Emphasys® Zephyr®

Endobronchial Valve System

Instructions for Use

STERILE EO

DO NOT RESTERILIZE
FOR SINGLE (1) USE ONLY
Keep dry. Store at room temperature.
Do not use if package is damaged or opened.
NON-PYROGENIC

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

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1. DEVICE DESCRIPTION

The Emphasys® Zephyr® Endobronchial Valve (Zephyr EBV) is an endobronchial implant that is intended to control airflow. 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 (Figure 1). It is implanted in the target bronchus using a flexible delivery catheter that is guided to the targeted bronchus by inserting it through the working channel of a bronchoscope.

The Zephyr EBV allows air to vent from the isolated lung segment during exhalation but does not allow refilling of this region during inhalation. With each respiratory cycle, the amount of air in the target lung segment is reduced. The Valve is designed to be a permanent implant.

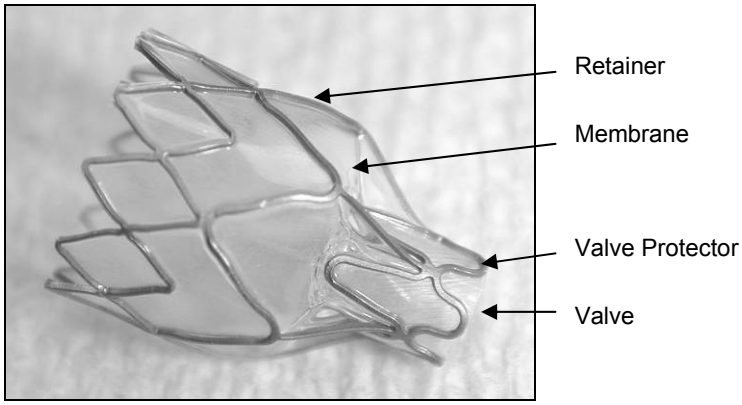


Figure 1: Emphasys Zephyr Endobronchial Valve

1.1. Required Equipment

- Adult flexible bronchoscope (working channel ≥ 2.8 mm)

1.2. System Components

- Emphasys Zephyr 4.0 Endobronchial Valve (Zephyr 4.0 EBV)
- Emphasys Zephyr 5.5 Endobronchial Valve (Zephyr 5.5 EBV)
- Emphasys Zephyr 4.0 Endobronchial Delivery Catheter (Zephyr 4.0 EDC)
- Emphasys Zephyr 5.5 Endobronchial Delivery Catheter (Zephyr 5.5 EDC)
- Emphasys Zephyr 4.0 Endobronchial Loader System (Zephyr 4.0 ELS)
- Emphasys Zephyr 5.5 Endobronchial Loader System (Zephyr 5.5 ELS)

2. INDICATIONS FOR USE

The Emphasys® Zephyr® Endobronchial Valve System (Zephyr EBV System), which consists of the implantable Zephyr Endobronchial Valve (Zephyr EBV), the Zephyr Endobronchial Delivery Catheter (Zephyr EDC) and the Zephyr Endobronchial Loader System (Zephyr ELS), is intended to improve FEV_1 and six minute walk test distance in patients with severe, heterogeneous emphysema who have received optimal medical management.

3. CONTRAINDICATIONS

The Zephyr EBV is contraindicated for:

- Patients for whom bronchoscopic procedures are contraindicated.
- Patients with evidence of active infection in the lung lobe targeted for valve therapy.
- Patients with known allergies to Nitinol (nickel-titanium) or silicone.

4. WARNINGS

The safety and efficacy of Zephyr Endobronchial Valve therapy has not been established in the following patient populations:

- Patients > 75 years of age.
- Patients who have not quit smoking.

- Alpha-1 antitrypsin deficiency.
- FEV_1 <15% of predicted value.
- Patients with DLco ≤ 15%.
- Large bullae in the non-targeted area of lung.
- Congestive heart failure or recent myocardial infarction.
- Prior lung transplant, LVRS, median sternotomy, or lobectomy.
- Pulmonary hypertension.
- Serious bleeding disorders.

5. PRECAUTIONS

- Read all labels and instructions prior to use.
- Carefully inspect product prior to use. Do not use if the product is damaged.
- The Zephyr EDC handle contains permanent magnets. These magnets have strong magnetic fields that may damage magnetic data storage media and electronic equipment if brought within two inches of the delivery catheter. The Zephyr EDC should be kept away from magnetic media such as electronic equipment, computer discs, credit cards and video tapes.

5.1. MRI Information

Non-clinical testing has demonstrated that the Zephyr EBV is MR Conditional immediately following implantation. The Zephyr EBV can be scanned safely under:

- Static magnetic field of 3 Tesla or less
- Spatial gradient field of 720 Gauss/cm or less
- Specific Absorption Rate (SAR) for 15 minutes of scanning:
  - Whole body average of 3.0 W/kg
  - Spatial peak of 5.8 W/kg

In non-clinical testing, the Zephyr EBV produced a temperature rise of less than or equal to 0.5°C at maximum MR system reported SAR of 3.0 W/kg for 15 minutes of MR scanning in a 3 Tesla MR scanner (Excite, Software G3.0-052B, General Electric Healthcare, Milwaukee, WI). This amount of heating is considered to be physiologically inconsequential and will not impose an additional risk or hazard to the patient undergoing an MRI procedure under these conditions.

MR image quality may be compromised if the area of interest is in the exact same area or relatively close to the position of the device. Therefore, it may be necessary to optimize MR imaging parameters to compensate for the presence of this implant.

