# A randomised trial of lung sealant *versus* medical therapy for advanced emphysema

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ABSTRACT   Uncontrolled pilot studies demonstrated promising results of endoscopic lung volume reduction using emphysematous lung sealant (ELS) in patients with advanced, upper lobe predominant emphysema. We aimed to evaluate the safety and efficacy of ELS in a randomised controlled setting.

Patients were randomised to ELS plus medical treatment or medical treatment alone. Despite early termination for business reasons and inability to assess the primary 12-month end-point, 95 out of 300 patients were successfully randomised, providing sufficient data for 3- and 6-month analysis.

57 patients (34 treatment and 23 control) had efficacy results at 3 months; 34 (21 treatment and 13 control) at 6 months. In the treatment group, 3-month lung function, dyspnoea, and quality of life improved significantly from baseline when compared to control. Improvements persisted at 6 months with >50% of treated patients experiencing clinically important improvements, including some whose lung function improved by >100%. 44% of treated patients experienced adverse events requiring hospitalisation (2.5-fold more than control, p=0.01), with two deaths in the treated cohort. Treatment responders tended to be those experiencing respiratory adverse events.

Despite early termination, results show that minimally invasive ELS may be efficacious, yet significant risks (probably inflammatory) limit its current utility.

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## Introduction

Lung volume reduction surgery (LVRS) improves quality of life, dyspnoea, lung function and exercise capacity, as well as mortality, in patients with severe upper lobe predominant emphysema and reduced exercise capacity [1, 2]. Although it is effective, LVRS involves major surgery in patients with limited respiratory reserve and is associated with substantial morbidity and mortality. In the National Emphysema Treatment Trial (NETT), non-high-risk LVRS patients had a 90-day mortality of 5.5%; 59% experienced serious complications [3]. While risk may have declined with refinements in technique, LVRS remains rarely performed [4], and efforts are ongoing to develop less invasive endoscopic approaches capable of achieving similar benefits [5–16]. Although some techniques have proven safer than LVRS, they have also been less efficacious, with insufficient risk-benefit data in randomised clinical trials to obtain US Food and Drug Administration (FDA) approval [5, 7, 13, 15].

The emphysematous lung sealant system (ELS) (AeriSeal System; Aeris Therapeutics, Inc. Woburn, MA, USA) is an endoscopic lung volume reduction (ELVR) technique that employs a synthetic polymer to irreversibly block small airways and collateral channels, promoting atelectasis, remodelling and scar formation, thereby reducing lung hyperinflation. By sealing lung tissue at the alveolar level, this approach addresses the problem of collateral ventilation, a limitation of ELVR approaches employing mechanical devices to collapse the lung by blocking proximal airways [17]. In open-label pilot studies, ELS durably reduced lung volume, improving lung function and quality of life with an acceptable safety profile [10, 18, 19].

Based on these promising findings, the AeriSeal System for Hyperinflation Reduction in Emphysema (ASPIRE) study was initiated. ASPIRE was an open-label, prospective, multicentre, randomised controlled trial comparing ELS treatment plus optimal medical therapy to optimal medical therapy alone in patients with advanced, upper lobe predominant emphysema. The study was terminated prematurely for business-related reasons after 95 out of 300 planned patients were randomised. However, accumulated data provide insight into the feasibility of using sealant therapy targeting the alveolar compartment in this high-risk population. Our results demonstrate that the procedure is technically simple, length of hospital stay generally brief, and surgical-level efficacy potentially achievable. Yet significant short-term side-effects associated with acute inflammation and infection risk may limit its potential utility in present form. Parts of this article have been reported in abstract form [20].

## Methods

### Patients

Between September 2012 and November 2013, 383 patients were screened at 37 centres; 241 were excluded and 47 were undergoing screening at study termination. 95 patients were randomised to ELS plus optimal medical therapy or optimal medical therapy alone [21]. Eligibility criteria included age ⩾40 years; former smoking (nonsmoking ⩾4 months) with ⩾20 pack-year history; upper lobe predominant emphysema on computed tomography (CT) (performed visually by site investigator and confirmed by study sponsor physicians); severe airflow obstruction with post-bronchodilator forced expiratory volume in 1 s ($FEV_1$) <50% predicted; hyperinflation, with total lung capacity >100% pred and residual volume >150% pred; single breath diffusing capacity of the lung for carbon monoxide 20–60% pred [19, 22]; dyspnoea despite guideline-optimised medical therapy; post-rehabilitation 6-min walking distance (6MWD) ⩾150 m [23]; carbon dioxide tension <65 mmHg; and oxygen saturation ⩾90% on ⩽4 L·min$^{-1}$ supplemental oxygen at rest. Exclusion criteria included prior lung volume reduction or lobectomy; clinically significant asthma or bronchiectasis; frequent severe chronic obstructive pulmonary disease (COPD) exacerbations; $\alpha_1$-antitrypsin deficiency; imaging consistent with active pulmonary infection, significant interstitial lung disease or pleural disease, giant bullous disease (predominant bulla >10 cm in diameter) or a new lung nodule >1 cm in diameter; active malignancy; HIV; recent myocardial infarction or stroke; pulmonary hypertension; impaired left ventricular function (ejection fraction <45%); body mass index <15 kg·m$^{-2}$ or >35 kg·m$^{-2}$; pregnancy/breastfeeding; significant abnormality in serum chemistries, complete blood count or coagulation indices; use of systemic corticosteroids at a daily dose greater than prednisone 20 mg (or equivalent immunosuppressive agents); or use of anticoagulant medication.

