ORIGINAL ARTICLE

A Multicenter Randomized Controlled Trial of Zephyr Endobronchial Valve Treatment in Heterogeneous Emphysema (LIBERATE)

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Abstract

Rationale: This is the first multicenter randomized controlled trial to evaluate the effectiveness and safety of Zephyr Endobronchial Valve (EBV) in patients with little to no collateral ventilation out to 12 months.

Objectives: To evaluate the effectiveness and safety of Zephyr EBV in heterogeneous emphysema with little to no collateral ventilation in the treated lobe.

Methods: Subjects were enrolled with a 2:1 randomization (EBV/standard of care [SoC]) at 24 sites. Primary outcome at 12 months was the ΔEBV–SoC of subjects with a post-bronchodilator FEV_1 improvement from baseline of greater than or equal to 15%. Secondary endpoints included absolute changes in post-bronchodilator FEV_1, 6-minute-walk distance, and St. George's Respiratory Questionnaire scores.

Measurements and Main Results: A total of 190 subjects (128 EBV and 62 SoC) were randomized. At 12 months, 47.7% EBV and 16.8% SoC subjects had a ΔFEV_1 greater than or equal to 15% ($P < 0.001$). ΔEBV–SoC at 12 months was statistically and clinically significant: for FEV_1, 0.106 L ($P < 0.001$); 6-minute-walk distance, +39.31 m ($P = 0.002$); and St. George's Respiratory Questionnaire, −7.05 points ($P = 0.004$). Significant ΔEBV–SoC were also observed in hyperinflation (residual volume, −522 ml; $P < 0.001$), modified Medical Research Council Dyspnea Scale (−0.8 points; $P < 0.001$), and the BODE (body mass index, airflow obstruction, dyspnea, and exercise capacity) index (−1.2 points). Pneumothorax was the most common serious adverse event in the treatment period (procedure to 45 d), in 34/128 (26.6%) of EBV subjects. Four deaths occurred in the EBV group during this phase, and one each in the EBV and SoC groups between 46 days and 12 months.

Conclusions: Zephyr EBV provides clinically meaningful benefits in lung function, exercise tolerance, dyspnea, and quality of life out to at least 12 months, with an acceptable safety profile in patients with little or no collateral ventilation in the target lobe.

Clinical trial registered with www.clinicaltrials.gov (NCT 01796392).

Keywords: chronic obstructive pulmonary disease; emphysema; lung reduction

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At a Glance Commentary

Scientific Knowledge on the Subject: Patients with severe heterogeneous or homogeneous emphysema and hyperinflation selected for little to no collateral ventilation between target and ipsilateral lobe benefit from Zephyr Endobronchial Valve treatment with significant clinical improvements over standard of care medical management in lung function, exercise tolerance, dyspnea, and quality of life out to 6 months.

What This Study Adds to the Field: This multicenter, prospective, randomized controlled clinical trial of the Zephyr Endobronchial Valve treatment in patients with heterogeneous emphysema distribution and little to no collateral ventilation demonstrates significant clinically meaningful benefits over current standard of care medical therapy in lung function, dyspnea, exercise capacity, and quality of life out to at least 12 months after the procedure.

Chronic obstructive pulmonary disease (COPD) is the third leading cause of mortality in the United States with 15.4 million physician visits, 1.5 million emergency department visits, and 726,000 hospitalizations each year (1). Patients with advanced emphysema, one of the diseases that comprises COPD, are characterized by hyperinflation that precipitates breathlessness and predisposes individuals to exacerbations and has a greater negative impact on health status than self-reported cardiovascular disease and diabetes (2, 3).

Many surgical procedures have been devised to treat this disease including costochondrectomy, phrenic crush, pneumoperitoneum, pleural abrasion, surgical lung denervation, and thoracoplasty. But apart from lung volume reduction surgery (LVRS), bullectomy, and lung transplantation all others have not proven to be viable (4). LVRS has been extensively studied, and in appropriately selected patients reduces hyperinflation improving lung function, dyspnea, exercise tolerance, and long-term survival (5–7). However, LVRS is underused because of concerns about the invasiveness of the procedure, increased associated perioperative morbidity and mortality, and narrow patient eligibility criteria (8–10). Zephyr Endobronchial Valves (Zephyr EBV, Pulmonx Corporation) are small duckbill valves inserted bronchoscopically into the lung to occlude an emphysematous lobe. Lobar deflation from the EBV leads to partial or full lobar atelectasis, thus reducing hyperinflation and mimicking the mechanisms of LVRS.

In the first randomized controlled trial of Zephyr EBV, VENT (Endobronchial Valve for Emphysema Palliation Trial), the coprimary endpoints of FEV_1 and 6-minute-walk distance (6MWD) achieved statistical but not clinically meaningful improvements between groups (11). *Post hoc* analysis showed that only patients with complete fissures in the treated lung and in whom lobar occlusion (occlusive positioning of valves in all segmental and subsegmental airways feeding the target lobe) was achieved had clinically meaningful outcomes (12, 13).

After VENT, subsequent short-term studies with Zephyr EBV have shown that by selecting patients with little to no collateral ventilation between target and ipsilateral lobes and performing post-procedure confirmation of lobar occlusion, similar benefits to LVRS can be achieved in patients with heterogeneous or homogeneous emphysema (14–17) but with less morbidity. All these studies included a control arm and followed subjects out to 3 or 6 months.

LIBERATE (Pulmonx Endobronchial Valves Used in Treatment of Emphysema) is the first large randomized controlled multicenter international study conducted in patients with severe heterogeneous emphysema and with little to no collateral ventilation in the target lung to evaluate the effectiveness, safety, and durability of benefit out to 12 months. The study compared Zephyr EBV treatment with standard medical management to standard medical management alone.

Some of the results have been previously reported in the form of an abstract (18).

Methods

This trial (NCT01796392) conducted under a U.S. Food and Drug Administration–approved Investigational Device Exemption for the Zephyr EBV enrolled patients between October 2013 and September 2016 at 24 sites (18 sites in the United States and 6 sites outside the United States). The study was approved by the respective institutional review boards or ethics committees at each site and all participating subjects

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A complete list of members of the LIBERATE Study Group may be found before the beginning of the References.

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Author Contributions: G.J.C. is the Principal Investigator of the study and collaborated on design of the study; advised on medical issues during the conduct of the study; actively recruited and treated patients in the study; and participated in acquisition of data, analysis and interpretation of the data, and development of the manuscript. R.S., S.W., H.R.-P., T.W., M.M.W., H.G.d.O., B.M., P.F.G.C., S. Hays, A.M., N.P., L.K., M.V., P.M.M., M.M., D.W.H., A.S., N.J., M.K., S. Hazelrigg, and G.K. are investigators in the study and actively recruited and treated patients in the study, participated in acquisition of data, and provided revisions to the manuscript. M.D., F.C.S., P.L.S., and D.-J.S. are investigators in the study and actively recruited and treated patients in the study, participated in acquisition of data, helped with the interpretation of the data, and provided revisions to the manuscript. B.A. managed the Study Database, oversaw the Database Snapshot and performed and directed all the statistical analyses per the Statistical Analysis Plan, helped with interpretation of the statistics and their inclusion in the manuscript, and reviewed and approved the final manuscript. N.S.S. oversaw the trial operations and analysis of the data per the prespecified statistical analysis plan, supported additional analyses requested by the authors, and approved of the decision to submit the manuscript for publication.

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provided written informed consent. The consent informed all subjects that their final enrollment in the study would be determined after the bronchoscopy procedure for collateral ventilation assessment with the Chartis Pulmonary Assessment System (510K Cleared K111764; Pulmonx Corporation).

The sample size was estimated using the results from the VENT trial (U.S. and European cohorts) (11, 12). Based on the results of these studies, the responder rate (FEV_1 improvement of $\geq$15%) in the Zephyr EBV treatment group was expected to be approximately 35% at 1 year. The responder rate for the control group was not expected to exceed 10% at 1 year. Assuming a two-sided 0.05 α level, study power of 90%, and 2:1 allocation random assignment, a sample size of 147 was expected to be adequate to test for superiority. The study sample size was increased to 183 to allow for 20% lost to follow-up and incomplete data. Each study site was allowed to enroll a maximum of 25 study participants.

