Segmental volume reduction using thermal vapour ablation in patients with severe emphysema: 6-month results of the multicentre, parallel-group, open-label, randomised controlled STEP-UP trial


Summary

Background Lung volume reduction of emphysematous lobes results in clinical improvement for patients with severe emphysema. However, some segments within a lobe are often substantially more diseased than others, thereby warranting a more targeted approach of the emphysematous parts of a lobe. We therefore did a study to assess whether or not selective sequential treatment of the more diseased upper lobe segments with bronchoscopic vapour ablation led to clinical improvement.

Methods For the multicentre, parallel-group, randomised, controlled, open-label Sequential Staged Treatment of Emphysema with Upper Lobe Predominance (STEP-UP) trial, adult patients aged 45–75 years with severe, upper lobe-predominant emphysema with a forced expiratory volume in 1 s (FEV₁) between 20% and 45%, substantial hyperinflation, and post-rehabilitation 6-min walk test (6MWT) greater than 140 m were enrolled from 13 hospital sites in Europe (ten sites) and Australia (three sites). A computer-generated blocked randomisation scheme (block size three per site based on a random table from an independent biostatistician) stratified by site was used to randomly assign enrolled patients 2:1 to segmental vapour ablation (treatment group) or standard medical management (control group). Patients and investigators were not masked to group assignment. The primary efficacy endpoints were statistically significant changes in FEV₁ and St George’s Respiratory Questionnaire (SGRQ-C) scores between trial groups at 6 months, analysed by intention to treat. This study is registered with ClinicalTrials.gov, number NCT01719263.

Findings Between June 30, 2013, and Oct 1, 2014, 134 patients were screened and 70 were enrolled and randomly assigned: 46 to the treatment group and 24 to the control group. One patient in the treatment group did not receive treatment because of physician decision post-randomisation; this patient is excluded from all analyses. The mean relative improvement in FEV₁ between the treatment group versus the control group was 14·7% (95% CI 7·8–21·5%; p<0·0001) and in SGRQ-C was –9·7 points (95% CI –15·7 to –3·7; p=0·0021). COPD exacerbation was the most common serious adverse event, occurring in 11 (24%) of 45 patients in the treatment group and one (4%) in the control group. One exacerbation resulted in a patient death 84 days after treatment; this was judged by the data and safety monitoring board to be possibly related to treatment. No pneumothorax occurred within 30 days of treatment.

Interpretation Compared with standard medical management, targeted thermal vapour ablation of more diseased segments and preservation of less diseased segments resulted in clinically meaningful and statistically significant improvements in lung function and quality of life at 6 months, with an acceptable safety profile.

Funding Uptake Medical.
Lung volume reduction technique on a sub-lobar basis to vapour ablation and the first use of any bronchoscopic therapy for emphysema using a segmental approach that targets only the more diseased segments for reduction and reduces the volume treated per session. Thermal ablation in particular was found to reduce individual segments without the need for complete lobar treatment. These criteria were incorporated into the design of the STEP-UP trial to find an optimum balance between vapour ablation’s efficacy and safety profiles.

**Evidence before this study**

We searched PubMed from Jan 1, 1999, up to Oct 1, 2015, using different terms associated with the treatment of emphysema, including: “lung volume reduction surgery”, “bronchoscopic lung volume reduction”, “severe emphysema”, “collateral ventilation”, and “intralobar heterogeneity”. We included only studies published in English. Successful lung volume reduction and minimal clinically important difference in lung function from vapour ablation have been previously reported in an early-phase feasibility study, the VAPOR trial, investigating a unilateral lobar approach. The early-phase experience with vapour ablation suggested that the occurrence and severity of serious adverse events typically increased with the volume of lung treated per session. Furthermore, our search emphasised the limitations of collateral ventilation and the need to target the whole lobe with endobronchial valve therapy. This finding established the need for a bronchoscopic therapy for emphysema using a segmental approach that targets only the more diseased segments for reduction and reduces the volume treated per session. Thermal ablation in particular was found to reduce individual segments without the need for complete lobar treatment. These criteria were