6. OVERVIEW OF CLINICAL STUDIES

The Zephyr EBV was initially evaluated in nonrandomized, prospective trials in patients with severe emphysema. Efficacy endpoints measured at 90 days demonstrated improvement in FEV_1, 6 minute walk test distance and quality of life scores. These improvements were achieved with reduced mortality and morbidity when compared to lung volume reduction surgery (LVRS).

The Endobronchial Valve for Emphysema PalliatioN Trial ("VENT Pivotal Trial") was a randomized, controlled, multicenter clinical trial designed to assess the safety and effectiveness of using the Zephyr EBV device in the palliation of patients with severe heterogeneous emphysema. Three hundred and twenty-one (321) patients were enrolled across thirty-one (31) clinical sites in the United States. Prior to randomization, all patients received optimized medical management including six to eight weeks of pulmonary rehabilitation. Patients were then randomized to either ongoing medical management (Control group) or Zephyr EBV therapy (Treatment group). Patients were randomized in a 2:1 ratio (2 Treatment : 1 Control). Follow-up contacts were scheduled at 2-3, 7-10, 30, 90 180 and 365 days. The study's co-primary efficacy endpoints were mean percent change from baseline in FEV_1 and 6 minute walk test (6MWT) at six months. The primary safety endpoint was the proportion of patients in each group experiencing one or more events specified as components of the Major Complications Composite (MCC) through six months of follow-up. The MCC components consisted of:

- Death, all-cause
- Empyema
- Massive hemoptysis resulting in respiratory failure or blood loss > 300cc in ≤ 24hr
- Pneumonia distal to the implanted valves
- Pneumothorax or prolonged air leak > 7 days
- Respiratory failure on mechanical ventilation for > 24 hours

7. ADVERSE EVENTS

Potential complications which may be associated with bronchoscopy and/or EBV implantation include, but are not limited to, the following:

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

7.1. Major Complications and Adverse Events – All Patients

Safety data analysis in the VENT study was based on the modified intention to treat patient cohort (i.e. randomized patients who received study-directed treatment and had any follow-up). The per-patient rates of study defined Major Complications and other adverse events observed in the VENT study are summarized in Table 1 and Table 2. The proportion of patients experiencing a Major Complication Composite event at six months or one year following Zephyr EBV therapy was not statistically significantly different than the rates observed in control patients.

Table 1: Per-Patient Major Complications Composite

	Primary Safety Endpoint 6 months			**Additional Safety Analysis 12 months (cumulative)**		
	EBV n=214	**Control n=87**	**p value**	**EBV n=214**	**Control n=87**	**p-value**
Major Complication Composite (MCC)	6.1%	1.2%	0.075	10.4%	4.6%	0.172
Death	2.8%	0.0%	0.187	3.7%	3.5%	1.000
Respiratory Failure with ≥ 24 hours ventilation	1.9%	1.2%	1.000	2.8%	2.3%	1.000
Massive Hemoptysis	0.5%	0.0%	1.000	0.5%	0.0%	1.000
Pneumothorax / air leak lasting > 7 days	1.4%	1.2%	1.000	1.9%	1.2%	1.000
Empyema	0.0%	0.0%	----	0.0%	0.0%	----
Pneumonia distal to implanted valve	1.4%	NA	----	4.2%	NA	----

Table 2: Per-Patient Adverse Events through 1 Year – All Patients

Event	Zephyr EBV n=214	Control n=87	p-value
All Cause Mortality [1]	3.7%	3.5%	1.0000
All Cardiovascular	7.9%	6.9%	1.0000
COPD/Emphysema Related			
Exacerbation w/o hospitalization	57.5%	50.6%	0.3069
Exacerbation with hospitalization	18.2%	10.3%	0.1174
Pneumonia not distal to valve	11.2%	10.3%	1.0000
Other pulmonary infection	8.4%	1.2%	**0.0174**
Any respiratory failure	3.3%	3.5%	1.0000
w/ ≥ 24 hours ventilation [1]	2.8%	2.3%	1.0000
Increased shortness of breath	9.8%	2.3%	**0.0295**
Hypoxemia	7.0%	0.0%	**0.0073**
New/worse hypercapnea	2.3%	1.2%	0.6765
Cough	6.1%	1.2%	0.0748
Bronchospasm	1.9%	0.0%	0.3277
Other Pulmonary/Thoracic Related			
Massive hemoptysis [1]	0.5%	0.0%	1.0000
Other hemoptysis	42.1%	2.3%	**<0.0001**
Pneumothorax	5.1%	2.3%	0.3602
Air leak > 7 days [1]	1.9%	1.2%	1.0000
Expanding pneumothorax	1.9%	2.3%	1.0000
Stable pneumothorax	1.4%	1.2%	1.0000
Empyema [1]	0.0%	0.0%	--
Pleural effusion	0.5%	0.0%	1.0000
Non-cardiac chest pain	16.4%	3.5%	**0.0018**
All Valve/Implant Related			
Expectoration/aspiration/migration	7.9%		--
Pneumonia distal to valve [1]	4.2%		--
Bronchial granulation tissue	7.9%		--
Bronchial trauma	0.5%		--
Other/General			
Nausea or vomiting	8.4%	1.2%	**0.0174**

[1] A component of the Major Complications Composite

7.2. Valve Migration

Migration from the implant site(s) is a known risk of Endobronchial Valve implantation. Implant location can be confirmed using chest x-ray, CT or bronchoscopy. During the VENT study, 23 valves (2.8%) in seventeen patients (7.9%) migrated from their original placement location. In 8 of these patients, one or more migrating valves were expectorated by the patient. The mean number of days post procedure for recorded migration events was 90 days (range 0 – 274 days).