Eligible emphysema patients were ex-smokers between 40 and 75 years of age, with post-bronchodilator (BD) FEV_1 between 15% and 45% predicted, TLC greater than 100% predicted, residual volume (RV) greater than or equal to 175% predicted, D_{LCO} greater than or equal to 20% predicted, and a 6MWD between 100 and 500 m after a supervised pulmonary rehabilitation program (complete inclusion and exclusion criteria provided in Section E1 in the online supplement). Target lobe selection was based on a greater than 50% destruction score (percentage of voxels less than −910 Hounsfield units on computed tomography [CT]) and heterogeneous emphysema defined as absolute difference of 15 or greater in destruction scores between the targeted and ipsilateral lobes determined by investigational sites using Myrian quantitative software (Intrasense; *see* Figure E1).

Eligible patients were assessed with the Chartis to determine collateral ventilation status between targeted and adjacent lobes before randomization (19) (additional details provided in Section E2). Figure E2 shows examples of "collateral ventilation negative" and "collateral ventilation positive" assessments on Chartis. Subjects deemed to have a "collateral ventilation negative" target lobe by Chartis were randomized in a 2:1 fashion (blocked design) immediately after the Chartis assessment to either the EBV or standard-of-care (SoC) groups (*see* Section E3). The bronchoscopy procedure for subjects randomized to SoC was terminated after the Chartis assessment and subjects recovered per institutional clinical practice. Subjects randomized to EBV underwent placement of Zephyr EBV valves during the same session with the intent to achieve complete lobar occlusion (20). Subjects assessed as "collateral ventilation positive" were exited from the study (*see* Section E2 for complete details).

Subjects randomized to SoC were discharged after post-bronchoscopy recovery. Subjects randomized to EBV were hospitalized for 5 nights regardless of clinical status and underwent daily chest radiographs (with the first taken within an hour of the bronchoscopy procedure) until discharge (*see* Figure E3 for postrandomization follow-up of study subjects). Frequency of chest radiographs for any hospitalization for an adverse event was at the discretion of the physician, but a chest radiograph was required on the day of discharge. Clinical staff was trained regarding the risk of a pneumothorax; equipment needed to treat a pneumothorax was kept bedside. At discharge, subjects were provided a wrist-band denoting "patient at risk of pneumothorax" and were instructed to seek immediate medical attention in the event of symptoms of a potential pneumothorax.

EBV subjects were contacted daily by telephone for 10 days after discharge; and evaluated during site visits at Day 7, Day 30, and Day 45 after discharge. At 45 days, a high-resolution CT scan was performed and assessed by an Independent Core Lab (MedQIA) to determine target lobe volume reduction (TLVR), and to verify whether complete lobar occlusion had been achieved. If necessary (TLVR <50%, and incomplete lobar occlusion), a repeat bronchoscopy and valve revision/replacement was recommended. All subjects had clinical visits at 45 days and 3, 6 , 9, and 12 months after bronchoscopy. To reduce variability in the collection of the spirometry data, all study sites used the ERT MasterScope (eResearch Technology), a central diagnostic station attached to a spirometer to capture the FEV_1 and FVC measurements (*see* Section E4). EBV-treated subjects are planned for annual follow-up for an additional 4 years. After the 12-month evaluation, if eligible, SoC group subjects were given the option to crossover to EBV treatment with planned follow-up for an additional 5 years.

Primary Outcome

The primary endpoint was the percentage of subjects in the EBV group at 1 year after the procedure who had an improvement in the post-BD FEV_1 of greater than or equal to 15% compared with the percentage of subjects achieving this improvement in the SoC group.

Secondary Outcomes

The secondary outcomes included difference between EBV and SoC groups in the absolute change at 1 year in FEV_1, St. George's Respiratory Questionnaire (SGRQ), and 6MWD. Additional effectiveness measures included TLVR at 45 days and 1 year after the procedure, RV, inspiratory capacity, TLC, FRC, D_{LCO}, modified Medical Research Council Dyspnea Scale (mMRC), BODE (body mass index, airflow obstruction, dyspnea, and exercise capacity) index, and for the EBV group only, the absolute and percent change in and the percentage of subjects achieving a TLVR minimal clinically important difference (MCID) of greater than or equal to 350 ml (19) relative to baseline.

Safety was assessed in the treatment period (procedure through 45 d) and longer-term period (46 d through 1 yr) through review of all adverse events solicited at all scheduled or unscheduled visits. An independent Clinical Events Committee (CEC) adjudicated serious adverse events (SAEs), device-related events, and select respiratory adverse events. A Data and Safety Monitoring Board provided study oversight to ensure patient rights and safety were respected and maintained.

Statistical Analyses

All statistical analyses were performed using SAS versions 9.3 (SAS Institute). The rationale for the sample size is provided in Section E5. Descriptive statistics included means, SD, and 95% confidence intervals. Continuous variables were compared with an analysis of covariance with the respective baseline value as the covariate, and categorical variables were compared with the Fisher exact test, a chi-square test, or a Cochran-Mantel-Haenszel test. Adverse event rates were compared using Poisson

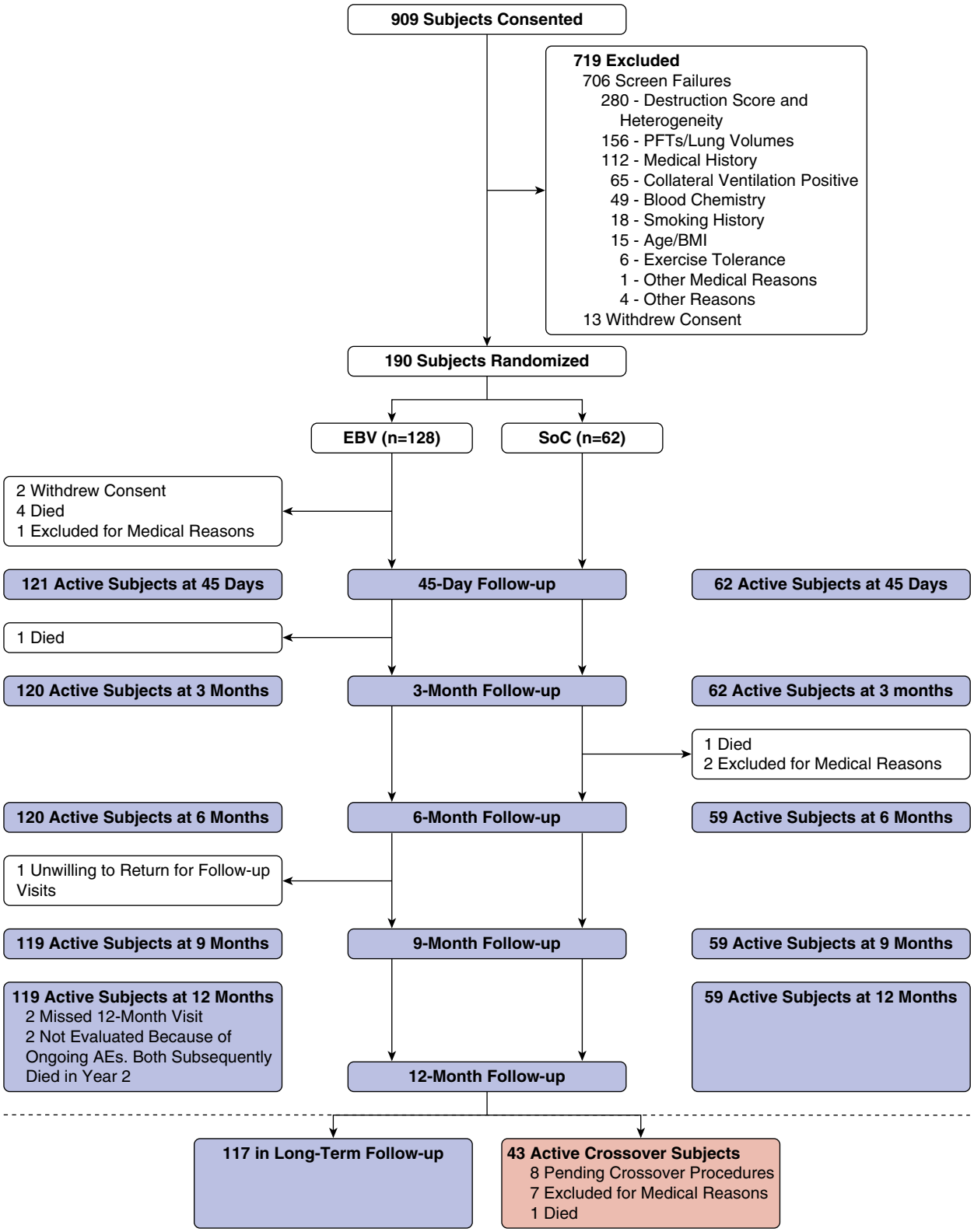

Figure 1. Consolidated Standards of Reporting Trials flow chart. AE = adverse event; BMI = body mass index; EBV = endobronchial valve; PFT = pulmonary function test; SoC = standard of care.

regression. An interim analysis was performed when 74 subjects had completed 12-month follow-up. To account for the interim analysis, the threshold for significance for the *Z*-statistic at 12 months was *Z* greater than or equal to 2.004. The Hochberg step-up procedure was used to control for multiple secondary endpoint analyses (21). Additional details are provided in Section E6.