### Study design

The planned study schema is presented in figure 1. Prior to participation, subjects provided written informed consent. Patients underwent screening, including medical history, physical examination, blood work, pulmonary function tests, 6MWD, chest CT, electrocardiogram, echocardiogram and questionnaires. Those meeting the study criteria underwent pre-randomisation pulmonary rehabilitation, after which they returned for baseline evaluation. Eligible patients were randomised in a 3:2 ratio (treatment:control) to ensure adequate statistical power if there was significant drop-out in the control arm; the randomisation sequence was computer-generated in blocks of five, stratified by site. As per the FDA mandate, a sham procedure was not

used, given the risks to control patients without potential benefit. Thus, patients and bronchoscopists were aware of treatment allocation; those conducting pulmonary function tests, 6MWD and questionnaires were blinded. After ELS (treatment group) or randomisation (control group), follow-up visits were planned at 3, 6, 9 and 12 months, followed by annual visits up to 5 years for treated patients. Control patients would be eligible for treatment after 12 months if they continued to meet inclusion/exclusion criteria and treatment was deemed safe. Patients were required to continue pulmonary rehabilitation post-randomisation. All patients, regardless of treatment allocation, continued optimal medical therapy, under the direction of their local physicians or study physicians. As the study was terminated prematurely, most randomised patients only underwent 3- or 6-month follow-up visits. The full protocol is provided in the online supplementary material.

### Procedure

ELS was performed under moderate sedation or general anaesthesia. Prior to intervention, patients received the first doses of a 7-day steroid taper and prophylactic antibiotic course to reduce the
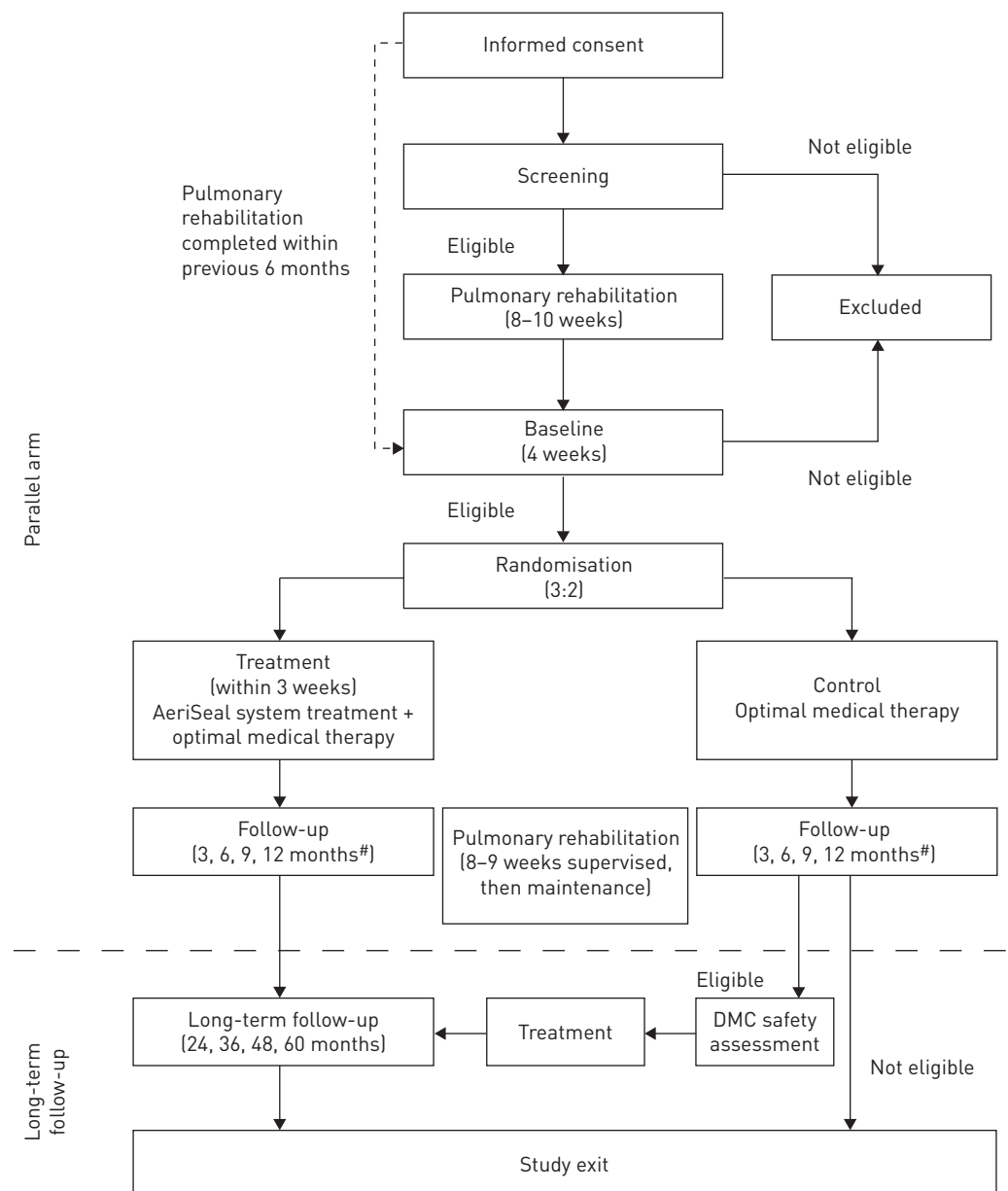


FIGURE 1 AeriSeal System for Hyperinflation Reduction in Emphysema study schema. DMC: data monitoring committee. [#]: telephone follow-up at 1, 2 and 3 weeks and 1, 2, 4, 5, 7, 8, 10 and 11 months.

post-treatment acute inflammatory response (PAIR: fever, dyspnoea, cough, chest pain and/or elevated inflammatory markers) observed in pilot studies [19]. Patients also received prophylactic nonsteroidal anti-inflammatory drugs for 3 days post-treatment, and stress-ulcer prophylaxis. Target treatment sites, the most severely damaged upper lobe segments, were identified by site investigators based on CT review and confirmed by study sponsor physicians. Based on pilot studies, two upper lobe sub-segments in each lung were treated; procedures were performed in a single session (online supplementary material) [10]. Post-treatment, patients were monitored in hospital for $\geqslant$1 night.

