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

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A Multicenter RCT of Zephyr® Endobronchial Valve Treatment in Heterogeneous Emphysema (TRANSFORM)

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At a Glance Commentary

Scientific knowledge on the subject:

Zephyr Endobronchial Valves properly placed in segmental and sub-segmental airways in patients with severe heterogeneous or homogeneous emphysema with no collateral ventilation between target and ipsilateral lobe have been shown to decrease

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hyperinflation by reducing target lobe volume, thereby providing clinical improvements in lung function, exercise tolerance and quality of life.

What this study adds to the field

This first, multicenter, prospective, randomized controlled clinical trial of the Zephyr Endobronchial valves (EBVs) confirms findings from 2 previous single-center RCTs that in patients with heterogeneous emphysema distribution and absence of collateral ventilation, these one-way valves improve lung function, dyspnea, exercise tolerance, and quality of life over current standard of care medical therapy.

Author Contributions

Samuel Kemp: SK is an Investigator at 2 individual sites over the course of the study, actively recruited and treated patients in the study, participated in acquisition of data, wrote the first draft of the manuscript and edited the manuscript after feedback from co-authors.

Dirk-Jan Slebos: DJS is an investigator in the study and actively recruited and treated patients in the study, participated in acquisition of data, and provided revisions to the manuscript.

Alan Kirk, MD: AK is an investigator in the study and actively recruited and treated patients in the study, participated in acquisition of data, and provided revisions to the manuscript.

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Abstract

Rationale: Single-center RCTs of Zephyr Endobronchial Valve (EBV) treatment have demonstrated benefit in severe heterogeneous emphysema. This is the first multicenter study evaluating this treatment approach.

Objectives: To evaluate the efficacy and safety of Zephyr EBVs in patients with heterogeneous emphysema and absence of collateral ventilation.

Methods: Prospective, multicenter 2:1 RCT of EBVs plus standard of care or standard of care (SoC) alone. Primary outcome at 3 months post-procedure was the percent of subjects with a FEV1 improvement from baseline of ≥12%. Changes in FEV1, RV, 6MWD, SGRQ, and mMRC were assessed at 3 and 6 months, and target lobe volume reduction (TLVR) on chest CT at 3 months.

Results: Ninety seven subjects were randomized to EBV (n=65) or SoC (n=32). At 3 months, 55.4% of EBV and 6.5% of SoC subjects had an FEV1 improvement ≥12% ($p<0.001$). Improvements were maintained at 6 months: EBV 56.3% vs SoC 3.2% ($p<0.001$), with a mean change in FEV1 at 6 months of 20.7±29.6% and -8.6±13.0%, respectively. 89.8% of EBV subjects had TLVR ≥350ml, mean 1.09±0.62L ($p<0.001$). Between group differences for changes at 6 months were statistically and clinically significant: ΔEBV–SoC for RV -700ml; 6MWD +78.7m; SGRQ -6.5 points; mMRC Dyspnea score -0.6 points; BODE Index -1.8 points (all $p<0.05$). Pneumothorax was the commonest adverse event, occurring in 19/65 (29.2%) of EBV subjects.

Conclusions: EBV treatment in hyperinflated patients with heterogeneous emphysema without collateral ventilation resulted in clinically meaningful benefits in lung function, dyspnea, exercise tolerance, and quality of life, with an acceptable safety profile.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive, life-threatening, lung disease characterized by airflow obstruction that results in breathlessness and predisposes afflicted individuals to exacerbations and serious illness (1). Patients with advanced emphysema remain one of the most at-risk sub-populations. It is estimated that over 300 million people globally have COPD, with considerable dyspnea due to lung hyperinflation, poor quality of life, few treatment options, and a reduced life expectancy (2,3,4).

Lung volume reduction surgery (LVRS) results in improvements in lung function, dyspnea, exercise tolerance, and long-term survival in appropriately selected patients with emphysema (5,6,7,8). Whilst LVRS has proven effective in selected populations, the technique is relatively under-utilized owing to concerns about the invasiveness of the procedure, morbidity, and the narrow patient eligibility criteria (9,10). Zephyr® endobronchial valves (EBV®, Pulmonx Corporation, Redwood City, CA) are one-way valves inserted via the bronchoscope into the airways of emphysematous lung, and are designed to cause lung deflation (and hence a reduction in hyperinflation) by allowing air and secretions out but preventing air entry.

Bronchoscopic lung volume reduction with Zephyr EBVs aims to provide the benefits seen with LVRS but with a reduction in morbidity. The VENT study achieved statistical but not clinically meaningful improvements in forced expiratory volume in 1 second (FEV_1) and six-minute walking distance (6MWD) between EBV-treated and control groups (11), with post-hoc analysis showing that improvements in these outcomes were clinically meaningful only in patients with no collateral ventilation (CV) between the

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target and ipsilateral lobes (11,12). Zephyr EBVs have been shown to cause target lobe volume reduction (TLVR) in patients without CV and where lobar occlusion is achieved (13,14). Clinically and statistically meaningful benefits in multiple outcome measures have been demonstrated in patients with heterogeneous (15,16) as well as homogeneous emphysema (16,17). Two single-center randomized controlled trials (15,16) have reported significant benefits of Zephyr EBVs over best medical care, and we now report the first multi-center study in patients with heterogeneous emphysema and without CV. Some of the results of this study have been previously reported in the form of an abstract (18).

Methods

Study Conduct: This randomized, controlled trial (NCT02022683) enrolled patients between June 2014 and June 2016 at 17 sites across Europe. The study was approved by the respective Ethics Committees at each site, and conducted in accordance with the Declaration of Helsinki (19). All participating subjects provided written informed consent.

Study Subjects: Eligible subjects were ex-smokers ≥40 years of age with severe emphysema. Key inclusion criteria were post-bronchodilator FEV_1 of between 15% and 45% predicted despite optimal medical management, total lung capacity (TLC) >100% predicted, residual volume (RV) ≥180% predicted, and a 6MWD of between 150m and 450m (complete criteria provided in online supplement – Section E1). High resolution computed tomography (HRCT) scans were analyzed at an independent imaging core laboratory using quantitative software (VIDA Diagnostics, Coralville, IA, USA) to measure lobar volumes and emphysema destruction by lobe. Heterogeneous

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emphysema was defined as a >10% difference in destruction scores between target and ipsilateral lobes.

Eligible patients underwent Chartis® (Pulmonx Corporation, Redwood City, CA) assessment to determine the presence of CV between target and adjacent lobes before randomization. The Chartis® Pulmonary Assessment System is a validated system designed to assess for the presence of collateral ventilation within isolated lung units. It consists of a Chartis console connected to a balloon catheter with a central channel which is used to occlude the target lobe, and to subsequently measure pressure and flow in order to calculate resistance to airflow in that lobe, and hence to quantify collateral ventilation (13). Figure E1 in the online supplement shows examples of CV negative and CV positive read-outs. Subjects who had a CV negative target were randomized in a 2:1 fashion (blocked design and concealed envelopes) immediately after the Chartis measurement into either the EBV group or the SoC group. The bronchoscopy procedure for subjects randomized to SoC was terminated and subjects recovered appropriately as per institutional standards. Subjects randomized to the EBV group underwent immediate placement of Zephyr EBVs with the intention of complete lobar occlusion (12,20). Subjects assessed to be CV positive were excluded. See online supplement Sections E2 and E3 for complete details.

Where there was more than one potential target lobe, the lobe with the highest destruction score and lowest perfusion as determined by scintigraphy was assessed for CV first. If the primary target lobe was CV positive, or if the CV status was not assessable, then the secondary target lobe was evaluated (for further information, see Figure E2 in the online supplement).

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Follow-up: Subjects randomized to SoC were discharged after standard post-bronchoscopy recovery, unless the treating physician deemed an admission necessary. Subjects randomized to EBVs were hospitalized for at least one day and discharged following a chest X-ray if there were no complications/serious adverse events (SAEs). Subjects were instructed to seek immediate medical attention in the event of symptoms of a potential pneumothorax. EBV subjects were evaluated at 45 days with a HRCT scan to assess TLVR, and to verify whether complete lobar occlusion had been achieved. If necessary (TLVR <50%, or incomplete lobar occlusion), a repeat bronchoscopy and valve revision/replacement was performed.

Outcome Measures: All subjects were assessed at 3 months post-bronchoscopy (SoC and EBV). For EBV subjects who underwent valve replacement or revision based on their 45 day HRCT scan, follow-up occurred 3 months after the revision bronchoscopy. Subjects in the SoC group were given the option of exiting the study following the 6 month evaluation if they wished to pursue EBV treatment, or to continue in follow-up until 12 months. Follow-up of the EBV group will continue to 24 months (see study scheme, Figure E3 in online supplement).

The primary endpoint was the percentage of subjects in the EBV group at 3 months post-procedure who had an improvement in the post-bronchodilator FEV_1 of ≥12% (protocol-defined minimal clinically important difference (MCID)) compared to the percentage of subjects in the SoC group.

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Secondary endpoints included comparison between EBV and SoC groups for the absolute and percent changes and responder rates (percentage of subjects achieving the MCID) at 3 and 6 months for FEV_1 (≥12%), RV (≤-430 mL), St. George's Respiratory Questionnaire (SGRQ) score (≤-4 points), 6MWD (≥26 meters), modified Medical Research Council (mMRC) dyspnea score (≤-1 point), and for the EBV group only, the absolute and percent change in TLVR at 45 days post-procedure and the percent of subjects meeting the TLVR MCID of ≥350mL (12) relative to baseline. Safety was assessed through review of all adverse events solicited at all scheduled or unscheduled visits.

Statistical Analyses: The sample size calculation of 78 subjects was based on proportions for the primary endpoint of a ≥12% improvement in FEV_1 at 47% (EBV) and 13% (SoC) estimated from the VENT study (11), a 2:1 randomization, 80% power, alpha = 0.05, a two-sided Chi-Square test, and 15% drop-out rate. For the intention-to-treat (ITT) analysis, missing data were imputed using the last observation carried forward method. All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary NC). Absolute and percent changes from baseline were analyzed using a fixed-effect one-way ANOVA (or ANCOVA with baseline as a covariate) model for normally distributed data; otherwise the Wilcoxon Rank-Sum test was used. Categorical variables were analyzed using a Chi-Square test. Details of the analysis populations in Section E4 in online supplement.

Results

Two hundred and seventy-three (273) subjects were screened, with 125 subjects meeting the inclusion/exclusion criteria. A total of 97 subjects deemed to be CV

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negative were randomized, 65 subjects to EBVs and 32 to SoC (see CONSORT diagram, Figure E4 in online supplement). The median(range) number of randomized subjects per center was 5(1-14). Baseline characteristics were similar in both groups, although the EBV group reported a worse respiratory related quality of life (p=0.042) and absolute but not percent predicted FEV1 (p=0.008). See Table 1 and Table E1 in online supplement.

Treatment details: A median of 4 valves (range 2 to 8) per subject were implanted in the 65 EBV subjects. Treatment distributions were 52% left upper lobe, 22% left lower lobe, 15% right upper lobe, 8% right upper and right middle lobe combined, and 3% right lower lobe. The median hospital stay for the treatment visit was 4 days (range 1 to 49 days) for the EBV group and 1 day (range 1 to 3 days) for the SoC group. At 45 days post-procedure, 89.8% of subjects achieved a TLVR of ≥350ml, with a mean of 1.09 ± 0.62L (p<0.001). Individual subject TLVR changes are provided in Figure E5 in the online supplement. Eighteen subjects underwent a repeat bronchoscopy, 17 of whom had a revision procedure, and 12 of those subsequently developed significant TLVR.

Primary outcome: At 3 months post-procedure, responder rates (≥12% improvement from baseline in FEV_1) in the ITT population were 55.4% in the EBV group and 6.5% in the SoC group (p<0.001), and for the per protocol (PP) population were 66.7% and 6.7%, respectively (p<0.001). These differences were maintained at 6 months: ITT (EBV vs SoC) 56.3% vs 3.2% (p<0.001), and PP 66.3% vs 3.3% (p<0.001), respectively (Figure 1).

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Secondary outcomes: Statistically and clinically significant improvements from baseline were seen at both 3 and 6 months in the EBV group compared to the SoC group for FEV_1 (Figure 2a), 6MWD (Figure 2b), and SGRQ score (Figure 2c). There was a decrease in RV ($p<0.001$, Figure 2d) and BODE Index (points, $p<0.001$, Figure 2e) in the EBV vs SoC group at both 3 and 6 months. The absolute and percent changes from baseline at 6 months are summarized in Table 2. Changes from baseline for EBV and SoC groups and differences between groups for the changes for the PP population are provided in Tables E2 to E9 in online supplement.

For each outcome measure, a significantly greater number of subjects in the EBV group met or exceeded the MCID (Table 3, and Table E10, and Figures E6, E7, and E8 in online supplement). In post-hoc analysis, 76.9% of the ITT population and 90.2% of the PP population achieved the MCID for at least one of FEV1, 6MWD, and SGRQ at 6 months. Following the 6 month evaluation, 30 of the 32 SoC subjects exited the study and opted for EBV treatment.