Results

Demographics

A total of 190 subjects who met the inclusion/exclusion criteria and were

Table 1. Baseline Demographics and Clinical Characteristics

Variable	EBV (*n* = 128)	SoC (*n* = 62)	*t* Test *P* Value
Sex, *n* (%)			NS
Male	56 (43.8)	33 (53.2)	
Female	72 (56.3)	29 (46.8)	
Age, yr	64.0 ± 6.85	62.5 ± 7.12	NS
BMI, kg/m^2	24.67 ± 3.90	24.32 ± 4.38	NS
Smoking history, pack-years	50.78 ± 26.88	48.59 ± 28.48	NS
Race, *n* (%)			
White	117 (91.4)	57 (91.9)	
Black/African American	8 (6.3)	3 (4.8)	
Other	3 (2.3)	2 (3.2)	
Clinical characteristics			
GOLD stage, *n* (%)			0.037
Stage III	54 (42.2)	16 (25.8)	
Stage IV	74 (57.8)	46 (74.2)	
Emphysema score of the target lobe at −910 HU*	70.9 ± 8.52	70.9 ± 8.77	NS
Heterogeneity index between target and ipsilateral lobes†	25.5 ± 9.85	26.1 ± 9.81	NS
Post-BD FEV_1, L	0.76 ± 0.25	0.75 ± 0.22	NS
Post-BD FEV_1, % predicted	28.0 ± 7.45	26.2 ± 6.28	NS
Post-BD FVC, L	2.60 ± 0.86	2.63 ± 0.79	NS
Post-BD FVC, % predicted	71.2 ± 15.99	68.5 ± 13.59	NS
Post-BD FEV_1/FVC ratio	0.30 ± 0.06	0.29 ± 0.06	NS
$D_{L_{CO}}$, ml CO/min/mm Hg	8.53 ± 3.48	8.34 ± 2.70	NS
$D_{L_{CO}}$, % predicted	34.6 ± 11.34	33.1 ± 9.84	NS
RV, L	4.71 ± 1.05	4.76 ± 0.90	NS
RV, % predicted	224.5 ± 42.45	224.6 ± 38.86	NS
TLC, L	7.54 ± 1.59	7.63 ± 1.37	NS
TLC, % predicted	133.5 ± 21.17	130.2 ± 12.44	NS
RV/TLC ratio	0.63 ± 0.09	0.63 ± 0.07	NS
IC, L	1.81 ± 0.70	1.78 ± 0.70	NS
IC/TLC ratio	0.24 ± 0.07	0.23 ± 0.07	NS
Vital capacity, L	2.74 ± 0.9	2.88 ± 0.9	NS
Pa_{O_2}, mm Hg	68.7 ± 11.62	67.8 ± 11.72	NS
Pa_{CO_2}, mm Hg	40.1 ± 4.91	41.3 ± 5.33	NS
6-min-walk distance, m	311 ± 81	302 ± 79	NS
SGRQ total score‡	55.15 ± 14.08	53.10 ± 14.14	NS
mMRC score§	2.4 ± 0.97	2.2 ± 0.83	NS
BODE index‖	5.34 ± 1.52	5.32 ± 1.56	NS¶
COPD Assessment Test	19.2 ± 6.32	19.3 ± 6.35	NS
Patients on continuous oxygen usage, *n* (%)	46 (35.9)	17 (27.4)	NS
Hospital admissions in the last year before screening			
For respiratory failure	0.4 ± 0.65	0.3 ± 0.52	
For pneumonia	0.2 ± 0.38	0.2 ± 0.39	
For COPD exacerbation	0.4 ± 0.48	0.3 ± 0.44	

Definition of abbreviations: BMI = body mass index; BODE = BMI, airflow obstruction, dyspnea, and exercise capacity; COPD = chronic obstructive pulmonary disease; EBV = Zephyr Endobronchial Valve; GOLD = Global Initiative for Chronic Obstructive Lung Disease; HU = Hounsfield units; IC = inspiratory capacity; mMRC = modified Medical Research Council Dyspnea Scale; NS = not significant; post-BD = post-bronchodilator; RV = residual volume; SGRQ = St. George's Respiratory Questionnaire; SoC = standard-of-care.

Values are means ± SD.

*Emphysema destruction score was assessed as the percentage of voxels of less than −910 HU on computed tomography.

†Heterogeneity index was assessed as the difference in the emphysema score between the target and the ipsilateral lobe.

‡SGRQ scores range from 0 to 100, with higher scores indicating worse quality of life.

§mMRC Dyspnea Scale ranges from 0 to 4, with higher scores indicating more severe dyspnea.

‖BODE index score ranges from 0 to 10 based on a multidimensional scoring system to include FEV_1, BMI, 6-minute-walk distance, and the mMRC dyspnea score. Higher scores denote a greater risk of mortality.

¶Wilcoxon signed rank test.

"collateral ventilation negative" for the target lobe according to Chartis assessment were randomized; 128 subjects (56 male/72 female) to EBV, and 62 subjects (33 male/29 female) to SoC (*see* Consolidated Standards of Reporting Trials diagram, Figure 1). Both groups were well matched for all baseline demographics and clinical characteristics, except for the Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage classification, with more GOLD stage IV subjects in the SoC group ($P = 0.037$) (Table 1; *see* Tables E1–E5).

Procedural Details

A median of four valves (range, 2–8) per subject were implanted in the 128 EBV subjects either under general anesthesia (64.8%) or conscious sedation (35.2%). Distribution of treated lobes was 66.4% left upper lobe, 11.7% left lower lobe, 10.9% right upper lobe, 6.3% right upper and right middle lobe combined, and 4.7% right lower lobe (*see* Table E6 for procedural details). Sixteen subjects (12.5%) with incomplete lobar occlusion and TLVR less than 50% verified through the high-resolution CT assessment at 45 days were eligible for valve adjustment; an additional two subjects were considered for valve adjustment by the investigator. Of these, 11 subjects underwent valve-adjustment procedures (*see* Table E7). A total of 35 subjects underwent 54 secondary procedures of which 11 procedures were for the protocol-allowed adjustment after verification of lobar occlusion, 28 procedures were for valve removals and/or subsequent valve replacement after an adverse event (adverse events requiring valve removal included 12 pneumothorax, two increased dyspnea, one respiratory failure, one hypoxemia, one subcutaneous emphysema, and one valve migration), 12 procedures were for clinical investigation (five for inspection of valves because of loss of atelectasis, three for lavage to clear mucus, four to investigate blood in sputum), and the remaining three procedures were for patient-requested valve removals for perceived lack of benefit. Eight subjects had all valves removed before to the 12-month evaluation.

Outcomes

Primary outcome. At 12 months after the procedure, 47.7% of the EBV subjects compared with 16.8% SoC subjects had a greater than or equal to 15% increase over baseline in post-BD FEV_1, with a between-group absolute difference of 31.0 (95% confidence interval, 18.0–43.9%; $P < 0.001$; intention-to-treat). The results of the primary effectiveness endpoint are shown graphically in Figure 2.

