



Zephyr[®]
Endobronchial Valve
System

Instructions for Use

Caution: Federal law restricts this device to sale by or on the order of a physician.

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1.0 Pulmonx Zephyr® Endobronchial Valve (EBV®) System Description

The Zephyr® Endobronchial Valve (Zephyr Valve) is an endobronchial implant designed to occlude airflow in the target lobe and thereby reduce lung volume. The device consists of a one-way silicone duckbill valve attached to a nickel-titanium (Nitinol) self-expanding retainer that is covered with a silicone membrane. It is implanted in the target bronchus during a bronchoscopy procedure using the Zephyr Endobronchial Delivery Catheter (EDC) that is guided to the targeted bronchus by inserting it through the working channel of an adult bronchoscope.

Successful lobar occlusion may require placement of multiple Zephyr Valves in bronchi of the target lobe. The Zephyr Valves permit air to vent out of the treated lobe during exhalation but do not permit refilling of this region during inhalation to reduce hyperinflation due to emphysema. Trapped air in the diseased lobe escapes through the Zephyr Valves until the lung volume of the treated lobe is reduced.

The Zephyr Valve is designed to be a permanent implant, but can be removed, if necessary.

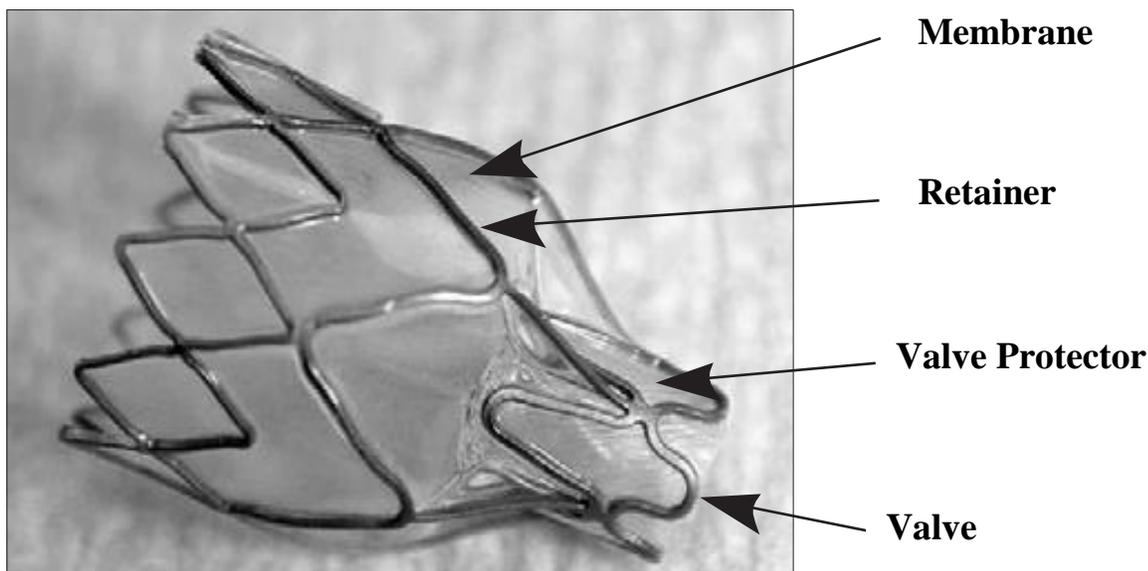


Figure 1 Zephyr Valve

1.1 Required Equipment

Adult flexible bronchoscope (working channel ≥ 2.8 mm)

1.2 System Components

- Zephyr 4.0 Endobronchial Valve (Zephyr 4.0 EBV)
- Zephyr 4.0-LP Endobronchial Valve (Zephyr 4.0-LP EBV)
- Zephyr 5.5 Endobronchial Valve (Zephyr 5.5 EBV)
- Zephyr 4.0 Endobronchial Delivery Catheter (Zephyr 4.0 EDC)
- Zephyr 4.0-J Endobronchial Delivery Catheter (Zephyr 4.0-J EDC)
- Zephyr 5.5 Endobronchial Delivery Catheter (Zephyr 5.5 EDC)

The Zephyr 4.0 EDC and Zephyr 4.0-J EDC, which have blue marker bands, are configured to deliver the Zephyr 4.0 EBV and Zephyr 4.0-LP EBV. The Zephyr 5.5 EDC, which has green marker bands, is configured to deliver the Zephyr 5.5 EBV.

2.0 Indications for Use

The Pulmonx Zephyr® Endobronchial Valves are implantable bronchial valves indicated for the bronchoscopic treatment of adult patients with hyperinflation associated with severe emphysema in regions of the lung that have little to no collateral ventilation.

3.0 Contraindications

The Zephyr Valve is contraindicated for:

- Patients for whom bronchoscopic procedures are contraindicated
- Patients with evidence of active pulmonary infection
- Patients with known allergies to Nitinol (nickel-titanium) or its constituent metals (nickel or titanium)
- Patients with known allergies to silicone
- Patients who have not quit smoking
- Patients with large bullae encompassing greater than 30% of either lung

4.0 Warnings

The Zephyr Valve should be used with caution and only after careful consideration in patients with:

- Prior lung transplant, LVRS, median sternotomy, or lobectomy
- Congestive heart failure or recent myocardial infarction
- FEV₁ <15% of predicted value

The Zephyr EDC handle contains strong permanent magnets. To avoid interference and possible patient/clinician harm, keep it more than 2 inches away from medical devices that could be affected by the magnetic fields, including, but not limited to pacemakers, cochlear implants, and neurostimulators. Additionally, strong magnetic fields may cause damage to magnetic data storage media and electronic equipment if brought within two inches of the Zephyr EDC.

5.0 Precautions

5.1 General Precautions

Read all labels and instructions prior to use. Use is restricted to a physician trained in the use of this device.

- The Zephyr Valve and EDC are intended for single-patient use only. Do not re-sterilize. No assurance of sterility can be made if devices are re-used.
- Do not attempt to reload a Zephyr Valve.
- Do not use the device if the sterilization barrier has been damaged or if the device is dropped after removal from sterile packaging.
- Performance of the Zephyr Valve has not been assessed in physiological conditions unique to air leak patients with an open thoracic window (also known as a Claggett Window or Eloesser Flap). The Zephyr Valve device may be subject to fracture due to unusual physical forces in this setting.
- Safety in uncontrolled pulmonary hypertension has not been evaluated.

- The Zephyr Valve was evaluated in patients with heterogenous emphysema in the pivotal trial, LIBERATE Study (Section 6.1). Limited data on the use of this device in homogenous emphysema patients came from the OUS IMPACT trial (Section 6.2).

5.2 Magnetic Resonance Imaging (MRI) Safety Information

Non-clinical testing has demonstrated the Zephyr Endobronchial Valve (i.e., 4.0 EBV, 4.0-LP EBV, and 5.5 EBV) is MR Conditional. A patient with this valve can be safely scanned in an MR system meeting the following conditions:

- Static magnetic field of 3.0 T, or less
- Maximum spatial field gradient of 4,000 gauss/cm (40 T/m)
- Maximum MR system reported, whole body averaged specific absorption rate (SAR) of 4 W/kg (First Level Controlled Operating Mode)

Under the scan conditions defined above, the Zephyr Endobronchial Valve (i.e., 4.0 EBV, 4.0-LP EBV, and 5.5 EBV) is expected to produce a maximum temperature rise of less than 2.7°C after 15 minutes of continuous scanning.

In non-clinical testing, the image artifact caused by the Zephyr Endobronchial Valve (i.e., 4.0 EBV, 4.0-LP EBV, and 5.5 EBV) extends approximately 5 mm from the valve when imaged with a gradient echo pulse sequence and a 3.0 T MRI system.

The Endobronchial Loader System (ELS) and the flexible Zephyr Endobronchial Delivery Catheter (EDC) are not tested for their compatibility with MR environment and are MR unsafe.

5.3 Target Lobe Selection

Zephyr Valves should be used in diseased lobes with little to no collateral ventilation from a neighboring lobe(s). The LIBERATE Study, IMPACT Trial, and TRANSFORM Study all assessed collateral ventilation utilizing the Chartis[®] Pulmonary Assessment System which provides a physiological measure of air flow.

Patients in whom the targeted lobe for treatment is not the most diseased (due to factors such as collateral ventilation or other abnormalities), who have a contralateral lung with a >60% emphysema destruction score (at -910 HU), could be at higher risk for a complex pneumothorax (defined as requiring removal of all valves or resulting in death) if a pneumothorax occurs. In the event the most diseased lobe is not the target lobe and the contralateral lung has >60% emphysema destruction score (at -910 HU), Zephyr Valve treatment should only be performed after careful consideration and appropriate discussion of the risk with the patient. Patient should be carefully observed post-procedure.

5.4 Pneumothorax Management

Pneumothorax is a commonly occurring side effect of Zephyr Valve treatment. In LIBERATE, seventy-six percent (76%) of pneumothoraces occur within the first 3 days of a procedure. Patients should remain in-hospital for the first 3 nights after a procedure and should be provided with clear instructions on recognizing symptoms of a pneumothorax and to seek emergent help if experiencing these symptoms.

In the event a pneumothorax occurs, pneumothorax management should be per expert recommendations¹. A chest x-ray must be completed within the first four (4) hours and then 24 hours after the procedure as routine clinical practice. Patient should be discharged according to the physician's clinical judgement.

6.0 Clinical Experience

The safety and effectiveness of the Zephyr Endobronchial Valve (EBV) in patients with little to no collateral ventilation in the treated lobe has been demonstrated in 3 multicenter randomized clinical studies in subjects with both severe heterogeneous and homogeneous emphysema and absence of collateral ventilation. These studies included:

- LIBERATE Study, see Section 6.1
- IMPACT Trial, see Section 6.2
- TRANSFORM Study, see Section 6.3

6.1 LIBERATE Study: Lung Function Improvement after Bronchoscopic Lung Volume Reduction with Pulmonx Endobronchial Valves used in Treatment of Emphysema

Study Objective

The LIBERATE Study was a prospective randomized, controlled study designed to assess the safety and effectiveness of bronchoscopic lung volume reduction (BLVR) using the Zephyr Endobronchial Valve (EBV) in treated study subjects compared to standard-of-care Control subjects to support a premarket approval application to FDA.

Study Design

The LIBERATE Study was a multicenter, prospective, randomized, controlled, one-way crossover study. Subjects were enrolled and randomized at 24 Investigational sites in the US and outside the US (OUS). Qualifying subjects with heterogeneous emphysema were randomized at a 2:1 ratio into either the Zephyr EBV treatment arm or Control (Standard of Care) arm. The subjects in the EBV arm had Zephyr EBVs placed in the target lobe to achieve lobar occlusion. Both the Zephyr EBV and Control group subjects continued to receive optimal medical management according to current clinical practice. Following their 12-month evaluation, the Control group subjects had an option to cross over to Zephyr EBV treatment, if eligible.

Key Inclusion Criteria

1. Signed Screening or Study Procedure Informed Consent using a form that was reviewed and approved by the IRB.
2. Age 40 to 75 years.
3. BMI less than 35 kg/m².
4. FEV₁ between 15% and 45% of predicted value at baseline exam
5. Post-rehabilitation 6-minute walk distance between 100 meters and 500 meters at baseline exam.
6. Stable with less than 20 mg prednisone (or equivalent) daily.

¹ Valipour, Arshang, et al. "Expert statement: pneumothorax associated with endoscopic valve therapy for emphysema-potential mechanisms, treatment algorithm, and case examples." *Respiration* 87.6 (2014): 513-521.

7. Nonsmoking for 4 months prior to screening interview.
8. Current Pneumococcus vaccination.
9. Current Influenza vaccination.
10. Little to no collateral ventilation (CV-) as determined using the Chartis System.

Key Exclusion Criteria

1. Clinically significant (greater than 4 tablespoons per day) sputum production.
2. Two or more COPD exacerbation episodes requiring hospitalization in the last year at screening.
3. Two or more instances of pneumonia episodes in the last year at screening.
4. History of exercise-related syncope.
5. Myocardial Infarction or congestive heart failure within 6 months of screening.
6. Prior lung transplant, LVRS, bullectomy or lobectomy.
7. Clinically significant bronchiectasis.
8. Unable to safely discontinue anti-coagulants or platelet activity inhibitors for 7 days.
9. Uncontrolled pulmonary hypertension (systolic pulmonary arterial pressure >45 mm Hg) or evidence or history of CorPulmonale as determined by recent echocardiogram (completed within the last 3 months prior to screening visit).
10. Pulmonary nodule requiring surgery as noted by chest X-ray or CT scan.
11. HRCT collected per CT scanning protocol within the last 3 months of screening date and evaluated by clinical site personnel using Myrian CT software (K071000) shows:
 - a. Parenchymal destruction score of greater than 75% in all three right lobes or both left lobes.
 - b. Emphysema heterogeneity score less than 15% (Not Applicable for Crossover subjects as of Revision H of protocol).
 - c. Large bullae encompassing greater than 30% of either lung.
 - d. Insufficient landmarks to evaluate the CT study using the software as it is intended.
12. Left ventricular ejection fraction (LVEF) less than 45% as determined by recent echocardiogram (completed within the last 3 months prior to screening visit).
13. Resting bradycardia (<50 beats/min), frequent multifocal PVCs, complex ventricular arrhythmia, sustained SVT.
14. Post-bronchodilator FEV₁ less than 15% or greater than 45% of predicted value at screening.
15. TLC less than 100% predicted (determined by body plethysmography) at screening.
16. RV less than 175% predicted (determined by body plethysmography) at screening.
17. DLCO less than 20% predicted value at screening.
18. 6-minute walk distance less than 100 meters or greater than 450 meters at screening.
19. PaCO₂ greater than 50 mm Hg (Denver greater than 55 mm Hg) on room air at screening.
20. PaO₂ less than 45 mm Hg (Denver less than 30 mm Hg) on room air at screening.

