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Title:

Improving Lung Function in Severe Heterogenous Emphysema with the Spiration® Valve System (EMPROVE): A Multicenter, Open-Label, Randomized, Controlled Trial

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Running Title: RCT of the Spiration® Valve System in Emphysema

Impact: The results of this multicenter, open-label, randomized, controlled trial highlights the effectiveness of the Spiration Valve System which along with the Zephyr valve, adds to the growing body of evidence for the use of one-way valves in the treatment of severe emphysema.

Author Contributions: G. Criner was involved in manuscript writing and as the corresponding author was provided full access to the data and had final responsibility for the decision to submit this original research for publication. All other coauthors were involved in data collection as principal investigators at their respective sites, and as reviewers of the manuscript. A medical writer was employed to rewrite sections that needed to be shortened to comply with the journal word limits and editorial assistance in ensuring that all journal requirements were met.

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At a Glance Commentary: While no medical therapy provides relief from the progressive disability of severe emphysema, improved lung function and survival has been seen with lung volume reduction surgery (LVRS). However, eligibility for LVRS is contingent upon the patient's overall health status and pattern of emphysema and is only offered at a limited number of centers. Thus, there is substantial need for less invasive treatment options for severe emphysema.

The Spiration® Valve System (SVS) consists of a one-way valve that blocks inspired airflow to distal portions of the lung affected by disease. Treatment of severe heterogeneous emphysema with the SVS in medically optimized participants achieved significant improvements in FEV_1, hyperinflation, TLV, dyspnea, and QoL measures compared with optimal medical management alone. SVS offers clinically relevant benefits to severely ill patients with emphysema.

The current study refined objective methods for using quantitative computed tomography as a tool to assess target lobe emphysema characteristics and determine eligibility for bronchoscopic lung volume reduction therapy.

Supplement: This article has an online data supplement, which is accessible from this issue's table of contents online at www.atsjournals.org.

Abstract

Rationale: Less invasive, non-surgical approaches are needed to treat severe emphysema.

Objective: Evaluate the effectiveness and safety of the Spiration® Valve System versus optimal medical management.

Methods: In this multicenter, open-label, randomized, controlled trial, subjects aged ≥40 years with severe, heterogeneous emphysema were randomized 2:1 to Spiration Valve System with medical management (treatment) or medical management alone (control).

Measurements: The primary efficacy outcome was the difference in mean forced expiratory volume in 1 second ($FEV_{1)}$ from baseline to 6 months. Secondary effectiveness outcomes included: difference in FEV_1 responder rates, target lobe volume reduction, hyperinflation, health status, dyspnea, and exercise capacity. The primary safety outcome was the incidence of composite thoracic serious adverse events. All analyses were conducted by determining the 95% Bayesian credible intervals (BCI) for the difference between treatment and control arms.

Main Results: Between October 2013 and May 2017, 172 participants (53.5% male, mean age 67.4) were randomized to treatment (n=113) or control (n=59). Mean FEV_1 showed statistically significant improvements between the treatment and control groups - between-group difference at 6 and 12 months, respectively of 0.101 liters (95% BCI: 0.060, 0.141) and 0.099 liters (95% BCI: 0.048, 0.151). At 6 months, the treatment group had statistically significant improvements in all secondary endpoints except 6 minute walk distance. Composite thoracic serious adverse event incidence through 6

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months was greater in the treatment group (31.0% vs 11.9%), primarily due to a 12.4% incidence of serious pneumothorax.

Conclusions: In patients with severe heterogeneous emphysema, the Spiration Valve System shows significant improvement in multiple efficacy outcomes, with an acceptable safety profile.

Trial Registration: ClinicalTrials.gov, NCT01812447, https://clinicaltrials.gov/ct2/show/NCT01812447.

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Introduction

Chronic obstructive pulmonary disease (COPD) affects an estimated 16 million US residents,[1] and is the fourth leading cause of death in the US.[2] Emphysema alone affects 4.7 million US residents and is associated with progressive physical activity limitations, dyspnea, and reduced quality of life (QoL).[3,4]

Pharmacologic COPD treatments have limited benefit.[5] Inhaled therapies reduce annual decline in forced expiratory volume in 1 second (FEV_1) more than placebo; however, observed declines have not been clinically relevant. Other guideline-recommended treatments include pulmonary rehabilitation (PR) and continuous oxygen therapy,[6] but no medical therapy provides relief from the progressive disability of severe emphysema.[5]

The National Emphysema Treatment Trial showed that lung volume reduction surgery (LVRS) improved survival compared with medical treatment in participants with upper-lobe emphysema and low exercise capacity, and also improved health status, dyspnea, exercise capacity, and lung function.[7] While effective, most qualifying individuals (80%) are ineligible for LVRS, primarily due to the potential morbidity associated with surgery and the pattern of emphysema and severity of lung function.[8,9] Thus, there is a substantial need for less invasive treatment options for severe emphysema.

The Spiration Valve System (SVS, formerly known as the Intrabronchial Valve, or IBV) consists of a one-way valve that blocks inspired airflow using a flexible umbrella design.

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This allows for bronchoscopic placement in selected airway regions, and limits airflow to distal portions of the lung affected by emphysema. The SVS has been evaluated in prior clinical studies using a bi-lateral, partial occlusion treatment methodology,[10,11] which proved ineffective. However, Eberhardt et al[12] along with other subsequent studies[13,14] showed that uni-lobar total occlusion may provide similar physiologic and clinical benefits to LVRS, including reduced hyperinflation, leading to improved lung function and clinical status, in a minimally invasive and potentially reversible manner.[15]

Previous studies using endobronchial valves to treat hyperinflated emphysematous patients have reported that absence of collateral ventilation is pivotal in achieving lobar atelectasis, the overall treatment goal of this therapy.[13,16,17] Collateral ventilation can be assessed using a balloon tipped catheter placed bronchoscopically to measure flow and pressure distally in the targeted lobe.[18] Alternatively, structural integrity of the fissure(s) adjacent to the targeted lobe can be assessed by quantitative high-resolution computed tomography (HRCT), which also acts as a marker for collateral ventilation and aids in patient and lobe selection.[19] The EMPROVE trial represents the largest multicenter study using HRCT analysis of fissure integrity for patient selection and targeted lobar treatment.

The results of the current research have been published in the form of two abstracts presented at the American Thoracic Society[18] and the European Respiratory Society[21] meetings in 2018.

Methods

The EMPROVE study was a prospective, open-label, randomized, controlled, multicenter trial to assess the safety and efficacy of the SVS procedure in participants with severe heterogeneous emphysema.

Participant population

Up to 220 participants were to be randomized from 41 investigational sites (Appendix 2), with the potential for the study to be stopped early for success or futility. Institutional Review Boards at each site approved the study, and all participants provided written informed consent (Appendix 1). Eligible participants were ≥40 years old, met American Thoracic Society/European Respiratory Society Guidelines criteria for management of stable COPD, and were able to perform a 6-minute walk test (6MWT) ≥140m. Disease severity was assessed by HRCT. Participants were required to have ≥40% emphysema destruction in the target lobe (assessed at -920 Hounsfield Units) and a ≥10% disease emphysema severity difference with the ipsilateral lobe. The target and ipsilateral lobes were required to be separated by an intact fissure, estimated visually to be ≥90% complete with no segmental vessels crossing between adjacent lobes (as assessed by the CT corelab; MedQIA, Los Angeles, CA). Eligible participants had severe dyspnea (Modified Medical Research Council scale [mMRC] ≥2); severe obstructive disease FEV_1 ≤45% of predicted, after bronchodilators; and hyperinflation defined as total lung capacity (TLC) ≥100% and residual volume (RV) ≥150% of predicted. Participants

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agreed to attend required follow-up visits and maintain consistent nutrition and exercise habits during the study period (Appendix 3).

All subjects who had not completed a pulmonary rehabilitation (PR) program in the prior 2 years were screened to determine if they should complete a PR program before entering the trial (Appendix 4). Baseline testing included pulmonary function, CT and quality of life assessments (Appendix 5). Randomization occurred within the electronic data capture system at a pre-procedure visit (2:1 randomization to treatment or control group). Patients in both the treatment and control groups received optimal medical management throughout the study; the treatment group additionally received bronchoscopic SVS placement.

Procedure

The SVS valve is designed for placement in selected regions of bronchial airways using a flexible bronchoscope, deployment catheter, and accompanying loader. The valve has a flexible umbrella that blocks inspired airflow to distal portions of lungs affected by disease, while allowing air and mucus to clear proximally from treated airways. Valves are removable using a flexible bronchoscope and forceps, if necessary. The valve comprises a frame made of a super-elastic, biocompatible alloy (Nitinol) and a polyurethane membrane (Figure 1). The membrane is held against the airway mucosa by 6 flexible struts, which expand and contract with airway movement during breathing. The valve is secured in position with 5 anchors and tips that gently penetrate the airway wall to a controlled depth.

An airway sizing system and calibrated balloon was used to determine the appropriate valve width size (5mm, 6mm, 7mm, and 9mm [the 9mm valve was introduced after initial 29 subjects had been randomized in the study]) to treat target lobe airways ranging from 4.75 to 8.75mm. The treatment algorithm called for the complete occlusion of one lobe; this was achieved by using one or more SVS valves to occlude all segments, i.e., lobar, segmental, and/or sub-segmental airways. HRCT imaging and, if necessary, lung perfusion was used to select treatment lobes. Either upper or lower lobes could be targeted for treatment; the right middle lobe was not treated in this study. When two lobes both met criteria for emphysema and heterogeneity, the lobe with the lowest perfusion was treated. To limit subsequent adverse events, physicians were asked to follow a checklist to limit procedure duration. Treated patients remained in the hospital for at least 1 day. The total duration of post procedural hospitalization was at the discretion of the local investigator and within the norms of clinical practice at the local center.

Outcome measures

Follow-up and outcome assessments were scheduled for 2 weeks, 1, 3, and 6 months, and annually through 2 or 5 years for the control and treatment groups, respectively. The primary effectiveness endpoint was mean change in FEV_1 post-bronchodilator from baseline to 6 months between treatment and control groups; 12-month results are also reported. Secondary effectiveness endpoints were: FEV_1 difference between responders, defined as a ≥15% improvement; target lobe volume (TLV) reduction, only

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assessed in the SVS treatment group, measured by quantitative computed tomography (QCT); hyperinflation, measured by the ratio of residual volume to total lung capacity (RV/TLC); health status and QoL, measured by St. George's Respiratory Questionnaire (SGRQ); dyspnea, measured by mMRC; and exercise capacity, measured by 6MWT. HRCT, plethysmography, and exercise assessments only occurred between baseline and 6 months; therefore, TLV, hyperinflation, and 6MWT data were not assessed at 12 months.

The primary safety endpoint was the incidence of pre-specified composite thoracic serious adverse events (SAEs, Appendix 6) through 6 months; secondary safety endpoints were the rate of each category of thoracic SAE and thoracic SAE rate per patient-year.

Statistical analysis

Analyses of SVS effectiveness and durability were conducted at 6 and 12 months, respectively. Utilizing a Bayesian adaptive design,[22,23] two interim analyses of sample size adequacy were conducted when 100 and 160 participants were enrolled, at which the predictive probability of eventual success was calculated. Based on these, enrollment could be stopped early for futility or probable eventual success, while follow-up continued until the last subject reached 6 months. The maximum possible sample size was 220 (Appendix 7). Subjects with missing data were included in the analysis via Bayesian multiple imputation. The primary effectiveness objective (superiority of SVS based on FEV_1 change from baseline to 6 months) was considered statistically

significant if the posterior probability (PP) exceeded 0.982, a pre-specified threshold value chosen to control type I error rate (under simulation) ≤ 0.025.