Safety outcomes: At 6 months, there were 44 respiratory related SAEs in 31 (47.7%) subjects in the EBV group compared to 4 events in 3 (9.4%) subjects in the SoC group ($p<0.001$, Fishers test), with most events occurring within 30 days of the procedure (Table 4). In the EBV group, the most common SAE was pneumothorax, which was managed according to a protocolized pneumothorax management flow chart (21, and Figure E9 in online supplement). Other respiratory related SAEs during the first 30 days in the EBV group included dyspnea (7.7%), COPD exacerbation (4.6%), and pneumonia (4.6%). A summary of all respiratory and non-respiratory adverse events is provided in Tables E11 and E12 in the online supplement.

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Pneumothorax: Over the 6 month follow-up period, there were 20 pneumathoraces in 19/65 (29.2%) EBV subjects, with a median time to onset of 1 day. Table E13 in the online supplement shows pneumothorax rate by lobe treated. In 14 subjects, the pneumothorax required an intervention and/or hospitalization and was therefore considered a SAE. Pneumothorax was managed by observation only in 8 cases, and placement of chest drains in 11 cases. In one case, the air leak was addressed surgically. Seven subjects underwent a second bronchoscopy for an adverse event, 5 for valve removal for pneumothorax management, one for valve replacement a day after the initial procedure due to expectoration of a valve, and one for loss of effect. One EBV subject died of in-hospital cardiac arrest as a complication of pneumothorax. There were no differences in any outcome measure at 3 or 6 months in the EBV cohort between subjects who experienced a pneumothorax (n=19) and those that did not (n=46). See tables E14 and E15 in the online supplement.

Discussion

This is the first multicenter, prospective RCT of Zephyr EBV treatment in patients with severe heterogeneous emphysema and absence of collateral ventilation. We found statistically and clinically significant improvements in lung function, exercise capacity, and quality of life associated with Zephyr EBV treatment compared with standard of care. Ninety percent of subjects experienced TLVR, indicating appropriate selection of CV negative patients and effective occlusion of the target lobe following EBV placement. Of significance, the EBV group had improvements that exceeded the MCIDs for FEV_1, SGRQ, RV, 6MWD, and mMRC at 6 months post-treatment.

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Post-hoc analysis of the VENT study (11,12) demonstrated the critical importance of the absence of CV and achieving complete lobar occlusion as necessary elements for successful lung volume reduction with EBVs. Whilst visual evaluation of fissure completeness has been useful in patient selection for bronchoscopic lung volume reduction with Zephyr EBVs (15), the physiologic assessment of air flow using the Chartis System has been more reliable (13,16). Using this approach, Klooster et al (16) successfully demonstrated significant improvements in lung function and exercise capacity in patients with severe emphysema characterized by an absence of CV. Similarly, Valipour et al (17) reported benefits in patients with homogeneous emphysema. The findings of the present multicenter RCT provide further confirmation that patients carefully selected for absence of CV experience significant, meaningful reduction in treated lobar volumes (mean 1.09 ± 0.62L, $p<0.001$) with benefits in lung function, dyspnea, exercise capacity, and quality of life following Zephyr EBV placement.

The magnitude of benefits seen in this study are comparable to those observed after LVRS (8), but with reduced morbidity. The mean change presented here in the 6MWD, a patient-centered outcome, is three times the MCID, and similar to values reported from a single center RCT (16). Zephyr EBV treatment has the added benefits of being suitable for both upper and lower lobe disease, as well as homogeneous disease (17), and is a reversible procedure. Valves were permanently removed in 7 subjects in our study with no associated complications.

There were a greater number of serious adverse events in the early post-procedure period (within the first 30 days) in the EBV group than in the SoC group (Table 4).

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Pneumothorax was the most common adverse event, and was managed according to published guidelines (21). The occurrence of pneumothoraces and air leaks is a common side-effect of thoracic procedures, ranging from 4% to 42% after CT-guided biopsy (22,23), 11.6% for endobronchial coil treatment (24), and up to 90% of patients within 30-days of LVRS (25). The frequency of pneumothorax in the present study (21.5%) was similar to other published Zephyr EBV treatment studies (16,17), and the occurrence of pneumothorax does not appear to negatively impact clinical outcomes (26). Of note, 94% (30/32) of the control subjects opted to exit the study and receive Zephyr EBV treatment after the 6 month evaluation.

Previous retrospective analyses have demonstrated a survival advantage where TLVR is achieved after Zephyr EBV placement (27,28,29). A reduction of more than 1 point in the BODE Index has been associated with a significant decrease in mortality (30,31) and the difference between groups in the change in BODE Index in this prospective trial was -1.8 points. This is compatible with the recent report by Klooster at al (32), and raises the hope of improved survival in our subjects. This will need to be confirmed in future studies and with longer follow up data.

One limitation of this study is the follow-up out to only 6 months, though earlier single center RCTs have reported 1-year follow-up data, demonstrating the durability of this treatment (33,34). Subjects in the EBV group will be followed out to 2 years, important for capturing events that may be infrequent in a 6 month window, such as exacerbations or mortality. Another limitation is the absence of a sham bronchoscopy in the SoC group, since the treatment involves an intervention with associated adverse events and the potential for a placebo effect. However, unlike other interventional devices for BLVR,

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the benefit of EBV treatment using a sham control has previously been demonstrated (15), and patients in the SoC arm in our study did undergo bronchoscopy for the purposes of Chartis examination (although this does not mitigate against any placebo effect associated with actual valve implantation).

Another potential limitation is the lack of mandatory pulmonary rehabilitation in the period prior to trial entry. Given the randomized nature of the trial, any changes or lack thereof associated with the potentially variable provision of pre-procedure PR should be balanced across the 2 groups, and therefore would not be expected to be a significant factor in any between group differences.

Whilst there was an apparent imbalance in the absolute FEV1, and to a lesser extent SGRQ, at baseline between the two groups (although not in the percent predicted FEV1), which could have affected outcome, ANCOVA models with baseline values as the covariate resulted in the same p-values as when using the t-test for all secondary endpoints, indicating that the group differences (EBV vs. SoC) are there despite the groups having different baseline values.

The benefits of EBV treatment for patients with severe heterogeneous emphysema reported here, and for homogeneous patients previously reported by Valipour et al (17), demonstrate that EBV placement is an effective treatment option in patients without CV regardless of emphysema distribution. The success of the treatment requires accurate patient selection including correct determination of the absence of CV between target and adjacent lobes, and expertise in the management of procedural complications.

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Conclusion

EBV treatment in hyperinflated subjects with heterogeneous emphysema without CV in the target lobe results in clinically meaningful and statistically significant benefits in lung function, dyspnea, exercise tolerance, and quality of life over current standard of care medical therapy. Benefits are in line with those seen with LVRS, and the consistent trial results, potential reduction in post-procedure morbidity, and reversibility of the procedure position Zephyr EBV treatment as a viable treatment option in those who remain symptomatic on maximal medical therapy.

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Disclosures

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Figure 1: Primary Endpoint - Percent of subjects achieving a 12% or greater Improvement in FEV_1 (L) at 3 Months.

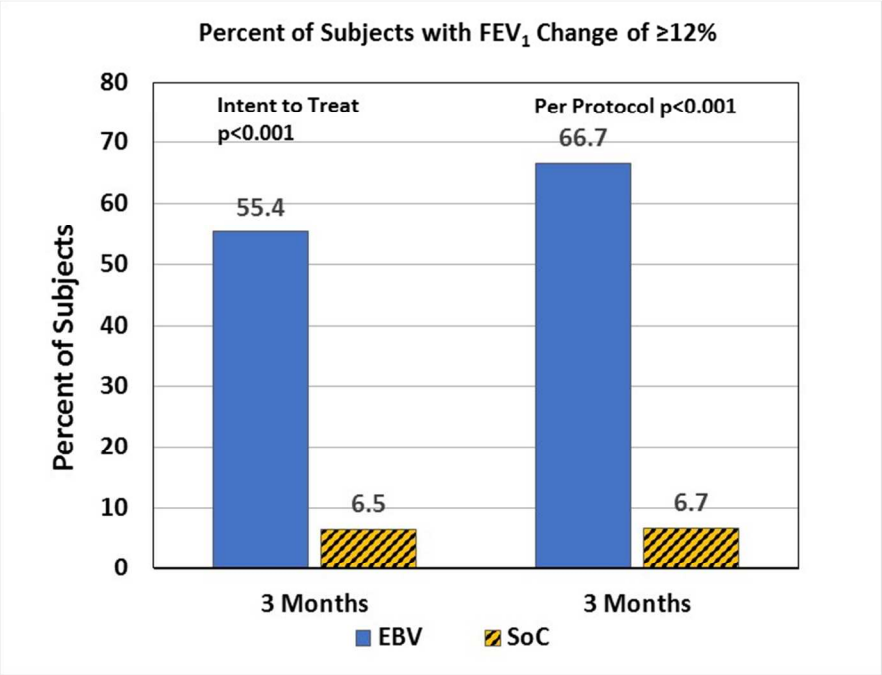

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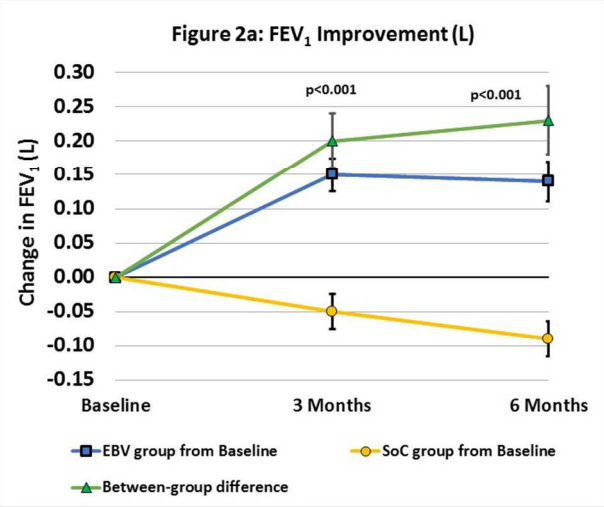
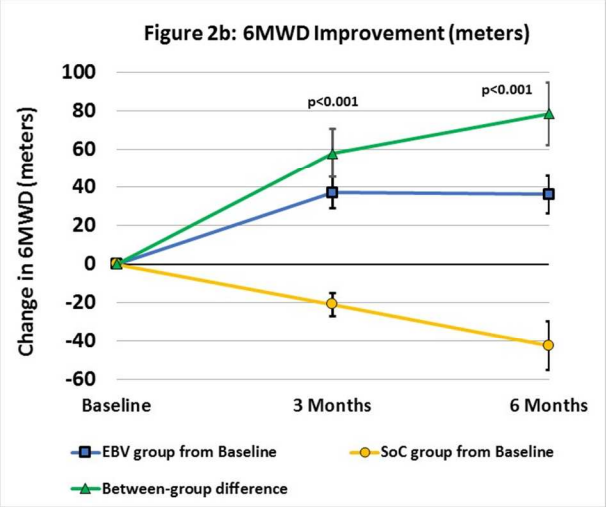
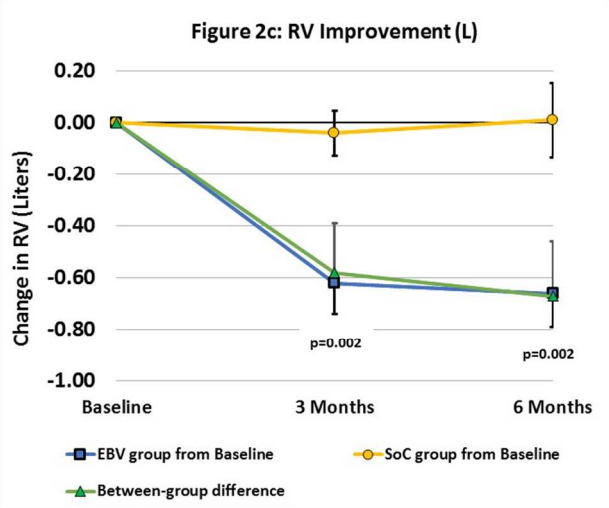
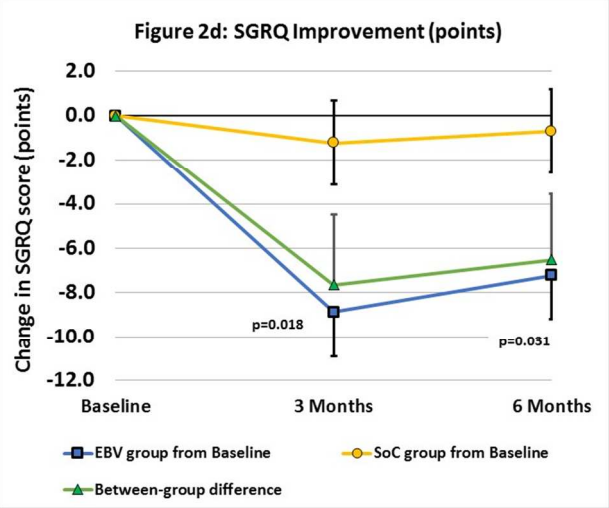
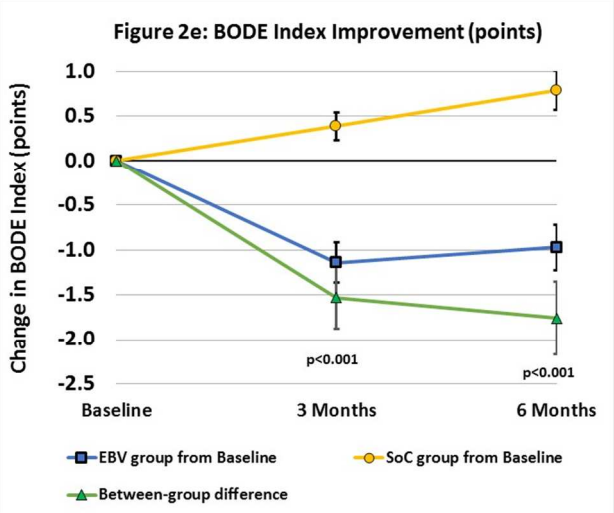
Figure 2: Absolute changes from Baseline in key outcome measures at 3 and 6 months











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Legend to Figure 2: Data presented are mean ± SEM for changes from baseline to 3 and 6 months post bronchoscopy for EBV (□), SoC (○), and difference between EBV and SoC (Δ). Figure 2a: FEV_1 (L); Figure 2b: 6-Minute Walk Distance (m); Figure 2c: RV (L); Figure 2d: St. George's Respiratory Questionnaire; and Figure 2e: BODE Index.