21. Elevated white cell count (>10,000 cells/ μ L) at screening.
22. Plasma cotinine level greater than 13.7 ng/ml (or arterial carboxyhemoglobin >2.5% if using nicotine products) at screening.
23. Evidence of collateral ventilation (CV+) as determined using the Chartis System.

Follow-up

Subjects in both arms were followed-up at 45-days, 3-months, 6-months, 9-months, and 1-year. Subjects in the Zephyr EBV treatment arm had additional daily phone call follow-ups for the first ten (10) days, and office visits at 7-days and 30-days.

Annual follow-up visits out to 5 years are planned for the Zephyr EBV treatment arm and Control Subjects that crossed over to the Zephyr EBV treatment arm after completing their 12 months follow-up.

Endpoints

The primary effectiveness endpoint was the percentage of study subjects in the Zephyr Endobronchial Valve (EBV) treatment arm who meet the threshold of $\geq 15\%$ improved forced expiratory volume in one second (FEV₁) as compared to the Control arm at 1 year.

The secondary effectiveness endpoints included:

- 1) FEV₁: Difference between study arms in absolute change from baseline for FEV₁ at 1 year.
- 2) Six-Minute Walk Distance (6MWD): Difference between study arms in absolute change from baseline for 6MWD at 1 year.
- 3) St. George's Respiratory Questionnaire: Difference between study arms in absolute change from baseline for SGRQ score at 1 year.

Other endpoints included additional measures of lung function, exercise capacity, breathlessness, and quality of life. Adverse Events and Serious Adverse Events² were evaluated for the Treatment Period (Day of Procedure to 45 days), and Long-Term Period (46 days after procedure to 12 months).

Demographics

A total of 190 subjects were randomized at 24 centers in US and OUS, 128 subjects in the Zephyr EBV group and 62 subjects in the Control group. Except for a higher proportion of GOLD Stage IV subjects in the Control group (74.2% vs 57.8% in the Zephyr EBV group), there were no other differences in any of the baseline demographic or clinical characteristics between the randomized groups showing that both groups were well matched with no confounders at Baseline. Subject baseline demographics and clinical characteristics are presented in **Table 1**.

² A serious adverse event (SAE) is any untoward medical occurrence that: results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, or results in persistent or significant disability/incapacity, or congenital anomaly/birth defect.

Table 1 LIBERATE Baseline Demographics and Clinical Characteristics

Variable	Zephyr EBV (n=128)	Control (n=62)	t-test p-value
Gender	56 Males (44%) 72 Females (56%)	33 Males (53%) 29 Females (47%)	0.278 ^b
Age (years)	64.0 ± 6.8	62.5 ± 7.1	0.161 ^a
BMI (kg/m ²)	24.67 ± 3.90	24.32 ± 4.38	0.577 ^a
Pack-Year smoking history	50.78 ± 26.88	48.59 ± 28.48	0.606 ^a
GOLD Stage ^c	54 (42.2%) Stage III 74 (57.8%) Stage IV	16 (25.8%) Stage III 46 (74.2%) Stage IV	0.037 ^b
Forced Expiratory Volume in 1 sec. (FEV ₁) (L)- Post-bronchodilator	0.763 ± 0.252	0.752 ± 0.217	0.767 ^a
Forced Expiratory Volume in 1 sec. (FEV ₁) (% predicted)- Post-bronchodilator	28.0 ± 7.45	26.2 ± 6.28	0.101 ^a
Residual Volume (RV) (L)	4.709 ± 1.046	4.759 ± 0.901	0.752 ^a
Residual Volume (% predicted)	224.5 ± 42.45	224.6 ± 38.86	0.987 ^a
Total Lung Capacity (TLC) (L)	7.537 ± 1.593	7.634 ± 1.369	0.683 ^a
Total Lung Capacity (% predicted)	133.5 ± 21.17	130.2 ± 12.44	0.256 ^a
FEV ₁ /FVC (%)	0.302 ± 0.063	0.294 ± 0.063	0.421 ^a
RV/TLC (%)	0.631 ± 0.086	0.626 ± 0.073	0.689 ^a
6 Minute Walk Distance (m)	311.33 ± 81.33	301.91 ± 78.54	0.450 ^a
SGRQ Total score	55.15 ± 14.09	53.10 ± 14.14	0.352 ^a
Values are means ± SD ^a P-value from two-sided t-test assuming equal variance. ^b P-value from two-sided Fisher's exact test. ^c Classification of airflow limitation severity in COPD (based post-bronchodilator FEV ₁): GLOBAL STRATEGY FOR THE DIAGNOSIS, MANAGEMENT, AND PREVENTION OF COPD (2017 REPORT)			

Results**Effectiveness**

The Primary Endpoint for the Study was met. A greater number of subjects in the Zephyr EBV group compared to the Control group achieved a Post-bronchodilator FEV₁ (L) improvement from Baseline of ≥15%; the difference between groups is 31.0% (p<0.001), see **Table 2** and **Figure 2**.

Table 2 Primary Analysis of the Primary Effectiveness Endpoint (Intent-to-Treat Population)

	Zephyr EBV (N=128)	Control (N=62)	Delta (95% CI)	Z-statistic	P-value
Percent of Subjects with $\geq 15\%$ Improved Post-Bronchodilator FEV ₁ at 1 Year	47.7%	16.8%	31.0% (18.0% to 43.9%)	4.130	<0.001

Note:

To account for the interim analysis, $Z > 2.004$ is the threshold for significance. Intermittent missing values imputed with linear interpolation. Truncated missing values imputed with multiple imputation (propensity score method). Death prior to 1-year endpoint imputed as failure. Values have been adjusted for multiple imputation. Averages across imputations are presented for Z and p-value.

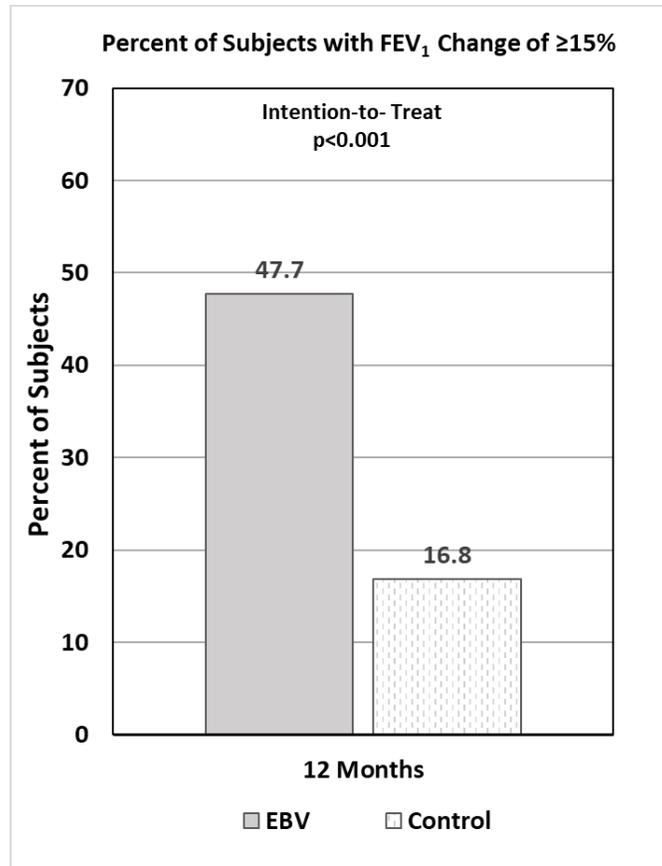


Figure 2 Primary Effectiveness Endpoint- Percent of Subjects with FEV₁ Improvement of $\geq 15\%$ at 12-months

The Secondary Endpoints for the Study were met. All three Secondary effectiveness endpoints showed statistically significant and clinically meaningful improvements in favor of Zephyr EBV treatment over the Control, see **Figure 3**.

The post-bronchodilator FEV₁ absolute change showed significantly greater mean improvement (volume increase) in the Zephyr EBV group compared to the Control group (Δ EBV – Control = + 0.106L, $p < 0.001$).

The Six-Minute Walk Distance showed significantly greater mean improvement (increased distance walked) in the Zephyr EBV group compared to the Control group (Δ EBV – Control = +39.31 meters, $p = 0.002$).

The St. George’s Respiratory Questionnaire (SGRQ) showed significantly greater mean improvement (score reduction) in the Zephyr EBV group compared to the Control group (Δ EBV – Control = –7.05, $p = 0.004$).

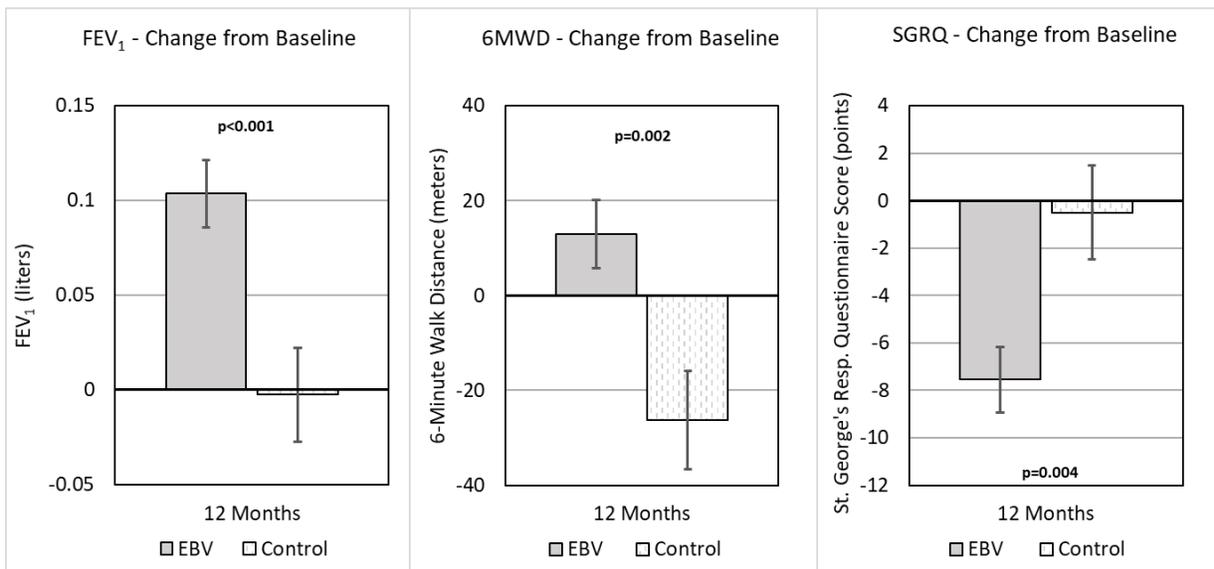


Figure 3 Secondary Effectiveness Endpoints

At 12-months, there was an improvement in all Lung Function Measures, Exercise Capacity and Quality of Life Measures, including dyspnea, in favor of the Zephyr EBV group. The mean differences between the Zephyr EBV and Control groups for the changes from Baseline to 12-months are shown in the **Table 3**. The durability of key and additional effectiveness outcomes is shown graphically in **Figure 4**.

Table 3 Zephyr EBV Group Changes from Baseline at 12-months (ITT Population)

Lung Function Measures	Zephyr EBV Group	Mean Change
Treated Lobe Volume Reduction (TLVR; L)	EBV from Baseline	1.142
Change in Residual Volume (RV; L)	Δ EBV - Control	-0.522
Change in Total Lung Capacity (TLC; L)	Δ EBV - Control	-0.288
Change in FEV ₁ /FVC ratio	Δ EBV - Control	0.01
Change in RV/TLC ratio	Δ EBV - Control	-0.05
Change in Forced Vital Capacity (FVC; L)	Δ EBV - Control	0.27
Change in Functional Residual Capacity (FRC; L)	Δ EBV - Control	-0.426
Change in Inspiratory Capacity (IC; L)	Δ EBV - Control	0.159
Change in IC/TLC ratio	Δ EBV - Control	0.034
Change in Diffusing Capacity (DLCO) (mL CO/min/mm Hg)	Δ EBV - Control	0.869
Patient-Reported Quality of Life Measures		
Change in SGRQ – Symptoms domain (points)	Δ EBV - Control	-0.88
Change in SGRQ – Activity domain (points)	Δ EBV - Control	-12.73
Change in SGRQ – Impacts domain (points)	Δ EBV - Control	-9.72
Change in CAT score (points)	Δ EBV - Control	-3.1
Change in mMRC Dyspnea score (points)	Δ EBV - Control	-0.8
Change in TDI Focal score (points)	Δ EBV - Control	4.3
Change in TDI Functional Impairment (points)	Δ EBV - Control	1.4
Change in TDI Magnitude of Task (points)	Δ EBV - Control	1.4
Change in TDI Magnitude of Effort (points)	Δ EBV - Control	1.5
Change in EXACT-PRO Total Score (points)	Δ EBV - Control	-3.8
EXACT Breathlessness Score (points)	Δ EBV - Control	-8.8
EXACT Cough and Sputum Score (points)	Δ EBV - Control	-1.1
EXACT Chest Symptoms Score (points)	Δ EBV - Control	-1.5
Change in BODE Index (points)	Δ EBV - Control	-1.2
Change in EQ-5D (points)	Δ EBV - Control	0.013
Change in EQ-5D (VAS) Health State Today (points)	Δ EBV - Control	2.911