**Methods**

**Study design and participants**

The study design and eligibility criteria have been reported previously.15 In brief, adult patients with upper lobe-predominant heterogeneous emphysema were enrolled from ten hospital sites in Europe and three in Australia. The key inclusion criteria were age 45–75 years, evidence of upper lobe-predominant heterogeneous emphysema (>15% difference in lung density between targeted upper lobe segment and its respective lower lobe, and hyperinflation).15 FEV1, between 20% and 45% predicted, total lung capacity at least 100% predicted, substantial hyperinflation, post-rehabilitation 6-min walk test (6MWT) greater than 140 m, and non-smoking for at least 6 months before study enrolment. Patients with incomplete fissures or collateral ventilation were not excluded from this trial. However, individuals with any condition that would interfere with the completion of study follow-up assessments or bronchoscopy or would adversely affect study outcomes, and those with pulmonary hypertension, clinically significant bronchiectasis, or recent COPD exacerbations, were excluded. The full inclusion and exclusion criteria are listed in the panel.

All enrolled patients provided a completed written informed consent form that was reviewed and approved by the institutional review board or ethics committee of all participating hospital sites. All participating sites provided ethics consent and protocol approval.

**Randomisation and masking**

All patients were screened and confirmed for treatment eligibility before randomisation. Randomisation to the treatment or control groups was based on a computer-generated blocked randomisation scheme (block size three per site). The blocking was separated by site and the exact blocking scheme was not disclosed to the sites or the sponsor. Since this study was open label, neither patients nor study personnel were masked to group assignment.
Inclusion criteria

- Age ≥40 and ≤75 years
- Heterogeneous emphysema with upper-lobe predominance
- Forced expiratory volume in 1 s between 20% and 45% predicted
- Total lung capacity ≥100% predicted
- Residual volume ≥150% predicted
- Post-rehabilitation 6-min walk test >140 m
- Marked dyspnoea scoring >2 on the modified Medical Research Council (mMRC) scale
- Arterial blood gas levels of: PaCO₂ ≤50 mm Hg; PaO₂ >50 mm Hg on room air
- Non-smoking for 6 months before study enrolment
- Optimised medical management (treatment consistent with GOLD guidelines)
- Evidence of completed pulmonary rehabilitation: ≥6 weeks outpatient or ≥3 weeks inpatient within 6 months of enrolment; or patient has or continues to participate in regular physical activity beyond activities of daily living (ie, a walking programme) for ≥6 weeks under the supervision of a health-care professional
- Mentally and physically able to cooperate with the study procedures and to provide informed consent to participate in the study

Exclusion criteria

- Any disorder or illness that would interfere with the completion of the study follow-up assessments, bronchoscopy, or that would adversely affect study outcome
- Diffusing capacity of the lungs for carbon monoxide <20% predicted
- Body-mass index <18 kg/m² or >32 kg/m²
- Pulmonary hypertension: peak systolic pulmonary arterial pressure >45 mmHg or mean pulmonary arterial pressure >35 mmHg; or right heart catheter measurements will be considered definitive over echocardiogram measurements
- Highly diseased lower lobes (density: tissue to air ratio of <11%)
- Clinically significant bronchiectasis
- Pneumothorax or plural effusions within previous 6 months
- Any history of heart and/or lung conditions, stroke, heart failure, transplant, lung volume reduction or resection, bullectomy, or implantable cardiac defibrillator implant
- Recent COPD exacerbation in preceding 6 weeks, or >3 COPD-related hospital admissions requiring antibiotics in past 12 months
- Daily use of systemic steroids or >5 mg prednisolone
- Single large bulla (defined as more than a third of the volume of the lobe) in upper lobe
- Coagulopathy or current use of anticoagulants

