Number of subjects with event (%)	Number of events	Number of subjects with event (%)	Number of events	Number of subjects with event (%)	Number of events
Treatment period	2 (13.3)	2	23 (27.1)	23	1 (16.7)	1	5 (35.7)	5	3 (37.5)	3
Long-term period	1 (6.7)	1	5 (6.3)	5	0 (0.0)	0	1 (7.1)	1	1 (12.5)	1

Table 34. Pneumothorax in the IMPACT study

Treatment group	Number of days after procedure	Severity	Hospitalization/ prolongation of hospitalization	Treatment	Valve removal	Outcome	Duration
EBV	1 day	Serious	Yes	Chest tube (≥5 days)	All	Resolved	41 days
EBV	6 days	Serious	Yes	Chest tube (≥5 days)	All	Resolved	11 days
EBV	1 day	Serious	Yes	Chest tube (≥5 days)	≥1	Resolved	17 days
EBV	1 day	Serious	Yes	Chest tube (≥5 days)	≥1	Resolved	15 days
EBV	1 day	Serious	Yes	Chest tube (≥5 days)	≥1	Resolved	11 days
EBV	1 day	Serious	Yes	Chest tube (≥5 days)	No	Resolved	9 days
EBV	1 day	Serious	Yes	Chest tube (≥5 days)	No	Resolved	9 days
EBV	1 day	Serious	Yes	Chest tube (≥5 days)	No	Resolved	18 days
EBV	2 days	Serious	Yes	Chest tube (≥5 days)	No	Resolved	13 days
EBV	2 days	Serious	Yes	Chest tube (≥5 days)	No	Resolved	15 days
EBV	17 days	Serious	Yes	Chest tube (≤5 days)	No	Resolved	8 days
EBV	50 days	Serious	Yes	Chest tube (≥5 days)	No	Resolved	15 days
EBV	36 days	Serious	No	Chest tube (number of days unknown)	No	Resolved	15 days
Crossover	2 days	Serious	Yes	Chest tube (≤5 days)	All	Resolved	6 days
Crossover	1 day	Serious	No	Chest tube (≥5 days)	≥1	Resolved	9 days
Crossover	1 day	Serious	Yes	Chest tube (number of days unknown)	≥1	Resolved	13 days
Crossover	1 day	Serious	Yes	Chest tube (≥5 days)	No	Resolved	12 days
Crossover	1 day	Serious	Yes	Chest tube (≥5 days)	No	Resolved	19 days
Crossover	5 days	Serious	Yes	Chest tube (≥5 days)	No	Resolved	12 days
Crossover	7 days	Serious	Yes	Chest tube (≥5 days)	No	Resolved	35 days
Crossover	8 days	Serious	Yes	Chest tube (≤5 days)	No	Resolved	7 days
Crossover	45 days	Serious	Yes	Chest tube (≤5 days)	No	Resolved	6 days
Crossover	2 days	Serious	Yes	Follow-up	No	Resolved	3 days
Crossover	4 days	Serious	Yes	Follow-up	No	Resolved	2 days
Crossover	4 days	Serious	Yes	Follow-up	No	Resolved	8 days
Crossover	5 days	Serious	Yes	Follow-up	No	Resolved	16 days

PMDA's view:

Given the principle of the treatment with the Zephyr EBV System, it will cause pneumothorax inevitably with some frequency as compared with non-surgical treatment. The LIBERATE study reported 38 cases

of pneumothorax in 38 subjects (29.7%) in the Zephyr EBV group during the treatment period and 8 cases in 8 subjects (6.6%) in the Zephyr EBV group during the long-term period, while this event did not occur in the control group. There were 3 cases of pneumothorax-associated deaths (2.3%) and 34 cases of serious adverse events (26.6%) within 45 days after the procedure. Because of its high incidence and severity, pneumothorax is considered an adverse event of the utmost concern in the treatment with the Zephyr EBV System.

Of the reported pneumothorax, 67% occurred within 3 days and 76% within 5 days after the first procedure. This indicates the need of careful post-procedural follow-up until the incidence of pneumothorax declines under inpatient conditions. Pneumothorax may involve thoracic cavity drainage. Furthermore, 12 cases in the LIBERATE study and 8 cases in the IMPACT study resulted in the removal of placed valves. Thus, decision making on valve removal will be required.