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Table 1: Baseline demographics and clinical characteristics

Variable	EBV (n=65)	SoC (n=32)	t-test p-value
Gender	37 Males / 28 Females	21 Males / 11 Females	NS
Age (years)	64.9 ± 8.0	63.0 ± 6.0	NS
BMI (kg/m^2)	23.7 ± 4.4	24.3 ± 5.3	NS
Smoking history (pack years)	42.0 ± 21.5	42.0 ± 20.2	NS
Clinical Characteristics			
GOLD Stage	Stage III: 26 (40%) Stage IV: 39 (60%)	Stage III: 18 (56%) Stage IV: 14 (44%)	NS
Emphysema score of the target lobe at -910 HU*	69.3 ± 9.3	68.4 ± 11.2	NS
Heterogeneity Index between target and ipsilateral lobe(s) †	21.8 ± 14.6	25.5 ± 15.8	NS
Forced Expiratory Volume in 1 sec. (L)	0.78 ± 0.24	0.94 ± 0.31	0.008
Forced Expiratory Volume in 1 sec. (% predicted)	29.8 ± 9.2	32.2 ± 8.4	NS
Residual Volume (% predicted)	249.4 ± 51.8	241.0 ± 41.4	NS
Total Lung Capacity (% predicted)	139.0 ± 18.9	137.3 ± 12.5	NS
6 Minute Walk Distance (m)	282 ± 94	320 ± 92	NS
SGRQ Total score ‡	64.3 ± 14.4	58.1 ± 13.3	0.042
mMRC score §	3.00 ± 0.77	2.88 ± 0.83	NS
BODE Index score **	6.14 ± 1.68	5.55 ± 1.77	NS††

Values are means ± SD.

* Emphysema destruction score was assessed as the percentage of voxels of less than −910 Hounsfield units on CT.

† Heterogeneity Index was assessed as the difference in the Emphysema score between the target and the ipsilateral lobe.

‡ St. George's Respiratory Questionnaire (SGRQ) scores range from 0 to 100, with higher scores indicating worse quality of life.

§ Modified Medical Research Council dyspnea (mMRC) scores 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, body-mass index, 6 Minute Walk Distance, and the modified MRC dyspnea score. Higher scores denote a greater risk of mortality.

††: Wilcoxon signed-rank test.

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Table 2: Mean changes from baseline in secondary outcome measures at 6-months (ITT)

Outcome Measure	Change from Baseline	EBV (n=65)	SoC (n=32)	Δ EBV – SoC Mean [95% CI]	p-value*
FEV_1	Liters (L)	0.14 ± 0.24	-0.09 ± 0.14	0.2 [0.1, -0.3]	<0.001
	Percent (%)	20.7 ± 29.6	-8.6 ± 13.0	29.3 [18.3, -40.4]	<0.001
RV	Liters (L)	-0.66 ± 1.04	0.01 ± 0.79	-0.7 [-1.1, -0.3]	0.002
6MWD	Meters	36.2 ± 76.9	-42.5 ± 68.2	78.7 [46.3, 111.0]	<0.001
SGRQ total score	Points	-7.2 ± 15.1	-0.7 ± 10.4	-6.5 [-12.4, -0.6]	0.031
mMRC Grade	Points	-0.56 ± 1.04	0.00 ± 0.86	-0.6 [-1.0, -0.1]	0.010
BODE Index score	Points	--0.97 + 2.01	0.79 ± 1.17	-1.8 [-2.6, -0.9]	<0.001†

Values are means ± SD.
*: Two sample t test
†: Wilcoxon signed-rank test
ANCOVA with baseline as covariate did not impact any outcomes

Table 3: MCID responders for key outcome measures in the ITT population at 6 months

Variable	EBV	SoC	p-value*
FEV_1 (L): (MCID ≥ +12%)[35,36]	36/64 (56.3%)	1/31 (3.2%)	< 0.001
RV (ml): (MCID ≤ -430 mL)[37]	37/64 (57.8%)	8/31 (25.8%)	0.003
SGRQ: (MCID ≤ -4 points)[38]	35/62 (61.7%)	11/32 (34.4%)	0.042
6MWD: (MCID≥ +26 meters)[39]	33/63 (52.4%)	4/31 (12.9%)	<0.001
mMRC: (MCID ≤ -1 point)[40]	29/64 (43.8%)	7/31 (22.6%)	0.032

FEV_1: Forced Expiratory Volume in 1 second; RV: Residual Volume; SGRQ: St. George's Respiratory Questionnaire; 6MWD: Six-Minute Walk Distance; mMRC: Modified Medical Research Council Dyspnea score
*: Chi-squared test

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Table 4: Serious adverse events during 6 months of follow up

	EBV (n=65)				SoC (n=32)			
Event	≤30 days Events	≤30 days Subjects (%)	>30 days to 6 months Events	>30 days to 6 months Subjects (%)	≤30 days Events	≤30 days Subjects (%)	>30 days to 6 months Events	>30 days to 6 months Subjects (%)
Pneumothorax	13	13 (20.0%) *	2¶	2 (3.1%)	0	0	0	0
Dyspnea	6	5 (7.7%)	2	2 (3.1%)	0	0	0	0
Pneumonia	3	3 (4.6%)	3	3 (4.6%)	0	0	1	1 (3.1%)
COPD Exacerbation	3	3 (4.6%)	4	3 (4.6%)	0	0	3	2 (6.3%)
Subcutaneous emphysema	1	1 (1.5%)	0	0	0	0	0	0
Hemoptysis	1	1 (1.5%)	0	0	0	0	0	0
Inhaled foreign body	1	1 (1.5%)	0	0	0	0	0	0
Lower Respiratory Tract Infection	1	1 (1.5%)	0	0	0	0	0	0
Death	1	1 (1.5%)‡	0	0	0	0	0	0
Bronchospasm	0	0	2	1 (3.1%)	0	0	0	0
Influenza	0	0	1	1 (1.5%)	0	0	0	0
EBV removal	0	0	1	1 (1.5%)	0	0	0	0

Serious Adverse Events were events leading to death or to serious deterioration in health that resulted in a life-threatening illness or injury, a permanent impairment of a body structure or body function, hospitalization or prolongation of existing hospitalization, or medical or surgical intervention to prevent permanent impairment to body structure or body function.

¶: One event occurred 58 days after initial placement and 3 days after a valve replacement procedure (valve previously removed due to pneumothorax); one event occurred 83 days after valve placement procedure.

‡: Also included in the count of Pneumothorax; subject died of cardiac arrest during hospitalization for a pneumothorax

*: p=0.004 Fisher's Exact Test (EBV vs SoC at ≤30 days)

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Online Data Supplement

A Multicenter RCT of Zephyr® Endobronchial Valve Treatment in Heterogeneous Emphysema (TRANSFORM)

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This supplementary material is provided by the authors to give readers additional information relating to the above-mentioned work.

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Section E1: Study Subjects: Inclusion and Exclusion criteria

Subjects enrolled in the Study had to meet the following Inclusion and Exclusion criteria:

Inclusion Criteria

1. Obtained informed consent.
2. Diagnosis of heterogeneous emphysema with a heterogeneity index of ≥10 % between target and adjacent lobes.
3. Subjects of both genders of at least 40 years of age.
4. 15 % predicted ≤ FEV_1≤ 45% predicted.
5. TLC > 100% and RV ≥ 180% predicted.
6. 150 meters ≤ 6MWT ≤ 450 meters.
7. Non-smoker >8 weeks prior to signing the Informed Consent.
8. CV negative target lobe.

   Additional inclusion criterion French CIP*:

   - If treated in France, Subject must be entitled to French social security

Exclusion criteria

1. Any contraindication for bronchoscopic procedure.
2. Evidence of active pulmonary infection.
3. History of 2 or more exacerbations requiring hospitalization over the past 12 months.
4. Known pulmonary hypertension that according to the physician will be unsuitable for EBV treatment.
5. Myocardial infarction or other relevant cardiovascular events in the past 6 months.
6. Significant bronchiectasis seen at CT scan.
7. Greater than two tablespoons of sputum production per day.
8. Prior LVR or LVRS procedure.

   French CIP wording*: Prior lung transplant, median sternotomy, LVR or LVRS procedure (including lobectomy).
9. Pulmonary nodule requiring follow-up within any lobe.
10. Pregnant or nursing women.

    French CIP wording*: Subject is pregnant or lactating, or plans to become pregnant within the study timeframe.
11. Hypercapnia ($paCO_2$ >7.33 kPa).
12. Current diagnosis of asthma.
13. > 25mg Prednisolone (or equivalent) use/days.
14. Any other condition that as judged by the investigator may make follow-up or investigations inappropriate.
15. Evidence of pleural adhesions or earlier pulmonary surgery.
16. Severe Bullous Emphysema (> 1/3 Hemithorax)
17. Any subject that according to the Declaration of Helsinki is unsuitable for enrollment.

    Additional exclusion criteria in French CIP*:

    - History of allergy to silicone and/or nitinol.
    - If treated in France, Subject is a "personne vulnerable" as defined by French regulation.
    - Simultaneous participation in another drug and/or medical device related clinical.

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Section E2: Study Design and Methods

Prospective, randomized, controlled, two-armed multi-center trial. Planned to enroll 78 subjects with heterogeneous emphysema at Study centers in Europe.

- Potential subjects with heterogeneous emphysema will be asked to sign the inform consent form and will thereafter initially be identified by visual read of a high-resolution computer tomography scan (HRCT) by the investigator. Subjects underwent baseline evaluations including medical history, physical examination, blood test, echocardiogram, measures lung volumes and lung function, scintigraphy, Six-Minute Walk Test (6MWD), and questionnaires including St. George's Respiratory Questionnaire (SGRQ), modified Medical Research Council (mMRC) Dyspnea score, and EQ-5D.
- Heterogeneity was confirmed using computerized software to determine the heterogeneity index (HI). Subjects with a HI (difference in destruction scores between potential target and ipsilateral lobe(s)) of ≥10% and a destruction score ≥50% in the potential target lobe were considered for enrollment into the Trial. In case of multiple target lobes, the lobe with the highest destruction score and lowest perfusion or ventilation as determined by scintigraphy was assessed for CV first. The scheme for target lobe determinations is shown in Figure E1.
- All potential study candidates then underwent a Chartis assessment to determine the extent of collateral ventilation (CV) between target and adjacent lobes. In case of multiple (2) target lobes, the lobe with the highest destruction score and lowest perfusion or ventilation as determined by scintigraphy was assessed for CV first. If the primary target lobe was CV positive or if the CV status was not assessable, then the secondary target lobe was evaluated for CV status. Only subjects with a CV negative (low collateral flow as determined by the investigator) target lobe and with an exhaled volume of >100 ml were considered. Subjects fulfilling all the eligibility criteria were considered enrolled and were randomized 2:1 into either the EBV group or the SoC group.
- Subjects randomized to EBV treatment arm had EBVs placed during a bronchoscopy procedure (under general anesthesia or sedation) to achieve lobar occlusion. Subjects in the SoC arm received standard treatment.
- Subjects in whom EBV were placed were monitored at the hospital at least 24 hours following valve placement to screen for signs of volume reduction, pneumothorax and any other side effects or complications and had a chest X-ray performed immediately prior to discharge. Following discharge, the subjects were recommended to avoid anything else but mild physical activity and bedrest for additional four days by the treating physician. Cough suppressants could be prescribed prophylactically.