7.3. Valve Removal

Zephyr Endobronchial Valves were shown to be removable in the VENT study. During the follow-up period, a total of 87 valve removal attempts were made in thirty-one patients. Individual valve removal was successful in 98% of attempts. In 10 patients, valve removal was precipitated by migration. In six patients removal was undertaken to reposition valves or to allow alternative treatments. In the remaining 15 patients, removal was performed for a range of reasons such as hemoptysis, pneumonia, granulation tissue formation, dyspnea, continuing COPD exacerbations, or patient request.

8. CLINICAL STUDIES – AGGREGATE RESULTS OF THE VENT TRIAL

8.1. Efficacy Results

The co-primary efficacy endpoints of the VENT study were FEV_1 and 6MWT using intent-to-treat analysis with multiple imputation. To meet these endpoints, the study had to show that at six months follow-up, the mean percent change from baseline was statistically higher in the treatment group for both variables.

Results for patients with imputed data showed the difference between treatment and control group to be 6.8% for FEV_1 and 5.8% for 6MWT. Both findings were highly statistically significant. Differences in the four secondary endpoints also reached statistical significance (Table 3).

Table 3: Primary and Secondary Efficacy Endpoint Results by Intent-to-Treat Analysis

	Mean Change from Baseline at 6 Months	
1° ENDPOINTS	**Delta (95% CI)**	**p-value**
FEV_1 (% change)	6.8 (2.1, 11.5)	**0.002**
6MWT (% change)	5.8 (0.5, 11.2)	**0.019**
2° ENDPOINTS		
SGRQ	-3.4 (-6.6, -0.3)	**0.017**
MMRC	-0.26 (-0.49, -0.02)	**0.018**
Cycle Ergometry Peak Workload (watts)	3.8 (0.2, 7.4)	**0.020**
Supplemental Oxygen Use (liters/day)	-12.0 (-76.7, 52.7)	**0.020**

Results for patients with available data showed the difference between treatment and control group means to be 7.2% for FEV_1 and 5.8% for 6MWT. Both findings were highly statistically significant. Differences in three of the four secondary endpoints also reached statistical significance (Table 4).

Table 4: Supportive Analysis: Efficacy Endpoint Results with Available Data

	Mean Change from Baseline at 6 Months				
1° ENDPOINTS	**Zephyr EBV Mean ± SD (n)**	**Control Mean ± SD (n)**	**Delta**	**(95% CI)**	**p-value**
FEV_1 (% change)	5.3 ± 19.6 (179)	-1.9 ± 12.2 (75)	7.2	(3.2, 11.2)	**<0.001**
6MWT (% change)	4.3 ± 22.7 (178)	-1.5 ± 22.5 (73)	5.8	(1.3, 11.7)	**0.008**
2° ENDPOINTS					
SGRQ	-2.7 ± 13.3 (158)	0.7 ± 9.7 (62)	-3.4	(-6.6, -0.2)	**0.019**
MMRC	-0.09 ± 1.04 (162)	0.21 ± 0.83 (67)	-0.30	(-0.56, -0.05)	**0.011**
Cycle Ergometry Peak Workload (watts)	0.1 ± 15.3 (166)	-4.4 ± 12.8 (69)	5.0*	(0.0, 5.0)*	**0.004**
Supplemental Oxygen Use (liters/day)	-17.1 ± 912.8 (171)	82.9 ± 744.0 (75)	-100.1	(-318.6, 118.4)	0.184

*Delta and 95% CI calculated using the median due to non-parametric distribution

8.2. Target Lobe Volume Changes at 6 Months

Lung lobe volumes were measured at follow-up and compared to baseline values. Treatment with Zephyr Endobronchial Valves resulted in a statistically significant reduction in target lobe volume at six months. Zephyr EBV treatment also resulted in a statistically significant increase in the volume of non-targeted lobes indicating a redistribution of airflow within the lung at six months (Table 5).

Table 5: Lung Volume Redistribution at 6 Months Following EBV Therapy

Target Lobe Volume Change (ml)			Non-Target Lobe Volume Change* (ml)		
Zephyr EBV Mean ± SD (n)	**Control Mean ± SD (n)**	**p-value**	**Zephyr EBV Mean ± SD (n)**	**Control Mean ± SD (n)**	**p-value**
-378.4 ± 530.1 (189)	-16.3 ± 134.7 (79)	**<0.001**	207.7 ± 340.2 (189)	-35.4 ± 169.8 (79)	**<0.001**

* Total volume change for all non-treated lobes in the treated lung

9. CLINICAL STUDIES – HIGH HETEROGENEITY PATIENT COHORT

Multivariate, mixed-model analyses were used to test the relationship between prespecified covariates and changes in the co-primary endpoints. Heterogeneity, defined as the difference in disease severity between lobes within the treated lung, remained in the mixed model analyses as a predictor of outcome for both co-primary endpoints. Based on these findings, the median heterogeneity (15%) was used to divide the study population into a high heterogeneity (≥15%) and low heterogeneity (<15%) groups for further analysis. Patients with high heterogeneity have less destruction and thus more potentially expandable lung parenchyma in the non-treated lobe compared with patients with less heterogeneous emphysema.