The prevention of pneumothorax is difficult due to the principle of the treatment with the Zephyr EBV System. It is also difficult to predict the onset of pneumothorax from the target lobe. Prior to the use of the Zephyr EBV System in Japan, the risk of serious pneumothorax should be appropriately communicated to not only healthcare professionals but also patients. In addition, all possible measures should be taken to ensure that pneumothorax is treated appropriately. Of 3 subjects who died of pneumothorax in the LIBERATE study, 1 subject presented with tension pneumothorax and failed to survive even during hospitalization, and another subject developed tension pneumothorax out of hospital and was taken to an emergency room. Given these cases, valve placement and post-procedural patient management should be implemented at medical institutions well-equipped for emergency treatment, including cardiorespiratory management and thoracic cavity drainage. Pleurodesis, bronchial occlusion, or other surgical treatment may be necessary depending on the severity and pathological condition of pneumothorax. Therefore, medical institutions may need to be adequately equipped to provide surgical treatment of pneumothorax. The criteria for doctors and medical institutions required in the post-marketing setting are described later in Section 6.B.(5).

COPD exacerbation

The applicant's explanation about the risk of COPD exacerbation:

In the LIBERATE study, there were 25 cases of COPD exacerbation in 25 subjects (19.5%) in the Zephyr EBV group and 7 cases in 7 subjects (11.3%) in the control group during the treatment period. Serious COPD exacerbation occurred in 10 subjects (7.8%, 10 cases) in the Zephyr EBV group and 3 subjects (4.8%, 3 cases) in the control group. There were 118 cases of COPD exacerbation in 69 subjects (56.6%) in the Zephyr EBV group and 70 cases in 35 subjects (56.5%) in the control group during the long-term period. Serious COPD exacerbation occurred in 28 subjects (23.0%, 40 cases) in the Zephyr EBV group and 19 subjects (30.6%, 29 cases) in the control group.

In the IMPACT study, there were 12 cases of COPD exacerbation in 12 subjects (27.9%) in the Zephyr EBV group and 2 cases in 2 subjects (4.0%) in the control group during the short-term period. Serious COPD exacerbation occurred in 6 subjects (14.0%, 6 cases) in the Zephyr EBV group and 1 subject (2.0%, 1 case) in the control group. There were 30 cases of COPD exacerbation in 17 subjects (39.5%) in the Zephyr EBV group and 23 cases in 19 subjects (38.0%) in the control group during the long-term

period. Serious COPD exacerbation occurred in 8 subjects (18.6%, 12 cases) in the Zephyr EBV group and 10 subjects (20.0%, 10 cases) in the control group.

In both studies, COPD exacerbation in the early postoperative period was a risk associated with the treatment with the Zephyr EBV System. In the LIBERATE study, however, the incidence of serious COPD exacerbation decreased during the long-term treatment. The benefits of valve placement is considered to outweigh a possible temporal increase in the risk COPD exacerbation.

PMDA's view:
Serious COPD exacerbation in the early postoperative period is a risk associated with the treatment with the Zephyr EBV System. In the LIBERATE study, COPD exacerbation commonly occurred during the treatment period (up to 45 days after the procedure), but its incidence was similar between Zephyr EBV and control groups during the long-term period (46 days to 12 months). COPD exacerbation in the early postoperative period did not result in death. Therefore, the risk associated with the treatment with the Zephyr EBV System is considered acceptable in light of expected benefits from appropriate postoperative risk measures.

Respiratory failure
The applicant's explanation about the risk of respiratory failure:
In the LIBERATE study, there were 2 cases of respiratory failure in 2 subjects (1.6%) in the Zephyr EBV group and none in the control group during the treatment period. Both cases were serious. During the long-term period of the study, there were 1 case of respiratory failure in 1 subject (0.8%) in the Zephyr EBV group and 3 cases in 2 subjects (3.2%) in the control group. All events were serious. One case of serious respiratory failure in 1 subject during the treatment period resulted in death.

In the IMPACT study, 1 case of respiratory failure, non-serious, occurred in 1 subject (2.0%) in the control group during the long-term period.

The fatal case of respiratory failure in the early postoperative period was due to the refusal of aggressive treatment. If the subject accepted aggressive treatment, the death could have been avoided. The Zephyr EBV group had a lower incidence of respiratory failure than the control group in the long-term postoperative period, indicating that the incidence of this adverse event increased only transiently after valve placement and is clinically acceptable.