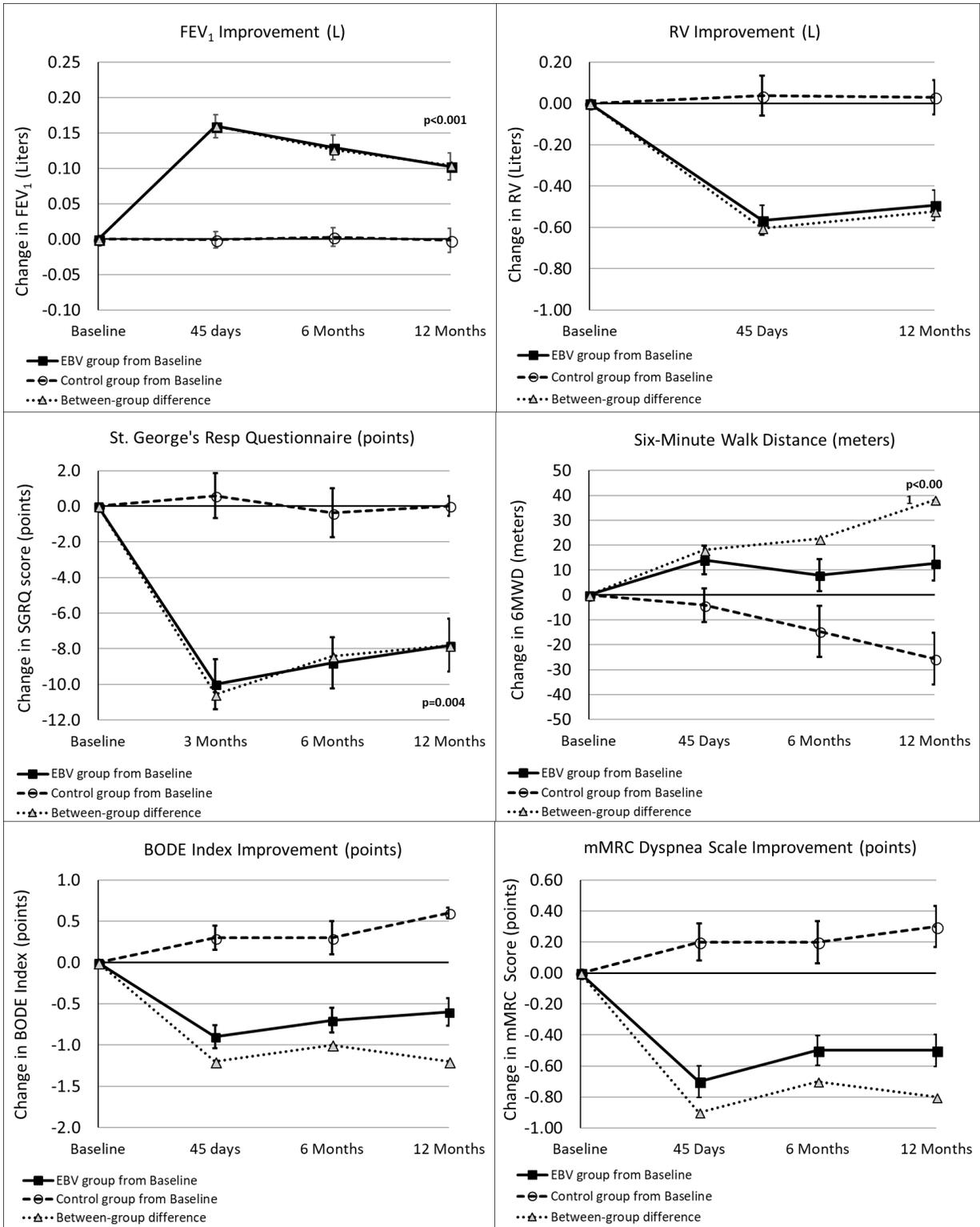


Figure 4 Durability of Key and Additional Effectiveness Outcomes

Adverse Events

The safety of the Zephyr EBV System was assessed by comparing adverse event profiles of the Zephyr EBV and Control group subjects for the Treatment Period (Day of procedure/ randomization to 45 days) and Longer-Term Period (46 days after the study procedure/ randomization until the 1-year follow-up visit).

There were a higher number of serious respiratory adverse events in the Zephyr EBV group compared to the SoC group during the Treatment Period (35.2% subjects versus 4.8 % subjects). The most common serious respiratory adverse events in the Zephyr EBV versus SoC subjects during the Treatment Period were pneumothorax in 26.6% versus 0.0% subjects, respectively; COPD exacerbations in 7.8% versus 4.8% subject, respectively; dyspnea in 1.6% versus 0.0% subjects, respectively; pleural effusion in 1.6% versus 0.0% subjects, respectively; and respiratory failure in 1.6% versus 0.0% subjects, respectively.

There was a total of 4 deaths (3.1%) in the Zephyr EBV group during the Treatment Period. There were no deaths in the Control group during the Treatment Period. The majority of pneumothoraces (76%) occurred within 3 days following a bronchoscopy procedure. Analyses of the pneumothoraces identified two variables that predicted subjects at higher-risk of having a complex pneumothorax (defined as requiring removal of all valves or resulting in death) and provide a means to prospectively identify these patients and consider mitigations. Specifically, patients in whom the targeted lobe for treatment is not the most diseased (due to factors such as collateral ventilation or other abnormalities), and the contralateral lung has >60% emphysema destruction score could be at higher risk for a complex pneumothorax (defined as requiring removal of all valves or resulting in death). Patients who experienced a pneumothorax following Zephyr EBV treatment experienced meaningful clinical benefit once they recovered from the pneumothorax event.

In the Longer-Term Period (46 days after the study procedure/ randomization until the 1-year follow-up visit), the frequency of respiratory serious adverse events was comparable with 33.6% of the Zephyr EBV group subjects and 30.6% of the Control group subjects experiencing one or more respiratory serious adverse events ($p=0.741$). Some of the higher number of adverse events in the Zephyr EBV group during this period were associated with protocol allowed bronchoscopy procedures for valve adjustment. Unlike the Treatment Period, during the Longer-Term Period the Control group had a higher frequency of COPD exacerbations that were serious adverse events (29 events in 19 (30.6%) subjects compared to 40 events in 28 (23.0%) subjects in the Zephyr EBV group), a higher frequency of pneumonias (6 events in 5 (8.1%) subjects compared to 7 events in 7 (5.7%) subjects in the Zephyr EBV group), and respiratory failure (3 events in 2 (3.2%) subjects compared to 1 event in 1 (0.8%) subject in the Zephyr EBV group). During the Longer-Term Period from 46 days to the 12-month visit date, death occurred in 0.8% of subjects in the Zephyr EBV group (1 subject), and 1.6% of the Control group (1 subject), both due to disease progression.

All adverse events occurring at an incidence rate of $\geq 3.0\%$ in either the Zephyr EBV or SoC groups during the Treatment Period (Day of procedure/ randomization to 45 days) and Longer-Term Period (46 days after the study procedure/ randomization until the 1-year follow-up visit) is provided in **Table 4**.

Table 4 Adverse Events Occurring in at Least 3% of Subjects in Either Group

	Treatment Period (Day of Procedure/ Randomization to 45 Days)		Longer-Term Period (45 Days from the Study Procedure/Randomization until 12-Month Visit Date)	
	Zephyr EBV (N=128)	Control (N=62)	Zephyr EBV (N=122)	Control (N=62)
Respiratory				
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%)
Dyspnea	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%)	1 (0.8%)	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%)
Death	4 (3.1%)	0 (0.0%)	1 (0.8%)	1 (1.6%)
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	1 (0.8%)	0 (0.0%)	7 (5.7%)	0 (0.0%)
Bronchitis	1 (0.8%)	0 (0.0%)	6 (4.9%)	3 (4.8%)
Lower respiratory tract congestion	3 (2.6%)	0 (0.0%)	5 (4.1%)	0 (0.0%)
Sinusitis	0 (0.0%)	0 (0.0%)	3 (2.5%)	3 (4.8%)
Respiratory failure	2 (1.6%)	0 (0.0%)	1 (0.8%)	2 (3.2%)
Pharyngitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (3.2%)
Non-Respiratory				
Headache	10 (7.8%)	1 (1.6%)	4 (3.3%)	0 (0.0%)
Nausea	10 (7.8%)	0 (0.0%)	1 (0.8%)	0 (0.0%)
Constipation	8 (6.3%)	0 (0.0%)	1 (0.8%)	0 (0.0%)

Functional Gastrointestinal disorder	6 (4.7%)	0 (0.0%)	1 (0.8%)	0 (0.0%)
Arrhythmia	5 (3.9%)	0 (0.0%)	2 (1.6%)	2 (3.2%)
Dizziness	4 (3.1%)	0 (0.0%)	1 (0.8%)	0 (0.0%)
Pyrexia	4 (3.1%)	1 (1.6%)	0 (0.0%)	0 (0.0%)
Infection	1 (0.8%)	1 (1.6%)	10 (8.2%)	4 (6.5%)
Urinary Tract Infection	1 (0.8%)	1 (1.6%)	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%)

Conclusion

At 1-year post-randomization, the difference between the Zephyr EBV Treatment group and Control group for the percentage of subjects meeting the threshold of $\geq 15\%$ improved in post-bronchodilator FEV₁ differs significantly (two-sided test, $p < 0.001$) in favor of the Zephyr EBV Treatment group.

The Zephyr Endobronchial Valve System is safe and effective for the treatment of adults with severe heterogeneous emphysema in regions of the lung that have little to no collateral ventilation.

6.2 IMPACT Study: A Multi-center, Prospective, Randomized, Controlled, one-way Crossover Investigation of Endobronchial Valve (EBV) Therapy vs. Standard of Care (SoC) in Homogeneous Emphysema

Study Objective

The objective of the IMPACT study, a prospective, randomized, controlled trial was to evaluate the safety and efficacy of the Zephyr EBV in patients with severe homogeneous emphysema.

Study Design

The IMPACT Study was a multicenter, prospective, randomized, controlled, one-way crossover study. Subjects were enrolled at 8 Investigational Sites in Europe. Qualifying subjects with homogeneous emphysema ($< 15\%$ heterogeneity index (difference in destruction scores between the target and ipsilateral lobes)), FEV₁ (% predicted) $\leq 45\%$, and Residual Volume $\geq 200\%$ predicted were randomized at a 1:1 ratio into either the EBV treatment arm or the Standard of Care (SoC) arm. The subjects in the Zephyr EBV arm had Zephyr EBVs placed in the target lobe to achieve lobar occlusion. Subjects randomized to the SoC group continued to receive optimal medical management according to clinical practice. SoC subjects were, crossed over to Zephyr EBV treatment after 6-month follow-up.

Follow-up

Study participants were followed up for a period of 12 months following randomization with assessments at 30 days (Zephyr EBV group only), 3-, 6- and 12-months post-enrollment. If eligible, subjects in the SoC arm, were crossed over to the Zephyr EBV treatment arm after completing their 6-months follow-up and they were followed up for an additional 6-months.

Endpoints

The primary endpoint was the percentage change in FEV₁ at 3-months relative to Baseline in the Zephyr EBV group, compared to the SoC group.

Other endpoints included other lung function parameters, exercise capacity, and quality of life measures. Adverse Events and Serious Adverse Events were evaluated for the Treatment Period (Day of Procedure to 30 days), and Long-Term Period (31 days after procedure to 6 months).

Demographics

A total of 93 subjects were randomized at 8 centers in Europe; there were 43 subjects in the Zephyr EBV group and 50 subjects in the SoC group. There were no statistical differences in demographic variables. Subject baseline demographics and clinical characteristics are presented in **Table 5**.

Table 5 IMPACT Baseline Demographics and Clinical Characteristics

Variable	Zephyr EBV (n=43)	SoC (n=50)	t-test p-value
Gender	20 Males (47%) 23 Females (53%)	16 Males (32%) 34 Females (68%)	NS
Age (years)	64.3 ± 6.3	63.2 ± 6.0	NS
BMI (kg/m ²)	23.7 ± 4.3	22.6 ± 3.7	NS
Pack-Year smoking history	41.5 ± 19.6	42.5 ± 22.0	NS
GOLD Stage	18 (42%) Stage III 25 (58%) Stage IV	23 (46%) Stage III 27 (54%) Stage IV	NS
Forced Expiratory Volume in 1 sec. (FEV ₁) (L)- Post-bronchodilator	0.76 ± 0.17	0.75 ± 0.19	NS
Forced Expiratory Volume in 1 sec. (FEV ₁) (% predicted) - Post-bronchodilator	28.4 ± 6.3	30.0 ± 6.6	NS
Residual Volume (RV) (L)	5.7 ± 1.1	5.2 ± 1.1	0.030
Residual Volume (% predicted)	277 ± 55	274 ± 63	NS
Total Lung Capacity (TLC) (L)	8.4 ± 1.6	7.6 ± 1.4	0.024
Total Lung Capacity (% predicted)	145 ± 21	144 ± 18	NS
FEV ₁ /FVC (%)	36.3 ± 7.2	35.8 ± 8.6	NS
RV/TLC (%)	69 ± 6	68 ± 7	NS
6 Minute Walk Distance (m)	308 ± 91	328 ± 93	NS
SGRQ Total score	63.2 ± 13.7	59.3 ± 15.6	NS
Values are means ± SD			

Results**Effectiveness**

The primary effectiveness endpoint for the study was met. The mean percent change in FEV₁ (L) from Baseline to 3-months in the Zephyr EBV group was an increase of 15.3% compared to a decrease of 3.4% in the SoC group (Observed cases). The mean group difference (EBV - SoC) for the change in FEV₁ from Baseline to 3-months was 18.8 ± 22.1% (mean ± SD; p < 0.001), see **Figure 5**. Similar changes were observed in the Intention to Treat (ITT) population. The mean percent change in FEV₁ (L) from Baseline to 3-months in the Zephyr EBV group was an increase of 13.7% compared to a decrease of 3.2% in the SoC group (ITT). The mean group difference (EBV - SoC) for the change in FEV₁ from Baseline to 3-months was 17.0 ± 21.4% (mean ± SD; p < 0.001).