9.1. Key Efficacy Outcome Measures at 6 and 12 Months

Efficacy results for the high heterogeneity group are given below in Table 6. In this completed cases cohort, Zephyr Endobronchial Valve therapy resulted in statistically significant improvements in FEV_1 and 6MWT at 6 and 12 months when compared to optimized medical management alone.

Table 6: Key Efficacy Measures - High Heterogeneity Group

METRIC	MEAN CHANGE FROM BASELINE					
	Zephyr EBV Mean ± SD	(n)	Control Mean ± SD	(n)	Delta (95% CI)	p-value
6 MONTH						
FEV_1 Δ (ml)	83.2 ± 184.3	(91)	-28.0 ± 83.9	(40)	111.2 (64.9, 157.5)	**<0.001**
6MWTΔ (meters)	19.2 ± 71.8	(90)	-25.2 ± 78.4	(38)	50.4* (20.2, 66.0)*	**<0.001**
FEV_1%	10.1 ± 22.3	(91)	-2.2 ± 11.3	(40)	12.3 (6.5, 18.1)	**<0.001**
6MWT%	7.3 ± 26.6	(90)	-5.9 ± 21.9	(38)	14.4* (6.3, 21.0)*	**<0.001**
12 MONTH						
FEV_1 Δ (ml)	110.8 ± 204.2	(87)	-21.5 ± 88.0	(41)	132.3 (81.1, 183.4)	**<0.001**
6MWTΔ (meters)	5.1 ± 83.1	(88)	-24.7 ± 78.8	(41)	26.6* (4.0, 51.0)*	**0.013**
FEV_1 %	13.6 ± 24.2	(87)	-1.6 ± 10.4	(41)	15.2 (9.1, 21.2)	**<0.001**
6MWT%	3.1 ± 29.2	(88)	-5.0 ± 19.2	(41)	8.2 (-0.4, 16.7)	**0.031**

*****Delta and 95% CI calculated using the median due to non-parametric distribution

9.2. Responder Analysis

The proportion of high heterogeneity patients meeting or exceeding prespecified thresholds of improvement at follow-up were calculated (Table 7). Zephyr Endobronchial Valve therapy resulted in a higher proportion of patients with 15% or greater improvements in FEV_1 and 6MWT at 6 months and in FEV_1 at 12 months following treatment.

Table 7: Responder Analysis - High Heterogeneity Group

	PROPORTION OF PATIENTS MEETING THRESHOLD				
	Zephyr EBV% (n)	Control% (n)	Odds Ratio	(95% CI)	p-value
6 MONTH					
FEV_1Δ ≥ 0%	65.9 (91)	32.5 (40)	4.0	(1.8, 8.9)	**<0.001**
FEV_1Δ ≥ 15%	35.2 (91)	12.5 (40)	3.8	(1.4,10.7)	**0.006**
6MWTΔ ≥ 0%	65.6 (90)	36.8 (38)	3.3	(1.5, 7.2)	**0.003**
6MWTΔ ≥ 15%	31.1 (90)	13.2 (38)	3.0	(1.1, 8.4)	**0.025**
12 MONTH					
FEV_1Δ ≥ 0%	66.7 (87)	51.2 (41)	1.9	(0.9, 4.1)	0.070
FEV_1Δ ≥ 15%	40.2 (87)	2.4 (41)	26.9	(3.5, 205.0)	**<0.001**
6MWTΔ ≥ 0%	62.5 (88)	39.0 (41)	2.6	(1.2, 5.6)	**0.011**
6MWTΔ ≥ 15%	25.0 (88)	17.1 (41)	1.6	(0.6, 4.2)	0.221

10. INDIVIDUALIZATION OF TREATMENT

10.1. Fissure Integrity

During the VENT trial, an imaging core lab assessed the integrity of each fissure at baseline. Each fissure was given a binary score of complete or incomplete. For data analysis, patients were considered to have complete fissures if all fissures bordering the target lobe were graded complete. Multivariate analysis identified fissure integrity as an additional predictor of FEV_1 improvement at follow-up.

10.2. Target Lobe Volume Changes at 6 Months

Target lobe volume reduction following valve implantation was greatest in the intact fissure patient group (Table 8). Volume changes in non-target lobes were also highest in this group.

Table 8: Lung Volume Redistribution at 6 Months Following EBV Therapy – Intact Fissure Group

Target Lobe Volume Change (ml)			Non- Target Lobe Volume Change* (ml)		
Zephyr EBV Mean ± SD (n)	**Control Mean ± SD (n)**	**p-value**	**Zephyr EBV Mean ± SD (n)**	**Control Mean ± SD (n)**	**p-value**
-712.5 ± 668.0 (68)	2.2 ± 111.5 (34)	**<0.001**	400.5 ± 427.3 (68)	-14.7 ± 123.7 (34)	**<0.001**

* Total volume change for all non-treated lobes in the treated lung

10.3. Impact of Fissure Integrity on FEV_1

The impact of fissure integrity on FEV_1 is given in Table 9 and Table 10. Endobronchial valve treatment in this group resulted in greater improvements at 6 and 12 months that were highly statistically significant.