Panel: STEP-UP trial inclusion and exclusion criteria

Procedures

Patients in the control group received standard medical management consistent with Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, which comprised removal of risk factors such as smoking, medical therapy with one or more bronchodilators, pulmonary rehabilitation (encouraged and recommended), and the use of inhaled corticosteroids. Patients in the treatment group received vapour ablation treatment of one to two segments during each treatment session in addition to standard medical management. During bronchoscopic vapour ablation treatment, lung volume reduction is induced thermally by the delivery of water vapour to individual upper lobe segments over the course of a stepped (two-stage) procedure. Water vapour is delivered by bronchoscopically positioning a balloon catheter into the target region. A balloon located at the tip of the catheter is inflated to occlude the target region and 3–10 s of water vapour is delivered. One segment was targeted during the first treatment session and up to two segments were targeted during the second session. The protocol restricted treatment to one upper lobe per session. CT quantitative analysis software (VIDA Diagnostics, Coralville, IA, USA) was used to do a sub-lobe analysis and measure the tissue mass and air volume of each segment. This analysis was used to ascertain the specific treatment time needed to achieve a target dose of 8–5 calories per gram of lung tissue. The sub-lobe analysis also established which segments to target based on volume and disease state as defined by tissue-to-air ratio—a measure of lung density. The details of this algorithm and the measure of lung density have been detailed previously. In brief, tissue to air ratio is calculated by allocation of voxels based on their density value to the appropriate air or tissue measurement. Tissue measurements are divided by the air measurements for each region to ascertain the ratio.

The first treatment session was scheduled within 1 week of the screening visit and the second treatment session was scheduled 13 weeks after the first treatment session. A follow-up high-resolution CT scan was scheduled for the treatment group only at the 6-month follow-up visit to assess lung volume reduction; this was not done in the control group because of ethics concerns related to radiation exposure. Follow-up clinic visits were scheduled by the study coordinator at 2, 8, 12, 21, and 26 weeks, with telephone follow-up calls at 4 and 17 weeks for both study groups. The treatment group had additional visits at 1, 14, and 15 weeks. Spirometry, exercise tolerance (6MWT), lung volumes from body plethysmography, and quality of life (COPD-specific version of the St George’s Respiratory Questionnaire [SGRQ-C]) were assessed at 12 and 26 weeks by the study coordinator at the clinic. Spirometry and SGRQ-C were also assessed at 8 and 21 weeks by the study coordinator at the clinic.

Outcomes

The primary efficacy endpoints were the change in FEV₁ and SGRQ-C scores between the treatment and control
groups at 6 months, analysed by intention to treat. Secondary efficacy endpoints were lung volume reduction as assessed by high-resolution CT, other spirometry measures (eg, forced vital capacity [FVC]), body plethysmography lung volume measures, COPD Assessment test (CAT), modified Medical Research Council dyspnoea scale (mMRC), diffusing capacity of the lungs for carbon monoxide (DLCO), and 6MWT. A binary responder analysis was also done to establish the minimal clinically important difference (MCID) in patients for the following parameters: FEV₁ (≥12%), SGRQ-C (≤–8 points), and 6MWT (≥26 m). Twenty-eight subjects were treated (n=46) and considered the segmental treatment status or location in order to maintain masking during high-resolution CT analysis. Safety was assessed mainly by a comparison of the occurrence of serious adverse events between the trial groups.

**Statistical analysis**
We calculated the sample size using 80% power, a type I error rate of 0.05, and a 2:1 randomisation allocation. We used Power Analysis version 11.0 and Sample Size version 11.0 software for the calculations. All patient data were entered into an electronic database (eClinicalOS, Morrisville, NC, USA). Analysis was done on the intention-to-treat population at 6 months. We used the Hochberg method to compensate for the multiple comparisons resulting from two endpoints and assessed whether or not the primary endpoint had been reached. This method allowed for two different scenarios to determine achievement of the primary endpoint for a positive trial: if both primary endpoints (FEV₁ and SGRQ-C) reached clinical significance at the 0.05 level, or if either one of the two endpoints reached clinical significance at the 0.025 level. No imputations were done for the analysis. We computed p values for discrete variables using Fisher’s exact test and p values for continuous variables (eg, sex) using the two-sample t test. A data and safety monitoring board and clinical events committee closely and independently monitored the safety of the STEP-UP trial. This study is registered at ClinicalTrials.gov, number NCT01719263.