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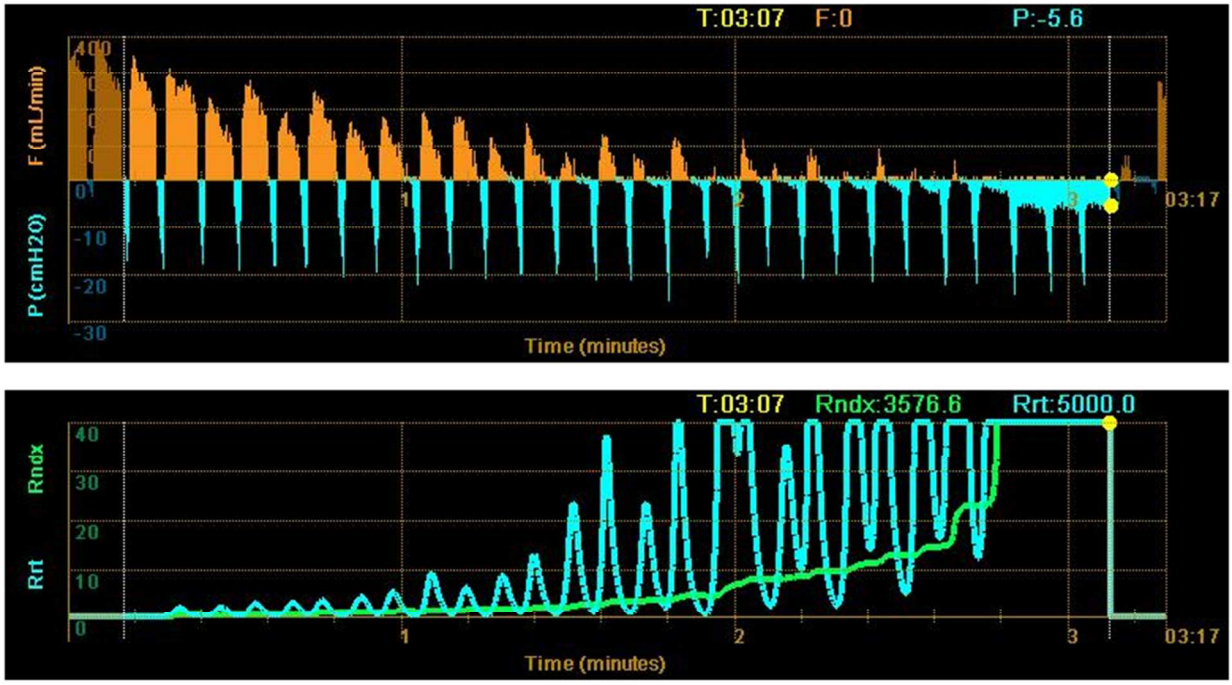
Figure E1: Examples of CV negative and CV positive read-outs from the Chartis system

CV Negative (CV-) Chartis assessment



CV Positive (CV+) Chartis assessment

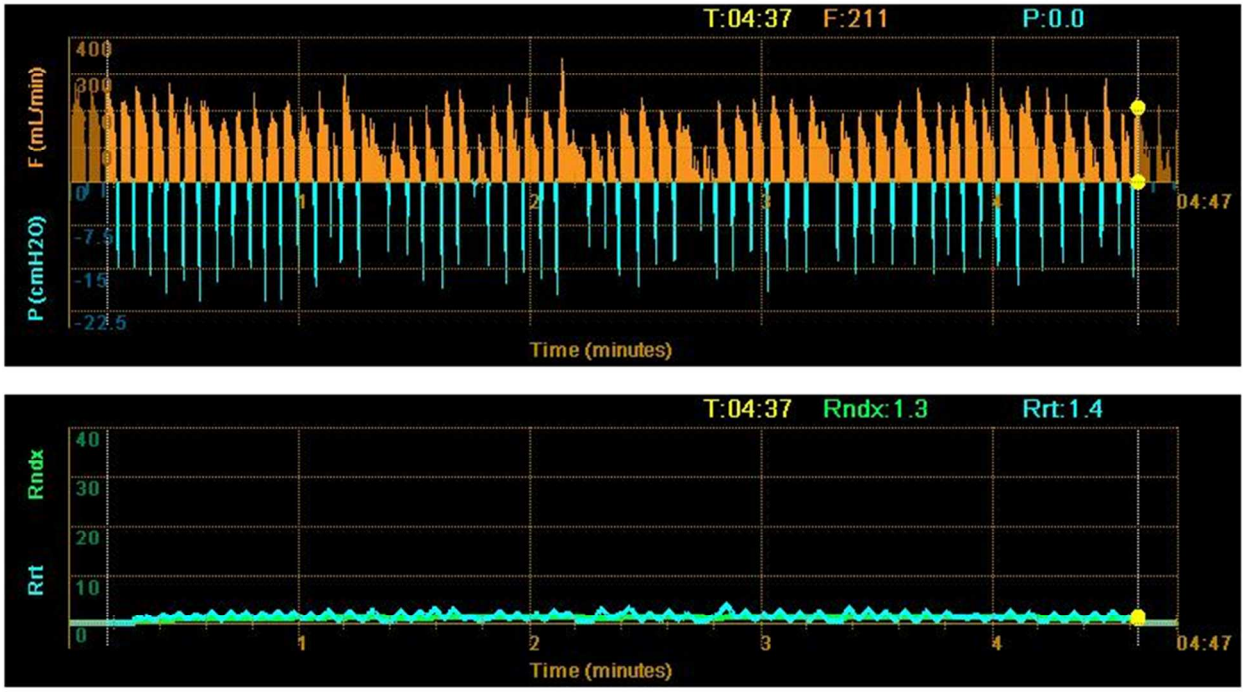


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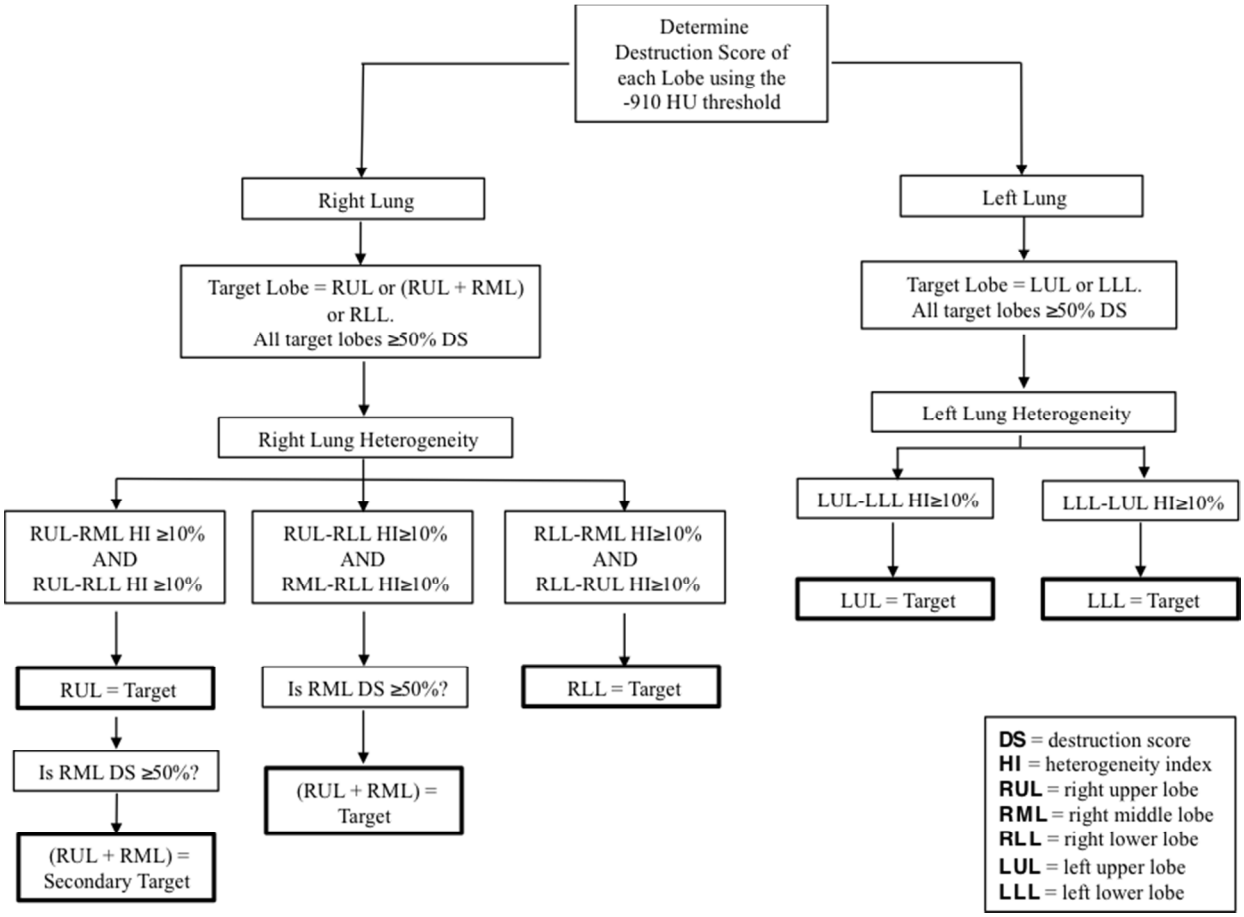
Figure E2: Target Lobe Selection



Note: RML is not a target lobe by itself. When RML is considered for treatment this will only be in combination with RUL.

- EBV group subjects had a HRCT performed at 45 days after the procedure to verify technical success of valve placement. Valve adjustment or valve replacement, if indicated to be necessary as per the HRCT, was considered part of the study procedure. In the case of a secondary valve procedure, the follow-up schedule was calculated from the date of the latest valve procedure. Valve adjustment/replacement could be performed only once for a study participant within the trial. A valve adjustment or valve replacement procedure was considered if:

    1. The 45-day HRCT scan, as read by the core radiology reading laboratory and measured using software designed to evaluate HRCT changes, showed less than 50% volumetric reduction in the EBV-treated lobe.
    2. The 45-day HRCT scan, as read by the core radiology reading laboratory, demonstrated signs indicative of incomplete occlusion, including no valve in a segmental airway, anatomic variation resulting in the valve not occluding accessory branches, leakage around the valve, and incorrect placement.

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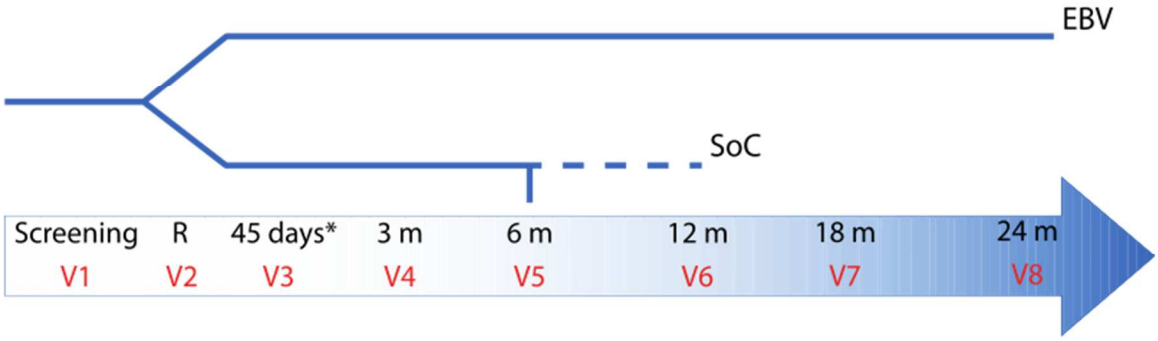
In addition to verifying technical success as judged by the HRCT scan, the TLVR was calculated relative to baseline.

- Subjects in both EBV and SoC arms performed assessments at 3 and 6 months. SoC subjects could exit the trial after the 6-month evaluation and thereafter receive EBV treatment. Any subjects remaining in the SoC group (declining valve treatment after the 6-month follow up) was followed up at 12 months where after they would exit the study. In addition to the 3, 6, and 12 months follow-up visits, subjects in the EBV group will be followed-up at 45 days, 18 and 24 months following valve placement.
- Adverse events were solicited during each visit and during any unscheduled visit.