PMDA's view:
Serious respiratory failure in the early postoperative period, although infrequent, is a risk associated with the treatment with the Zephyr EBV System that is potentially life threatening. In light of the target patient population of the Zephyr EBV System, however, this adverse event is expected to occur at a certain frequency. The treatment with the Zephyr EBV System must be performed based on the recognition of respiratory failure as a Zephyr EBV System-associated risk, and at medical institutions adequately equipped for the treatment of this adverse event. The criteria for physicians and medical institutions in the post-marketing setting are described later in Section 6.B.(5).

Pneumonia

The applicant's explanation about the risk of pneumonia:

In the LIBERATE study, there were 6 cases of pneumonia in 6 subjects (4.7%) in the Zephyr EBV group and none in the control group during the treatment period. Serious pneumonia occurred in 1 subject (0.8%, 1 case). There were 12 cases of pneumonia in 11 subjects (9.0%) in the Zephyr EBV group and 7 cases in 6 subjects (9.7%) in the control group during the long-term period. Serious pneumonia occurred in 7 subjects (5.7%, 7 cases) in the Zephyr EBV group and 5 subjects (8.1%, 6 cases) in the control group. Pneumonia in 2 cases in 2 subjects in the Zephyr EBV group needed to be managed by removal of all valves placed.

In the IMPACT study, 1 case of non-serious pneumonia occurred in 1 subject (2.0%) in the control group in the short-term. There were 1 case of pneumonia in 1 subject (2.3%) in the Zephyr EBV group and 3 cases in 3 subjects (6.0%) in the control group in the long-term. Serious pneumonia occurred in 1 subject (2.3%, 1 case) in the Zephyr EBV group and in 2 subjects (4.0%, 2 cases) in the control group.

Standard medical treatment with wide-spectrum antibiotics is recommended to manage pneumonia. When pneumonia occurs in a lobe distal to the valve placement site and does not respond to antibiotic treatment, valve removal should be considered.

PMDA's view:

Although pneumonia may occur in the early postoperative period, no serious cases have been reported and thus is clinically acceptable. PMDA instructed the applicant to communicate the possibility of the removal of all Valves in the treatment of pneumonia through the training sessions and the instructions for use, and to investigate the incidence of pneumonia and whether pneumonia is appropriately manageable in Japan through the post-marketing surveillance later described. The applicant accepted it.

Haemoptysis

The applicant's explanation about the risk of haemoptysis:

In the LIBERATE study, there were 14 cases of haemoptysis in 11 subjects (8.6%) in the Zephyr EBV group and 1 case in 1 subject (1.6%) in the control group during the treatment period. No serious haemoptysis were observed. There were 12 cases of haemoptysis in 12 subjects (9.8%) in the Zephyr EBV group and none in the control group during the long-term period. Serious haemoptysis occurred in 2 subjects (1.6%, 2 cases). Serious haemoptysis in 1 case of 1 subject during the long-term period resulted in death. In the IMPACT study, 1 case of non-serious haemoptysis occurred in 1 subject (2.3%) in the Zephyr EBV group in the short-term. In patients who are on anticoagulants or antiplatelets, even slight bleeding in the airway may lead to a serious outcome. However, the development of complications can be minimized by carefully assessing the risks of bronchoscopic diagnosis and intervention. For the case of Zephyr EBV System-related death that occurred at approximately 2 years after the procedure in the LIBERATE study, haemoptysis itself resolved after appropriate intervention and the incidence of haemoptysis-associated death was low. For these reasons, the adverse event can be clinically acceptable.

PMDA's view:
Postoperative haemoptysis, although infrequent, is a potentially life threatening risk associated with the treatment with the Zephyr EBV System. The treatment with the Zephyr EBV System must be performed based on the recognition of postoperative haemoptysis as a Zephyr EBV System-associated risk and at medical institutions adequately equipped for the treatment of this adverse event. PMDA instructed the applicant to communicate the relevant information through the training sessions and the instructions for use, and to investigate the incidence of haemoptysis and whether haemoptysis is appropriately manageable in Japan through the post-marketing surveillance later described. The applicant accepted it.

Death
PMDA's view:
Death due to pneumothorax or respiratory failure occurred in 4 subjects in the early postoperative period in the LIBERATE study. As mentioned, safety in the use of the Zephyr EBV System must be ensured by performing it in appropriately selected patients and at medical institutions equipped for complication management. The incidence and time-course of deaths in Japan should be collected through the post-marketing surveillance.