Secondary outcomes. All three secondary endpoints improved in favor of EBV and met statistical significance (Table 2 and Figure 3); the difference of means between EBV and SoC groups from baseline to 12 months for the absolute change in FEV_1 was 0.106 L (17.96% for percent change in FEV_1; $P < 0.001$) (Figure 3A), 6MWD was 39.3 m ($P = 0.002$) (Figure 3B), and SGRQ was −7.05 points ($P = 0.004$) (Figure 3C). Improvements in FEV_1, 6MWD, and SGRQ score after EBV treatment were evident as early as 45 days after the procedure and persisted out to at least 12 months (Figure 4).

There were two measures at baseline that were imbalanced between the EBV and SoC groups at a two-sided 0.10 level, mMRC ($P = 0.091$) and GOLD stage classification based on the percent predicted FEV_1 ($P = 0.037$); however, there was no imbalance between groups based on FEV_1. The interaction terms from logistic regression or from analysis of covariance with factors of treatment group and baseline value for mMRC or GOLD stage classification as covariate were not significant for the primary endpoint ($P = 0.799$ and $P = 0.906$ for mMRC and GOLD, respectively), or any of the secondary endpoints. Thus, neither of these variables had an impact on the primary or secondary effectiveness endpoints. The *P* value for the logistic regression with factors of treatment group, investigational site, and treatment group by investigational site interaction did not show any investigational site effect ($P = 0.785$).

A significantly greater percentage of subjects in the EBV group than in the SoC group met or exceeded the MCID for FEV_1 (change of ⩾15% and ⩾12%), SGRQ (change of ⩽−4 points), and 6MWD (change of ⩾25 m), indicating meaningful clinical benefit was achieved (Figure 5; 6-mo responder data in Figure E4). Correspondingly, a higher percentage of subjects in the SoC group consistently either declined or had no change compared with the EBV group across these endpoints (Figure 6). Individual subject responses to each of these measures are presented graphically in Figure E5.

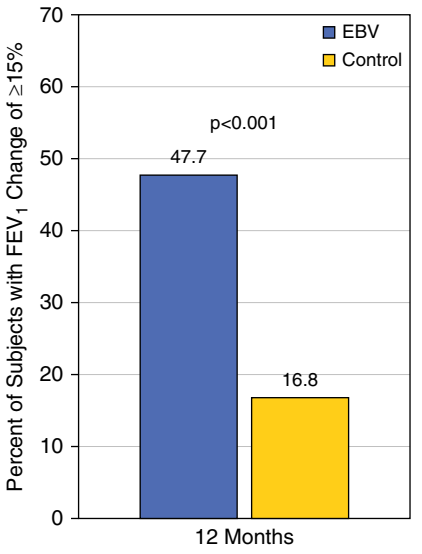

Figure 2. Percent of subjects with FEV_1 change from baseline to 12 months of ⩾15%. Bars represent the percent of subjects with an FEV_1 (L) improvement of ⩾15% from baseline to 12 months. Blue bar = endobronchial valve group; yellow bar = standard-of-care group. *P* value for chi-square test. EBV = Zephyr Endobronchial Valve.

At 45 days after the procedure, 79.1% of subjects achieved a TLVR of greater than or equal to 350 ml, with a mean reduction of 1.03 ± 0.68 L ($P < 0.001$) and at 12 months, 84.2% of subjects achieved a TLVR of greater than or equal to 350 ml, with a mean reduction of 1.14 ± 0.70 L ($P < 0.001$) (Figure 5).

Consistent with a durable TLVR at 12 months in the EBV group, there was a significant reduction in hyperinflation as measured by RV (decrease of 522 ml; $P < 0.001$; EBV – SoC) and RV/TLC ratio (decrease of 0.05; $P < 0.001$; EBV – SoC) (Table 2). At 12 months, RV decrease of 310 ml or more was achieved by 61.6% EBV subjects compared with 22.4% subjects in the SoC group (Figure 5). There was a significant improvement in gas exchange in the EBV compared with SoC groups (increase in D_{LCO} of 0.870 ml CO/min/mm Hg; $P = 0.013$; EBV – SoC). The mMRC dyspnea score improved in favor of EBV with a between-group change of −0.8 points ($P < 0.001$) with a greater number of subjects in the EBV group (47.8%) than in the SOC group (18.6%) meeting or exceeding the MCID of −1 point change; $P < 0.001$).

Subjects in the EBV group had a greater reduction from baseline in the

multicomponent composite BODE index than those in the SoC group, with a mean difference between groups of −1.2 points ($P < 0.001$) at 12 months. More subjects in the EBV than in the SoC group were responders achieving a MCID change of −1 point or less (58.0% vs. 24.1%, respectively; $P < 0.001$) (Figure 6). Supplemental oxygen usage at 12 months in the EBV and SoC group subjects was evaluated to compare change in oxygen usage from baseline. A larger proportion of EBV subjects than SoC subjects (15.7% vs. 6.9%, respectively) used less oxygen, whereas a larger proportion of SoC subjects than EBV subjects (22.4% vs. 11.3%, respectively) used more oxygen, at 12 months than their baseline usage; the distribution of oxygen change categories was statistically significant ($P = 0.019$) when comparing EBV with SoC (*see* Table E8).

Subgroup Analyses

Subjects with no valves at 12-month evaluation. Eight subjects who had all valves removed before their 12-month evaluation (five for a pneumothorax, two for increased dyspnea, and one for pneumonia) did not achieve any benefit when compared with EBV subjects with valves (*see* Table E9). Outcomes for subjects with no valves at 12 months were not dissimilar from the SoC group (Table 2).

Type of anesthesia used. The percent of subjects achieving an FEV_1 improvement of greater than or equal to 15% based on the type of anesthesia used for the EBV procedure were similar with 49.2% in the conscious sedation group and 46.9% in the general anesthesia group. Adverse events occurring at a frequency of 3% or greater for the subgroups of anesthesia type are provided in Table E10.

Table 2. Effectiveness Endpoints for the Intention-to-Treat* Population

Outcome	EBV (*n* = 128)	SoC (*n* = 62)	Between-Group Difference EBV − SoC (95% CI)	*P* Value
Primary endpoint†				
Percent of subjects with post-BD FEV_1 (L) improvement of ⩾15%	47.7	16.8	31.0 (18.0 to 43.9)	<0.001
Secondary endpoints‡ (change from baseline to 12 mo)				
Post-BD FEV_1‡				
Volume, L	0.104 ± 0.200	−0.003 ± 0.194	0.106 (0.047 to 0.165)	<0.001
Percent change, %	17.16 ± 27.93	−0.80 ± 26.94	17.96 (9.84 to 26.09)	<0.001
6MWD, m	12.98 ± 81.54	−26.33 ± 81.50	39.31 (14.64 to 63.98)	0.002‡
SGRQ score, points	−7.55 ± 15.71	−0.50 ± 15.50	−7.05 (−11.84 to −2.27)	0.004‡
TLVR				
Volume, L	−1.142 ± 0.702	NA		
Percent change, %	63.8 ± 36.16	NA		
Additional endpoints (change from baseline to 12 mo)§				
FEV_1, % predicted‖	4.0 ± 7.84 (128)	−0.3 ± 4.41 (62)	4.2 (2.1 to 6.4)	<0.001
RV, L	−0.49 ± 0.83 (112)	0.03 ± 0.66 (58)	−0.522 (−0.77 to −0.27)	<0.001
FRC, L	−0.412 ± 0.768 (112)	0.014 ± 0.509 (58)	−0.425 (−0.65 to −0.20)	<0.001
TLC, L	−0.319 ± 0.621 (112)	−0.031 ± 0.467 (58)	−0.288 (−0.47 to −0.11)	0.002
RV/TLC	−0.045 ± 0.079 (112)	0.005 ± 0.059 (58)	−0.050 (−0.07 to −0.03)	<0.001
IC/TLC	0.03 ± 0.07 (112)	−0.004 ± 0.04 (58)	0.03 (0.02 to 0.05)	<0.001
D_{LCO}, ml CO/min/mm Hg	0.559 ± 2.410 (112)	−0.310 ± 1.533 (57)	0.870 (0.18 to 1.56)	0.013
D_{LCO}, % predicted	1.80 ± 8.44 (112)	−1.01 ± 6.39 (57)	2.82 (0.31 to 5.33)	0.014
mMRC, points	−0.5 ± 1.17 (113)	0.3 ± 1.03 (59)	−0.8 (−1.1 to −0.4)	<0.001
BODE index, points	−0.6 ± 1.76 (112)	0.6 ± 1.51 (58)	−1.2 (−1.8 to −0.7)	<0.001

Definition of abbreviations: 6MWD = 6-minute-walk distance; BODE = body mass index, airflow obstruction, dyspnea, and exercise capacity; CI = confidence interval; EBV = Zephyr Endobronchial Valve; IC = inspiratory capacity; mMRC = modified Medical Research Council Dyspnea Scale; NA = not applicable; post-BD = post-bronchodilator; RV = residual volume; SGRQ = St. George's Respiratory Questionnaire; SoC = standard-of-care; TLVR = target lobe volume reduction.