Primary and secondary safety analyses were conducted by determining the 95% Bayesian credible intervals (BCI) for the difference and ratio of composite SAE probabilities, as well as each individual thoracic SAE category, in the treatment and control groups (Appendix 8). Secondary effectiveness endpoints were computed as the difference between treatment and control groups at 6 and 12 months compared to baseline. Statistical analysis was conducted in the R statistical language (version 3.4.0; R Foundation for Statistical Computing, Vienna, Austria).

Results

The trial was conducted from October 8, 2013 to May 3, 2017 at 41 clinical sites (Appendix 1) with 172 participants ultimately randomized to treatment (n=113, 65.7%) and control (n=59, 34.3%) groups at 31 clinical sites (Figure 2). Enrollment was stopped when the predictive probability of success with the existing cohort was >0.999. By 6 months in the treatment group, 6 subjects had died and 107 had an evaluable visit. By 12 months, 96 subjects had evaluable visits. In the control group (n=59), 8 participants withdrew and 1 died, leaving 50 evaluable subjects at 6 months. By 12 months, 43 subjects had an evaluable visit.

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Treatment and control group participants had similar baseline characteristics. Demographic data, use of pulmonary medications and supplemental oxygen, medical history, lung function, arterial blood gas results, exercise tolerance, SGRQ, mMRC dyspnea scores, and HRCT characteristics were all comparable (Table 1; Appendix 9: Table S2). The only demographic difference was sex; the control group had approximately 15% more males.

Mean procedure duration, defined as the time between bronchoscope insertion and removal, was 24.3 minutes (range, 9 to 73 minutes). The mean and median duration of hospitalization was 3.83 days and 1 day, respectively (Appendix 10: Table S3). Target lobes, defined by pre-procedural imaging, were primarily on the left side (82.3%) with 58.4% being the left upper lobe (Appendix 10: Table S4). QCT was used for target lobe selection in 97.4% of cases. In the remaining 3 cases where two potential target lobes were identified by QCT, perfusion scan results were used, and final determination of the target lobe was by the CT corelab. A total of 476 valves were placed in 113 treatment group participants (mean number per participant, 3.83±1.48) (Appendix 10: Table S5).

Efficacy outcomes

The SVS treatment group had significant FEV_1 improvements (Figure 3). At 6 months, the treatment group improved by 0.099 liters on average from baseline (95% BCI: 0.069, 0.128), whereas the control group changed by -0.002 liters (95% BCI: -0.030, 0.026), for a between-group difference of 0.101 liters (95% BCI: 0.060, 0.141). At 12 months, the treatment group improved by 0.067 liters on average (95% BCI: 0.031,

0.103), while the control group decreased by -0.032 liters (95% BCI: -0.069, 0.005), for a between-group difference of 0.099 liters (95% BCI: 0.048, 0.151). (Appendix 11: Table S6).

Secondary effectiveness outcomes were also improved in the SVS treated group. At 6 and 12 months, the between-group difference in FEV_1 responder rates (improvement ≥15%) was estimated at 25.7% (95% BCI: 12.5%, 37.5%; 0.9998 PP) and 30.4% (95% BCI: 16.8%, 42.5%; 0.9999 PP), respectively, in favor of SVS (Table 3; Appendix 11: Table S7-S9).

At 6 months, treatment group participants had a significant reduction in TLV as measured by QCT (-0.974 L [95% BCI: -1.119, -0.829]), with a 1.0000 PP for mean change <0 (Table 2; Appendix 11: Table S10). Using a 350 ml reduction in TLV as a threshold, 75% of the SVS treated group achieved a clinically meaningful improvement, with 40% of the entire treatment cohort achieving complete atelectasis of the target lobe.

The SVS treatment group also had significantly greater mean RV/TLC improvement. The between-group difference at 6 months was -0.039 (95% BCI: -0.058, -0.020; 1.0000 PP) in favor of SVS (Table 2; Appendix 11: Table S11a).

There was significantly greater mean improvement in SGRQ (health status) for SVS treatment vs control groups at 6 months, with a between-group difference of -13.0

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points (95% BCI: -17.4, -8.5; 1.0000 PP). Results at 12 months were -9.5 points (95% BCI: -14.4, -4.7; 1.0000 PP) (Table 2; Appendix 11: Table S12).

Dyspnea, as measured by mMRC, was significantly improved with SVS treatment, with a between-group difference of -0.6 (95% BCI: -0.9, -0.3; 1.0000 PP) at 6 months and -0.9 (95% BCI: -1.2, -0.6; 1.0000 PP) at 12 months (Table 2; Appendix 11: Table S13).

While not a secondary endpoint of the study, the COPD assessment test (CAT) scores were improved by 4.3 points at 6-months and 5.3 points at 12-months in the treatment group compared to the control group and were statistically significant at both time points (Appendix 11: Table S16).

Change in exercise capacity, measured by 6MWT was not statistically significant at 6 months, with a between-group difference of 6.9 meters (95% BCI: -14.2, 28.2; 0.7438 PP) (Table 2; Appendix 11: Table S14).

Table 3 provides responder rates for all secondary efficacy outcomes.

Safety outcomes

Short-term (0-6 months)

At 6 months, the incidence of composite thoracic SAEs was 31.0% in the treatment group and 11.9% in the control group for a statistically significant between-groups difference of 19.1% (95% BCI: 5.9 – 29.7). The higher treatment group incidence was

primarily due to a 12.4% (95% BCI: 4.6 – 18.6) increased incidence of serious pneumothorax (Appendix 12: Table S17-S18), which was statistically significant. Over this time, 32 monitored events of pneumothorax were reported, with 18 protocol-defined (Appendix 6) serious incidents in 16 (14.2%) of 113 treatment group participants, and 14 non-serious pneumothorax events in 13 (11.5%) treatment group participants. The majority (66%) of these pneumothorax events occurred within 3 days of the procedure, within the average hospital stay duration (Appendix 12: Figure S1). Of the 16 subjects with serious pneumothorax events, 11 (69%) had ≥1 valve removed per the defined pneumothorax management protocol (Appendix 5). Five (5) of these subjects had valves re-implanted upon cessation of the pneumothorax and this subset showed a TLV reduction of -834.0 ml compared to the only -19.2 ml in those that did not have valves replaced. There were no other statistically significant between-group differences in thoracic SAEs by category.

There were six (5.3%) deaths in the treatment group and one (1.7%) death in the control group (Appendix 12: Table S19). This difference between groups was not statistically significantly. Only one death (occurring at Day 95 post-SVS procedure) was adjudicated by the study clinical events committee as possibly related to the device due to pneumothorax in the contralateral untreated lobe, which did not resolve before death (Table S20).

There were no statistically significant between-group differences for non-thoracic SAEs, with 11.5% and 3.4% non-thoracic SAEs in the treatment and control groups,

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respectively (Appendix 12: Table S19).

Long-term (6-12 months)

Between 6 and 12 months, the incidence of composite thoracic SAEs was 21.4% in the treatment group vs 10.6% in the control group (Appendix 12: Table S17), with a between-groups difference of 10.7% (95% BCI: -3.0 – 21.2), which was not statistically significant. There were no statistically significant between-group differences in thoracic SAEs by category. There were 3 non-serious events of pneumothorax in 2 of 113 (1.7%) treatment subjects and no additional serious pneumothorax events (Appendix 12: Figure S1). Three SAEs were adjudicated as device-related (1 case of infection, 1 of pneumonia, and 1 death). There were 4 (3.9%) deaths in the treatment group (one of which was device related) and 3 (6.4%) in the control group (Appendix 12: Table S17 and Table S19, Death details in Table S21). There were no unanticipated device-related SAEs or migration, erosion, or expectoration reported through 12-month follow-up.

There were no statistically significant between-group differences for non-thoracic SAEs, with rates of 12.6% and 12.8% in the treatment and control groups, respectively (Appendix 12: Table S19).

Discussion

The EMPROVE trial evaluated the safety and efficacy of the Spiration® Valve System compared to optimal medical management in patients with severe heterogeneous emphysema. While prior SVS trials using bilateral, partial occlusion of the target lobe

did not show consistent improvement [10,11], the results of the EMPROVE trial, with single-lobe, total lobar occlusion, shows marked benefits. At 6 months, the primary outcome and a majority of secondary outcome measures were improved in the SVS-treatment group compared to the control group. There was a significant between-group increase in mean FEV_1 from baseline (0.101 liters) and a 25.7% between-group difference in FEV_1 responder rates (defined as improvement of ≥15%). These results persisted at 12 months. The SVS-treatment group also saw significant reductions in TLV, hyperinflation, and dyspnea. Improved health status and QoL was observed as an 8.1-point mean reduction in the SGRQ, which exceeds the 4-point minimum score change defined as clinically relevant.[24] These efficacy results are very comparable to other randomized clinical trials using one-way valves in a unilateral lobar treatment paradigm.[13,14,16,25]

Although the SVS-treatment group performed better on the 6MWT than the control group (between-group difference: 6.9 meters), this difference was not statistically significant. In contrast, patients who underwent endobronchial valve treatment in the recent LIBERATE trial performed significantly better on 6MWT than control. This improvement is not surprising, as LIBERATE patients were required to maintain a supervised PR program throughout study follow-up,[25] and PR has been shown to improve exercise capacity in patients with COPD.[26] The EMPROVE study was designed with the understanding that only ~40% of COPD patients actually adhere to a PR program due to problems with access and prohibitive cost.[27] As such, EMPROVE subjects were required to have been in a PR program in the 2 years prior to study enrollment (Appendix 4), but were not mandated to maintain a supervised PR program

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throughout the study follow-up with only 34.5% and 32.7% of EMPROVE treatment and control subjects, respectively, maintaining a PR regimen through the 12-month follow-up. Thus, the difference between the two trials highlights the importance of additional exercise training by way of pulmonary rehabilitation in translating improved lung function into enhanced exercise performance.

Mean procedure time in EMPROVE (24 minutes) was also shorter than that observed in the LIBERATE trial (34 minutes).[25] This is relevant because shorter procedure times have been associated with fewer procedure-related complications.[11] In the EMPROVE study, post-SVS treatment risks were generally minor and tended to diminish over time. The primary safety outcome, incidence of composite thoracic SAE, was greater in the treatment than control group (31.0% and 11.9%, respectively). However, pneumothorax was the only individual SAE with significantly higher treatment group incidence, similar to comparable studies.[13,25,] Early-onset pneumothorax in the treatment group likely resulted from lung conformation changes due to acute reduction in lung volume by valve therapy, triggering rapid ipsilateral non-targeted lobe expansion, a recognized indicator of successful target lobe occlusion.[28] There was no statistically significant difference in mortality between the study groups at any time point. The 5.3% mortality rate in the treatment group is similar to the 3.1% - 5.0% documented in other randomized valve trials,[11,25,29] and lower than the 7.9% - 12% documented in randomized LVRS trials.[7] There were no unanticipated device-related SAEs.

The results of the EMPROVE trial also demonstrate that using HRCT analysis for fissure integrity ≥ 90% is a useful method to select patients for lack of collateral ventilation that are most likely to achieve targeted lobe atelectasis and improved clinical outcomes. The procedural time for SVS performance was less than other trials using physiological assessment for collateral ventilation and avoids added procedural costs.[32,33] Moreover, in a broader clinical context, HRCT quantitative assessment of fissure integrity may be easier to implement.