Table 9: Key Efficacy Measures – Intact Fissure Group

METRIC	MEAN CHANGE FROM BASELINE					
	Zephyr EBV Mean ± SD	**(n)**	**Control Mean ± SD**	**(n)**	**Delta (95% CI)**	**p-value**
6 MONTH						
FEV_1 Δ (ml)	101.6 ± 183.5	(68)	-34.6 ± 84.5	(33)	136.2 (83.2, 189.1)	**<0.001**
FEV_1%	13.5 ± 22.9	(68)	-2.7 ± 10.2	(33)	16.2 (9.7, 22.8)	**<0.001**
12 MONTH						
FEV_1 Δ (ml)	132.8 ± 191.8	(68)	-16.6 ± 87.5	(32)	149.4 (93.9, 204.8)	**<0.001**
FEV_1 %	17.2 ± 23.8	(68)	-1.7 ± 9.6	(32)	18.9 (12.3, 25.6)	**<0.001**

Table 10: Responder Analysis – Intact Fissure Group

	PROPORTION OF PATIENTS MEETING THRESHOLD				
	Zephyr EBV% (n)	**Control% (n)**	**Odds Ratio**	**(95% CI)**	**p-value**
6 MONTH					
FEV_1Δ ≥ 0%	72.1 (68)	42.4 (33)	3.5	(1.5, 8.4)	**0.004**
FEV_1Δ ≥ 15%	42.7 (68)	6.1 (33)	11.5	(2.6, 52.1)	**<0.001**
12 MONTH					
FEV_1Δ ≥ 0%	76.5 (68)	40.6 (32)	4.8	(1.9, 11.7)	**0.001**
FEV_1Δ ≥ 15%	45.6 (68)	6.3 (32)	12.6	(2.8, 56.8)	**<0.001**

11. PATIENT SELECTION

Clinical criteria that should be considered in determining whether a patient has advanced, heterogeneous emphysema similar to that evaluated in the VENT study include but are not limited to:

- FEV_1 ≥15% and ≤ 45%
- RV ≥ 150%
- TLC ≥ 100%
- At least one major lobe (RUL, RLL, LUL, LLL) with at least 50% of the lung volume destroyed by emphysema
- At least a 15% difference between the upper and lower lobes of the target lung, in the percentage of tissue destroyed by emphysema

12. VALVE TARGETING

The goal of Zephyr valve therapy is to completely isolate the most diseased lobe in the most heterogeneous lung. This maximizes volume reduction and airflow redistribution leading to clinical benefit. To identify the best lobe to target, the following treatment algorithm should be followed:

1. **Assess Disease Severity**
   - Radiographically assess the severity of disease destruction within each lobe of each lung.
   - Ensure that at least one upper or lower lobe has destruction sufficient to warrant treatment.
   - In the VENT study, this threshold was 50% of target lobe volume destroyed by emphysema.

2. **Assess heterogeneity**
   - Radiographically assess the relative severity of the upper and lower lobes in each lung.
   - A difference in degree of destruction between the upper and lower lobes should be readily apparent.

3. **Select Target Lung and Lobe**
   - If only one lung has sufficient disease severity and heterogeneity as identified above, then select that lung for treatment and place valves in the lobe (upper or lower) with greater disease severity.
   - If both lungs appear suitable for treatment, consider treating the lung with the greater heterogeneity.

4. **Valve Placement**
   - Valves should be placed in all airways necessary to fully occlude the target lobe.
   - Accurate valve placement and airtight airway wall contact are necessary to optimize air redistribution and volume reduction.

5. **Other considerations**
   - <u>Right Middle Lobe:</u> If the right middle lobe is significantly more destroyed than the other lobes in the right lung, treatment of the right upper or lower lobes may result in hyperinflation of the middle lobe following therapy as air is preferentially redirected into the less compliant middle lobe. In patients with this disease distribution, consider treating the left lung instead.

   - <u>Fissures:</u> Fissure integrity may be considered in valve targeting. Lobes surrounded by intact fissures tend to exhibit greater volume reduction.

   - <u>Destruction vs. Heterogeneity</u>: In cases where both lungs are eligible for treatment, one lung may have greater heterogeneity but much lower destruction than the other lung. In such cases, it may be warranted to treat the lung with the greater destruction.

   Note that in the VENT study, the left upper lobe and lingula were considered one anatomical unit. . When treatment of the left upper lobe was specified, both regions were isolated with valves. Bilateral treatment (treating both lungs in one setting) and right middle lobe treatment were not evaluated in the VENT study.

13. OPERATOR INSTRUCTIONS

13.1. Delivery Catheter Preparation

Remove the delivery catheter from the packaging tray as follows (see Figure 2):

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.

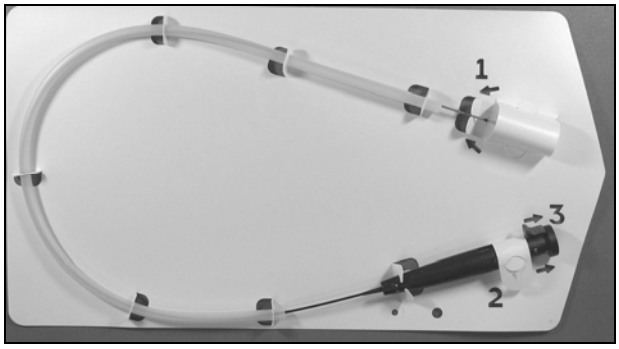


Figure 2: EDC Package Tray

13.2. Zephyr EBV Loading

The Zephyr EBV is packaged inside the Zephyr ELS (see Figure 3). To load the Zephyr EBV, perform the following steps:

a) Pull the Locking Clip from the loader funnel assembly (see Figure 4).