### Outcome measures

Assessment of primary and secondary efficacy end-points, intended at 12-month follow-up, was available only at 3 and 6 months. The planned primary efficacy end-point was mean percentage change in post-bronchodilator FEV1 from baseline to 12 months. Secondary efficacy end-points included proportion of patients achieving minimal clinically important differences (MCID) in FEV1 (MCID $\geqslant$100 mL and 12%); [24] dyspnoea quantified by the modified Medical Research Council dyspnoea scale (mMRC) (0–4, a higher score indicating more severe dyspnoea and MCID $\geqslant$1 U decrease) [25]; and disease-specific quality of life measured by St George's Respiratory Questionnaire (SGRQ) (0–100: a higher score indicating worse quality of life and MCID $\geqslant$4 U decrease) [26]; as well as changes in 6MWD [27] and upper lobe volume (measured by quantitative CT) at 12 months. Adverse events were recorded, focusing on serious adverse events, including deaths and those requiring hospitalisation.

### Study administration and oversight

The study was sponsored by Aeris Therapeutics, Inc. The protocol was developed by the sponsor in collaboration with the Center for Devices and Radiological Health of the FDA and an independent data monitoring committee (DMC), comprising three physicians and a statistician. The protocol was approved by the institutional review boards and ethics committees of participating centres. The DMC assisted with developing safety-related stopping rules, reviewed safety data bi-annually and evaluated deaths. Recommendations were forwarded to the sponsor. An independent, blinded medical assessment committee reviewed and adjudicated all serious adverse events and a pre-defined subset of respiratory-related adverse events (i.e. pneumonia, pneumothorax, respiratory failure, haemoptysis and COPD exacerbation).

### Study termination

The study was stopped prematurely due to lack of company financing. While the adverse event rate was higher than anticipated, the DMC did not recommend trial termination. At termination, a group of participating physicians obtained data collected per protocol from the sponsor, providing the content for this article.

### Statistical analysis

Given the early termination of the trial, descriptive statistics for subjects at baseline and 3 and 6 months post-randomisation are presented. Efficacy analyses using interim assessments were performed according to intention-to-treat in subjects with available data. Safety analyses used the as-treated population. As sample sizes were limited, continuous variables are presented as median (interquartile range) and dichotomous variables as n (%), unless otherwise stated. Non-parametric tests were used for between-group comparisons and p-values reported.

## Results

### Study patients

61 patients were randomised to ELS; 34 to control treatment (fig. 2). Study groups were well matched at baseline (table 1), except control patients had more upper lobe predominant emphysema on CT. 59 of those randomised to treatment received ELS, two did not. One withdrew prior to treatment; the study was terminated before treating the other. At study termination, results were available for 57 patients (34 in the treatment group and 23 in the control group) at 3 months and 34 patients (21 in the treatment group and 13 in the control group) at 6 months. One control patient withdrew on day 81 to pursue alternative therapy.

### Procedural details

All patients were successfully treated at two sub-segments in each upper lobe. 28 procedures were performed under general anaesthesia and 31 under conscious (moderate) sedation. Mean±SD duration of ELS was 23±8 min (median 22 min, minimum 8 min and maximum 47 min). Patients spent mean±SD 5.3±17.9 days (median 1 day, minimum 1 day per protocol and maximum 120 days) in the hospital post-procedure. ELS was well tolerated. No adverse events occurred during the technical procedure, and

TABLE 1 Baseline characteristics of randomised patients

| | Treatment | Control | p-value |
|---|---|---|---|
| **Subjects n** | 61 | 34 | |
| **Demographics** | | | |
| Age years | 65 (58–69) | 64 (58–69) | 0.69 |
| Male | 35 (57) | 21 (62) | 0.68 |
| White[#] | 58 (95) | 33 (97) | 0.99 |
| BMI kg·m$^{-2}$ | 25.2 (21.9–27.9) | 25.7 (21.4–28.3) | 0.90 |
| Smoking pack-years | 50 (37–77) | 50 (39–65) | 0.97 |
| Supplemental oxygen | 41 (67) | 25 (74) | 0.52 |
| **Lung function[¶]** | | | |
| FEV$_1$ L | 0.78 (0.65–1.02) | 0.90 (0.70–1.06) | 0.274 |
| FEV$_1$ % pred | 29 (23–35) | 30 (27–38) | 0.132 |
| FVC L | 2.39 (1.97–3.02) | 2.52 (2.02–3.18) | 0.630 |
| TLC L | 7.42 (6.18–8.58) | 6.99 (6.16–7.94) | 0.338 |
| TLC % pred | 124 (115–139) | 120 (108–133) | 0.088 |
| RV L | 4.35 (3.73–5.19) | 4.04 (3.70–4.53) | 0.159 |
| RV % pred | 200 (168–231) | 179 (168–215) | 0.140 |
| $D_{LCO}$ mL·min$^{-1}$·mmHg$^{-1}$ | 7.90 (6.13–10.36) | 8.06 (7.18–10.91) | 0.378 |
| $D_{LCO}$ % pred | 33 (26–39) | 36 (28–46) | 0.235 |
| **Arterial blood gases[+]** | | | |
| $P_{aO_2}$ mmHg | 70 (64–78) | 71 (63–78) | 0.917 |
| $P_{aCO_2}$ mmHg | 41 (37–45) | 41 (37–44) | 0.837 |
| **Exercise performance** | | | |
| 6MWD m | 313 (236–363) | 293 (247–420) | 0.277 |
| **CT[§]** | | | |
| Emphysema % | 34.5 (27.8–44.4) | 30.0 (20.6–39.3) | 0.052 |
| Heterogeneity index | 1.45 (1.27–1.72) | 1.60 (1.40–2.06) | 0.035 |
| **Questionnaires** | | | |
| mMRC U | 3.0 (2.0–3.0) | 2.0 (2.0–3.0) | 0.452 |
| SGRQ U | 54 (46–65) | 58 (45–74) | 0.508 |
| **Medication use** | | | |
| Short-acting bronchodilator | 51 (84) | 26 (77) | 0.395 |
| Long-acting bronchodilator[f] | 48 (79) | 23 (68) | 0.235 |
| Inhaled corticosteroid | 47 (77) | 21 (62) | 0.113 |
| Oral corticosteroid | 9 (15) | 3 (9) | 0.623 |