**Role of the funding source**
The funder of the study (Uptake Medical Corp, Tustin, CA, USA) had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All study management and data collection was done by the study sites and was monitored and audited by clinical research organisations (Acromion and Novotech [for Australia]). All safety data were reviewed and adverse events were adjudicated by the data and safety monitoring board. The authors of the study had full access to all the data in the study and had final responsibility for the decision to submit for publication, including the report content and conclusions.

**Results**
Between June 30, 2013, and Oct 1, 2014, 134 patients were screened and 70 were enrolled from the 13 centres in Australia and Europe. Enrolment per centre ranged from one to 13 patients, and the median number of patients enrolled per site was four. The maximum relative enrolment from a single site was 19%; this site was the Alfred Hospital (Melbourne, VIC, Australia). Centre had a enrolment from a single site was 19%; this site was the Alfred Hospital (Melbourne, VIC, Australia). Centre had a.
One patient in the treatment group did not receive treatment because of physician decision post-randomisation. This patient was excluded from all analyses in this report. Of the 45 patients who received treatment, two missed their 3-month 6MWT follow-up, one missed their 3-month spirometry follow-up, and one patient died from exacerbation. Three patients missed their 6-month spirometry follow-up. Of these three patients, two missed their entire 6-month follow-up visit. Of the 24 patients in the control group, four missed their 3-month 6MWT follow-up. Of these four patients, one missed their entire 3 month follow-up visit and one withdrew from the study. Figure 1 shows the enrolment, randomisation, and attendance during follow-up visits for the study.

Table 1 shows the enrolment, randomisation, and attendance during follow-up visits for the study.

Table 1 shows the baseline characteristics of patients in each trial group. Fissure completeness was assessed by high-resolution CT analysis software. Incomplete fissures (90% threshold), which are often indicative of collateral ventilation, were recorded in at least one lung in 78% of all enrolled patients in both groups.21,22

Vapour ablation therapy was given to 45 patients in the treatment group. Of these patients, five received only a single vapour treatment and did not proceed to the second treatment session for the following reasons: one was not eligible because of extensive improvement at 3 months, two were excluded because of health-related complications, one patient was discovered to be currently on anticoagulants, and one patient died before the second treatment session. During the first treatment session, 11 patients received conscious sedation and 34 received general anaesthesia. During the second treatment session, seven patients received conscious sedation and 33 received general anaesthesia. The treating physician or the anaesthetist was responsible for choosing the use of conscious versus general sedation. This decision was dictated by each site's standard of practice and experience. Of the 40 patients who received the second treatment session, 32 patients had two segments treated and eight patients had one segment treated. The less diseased segments were preserved and more diseased segments were treated. On average, the treated segments had a density (as measured by the tissue-to-air ratio) of 8·5% (SD 1·8%) at baseline. The preserved segments had a higher average density of 10·4% (SD 2·2%), indicating that the untreated segments were healthier than the treated segments.

Lung volume reduction was assessed by analysis of the high-resolution CT scans at 6 months post-ablation with use of high-resolution CT analysis software. High-resolution CT scans were not obtained for the control group because of ethics concerns related to radiation exposure. High-resolution CT scan analysis was available for 40 of 45 patients in the treatment group at 6 months. Of these 40 individuals, 36 received two treatments. High-resolution CT scan analysis was unavailable for five patients in the treatment group, either because the scans were not acquired at 6 months (three patients), or a non-conforming high-resolution CT was acquired at 6 months and could not be analysed by the software (one patient), or a high-resolution CT was acquired before the 6-month visit as clinically indicated because of the occurrence of pneumothorax and thus could not be assessed for lung volume reduction (one patient). The mean reduction for segments was –42% (SD 26%) for segments treated during session 1 and –33% (SD 20%) for segments treated during treatment session 2 (table 2). An ad-hoc Pearson correlation was done between the tissue volume change of treated segments and the absolute change in FEV₁ (r=−0·47) and SGRQ-C (r=0·37). Because this is a sub-lobar reduction, portions of the healthier, preserved neighbouring segments of the targeted lobe expanded as the diseased, treated segments shrank (figure 2). Nearly three-quarters of these neighbouring segments expanded neighbouring segmental reduction. For this reason, lobar volume reduction of the target lobe is less relevant than with lobar volume reduction where all segments are reduced.