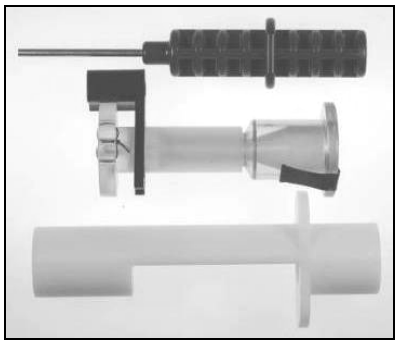


Figure 3: Emphasys Loader System

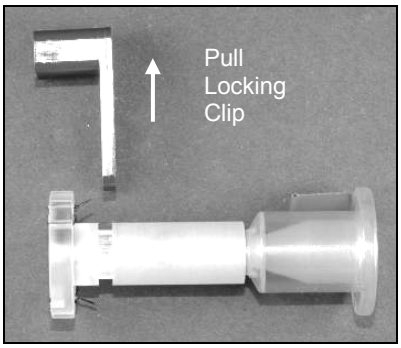


Figure 4: Locking Clip Removal

b) Pull the Zephyr EBV into the funnel cartridge of the loader by pulling the ends of the funnel assembly until the EBV device stops advancing within the funnel (this is indicated by an increase in resistance while pulling), (see Figure 5).

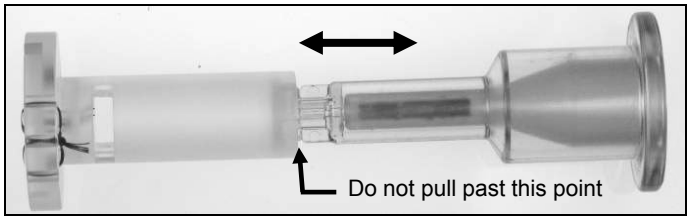
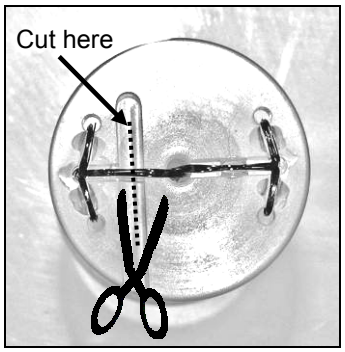


Figure 5: Funnel Loading

c) Cut the cord bundle that lays across the groove in the end of the funnel assembly and pull the two parts of the funnel assembly until completely separated (see Figure 6 and Figure 7).



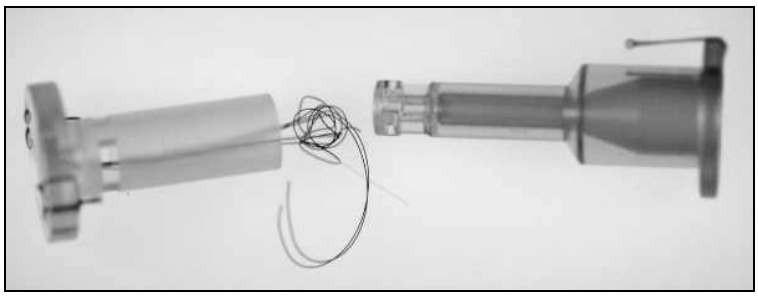


Figure 6: Cord Cutting **Figure 7: Funnel Assembly Separation**

d) Remove the tape from the end of the loader funnel assembly and remove the funnel cartridge. Confirm that the Zephyr EBV is completely pulled into the small diameter portion of the funnel cartridge and that there are no monofilament strands attached to the valve (see Figure 8).

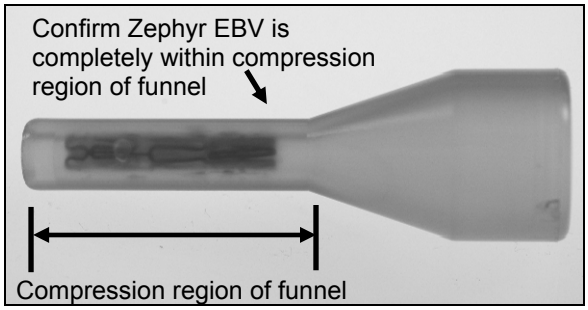


Figure 8: Confirm Zephyr EBV Position

e) Place the Zephyr EDC housing in the loading cylinder and slide the proximal end up to the housing stop (see Figure 9). Verify that the handle actuator is fully retracted.

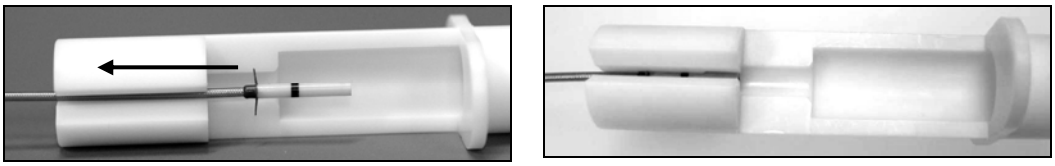


Figure 9: Housing Insertion

f) Place the funnel cartridge into the loading cylinder and use the handle end of the pusher to slide the funnel cartridge over the end of the EDC housing. Gently apply force until the pusher is snug against the loader body to insure funnel cartridge is over the end of the EDC housing (see Figure 10)

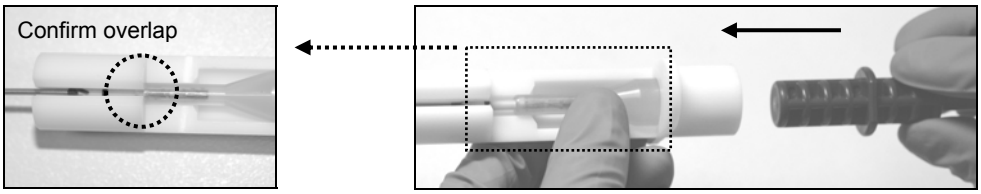


Figure 10: Funnel Cartridge Insertion

g) Insert the pusher tip into the funnel and gently apply force, pressing the compressed Zephyr EBV into the Zephyr EDC housing (see Figure 11). Carefully, hold the funnel cartridge in place to insure the funnel cartridge is over the end of the EDC housing.