Data are presented as median (interquartile range) or n (%), unless otherwise stated. BMI: body mass index; FEV$_1$: forced expiratory volume in 1 s; % pred: % predicted; FVC: forced vital capacity; TLC: total lung capacity; RV: residual volume; $D_{LCO}$: single breath diffusing capacity of the lung for carbon monoxide; $P_{aO_2}$: arterial oxygen tension; $P_{aCO_2}$: arterial carbon dioxide tension; 6MWD: 6-min walking distance; CT: computed tomography; mMRC: modified Medical Research Council dyspnoea scale; SGRQ: St George's Respiratory Questionnaire. [#]: race was self-reported. [¶]: all lung function measures were obtained post-bronchodilator. [+]: arterial blood gas measurements were performed while patients were breathing ambient air. [§]: per cent emphysema was defined as the percentage of total lung tissue with a density <-950 HU. Heterogeneity index = [% voxels in the right upper lobe+left upper lobe <-910 HU]/[% voxels in the right lower lobe+left lower lobe <-910 HU] [10], with higher indices indicating more pronounced upper lobe predominant emphysema. [f]: long-acting bronchodilator includes long-acting β-agonists, long-acting anticholinergics or both.

there were no procedure-related deaths. In general, patients were hospitalised longer than the required observation period for respiratory insufficiency in the setting of anticipated PAIR.

*Efficacy outcomes*

At 3 months, FEV$_1$ improvement was 11.4% (2.0–32.0%) and 110 mL (18–211 mL) in the treatment group *versus* -2.1% (-4.9–9.0%) and -20 mL (-48–60 mL) in controls (p=0.0037). There were also improvements in health-related quality of life (change in SGRQ -11 U (-18–-1 U) *versus* -4 U (-6–3 U), p=0.026) and dyspnoea (change in mMRC -1.0 U (-2.0–0 U) *versus* 0 U (-0.8–0.8 U), p=0.005) in the treatment group compared with controls.

Improved lung function, exercise capacity and health-related quality of life were observed at 6 months in treatment *versus* control groups. Change in FEV$_1$ change was 18.9% (-0.7–41.9%) and 100 mL (0–370 mL) in the treatment group *versus* 1.3% (-8.2–12.9%) and 10 mL (-90–100 mL) in controls (p=0.043). Treated patients
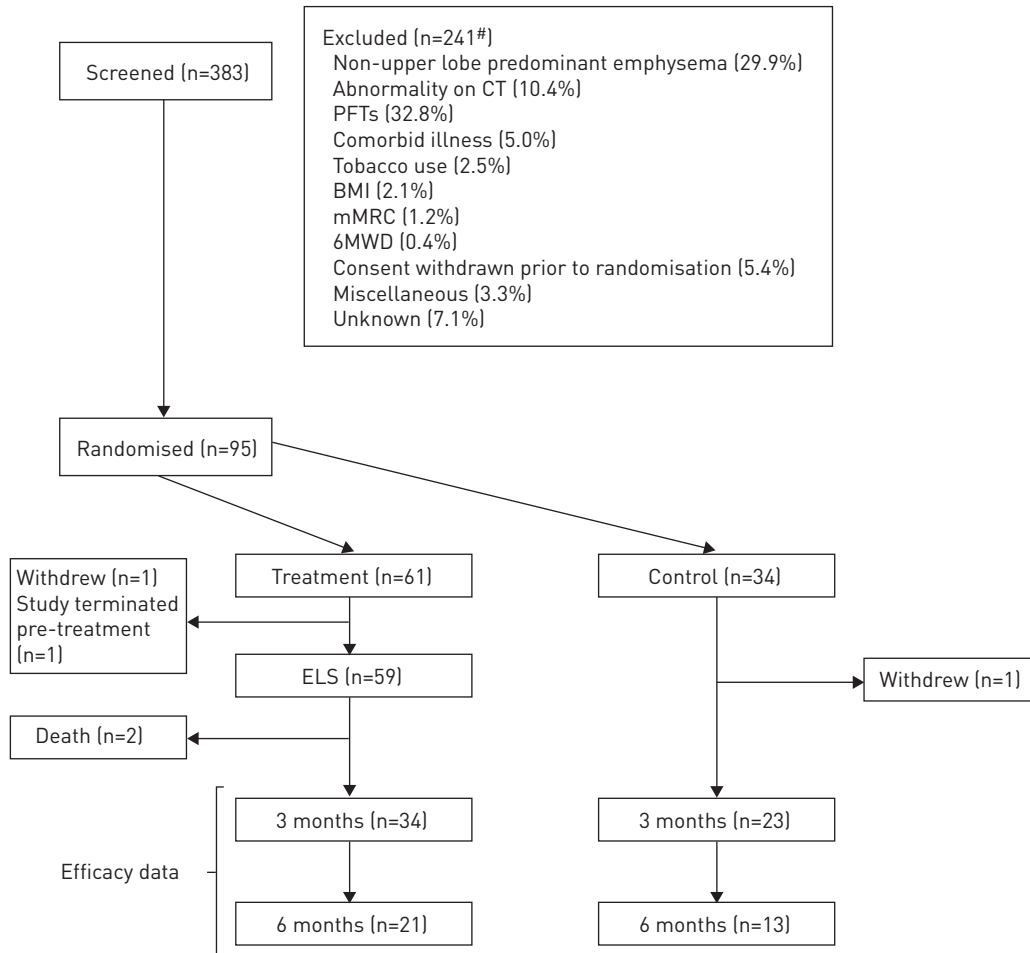
FIGURE 2 Consort diagram summarising enrolment, allocation, and follow-up. CT: computed tomography; PFTs: pulmonary function tests; BMI: body mass index; mMRC: modified Medical Research Council dyspnoea scale; 6MWD: 6-min walking distance; ELS: emphysematous lung sealant system. #: 47 patients were undergoing screening at the time of study termination.