The Zephyr EBV group showed further increasing deaths than the control group even after 1 year. The causes of these deaths were COPD exacerbation, pneumonia, respiratory failure, and traffic injury, none of which were related to the Zephyr EBV System other than the deaths of 2 subjects with pneumonia requiring the removal of all valves and Zephyr EBV System-associated haemoptysis. As mentioned, PMDA instructed the applicant to collect relevant information through the training sessions and the instructions for use, and to investigate the incidence and time-course of deaths in Japan in the post-marketing surveillance. The applicant accepted it.

Valve migration and expectoration
The applicant's explanation about the risk of valve migration and expectoration:
In the LIBERATE study, there were 3 cases of valve migration in 3 subjects (2.3%) and valve expectoration in 2 subjects (1.6%). The events occurred from 1 day through 5 months after the procedure. None of the events resulted in death or serious outcome. In the IMPACT study, 2 cases of valve migration occurred in 1 subject (2.3%) in the short-term and both were serious. There were 2 cases of valve expectoration in 1 subject (2.3%), 1 case of valve dislocation in 1 subject (2.3%), and 1 case of valve replacement in 1 subject (2.3%). The case of valve dislocation in 1 subject (2.3%) was serious. The valve migration observed in the clinical studies may likely to occur by improper valve size choice or positioning. Because valve migration can aggravate dyspnoea, the valve position should be checked by a chest X-ray or computerized tomography in the early postoperative period. If valve migration is suspected, the valve position should be assessed bronchoscopically and the valve should be replaced as necessary. Valve migration occurs infrequently, and a migrated valve is locatable and removable or can be replaced, thus is clinically acceptable

PMDA's view:
None of valve migrations has led a severe outcome. The following measures will help reduce the risk of valve migration and secure the safety of patients in whom valve migration has been found. These measures should be communicated through training and the guidelines for proper use.

- Determine the size of the airway before valve placement and select the appropriate valve size.
- Check the position of the valve in X-ray imaging, CT scanning, or bronchoscopy.
- Suspect valve migration when an abrupt decline in valve effect (e.g., lung function deterioration) is observed, and examine the lobe.
- Consider endoscopic valve removal and replacement if valve migration is observed.

PMDA's view on the safety of the Zephyr EBV System:
The treatment with the Zephyr EBV System is accompanied by adverse events, including pneumothorax, COPD exacerbation, and respiratory failure, in the relatively early postoperative period. These adverse events are risks leading to severe outcomes or death. Taking these risks into consideration, the Zephyr EBV System should be used in patients who truly need the treatment as determined by qualified physicians. The procedure should be performed by physicians with full understanding of possible adverse events during and after the procedure, and at medical institutions appropriately equipped for the treatment of possible adverse events. The facts that the management of postoperative pneumonia may require the removal of all valves and that the Zephyr EBV System-associated haemoptysis may occur should be communicated through the training sessions and the guidelines for proper use. Training, and establishment of the guidelines for proper use and approval conditions as later described are essential.

6.B.(5) Post-marketing safety measures

The applicant plans to provide users (physicians and other healthcare professionals) with training opportunities similar to those provided overseas (Table 35) and explained that the details of the training programs would be prepared jointly with the academic societies involved (e.g., the Japan Society for Respiratory Endoscopy).

Table 35. Outline of training programs

E-learning	The outline of the Zephyr EBV System, patient selection, directions for use, placement method, and clinical study data including complications are reviewed.
Face-to-face training	A training program for physicians to learn about appropriate patient selection, procedure, and procedure-related complications, etc. This program provides an opportunity to practice the skills using a lung model.
Training for healthcare professionals other than physicians	A series of lectures on bronchoscopy for healthcare professionals

PMDA's view:
The Zephyr EBV System is Japan's first bronchial valve for the treatment of severe emphysema. Valve placement must be performed with a good understanding of the ways of diagnosis of hyperinflation and target lobe selection based on the results of prior pulmonary function test, CT scans, etc.; the selection of appropriate valve size that fits on the bronchus; how to identify eligible patients based on collateral ventilation measured with the Chartis System; and the procedures. The applicant presented the outline of training that includes lecture and practice sessions, which allow users to understand the Zephyr EBV System and acquire the procedural skills, and is considered reasonable. For the proper use of the Zephyr EBV System, requirements for treating physicians and medical institutions should be defined in view of

patient eligibility criteria determined based on the patient inclusion/exclusion criteria in the foreign clinical studies, as well as risk measures. In addition to the above training programs, guidelines for proper use (e.g., requirements for users and medical institutions, and details of candidate patients for the treatment, including clinical signs and findings from respiratory function test) should be prepared for the devices used in BLVR, in cooperation with the academic societies involved. The Zephyr EBV System has a potential risk of severe outcome or death, and thus should only be used for patients who have disabling symptoms despite optimal non-surgical therapies. Such advice should be provided in the guidelines for proper use, and presented in the form of approval conditions 1 and 2.

