

A MULTICENTER RANDOMIZED CONTROLLED TRIAL OF ZEPHYR **ENDOBRONCHIAL VALVE** TREATMENT IN HETEROGENEOUS EMPHYSEMA (LIBERATE)

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Are Zephyr valves effective and safe at 12 months

THE CLINICAL QUESTION

follow-up when used for endobronchial lung volume reduction in patients with heterogeneous emphysema with little to no collateral ventilation in the treated lobes?

lung function, exercise capacity, dyspnea and quality of life in patients with emphysema and

TAKE HOME MESSAGE

negative collateral ventilation who underwent EBV placement at 12 months follow-up. The improvements are of the same magnitude as those seen after LVRS but with less mortality and morbidity. Further long-term validation of these benefits is still pending. The rate of pneumothorax was considerable and associated with 4 deaths. A thoughtful

This is the first trial to demonstrate improvement in



multidisciplinary approach to patient selection, determination of target lobe, and management of potential life-threatening pneumothoraces are key for good outcomes. BACKGROUND

COPD is the 3rd leading cause of mortality in the U.S. Hyperinflation

as a result of emphysema leads to dyspnea and predisposes patients

improves lung function, dyspnea, exercise tolerance, and long-term

to exacerbations.

survival in very highly selected patients (upper lobe predominant emphysema and low exercise performance on CPET). LVRS is underused due to its invasiveness, increased perioperative morbidity and mortality, and narrow patient eligibility criteria.

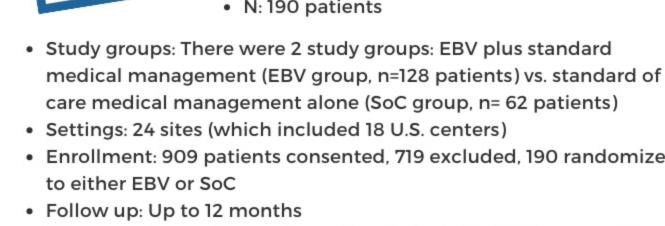
Lung volume reduction surgery (LVRS) reduces hyperinflation and

- Lobar deflation using EBV reduces hyperinflation and mimics the mechanisms of LVRS. Prior studies showed that only patients with complete fissures and complete lobar occlusion had meaningful clinical improvement. This was valid for both heterogeneous and homogenous severe emphysema patients with less morbidity than LVRS. All these studies included a control arm, and subjects were followed for 3 or 6 months.
- STUDY DESIGN Type of trial: Multicenter, randomized controlled trial Randomization: Patients underwent 2:1

Study groups: There were 2 study groups: EBV plus standard

N: 190 patients

using the Chartis System.



Enrollment: 909 patients consented, 719 excluded, 190 randomized

allocation random assignment after

confirmation of negative collateral ventilation

POPULATION

Primary outcome: Percentage of patients in the EBV group at 1-year

- Inclusion criteria Age 40 to 75 years BMI < 35 kg/m2
 - COPD stable with < 20mg prednisone (or equivalent) daily. Nonsmoking for 4 months prior to screening interview Completed a supervised pulmonary rehabilitation program or is regularly performing maintenance respiratory rehabilitation if initial

Post-rehabilitation 6MWD between 100 and 500 meters at baseline

Little or no collateral ventilation (CV-) as determined using the Chartis System during bronchoscopy

Exclusion criteria

exam

Uncontrolled COPD/bronchitis Clinically significant (> 4 tablespoons/day) sputum production or

Unplanned weight loss >10%

echocardiogram (3 months prior)

 Pulmonary nodule requiring surgery as noted by chest X-ray or CT scan. Cardiac/vascular conditions

MI or CHF within 6 months of screening. LVEF < 45% in recent

 Uncontrolled pulmonary hypertension (PASP >45 mm Hg) or evidence of cor pulmonale in a recent echocardiogram (3 months prior) Unable to safely discontinue anticoagulants or antiplatelets for 7

Also includes dysrhythmia that might pose a risk during exercise or

 Emphysema heterogeneity score <15% Large bullae encompassing >30% of either lung PFT outside severity range of obstruction or diffusion capacity, or

Pulmonary conditions that required or might require surgery

carboxyhemoglobin >2.5% if using nicotine products) at screening Baseline Characteristics (No significant differences in all variables, except in GOLD stage, which was higher in the SoC group) EBV group: Age 64 +/-6.8, on continuous oxygen 35.9%. GOLD stage III and IV in EBV group was 42% and 57% respectively, compared to 25% and 74% in the SoC group

 EBV group: Emphysema score at target lobe 70.0±8.5. Post FEV1 (L) 0.76±0.25, TLC (%) 133.5±21, RV (%) 224.5±42, DLCO (%) 34.6±11, and