had improvements in 6MWD compared with controls (31.0 m (0–41.3 m) *versus* -22.0 m (-41.3–9.3 m), p=0.019; data not collected at 3 months) as well as in SGRQ (-12 U (-22–-5 U) and -3 U (-5–1 U) in treatment and control groups, respectively; p=0.0072). There was no difference in dyspnoea between groups at 6 months (mMRC -1.0 U (-1.0–0 U) in treated patients *versus* 0 U (-1.0–0 U) controls; p=0.57). $FEV_1$ and SGRQ at baseline, 3 months and 6 months for each patient with 6-month follow-up data are plotted in online figure S1. The proportions of patients in each group achieving MCID in measured variables at 3 and 6 months are presented in table 2. Figure 3 depicts changes in $FEV_1$ at 6 months for individual patients. >50% of treated patients had a MCID in $FEV_1$ at 6 months *versus* 15% of control patients. Baseline and 6-month CT images for one treated patient demonstrate radiographic evidence of upper lobe deflation and lower lobe inflation with corresponding improvement in airflow obstruction (fig. 4).

### Adverse events

Two deaths occurred in the treatment group, both beyond the immediate peri-procedure period. One was due to a myocardial infarction 55 days after treatment in a patient treated for a COPD exacerbation/ pneumonia ~40 days following intervention. The second death occurred in a patient who developed pneumonia at a treatment site and died of sepsis 65 days post-procedure. There were no deaths in the control group (p-value for mortality difference 0.80). Three patients in the treatment group experienced four episodes of respiratory failure requiring invasive mechanical ventilation. Two of these patients required tracheostomy, but were eventually decannulated. There were no episodes of respiratory failure in the controls. 44% of treated patients and 18% of controls experienced adverse events requiring hospitalisation (p=0.0098) at any time during the study. The majority of events were respiratory (77% and 89% of events in

the treatment and control groups, respectively). Serious adverse events are summarised in table 3. Figure 5 shows examples of treatment-associated pulmonary complications, including pulmonary infiltrate, pleural effusion and possible lung abscess. For each patient with 6 months follow-up, the number of adverse events

TABLE 2 Proportion of patients achieving minimally clinically important differences in measured variables

|  | 3 months | | | 6 months | | |
|---|---|---|---|---|---|---|
|  | Treatment | Control | p-value | Treatment | Control | p-value |
| Subjects n | 34 | 23 | | 21 | 13 | |
| FEV1[#] | 47.1 | 8.7 | 0.001 | 52.4 | 15.4 | 0.068 |
| SGRQ[¶] | 58.8 | 47.8 | 0.414 | 76.2 | 46.2 | 0.159 |
| mMRC[+] | 55.9 | 26.1 | 0.026 | 52.4 | 38.5 | 0.664 |
| 6MWD[§] | NA | NA | NA | 52.4 | 0 | 0.0025 |