Strengths and Limitations

Strengths of the EMPROVE trial include its use of an adaptive sample size, thus shortening overall enrollment time, and planned long-term follow-up: 5 and 2 years for the treatment and control groups, respectively. A key study limitation was the lack of TLV and hyperinflation assessments at 12 months, which would have provided mechanistic data to support improvements in functional and QoL parameters. Additionally, the EMPROVE study, and other recent multicenter, randomized controlled trials, did not blind either subjects or assessors.[16,25,34] While this may introduce bias to the QoL assessments and the 6MWT, it is unlikely that measures such as lung function, TLV, and hyperinflation would be affected by this approach.

Conclusion

Treatment of severe heterogeneous emphysema with the SVS in medically optimized participants selected for fissure integrity ≥ 90% by quantitative HRCT achieved significant improvements in FEV_1, hyperinflation, TLV, dyspnea, and QoL measures

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compared with optimal medical management alone. The SVS offers clinically relevant benefits for severely ill patients with emphysema and while there are risks with the therapy they are primarily manageable and tend to diminish over time.

The results of the EMPROVE Trial and other randomized trials of valve therapy have led to the inclusion of endobronchial valve therapy as an important component of the clinical therapy recommendations for the underserved patient population with severe emphysema.[35,36]

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Additional contributions: Safety oversight of the Study was provided by a Data and Safety Monitoring Board comprising: John Beamis, MD (Chair), Greg Campbell, PhD (Statistician), Frank Detterbeck, MD, Barry Make, MD and Jonathon Truwit, MD. The Clinical Events Committee (CEC) adjudicated adverse events and comprised: Matthew Brenner, MD (Chair), Richard Helmers, MD, Eric Vallières, MD, Roger Yusen, MD. The study Medical Monitors were Robert Kruklitis, MD and Daniel Nader, MD.

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Figure Legends

Figure 1: Spiration Valve. Key components of the Spiration Valve.

Figure 2: Study Subject Disposition Flow Chart

Figure 3: Change in FEV_1 at 6 and 12 Months

Mean ± 95% BCI

BCI=Bayesian credible interval; FEV_1= Forced expiratory volume in 1 second; PP=Posterior Probability; SVS=Spiration Valve System.

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Tables

Table 1: Subject Demographics and Baseline Characteristics

	Treatment Group (N = 113)		Control Group (N = 59)		Difference (T – C)
	N	Mean ± SD or N (%)	N	Mean ± SD or N (%)	95% BCI
Sex (Male)	113	54 (47.8%)	59	38 (64.4%)	(-30.9%, -0.8%)
Age (Years)	113	66.7 ± 6.6	59	68.1 ± 6.4	(-3.4, 0.7)
BMI (kg/m^2)	113	25.3 ± 4.3	59	24.6 ± 5.2	(-0.8, 2.3)
FEV_1 (L)	113	0.825 ± 0.264	59	0.792 ± 0.260	(-0.051, 0.116)
FEV_1 (% Predicted, L)	113	30.8 ± 8.1	59	28.5 ± 8.5	(-0.4, 5.0)
FVC (L)	113	2.492 ± 0.754	59	2.633 ± 0.757	(-0.384, 0.101)
FVC (% Predicted, L)	113	70.2 ± 16.5	59	70.5 ± 16.7	(-5.6, 5.0)
TLC (L)	113	7.215 ± 1.530	59	7.649 ± 1.431	(-0.904, 0.035)
TLC (%Predicted, L)	113	126.5 ± 14.5	59	128.2 ± 17.0	(-6.9, 3.5)
RV (L)	113	4.573 ± 1.253	59	4.848 ± 1.199	(-0.665, 0.115)
RV (%Predicted, L)	113	207.5 ± 45.0	59	213.4 ± 49.3	(-21.3, 9.4)
RV/TLC Ratio	113	0.632 ± 0.080	59	0.632 ± 0.086	(-0.028, 0.026)
Prescribed O_2 - Proportion - (L/min)	113	51 (45.1%) 1.18 ± 1.43	59	27 (45.8%) 1.16 ± 1.47	(-15.7, 14.9) (-0.45, 0.49)
PO_2 (mmHg)	112	67.9 ± 10.2	59	68.0 ± 11.6	(-3.6, 3.5)
PCO_2 (mmHg)	112	40.2 ± 5.7	59	40.9 ± 6.0	(-2.7, 1.1)
Pulmonary Rehabilitation - Prior to enrollment - During follow-up period	113	 113 (100%) 39 (34.5%)	59	 59 (100%) 18 (30.5%)	 (-11.8, 13.4)
6MWT (meters)	113	303.5 ± 84.6	59	306.9 ± 104.2	(-34.8, 28.0)
Dyspnea (mMRC)	113	2.7 ± 0.7	59	2.7 ± 0.6	(-0.2, 0.2)
COPD Assessment Test	113	21.8 ± 6.8	59	20.0 ± 6.3	(-0.3, 3.9)
SGRQ Total	113	57.2 ± 14.8	59	54.6 ± 13.6	(-1.9, 7.1)
Target Lobe Volume (L)	113	1.843 ± 0.602	59	1.820 ± 0.456	(-0.140, 0.187)
Target Lobe	113		59		
Left Lower		27 (23.9%)		9 (15.3%)	(-4.2%, 19.5%)
Left Upper		66 (58.4%)		37 (62.7%)	(-17.8%, 12.0%)
Right Lower		7 (6.2%)		7 (11.9%)	(-15.9%, 2.8%)
Right Upper		13 (11.5%)		6 (10.2%)	(-9.4%, 10.1%)
Emphysema Severity (%)	113	63.6 ± 10.1	59	61.6 ± 11.6	(-1.6, 5.5)
Emphysema Heterogeneity (%)	113	25.3 ± 12.0	59	23.3 ± 11.6	(-1.8, 5.8)

* Heterogeneity calculated as the difference in emphysema severity between the target and ipsilateral lobe; 6MWT = 6-minute walk test; BCI = Bayesian credible interval; BMI = body mass index; C = control; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; mMRC = Modified Medical Research Council; O_2 = oxygen; PCO_2 = partial pressure of carbon dioxide; PO_2 = partial pressure of oxygen; RV = residual volume; SD = standard deviation; SGRQ = St. George's Respiratory Questionnaire; T = treatment; TLC = total lung capacity.

Table 2: Secondary Effectiveness Outcomes

Outcome Measure described as change from baseline		Treatment Group Mean ± SD (N)	Control Group Mean ± SD (N)	Difference between groups (95% BCI)	Posterior probability of superiority
TLV	**6 months**	-0.974 ± 0.74 (102)	NA	-0.974 (-1.12, -0.83)*	1.0000
RV	**6 months**	-0.402 ± 0.85 (105)	-0.042 ± 0.58 (50)	-0.361 (-0.59, -0.13)	0.9990
RV/TLC	**6 months**	-0.035 ± 0.08 (105)	0.005 ± 0.04 (50)	-0.039 (-0.06, -0.02)	1.0000
SGRQ	**6 months**	-8.1 ± 17.1 (105)	4.8 ± 10.6 (50)	-13.0 (-17.4, -8.5)	1.0000
	12 months	-5.8 ± 16.8 (95)	3.7 ± 10.9 (41)	-9.5 (-14.4, -4.7)	1.0000
mMRC	**6 months**	-0.6 ± 1.0 (107)	-0.0 ± 0.6 (50)	-0.6 (-0.9, -0.3)	1.0000
	12 months	-0.6 ± 1.1 (94)	0.2 ± 0.6 (41)	-0.9 (-1.2, -0.6)	1.0000
6MWT	**6 months**	-4.4 ± 76.7 (102)	-11.3 ± 51.4 (48)	6.9 (-14.2, 28.2)	0.7438

* Compared to Baseline; 6MWT = 6-minute walk test; BCI = Bayesian credible interval; FEV_1 = forced expiratory volume in 1 second (L); mMRC = modified Medical Research Council (points); RV = residual volume (L); SD=standard deviation; SGRQ = St. George's Respiratory Questionnaire (points); TLC = total lung capacity; TLV = target lobe volume (L).
Pre-specified hierarchy of testing: TLV, Hyperinflation (RV/TLC), SGRQ, Dyspnea (mMRC), 6MWT, all at 6 months.

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Table 3: Responder Rates for all Effectiveness Outcomes

Outcome Measure Responder Rates	Treatment Group n/N (%)	Control Group n/N (%)
FEV_1 (≥15% improvement)		
6 months	39/106 (36.8%)	5/50 (10.0%)
12 months	32/86 (37.2%)	2/39 (5.1%)
TLV (≥ 350ml reduction)		
6 months	76/102 (74.5%)	NA
RV (≥ 310ml reduction)		
6 months	53/105 (50.5%)	16/50 (32.0%)
SGRQ (≥ 4 point reduction)		
6 months	57/105 (54.3%)	9/50 (18.0%)
12 months	48/95 (50.5%)	9/41 (22.0%)
mMRC (≥ 1 point reduction)		
6 months	57/107 (53.3%)	9/50 (18.0%)
12 months	46/94 (48.9%)	3/41 (7.3%)
6MWT (≥ 25m improvement)		
6 months	33/102 (32.4%)	11/48 (22.9%)

6MWT = 6-minute walk test; FEV_1 = forced expiratory volume in 1 second; RV = residual volume; SGRQ = St. George's Respiratory Questionnaire;

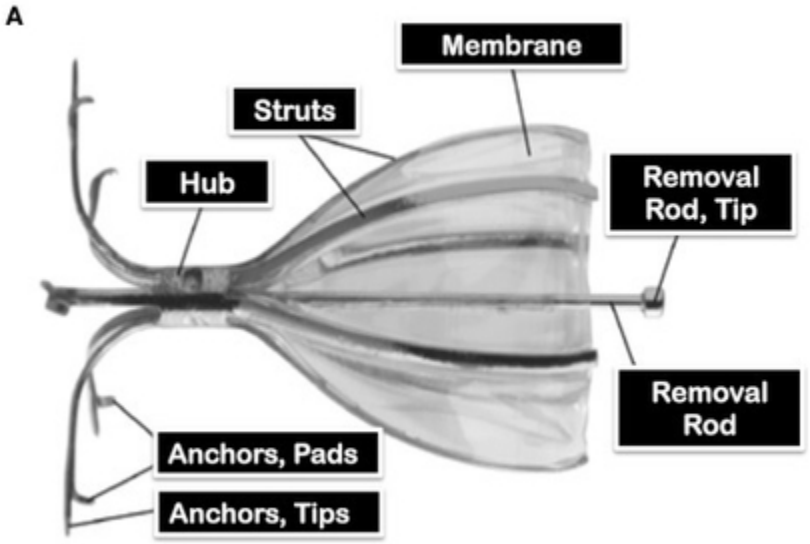

Figure 1: Spiration Valve. Key components of the Spiration Valve.