There were statistically significant and clinically meaningful improvements from Baseline in the Zephyr EBV versus the SoC group at 3-months and 6-months for FEV₁

(L), RV (L), 6MWD (m), St. Georges Respiratory Questionnaire (SGRQ) score, and mMRC Dyspnea Scale score (see Figure 6).

For the Zephyr EBV group followed out to 12-months, while all variables showed an improvement from Baseline, statistical significance was obtained for RV (Liter and % change), and the SGRQ score. At this timepoint, no SoC Control group subjects were available for comparison.

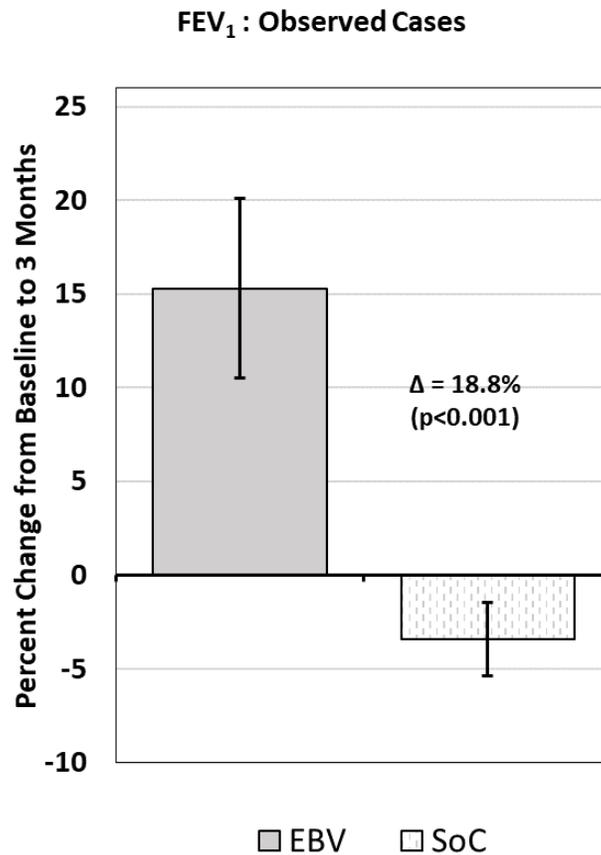


Figure 5 Primary Effectiveness Endpoint- Percent Change in FEV₁ from Baseline to 3-months

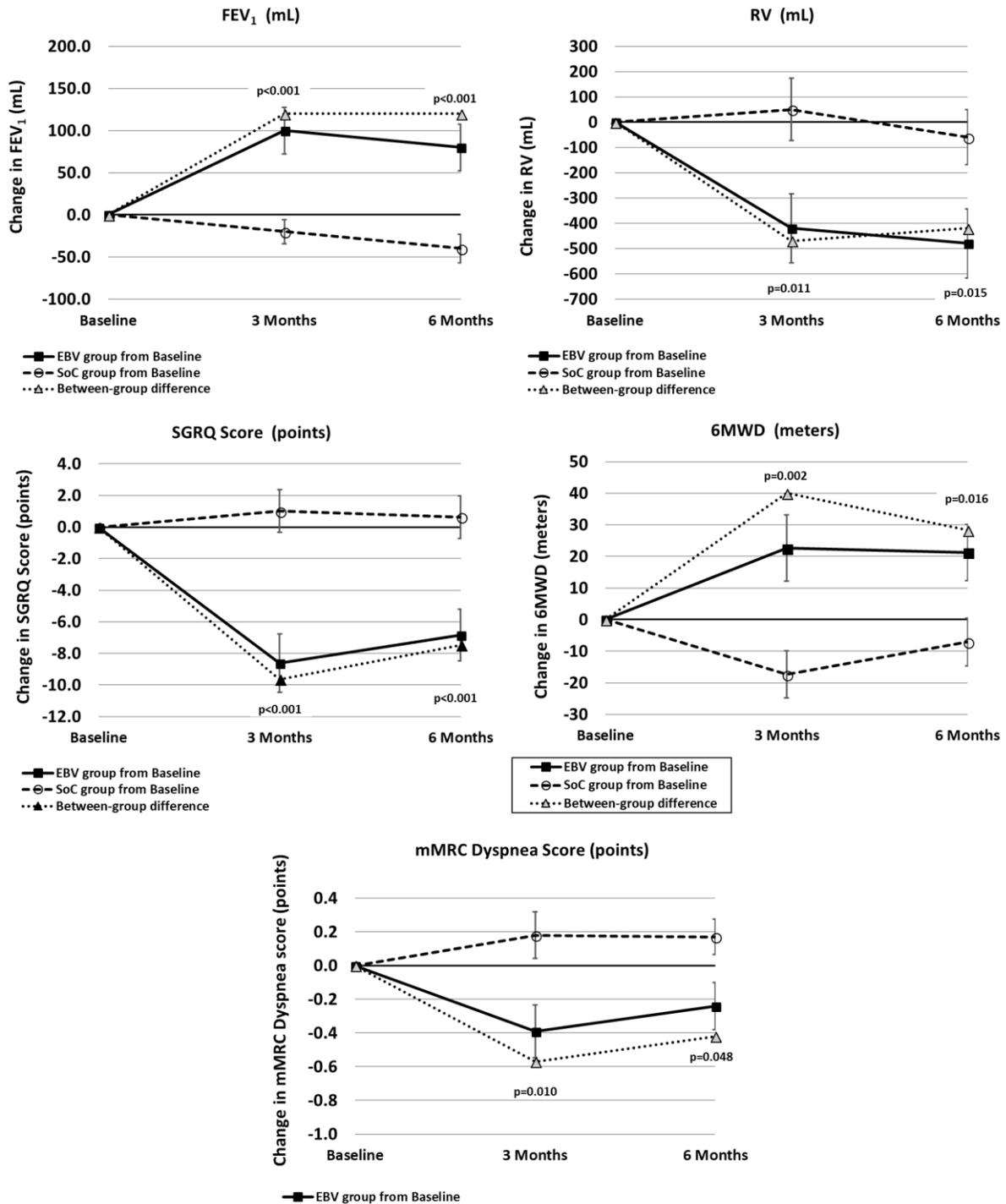


Figure 6 Effectiveness Endpoints

Adverse Events

The safety of the Zephyr EBV System was assessed by comparing adverse event profiles of the Zephyr EBV and SoC group subjects. Adverse event profiles are compared for the Treatment Period (day of procedure to 30 days) and Longer-Term Period (31 days from procedure day to 6-months).

There were a higher number of serious respiratory adverse events in the Zephyr EBV group compared to the SoC group during the Treatment Period (44.2% subjects versus 2.0% subjects). The most common serious respiratory adverse events in the Zephyr EBV versus SoC subjects during the Treatment Period were pneumothorax in 23.3% versus 0.0%, respectively; and COPD exacerbations in 14.0% versus 2.0% subjects, respectively. All pneumothoraces were managed using standard techniques that included chest tube placement and/or careful observation.

There were a comparable number of serious respiratory adverse events in the Zephyr EBV group compared to the SoC group during the Longer-Term Period (34.9% subjects versus 26.0% subjects). The most common respiratory adverse events in the Zephyr EBV versus SoC subjects during the Longer-Term Period were COPD exacerbations in 18.6% versus 20.0% subjects, respectively; dyspnea in 4.7% versus 0.0% subjects, respectively; pneumothorax in 4.7% versus 0.0% subjects, respectively; pneumonia in 2.3% versus 4.0% subjects, respectively; and hypercapnia in 0.0% versus 6.0% subjects, respectively.

There were 2 deaths in the SoC group that occurred in the Longer-Term Period and none in the Zephyr EBV group. There was one death in the Zephyr EBV group that occurred beyond 12-months after the EBV implantation.

All adverse events occurring at an incidence rate of $\geq 3.0\%$ in either the Zephyr EBV or SoC groups during the Treatment Period (Day of procedure to 30 days) or the Longer-Term Period (31 days from procedure day to 6-months) is provided in **Table 6**.

Table 6 Adverse Events Occurring in at Least 3% of Subjects in Either Group

	Treatment Period (Day of procedure to 30 days)		Longer-Term Period (31 days from procedure day to 6-months)	
	Zephyr EBV (N=43)	SoC (N=50)	Zephyr EBV (N=43)	SoC (N=50)
Respiratory				
COPD Exacerbation	12 (27.9%)	2 (4.0%)	17 (39.5%)	19 (38.0%)
Pneumothorax	10 (23.3)	0 (0.0%)	2 (4.7%)	0 (0.0%)
Cough	4 (9.3%)	0 (0.0%)	2 (4.7%)	1 (2.0%)
Common cold	3 (7.0%)	2 (4.0%)	4 (9.3%)	5 (10.0%)
Thoracic pain	3 (7.0%)	0 (0.0%)	1 (2.3%)	1 (2.0%)
Death	0 (0.0%)	0 (0.0%)	0 (0.0%)*	2 (4.0%)
Diagnostic bronchoscopy	0 (0.0%)	0 (0.0%)	2 (4.7%)	0 (0.0%)
Dyspnea	1 (2.3%)	0 (0.0%)	2 (4.7%)	2 (4.0%)
Pleural effusion	1 (2.3%)	0 (0.0%)	2 (4.7%)	0 (0.0%)
Pulmonary infection	2 (4.7%)	0 (0.0%)	2 (4.7%)	1 (2.0%)
Pulmonary shunt	2 (4.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pneumonia	0 (0.0%)	1 (2.0%)	1 (2.3%)	3 (6.0%)
Hypercapnia	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (6.0%)
Pulmonary lesion	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (6.0%)
Non-Respiratory				
Diarrhea	2 (4.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Insomnia	2 (4.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Tachycardia	0 (0.0%)	1 (2.0%)	2 (4.7%)	0 (0.0%)
Urinary tract infection	1 (2.3%)	0 (0.0%)	2 (4.7%)	0 (0.0%)

* There was one death in the EBV group that occurred 12-months after the EBV implantation.

Note: The Treatment Period adverse events include events from the Index procedure as well as events from subsequent bronchoscopy procedures (valve adjustment, valve removal, and/or valve replacement) with onset restricted to a 30-day post procedure window.

Conclusion

Results of the IMPACT clinical study demonstrated that the Zephyr EBV treatment provided clinically meaningful improvement at 6-months post-randomization in lung function, dyspnea, exercise capacity, and Quality of Life in patients with homogeneous emphysema. The Zephyr EBV treatment is associated with a transient increase in respiratory adverse events that can be managed with standard therapies. There were no deaths in the first year of follow-up.

6.3 TRANSFORM Study: Multi-center, Prospective, Randomized, Controlled Trial of Zephyr® Endobronchial Valve (EBV®) Treatment vs. Standard of Care (SoC) in Heterogeneous Emphysema

Study Objective

The objective of the TRANSFORM study, a prospective, randomized, controlled study was to compare clinical outcomes of the Zephyr EBV treatment vs. Standard of Care (SoC) in patients with severe heterogenous emphysema.

Study Design

The TRANSFORM Study was a multicenter, prospective, randomized, controlled study conducted at 17 centers in Europe. Qualifying subjects with heterogenous emphysema ($\geq 10\%$ heterogeneity index (difference in destruction scores between the target and ipsilateral lobes)), FEV_1 (% predicted) $\leq 45\%$, and Residual Volume $\geq 180\%$ predicted were randomized at a 2:1 ratio into either the Zephyr EBV treatment or the SoC Control arm. The subjects in the Zephyr EBV arm had Zephyr EBVs placed in the target lobe to achieve lobar occlusion. The subjects randomized to the SoC group continued to receive optimal medical management according to clinical practice.

Follow-up

Study participants in both arms were followed-up at 45-days, 3-months and 6-months. Subjects in the SoC group were required to complete a minimum 6 months follow-up. After the 6 months follow-up, SoC group subjects could opt out of the study and pursue Zephyr EBV treatment, which is commercially available in Europe or remain in the study for an additional 6 months.

Endpoints

The primary endpoint was the percentage of trial participants in the Zephyr EBV treatment arm meeting the minimally clinically important difference (MCID) of $>12\%$ improved post-bronchodilator forced expiratory volume in one second (FEV_1) compared to the percentage in the control arm at 3 months post-procedure.

Other endpoints included various lung function, exercise capacity, quality life measures. Adverse Events and Serious Adverse events were evaluated for the Treatment Period (Day of Procedure to 45 days), and Longer-Term Period (46 days from procedure day to 6-months).

Subjects in the Zephyr EBV group, and any subjects remaining in the SoC group (i.e. any subject who had not received Zephyr EBV past the 6-months follow up and exited the trial) were followed up for a period of 12 months following randomization. The Zephyr EBV group are planned to be followed up at 18- and 24-months following treatment.