Figure E3: Study Scheme



V1: Screening
V2: Bronchoscopy to determine CV status and randomization is CV negative (CV-)
V3: 45 Day – HRCT for EBV group only
V4: 3-month assessment
V5: 6-month assessment; exit of SoC subjects if choosing to pursue EBV treatment
V6: 12-month assessment
V7: 18-month assessment – EBV only
V8: 24-month assessment – EBV only

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Section E3: Randomization

Subjects were randomly assigned at a 2:1 ratio to the EBV treatment group or the SoC group during the bronchoscopy procedure. Once CV negative status was confirmed, two study participants were randomized to the EBV Treatment arm for every one (1) participant randomized to the SoC arm using a blocked design to assure the 2:1 balance from start. Each site was provided with sealed envelopes with consecutive numbering. The envelopes were brought into the bronchoscopy suite and the seal was broken once the CV negative status has been confirmed; the enclosed document was marked “EBV” or “SoC”.

Section E4: Analysis population

During statistical analysis of the study results the patient population may be divided into subgroups, for example:

- Intention-to-treat (ITT): all patients included in the study whether or not treated according to protocol.
- Per-protocol (PP): all patients that meet the following criteria:
    1. Meets inclusion/exclusion criteria. Prospective deviations preapproved by Sponsor does not cause removal from the PP group.
    2. Received treatment (EBV or SoC). Any valve removed has been replaced before 3-month assessment.

Safety analyses were performed on the ITT population.

Section E5: Handling of Missing Data

If the FEV_1 (L) data from the 3-month follow-up visit have failed to be collected, then this subject’s data for this parameter was excluded from the statistical analysis. Available data for other measures was analyzed.

For the Intention to Treat analyses, for a missed visit, values for all variables were imputed using the Last Observation Carried Forward (LOCF) method. For a completed visit, no imputation was done for a single missing variable.

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Figure E4: CONSORT Flow Diagram

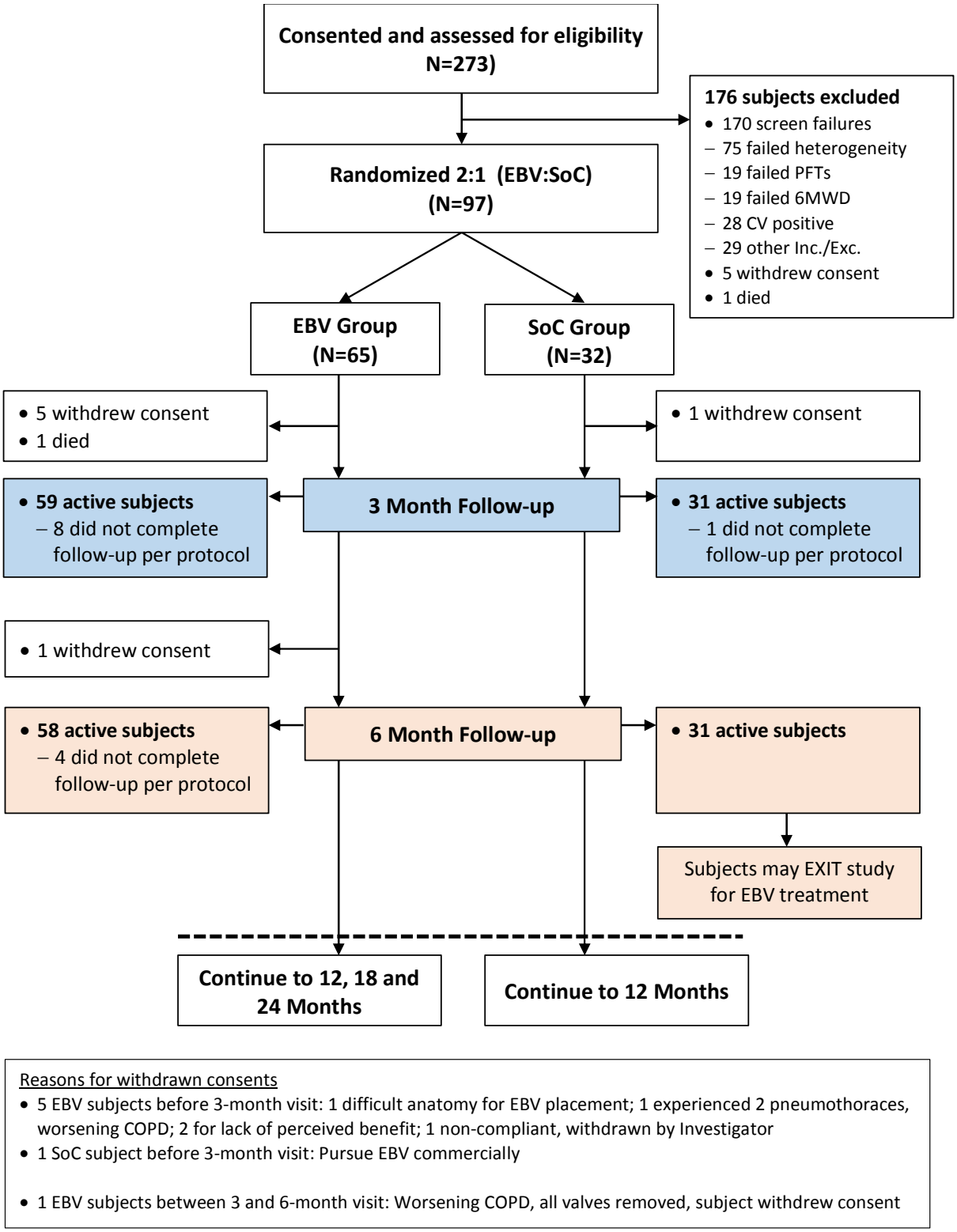

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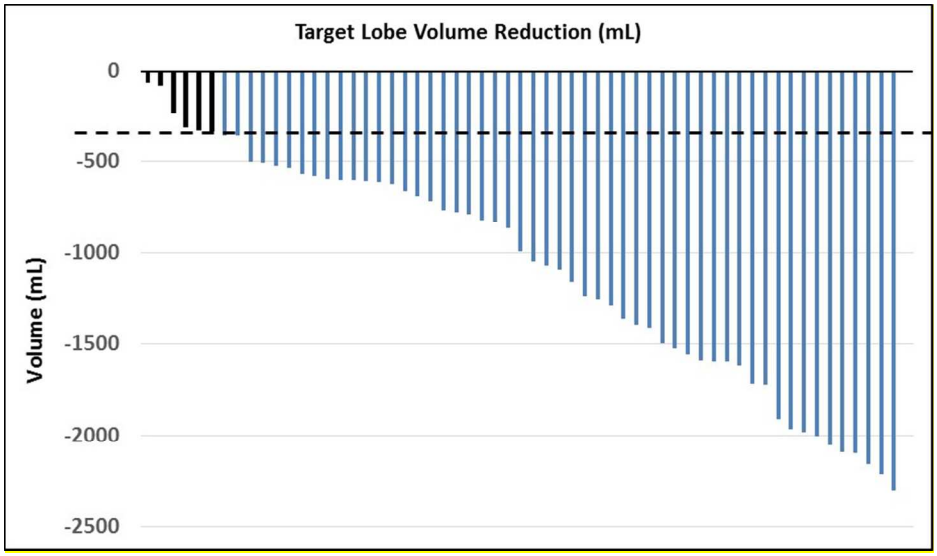
Figure E5: Responders based on Target Lobe Volume Reduction of ≥350mL



Legend for Figure E5: Each bar represents an individual subject. Blue bars represent subjects that had a Target Lobe Volume reduction of equal to or greater than 350mL. Black bars represent subjects who did not achieve a TLVR of ≥350mL. Dotted line represents a target volume of 350mL.

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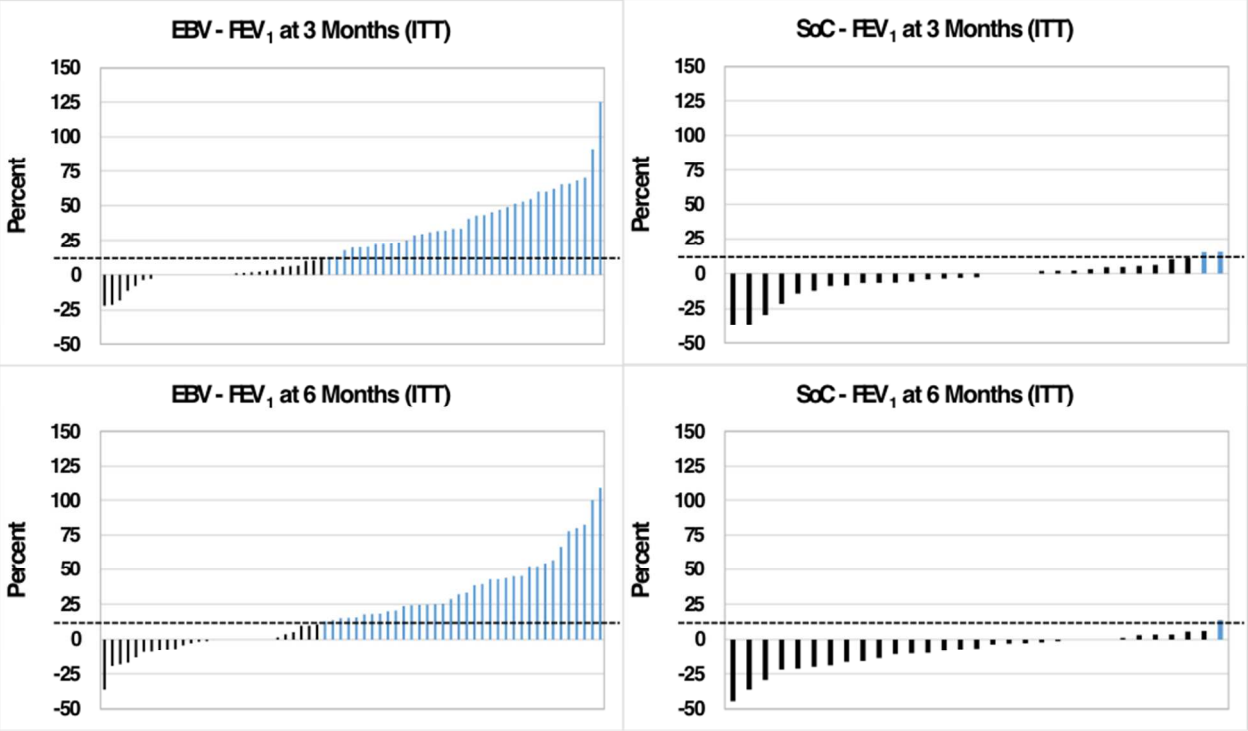
Figure E6: Responders based on Minimal Clinically Important Difference for Forced Expiratory Volume in 1 Second (%) (ITT population)



Legend for Figure E6: Each bar represents an individual subject. Blue bars represent subjects that met or exceeded the minimal clinical important difference (MCID) for FEV_1 of ≥12% improvement in FEV_1 (L). Black bars represent subjects who did not meet the MCID. Dotted line represents the MCID.

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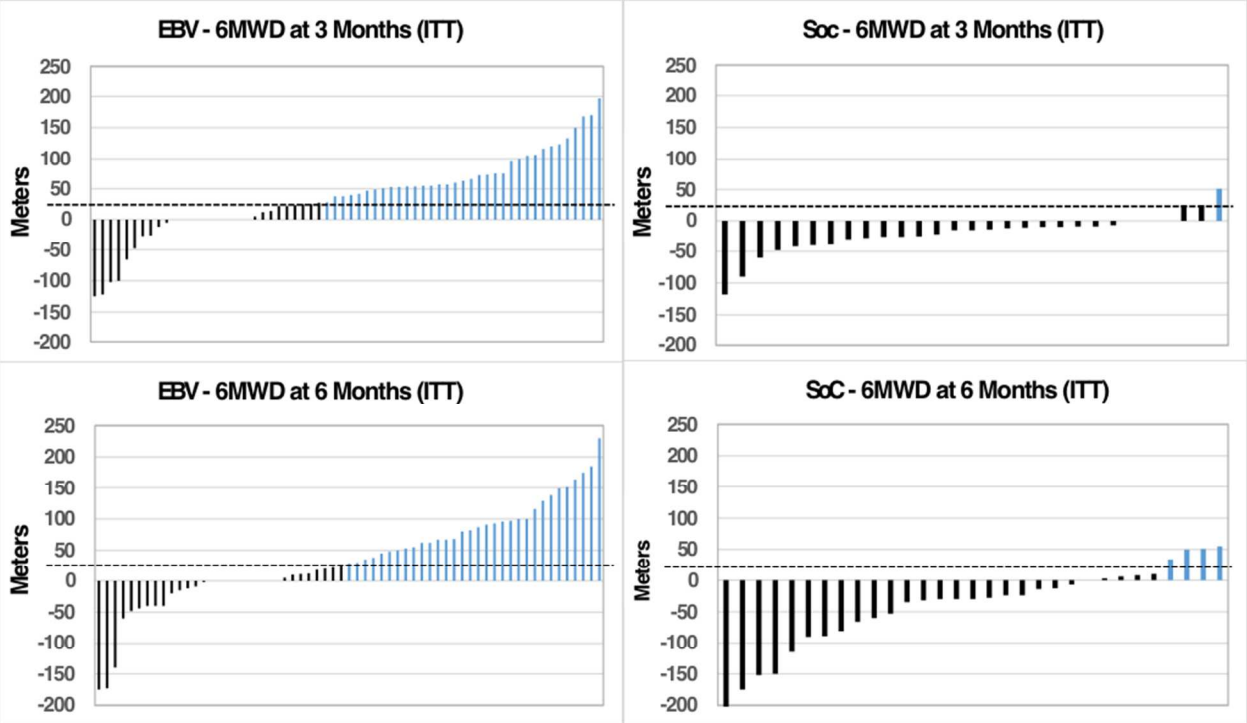
Figure E7: Responders based on Minimal Clinically Important Difference for Six-Minute Walk Distance (6MWD) in meters (ITT population)



Legend for Figure E7: Each bar represents an individual subject. Blue bars represent subjects that met or exceeded the minimal clinical important difference (MCID) for 6-Minute Walk Distance (26 meters). Black bars represent subjects who did not meet the MCID. Dotted line represents the MCID.