Values are mean ± SD or mean ± SD (*n*) unless otherwise indicated.

*Intention-to-treat analysis set included all subjects who were randomized. Data for the primary and secondary endpoints were imputed for 13 EBV subjects and three SoC subjects.

†Truncated missing values imputed with multiple imputation (propensity score method). Death before 12-month endpoint imputed as failure. The *P* value is from a chi-square test.

‡Truncated missing values imputed with multiple imputation (propensity score method). Death before 12-month endpoint imputed no change. Values have been adjusted for multiple imputation. *P* values, least squares mean, SD, and confidence intervals are calculated from analysis of covariance with factor of treatment group and the respective baseline value as a covariate (with values adjusted for multiple imputation).

§No imputation of missing values. Observed means, SD, and confidence intervals are presented together with the number of subjects included. *P* values are from analysis of covariance with factor of treatment and the respective baseline value as a covariate.

‖For subjects with missing data at 12 months, FEV_1% predicted values were derived from the volume (L) values that were imputed for the primary endpoint analysis.

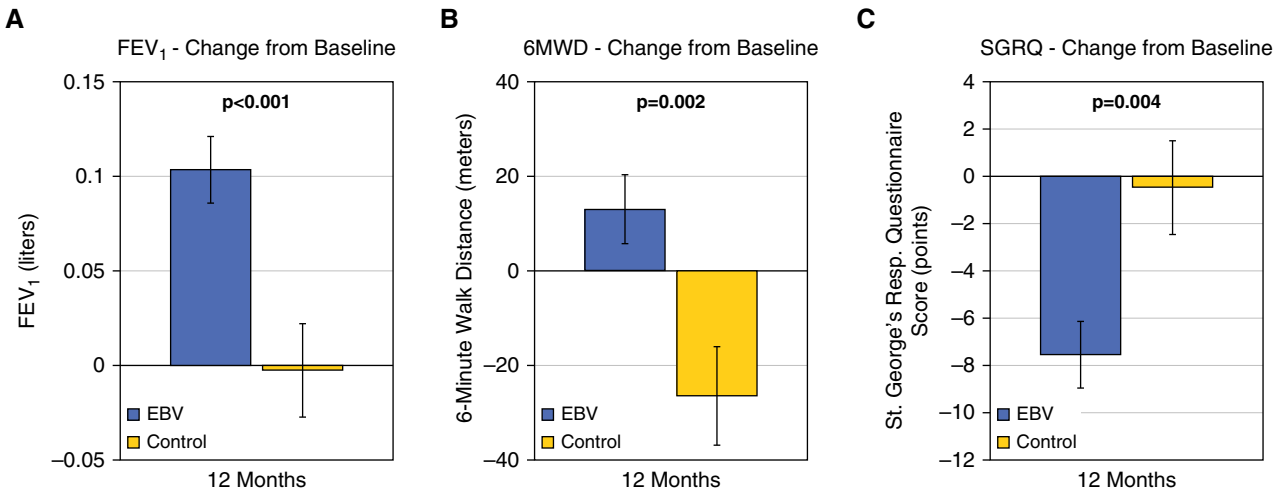

Figure 3. Secondary endpoints. (*A–C*) Changes from baseline to 12 months for FEV_1 (*A*), 6-minute-walk distance (*B*), and St. George's Respiratory Questionnaire (*C*). Values are least squares means ± SEM for $n = 128$ (endobronchial valve) and $n = 62$ (standard of care). *P* values, least squares mean, and SEMs from an analysis of covariance with factor of treatment and the respective baseline value as a covariate. Values have been adjusted for multiple imputation. Truncated missing values imputed with multiple imputation (propensity score method). Missing values imputed as baseline carried forward for subjects that died before completing 12-month visit. To control the familywise type I error rate at 5%, the Hochberg step-up procedure was used. 6MWD = 6-minute-walk distance; EBV = Zephyr Endobronchial Valve; SGRQ = St. George's Respiratory Questionnaire.

Upper versus lower lobe treatments. Similar benefits were seen in the upper lobe and lower lobe subgroups with 45.9% upper lobe treated subjects and 57.1% lower lobe treated subjects with an FEV_1 improvement of greater than or equal to 15%. The secondary endpoint results for these subgroups are provided in Table E11.

Adverse Events

A summary of all adverse events occurring at a frequency of 3% or more is provided in Table E12. Of the 501 EBVs that were implanted, two EBVs (in two subjects) were expectorated and three EBVs (in three subjects) migrated throughout the 12-month follow-up for a 0.4% expectoration rate and 0.6% migration rate. Investigator-reported respiratory SAEs listed in Table 3 show that significantly more subjects in the EBV group (35.2%) than in the SoC group (4.8%) experienced respiratory SAEs in the treatment period (day of procedure/randomization to 45 d) immediately after the bronchoscopy procedure ($P < 0.001$). This difference was primarily caused by a higher frequency of pneumothoraces in the EBV group during the treatment period, which were managed according to previously published and protocolized pneumothorax management algorithm (22) (*see* Figure E6). Select respiratory SAEs with onset after the most recent bronchoscopy procedure are summarized in Table E13.

However, during the longer-term period (>46 d until 12-mo visit), the frequency of events was comparable between groups with 33.6% of the EBV group subjects and 30.6% of the SoC group subjects experiencing one or more respiratory SAEs. During the longer-term period (Table 3), there was a lower frequency of SAEs (COPD exacerbations, pneumonias, and respiratory failure) in the EBV group than in the SoC group (23.0% vs. 30.6%, 5.7% vs. 8.1%, and 0.8% vs. 3.2%, respectively), although none of these differences reached statistical significance. Over the 12-month follow-up, there were no episodes of hemoptysis (defined as >200 ml blood loss in <24 h).

Table 4 shows the rates of respiratory SAEs (i.e., annualized rates based on the time of occurrence). Investigator-reported event rates are compared with the CEC adjudicated event rates; CEC adjudication removed any investigator bias on nomenclature and attribution of adverse events by using standardized definitions. Based on the CEC adjudication, during the treatment period, only the pneumothorax rate was significantly different between groups with 0.275 events/45 days in the EBV group compared with no events in the SoC group ($P < 0.001$). During the longer-term period, CEC-adjudicated pneumothorax rates continued to be significantly different between groups with 0.074 events/yr compared with no events in the SoC group ($P = 0.013$). However, during the longer-term period, serious COPD exacerbations and respiratory failure events rates trended to be lower in the EBV group than in the SoC group with 0.352 events/yr compared with 0.573 events/yr ($P = 0.053$) and 0.019 events/yr compared with 0.099 events/yr ($P = 0.033$), respectively.

Pneumothorax

The major post-procedural complication was pneumothorax with 46 pneumothorax events occurring in 44 EBV subjects (34.4%) during the 12-month period. Eight of these events did not require any intervention (observation only). A total of 38 of the 46 pneumothoraces (83%) were managed with a placement of a chest tube; 12 of these events also required the removal of at least one valve. None of the pneumothoraces occurring in the longer-term period required the removal of any valves for their management. A total of 43 of the 46 pneumothoraces occurred within 13 days of a recent bronchoscopy procedure, of which 35 (76%) occurred within the first 3 days as shown in Figure 7, for a median event onset time of 1.0 day from a recent bronchoscopy procedure.