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

7.A Summary of the data submitted

The applicant's explanation:

The applicant plans to provide training opportunities to all treating physicians on the use of the Zephyr EBV System. The placement of the Zephyr EBV System employs the standard bronchoscopic procedure. The use-results survey will not be necessary because of not much difference in medical environment in Japan from other countries' including the US, and demonstrated safety and efficacy of BLVR with the Zephyr EBV System in the study in Asian patients by Park, et al.[7] in Korea.

7.B Outline of the review conducted by PMDA

PMDA's view:

The results of the foreign clinical studies can be extrapolated to the evaluation of the efficacy and safety of the Zephyr EBV System in Japan. However, there is no bronchial valve approved for the treatment of severe emphysema in Japan. Further information need to be collected through a use-results survey to confirm whether an appropriate risk management and treatment can be ensured for adverse events that were reported in the LIBERATE or IMPACT study in the medical environment in Japan. Accordingly, the applicant was instructed to conduct a use-results survey, and the applicant submitted the following draft of use-results survey.

Table 36. Summary of use-results survey (draft)

Objective		To evaluate the efficacy and safety of the Zephyr EBV System in patients who are on optimal non-invasive treatment for severe COPD accompanied by severe emphysema and hyperinflation with little or no documented collateral ventilation and are eligible for bronchoscopic treatment.
Survey period	Preparation	12 months
	Registration	3 years
	Follow-up	12 months (preparatory period, 2 months)
	Analysis	10 months
Survey items		Demographics, prior therapies at baseline, respiratory parameters (lung function and vital capacity), high resolution CT images, details of the procedure, and all adverse events
Key survey items		• FEV1, RV, TLC, 6MWD, mMRC, BODE index, SGRQ, high resolution CT (HRCT) images, procedural information, and treated lobe volume reduction (TLVR) • Adverse events of special interest: COPD exacerbation, haemoptysis, pneumothorax, pneumonia, respiratory failure, valve migration, valve expectoration; safety • Serious respiratory adverse events: Safety
Analysis items		Incidence of pneumothorax within 45 days after the procedure, device- or procedure-related COPD exacerbation, pneumonia, haemoptysis, valve expectoration, valve migration, incidence of all serious adverse events not limited to respiratory failure, change in lung function (FEV1), change in exercise tolerance (6MD), and change in QOL (SGRQ)
Planned sample size		140 (all-case surveillance)

The planned sample size of 140 was determined to assess the comparability of the incidence of pneumothorax between the use-results survey and the LIBERATE study based on the presumed incidence of approximately 30% within 45 days after the placement, with a half-width value of <10% and a 2-sided 95% confidence interval. The survey period and items were the same as those of the LIBERATE study.

PMDA concluded that the draft use-results survey submitted by the applicant was acceptable for the following reasons: The survey design allows for the comparison of the incidence of pneumothorax, which is the adverse event of most concern in BLVR, with that in the LIBERATE study; the planned sample size is large enough to clarify how pneumothorax has been treated in Japan; data on respiratory adverse events are collectable as key survey items; and lung function, etc. is also assessable.

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 compliance 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 Zephyr EBV System is a bronchial valve intended for patients who have been on optimal non-invasive treatment for severe COPD accompanied by severe emphysema and hyperinflation with little or no collateral ventilation as determined using a physiological measure. The Zephyr EBV System works to occlude airflow into a hyperinflated lung lobe, remove the air trapped in it, thereby reducing its volume.

The review of the application for the Zephyr EBV System focuses on its efficacy and safety and post-marketing safety measures. Based on comments raised in the Expert Discussion, PMDA have reached the following conclusions:

(1) Efficacy and safety of the Zephyr EBV System

The LIBERATE study showed the primary endpoint of 47.7% in the Zephyr EBV group and 16.8% in the control group. A significantly higher percentage of subjects in the Zephyr EBV group, as compared to the control group, achieved the threshold of ≥15% improvement in FEV1. There were 26 cases of severe pneumothorax, which occurred at a high incidence of 57% and were severe. In light of the difficulty in preventing pneumothorax in the treatment employing the Zephyr EBV System, the selection of medical institutions is essential for the use of it in Japan to take all possible appropriate measures to manage pneumothorax developing. In view of the potential benefits of the Zephyr EBV System, its risk is considered acceptable as long as efforts are made to minimize the impact of pneumothorax on patient's life prognosis. On the basis of the analysis of the event and other serious adverse events, PMDA concluded that the safety of the Zephyr EBV System is clinically acceptable.