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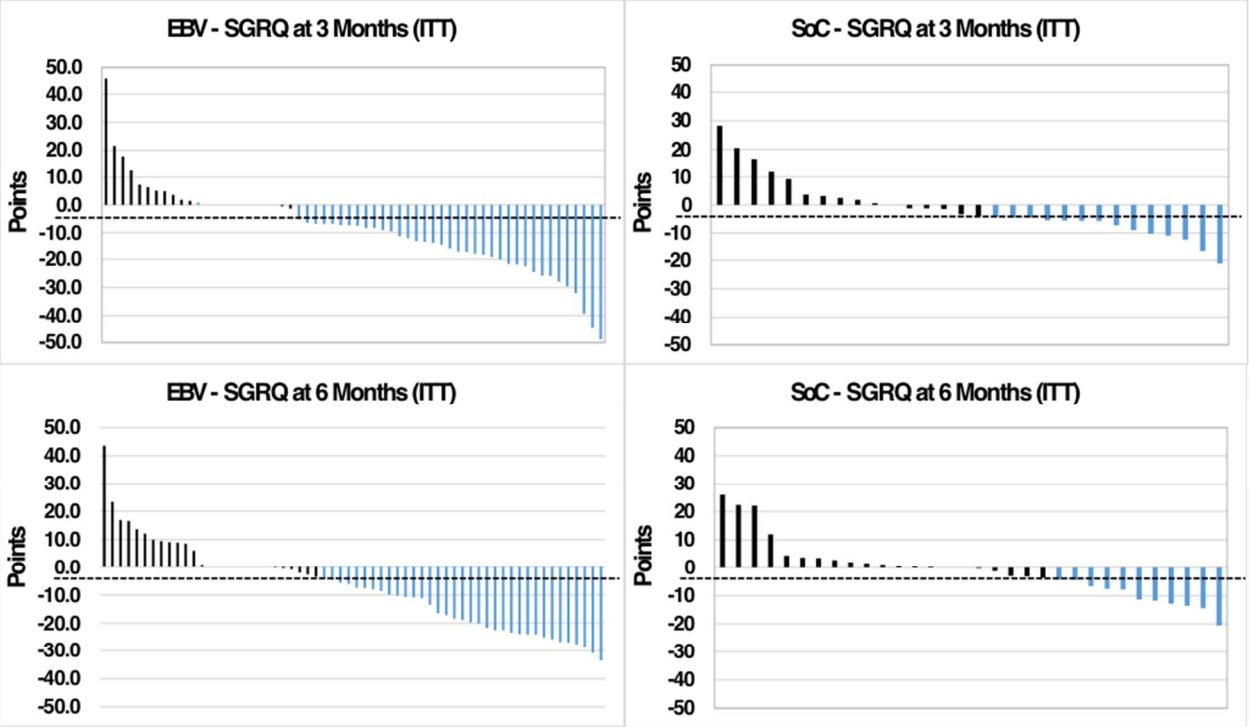
Figure E8: Responders based on Minimal Clinically Important Difference for St. George's Respiratory Questionnaire Score (points) (ITT population)



Legend for Figure E8: Each bar represents an individual subject. Blue bars represent subjects that met or exceeded the minimal clinical important difference (MCID) for St. George's Respiratory Questionnaire (-4 points). Black bars represent subjects who did not meet the MCID. Dotted line represents the MCID.

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Figure E9: Pneumothorax Treatment Algorithm

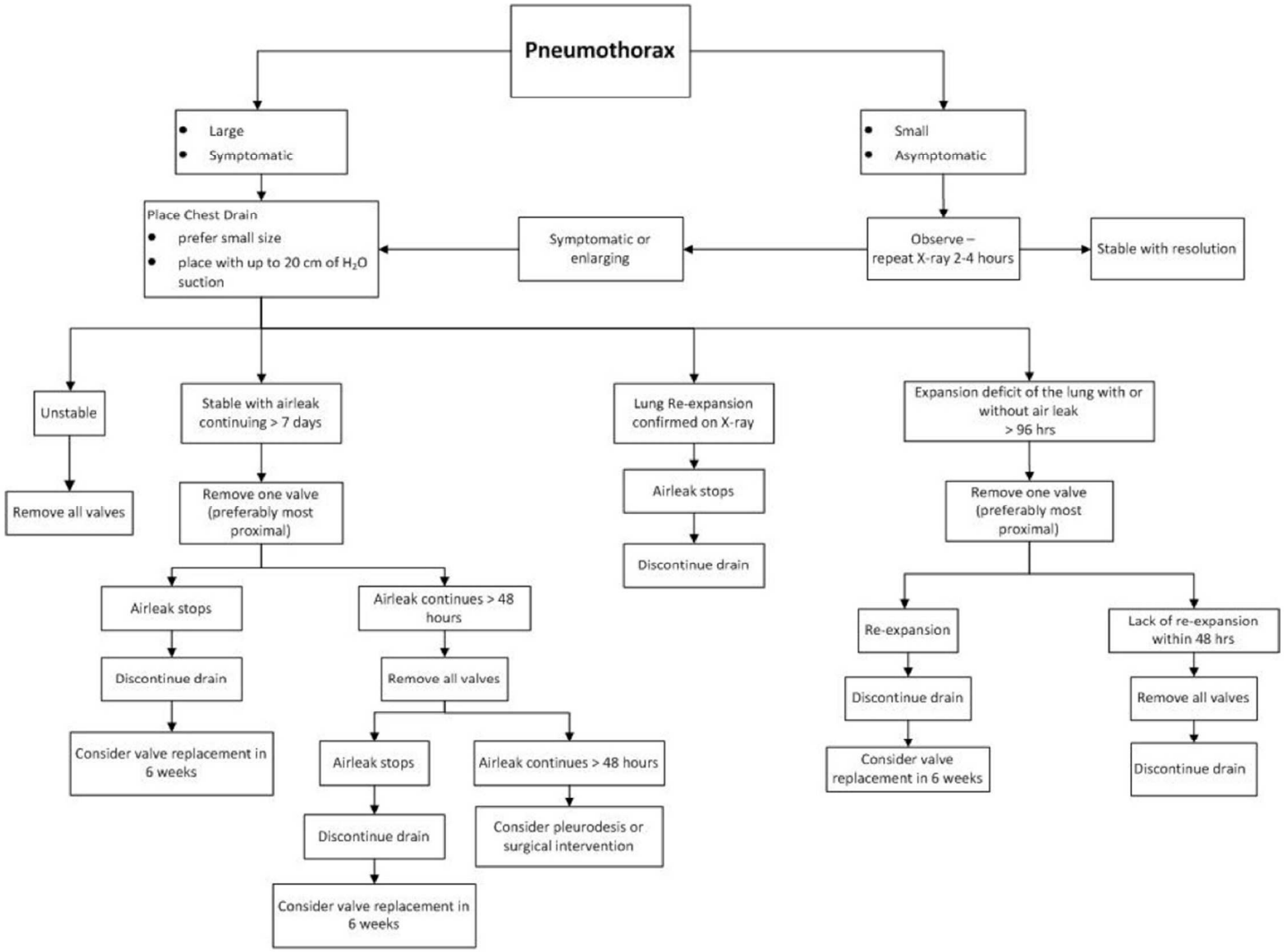

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Table E1: Baseline Absolute Values

Variable	Group	n	Mean	SD	Min	Median	Max	t-test p-value
Emphysema score	EBV	65	69.28	9.30	42.00	70.00	88.00	0.692
	SoC	32	68.42	11.23	41.00	70.00	86.00	
Heterogeneity index	EBV	65	21.77	14.59	-17.00	20.00	64.00	0.252
	SoC	32	25.50	15.79	5.00	22.50	63.00	
FEV1 (L)	EBV	65	0.78	0.24	0.37	0.76	1.40	0.008
	SoC	32	0.94	0.31	0.47	0.87	1.61	
FEV1 (% predicted)	EBV	65	29.75	9.18	15.00	28.00	48.00	0.214
	SoC	32	32.16	8.35	17.00	32.00	49.00	
RV (L)	EBV	64	5.47	1.26	3.10	5.38	8.37	0.764
	SoC	32	5.39	1.16	3.36	5.29	8.56	
RV (% predicted)	EBV	64	249.44	51.76	161.00	238.00	409.00	0.423
	SoC	32	240.97	41.39	166.00	243.50	364.00	
TLC (L)	EBV	64	8.12	1.54	5.30	8.13	12.49	0.200
	SoC	32	8.55	1.56	5.74	8.74	11.12	
TLC (% predicted)	EBV	64	138.97	18.88	102.00	136.50	209.00	0.648
	SoC	32	137.28	12.48	117.00	139.00	163.00	
FEV1/FVC (%)	EBV	65	32.70	8.13	18.90	31.46	56.17	0.508
	SoC	32	31.57	7.32	19.48	31.03	49.12	
RV/TLC (%)	EBV	64	67.20	7.79	50.58	68.09	87.16	0.016
	SoC	32	63.13	7.47	52.08	62.63	78.46	
DLco (mmol/min/kPa)	EBV	59	2.50	1.49	0.33	2.20	8.90	0.370
	SoC	31	2.81	1.63	0.47	2.86	8.07	
DLco (% predicted)	EBV	60	32.32	13.11	8.00	32.50	82.00	0.304
	SoC	31	35.35	13.55	13.00	36.00	74.00	
SGRQ total score	EBV	64	64.34	14.39	32.94	65.08	93.29	0.042
	SoC	32	58.07	13.26	18.46	59.94	81.10	
6MWD (m)	EBV	65	282.46	94.41	150.00	260.00	484.00	0.065
	SoC	32	320.25	91.79	150.00	327.50	470.00	

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Table E1: Baseline Absolute Values								
Variable	**Group**	**n**	**Mean**	**SD**	**Min**	**Median**	**Max**	**t-test p-value**
MRC breathlessness grade	EBV	65	3.00	0.77	1.00	3.00	4.00	0.466
	SoC	32	2.88	0.83	1.00	3.00	4.00	
BODE index	EBV	65	6.14	1.68	3.00	6.00	9.00	0.116
	SoC	31	5.55	1.77	3.00	5.00	9.00	
PaO2 (kPa)	EBV	63	9.22	1.30	6.87	9.00	13.16	0.365
	SoC	32	8.96	1.33	5.73	9.15	11.00	
PaCO2 (kPa)	EBV	63	5.31	0.66	3.76	5.24	7.07	0.213
	SoC	32	5.13	0.61	4.08	5.14	6.44	

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Table E2: Changes from Baseline to 3 Month Follow-up for ITT Population								
Variable	**Group**	**n**	**Mean**	**SD**	**Min**	**Median**	**Max**	**t-test p-value**
Change (%) FEV1 (L)	EBV	65	23.21	28.49	-21.93	19.67	125.00	<.001
	SoC	31	-4.01	12.95	-36.61	-2.67	15.48	
Change FEV1 (L)	EBV	65	0.15	0.20	-0.26	0.13	0.72	<.001
	SoC	31	-0.05	0.14	-0.41	-0.02	0.14	
Change FEV1 (% predicted)	EBV	65	6.22	8.03	-7.00	5.00	33.00	<.001
	SoC	31	-1.61	5.08	-16.00	-1.00	7.00	
Change DLco (mmol/min/kPa)	EBV	58	0.07	1.03	-5.19	0.14	2.33	0.723
	SoC	29	0.00	0.57	-1.49	0.00	1.37	
Change DLco (% predicted)	EBV	59	2.78	8.84	-30.00	3.00	28.00	0.062
	SoC	29	-0.72	6.54	-17.00	0.00	15.00	
Change SGRQ total score	EBV	60	-8.87	15.70	-48.88	-7.45	46.08	0.018
	SoC	30	-1.22	10.44	-21.16	-3.65	28.31	
Change 6MWD (m)	EBV	64	37.22	65.11	-125.00	39.00	197.00	<.001
	SoC	29	-20.86	32.46	-118.00	-15.00	51.00	
Change MRC breathlessness grade	EBV	64	-0.59	1.03	-3.00	0.00	2.00	0.002
	SoC	32	0.03	0.59	-1.00	0.00	1.00	
Change BODE index	EBV	63	-1.14	1.75	-6.00	-1.00	3.00	<.001
	SoC	28	0.39	0.83	-1.00	0.00	2.00	