Subjects with pneumothorax ($n = 44$) experienced similar benefits at 12 months to subjects without a pneumothorax ($n = 84$);

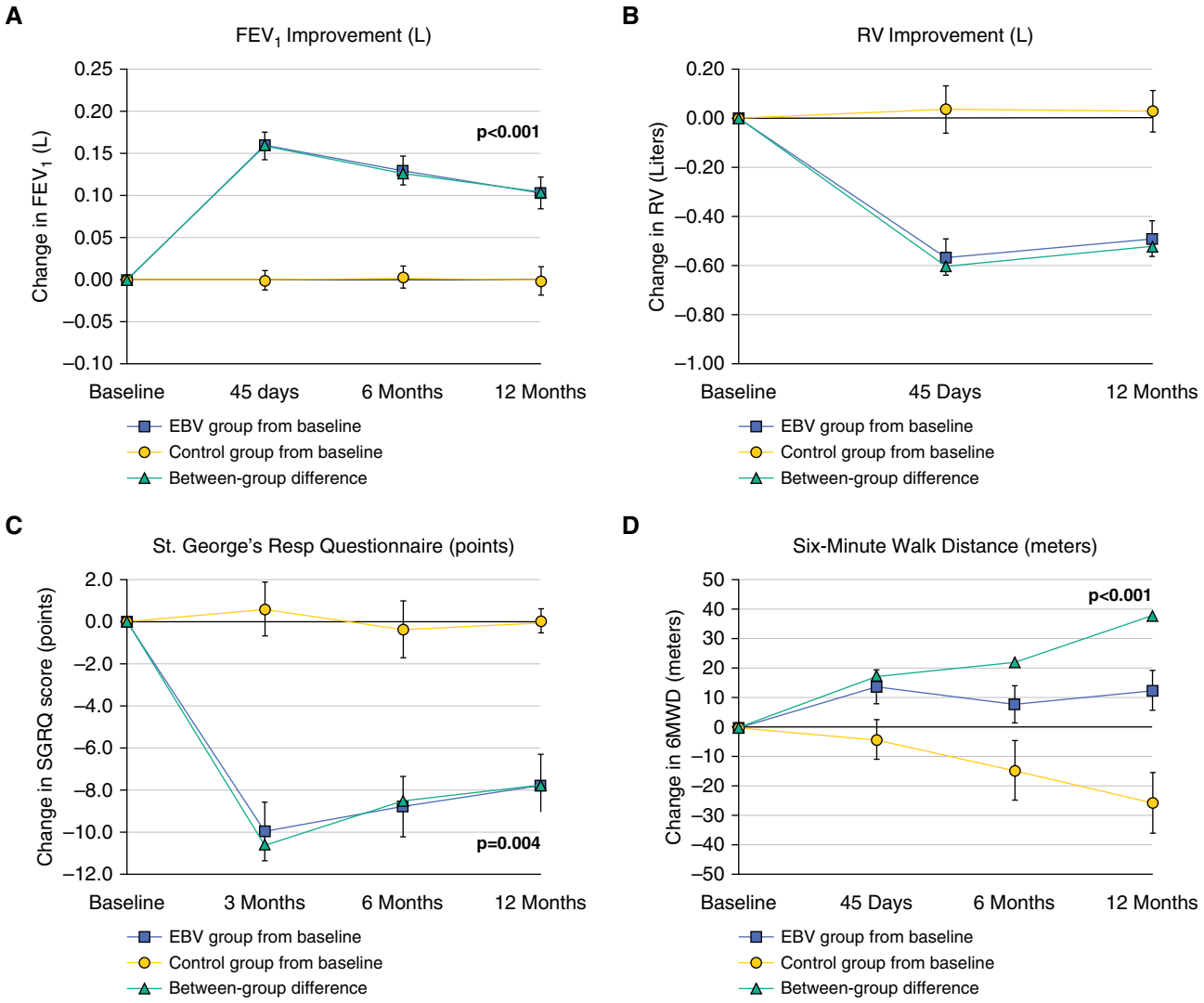

Figure 4. Changes over time from baseline out to 12 months for key outcomes. Data presented are raw means ± SEM for changes from baseline to later time points after the bronchoscopy for EBV (blue square), standard of care (yellow circle), and difference between EBV and standard of care (green triangle). (*A*) FEV_1. (*B*) Residual volume. (*C*) St. George's Respiratory Questionnaire. (*D*) 6-minute-walk distance. 6MWD = 6-minute-walk distance; EBV = Zephyr Endobronchial Valve; RV = residual volume; SGRQ = St. George's Respiratory Questionnaire.

(*see* Table E14). Exploratory analyses of subjects who experienced either a "complex" pneumothorax (defined by either death or removal of all EBVs) or a "simple" pneumothorax (all other pneumothoraces) showed that subjects were at higher risk of a "complex" pneumothorax if the lobe with maximum destruction score is not treated, and the nontreated contralateral lung destruction score is greater than 60%. Qualitative assessment of CTs of the EBV group by an independent thoracic radiologist (Imaging Core Lab) of radiologic features that included presence or absence of pleural adhesions, intraparenchymal scars, blebs, bullae, and paraseptal cysts in target and nontarget lobes did not identify any variable that was statistically significant in predicting the occurrence of a pneumothorax.

Mortality

During the treatment period, there were four deaths in the EBV group (3.1% of subjects; three from a pneumothorax on Day 3, Day 3, and Day 13, and one from respiratory failure on Day 11) compared with none in the SoC group. The three pneumothorax-related deaths occurred in subjects who were not treated in the most diseased lobe. Of the four deaths in the EBV group, three were considered "definitely related" and one "probably related" to the EBV treatment. During the longer-term period, there was one death (0.8%) in the EBV group on Day 147 resulting from a COPD exacerbation that was not related to the device, and one cardiac arrhythmia related in the SoC group (1.6%) on Day 141.

Discussion

Bronchoscopic lung volume reduction (BLVR) with Zephyr EBV is a breakthrough approach for reducing hyperinflation in patients with severe emphysema. This multicenter randomized controlled trial demonstrates that Zephyr EBV treatment in

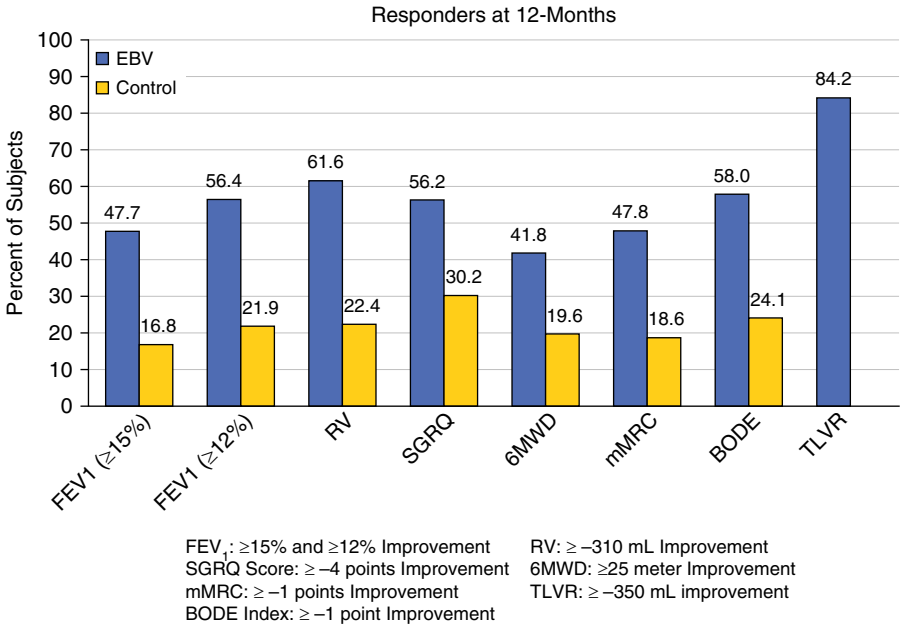

Figure 5. Responders based on minimal clinically important difference for assessed variables. 6MWD = 6-minute-walk distance; BODE = body mass index, airflow obstruction, dyspnea, and exercise capacity; EBV = Zephyr Endobronchial Valve; mMRC = modified Medical Research Council Dyspnea Scale; RV = residual volume; SGRQ = St. George's Respiratory Questionnaire; TLVR = target lobe volume reduction.

patients with severe emphysema selected for little to no collateral ventilation between the treated and the ipsilateral lobe resulted in significant lobar volume reduction, with consequent reduction in hyperinflation, and clinically meaningful improvements in dyspnea, lung function, exercise-capacity, and quality of life. Similar results have been reported previously (14–17).