36x24mm (300 x 300 DPI)

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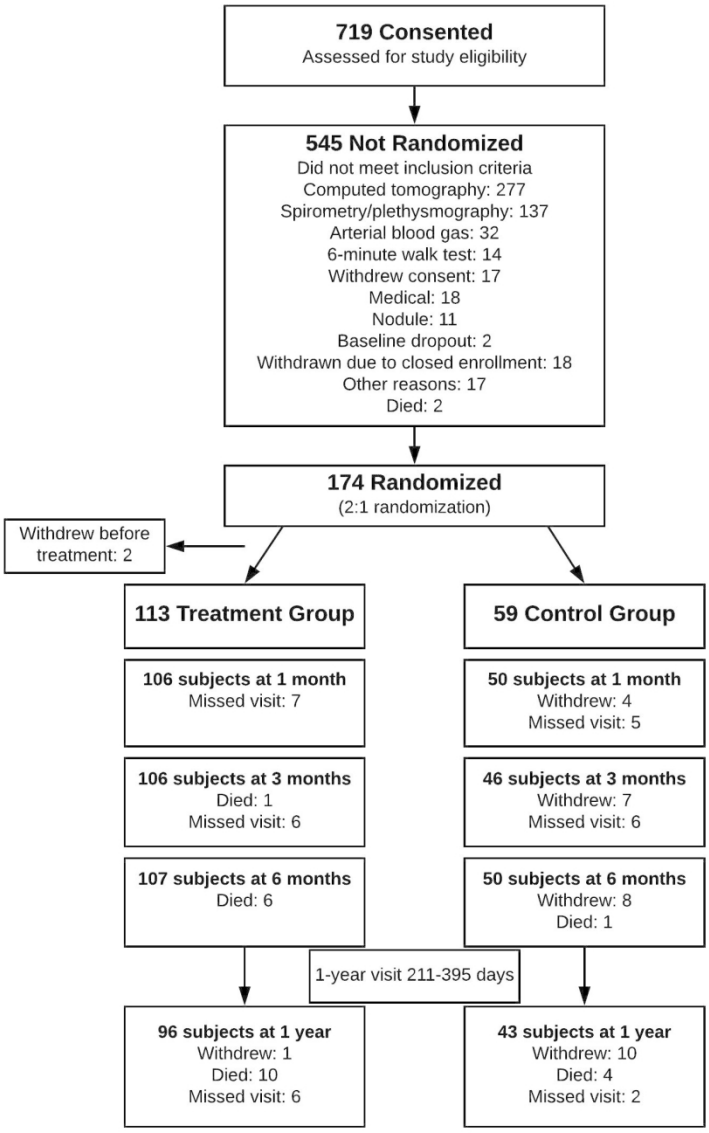

Figure 2: Study Subject Disposition Flow Chart

123x190mm (300 x 300 DPI)

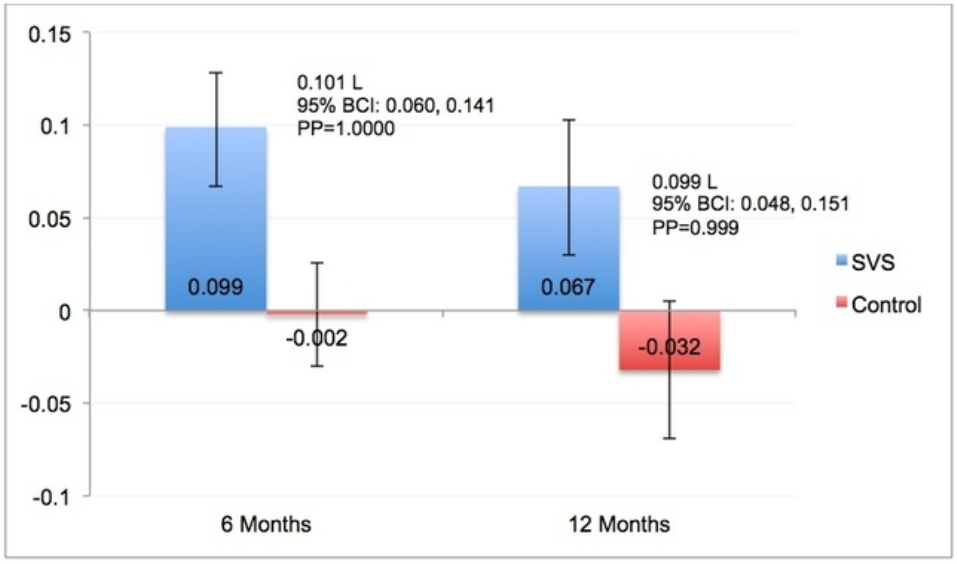

Figure 3: Change in FEV1 at 6 and 12 Months
Mean ± 95% BCI
BCI=Bayesian credible interval; FEV1= Forced expiratory volume in 1 second; PP=Posterior Probability; SVS=Spiration Valve System.

56x32mm (300 x 300 DPI)

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Online Data Supplement

Title: Improving Lung Function in Severe Heterogenous Emphysema with the Spiration® Valve System (EMPROVE): A Multicenter, Open-Label, Randomized, Controlled Trial

Authors: Gerard J. Criner, MD; Antoine Delage, MD; Kirk Voelker, MD; D. Kyle Hogarth, MD; Adnan Majid, MD; Michael Zgoda, MD; Donald R. Lazarus, MD; Roberto Casal, MD; Sadia B. Benzaquen, MD; Robert C. Holladay, MD; Adam Wellikoff, MD; Karel Calero, MD; Mark J. Rumbak, MD; Paul R. Branca, MD; Muhanned Abu-Hijleh, MD; Jorge M. Mallea, MD; Ravi Kalhan, MD; Ashutosh Sachdeva, MD; C. Matthew Kinsey, MD; Carla R. Lamb, MD; Michael F. Reed, MD; Wissam B. Abouzgheib, MD; Phillip V. Kaplan, DO; Gregory X. Marrujo, MD; David W. Johnstone, MD; Mario G. Gasparri, MD; Arturo A. Meade, MD; Christopher A. Hergott, MD; Chakravarthy Reddy, MD; Richard A. Mularski, MD; Amy Hajari Case, MD; Samir S. Makani, MD; Ray W. Shepherd, MD, Benson Chen, MD; Gregory E. Holt, MD; Simon Martel; for the EMPROVE Study Group.

Trial Registration: www.clinicaltrials.gov Identifier NCT01812447.

EMPROVE ONLINE DATA SUPPLEMENT APPENDICES

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Appendix 1. **Informed Consent and Medical Management Evaluation**

Subjects were required to sign the informed consent prior to screen testing, the run-in period, baseline testing, and enrollment. This study and the informed consent form and all appropriate amendments were reviewed by a qualified Institutional Review Board (IRB). A list of all IRBs and their initial approval date is provided below:

1. University of Cincinnati Hospital (06/05/13)
2. University of Texas Southwestern Medical Center (06/12/13)
3. University of Utah Health Sciences (07/18/13)
4. Kaiser Permanente Riverside Medical Center (06/18/13)
5. Sarasota Memorial Hospital (07/11/13)
6. University of Chicago Medical Center (07/30/13)
7. University of Tennessee Medical Center (06/18/13)
8. Virginia Commonwealth University (08/01/13)
9. Beth Israel Deaconess Medical Center (8/20/13)
10. Carolinas Medical Center (8/21/13)
11. Florida Hospital (07/02/13)
12. University of Maryland Hospital (09/30/13)
13. Medical College of Wisconsin (09/25/13)
14. University of Pennsylvania (11/15/13)
15. Piedmont Hospital (11/05/13)
16. Michael E. DeBakey VA Medical Center (09/04/13)
17. University of California Medical Center at Los Angeles (07/02/13)
18. University of Washington Medical Center (12/16/13)
19. Lahey Hospital & Medical Center (09/11/13)
20. Penn State Milton S. Hershey Medical Center (10/07/13)
21. Mayo Clinic, Jacksonville (09/12/13)
22. Kaiser Permanente Northwest (01/15/14)

23. University of California San Diego Medical Center (10/24/13)
24. Louisiana State University Hospital (03/10/14)
25. The Cooper Health System (02/12/14)
26. Sparks Regional Medical Center (02/14/14)
27. University of Vermont Medical Center (07/01/14)
28. Tampa General Hospital (05/12/14)
29. Northwestern Memorial Hospital (10/23/14)
30. University of Minnesota Medical Center (09/01/14)
31. Detroit Clinical Research Center (10/28/15)
32. Laval Hospital (09/15/15)
33. Vancouver General Hospital (UBC) (12/09/15)
34. Weill Cornell Medicine (Cornell New York Presbyterian Hospital) (08/08/16)
35. California Pacific Medical Center (06/05/15)
36. University of Calgary (10/01/15)
37. The Ottawa Hospital (09/18/15)
38. Vanderbilt University Medical Center (11/09/15)
39. Miami VA Healthcare System (12/11/15)
40. Temple University Hospital (07/14/16)
41. University of Pittsburgh Medical Center (12/29/16)

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Appendix 2. Clinical Sites and Study Investigators

Table S1. Study Investigators and Enrollment by Clinical Site

Pivotal Clinical Site	Site ID	Subjects Randomized	Principal Investigator
University of Cincinnati Hospital	01	7	Sadia Benzaquen
University of Texas Southwestern Medical Center at Dallas	02	6	Muhanned Abu-Hijleh
University of Utah Health Sciences	03	3	Chakravarthy Reddy
Kaiser Permanente Riverside Medical Center	04	3	Gregory Marrujo
Sarasota Memorial Hospital	05	14	Kirk Voelker
University of Chicago	06	9	Kyle Hogarth
University of Tennessee Medical Center	07	6	Paul Branca
Virginia Commonwealth University	08	2	Ray Shepherd
Beth Israel Deaconess Medical Center	09	7	Adnan Majid
Carolinas Medical Center	10	7	Michael Zgoda
Florida Hospital Orlando*	11	0	Jorge Guerrero
University of Maryland	12	5	Ashutosh Sachdeva
Medical College of Wisconsin	13	3	David Johnstone Mario Gaspari
University of Pennsylvania*	14	0	Andrew Haas
Piedmont Hospital	15	2	Amy Case
Michael DeBakey VA Medical Center	16	7	Donald Lazarus Roberto Casal
University of California Medical Center at Los Angeles*	17	0	Christopher Cooper
University of Washington Medical Center*	18	0	Douglas Wood
Lahey Hospital & Medical Center	19	4	Carla Lamb
Penn State Milton S. Hershey Medical Center	20	4	Michael Reed
Mayo Clinic, Jacksonville	21	5	Jorge Maella
Kaiser Permanente Northwest	22	2	Richard Mularski
University of California Medical Center at San Diego	23	2	Samir Makani
Louisiana State University Hospital	24	6	Robert Holladay Adam Wellikoff
The Cooper Health System*	25	4	Wissam Abouzgheib
Sparks Regional Medical Center	26	3	Arturo Meade
University of Vermont Medical Center	27	5	Matt Kinsey
Tampa General Hospital	28	6	Karel Calero Mark Rumbak
Northwestern Memorial Hospital	29	5	Ravi Kalhan
University of Minnesota*	30	0	Erhan Dincer
Beaumont Botsford Hospital	31	3	Phillip Kaplan
Laval University, Quebec	32	16	Simon Martel Antoine Delage
Vancouver General Hospital*	33	0	Jeremy Road
Cornell NYPH*	34	0	Eugene Shostak
California Pacific Medical Center	35	1	Benson Chen
University of Calgary	36	3	Christopher Hergott
The Ottawa Hospital*	37	0	Kayvan Amjadi
Vanderbilt University Medical Center	38	0	Otis Rickman

Miami VA Healthcare System	39	1	Gregory Holt
Temple University Hospital	40	21	Gerard Criner
University of Pittsburgh Medical Center*	41	0	Frank Sciurba
Total		**172**	

*Site Closed

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Appendix 3. Detailed Inclusion and Exclusion Criteria

Additional Inclusion Criteria

- Subject has abstained from cigarette smoking for 4 months and is willing to abstain throughout the study
- Investigator has confirmed that medical management is within standard of care and subject has been stable and without a COPD exacerbation for ≥6 weeks
- Subject provides informed consent and is willing and able to participate in a controlled study and return for all study examinations
- Subjects with α-1 antitrypsin deficiency must have confirmatory blood test