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Table E3: Changes from Baseline to 6 Month Follow-up for ITT Population

Variable	Group	n	Mean	SD	Min	Median	Max	t-test p-value
Change (%) FEV1 (L)	EBV	64	20.70	29.58	-36.36	15.54	108.86	<.001
	SoC	31	-8.64	13.03	-44.54	-6.67	13.79	
Change FEV1 (L)	EBV	64	0.14	0.24	-0.40	0.11	0.86	<.001
	SoC	31	-0.09	0.14	-0.53	-0.05	0.12	
Change FEV1 (% predicted)	EBV	64	5.45	8.77	-16.00	4.00	29.00	<.001
	SoC	31	-2.87	4.44	-14.00	-2.00	4.00	
Change DLco (mmol/min/kPa)	EBV	58	0.09	1.42	-5.95	0.23	3.15	0.062
	SoC	28	-0.47	0.99	-2.95	-0.15	0.86	
Change DLco (% predicted)	EBV	59	4.02	12.39	-31.00	2.00	65.00	0.004
	SoC	28	-3.60	7.74	-19.00	-2.00	10.00	
Change SGRQ total score	EBV	62	-7.22	15.10	-33.57	-6.80	43.58	0.031
	SoC	32	-0.70	10.36	-20.46	-0.12	25.97	
Change 6MWD (m)	EBV	63	36.17	76.93	-175.00	29.00	230.00	<.001
	SoC	31	-42.48	68.15	-236.00	-30.00	55.00	
Change MRC breathlessness grade	EBV	64	-0.56	1.04	-3.00	0.00	1.00	0.010
	SoC	31	0.00	0.86	-2.00	0.00	2.00	
Change BODE index	EBV	61	-0.97	2.01	-6.00	-1.00	4.00	<.001
	SoC	28	0.79	1.17	-1.00	0.50	3.00	

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Table E4: Changes from Baseline to 3 Month Follow-up for PP Population

Variable	Group	n	Mean	SD	Min	Median	Max	t-test p-value
Change (%) FEV_1 (L)	EBV	51	27.76	29.82	-21.93	23.29	125.00	<.001
	SoC	30	-4.14	13.14	-36.61	-2.90	15.48	
Change FEV_1 (L)	EBV	51	0.18	0.21	-0.26	0.18	0.72	<.001
	SoC	30	-0.05	0.14	-0.41	-0.02	0.14	
Change FEV_1 (% predicted)	EBV	51	7.52	8.49	-7.00	7.00	33.00	<.001
	SoC	30	-1.67	5.16	-16.00	-1.00	7.00	
Change DLco (mmol/min/kPa)	EBV	45	0.24	0.77	-1.81	0.27	2.33	0.155
	SoC	28	0.00	0.58	-1.49	-0.01	1.37	
Change DLco (% predicted)	EBV	45	4.02	8.55	-16.00	4.00	28.00	0.014
	SoC	28	-0.74	6.66	-17.00	0.00	15.00	
Change SGRQ total score	EBV	48	-10.73	16.65	-48.88	-10.35	46.08	0.008
	SoC	28	-1.16	10.80	-21.16	-3.65	28.31	
Change 6MWD (m)	EBV	50	47.80	66.60	-125.00	52.00	197.00	<.001
	SoC	28	-21.61	32.81	-118.00	-15.00	51.00	
Change MRC breathlessness grade	EBV	51	-0.67	1.11	-3.00	0.00	2.00	0.001
	SoC	30	0.07	0.58	-1.00	0.00	1.00	
Change BODE index	EBV	50	-1.38	1.84	-6.00	-1.00	3.00	<.001
	SoC	27	0.41	0.84	-1.00	0.00	2.00	

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Table E5: Changes from Baseline to 6 Month Follow up for PP Population

Variable	Group	n	Mean	SD	Min	Median	Max	t-test p-value
Change (%) FEV_1 (L)	EBV	50*	25.05	31.33	-36.36	21.05	108.86	<.001
	SoC	30	-8.92	13.16	-44.54	-6.90	13.79	
Change FEV_1 (L)	EBV	50	0.17	0.26	-0.40	0.15	0.86	<.001
	SoC	30	-0.09	0.14	-0.53	-0.07	0.12	
Change FEV_1 (% predicted)	EBV	50	6.67	9.43	-16.00	5.00	29.00	<.001
	SoC	30	-2.97	4.48	-14.00	-2.00	4.00	
Change DLco (mmol/min/kPa)	EBV	45	-0.38	0.94	-2.85	0.46	3.15	<.001
	SoC	27	-0.49	1.00	-2.95	-0.20	0.86	
Change DLco (% predicted)	EBV	45	5.78	13.30	-31.00	6.00	65.00	0.001
	SoC	27	-3.73	7.86	-19.00	-2.00	10.00	
Change SGRQ total score	EBV	50	-8.89	16.06	-33.57	-10.11	43.58	0.014
	SoC	30	-0.60	10.69	-20.46	-0.12	25.97	
Change 6MWD (m)	EBV	49	47.71	82.82	-175.00	53.00	230.00	<.001
	SoC	29	-44.31	70.03	-236.00	-30.00	55.00	
Change MRC breathlessness grade	EBV	51	-0.65	1.13	-3.00	-1.00	1.00	0.006
	SoC	29	0.03	0.87	-2.00	0.00	2.00	
Change BODE index	EBV	48	-1.21	2.18	-6.00	-1.00	4.00	<.001
	SoC	27	0.81	1.18	-1.00	1.00	3.00	

*Consort diagram in figure E4 shows 51 EBV patients completed the study. FEV1 was not recorded for 1 subject at 6 months. All other assessments were completed. For the PP population, LOCF was only done for FEV1 where none of the data for a visit was available i.e. there was a missed visit.

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Table E6: Difference between groups for Changes from Baseline to 3 Month Follow up for ITT Population

Variable	Group	Mean	SD	95% CI	t-test p-value
Change (%) FEV1 (L)	Δ EBV-SoC	27.22	24.62	16.55 - 37.89	<.001
Change FEV1 (L)	Δ EBV-SoC	0.20	0.18	0.12 - 0.28	<.001
Change FEV1 (% predicted)	Δ EBV-SoC	7.83	7.22	4.70 - 10.96	<.001
Change DLco (mmol/min/kPa)	Δ EBV-SoC	0.07	0.09	-0.34 - 0.48	0.723
Change DLco (% predicted)	Δ EBV-SoC	3.50	8.16	-0.18 - 7.18	0.062
Change (%) RV (L)	Δ EBV-SoC	-10.59	14.68	-17.04 - -4.13	0.002
Change RV (L)	Δ EBV-SoC	-0.58	0.84	-0.95 - -0.21	0.002
Change RV (% predicted)	Δ EBV-SoC	-28.33	38.85	-45.40 - -11.26	0.001
Change FEV1/FVC (%)	Δ EBV-SoC	2.3	5.8	-0.2 - 4.8	0.074
Change RV/TLC (%)	Δ EBV-SoC	-5.2	7.3	-8.4 - -2.0	0.002
Change SGRQ total score	Δ EBV-SoC	-7.64	14.18	-13.95 - -1.34	0.018
Change 6MWD (m)	Δ EBV-SoC	58.08	57.09	32.70 - 83.46	<.001
Change MRC breathlessness grade	Δ EBV-SoC	-0.63	0.91	-1.02 - -0.23	0.003
Change BODE index	Δ EBV-SoC	-1.54	1.53	-2.23 - -0.85	<.001

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Table E7: Difference between groups for Changes from Baseline to 6 Month Follow up for ITT Population

Variable	Group	Mean	SD	95% CI	t-test p-value
Change (%) FEV1 (L)	Δ EBV-SoC	29.34	25.44	18.28 - 40.39	<.001
Change FEV1 (L)	Δ EBV-SoC	0.23	0.21	0.14 - 0.32	<.001
Change FEV1 (% predicted)	Δ EBV-SoC	8.32	7.65	4.99 - 11.64	<.001
Change DLco (mmol/min/kPa)	Δ EBV-SoC	0.56	1.30	-0.03 - 1.16	0.062
Change DLco (% predicted)	Δ EBV-SoC	7.62	11.12	2.55 - 12.70	0.004
Change (%) RV (L)	Δ EBV-SoC	-13.10	17.55	-20.73 - -5.48	<.001
Change RV (L)	Δ EBV-SoC	-0.67	0.97	-1.09 - -0.25	0.002
Change RV (% predicted)	Δ EBV-SoC	-32.41	44.67	-51.82 - -13.00	0.001
Change FEV1/FVC (%)	Δ EBV-SoC	2.9	5.2	0.7 - 5.2	0.011
Change RV/TLC (%)	Δ EBV-SoC	-6.4	7.7	-9.7 - -3.0	<.001
Change SGRQ total score	Δ EBV-SoC	-6.52	13.69	-12.44 - -0.61	0.031
Change 6MWD (m)	Δ EBV-SoC	78.66	74.18	46.34 - 110.98	<.001
Change MRC breathlessness grade	Δ EBV-SoC	-0.56	0.98	-0.99 - -0.14	0.010
Change BODE index	Δ EBV-SoC	-1.75	1.79	-2.56 - -0.94	<.001

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Table E8: Difference between groups for Changes from Baseline to 3 Month Follow up for PP Population

Variable	Group	Mean	SD	95% CI	t-test p-value
Change (%) FEV1 (L)	Δ EBV-SoC	31.90	25.02	20.44 - 43.36	<.001
Change FEV1 (L)	Δ EBV-SoC	0.23	0.19	0.14 - 0.32	<.001
Change FEV1 (% predicted)	Δ EBV-SoC	9.19	7.44	5.78 - 12.60	<.001
Change DLco (mmol/min/kPa)	Δ EBV-SoC	0.24	0.71	-0.09 - 0.58	0.155
Change DLco (% predicted)	Δ EBV-SoC	4.76	7.88	0.98 - 8.54	0.014
Change (%) RV (L)	Δ EBV-SoC	-12.40	14.96	-19.36 - -5.45	<.001
Change RV (L)	Δ EBV-SoC	-0.67	0.84	-1.06 - -0.28	0.001
Change RV (% predicted)	Δ EBV-SoC	-33.67	39.83	-52.18 - -15.16	<.001
Change FEV1/FVC (%)	Δ EBV-SoC	2.8	6.2	-0.0 - 5.7	0.051
Change RV/TLC (%)	Δ EBV-SoC	-6.0	7.4	-9.5 - -2.5	<.001
Change SGRQ total score	Δ EBV-SoC	-9.57	14.79	-16.57 - -2.56	0.008
Change 6MWD (m)	Δ EBV-SoC	69.41	56.94	42.64 - 96.17	<.001
Change MRC breathlessness grade	Δ EBV-SoC	-0.73	0.95	-1.17 - -0.30	0.001
Change BODE index	Δ EBV-SoC	-1.79	1.57	-2.53 - -1.04	<.001

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Table E9: Difference between groups for Changes from Baseline to 6 Month Follow up for PP Population

Variable	Group	Mean	SD	95% CI	t-test p-value
Change (%) FEV1 (L)	Δ EBV-SoC	33.98	26.09	21.98 - 45.97	<.001
Change FEV1 (L)	Δ EBV-SoC	0.26	0.22	0.16 - 0.36	<.001
Change FEV1 (% predicted)	Δ EBV-SoC	9.64	7.96	5.98 - 13.30	<.001
Change DLco (mmol/min/kPa)	Δ EBV-SoC	0.87	0.96	-0.41 - 1.34	<.001
Change DLco (% predicted)	Δ EBV-SoC	9.51	11.58	3.89 - 15.13	0.001
Change (%) RV (L)	Δ EBV-SoC	-15.25	18.20	-23.62 - -6.89	<.001
Change RV (L)	Δ EBV-SoC	-0.78	0.99	-1.24 - -0.33	<.001
Change RV (% predicted)	Δ EBV-SoC	-38.77	45.73	-59.79 - -17.74	<.001
Change FEV1/FVC (%)	Δ EBV-SoC	3.2	5.5	0.7 - 5.7	0.014
Change RV/TLC (%)	Δ EBV-SoC	-7.6	7.9	-11.2 - -4.0	<.001
Change SGRQ total score	Δ EBV-SoC	-8.29	14.31	-14.87 - -1.71	0.014
Change 6MWD (m)	Δ EBV-SoC	92.02	78.35	55.46 - 128.58	<.001
Change MRC breathlessness grade	Δ EBV-SoC	-0.68	1.04	-1.16 - -0.20	0.006
Change BODE index	Δ EBV-SoC	-2.02	1.89	-2.93 - -1.12	<.001