Except for a higher proportion of categorically defined GOLD stage IV subjects in the SoC group, the EBV and SoC groups were well matched for baseline demographics and clinical characteristics; including mean post-BD FEV_1. However, this difference did not impact either the primary or secondary effectiveness outcomes based on analysis of covariance with baseline GOLD stage as a covariate.

The study met its primary endpoint with 47.7% EBV subjects compared with 16.8% SoC subjects achieving an improvement in FEV_1 of greater than or equal to 15% ($P < 0.001$). Although the MCID cut off for change in FEV_1 is highly variable, ranging from 10% to 15% (23), this threshold of 15% for the responder analysis was based on discussion with the Food and Drug Administration as the *a priori* threshold that they required for the pivotal U.S. trial. The absolute difference in means for FEV_1 of 0.106 L signifies a meaningful important clinical change (24).

Importantly, 79.1% of patients in the EBV group achieved the MCID for TLVR at 45 days; and 84.2% at 12 months confirming proper patient selection with Chartis and successful lobar occlusion. The overall mean change in target lobe volume radiographically determined by high-resolution CT at 12 months was a reduction of 1.14 L, which corresponded to a mean reduction in RV of 0.5 L (or a 10.38% decrease from baseline). TLVR and consequent reduction in RV are consistent with the proposed mechanism of action of EBV and are comparable with changes after LVRS (25).

The major significant side effect associated with the EBV procedure in the short-term treatment period was pneumothorax. Targeted lobar deflation likely causes inflation of the ipsilateral lobe, which can result in a tear of the already compromised parenchymal tissue of the emphysematous ipsilateral lobe, resulting in a pneumothorax. As seen in this study and reported previously (17, 26) subjects experiencing a pneumothorax attained the same level of benefit over the long-term as those without pneumothorax. The three

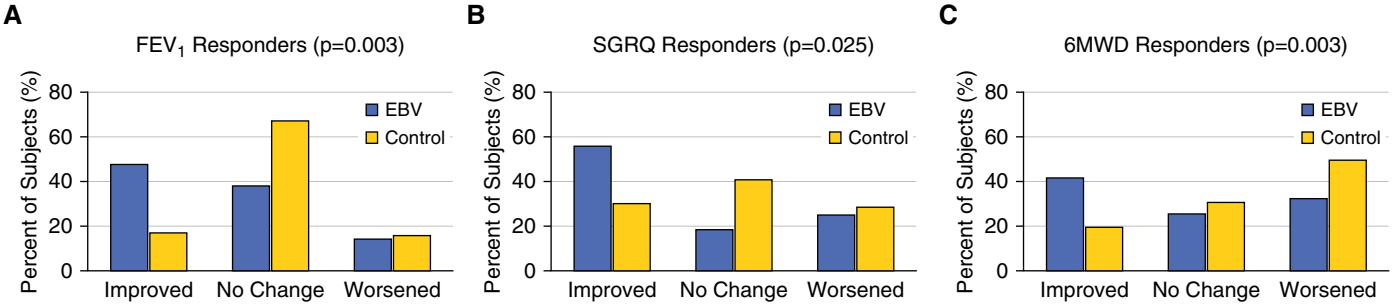

Figure 6. Responders based on minimal clinically important difference for FEV_1, SGRQ, and 6MWD. Percent of subjects categorized as improved, no change, or worsened based on minimal clinically important difference for each measure. (*A*) FEV_1: improved is ⩾15% change; no change is >−15% to <15% change; and worsened is ⩽−15% change. (*B*) SGRQ: improved is ⩽−4 points change; no change is >−4 to <4 points change; and worsened is ⩾4 points change. (*C*) 6MWD: improved is ⩾25 m change; no change is >−25 to <25 m change; and worsened is ⩽−25 m change. Intermittent missing values imputed with linear interpolation. Truncated missing values imputed with multiple imputation (propensity score method). Death before 1-year endpoint was imputed as worsened. *P* value from Cochran-Mantel Haenszel test for row means scores adjusted for multiple imputation using Wilson-Hilferty transformation. 6MWD = 6-minute-walk distance; EBV = Zephyr Endobronchial Valve; SGRQ = St. George's Respiratory Questionnaire.

Table 3. Serious Adverse Events Occurring in at Least 3.0% of Subjects in Either Group

	Treatment Period Day of Procedure/Randomization to 45 Days		Longer-Term Period 46 Days from the Study Procedure/Randomization until 12-Month Visit Date	
	EBV ($n = 128$)	SoC ($n = 62$)	EBV ($n = 122$)	SoC ($n = 62$)
Death	4 (3.1)*	0 (0.0)	1 (0.8)	1 (1.6)
Pneumothorax	34 (26.6)†	0	8 (6.6)	0
COPD exacerbation	10 (7.8)	3 (4.8)	28 (23.0)	19 (30.6)
Pneumonia	1 (0.8)	0	7 (5.7)	5 (8.1)
Respiratory failure	2 (1.6)	0	1 (0.8)	2 (3.2)
Arrhythmia	0	0	1 (0.8)	2 (3.2)
Diverticulitis	0	0	1 (0.8)	2 (3.2)

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; EBV = Zephyr Endobronchial Valve; SoC = standard of care.
Data are shown as *n* (%). Counts reflect number of subjects reporting one or more serious adverse events. Subjects are counted once.
*Two subjects had do-not-resuscitate orders that prevented further intervention.
†$P < 0.05$, Fisher exact test.

pneumothorax-related deaths that occurred in subjects that were not treated in the most diseased lobe because of the heterogeneity requirement (difference in heterogeneity score of 15 between target and ipsilateral lobes) and the absence of collateral ventilation may imply that subjects with reduced capacity in the nontreated contralateral lung experience higher risk from the insult of single-lung ventilation during the pneumothorax event. Physicians performing EBV treatment must be trained on appropriate patient and lobe selection for treatment and anticipate and recognize a pneumothorax, which can be readily managed using standard approaches (22).

The difference between groups for the change from baseline to 12 months of 39 m in the 6MWD is meaningful and demonstrates the persistent benefit EBV treatment provides in improving exercise tolerance in this patient group (27–29). The absolute mean change in 6MWD in the EBV group at 12 months compared with baseline was only 13 m. However, left untreated, the decline in 6MWD in patients with COPD at GOLD stage III/IV would be expected to be significant over time (30). As an example, in the NETT (National Emphysema Treatment Trial) study, untreated control patients in the non–high-risk group showed declines of 40 m in the 6MWD at 1 year (5). In this study, the 6MWD in the SoC group declined by 26.3 m from baseline to 12 months. Although there was a wide range of baseline 6MWD, there was no correlation between baseline 6MWD and key outcomes of FEV_1, 6MWD, or SGRQ in contrast to NETT where substantial benefit was seen only in patients with low exercise tolerance (31). Although not powered to demonstrate this change, there was a reduction in the rate of respiratory failure events ($P = 0.033$) and a trend for a reduction in COPD exacerbations resulting in hospitalizations ($P = 0.053$) and in the longer-term period between EBV and SoC. These

Table 4. Respiratory Serious Adverse Events Rates: Site Reported and CEC Adjudicated Event Rates

Serious Respiratory Adverse Events	Treatment Period Day of Procedure/Randomization to 45 Days: Serious Adverse Event Rates (*Events/45 d*)			Longer-Term Period 46 Days from the Study Procedure/Randomization until 12-Month Visit Date: Serious Adverse Event Rates (*Events/yr*)		
	EBV ($n = 128$)	SoC ($n = 62$)	*P* Value*	EBV ($n = 128$)	SoC ($n = 62$)	*P* Value*
Pneumothorax						
Investigator reported	0.267	0.00	<0.001	0.074	0.00	0.013
CEC adjudicated	0.275	0.00	<0.001	0.074	0.00	0.013
COPD exacerbations						
Investigator reported	0.079	0.047	0.423	0.371	0.573	0.080
CEC adjudicated	0.110	0.047	0.150	0.352	0.573	0.053
Pneumonia						
Investigator reported	0.008	0.00	0.369	0.065	0.118	0.287
CEC adjudicated	0.024	0.00	0.120	0.056	0.118	0.196
Hemoptysis						
Investigator reported	—	—	—	0.019	0.00	0.215
CEC adjudicated	—	—	—	0.028	0.00	0.129
Respiratory failure						
Investigator reported	0.016	0.00	0.204	0.009	0.059	0.078
CEC adjudicated	0.024	0.00	0.120	0.019	0.099	0.033

Definition of abbreviations: CEC = Clinical Events Committee; COPD = chronic obstructive pulmonary disease; EBV = endobronchial valve; SoC = standard of care.
**P* value from Poisson regression adjusted for each subject's length of follow-up.