Data are presented as %, unless otherwise stated. FEV1: forced expiratory volume in 1 s; SGRQ: St George's Respiratory Questionnaire; mMRC: modified Medical Research Council dyspnoea scale; 6MWD: 6-min walking distance; NA: not available. [#]: MCID $\geqslant$12% and 100 mL [24] increase in post-bronchodilator FEV1 from baseline; [¶]: MCID $\geqslant$4 unit decrease from baseline [26]; [+]: MCID $\geqslant$1 unit decrease from baseline [25]; [§]: MCID 26 m increase from baseline [27].
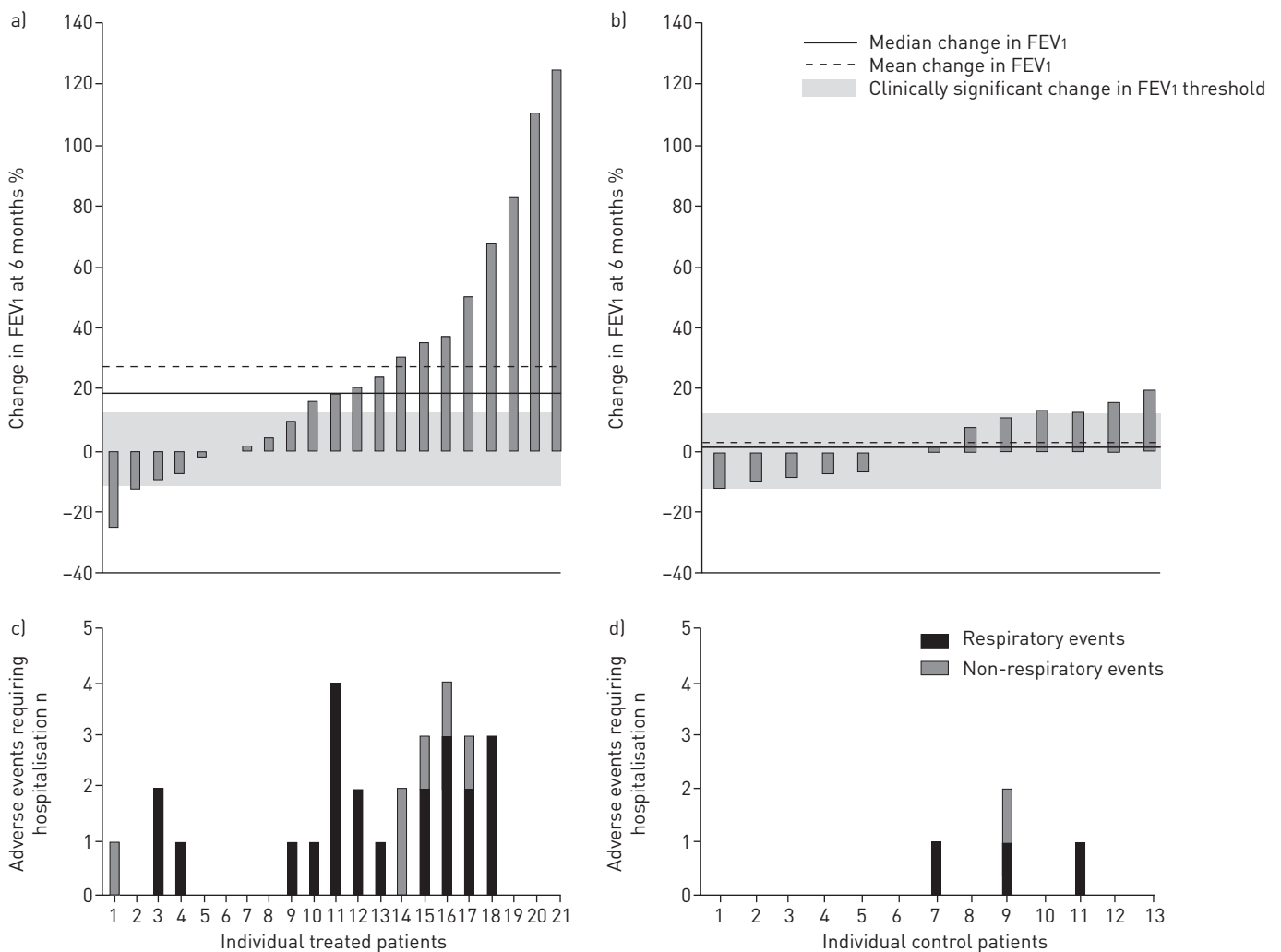


FIGURE 3 Percentage change in forced expiratory volume in 1 s (FEV1) from baseline to 6-month follow-up for a) treated patients and b) control patients. Each bar represents an individual patient. The regions outside the shaded zone indicate clinically significant changes in FEV1. Adverse events requiring hospitalisation for the corresponding individual c) treated patients and d) control patients.

requiring hospitalisation is presented in figure 3, concurrent with change in FEV1. In treated patients, there was a trend toward FEV1 responders (those with a MCID in FEV1) being more likely than nonresponders to have had respiratory adverse events (67% *versus* 27%, p=0.139).
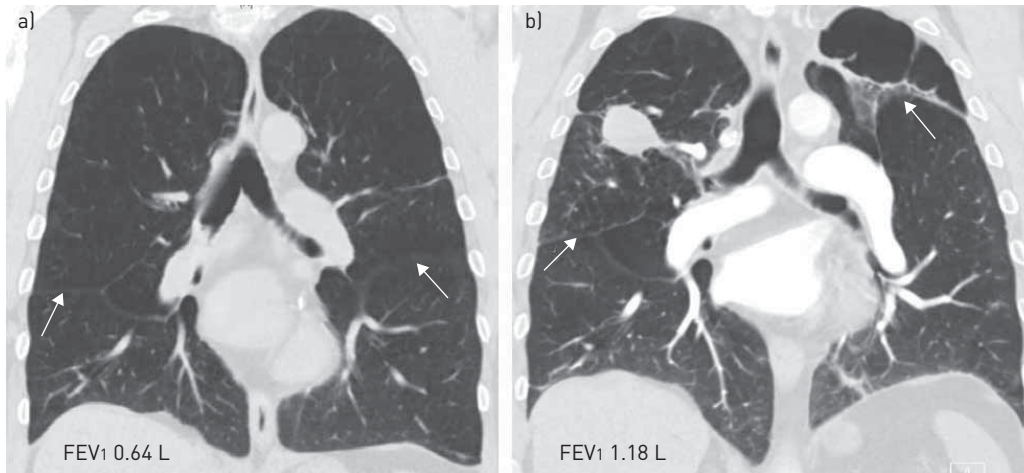


FIGURE 4 Coronal images at equivalent anatomic locations from chest computed tomographic (CT) scans of the same patient at various time points, with corresponding forced expiratory volume in 1 s (FEV1). The patient had a complicated post-treatment course with repeated admissions for fevers and pneumonia *versus* pneumonitis. ~6 months after treatment (after termination of the study) the patient was found to have a pulmonary embolus in the left upper lobar artery extending into segmental and subsegmental arteries. Given the location of the clot within collapsed/treated areas, there was suspicion of *in situ* thrombosis. The patient was treated with anticoagulant therapy. a) Baseline chest CT; b) clinically-acquired chest CT taken almost 6 months post-treatment demonstrates a treatment site in the right upper lobe. Compared with the baseline CT, the diaphragms and fissures (arrows) are now elevated, consistent with deflation. The patient's FEV1 improved 84% from baseline (follow-up spirometry obtained outside the study).