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Table E10: MCID responders for key outcome measures in the PP population at 6 months

Variable	EBV Group	SoC Group	p-value*
FEV_1 (L): (MCID ≥ +12%)	33/50 (66.0%)	1/30 (3.3%)	< 0.001
RV (ml): (MCID ≤ -430 mL)	34/50 (68.0%)	8/30 (26.7%)	<0.001
SGRQ: (MCID ≤ -4 points)	33/50 (66.0%)	10/30 (33.3%)	0.005
6MWD: (MCID≥ +26 meters)	32/49 (65.3%)	4/29 (13.8%)	<0.001
mMRC: (MCID ≤ -1 point)	26/51 (51.0%)	6/29 (20.7%)	0.008

FEV_1: Forced Expiratory Volume in 1 second; RV: Residual Volume; SGRQ: Sr. George's Respiratory Questionnaire' 6MWD: Six Minute Walk Distance; mMRC: Modified Medical Research Council Dyspnea score

*: Chi-squared test

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Table E11: Respiratory Adverse Events over 6 Months

	Adverse Events					Subjects with Adverse Events				
Event	EBV No. of events	EBV % of events	SoC No. of events	SoC % of events	Fisher p-valve	EBV No. of subjects	EBV % of subjects	SoC No. of subjects	SoC % of subjects	Fisher p-value
Respiratory AEs	148	96.1	26	57.8	<.001	59	90.8	13	40.6	<.001
Bleeding bulla right lung	1	1.5	0	0.0	1.000	1	1.5	0	0.0	1.000
Bronchitis	1	1.5	1	3.1	1.000	1	1.5	1	3.1	1.000
Bronchospasm	2	3.0	1	3.1	1.000	1	1.5	1	3.1	1.000
COPD Exacerbation	39	48.8	13	36.1	0.231	24	36.9	9	28.1	0.496
Chest infection	10	14.5	5	14.3	1.000	6	9.2	2	6.3	1.000
Chest pain	6	9.2	0	0.0	0.173	6	9.2	0	0.0	0.173
Common cold	2	3.1	0	0.0	1.000	2	3.1	0	0.0	1.000
Cough	4	6.2	0	0.0	0.299	4	6.2	0	0.0	0.299
Desaturation	1	1.5	0	0.0	1.000	1	1.5	0	0.0	1.000
Dyspnea	23	32.4	1	3.1	<.001	17	26.2	1	3.1	0.005
EBV removal	2	3.1	0	0.0	1.000	2	3.1	0	0.0	1.000
Emphysema	1	1.5	0	0.0	1.000	1	1.5	0	0.0	1.000
Hemoptysis	4	6.2	0	0.0	0.299	4	6.2	0	0.0	0.299
Hyperventilation	0	0.0	1	3.1	0.330	0	0.0	1	3.1	0.330
Influenza	1	1.5	1	3.1	1.000	1	1.5	1	3.1	1.000
Inhaled foreign body	1	1.5	0	0.0	1.000	1	1.5	0	0.0	1.000
Lower Respiratory Tract Infection	2	3.1	0	0.0	1.000	2	3.1	0	0.0	1.000
Mucus	1	1.5	0	0.0	1.000	1	1.5	0	0.0	1.000
Mucus production	3	4.6	0	0.0	0.549	3	4.6	0	0.0	0.549
Pneumonia	8	12.1	1	3.1	0.264	7	10.8	1	3.1	0.265
Pneumothorax	20	30.3	0	0.0	<.001	19	29.2	0	0.0	<.001
Post-operative pain	1	1.5	0	0.0	1.000	1	1.5	0	0.0	1.000
Pulmonary infection	1	1.5	0	0.0	1.000	1	1.5	0	0.0	1.000
Purulent Sputum	0	0.0	1	3.1	0.330	0	0.0	1	3.1	0.330
Quincke's Oedema of the Lingula	1	1.5	0	0.0	1.000	1	1.5	0	0.0	1.000
Respiratory infection	2	3.1	0	0.0	1.000	2	3.1	0	0.0	1.000
Sinusitis	0	0.0	1	3.1	0.330	0	0.0	1	3.1	0.330
Sore throat	1	1.5	0	0.0	1.000	1	1.5	0	0.0	1.000
Thoracic pain	4	6.2	0	0.0	0.299	4	6.2	0	0.0	0.299

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Table E11: Respiratory Adverse Events over 6 Months										
	Adverse Events					Subjects with Adverse Events				
Event	EBV No. of events	EBV % of events	SoC No. of events	SoC % of events	Fisher p-valve	EBV No. of subjects	EBV % of subjects	SoC No. of subjects	SoC % of subjects	Fisher p-value
Upper Respiratory Tract Infection	4	6.1	0	0.0	0.300	3	4.6	0	0.0	0.549
Valve dislocation	1	1.5	0	0.0	1.000	1	1.5	0	0.0	1.000
Wheezing	1	1.5	0	0.0	1.000	1	1.5	0	0.0	1.000

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Table E12: Non-Respiratory Adverse Events over 6 Months

	Adverse Events					Subjects with Adverse Events				
Event	EBV No. of events	EBV % of events	SoC No. of events	SoC % of events	Fisher p-valve	EBV No. of subjects	EBV % of subjects	SoC No. of subjects	SoC % of subjects	Fisher p-value
Non-Respiratory AEs	43	50.0	12	33.3	0.112	22	33.8	8	25.0	0.485
Abdominal pain	1	1.5	0	0.0	1.000	1	1.5	0	0.0	1.000
Allergic reaction	2	3.0	0	0.0	1.000	1	1.5	0	0.0	1.000
Anxiety	1	1.5	0	0.0	1.000	1	1.5	0	0.0	1.000
Asthenia	0	0.0	1	3.1	0.330	0	0.0	1	3.1	0.330
Back pain	1	1.5	0	0.0	1.000	1	1.5	0	0.0	1.000
Bruises left side arms and legs (traffic accident)	1	1.5	0	0.0	1.000	1	1.5	0	0.0	1.000
Chronic flebothrombosis	1	1.5	0	0.0	1.000	1	1.5	0	0.0	1.000
Cushingoid face	1	1.5	0	0.0	1.000	1	1.5	0	0.0	1.000
Diarrhea	1	1.5	0	0.0	1.000	1	1.5	0	0.0	1.000
Diverticulitis	1	1.5	0	0.0	1.000	1	1.5	0	0.0	1.000
Dizziness	1	1.5	0	0.0	1.000	1	1.5	0	0.0	1.000
Edema	3	4.5	0	0.0	0.549	2	3.1	0	0.0	1.000
Fever	0	0.0	1	3.1	0.330	0	0.0	1	3.1	0.330
Foot fracture	1	1.5	0	0.0	1.000	1	1.5	0	0.0	1.000
Fungal infection	1	1.5	0	0.0	1.000	1	1.5	0	0.0	1.000
Gastric reflux	1	1.5	0	0.0	1.000	1	1.5	0	0.0	1.000
Headache	2	3.1	0	0.0	1.000	2	3.1	0	0.0	1.000
Heart failure	2	3.1	0	0.0	1.000	2	3.1	0	0.0	1.000
Hoarseness	1	1.5	0	0.0	1.000	1	1.5	0	0.0	1.000
Hypercholesterolemia	0	0.0	1	3.1	0.330	0	0.0	1	3.1	0.330
Hypertension	3	4.6	1	3.1	1.000	3	4.6	1	3.1	1.000
Hyperthyroidism	1	1.5	1	3.1	1.000	1	1.5	1	3.1	1.000
Hypotension	1	1.5	0	0.0	1.000	1	1.5	0	0.0	1.000
Mucositis	1	1.5	0	0.0	1.000	1	1.5	0	0.0	1.000
Musculoskeletal event	0	0.0	1	3.1	0.330	0	0.0	1	3.1	0.330
Nausea	2	3.1	0	0.0	1.000	2	3.1	0	0.0	1.000
Radiomucositis	0	0.0	1	3.1	0.330	0	0.0	1	3.1	0.330
Rheumatoid arthritis	1	1.5	0	0.0	1.000	1	1.5	0	0.0	1.000

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Table E12: Non-Respiratory Adverse Events over 6 Months

	Adverse Events					Subjects with Adverse Events				
Event	EBV No. of events	EBV % of events	SoC No. of events	SoC % of events	Fisher p-valve	EBV No. of subjects	EBV % of subjects	SoC No. of subjects	SoC % of subjects	Fisher p-value
Rib fracture	0	0.0	1	3.1	0.330	0	0.0	1	3.1	0.330
Right shoulder pain	0	0.0	1	3.1	0.330	0	0.0	1	3.1	0.330
Skin rash	1	1.5	0	0.0	1.000	1	1.5	0	0.0	1.000
Squamous carcinoma	0	0.0	1	3.1	0.330	0	0.0	1	3.1	0.330
Supraventricular tachycardia	2	3.1	0	0.0	1.000	2	3.1	0	0.0	1.000
Throat pain	1	1.5	0	0.0	1.000	1	1.5	0	0.0	1.000
Tiredness	1	1.5	0	0.0	1.000	1	1.5	0	0.0	1.000
Tooth pain	1	1.5	0	0.0	1.000	1	1.5	0	0.0	1.000
Unspecified infection	3	4.6	0	0.0	0.549	3	4.6	0	0.0	0.549
Urinary tract infection	0	0.0	1	3.1	0.330	0	0.0	1	3.1	0.330
Urosepsis	1	1.5	0	0.0	1.000	1	1.5	0	0.0	1.000
Vertebral fracture	0	0.0	1	3.1	0.330	0	0.0	1	3.1	0.330
Viral infection	1	1.5	0	0.0	1.000	1	1.5	0	0.0	1.000
Wound infection	1	1.5	0	0.0	1.000	1	1.5	0	0.0	1.000

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Table E13: Occurrence of Pneumothorax by Lobe Treated			
Treated lobe	**Number of subjects with pneumothorax**	**Total number of subjects treated per lobe**	**% Subjects with pneumothorax by Lobe Treated**
LUL	11 (12 events)	34	32.4
LLL	6	14	42.9
RUL	2	10	20.0
RUL+RML	0	5	0.0
RLL	0	2	0.0
Total	19 (20 events)	65	

Table E14: EBV Subjects with Pneumothorax and No Pneumothorax: Difference between groups for Changes from Baseline to 3 Month Follow up (ITT)					
Variable	**Group**	**Mean**	**SD**	**95% CI**	**t-test p-value**
Change (%) FEV1 (L)	Δ Pneu-No Pneu	1.17	28.71	-14.48 - 16.81	0.882
Change FEV1 (L)	Δ Pneu-No Pneu	0.02	0.20	-0.09 - 0.13	0.764
Change FEV1 (% predicted)	Δ Pneu-No Pneu	0.27	8.09	-4.14 - 4.69	0.901
Change DLco (mmol/min/kPa)	Δ Pneu-No Pneu	0.02	1.04	-0.58 - 0.62	0.941
Change DLco (% predicted)	Δ Pneu-No Pneu	0.42	8.92	-4.71 - 5.55	0.870
Change SGRQ total score	Δ Pneu-No Pneu	-1.07	15.82	-9.99 - 7.86	0.812
Change 6MWD (m)	Δ Pneu-No Pneu	18.71	65.07	-17.45 - 54.87	0.305
Change MRC breathlessness grade	Δ Pneu-No Pneu	-0.18	1.04	-0.76 - 0.40	0.351
Change BODE index	Δ Pneu-No Pneu	-0.61	1.74	-1.60 - 0.38	0.174

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Table E15: EBV Subjects with Pneumothorax and No Pneumothorax: Difference between groups for Changes from Baseline to 6 Month Follow up (ITT)

Variable	Group	Mean	SD	95% CI	t-test p-value
Change (%) FEV1 (L)	Δ Pneu-No Pneu	4.70	29.74	-11.56 - 20.96	0.566
Change FEV1 (L)	Δ Pneu-No Pneu	0.04	0.24	-0.09 - 0.17	0.567
Change FEV1 (% predicted)	Δ Pneu-No Pneu	1.53	8.82	-3.29 - 6.35	0.529
Change DLco (mmol/min/kPa)	Δ Pneu-No Pneu	0.11	1.43	-0.72 - 0.94	0.787
Change DLco (% predicted)	Δ Pneu-No Pneu	-1.90	12.46	-9.08 - 5.27	0.598
Change SGRQ total score	Δ Pneu-No Pneu	1.69	15.21	-6.82 - 10.20	0.693
Change 6MWD (m)	Δ Pneu-No Pneu	2.99	77.55	-39.58 - 45.56	0.889
Change MRC breathlessness grade	Δ Pneu-No Pneu	-0.22	1.04	-0.80 - 0.36	0.307
Change BODE index	Δ Pneu-No Pneu	-0.20	2.02	-1.34 - 0.93	0.546

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