Exclusion Criteria

- Severe gas exchange abnormality in either PCO_2 or PO_2
    - PCO_2 >5 mm Hg or
    - PO_2 <45 mm Hg on room air
- Co-existing major medical disease, alcoholism, or drug abuse potential that:
    - Will limit evaluation, participation, or follow-up during 6-month study period
    - Includes neurological or musculoskeletal conditions that may interfere with testing
- BMI <15 kg/m^2
- Hospitalization for COPD exacerbation or respiratory infections in the 3 months prior to baseline testing
- Bronchitis with sputum production >4 tablespoons or 60 ml per day
- Active asthma component to disease or requires more than 15 mg of prednisone daily
- Presence of giant bulla (>1/3 volume in either lung)
- Severe pulmonary hypertension based on clinical evaluation
- Prior lung volume reduction surgery or major lung procedures (lobectomy or greater)

- Lung nodule anticipated to require evaluation or intervention during 6-month study period
- Demonstrated unwillingness or inability to complete screening or baseline data collection procedures
- Diffuse emphysema pattern
- Classified as American Society of Anesthesiologists Class >P4 (assessing fitness for surgery), including presence of co-morbidity that could significantly increase risk of a bronchoscopy procedure
- Participated in a study of an investigational drug or device within the 30 days prior to participation in this study or currently participating in another clinical study

Appendix 4. **Concomitant Medications**

- Medication could include 3 types of inhaled bronchodilators in common clinical use:
    - Short-acting β-agonists
    - Long-acting β-agonists
    - Long-acting anti-cholinergic drugs
- Inhaled corticosteroids could be discontinued or continued during the study period
    - Inhaled steroids could not be added during the study period
    - Oral corticosteroids (eg, prednisone) were minimized prior to run-in period
    - Patients were not eligible for enrollment if using >15 mg prednisone or equivalent per day
    - Patients able to successfully taper steroid dose could be considered for enrollment
- Oral methylxanthines (ie, theophylline) and other approved respiratory medications could be discontinued or continued during study period, but could not be added to participant's medical regimen during study period.

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Supplemental Oxygen, COPD Exacerbations, and Pulmonary Rehab

- Supplemental oxygen, if prescribed, was to remain stable during study period. Any changes to prescribed oxygen were explained and documented in participant's clinical records.
- COPD exacerbations were treated by each participant's physician. Intermittent oral and intravenous glucocorticoids were allowed for COPD exacerbations.
- All participants were assessed to determine if they should complete a pulmonary rehabilitation (PR) program prior to participating. Those who completed a PR program in 2 years prior to consent were not required to participate in another. If they had not completed a PR program in the last 2 years, the study investigator determined if the patient was likely to clinically benefit from a PR program. If no, patients were not required to complete a PR program; if yes, patients were required to complete a certified outpatient or supervised home-based PR program.

Appendix 5. Study Design and Methods

Participants considered eligible after screening tests were evaluated for stable medical management, which was required before starting the 6-week run-in period. Participants were deemed stable based on ACP/ACCP/ATS/ERS Guidelines for Management of Stable COPD.[1] The evaluation included details on COPD medications, oxygen use, and pulmonary rehabilitation. Any changes required to achieve participant stability had to be made before the start of the 6-week run-in period. Participants were expected to maintain stable medical management during the 6-month primary endpoint period and not elect any additional interventions to treat their emphysema.

Run-in and Baseline Testing

A 6-week run-in period was required to allow a subject to achieve treatment stability and observe that a COPD exacerbation has not occurred prior to baseline testing. The run-in was repeated if patients experienced a COPD exacerbation, or if significant medical management changes were required during the initial 6 weeks.

Baseline testing followed the 6-week run-in period and consisted of patient history and physical examination and evaluation of pulmonary function and morphology, including the following:

- Office evaluation
    - Age, sex, height, weight, BMI, ethnicity, race
    - General physical examination
    - Detailed pulmonary examination with record of pulmonary medications
    - Vital signs
    - Pulmonary examination with review of pulmonary medications and notation of any changes and why
    - SpO2 and O2 level if O2 prescribed
- Clinical laboratory tests

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    - Routine blood tests
    - Urine or serum cotinine test
    - α1-Antitrypsin level with confirmatory blood test, and phenotyping, if indicated
    - Female participants of childbearing potential: serum human chorionic gonadotropin pregnancy test within 7 days of procedure
- Physiologic testing
    - 6MWT with prescribed oxygen, if any
    - Pulmonary function tests (PFT) including
        - Spirometry post-bronchodilator (eg albuterol MDI 2 puffs)
        - Lung volume by plethysmography (TLC)
- Imaging studies
    - High resolution computed tomography (HRCT) scan for assessing high heterogeneity and inter-lobar fissures
    - Proportion of lobar lung parenchyma destroyed by emphysema was established by HRCT
    - HRCT to determine lobe volumes including target lobe volume
- Questionnaires
    - Medical Research Council, Modified (mMRC) Questionnaire (administered by a trained interviewer or an investigator)
    - St. George's Respiratory Questionnaire (SGRQ)
    - COPD Assessment Test (CAT)
    - SF-36 Health Survey (SF-36)
    - Quality of Well Being Questionnaire – Utility Scale (QWB)

Management of Pneumothorax

Pneumothorax after valve placement can be an effect of the desired treatment response that is associated with complete lobe treatment and atelectasis. The management of pneumothorax is

an integral part of valve treatment. The origin of pneumothoraces is thought to be from the rupture of stretched, diseased tissue adjacent to the volume-reduced lobe.

The EMPROVE study used the following management guidelines for pneumothorax events. However, clinical management of pneumothorax varied depending on clinical circumstances, so exceptions to these guidelines were expected.

- A small and minimally symptomatic pneumothorax was to be observed or aspirated.
- A large or symptomatic pneumothorax was to require tube thoracostomy drainage for lung expansion.
- If there was a persistent air leak after 3 days of tube drainage, 1 valve was to be removed from the treated lobe to allow expansion of the lobe (if the left upper-lobe was the treatment lobe, the removal would be from a lingular segment). For those patients whose persistent air leak then resolved within 4 days of valve removal, discharge would occur with replacement of the 1 valve scheduled in 6 weeks. During the valve replacement procedure, if previously placed valves were observed to be sub-optimally placed, the investigator may remove and replace any sub-optimally placed valves.
- If the leak did not resolve within 4 days of valve removal, the remaining valves were to be removed. These subjects were to be followed for any AEs until the event subsided, or in case of permanent impairment, until the event stabilized and the overall clinical outcome had been ascertained, at which time the subject was to be withdrawn from the study.
    - This event was to be considered an SAE, belonging to the category of "Pneumothorax requiring surgical intervention or prolonged air leak >7 days defined as the time from chest tube insertion to the time the air leak is not present."

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Appendix 6. **Individual Serious Adverse Events (SAEs) Included in the Thoracic SAE Composite**

- Acute asthma or bronchospasm requiring admission to an intensive or critical care unit
- Acute exacerbation of COPD that is acute onset, life threatening, and requires hospitalization
- Airway injury from valve placement, valve migration, or airway stenosis from a valve, requiring surgical intervention
- Death from the procedure or device
- Massive hemoptysis (estimated over 300 ml in 24 hours and requiring transfusion, surgery, or arterial embolization) attributed to the procedure or device
- Pneumonia in the valve-treated lobe that requires hospitalization, IV antibiotics, and valve removal
- Pneumonia NOT in the valve-treated lobe that is life-threatening, acute onset, and requires hospitalization and IV antibiotics
- Pneumothorax requiring surgical intervention or prolonged air leak > 7 days defined as the time from chest tube insertion to the time the air leak is not present
- Respiratory failure that requires mechanical ventilatory support for > 24 hours
- Tension pneumothorax that is life-threatening, acute onset, and requires hospitalization and treatment

Appendix 7. **Sample Size Rationale**

This study was designed to adaptively determine the appropriate sample size via a Bayesian adaptive design.[2,3] Though the pre-specified analysis used Bayesian methods, the choice of maximum sample size was guided by the usual considerations for a t-test with one-sided α = 0.025: using conservative assumptions (difference in means = 100mL, sd = 200mL in each group, 2:1 allocation ratio), a sample size of 165 (110 treatment, 55 control) subjects is required to achieve 85% power. Allowing for missing data and a modest sample size increase to compensate for power loss caused by interim analyses, a maximum of N=220 subjects was chosen. Interim analyses at N=100 and N=160 enrollments were planned, at which the trial could stop enrolling for futility (based on a low predictive probability of success) or eventual success (based on a high predictive probability of success). In this adaptive design, the sole analysis to determine success occurs 6 months after enrollment stop (thus avoiding enrollment over-runs during the last 6 months of follow-up). Randomization followed a 2:1 (Treatment:Control) allocation ratio and was stratified by site, using a blocked randomization scheme with blocks of randomly varying sizes.

Bayesian statistical modeling was used to predict 6-month FEV_1 change-from-baseline measures from the change-from-baseline measures at 1 month and 3 months. For those with outcomes at all time points, a linear regression of 6-month FEV_1 outcome on the earlier FEV_1 measures (1-month and 3-month) was used to establish posterior distributions for the regression coefficients, from which 6-month FEV_1 observations were predicted for those who were missing only the 6-month measure. Similar regression models were used to predict 6-month outcomes for those with baseline and 1-month data, baseline and 3-month data, and only baseline data. Imputing 6-month values multiple times and combining each set of imputed values with the observed 6-month data, a set of posterior probabilities of superiority was obtained. The proportion of posterior probabilities exceeding the pre-specified threshold of

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0.982 determined the predictive probability of eventual success on which stopping decisions were based..

Appendix 8. **Statistical Analysis Methods**

The primary effectiveness objective was to establish that the Spiration Valve System is superior to control as assessed by change from baseline in FEV_1. The hypothesis of interest is

$$H: \quad \mu t > \mu c,$$

where μt and μc, represent the mean FEV_1 change from baseline for the Treatment and Control Groups, respectively. The Spiration Valve System will be declared to be superior to control if it can be established that the posterior probability Pr(H | data) > Ψ, where Ψ is a pre-specified threshold value that is chosen to achieve a type I error rate (under simulation) of at most 0.025. The value Ψ specified for this trial is Ψ = 0.982, noticeably greater than a value of 0.975 that might be expected in a design without interim analyses.

Flat or diffuse prior distributions are specified for all secondary effectiveness analyses. For any hypothesis test, a posterior probability greater than 97.5% for the specified hypothesis will be considered to constitute evidence in favor of the hypothesis, in the same sense that a frequentist analysis would reject a null hypothesis when p < 0.025 and call it “statistically significant.”

Secondary effectiveness measures are formally tested in the following pre-specified hierarchy, using a posterior probability threshold of 0.975 to determine significance and continuation of testing:

- Target lobe volume (baseline to 6 months
- Hyperinflation (baseline to 6 months)

- SGRQ (baseline to 6 months)
- Dyspnea (baseline to 6 months)
- 6MWT (baseline to 6 months)
- FEV_1 Responders (proportions who achieve ≥ 15% improvement from baseline to 6 months)

For the primary safety objective, the statistical analyses will consist of presenting 95% Bayesian credible intervals for the difference and ratio of the probability of the composite SAE in the treatment and control groups. Independent beta (1,1) prior distributions will be used for the probability of an event in the treatment and control groups (πT and πC). The 95% Bayesian credible intervals will be presented for the difference in the probabilities, πT–πC, and for the ratio of these probabilities, πT/πC. The 95% Bayesian credible intervals will be those ranging from the 2.5th to the 97.5th percentiles.