Primary outcomes: There was a ≥15% increase in post-bronchodilator FEV1 at 12 months post-procedure favoring the EBV group (47.7% vs 16.8% in the SoC group), with a between group absolute difference of 31.0% (95%)

Secondary outcomes:

0.003±0.1)

(-26.3±81)

(- 0.50±15)

Adverse events (AE):

- post-procedure who had an improvement in post-bronchodilator FEV1 of ≥15% compared with that in the SoC group.
- supervised therapy occurred more than 6 months prior FEV1 between 15% and 45% of predicted value at baseline exam

Current Pneumococcus and Influenza vaccination

- clinically significant bronchiectasis ≥2 COPD exacerbations requiring hospitalization or ≥2 pneumonia episodes in the last year at screening Concern of malignancy
- days Arrythmias including resting bradycardia (<50 beats/min), frequent multifocal PVCs, complex ventricular arrhythmia, sustained SVT.

training

 Prior lung transplant, LVRS, bullectomy or lobectomy HRCT within 3-months of screening date with the following: Parenchymal destruction score > 75% in all three right lobes or

both left lobes

RV <175% predicted

Other lab tests

DLCO <20% predicted

6MWD test (m) 311±81

6MWD < 100 meters or > 450 meters

- PaCO2 < 45 mm Hg or > 50mm Hg on room air Presence of alpha-1 anti-trypsin deficiency Plasma cotinine level greater than 13.7 ng/ml (or arterial
- **OUTCOMES**

(n=34, 26.6%), COPD exacerbation (n=10, 7.8%), death (n=4, 3.1%), respiratory failure (n=2, 1.6%)The SoC group had a higher incidence of

- longer-term AEs, except for pneumothorax (EBV group n=8, 6.6% vs 0 in the SoC group) Control group, longer term AEs (45 days to 12) months): The most common was COPD exacerbation (n=19, 30.6% vs n=28, 23% in the EBV group) In the both EBV and SoC groups, the rate of 5.7% and n=5, 8.1% respectively)

Randomized Controlled Trial of Zephyr Endobronchial Valve Treatment in Heterogeneous Emphysema (TRANSFORM). Am J Respir Crit Care

Med. 2017 Dec 15;196(12):1535-1543

The study was funded by PulmonX, the

manufacturer of the valve used in this study.

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NationalEmphysema Treatment Trial (NETT) Part II: lessons learned

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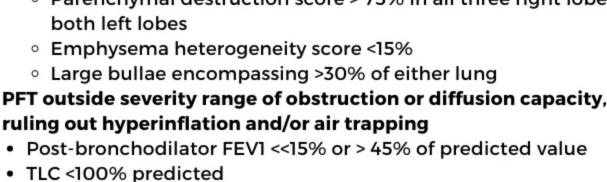
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FUNDING

Zephyr Endobronchial Valve Treatment in

Heterogeneous Emphysema (LIBERATE). Am J

Respir Crit Care Med. 2018 Nov 1;198(9):1151-1164



The secondary outcomes included differences between EBV and SoC groups in the absolute change at 12 months in FEV1, SGRQ, and 6MWD. All these outcomes improved in favor of the EBV group and were statistically significant. They were observed as early as 45 days and persisted to at least 12 months.

Increase of FEV1 (L): EBV (0.104±0.2) vs SoC (-

Increase of 6MWD (m): EBV (12.98±81) vs SoC

Decrease of SGRQ (points): EBV (-7.55±15) vs SoC

The EBV group had a significant number of earlier

pneumothorax that was associated with death in 4

pneumothorax-related deaths occurred in patients

EBV group, early AEs (<45 days): Pneumothorax

AEs. The most concerning was the rate of

cases (3 definitely, 1 probably related). All the

CI, 18.0-43.9%; P=0.001; intention-to-treat).

- pneumonia increased as a longer-term AE (n=7, COMMENTARY
- Research question: Do the initial benefits observed at 12 months for patients who underwent bronchoscopic LVR with the Zephyr EBV persist at years 3 and 5?

(MCID) cut off when compared to prior EBV studies.

This is a multicenter randomized controlled trial (2:1 allocation),

homogeneously well-matched groups that adhered to a very strict

undergoing EBV for BLVR. The primary end-point (≥15% increase in FEV1) represented a higher minimal clinically important difference

protocol and had the longest follow-up to date (12 months) in patients

Study Limitations and Potential for Bias: The very strict study protocol did not allow expansion to patients with homogeneous disease, led to

a high rate of screening, and prevented bronchoscopy for valve

revision in those patients who might have benefited from it.

- SUGGESTED READING 1. Kemp SV, Slebos DJ, Kirk A, Kornaszewska M, et al. A Multicenter
 - ARTICLE CITATION Criner GJ, Sue R, Wright S, Dransfield M, et al. A Multicenter Randomized Controlled Trial of

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