While the LIBERATE study targeted patients with severe heterogenous emphysema, the IMPACT study in patients with severe homogenous emphysema yielded similar results to that of the LIBERATE study. The results of the IMPACT study supplemented the results of the LIBERATE study, and these studies demonstrated the efficacy and safety of the Zephyr EBV System, regardless of whether lesions are homogenous or heterogenous.

The Zephyr EBV System is a promising treatment option following non-surgical therapies for patients for whom LVRS is conventionally indicated. LVRS is a highly invasive procedure and has been reported to lead to poor life prognosis as compared with medical treatment. Currently, LVRS is performed only in limited cases. In contrast, BLVR with the Zephyr EBV System is safe and less invasive as compared with LVRS and provides clinically significant efficacy. Due to its less-invasiveness, the procedure with the Zephyr EBV System also causes fewer serious adverse events and provides better life prognosis than LVRS. The risk and benefit balance of the Zephyr EBV System has been maintained within the clinically acceptable range. The introduction of the Zephyr EBV System to clinical setting in Japan is of clinical significance. At the same time, BLVR with the Zephyr EBV System has a risk of serious outcome or death. As mentioned, it is essential that the Zephyr EBV System is used at medical institutions that are capable of determining patient eligibility and managing expected adverse events properly under an established regime. Adherence to the guidelines for proper use, which will be developed in cooperation with the academic societies involved, and the conduct of a use-results survey are necessary.

(2) Post-marketing safety measures

The Zephyr EBV System is Japan's first bronchial valve intended for the treatment of severe emphysema. Valve placement warrants a good understanding of the ways to select eligible patients and determine the target lobe, and of the series of procedures for use including the selection of appropriate valve size that fits on the bronchus and the judgement of eligibility based on the status of collateral ventilation as measured using the Chartis System. To ensure that the Zephyr EBV System is used in a safe and effective

manner, appropriate training for physicians is important. The academic societies involved plan to jointly develop the guidelines for proper use of the Zephyr EBV System, which mandates product training. The post-marketing safety measures proposed by the applicant are reasonable and will be advised in the form of approval conditions 1 and 2.

To verify the outcomes of the treatment with the Zephyr EBV System in the clinical settings in Japan with the above safety measures taken into account, a use-results survey is required. The appropriate duration of use-results survey is 6 years. This requirement should be added as approval condition 3. To estimate long-term prognosis, the submitted long-term results from the clinical studies need to be analyzed. In this context, the applicant is required to report over years and take necessary measures, and this requirement is to be added as approval condition 4.

As a result of its review, PMDA concludes that the Zephyr EBV System may be approved for the intended use modified as shown below.

Intended Use

The Zephyr EBV System is a one-way valve that is placed in the bronchus to occlude airflow into the target lung lobe. The Zephyr EBV System is intended for patients aged 18 years or older who are on optimal non-invasive treatment for COPD associated with severe emphysema and hyperinflation with little or no collateral ventilation from a neighboring lobe as determined by physiological measures and are eligible for bronchoscopic treatment.

Approval Conditions

The applicant is required to:

1. Ensure that the product is used by physicians with adequate knowledge and experience in treating COPD who have competency to select eligible patients according to pathological condition, adequate procedural skills, and knowledge about complications, etc. associated with the procedure, and at medical institutions that have an established treatment system for the disease. For these purposes, the applicant is expected to disseminate the guidelines for proper use developed jointly with academic societies involved, provide learning opportunities, and take other necessary measures.
2. Ensure the proper use of the product by necessary measures such as the provision of the proper use guidelines developed by academic societies involved and learning opportunities for physicians.
3. Conduct a use-results survey in the post-marketing setting involving all Japanese patients treated with the product until obtaining data of a certain number of cases, report survey results to the Pharmaceuticals and Medical Devices Agency, and take appropriate measures as necessary.
4. Report the analysis results to the Pharmaceuticals and Medical Devices Agency on the long-term prognosis of the patients who participated in the clinical studies included in this submission, and take 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 6 years.

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

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