For the secondary safety objective, the rate of each individual thoracic serious adverse event will be analyzed. Calculations for each event will count subjects only once if they have more than one occurrence of each serious adverse event. The statistical analyses will consist of presenting 95% Bayesian credible intervals for the probabilities of each SAE. Independent beta (1,1) prior distributions will be used for the probability of an event in the treatment and control groups (πT and πC). The 95% Bayesian credible intervals will be presented for πT and πC as well as for the difference πT–πC and the ratio πT/πC.

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Appendix 9. Additional Baseline Characteristics

Table S2. Pulmonary Medications and Use of Supplemental Oxygen

Baseline Medication	Treatment % (n/N)	Control % (n/N)
Monotherapy	7.1% (8/113)	6.8% (4/59)
Combination therapy	92.9% (105/113)	93.2% (55/59)
Bronchodilator	100% (113/113)	100% (59/59)
Steroid	81.4% (92/113)	84.7% (50/59)
Long-acting beta-agonist bronchodilator and inhaled corticosteroid	76.1% (86/113)	79.7% (47/59)
Methylxanthines	5.3% (6/113)	11.9% (7/59)
Short acting beta agonist bronchodilator and short acting muscarinic antagonist	7.1% (8/113)	6.8% (4/59)
Short acting muscarinic antagonist	7.1% (8/113)	6.8% (4/59)
Long acting muscarinic antagonist	0.9% (1/113)	0.0% (0/59)
PDE-4 inhibitor	12.4% (14/113)	1.7% (1/59)
Mucolytic	1.8% (2/113)	0.0% (0/59)
Leukotriene receptor antagonist	4.4% (5/113)	8.5% (5/59)
Supplemental Oxygen	45.1% (51/113)	45.8% (27/59)

Appendix 10. Procedure Details

Table S3. Procedure Times and Hospital Stay by Group

	N	Mean	Standard deviation	Max	Min	Median
Procedure time (min)	113	24.26	11.43	73	9	22
Hospital stay (days)	113	3.81	10.12	95*	1	1

* 1 Patient not discharged, died at 95 days.

Table S4. Target Lobe Treated

Target lobe	Number of subjects (N=113)	Percent
Left upper lobe	66	58.4%
Left lower lobe	27	23.9%
Right upper lobe	13	11.5%
Right lower lobe	7	6.2%

Table S5. Valves Used and Placed During Initial Procedure

Category	Count	Number of subjects
Total valves used	536	113
Total valves used but not placed	60	12
Total valves placed	476	113

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Appendix 11. Additional Results: Primary and Secondary Efficacy Assessments

The pre-specified analysis included Bayesian multiple imputation for missing data, however, completers only analysis (without Bayesian imputation) is also included,

Table S6: FEV_1 - Means and Change from Baseline through 12 Months

FEV_1 (L)	Treatment Group	Control Group	Difference (T–C)	
	Mean ± SD (N) [min, median, max]	Mean ± SD (N) [min, median, max]	Estimate*, (95% BCI)	Posterior Probability of ($\mu_T > \mu_C$)
Baseline	0.825 ± 0.264 (113) [0.410, 0.790, 1.460]	0.792 ± 0.260 (59) [0.370, 0.760, 1.530]		
1 Mo	0.974 ± 0.324 (102) [0.350, 0.920, 1.990]	0.808 ± 0.221 (50) [0.440, 0.790, 1.460]		
3 Mo	0.940 ± 0.315 (105) [0.350, 0.900, 2.020]	0.820 ± 0.239 (45) [0.400, 0.820, 1.320]		
6 Mo	0.937 ± 0.296 (106) [0.340, 0.905, 1.820]	0.811 ± 0.274 (50) [0.440, 0.750, 1.700]		
12 Mo	0.920 ± 0.301 (86) [0.330, 0.860, 1.760]	0.790 ± 0.257 (39) [0.410, 0.770, 1.460]		
1 Mo – Baseline	0.145 ± 0.173 (102) [-0.190, 0.105, 0.750]	-0.000 ± 0.101 (50) [-0.260, -0.005, 0.240]		
3 Mo – Baseline	0.121 ± 0.172 (105) [-0.330, 0.110, 0.680]	-0.003 ± 0.102 (45) [-0.340, 0.000, 0.180]		
6 Mo – Baseline	0.099 ± 0.154 (106) [-0.260, 0.080, 0.530] 95% BCI: (0.069, 0.128)	-0.002 ± 0.098 (50) [-0.240, -0.010, 0.210] 95% BCI: (-0.030, 0.026)		
	Completers Only – Without Predictions		0.101 (0.060, 0.141)	1.0000
	With Predictions for Missing Values		0.097 (0.057, 0.138)	1.0000
12 Mo - Baseline	0.067 ± 0.167 (86) [-0.280, 0.060, 0.600] 95% BCI: (0.031, 0.103)	-0.032 ± 0.114 (39) [-0.300, -0.030, 0.390] 95% BCI: (-0.069, 0.005)		
	Completers Only – Without Predictions		0.099 (0.048, 0.151)	0.9999
	With Predictions for Missing Values		0.088 (0.037, 0.137)	0.9997

BCI = Bayesian credible interval; C = control; Mo = month; N = total of number of patients randomized/enrolled/treated; SD = standard deviation; T = treatment; FEV1 = forced expiratory volume in 1 second.
*Posterior median

Table S7: FEV_1 Responders (Defined as ≥15% Improvement)

FEV_1 Responder Rate (≥15% Improvement)	Treatment Group n/N (%)	Control Group n/N (%)	Difference (T–C) Estimate*, (95% BCI)	Difference (T–C) Posterior Probability of ($p_T > p_C$)
1 Mo	47/102 (46.1%)	6/50 (12.0%)		
3 Mo	50/105 (47.6%)	4/45 (8.9%)		
6 Mo	39/106 (36.8%)	5/50 (10.0%)		
	Completers Only – Without Predictions		25.7% (12.5, 37.5)	0.9998
	With Predictions for Missing Values		23.4% (10.7, 35.8)	0.9998
12 Mo	32/86 (37.2%)	2/39 (5.1%)		
	Completers Only – Without Predictions		30.4% (16.8, 42.5)	0.9999
	With Predictions for Missing Values		24.9% (12.0, 37.3)	0.9999

BCI = Bayesian credible interval; C = control; FEV_1 = forced expiratory volume in 1 second; Mo = month; N = total of number of patients randomized/enrolled/treated; n = number of patients in the subset at the given time point; T = treatment.
*Posterior median

Table S8. FEV_1 Responders with ≥12% Improvement

FEV_1 Responder ≥ 12% improvement	Treatment Group n/N (%)	Control Group n/N (%)	Difference (T–C) Estimate*, (95% BCI)	Difference (T–C) Posterior Probability of ($p_T > p_C$)
1 Mo	50/102 (49.0%)	10/50 (20.0%)		
3 Mo	53/105 (50.5%)	7/45 (15.6%)		
6 Mo	46/106 (43.4%)	8/50 (16.0%)		
	Completers Only – Without Predictions		26.4% (11.8, 39.5)	0.9997
	With Predictions for Missing Values		24.2% (10.3, 37.8)	0.9996
12 Mo	36/86 (41.9%)	4/39 (10.3%)		
	Completers Only – Without Predictions		30.1% (14.8, 43.4)	0.9999
	With Predictions for Missing Values		27.2% (13.4, 40.6)	0.9999

BCI = Bayesian credible interval; C = control; FEV_1 = forced expiratory volume in 1 second; Mo = month; N = total of number of patients randomized/enrolled/treated; n = number of patients in the subset at the given time point; SD = standard deviation; T = treatment.
*Posterior median

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Table S9. FEV_1 Responders with ≥20% Improvement

FEV_1 Responder ≥ 20% improvement	Treatment Group n/N (%)	Control Group n/N (%)	Difference (T–C) Estimate*, (95% BCI)	Difference (T–C) Posterior Probability of ($p_T > p_C$)
1 Mo	44/102 (43.1%)	4/50 (8.0%)		
3 Mo	40/105 (38.1%)	3/45 (6.7%)		
6 Mo	35/106 (33.0%)	2/50 (4.0%)		
	Completers Only – Without Predictions		27.7% (16.3, 38.2)	1.0000
	With Predictions for Missing Values		25.5% (14.4, 36.4)	1.0000
12 Mo	28/86 (32.6%)	1/39 (2.6%)		
	Completers Only – Without Predictions		28.2% (15.9, 39.6)	1.0000
	With Predictions for Missing Values		24.1% (12.6, 35.4)	1.0000

BCI = Bayesian credible interval; C = control; FEV_1 = forced expiratory volume in 1 second; Mo = month; N = total of number of patients randomized/enrolled/treated; n = number of patients in the subset at the given time point; SD = standard deviation; T = treatment.
*Posterior median

Table S10. Target Lobe Volume - Means and Change From Baseline Through 6 Months

TLV (L)	Treatment Group Mean ± SD (N) [min, median, max]	Estimate*, (95% BCI)	Posterior Probability of ($\mu_T < 0$)
BL	1.843 ± 0.602 (113) [0.980, 1.670, 3.831]		
6 Mo	0.869 ± 0.856 (102) [0.000, 0.886, 3.437]		
6 Mo – BL	-0.974 ± 0.736 (102) [-3.403, -0.974, 0.280]		
	Completers Only – Without Predictions	-0.974 (-1.119, -0.829)	1.0000

BCI = Bayesian credible interval; BL = baseline; C = control; Mo = month; N = total of number of patients randomized/enrolled/treated; SD = standard deviation; T = treatment; TLV = target lobe volume.
*Posterior median

Table S11a: Hyperinflation (RV/TLC) - Means and Change From Baseline Through 6 Months

Hyperinflation (RV/TLC)	Treatment Group	Control Group	Difference (T–C)	
	Mean ± SD (N) [min, median, max]	Mean ± SD (N) [min, median, max]	Estimate*, (95% BCI)	Posterior Probability of ($\mu_T < \mu_C$)
BL	0.632 ± 0.080 (113) [0.443, 0.636, 0.836]	0.632 ± 0.086 (59) [0.453, 0.648, 0.817]		
3 Mo	0.594 ± 0.092 (103) [0.367, 0.596, 0.823]	0.632 ± 0.081 (45) [0.411, 0.643, 0.762]		
6 Mo	0.595 ± 0.099 (105) [0.318, 0.602, 0.826]	0.628 ± 0.084 (50) [0.443, 0.633, 0.795]		
3 Mo – BL	-0.036 ± 0.080 (103) [-0.312, -0.024, 0.123]	0.010 ± 0.046 (45) [-0.059, 0.008, 0.150]		
6 Mo – BL	-0.035 ± 0.080 (105) [-0.253, -0.030, 0.136] 95% BCI: (-0.050, -0.019)	0.005 ± 0.039 (50) [-0.087, 0.005, 0.103] 95% BCI: (-0.007, 0.016)		
	Completers Only – Without Predictions		-0.039 (-0.058, -0.020)	1.0000
	With Predictions for Missing Values		-0.039 (-0.058, -0.020)	1.0000

BCI = Bayesian credible interval; BL = baseline; C = control; Mo = month; N = total of number of patients randomized/enrolled/treated; RV = residual volume; SD = standard deviation; T = treatment; TLC = total lung capacity.
*Posterior median