Demographics

A total of 97 subjects were randomized at 17 Investigational Sites with 65 subjects randomized to the Zephyr EBV group and 32 subjects randomized to the SoC group. There were no statistical differences in demographic variables. Subject baseline demographics and clinical characteristics are presented in **Table 7**.

Table 7 TRANSFORM Baseline Demographics and Clinical Characteristics

Variable	Zephyr EBV (n=65)	SoC (n=32)	t-test p-value
Gender	37 Males / 28 Females	21 Males / 11 Females	NS
Age (years)	64.9 ± 8.0	63.0 ± 6.0	NS
BMI (kg/m ²)	23.7 ± 4.4	24.3 ± 5.3	NS
Smoking history (pack years)	42.0 ± 21.5	42.0 ± 20.2	NS
GOLD Stage	Stage III: 26 (40%) Stage IV: 39 (60%)	Stage III: 18 (56%) Stage IV: 14 (44%)	NS
Forced Expiratory Volume in 1 sec. (L) - Post-bronchodilator	0.78 ± 0.24	0.94 ± 0.31	0.008
Forced Expiratory Volume in 1 sec. (% predicted) - Post-bronchodilator	29.8 ± 9.2	32.2 ± 8.4	NS
Residual Volume (L)	5.47 ± 1.26	5.39 ± 1.16	NS
Residual Volume (% predicted)	249.4 ± 51.8	241.0 ± 41.4	NS
Total Lung Capacity (L)	8.12 ± 1.54	8.55 ± 1.56	NS
Total Lung Capacity (% predicted)	139.0 ± 18.9	137.3 ± 12.5	NS
FEV ₁ /FVC (%)	32.7 ± 8.13	31.57 ± 7.32	NS
RV/TLC (%)	67.2 ± 7.79	63.13 ± 7.47	0.016
6-Minute Walk Distance (m)	282 ± 94	320 ± 92	NS
SGRQ Total score	64.3 ± 14.4	58.1 ± 13.3	0.042
Values are means ± SD			

Results**Effectiveness**

The primary effectiveness endpoint for the study was met. At 3-months post-procedure, responder rates ($\geq 12\%$ improvement from Baseline in FEV₁) in the ITT (Intention-to-Treat) population were 55.4% in the Zephyr EBV group and 6.5% in the SoC group ($p < 0.001$), see **Figure 7**.

Statistically and clinically significant improvements from Baseline were seen at both 3- and 6-months in the Zephyr EBV group compared to the SoC group (see **Figure 8**).

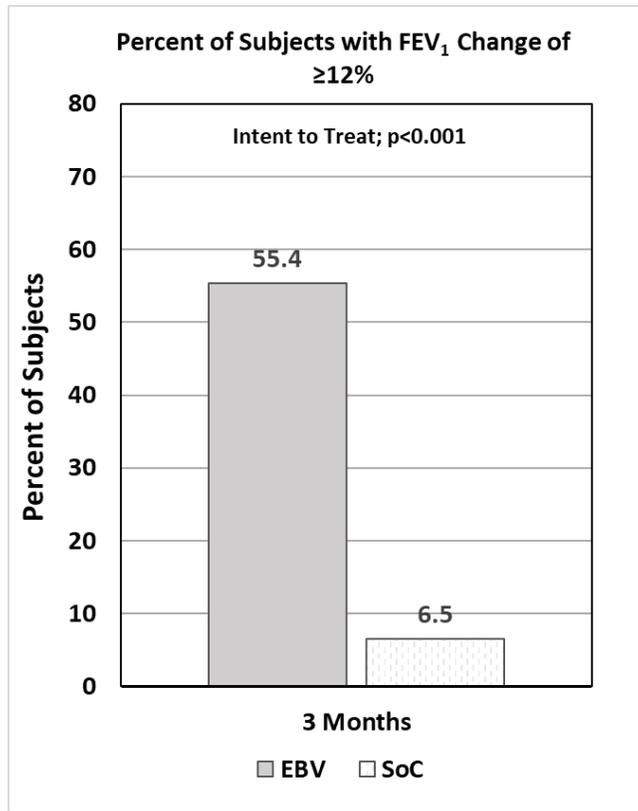


Figure 7 Primary Effectiveness Endpoint- Percent of Subjects with FEV₁ ≥12% at 3-months

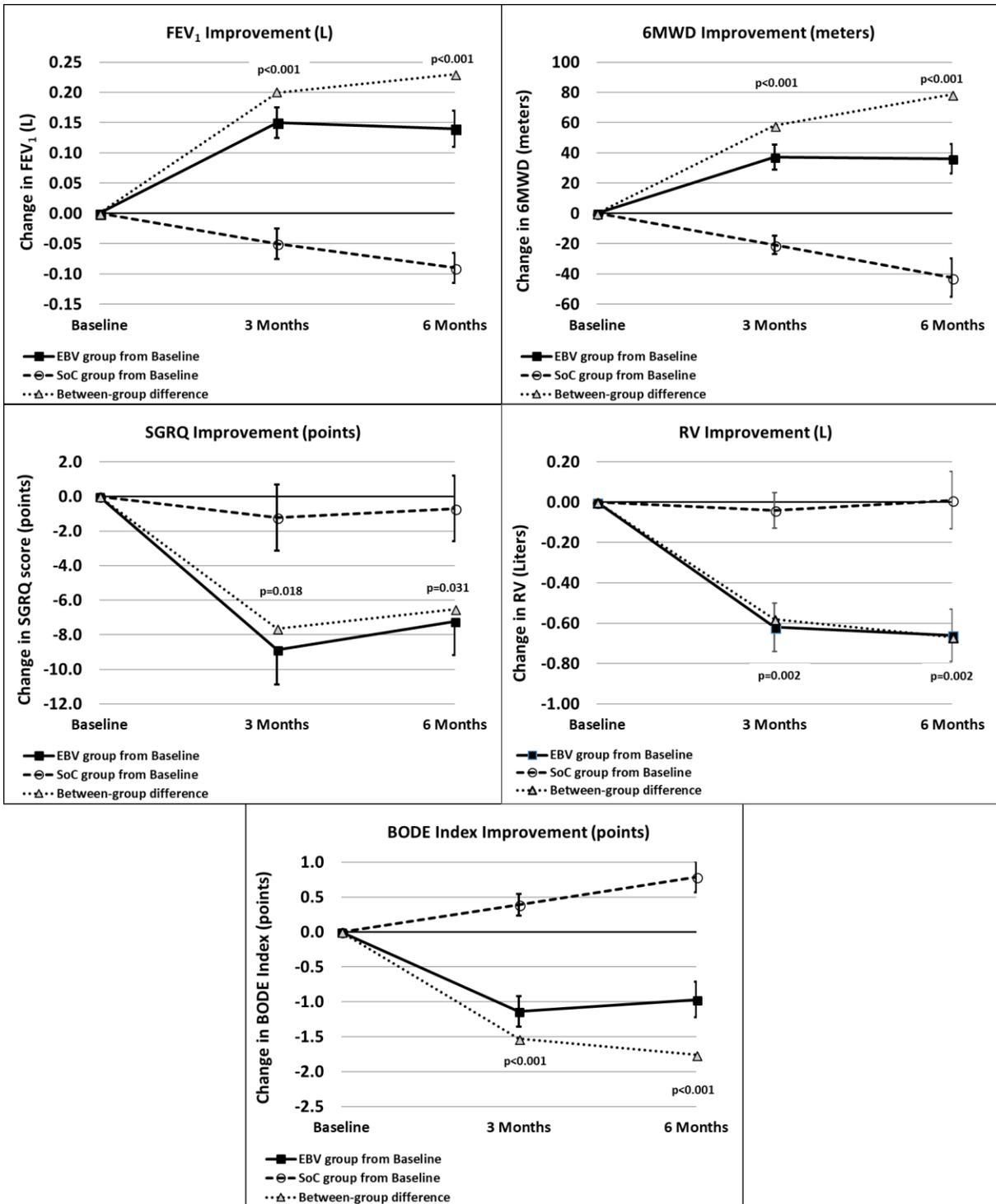


Figure 8 Effectiveness Endpoints

Adverse Events

The safety of the Zephyr EBV System was assessed by comparing adverse event profiles of the Zephyr EBV and SoC group subjects for the Treatment Period (day of procedure to 45 days) and Longer-Term Period (46 days from procedure day to 6-months).

There were a higher number of serious respiratory adverse events in the Zephyr EBV group compared to the SoC group during the Treatment Period (38.5 % subjects versus 3.1% subjects). The most common serious respiratory adverse events in the Zephyr EBV versus SoC subjects during the Treatment Period were pneumothorax in 20.0% versus 0.0%, respectively; dyspnea in 7.7% vs. 0.0%, respectively; COPD exacerbations in 6.2% versus 3.1% subjects, respectively; and pneumonia in 4.6% versus 0.0% subjects, respectively. The pneumothoraces were managed using standard techniques that included chest tube placement and/or careful observation, and in once case surgery. There was one death during the Treatment Period in the Zephyr EBV group.

There were a comparable number of serious respiratory adverse events in the Zephyr EBV group compared to the SoC group during the Longer-Term Period (15.4 % subjects versus 9.4% subjects). The most common serious respiratory adverse events in the Zephyr EBV versus SoC subjects during the Longer-Term Period were COPD exacerbations in 4.6% versus 6.3% subjects, respectively; pneumonia in 4.6% vs. 3.1%, respectively; dyspnea in 3.1% vs. 0.0%, respectively; and pneumothorax in 3.1% vs. 0.0%, respectively.

A summary of the adverse events based on the occurrence at an incidence rate of $\geq 3.0\%$ in either the Zephyr EBV or Control groups during either the Treatment Period (day of procedure to 45 days) and Longer-Term Period (46 days from procedure day to 6-months) is provided in **Table 8**.

Table 8 Adverse Events Occurring in at Least 3% of subjects in Either Group

	Treatment Period (Day of procedure to 45 days)		Longer-Term Period (46 days from procedure day to 6-months)	
	Zephyr EBV (N=65)	SoC (N=32)	Zephyr EBV (N=65)	SoC (N=32)
Respiratory				
Pneumothorax	18 (27.7%)	0 (0.0%)	2 (3.1%)	0 (0.0%)
Dyspnea	13 (20.0%)	0 (0.0%)	8 (12.3%)	1 (3.1%)
COPD Exacerbation	10 (15.4%)	3 (9.4%)	19 (29.2%)	8 (25.0%)
Chest pain	6 (9.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Chest infection	4 (6.2%)	2 (6.3%)	4 (6.2%)	2 (6.3%)
Cough	3 (4.6%)	0 (0.0%)	1 (1.5%)	0 (0.0%)
Hemoptysis	3 (4.6%)	0 (0.0%)	1 (1.5%)	0 (0.0%)
Mucus production	3 (4.6%)	0 (0.0%)	1 (1.5%)	0 (0.0%)
Pneumonia	3 (4.6%)	0 (0.0%)	4 (6.2%)	1 (3.1%)
Bronchospasm	0 (0.0%)	1 (3.1%)	1 (1.5%)	0 (0.0%)
Common cold	2 (3.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Thoracic pain	2 (3.1%)	0 (0.0%)	2 (3.1%)	0 (0.0%)
Upper Respiratory Tract Infection	2 (3.1%)	0 (0.0%)	2 (3.1%)	0 (0.0%)
Purulent Sputum	0 (0.0%)	1 (3.1%)	0 (0.0%)	0 (0.0%)
Bronchitis	0 (0.0%)	0 (0.0%)	1 (1.5%)	1 (3.1%)
EBV Removal	0 (0.0%)	0 (0.0%)	2 (3.1%)	0 (0.0%)
Hyperventilation	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.1%)
Influenza	0 (0.0%)	0 (0.0%)	1 (1.5%)	1 (3.1%)
Respiratory Infection	0 (0.0%)	0 (0.0%)	2 (3.1%)	0 (0.0%)
Sinusitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.1%)
Non-Respiratory				
Asthenia	0 (0.0%)	1 (3.1%)	0 (0.0%)	0 (0.0%)
Hypertension	2 (3.1%)	0 (0.0%)	1 (1.5%)	1 (3.1%)
Unspecified Infection	2 (3.1%)	0 (0.0%)	1 (1.5%)	0 (0.0%)
Fever	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.1%)
Headache	0 (0.0%)	0 (0.0%)	2 (3.1%)	0 (0.0%)
Heart Failure	0 (0.0%)	0 (0.0%)	2 (3.1%)	0 (0.0%)
Hypercholesterolemia	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.1%)
Hyperthyroidism	1 (1.5%)	0 (0.0%)	0 (0.0%)	1 (3.1%)
Musculoskeletal event	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.1%)
Radiomucositis	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.1%)
Rib fracture	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.1%)
Right shoulder pain	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.1%)
Squamous carcinoma	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.1%)
Urinary tract infection	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.1%)
Vertebral fracture	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.1%)

Note: The Treatment Period adverse events include events from the Index procedure as well as events from subsequent bronchoscopy procedures (valve adjustment, valve removal, and/or valve replacement) with onset restricted to a 45-day post procedure window.

Conclusion

Results of the TRANSFORM clinical study demonstrated that the Zephyr EBV treatment provided clinically meaningful improvement at 6-months post-randomization in lung function, dyspnea, exercise capacity, and Quality of Life in patients with severe emphysema. The Zephyr

EBV treatment is associated with a transient increase in respiratory adverse events that can be managed with standard therapies.