The primary efficacy endpoints, the between-group differences in FEV₁ (% and the SGRQ-C total score (points), are reported at 3 and 6 months following the first scheduled treatment session (or the randomisation date for the control group). At 3 months, the average difference in FEV₁, between trial groups was 10·1% (95% CI 3·2–16·9; p=0·0047) and at 6 months it was 14·7%
The diseased, treated LB3 segment (red) was effectively reduced in volume post-vapour ablation. The healthier, preserved LB1 segment (green) expanded post-vapour ablation.

Table 2: Segmental and lobar tissue volume changes at 6 months in the treatment group

<table>
<thead>
<tr>
<th></th>
<th>First treatment (n=40) % volume change at 6 months</th>
<th>Second treatment (n=36) % volume change at 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced segment(s)</td>
<td>-42% (26%)</td>
<td>-33% (20%)</td>
</tr>
<tr>
<td>Preserved segment(s)</td>
<td>+11% (32%)</td>
<td>+11% (21%)</td>
</tr>
<tr>
<td>Treated upper lobe</td>
<td>-12% (15%)</td>
<td>-16% (13%)</td>
</tr>
<tr>
<td>Preserved middle lobe or lingula</td>
<td>+14% (54%)</td>
<td>+8% (10%)</td>
</tr>
<tr>
<td>Preserved lower lobe</td>
<td>+8% (12%)</td>
<td>+8% (14%)</td>
</tr>
</tbody>
</table>

Data are n or mean change (SD). The lingula was treated for one patient. In this case, there was a tissue volume change of -100% in the treated region.

Figure 2: Radiographic image of treated (red) and preserved (green) segments for a STEP-UP patient at baseline and 6 months post-treatment

The diseased, treated LB3 segment (red) was effectively reduced in volume post-vapour ablation. The healthier, preserved LB1 segment (green) expanded post-vapour ablation.

(7.8–21.5; p<0.0001). The mean difference in SGRQ-C between trial groups at 3 months was −6.6 points (95% CI −12.4 to −0.9; p=0.0243) and at 6 months was −9.7 points (−15.7 to −3.7; p=0.0021). Table 3 shows the results for the primary efficacy endpoints and individual patient data are in appendix pp 3–4.

FEV₁, forced vital capacity, and residual volume showed significant (p<0.05) between-group improvements at 6 months (table 4). Responses were recorded even after one treatment session (table 5). Improvements in the 6MWT, BODE index, and mMRC scores were not statistically significant between trial groups but were statistically significant compared with baseline values for both groups at 3 months and at 6 months (appendix p 7).

The binary responder analysis was done at 3 months and 6 months to indicate the minimal clinically important difference in pulmonary function (FEV₁ ≥12%), quality of life (SGRQ-C ≤−8 points), and exercise tolerance (6MWT ≥26 m). The 8-point threshold was used for SGRQ-C to keep consistent with the most rigorous assessment of SGRQ in previous publications. Results using the accepted 4-point threshold are also presented (table 5). At least two-thirds of patients in the treatment group had a minimal clinically important difference for the two primary endpoints of either FEV₁ or SGRQ-C at 6 months (table 5). The proportion of patients who achieved a minimal clinically important difference in the individual parameters increased after the second treatment (table 5).

Of the patients who achieved a minimal clinically important difference in FEV₁, the mean improvement was 24% (SD 10%). Of patients that achieved a minimal clinically important difference in SGRQ-C, the mean improvement was 20 points (SD 11). Figure 3 shows the between-group improvements in FEV₁, SGRQ-C, and 6MWT.