Table S11b: Residual Volume (RV) Means and Change From Baseline Through 6 Months

Residual Volume (L)	Treatment Group	Control Group	Difference (T–C)	
	Mean ± SD (N) [min, median, max]	Mean ± SD (N) [min, median, max]	Estimate*, (95% BCI)	Posterior Probability of ($\mu_T < \mu_C$)
Baseline	4.573 ± 1.253 (113) [2.740, 4.280, 8.770]	4.848 ± 1.199 (59) [2.840, 4.720, 8.600]		
3 Mo	4.147 ± 1.302 (103) [2.000, 3.940, 8.310]	4.898 ± 1.268 (45) [3.190, 4.660, 8.500]		
6 Mo	4.191 ± 1.309 (105) [1.940, 3.980, 8.670]	4.730 ± 1.172 (50) [3.160, 4.485, 8.230]		
3 Mo – Baseline	-0.410 ± 0.900 (103) [-5.280, -0.340, 1.500]	0.104 ± 0.562 (45) [-1.110, 0.140, 2.280]		
6 Mo – Baseline	-0.402 ± 0.849 (105) [-3.360, -0.330, 1.630] 95% BCI: (-0.567, -0.238)	-0.042 ± 0.583 (50) [-1.190, -0.035, 1.340] 95% BCI: (-0.208, 0.124)		
	Completers Only – Without Predictions		-0.361 (-0.594, -0.127)	0.9990
	With Predictions for Missing Values		-0.362 (-0.594, -0.129)	0.9989

BCI = Bayesian credible interval; BL = baseline; C = control; Mo = month; N = total of number of patients randomized/enrolled/treated; RV = residual volume; SD = standard deviation; T = treatment.
*Posterior median

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Table S12: SGRQ - Means and Change From Baseline Through 12 Months

SGRQ (points)	Treatment Group	Control Group	Difference (T–C)	
	Mean ± SD (N) [min, median, max]	Mean ± SD (N) [min, median, max]	Estimate*, (95% BCI)	Posterior Probability of ($\mu_T > \mu_C$)
BL	57.2 ± 14.8 (113) [23.6, 59.0, 92.9]	54.6 ± 13.6 (59) [31.8, 53.2, 84.7]		
1 Mo	51.0 ± 16.2 (105) [12.8, 50.8, 86.2]	56.3 ± 14.8 (50) [24.8, 57.7, 83.7]		
3 Mo	49.1 ± 17.2 (106) [5.4, 49.8, 97.9]	56.3 ± 16.7 (43) [21.4, 57.7, 80.5]		
6 Mo	49.0 ± 17.2 (105) [8.7, 47.8, 87.3]	59.4 ± 15.8 (50) [24.9, 62.6, 84.4]		
12 Mo	50.7 ± 18.5 (95) [11.1, 50.5, 86.7]	57.0 ± 16.6 (41) [26.9, 55.8, 89.9]		
1 Mo – BL	-6.5 ± 15.9 (105) [-51.0, -5.6, 48.8]	2.8 ± 8.4 (50) [-13.2, 2.9, 21.2]		
3 Mo – BL	-8.0 ± 17.6 (106) [-52.0, -6.9, 57.3]	4.2 ± 10.7 (43) [-22.1, 3.4, 26.0]		
6 Mo – BL	-8.1 ± 17.1 (105) [-48.3, -5.6, 27.6] 95% BCI: (-11.5, -4.8)	4.8 ± 10.6 (50) [-16.9, 4.3, 28.2] 95% BCI: (1.8, 7.8)		
	Completers Only – Without Predictions		-13.0 (-17.4, -8.5)	1.0000
	With Predictions for Missing Values		-12.9 (-17.3, -8.5)	1.0000
12 Mo – BL	-5.8 ± 16.8 (95) [-50.1, -4.7, 36.4] 95% BCI: (-9.2, -2.4)	3.7 ± 10.9 (41) [-15.3, 2.4, 33.7] 95% BCI: (0.3, 7.2)		
	Completers Only – Without Predictions		-9.5 (-14.4, -4.7)	1.0000
	With Predictions for Missing Values		-8.7 (-13.4, -4.0)	0.9999

BCI = Bayesian credible interval; BL = baseline; C = control; Mo = month; N = total of number of patients randomized/enrolled/treated; SD = standard deviation; SGRQ = St. George's Respiratory Questionnaire; T = treatment.
*Posterior median

Table S13: mMRC Dyspnea Score - Means and Change From Baseline Through 12 Months

mMRC Score	Treatment Group	Control Group	Difference (T–C)	
	Mean ± SD (N) [min, median, max]	Mean ± SD (N) [min, median, max]	Estimate*, (95% BCI)	Posterior Probability of ($\mu_T > \mu_C$)
BL	2.7 ± 0.7 (113) [1.0, 3.0, 4.0]	2.7 ± 0.6 (59) [2.0, 3.0, 4.0]		
1 Mo	2.3 ± 1.0 (106) [0.0, 2.0, 4.0]	2.7 ± 0.7 (50) [1.0, 3.0, 4.0]		
3 Mo	2.2 ± 1.1 (106) [0.0, 2.0, 4.0]	2.7 ± 0.7 (45) [1.0, 3.0, 4.0]		
6 Mo	2.1 ± 1.0 (107) [0.0, 2.0, 4.0]	2.6 ± 0.9 (50) [1.0, 3.0, 4.0]		
12 Mo	2.1 ± 1.1 (94) [0.0, 2.0, 4.0]	2.9 ± 0.8 (41) [1.0, 3.0, 4.0]		
1 Mo – BL	-0.4 ± 0.9 (106) [-3.0, 0.0, 2.0]	0.0 ± 0.6 (50) [-1.0, 0.0, 2.0]		
3 Mo – BL	-0.5 ± 1.0 (106) [-4.0, 0.0, 2.0]	0.1 ± 0.5 (45) [-1.0, 0.0, 1.0]		
6 Mo – BL	-0.6 ± 1.0 (107) [-3.0, -1.0, 2.0] 95% BCI: (-0.8, -0.4)	-0.0 ± 0.6 (50) [-2.0, 0.0, 1.0] 95% BCI: (-0.2, 0.1)		
	Completers Only – Without Predictions		-0.6 (-0.9, -0.3)	1.0000
	With Predictions for Missing Values		-0.6 (-0.9, -0.3)	1.0000
12 Mo – BL	-0.6 ± 1.1 (94) [-4.0, 0.0, 1.0] 95% BCI: (-0.9, -0.4)	0.2 ± 0.6 (41) [-1.0, 0.0, 2.0] 95% BCI: (0.0, 0.4)		
	Completers Only – Without Predictions		-0.9 (-1.2, -0.6)	1.0000
	With Predictions for Missing Values		-0.8 (-1.1, -0.5)	1.0000

BCI = Bayesian credible interval; BL = baseline; C = control; mMRC = Modified Medical Research Council; Mo = month; N = total of number of patients randomized/enrolled/treated; SD = standard deviation; T = treatment.
*Posterior median

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Table S14: 6MWT - Means and Change From Baseline Through 6 Months

6MWT (m)	Treatment Group	Control Group	Difference (T–C)	
	Mean ± SD (N) [min, median, max]	Mean ± SD (N) [min, median, max]	Estimate*, (95% BCI)	Posterior Probability of ($\mu_T > \mu_C$)
BL	303.5 ± 84.6 (113) [118.0, 302.0, 508.0]	306.9 ± 104.2 (59) [78.0, 283.5, 557.0]		
3 Mo	301.3 ± 88.4 (104) [60.0, 300.0, 520.0]	327.5 ± 95.7 (45) [154.0, 314.0, 542.0]		
6 Mo	306.8 ± 100.4 (102) [61.0, 315.8, 604.0]	307.5 ± 122.9 (48) [60.0, 308.4, 553.0]		
3 Mo – BL	-6.6 ± 68.0 (104) [-263.0, 6.5, 120.0]	0.3 ± 49.3 (45) [-221.7, 3.0, 114.0]		
6 Mo – BL	-4.4 ± 76.7 (102) [-289.0, 0.0, 331.0] 95% BCI: (-19.4, 10.7)	-11.3 ± 51.4 (48) [-161.0, -6.0, 126.0] 95% BCI: (-26.2, 3.6)		
	Completers Only – Without Predictions		6.9 (-14.2, 28.2)	0.7438
	With Predictions for Missing Values		5.0 (-16.2, 26.2)	0.6821

6MWT = Six-minute walk test; BCI = Bayesian credible interval; BL = baseline; C = control; Mo = month; N = total of number of patients randomized/enrolled/treated; SD = standard deviation; T = treatment.
*Posterior median

Table S15: Forced Vital Capacity (FVC) - Means and Change From Baseline Through 12 Months

FVC (L)	Treatment Group	Control Group	
	Mean ± SD (N) [min, median, max]	Mean ± SD (N) [min, median, max]	Mean Difference (T-C) P value
Baseline	2.492 ± 0.754 (113) [0.960, 2.390, 4.930]	2.633 ± 0.757 (59) [1.050, 2.630, 4.580]	
6 Mo	2.666 ± 0.790 (106) [1.090, 2.535, 5.660]	2.593 ± 0.741 (50) [1.130, 2.560, 4.320]	
12 Mo	2.663 ± 0.790 (86) [1.030, 2.480, 5.820]	2.522 ± 0.729 (39) [1.010, 2.610, 4.230]	
6 Mo – Baseline	0.147 ± 0.485 (106) [-1.010, 0.100, 1.820]	-0.098 ± 0.252 (50) [-0.600, -0.105, 0.540]	0.245 P=0.001
12 Mo - Baseline	0.097 ± 0.536 (86) [-1.180, 0.090, 1.980]	-0.103 ± 0.369 (39) [-1.010, -0.080, 0.600]	0.200 P=0.037

T= Treatment; C = control; Mo = month; N = total of number of patients randomized/enrolled/treated; SD = standard deviation; FVC = Forced Vital Capacity.

Table S16: COPD Assessment Test (CAT) - Means and Change From Baseline Through 12 Months

COPD Assessment Test (points)	Treatment Group	Control Group	Difference (T–C)	
	Mean ± SD (N) [min, median, max]	Mean ± SD (N) [min, median, max]	Estimate*, (95% BCI)	Posterior Probability of ($\mu_T > \mu_C$)
Baseline	21.8 ± 6.8 (113) [7.0, 21.0, 38.0]	20.0 ± 6.3 (59) [7.0, 19.0, 31.0]		
6 Mo	18.9 ± 7.5 (106) [4.0, 18.0, 38.0]	21.7 ± 7.0 (50) [7.0, 23.0, 34.0]		
12 Mo	19.8 ± 7.7 (91) [3.0, 20.0, 39.0]	23.2 ± 7.5 (41) [8.0, 25.0, 36.0]		
6 Mo – Baseline	-3.0 ± 7.8 (106) [-25.0, -2.0, 17.0] 95% BCI: (-4.5, -1.5)	1.6 ± 5.3 (50) [-11.0, 1.5, 11.0] 95% BCI: (0.1, 3.1)		
	Completers Only – Without Predictions		-4.5 (-6.6, -2.4)	1.0000
	With Predictions for Missing Values		-4.4 (-6.5, -2.4)	1.0000
12 Mo - Baseline	-2.3 ± 8.1 (91) [-20.0, -2.0, 20.0] 95% BCI: (-4.0, -0.6)	3.0 ± 5.7 (41) [-5.0, 2.0, 17.0] 95% BCI: (1.3, 4.8)		
	Completers Only – Without Predictions		-5.3 (-7.8, -2.9)	1.0000
	With Predictions for Missing Values		-4.7 (-7.1, -2.3)	1.0000

BCI = Bayesian credible interval; BL = baseline; C = control; Mo = month; N = total of number of patients randomized/enrolled/treated; SD = standard deviation; T = treatment.
*Posterior median

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Appendix 12. Additional Results: Safety Assessments