7.0 Adverse Events

Probable adverse events include, but are not limited to, the following:

Acute respiratory distress syndrome	Hypoxemia
Airway erosion	Iatrogenic injuries
Airway stenosis	Impaired lung function
Aphonia	Increased mucus secretions
Bowel function impairment	Infection
Bronchitis	Insomnia
Bronchospasm	Musculoskeletal event
Chest Pain	Myocardial infarction
COPD exacerbation	Nausea/vomiting
Cough	Pain
Death	Pleural effusion
Disorientation/anxiety	Pneumonia
Dyspnea	Pneumothorax
Empyema	Pulmonary embolism
Epistaxis	Pulmonary shunting
Fever	Residual volume increase
Granulation tissue / ulceration formation	Respiratory failure
Headache	Sepsis
Heart arrhythmia	Shortness of breath
Heart Failure	Sore throat
Hematoma	Stroke/CVA/TIA
Hemoptysis	Systemic inflammatory response syndrome (SIRS)
Hemothorax	Valve migration/expectoration
Hypotension	Vocal cord injury
Hypercapnia	Wheeze or whistling

- Migration from the implant site(s) is a known risk of Zephyr Valve implantation. Implant location can be confirmed using chest X-ray, High Resolution Computed Tomography (HRCT) or visually via bronchoscopy.
- Physicians are advised to monitor suspected hemoptysis closely and to consider bronchoscopy, a CT scan and/or an evaluation of hypoxemia for any patient that reports expectoration of blood after EBV implantation.
- Pneumothorax is a commonly occurring side effect of the Zephyr Valve treatment. Physicians are advised to monitor subject post-procedure for pneumothorax. In the event a pneumothorax occurs, pneumothorax management should be per expert recommendations¹. A chest x-ray must be completed within the first four (4) hours and then 24 hours after the procedure as routine clinical practice. A pneumothorax is not always visible with standard chest x-ray imaging, therefore performing a CT scan of the chest without contrast to evaluate for a pneumothorax may be necessary. Keep chest drainage set easily accessible and consider placement of a small-bore catheter if any size

pneumothorax is identified. Patient should be discharged according to the physician's clinical judgement and should be provided with clear instructions on recognizing symptoms of a pneumothorax and to seek emergent help if experiencing these symptoms.

8.0 Operator's Instructions

Patient selection, target lobe selection, target airway sizing, and optimal valve placement are covered in Pulmonx's Training Program. Use is restricted to a physician trained in the use of this device.

Target lobe should have little to no collateral ventilation. Collateral ventilation may be assessed using a physiological measure of air flow (Chartis Pulmonary Assessment System) and/or validated quantitative CT techniques.

Multiple valves are required to achieve the lobar occlusion of the target lobe. The number of valves required to achieve complete lobar occlusion is a function of the patient's target lobe and airway anatomy. **Note:** In the LIBERATE trial, the median number of valves used per procedure was 4. The maximum number of valves used during a procedure was 8.

Note: Of patients experiencing a pneumothorax in the LIBERATE Study, those patients in whom the treated lobe was not the most diseased lobe (due to factors such as heterogeneity, collateral ventilation or other abnormalities) and in whom the contralateral lung had >60% emphysema destruction score (at -910 HU) had a higher risk for a complex pneumothorax (defined as requiring removal of all valves or resulting in death). In the event the most diseased lobe is not the target lobe and the contralateral lung has >60% emphysema destruction score (at -910 HU), Zephyr Valve treatment should only be performed after careful consideration and appropriate discussion of the risk with the patient. Patient should be carefully observed post-procedure.

8.1 Delivery Catheter Preparation

For Zephyr Endobronchial Delivery Catheters packaged in a tray, remove the Endobronchial Delivery Catheter (EDC) from the packaging tray as follows (see **Figure 9**):

Step 1 – press down tab 1 to release the distal end of the catheter

Step 2 – pull tab 2 to free the delivery catheter handle

Step 3 – slide the delivery catheter out of the packaging tube

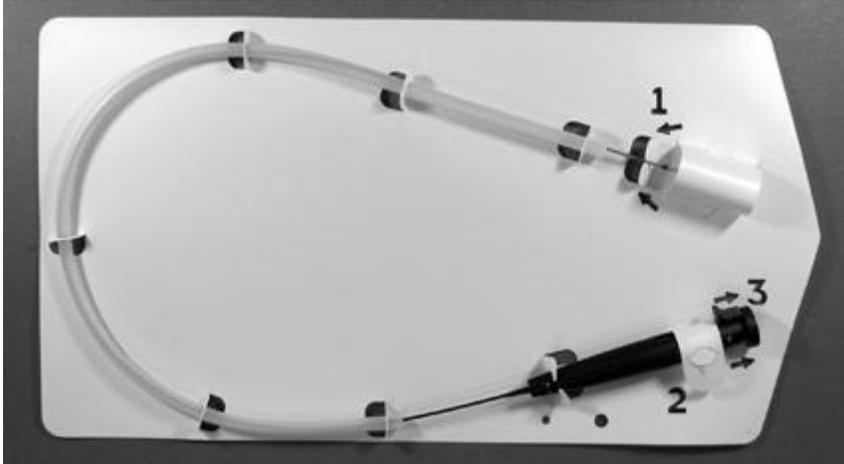


Figure 9 EDC Package Tray

8.2 Zephyr Endobronchial Valve Loading

- a. The Zephyr Endobronchial Valve (Zephyr Valve) is packaged inside the Endobronchial Loader System, or ELS (**Figure 10**). To load the Zephyr Valve, remove the Pusher from the side of the ELS (see **Figure 11**).



Figure 10 Endobronchial Loader System (ELS)

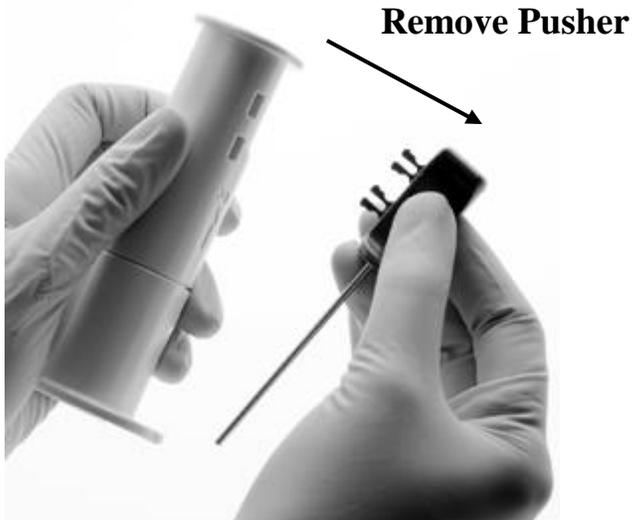


Figure 11 Pusher Removal

- b. Pull the Zephyr Valve into the funnel cartridge of the ELS by gently pulling the ends of the ELS apart until the monofilament strand is completely detached (see **Figure 12**).

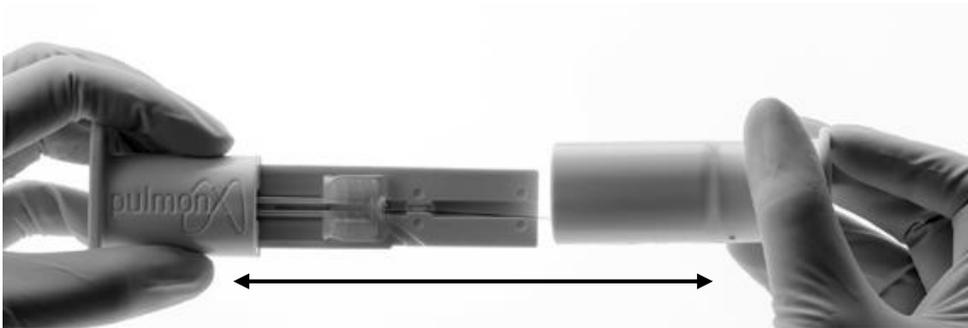


Figure 12 Endobronchial Loader System (ELS) Separation

- c. Discard the cap of the ELS. Confirm that the Zephyr Valve is completely pulled into the compression region of the funnel cartridge under the thumb lever and that there are no monofilament strands attached to the valve (see **Figure 13**).

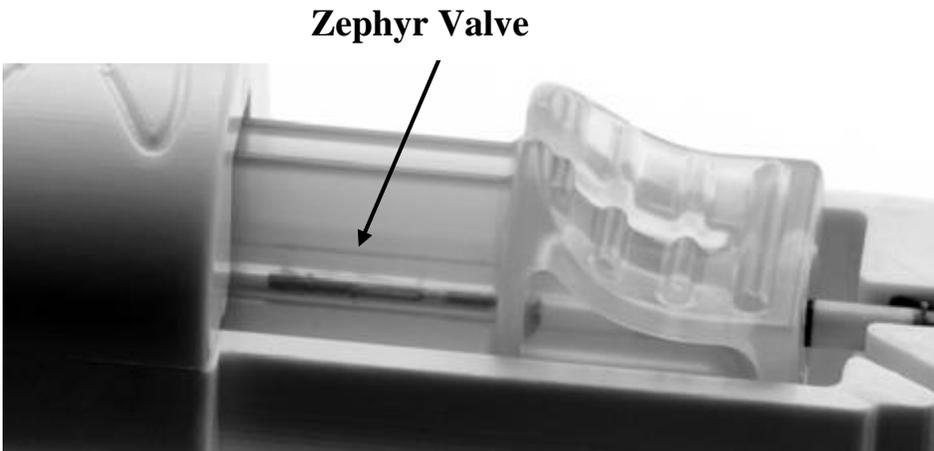


Figure 13 Confirm Zephyr Valve Position

- d. Retract the spring-loaded funnel cartridge, and place the EDC housing in the loading groove, sliding the proximal end up to the housing stop (see **Figure 14**). Verify that the handle actuator of the EDC is fully retracted.

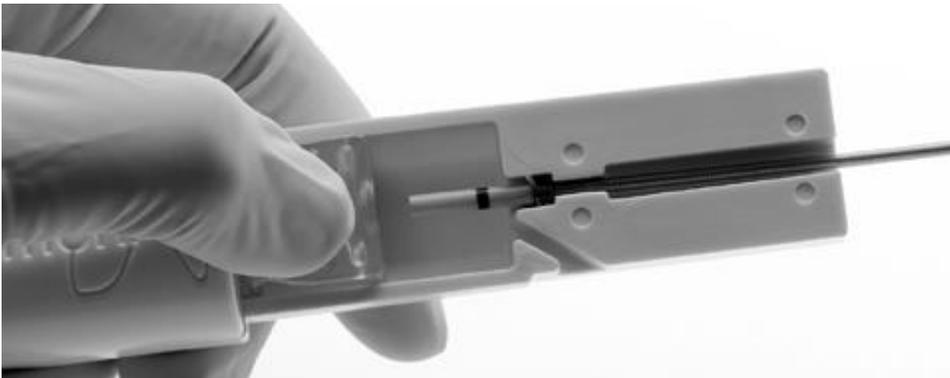


Figure 14 Housing Insertion

- e. Slowly release the thumb lever of the funnel cartridge, ensuring that it covers the end of the EDC housing (see **Figure 15**).

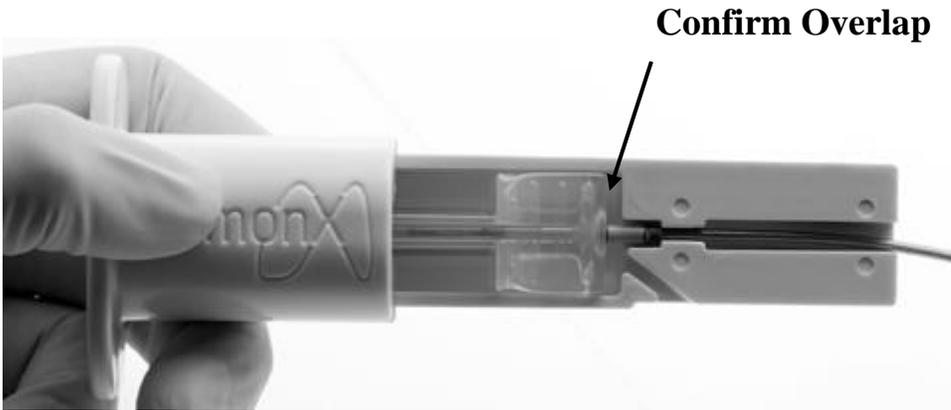


Figure 15 Funnel Cartridge Release

- f. Insert the pusher tip into the bottom of the ELS base and *gently* apply force until the pusher is snug against the ELS body pressing the compressed Zephyr Valve into the EDC housing (see **Figure 16**).



Figure 16 Zephyr Valve Loading

- g. Remove the pusher from the ELS. Retract the funnel cartridge from the EDC housing and remove the catheter from the loading groove. Discard the ELS. Verify that the Zephyr Valve is seated within the EDC housing (see **Figure 17**). Verify that the EDC housing is not damaged prior to and after loading. Replace the EDC if the housing appears damaged.