TABLE 3 Serious adverse events

| | 0–30 days Patients (events) | | 31–60 days Patients (events) | | 61–90 days Patients (events) | | >90 days Patients (events) | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | Treatment | Control | Treatment | Control | Treatment | Control | Treatment | Control |
| **Death** | | | 1 (1) | | 1 (1) | | | |
| **Respiratory failure#** | 3 (3) | | 1 (1) | | | | | |
| **Pneumonia** | 2 (3) | | 6 (7) | | 4 (5) | | 3 (3) | 2 (2) |
| **COPD exacerbation** | 5 (5) | 2 (2) | 1 (1) | 1 (2) | 1 (1) | | 4 (6) | 1 (1) |
| **PAIR** | 4 (5) | | 1 (1) | | | | | |
| **Pneumothorax** | 1 (2) | | | | | | | |
| **Lung cavity** | | | | | | | 1 (1) | |
| **Lung mass** | | | | | | | | 1 (1) |
| **Dyspnoea** | 1 (1) | | | | | | | |
| **Myocardial infarction** | | | 1 (1) | | | | | |
| **Chest pain** | | | 1 (1) | | | | | |
| **Tachyarrhythmia** | | | | | | | 1 (1) | 1 (1) |
| **Sepsis** | | | 1 (1) | | 1 (1) | | | |
| **Fever** | | | 1 (1) | | | | | |
| **Acute kidney injury** | | | 1 (1) | | | | | |
| **Urinary tract infection** | | | | | 1 (1) | | 1 (1) | |
| **Ileus** | | | 1 (1) | | | | | |
| **Inguinal hernia** | | | | | | | 1 (1) | |
| **Depression** | | | 1 (1) | | | | | |

Data are presented as n (n). Respiratory events are highlighted in grey. COPD: chronic obstructive pulmonary disease; PAIR: post-treatment acute inflammatory response (fever, dyspnoea, cough, chest pain and/or elevated inflammatory markers). #: respiratory failure was considered an outcome rather than an event, so was not included in the composite of respiratory events.
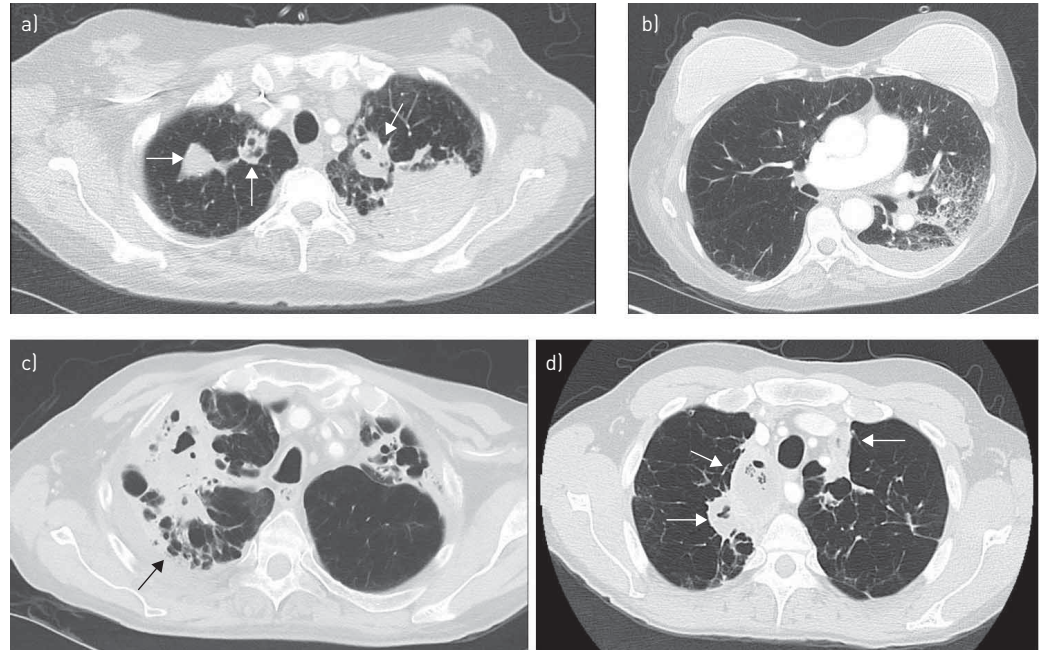
FIGURE 5 Axial images from chest computed tomography (CT) scans (performed for clinical indications) of patients treated with the emphysematous lung sealant system, displaying the appearance of the lungs and potential complications post-treatment. a, b) CT obtained 66 days after treatment when patient 1 presented with dyspnoea and abdominal pain. The patient was treated with broad-spectrum antibiotics for pneumonia. A thorough abdominal work-up was negative. Steroids were added to reduce potential systemic inflammation as a result of her treatment (C-reactive protein 66.3 mg·L$^{-1}$); her symptoms improved rapidly. a) Bilateral apical opacities consistent with treatment sites (arrows), as well as dense consolidation in the posterior left upper lobe (beyond expected treatment site). b) Ground glass opacification in the untreated left lower lobe and a small pleural effusion. c) CT scan obtained 70 days after treatment when patient 2 presented with persistent shortness of breath and fevers despite treatment with broad-spectrum antibiotics. CT shows bilateral upper lobe consolidation and a right-sided pleural effusion (arrow; transudative). The patient's condition improved upon treatment with steroids. d) CT obtained 23 days after treatment when patient 3 presented with fever, lethargy, and rust-colored sputum. CT demonstrates consolidation and complex air-fluid collections bilaterally, which may indicate lung abscesses rather than post-treatment changes (arrows). The patient improved upon treatment with broad-spectrum antibiotics.