Table S17: Composite of Thoracic SAEs – Short-Term (0-6 Months) and Long-Term (6-12 Months)

	Treatment Group (N = 113)	**Control Group** (N = 59)	**Difference** (T–C)		**Treatment Group (N = 103)**	**Control Group** (N = 47)	**Difference** (T–C)	
	%	%	%	(95% BCI)	**%**	%	%	(95% BCI)
	Short-Term (0 – 6 Months)				**Long-Term (6 – 12 Months)**			
Acute exacerbation of COPD	16.8	10.2	6.6	(-5.1, 16.0)	13.6	8.5	5.1	(-7.4, 14.2)
Death from procedure or device	0.0	0.0	0.0	(-5.3, 2.3)	1.0	0.0	1.0	(-5.9, 4.1)
Pneumonia in the valve-treated lobe	1.8	0.0	1.8	(-3.9, 5.2)	1.0	0.0	1.0	(-5.9, 4.1)
Pneumonia not in the valve-treated lobe	7.1	1.7	5.4	(-2.4, 11.1)	7.8	2.1	5.6	(-3.8, 11.9)
Pneumothorax requiring surgical intervention or prolonged air leak > 7 days	12.4	0.0	12.4	(4.6, 18.6)	0.0	0.0	0.0	(-6.6, 2.4)
Tension pneumothorax	1.8	0.0	1.8	(-3.9, 5.2)	0.0	0.0	0.0	(-6.6, 2.4)
Respiratory failure	2.7	0.0	2.7	(-3.2, 6.4)	1.0	0.0	1.0	(-5.9, 4.1)
TOTAL	**31.0%**	**11.9%**	**19.1%**	**(5.9, 29.7)**	**21.4%**	**10.6%**	**10.7%**	**(-3.0, 21.2)**

BCI = Bayesian credible interval; C = control; COPD = chronic obstructive pulmonary disease; N = total of number of patients randomized/enrolled/treated; SAE = serious adverse event; T = treatment.

Figure S1. Pneumothorax Events Through 12 Months

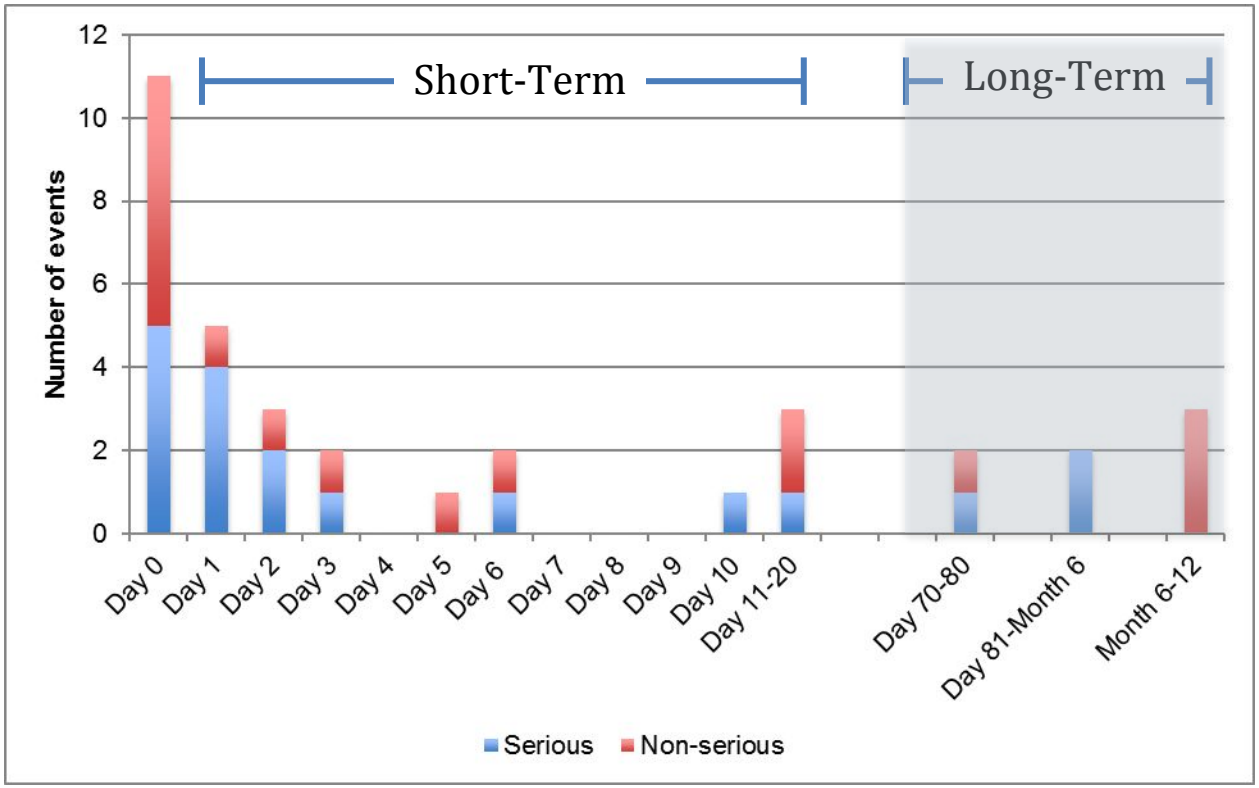

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Table S18. Composite of Thoracic SAE Rates – Short-Term (0-6 Months) and Long-Term (6-12 Months)

	Treatment Group (N = 113)	Control Group (N = 59)	Treatment Group (N = 103)	Control Group (N = 47)
	(Pt-Yrs = 63.52)	(Pt-Yrs = 30.47)	(Pt-Yrs = 48.81)	(Pt-Yrs = 22.17)
	Events/Pt-Yr (95% BCI)			
	Short-Term (0 – 6 Months)		**Long-Term (6 – 12 Months)**	
Acute exacerbation of COPD that is acute onset, life threatening, and requires hospitalization	0.35 (0.20, 0.49)	0.20 (0.09, 0.43)	0.41 (0.26, 0.62)	0.18 (0.06, 0.43)
Death from the procedure or device	0.0	0.0	0.02 (0.00, 0.10)	0.0
Pneumonia in the valve-treated lobe that requires hospitalization, IV antibiotics, and valve removal.	0.03 (0.01, 0.10)	0.0	0.02 (0.00, 0.10)	0.0
Pneumonia NOT in the valve-treated lobe that is life-threatening, acute onset, and requires hospitalization and IV antibiotics	0.16 (0.08, 0.28)	0.03 (0.00, 0.15)	0.23 (0.12, 0.39)	0.05 (0.00, 0.21)
Pneumothorax requiring surgical intervention or prolonged air leak > 7 days defined as the time from chest tube insertion to the time the air leak is not present	0.25 (0.15, 0.40)	0.0	0.0	0.0
Respiratory failure that requires mechanical ventilatory support for > 24 hours	0.08 (0.03, 0.17)	0.0	0.02 (0.00, 0.10)	0.0
Tension pneumothorax that is life-threatening, acute onset, and requires hospitalization and treatment	0.03 (0.01, 0.10)	0.0	0.0	0.0
Composite	**0.90 (0.69, 1.15)**	**0.23 (0.10, 0.45)**	**0.70 (0.49, 0.96)**	**0.23 (0.09, 0.49)**

BCI = Bayesian credible interval; C = control; COPD = chronic obstructive pulmonary disease; IV = intravenous; N = total of number of patients randomized/enrolled/treated; Pt-Yrs = patient-years; SAE = serious adverse event.

Table S19. Composite of Non-Thoracic SAEs – Short-Term (0-6 Months) and Long-Term (6-12 Months)

	Treatment Group (N = 113)	**Control Group** (N = 59)	**Difference** (T–C)		**Treatment Group (N = 103)**	**Control Group** (N = 47)	**Difference** (T–C)	
	%	%	%	(95% BCI)	**%**	%	%	(95% BCI)
	Short-Term (0 – 6 Months)				**Long-Term (6 – 12 Months)**			
Acute onset abdominal pain requiring urgent hospitalization or extended hospitalization	0.0	0.0	0.0	(-5.3, 2.3)	2.9	0.0	2.9	(-4.3, 6.9)
Cardiac rhythm disturbance requiring acute medical intervention	0.9	0.0	0.9	(-4.6, 3.8)	2.9	0.0	2.9	(-4.3, 6.9)
Death from any cause not from the investigational procedure or device	5.3**	1.7	3.6	(-3.9, 8.9)	2.9	6.4	-3.5	(-13.9, 3.0)
Emergent surgery that is not due to trauma	0.0	1.7	-1.7	(-8.2, 1.3)	1.0	0.0	1.0	(-5.9, 4.1)
Infection at any site that is life threatening and requires hospitalization and IV antibiotics	3.5	0.0	3.5	(-2.5, 7.7)	1.0	0.0	1.0	(-5.9, 4.1)
Thrombosis or thromboembolism requiring medical management and acute hospitalization	0.0	0.0	0.0	(-5.3, 2.3)	1.0	0.0	1.0	(-5.9, 4.1)
Other	7.1	3.4	3.7	(-4.9, 9.9)	5.8	6.4	-0.6	(-11.4, 6.7)
TOTAL	**11.5%**	**3.4%**	**8.1%**	**(-1.1, 15.2)**	**12.6%**	**12.8%**	**-0.1%**	**(-13.4, 10.0)**

BCI = Bayesian credible interval; C = control; IV = intravenous; N = total of number of patients randomized/enrolled/treated; SAE = serious adverse event; T = treatment.
**One death adjudicated as “possibly” device related.

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Table S20. Summary of Deaths 0-6 Months

Study Group	Days from Enrolled	CEC Device Relationship	CEC Procedure Relationship	Details
Control	156	Definitely not related	Definitely not related	Subject died prior to their 6M study visit from complications following surgery on the jaw (cancer).
Treatment	26	Definitely not related	Definitely not related	Subject died due to complications during hospitalization for exacerbation of COPD including arrhythmia, staph infection, renal failure, ileus & volvulus, and septic shock with multi-organ failure.
Treatment	189	Probably not related	Definitely not related	Subject died as a result of bilateral pleural effusion and hypercapnic respiratory failure, complicated by MRSA infection.
Treatment	188	Definitely not related	Definitely not related	Subject died as a result of a myocardial infarction.
Treatment	178	Definitely not related	Definitely not related	Subject died as a result of aspiration leading to infection and respiratory failure.
Treatment	179	Definitely not related	Definitely not related	Subject died due to complications during hospitalization for exacerbation of COPD.
Treatment	95	Possibly related	Probably not related	Subject died due to right-sided (contralateral) pneumothorax which did not resolve and led to hypoxia and cardiac arrest.

Table S21. Summary of Deaths 6-12 Months

Study Group	Days from Enrolled	CEC Device Relationship	CEC Procedure Relationship	Details
Control	303	Definitely not related	Definitely not related	Subject died in hospice due to declining health.
Control	336	Definitely not related	Definitely not related	Subject died due to unknown reasons –death certificate or medical records were not obtainable.
Control	233	Definitely not related	Definitely not related	Subject died as a direct result of trauma sustained in a car accident.
Treatment	353	Probably related	Definitely not related	Subject died from treatment of an acute lung abscess in the valve-treated left lower-lobe.
Treatment	342	Probably not related	Definitely not related	Subject “coded” in the parking lot of the hospital and was not resuscitated due to a DNR.
Treatment	271	Definitely not related	Definitely not related	Subject died from complications related to pneumonia in the ipsilateral lobe.
Treatment	281	Probably not related	Definitely not related	Subject died in hospice after hospitalization for COPD exacerbation leading and chronic respiratory failure.

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