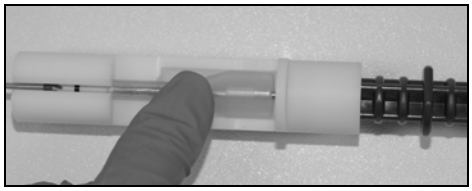


Figure 11: Zephyr EBV Loading

h) Slide the empty funnel away from the Zephyr EDC housing and remove the catheter from the loading cylinder. Verify that the Zephyr EBV device is seated within the Zephyr EDC housing. Verify that the Zephyr EDC housing is not damaged prior to and after loading. Replace the Zephyr EDC if the housing appears damaged.

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

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

13.3. 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 the tip. This can be performed in or out of the patient. Advance the bronchoscope up to the carina proximal to the target bronchus.

Advance the Zephyr 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 accept the EBV device (the minimum depth mark must be distal to the proximal carina of the target bronchus). Next, advance the Zephyr EDC into the target bronchus such that the diameter gauge located on the proximal end of the Zephyr EDC housing is flush with the carina of the target bronchus (see Figure 12). Using the diameter gauge located on the proximal end of the Zephyr EDC housing, verify that the target bronchial diameter is between the span of the large pair and the small pair of gauges. Locate the housing within the target bronchus such that the minimum depth mark is distal to the carina.

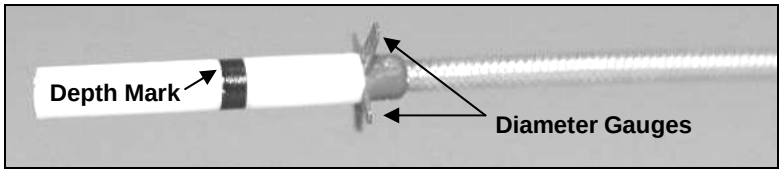


Figure 12: Depth Mark and Diameter Gauges

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

Precaution: *Placement of the Zephyr EBV 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 EBV device may impair the ability of the Zephyr EBV device to completely occlude the airway.*

Precaution: *Confirm free movement of the Zephyr EDC within the bronchoscope. If movement in the bronchoscope appears too constrained, change to a larger working channel bronchoscope.*

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

13.4. Emphasys Zephyr EBV Deployment

To ensure that the Zephyr EBV is not placed in a segment distal to the target bronchus, partially deploy the Zephyr EBV by slowly advancing the actuator on the EDC handle by 0.25" – 0.5" (see Figure 13). Position the EDC such that the flared distal end of the partially deployed Zephyr EBV is positioned immediately proximal to the carina distal to the target bronchi and complete deployment by slowly advancing the Zephyr EDC actuator fully forward. Note that the housing retracts as the Zephyr EBV is deployed; thus, positioning the catheter housing distal to the bronchoscope tip facilitates retraction of the housing and precise deployment of the Zephyr EBV.

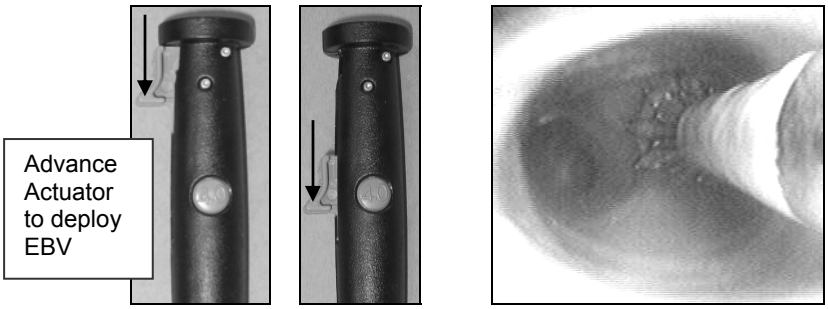


Figure 13: Actuator Advancement and Partial Deployment

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

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

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

Clinical results have indicated that in patients with markedly heterogeneous disease distribution, the most significant improvements have occurred when entire target lobes are treated. It is recommended that all bronchi leading to the targeted lobe be treated.

Following placement, verify that the valve is intact and functioning properly. The retainer of the deployed Zephyr EBV device should be seated distal to the carina such that none of the large retainer tips project out of the target bronchus (see Figure 14). Verify that the duckbill valve is not inverted or wedged open following deployment. If it is inverted, attempt to revert the valve using bronchoscopic suction. If the Zephyr EBV is not positioned correctly or if the valve does not appear to be functioning properly, remove and replace with a new Zephyr EBV.