## Discussion

At termination of this randomised controlled trial, ELS therapy compared to medical treatment produced encouraging physiological, functional, and quality-of-life benefits for up to 6 months in patients with severe upper lobe predominant emphysema. While treatment was associated with frequent adverse events and the time for primary end-point data collection was not reached, accrued data suggest that this novel approach, utilising a polymer sealant that flows into the alveolar compartment and collapses the hyperinflated lung is procedurally well-tolerated and can be highly effective in this high-risk group. >50% of patients randomised to treatment experienced MCID in FEV1, SGRQ, mMRC and 6MWD at 6 months.

These findings are consistent with ELS pilot studies [10, 18, 19]. In 20 patients undergoing bilateral upper lobe treatment with ELS, KRAMER et al. reported significant improvements in FEV1, dyspnoea and hyperinflation at 12 months, confirming the efficacy of this approach [10]. Long-term follow-up of this cohort for 2 years revealed a trend toward improvement in FEV1 (mean±SD change 14.5±33.1%, p=0.058) with eight out of 16 patients achieving a MCID in FEV1, suggesting durability of this approach [28]. The current randomised study extends this work by adding a critical control arm.

In our limited data set, efficacy results with ELS approached those of surgical lung volume reduction, although overall adverse events were also prominent. In NETT, the mean percentage change in FEV1 from baseline to 6 months for non-high risk LVRS patients was 28.5±33.6% compared with 27.5±40.1% in ASPIRE (fig. 3) [1]. Improvements in respiratory-specific health-related quality of life were also comparable (mean absolute change in SGRQ was -11±15 U in NETT versus -12±15 U in this study at 6 months) [1]. 90-day all-cause mortality after LVRS was 5.5% (non-high-risk patients) [3] and 3.4% post-ELS therapy. While the combined incidence of post-treatment respiratory failure and pneumonia in the first 30 days following ELS was lower than following surgery (10.2% versus 54% in NETT) [3], in ASPIRE, adverse events

continued through later follow-up (overall incidence of post-ELS respiratory failure and pneumonia 37%), potentially indicative of distinct pathological mechanisms between surgical and sealant-based approaches.

Ongoing adverse events following ELS may result from intense subacute inflammation arising from chemically-induced collapse and scarring of hyperinflated lung tissue. In a separate study of 29 patients treated with ELS, mean C-reactive protein (CRP) level 3 months post-treatment rose three-fold compared to baseline, indicative of significant inflammation. By 6 months, CRP dropped below baseline, remaining so at 1 year [29]. Given the premature termination of this study, the incidence of ELS-related adverse events after this potential "inflammatory window" remains unclear, although in the pilot study [28], no COPD exacerbations or pneumonia occurred after the first year.

ELS in its current form has clear limitations. Beyond adverse events, the therapy is irreversible, in contrast to other ELVR techniques. Still, the potential benefits of technological and procedural modifications, though speculative, merit consideration. For example, all patients received treatment at two upper lobe subsegments in a single session. While a staged procedure may have prolonged the inflammatory response, the intensity of the response may have been attenuated. It is possible that treating the most diseased side first, and potentially only, may have resulted in adequate efficacy with reduced risk. Changes in sealant formulation that reduce chemical irritation may also help achieve an ELS-like product with an improved safety profile. Moreover, the small number of participants with follow-up data precluded our ability to determine patient-specific characteristics predictive of those most likely to achieve benefit and those most likely to experience harm.

Such modifications may not positively alter the risk:benefit profile of ELS. Indeed, treatment responders in this study tended to have more respiratory adverse events. Considering data from available randomised controlled trials, it is possible that safer ELVR therapies may intrinsically be associated with reduced efficacy (*i.e.* endobronchial valves and airway bypass) [5, 13], while more effective treatments may have more severe side-effects [9, 11, 16], even when the mechanism of action is not clearly linked with inflammation [9, 16]. For example, while >50% of patients treated with vapuor ablation or airway coil therapy experienced clinically important improvements in $FEV_1$, SGRQ and 6MWD, the incidence of serious respiratory adverse events at 90 days was 57% and 39% in each study, respectively [9, 11]. Even with endobronchial valves, which have generally proven less efficacious, greatest response (*i.e.* in cases with intact fissures and lobar occlusion) has been linked with higher risk (more pneumothoraces) [5, 30, 31]. Thus, changing the anatomical structure of the lung sufficiently to achieve clinical benefit may inherently incur higher risk, even if achieved through a less invasive, endoscopic approach and regardless of method or degree of inflammation.

Despite its early termination, this study provides controlled proof of concept of sealant-based ELVR. The procedure itself was associated with low morbidity and high technical success, yet efficacy was offset by significant cumulative adverse events. For patients with advanced emphysema and few options, these results are disappointing. At a time when access to lung transplantation for end-stage emphysema is becoming more restricted due to new organ allocation guidelines [32], and patients are often too sick to undergo surgery, minimally invasive therapies are desperately needed, yet remain unapproved in USA. If effective ELVR therapy is ultimately determined to have a high inherent risk, independent of technique, then such treatments may be restricted to only the healthiest, most functional patients with end-stage lung disease, leaving a significant residual unmet medical need. Alternatively, we may need to re-examine the acceptable balance of therapy-related side-effects against the potential for significant clinical benefit in end-stage emphysema.

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