Figure 17 Inspect Zephyr Valve in EDC Housing (5.5 EDC shown)

Precaution: *Bending the Zephyr EDC when locked in the ELS may damage the Zephyr EDC shaft.*

Precaution: *Use only moderate force to push the Zephyr Valve into the housing of the EDC. If resistance is met while loading the Zephyr Valve, do not force the pusher. Discard the valve and EDC. Excessive loading forces may result in damage to the Zephyr Valve.*

8.3 Delivery Catheter Placement

Advance the Zephyr EDC into the working channel of the bronchoscope until the tip of the housing can be seen via the bronchoscope camera. The bronchoscope must be straight before the catheter can be advanced out of the end of working channel. This can be performed in or out of the patient. The EBV is intended to be placed in segmental and sub-segmental airways. Advance the bronchoscope up to the ostium of the target bronchus. Advance the EDC into the target bronchus such that the minimum depth mark on the housing can be visualized. The minimum depth mark can be used to verify that the target bronchus is long enough to accommodate the Zephyr Valve (the minimum depth mark must be distal to the ostium of the target bronchus). When verifying target bronchus length using an EDC with two minimum depth marks, the distal marker shows the minimum depth needed for the LP EBV; the proximal marker shows the minimum depth for standard Zephyr EBVs (see **Figure 18**). Next, advance the EDC into the target bronchus such that the diameter gauge located on the proximal end of the EDC housing is flush with the ostium of the target bronchus. Verify that the target bronchial diameter is between the large and small diameter gauges. The recommended sizing for the Zephyr Valves is below:

Zephyr Valve	Intended Diameter
Zephyr 4.0 EBV	4.0 - 7.0 mm
Zephyr 4.0-LP EBV	
Zephyr 5.5 EBV	5.5 - 8.5 mm

Warning: *Do not place Zephyr Valves in bronchi lower than the recommended diameter; this may compromise the valve function.*

Warning: Safety factor of normal functioning Zephyr Valves at the lower recommended diameter has not been evaluated.

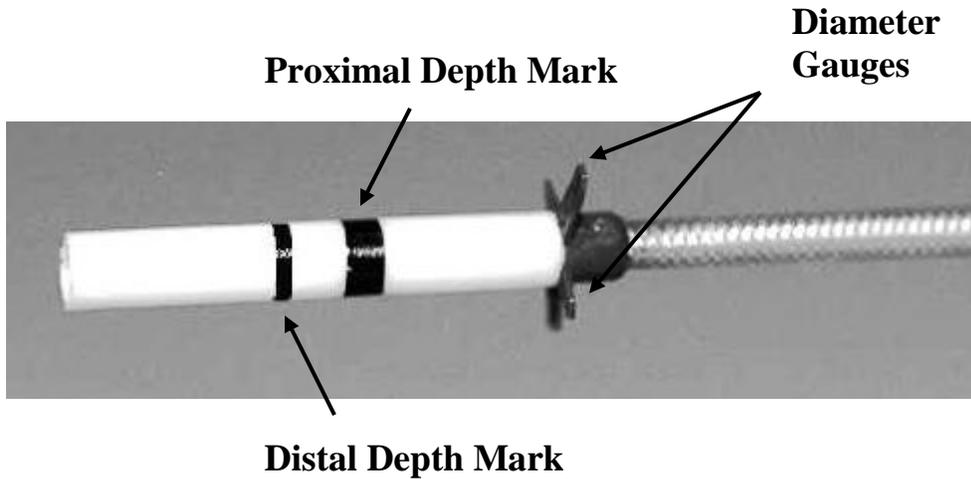


Figure 18 Minimum Depth Marks and Diameter Gauges

It is recommended that more tortuous and distal bronchi are treated first. Zephyr Valve placement can shift the bronchi such that access to tortuous and distal bronchi can be made more difficult.

Precaution: Standard Zephyr Valve (non-LP) placement using the distal depth mark on a dual mark EDC could potentially result in valve misplacements.

Precaution: Placement of the Zephyr Valve in bronchi of insufficient length may compromise valve function.

Warning: Iatrogenic injury from the Zephyr EDC may occur if excessive forces are applied during use especially in more tortuous bronchi when the delivery catheter housing is partially retracted into the bronchoscope.

Precaution: Under-sizing or over-sizing of the Zephyr Valve may impair the ability of the Zephyr Valve to completely occlude the airway or compromise the functioning of the silicone valve

Precaution: Ensure the working channel of the bronchoscope is adequate for the free movement of the Zephyr EDC (working channel ≥ 2.8 mm).

Precaution: Advancing a Zephyr EDC through an articulated bronchoscope may result in damage to the bronchoscope and delivery catheter.

8.4 Zephyr Valve Deployment

Locate the housing within the target bronchus such that the proximal minimum depth mark is distal to the ostium. To ensure that the Zephyr Valve is not misplaced in a segment distal to the

target bronchus, partially deploy the Zephyr Valve by slowly advancing the actuator on the Zephyr EDC handle by 6 to 12 mm (see **Figure 19**). Position the EDC such that the flared distal end of the partially deployed Zephyr Valve is positioned against the carina distal to the target bronchus and complete deployment by slowly advancing the EDC actuator fully forward (see **Figure 19**).

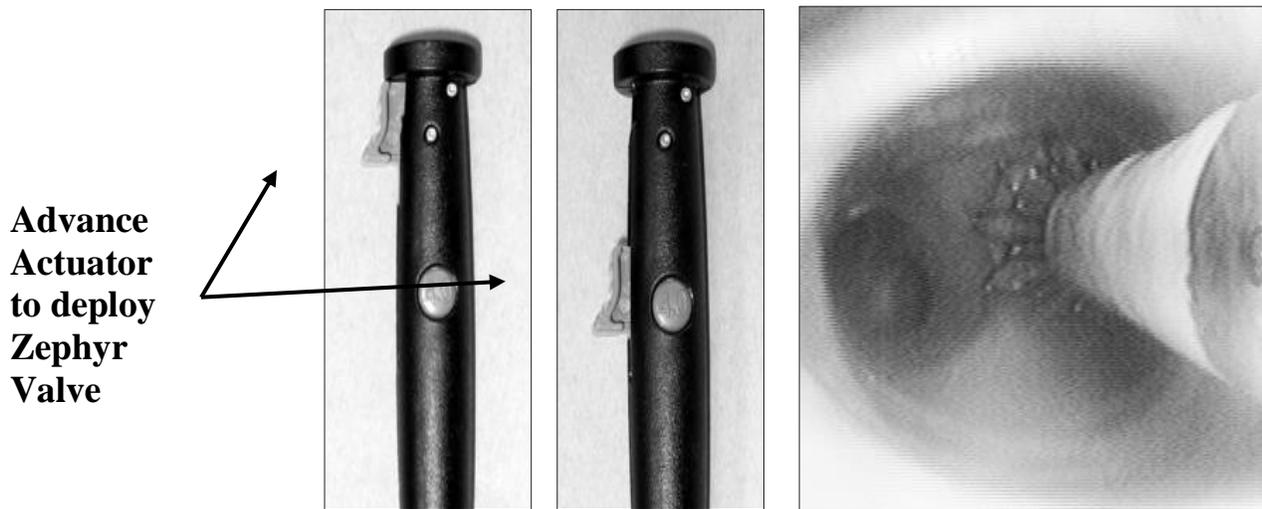


Figure 19 Actuator Advancement and Partial Deployment

If the length of the target bronchus can accommodate the Zephyr Valve without risking misplacement in a distal segment, confirm that the Zephyr EDC proximal depth mark is distal to the ostium of the target bronchus (see **Figure 20**). Slowly advance the actuator on the EDC to deploy the Zephyr Valve.

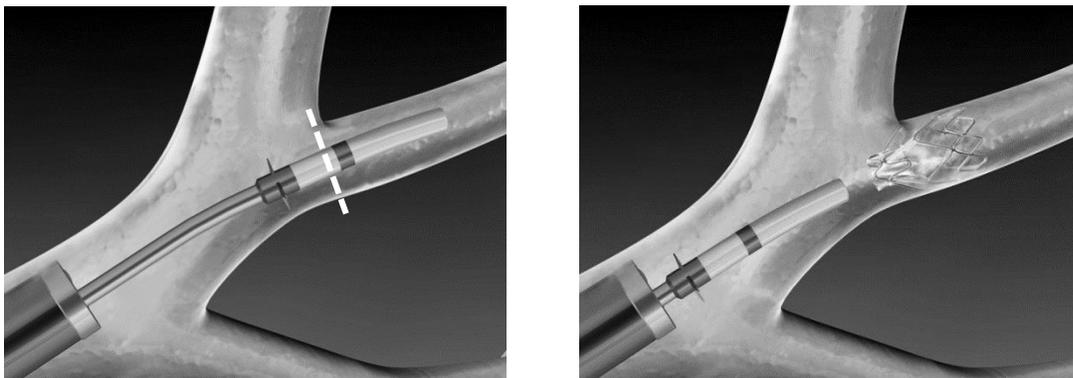


Figure 20 Deployment in Bronchus with Sufficient Length

Note that the housing retracts as the Zephyr Valve is deployed; thus, positioning the catheter housing distal to the bronchoscope tip facilitates retraction of the housing and precise deployment of the Zephyr Valve.

Prior to withdrawing the EDC, retract the bronchoscope into the patient's trachea and straighten the tip.

Precaution: *Use only moderate force to deploy the Zephyr Valve. If resistance is met while deploying, stop and remove the system. Replace the system with a new Zephyr Valve and Zephyr EDC.*

Warning: *Do not place the Zephyr EBV such that the distal end of the retainer is placed beyond the distal carina of the target bronchus thereby leaving a side branch untreated. This position may also result in proximal migration of the implanted Zephyr EBV.*

Precaution: *The Zephyr EDC may be loaded and used for deployment four times before discarding.*

Following placement, verify that the EBV is intact and functioning properly under direct visualization with the bronchoscope. The retainer of the deployed Zephyr Valve should be seated distal to the ostium such that none of the large retainer tips project out of the target bronchus (see **Figure 21**). Verify that the duckbill valve is not inverted or wedged open following deployment. If the Zephyr Valve is not positioned correctly or if the valve does not appear to be functioning properly, remove and replace with a new Zephyr Valve.

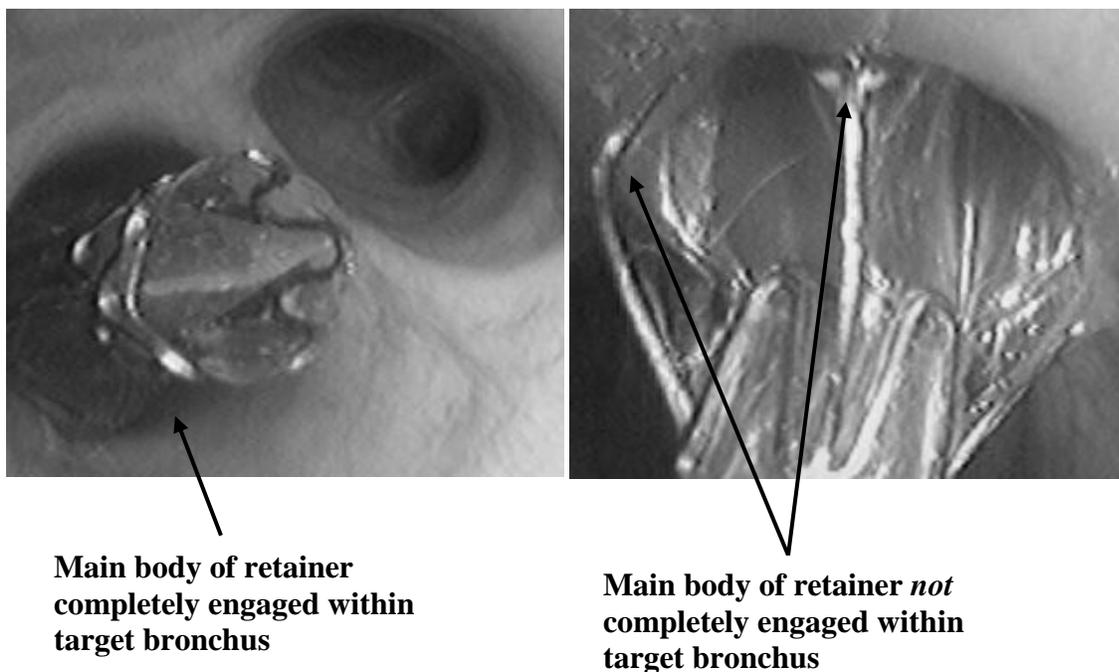


Figure 21 Zephyr Valve Device Positioning

Warning: Airway occlusion may be impaired if the Zephyr Valve retainer extends proximally beyond the ostium. Furthermore, this position may result in proximal migration or dislodgment of the implanted Zephyr Valve especially in short airways such as the superior bronchus of the lower lobes.

Multiple valves are required to achieve the lobar occlusion of the target lobe. The above steps must be repeated to place multiple valves in the segmental or sub-segmental airways of the target lobe. The number of valves required to achieve complete lobar occlusion, with the above mentioned optimal valve placement, is a function of the patient's target lobe and airway anatomy.

Note: In the LIBERATE trial, the median number of valves used per procedure was 4. The maximum number of valves used during a procedure was 8.

8.5 Zephyr Valve Removal

Following implantation, if the Zephyr Valve retainer is migrating within the airway during respiration, the Zephyr Valve is too small for the bronchus. Remove the device and select a larger size or implant devices in the next distal airways. Removal may be accomplished by using rat-tooth graspers to grip the valve protector portion of the retainer (via the bronchoscope working channel) (See **Figure 22**).



Figure 22 Grasping the Retainer

Precaution: Attempting to reposition the Zephyr Valve by grasping the valve protector portion of the retainer may result in device damage.

Precaution: Use caution when carefully removing a Zephyr Valve to avoid vocal cord injury. Once a Zephyr Valve is removed it cannot be reused.