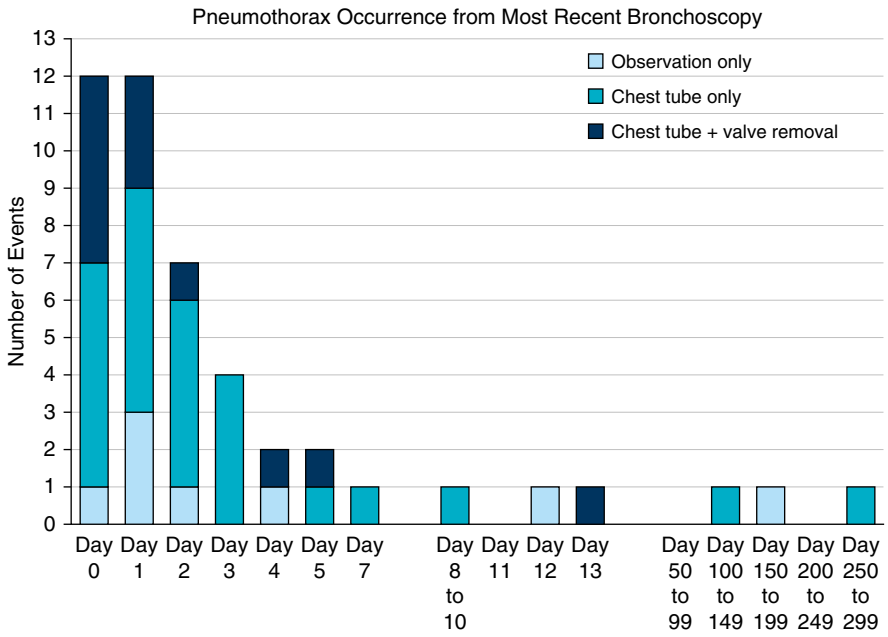

Figure 7. Pneumothorax occurrence from the most recent bronchoscopy. Data represent time of pneumothorax occurrences after the most recent bronchoscopy procedure. Each bar represents the number of events per time period color coded for management of the event: light blue = observation only; turquoise = chest tube only; dark blue = chest tube plus valve removal.

improvements resulting from a reduction in hyperinflation and improved lung function are consistent with similar findings after LVRS and warrant further study (32).

Although prior randomized clinical trials of BLVR with Zephyr EBV treatment demonstrated improvements in lung function, exercise capacity, dyspnea, and quality of life compared with control subjects over a short-term period of 6 months, the LIBERATE study is the first trial to evaluate these outcomes compared with a control group over a longer period of at least 12 months while reinforcing the suitability of Zephyr EBV for both upper and lower lobe disease, and a wider range of baseline lung function (<20% compared with NETT) and baseline exercise tolerance. An additional important outcome in LIBERATE is the strong signal for the potential to reduce respiratory failure and COPD exacerbations requiring hospitalization in the longer term, both being important goals of therapy for these patients. Taken together with the previous demonstration of its effectiveness in patients with both heterogeneous (14, 15, 17) and homogeneous (15, 16) emphysema selected for little to no collateral ventilation, unilateral EBV treatment now provides a viable treatment option for a group of patients with emphysema that is currently lacking. Unlike surgery or other bronchoscopic interventions (33–36) EBVs are readily removable, allowing the procedure to be reversed if a patient does not respond or has complications.

The 27% frequency of pneumothorax SAEs in the treatment period is consistent with previous studies (16, 17) and the occurrence of pneumothorax does not seem to negatively impact clinical outcomes as seen in this study and previously reported by Gompelmann and coworkers (26) and Kemp and coworkers (17). Seventy-six percent of the pneumothoraces occurred within 3 days after the most recent bronchoscopy (index procedure for those who did not have a secondary bronchoscopy), and 85% were within 5 days after the most recent bronchoscopy procedure. These statistics support a minimum 3-day hospital stay after EBV procedure to ensure timely management of a pneumothorax if it occurs. As in previous studies, the specific algorithm for managing pneumothorax after EBV procedures developed by experts (22) was used to manage this consequence of the procedure during the present study and highlights the need for physicians performing this procedure to have expertise in the management of procedural complications. One pneumothorax-related death at 13 days post-EBV procedure underlines the need to provide patients with clear instructions on recognizing symptoms of a pneumothorax and to seek emergent help if experiencing these symptoms.

The study has certain limitations. First, although many subjects did not meet the very strict inclusion/exclusion criteria that included baseline lung function measures, prior medical history, and so forth, 40% (280/706) of the screen failures were related to destruction score and heterogeneity requirements, the thresholds for which were arbitrarily chosen at the time the study was designed. Subsequent experience with homogenous patients in other trials (15, 16) has established the applicability of this therapy to a broader population. Similarly, the inclusion of subjects with little or no collateral ventilation was limited to their assessment with Chartis, which uses physiologic measures of airflow and airway resistance for assessing collateral ventilation status. The more recent evolution of novel quantitative CT (QCT) techniques now enables the noninvasive screening of subjects for collateral ventilation, with immediate exclusion of subjects with less than 80% complete fissure on QCT, Chartis requirement only in subjects with greater than 80% to less than 95% complete fissure on QCT, and treatment with EBV of subjects with greater than 95% complete fissure on QCT without Chartis (37, 38). This approach could have streamlined the screening out of subjects with completely absent fissures and perhaps reduced some screening bronchoscopies in this study.

A second limitation of the study was allowing a repeat bronchoscopy for valve revision/replacement only in subjects with TLVR less than 50%, and incomplete lobar occlusion based on the 45-day CT assessment by the Imaging Core Lab. These dual criteria were too restrictive and prevented many subjects from potentially benefitting from a revision procedure. In clinical practice (20), repeat bronchoscopies for valve revision are performed based on clinical judgment if a patient has a lack of clinical response or experiences a sudden late loss of benefit.

The observed benefit to risk profile of EBV treatment must be assessed considering the limited treatment options for patients

with severe emphysema. LIBERATE shows improvements over nontreated control subjects at the same magnitude as those seen after LVRS (EBV vs. LVRS: FEV_1 [29], 17% vs. 19%; 6MWD [5], 39.3 vs. 44.7 m; SGRQ score [9], −7.05 vs. −13.9 points). However, Zephyr EBV treatment has less morbidity than LVRS: pneumothorax requiring chest tube (EBV vs. LVRS: <30% vs. >90%), respiratory failure (EBV vs. LVRS: <30% vs. >90%), and pneumonia (EBV vs. LVRS: 4% vs. 18%). Specifically, 90-day mortality after EBV is lower than LVRS with a rate of 3.1% compared with 5.0% in the LVRS non-high-risk group (39). Although the risks associated with LVRS are considered acceptable, this approach remains relatively underused (40). The only other remaining alternative of lung transplantation has a limitation of strict patient eligibility superimposed over the limited availability of donor lungs (41).

Conclusions

Zephyr EBV treatment in carefully selected patients with little or no collateral ventilation in the target lobe provides clinically meaningful and statistically significant benefits in lung function, exercise tolerance, dyspnea, and quality of life over current SoC medical therapy out to at least 12 months. The benefits are comparable with those seen with LVRS but with a reduction in post-procedure morbidity. BLVR with the Zephyr EBV provides a viable treatment option for patients with severe emphysema and hyperinflation. ■

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