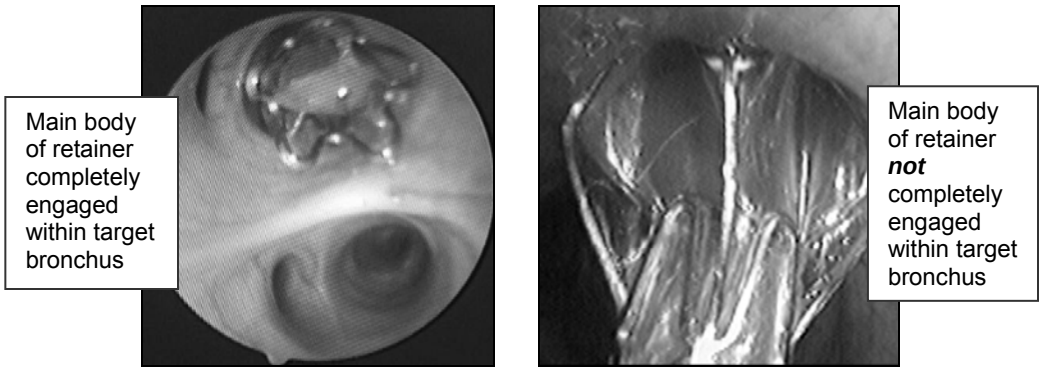


Figure 14: Zephyr EBV Device Positioning

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

Following implantation, if the Zephyr EBV retainer is moving proximally or distally within the airway during respiration, the Zephyr EBV is too small for the bronchus. Remove the device and select a larger size or implant devices in the next more distal airways.

Removal may be accomplished by using rat-tooth graspers, inserted through the bronchoscope working channel, to grip the valve protector portion of the retainer (see Figure 15).

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

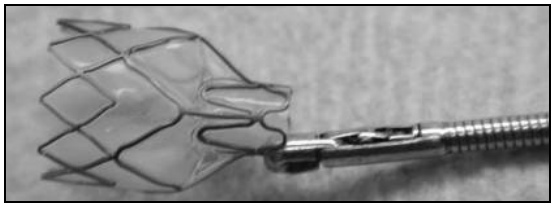


Figure 15: Grasping the Retainer

13.5. Post-Procedure

Post-procedure, it is recommended that patients with radiographic evidence of atelectasis be kept in-hospital under observation for at least two days post-procedure.

Warning: *Pneumothorax is an expected response to atelectasis. The user should be prepared to observe and/or treat a pneumothorax that develops subsequent to atelectasis.*

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

13.6. Valve Placement Optimization

If post-procedure volume reduction is less than anticipated, consider evaluating valve placement accuracy using bronchoscopy or HRCT imaging. Suboptimal valve placement can lead to air leaking past the implanted valves. For example, the distal part of the device may be inadvertently placed down one arm of an airway bifurcation leaving the other arm of the branch open (see Figure 16). If improper placement is suspected, consider removing and replacing the valve(s).

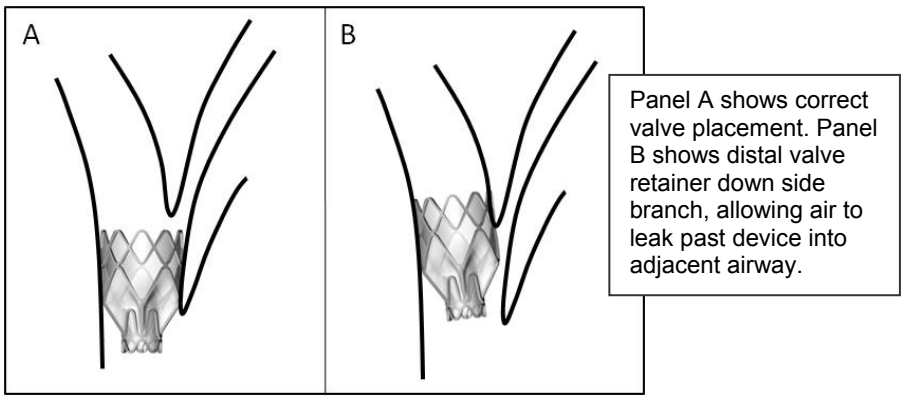


Figure 16: Valve Placement

14. PATIENT INFORMATION

In addition to these Instructions for Use, a Patient Implant Card is shipped with each Zephyr Endobronchial Valve. The card identifies the patient as a valve recipient and allows clinical contact information to be provided. Fill out the Zephyr Implant Card and provide to the patient.

A Patient Guide containing information about emphysema and the Zephyr Endobronchial Valve procedure may also be found on-line at www.emphasysmedical.com.

15. HOW SUPPLIED

15.1. Contents

The Zephyr Endobronchial Valve and Loader System are packaged together, one (1) valve and one (1) loader system per package. The Zephyr Delivery Catheter is packaged separately, one (1) catheter per package.

15.2. Sterility

The Zephyr system components are supplied sterilized by ethylene oxide gas. Contents are sterile and non-pyrogenic if packaging is unopened and undamaged.

15.3. Storage

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

16. PATENTS

Protected under one or more of the following patents: United States Nos: 5954766, 6632243, 6679264, 6694979, 6840243, 6901927, 6904909, 6941950, 7033387, 7165548, 7276077. Other U.S. patents pending. Foreign patents issued and pending.

17. GRAPHIC SYMBOLS CONTAINED IN DEVICE LABELING

LOT	Batch Code		Do Not Re-sterilize
REF	Catalog Number		Do Not Reuse
STERILE EO	Sterilized Using Ethylene Oxide		Attention, See Instructions for Use
	Use By		Consult Instructions for Use
	Date of Manufacture		Do Not Use if Package Is Damaged or Opened
	Keep Dry	MR	MR Conditional

Emphasys Medical, Inc.
700 Chesapeake Drive
Redwood City, California, USA 94063
650.364.0400