Precaution: It is recommended that bronchoscopic aspiration of mucous be considered if there is evidence of an increase in mucous production post-procedure.

9.0 Storage

Store the packaged Zephyr Endobronchial Valve System and accessories at room temperature. Do not expose to extreme heat or moisture.

10.0 Patents and Trademarks

Zephyr Endobronchial Valve (EBV): This product and/or its use are covered by one or more of the following United States patents: 5,954,766; 6,527,761; 6,632,243; 6,679,264; 6,840,243; 6,901,927; 6,904,909; 6,941,950; 7,011,094; 7,033,387; 7,165,548; 7,276,077; 7,662,181; 7,670,373; 7,798,147; 7,854,228; 8,136,520; 8,251,067; 8,357,139; 8,474,460. Other U.S. patents pending. This product and/or its use are covered by one or more of the following international patents: AU2001243416; AU2001260840; AU2002347900; DE60221139; DE60323502.6; EP1434615; EP1524942; FR1434615; FR1524942; GB1434615; GB1524942; IR1524942; IT1524942. Other international patents pending.

Endobronchial Loader System (ELS): This product and/or its use are covered by one or more of the following United States patents: 7,771,472; 7,717,115; 7,814,912; 8,100,959; 8,388,682; 8,409,168. Other U.S. and international patents pending.

11.0 Symbols

	Caution: Federal law restricts this device to sale by or on the order of a physician		Do Not Re-sterilize
	Batch Code		Do Not Reuse
	Catalog Number		Diameter Range
	Contents		Date of Manufacture
	Non-Pyrogenic		Manufacturer
	Sterilized Using Ethylene Oxide		Consult Instructions for Use
	Use By		Do Not Use if Package is Damaged or Opened
	Caution, consult accompanying documents		MR Conditional
	Keep Dry		Temperature Limit



Zephyr® Endobronchial Valve-

A New Treatment for Severe Emphysema

This brochure describes a new procedure for treating severe emphysema in adults

Caution: Federal law restricts this device to sale by or on the order of a physician.

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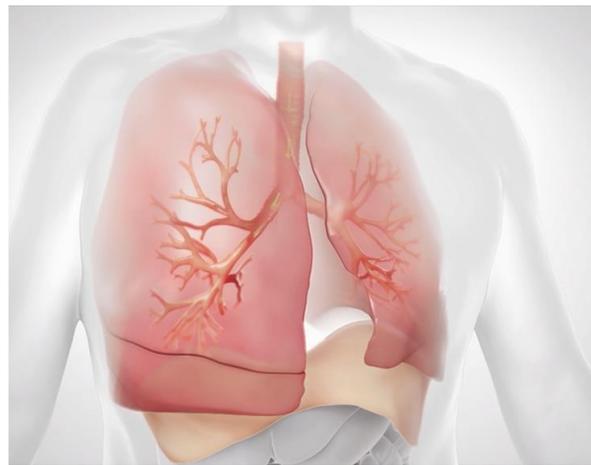
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What is Severe Emphysema?

Emphysema is a form of chronic obstructive pulmonary disease or COPD. In severe emphysema, parts of the lungs are damaged, which traps air in your lungs. This causes the diseased parts of the lung to get larger and put pressure on the healthy parts of your lungs and diaphragm. As a result, you may find it difficult to breath properly and take full, deep breaths.



Healthy Lung



Lung with Emphysema

This constant shortness of breath can make it difficult to do everyday activities and to enjoy many aspects of your life — such as walking, bathing, dressing, gardening, preparing meals, and going out with family or friends – without stopping for air, resting or requiring help.

Zephyr® Endobronchial Valve – A New Treatment Option for Severe Emphysema

Your doctor offers a new procedure to help patients with severe emphysema. It is called the Zephyr® Valve treatment. The Zephyr Valve treatment is a procedure that allows a doctor to place one or more small valves in your airways, which release trapped pockets of air to improve your ability to breathe. It is not a medicine and it is not surgery.

Other Treatment Options

Emphysema cannot be cured; however, treatment may help reduce symptoms, improve quality of life, and slow progression of the disease.

Current Emphysema Treatment Options:

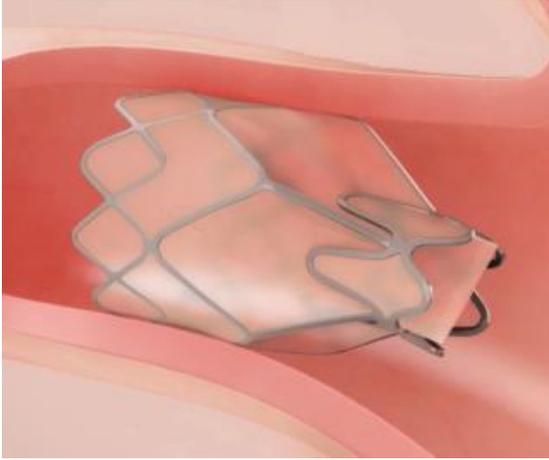
- Stop smoking
- Medication
- Long Term Oxygen Therapy
- Pulmonary rehabilitation
- Surgical lung volume reduction
- Lung transplant

What is Zephyr Valve?

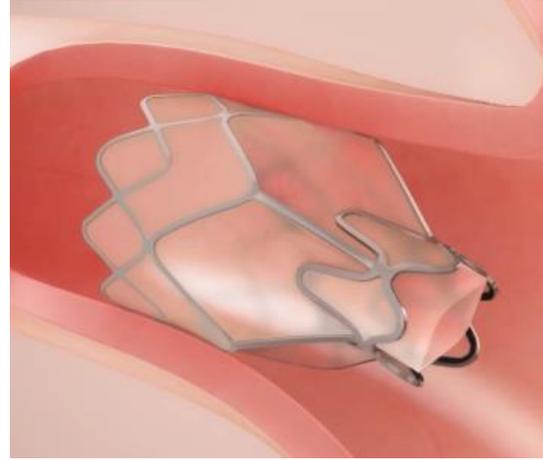
The Zephyr Valves are as tiny as a pencil eraser and are placed into diseased areas of your lungs in a short procedure.



The Zephyr Valves stop air from entering the diseased lung areas but allow air that is trapped and fluid in the lungs to escape when you breathe out. This allows healthy parts of your lungs to expand and work better. This will decrease shortness of breath.



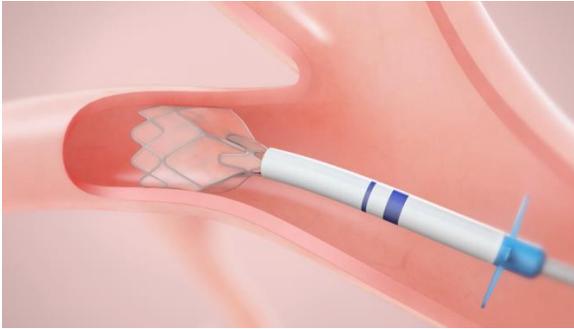
Zephyr Valve is closed when breathing in, stopping air from entering the damaged part of the lung



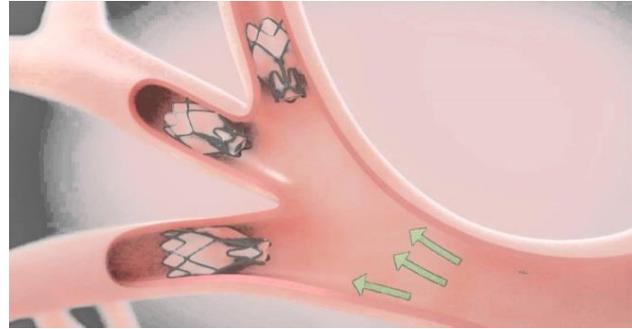
Zephyr Valve is open when breathing out, letting out trapped air from the damaged part of the lung

What is the Zephyr Valve treatment?

If your doctor agrees that you are good candidate, you will be sent to a specialist to decide if you qualify for treatment. The 30 to 60 minute Zephyr Valve procedure is performed in a hospital. The doctor will give you medicine to make you sleepy and insert a small tube with a camera (called a bronchoscope) into your lungs through your nose or mouth. The doctor will use the same tube to place between 3 to 5 Zephyr Valves in the airways in part of the lung being treated. The valves stop air from entering the treated part of the lung and allow previously trapped air to escape. After the procedure, you will continue to use the medicines that your doctor has prescribed for your condition.



Placement of Zephyr Valve



Multiples Zephyr Valves in Place

You can go home after 3 to 5 days unless you have side effects such as a small tear in the lung tissue, which can happen in up to 1 in 3 procedures. If this happens your doctor may put a small tube in your chest to let out the air from the tear, and you may need to stay in the hospital up to a week longer for the tissue to heal.

Who can have Zephyr Valve treatment?

The Zephyr Valve is used to treat patients whose lungs are increased in size by trapped air due to severe emphysema. Before you are treated, your doctor will give you a test to check that the blocked part(s) of your lung cannot refill with air from side passages from other parts of your lung.

Who cannot have Zephyr Valve treatment?

You cannot have this treatment if you:

- Are unable to have a bronchoscopic procedure
- Have an active lung infection
- Have an allergy to Nitinol, nickel, titanium, or silicone
- Have not stopped smoking
- An air pocket (bullae) that is greater than 1/3 of the size of the lung

Talk with your doctor

If one of the following is true for you, to see if you can have the Zephyr Valve procedure:

- Have had a lung transplant, lung volume reduction surgery, or any other major procedure on your lungs
- Have heart disease or had a recent heart attack
- Have a Claggett Window or Eloesser Flap

Clinical Studies

The Zephyr Valve has been studied in multiple clinical trials with patients in the United States, Europe, and Brazil. In these clinical trials, the Zephyr Valve was placed in over 1,000 patients with severe emphysema. In these studies, patients who had Zephyr Valves and were taking their normal emphysema medicines were able to breathe better, could do more exercise and had better quality of life than patients who did not have the Zephyr Valves.

Risks

What are the side effects of Zephyr Valve treatment?

In the most recent LIBERATE clinical trial, patients receiving Zephyr Valves had an increased risk of the following side effects in the first 45 days (in order of severity):

- Death
- Air Leak, also known as Pneumothorax (tear in the lung)
- Pneumonia
- Worsening of Emphysema Symptoms
- Coughing up Blood
- Shortness of Breath
- Chest Pain or Chest Discomfort
- Cough

This list does not include all the side effects that were seen in the clinical trials. You should talk with your doctor for more information regarding the Zephyr Valve procedure.

After the first 45 days, the LIBERATE patients who received the Zephyr Valve did not have an increased risk of side effects. , About 1 in 5 patients in LIBERATE had a second bronchoscope procedure to adjust the valves position or to manage side effects.

Benefits

Zephyr Valves provides significantly more benefit than medicine alone

In the LIBERATE clinical trial, at 1-year, the patients who received the Zephyr Valve experienced the following benefits compared to patients on medications alone.

- Increased exercise capacity- they could walk further
- Could do more daily life activities, such as walking, gardening, and getting ready in the morning, with less shortness of breath
- Increased lung function, as measured by FEV₁
- Better quality of life

What happens if you decide to have Zephyr Valve treatment for your severe emphysema?

- Your doctor will do an examination and perform lung function tests to determine if you are a good candidate.
- At the time of your procedure, your doctor will give you medicine that will make you sleepy and insert a flexible tube with a camera (called a bronchoscope) into your lungs through your nose or mouth.
- Your doctor will place the Zephyr Valves using the bronchoscope. The number of valves will be dependent on the structure of your lungs.

- The procedure should last between 30 to 60 minutes
- After the procedure the bronchoscope is removed from your nose or mouth.
- You will be carefully observed as you wake up and recover.

What happens after your Zephyr Valve treatment?

- You will be monitored closely by your doctor.
- You can go home after 3 to 5 days unless you have side effects like a tear in the lung tissue, which can happen up to 1 in 3 procedures. If this happens your doctor may put a small tube in your chest to let out the air from the tear and may need to stay in the hospital up to a week longer for the tissue to heal.
- Your doctor may recommend that you take antibiotics or steroid medicines after your Zephyr Valve procedure.
- You will be given a wallet-sized patient information card (patient ID card) that says you have one or more Zephyr Valve implants in your lung. It will also have the contact information of your doctor. Please keep this card with you at all times and show it to anyone who gives you medical care, including any emergency room medical staff. Please show your patient ID card to anyone who plans to perform an MRI scan.
- You will continue to use the medicines that your doctor has prescribed for your severe emphysema.
- After your airways recover from treatment, you will go back to your doctor for a checkup.

About 1 in 5 patients require an adjustment procedure. Zephyr Valves are removable. If you should require an adjustment procedure, one or more valves that have been previously placed are removed and replaced. During this procedure, your doctor may also place more valves as necessary to treat your lungs.

When should you seek medical help?

It is especially important to pay attention to symptoms within the first 2 weeks after any procedure.

- The risk of a tear in the lung (pneumothorax) is increased during the initial period post-procedure. This is a serious condition and requires (or may require) immediate emergency treatment. Patients should report to their local medical facility if they experience sudden chest pain, shortness of breath, rapid breathing or coughing, rapid heart rate, or sudden dizziness.
- If you cough up any blood or there is blood in your sputum, you should immediately go to your local medical facility or your doctor's office to be checked.
- Tell your doctor if you are having breathing symptoms or any other symptoms whether or not they are related to your breathing.

Where to get more information about the Zephyr Endobronchial Valve treatment for your emphysema.

Talk to your doctor

www.MyLungsMyLife.com

Call: 1-866-300-4550

Pulmonx Corporation

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Redwood City, CA 94063

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