Serious adverse events were monitored during the course of the study in both trial groups as the primary safety endpoint. The occurrence of adverse events within the first 90 days of treatment is expected in the studied population because, as is common to published randomised controlled trials of any bronchoscopic lung volume reduction therapy, an increase in serious adverse events in the treatment group was noted during the post-treatment phase. In the STEP-UP study, exacerbations and pneumonia 90 days post-treatment 1 and 2 were significantly more common in the treatment group than in the control group and resolved with standard of care with no mechanical ventilation or respiratory failure. Notably, one case of pneumothorax occurred during the 90 days post-treatment 1 and 2 period; however, it was asymptomatic and non-serious since it resolved without the need for chest tube insertion or surgery and did not result in prolonged hospital stay, mechanical ventilation, respiratory failure, or death. No cases of major haemoptysis requiring admission to hospital occurred within 90 days of the first treatment session. In the treatment group, six patients had pneumonia or pneumonitis and six had COPD exacerbations requiring hospital admission within the same timeframe. One patient died 84 days after treatment from complications related to COPD exacerbation. This death was reviewed by the data and safety monitoring board and was judged to be possibly related to treatment. Following the second treatment session, one patient had pneumothorax (76 days after treatment), one had major haemoptysis, three had pneumonia or pneumonitis, and six had COPD exacerbations necessitating admission to hospital within 90 days of ablation. The patient with pneumothorax did not need surgery or chest tube insertion and made a full recovery. The case of major haemoptysis was controlled through balloon tamponade and did not need any other intervention. The patient made a full recovery. Of the patients who did not receive a second treatment, one had two occurrences of pneumonia or pneumonitis more than 90 days after treatment session 1. The occurrence of these respiratory serious adverse events is reported in table 6.

COPD exacerbation occurred in 11 (24%) of 45 patients in the treatment group after up to two sessions of treatment with vapour. The mean duration of hospital stay for these events was 7 days (SD 6). The incidence of pneumonia or pneumonitis was 18% with mean duration
of hospital stay of 11 days (SD 7). Overall, the procedure was well tolerated with routine hospital ward recovery before discharge, there were no cases of respiratory failure, and no patients needed admission to intensive care. All adverse events were manageable post-treatment and were resolved with standard medical care with the exception of one patient.

Discussion
The STEP-UP study with a staged treatment strategy targeting only the more diseased segments of an upper lobe has shown that this treatment approach leads to statistically and clinically significant improvements compared with standard care. Compared with standard care, both the primary efficacy endpoints of FEV₁ and SGRQ-C total score in the STEP-UP study were statistically significant at 3 months (before treatment session 2) and at 6 months post-vapour ablation therapy. Furthermore, around two-thirds of patients in the treatment group had a minimal clinically important difference in FEV₁ (≥12%) or SGRQ-C (≤–8 points) at the 3-month and 6-month follow-up visits. The results at 3 months suggest that the treatment of one segment alone can positively affect lung function and quality of life. This targeted treatment strategy preserves less diseased segments. Since emphysema is an inexorable progressive disease, a strategy that preserves lung tissue might be highly desirable. The statistically significant results at 6 months suggest that staged ongoing treatment can capture additional improvements over time, which allows a personalised approach to treatment of the most diseased segments at the initial stage, assessment of patient response, and consideration of further treatment on an individual basis.

The ability of vapour ablation to reduce emphysematous segments irrespective of interlobar or intralobar collateral ventilation allows for precise targeting of only the more diseased segments of a lobe.21,22,24 Interlobar collateral ventilation is often associated with incomplete fissures, which were observed in most of the patients in the
STEP-UP trial. The percentage of STEP-UP patients with collateral ventilation was higher than in most studies, which might be due to a propensity for some STEP-UP trial sites to pre-screen out patients with no collateral ventilation for valve treatment.

All adverse events that occurred during STEP-UP were managed with standard medical care with the exception of one patient (the one who died). The staged treatment seems to have a more favourable safety profile than lobar reduction where all upper lobe segments are reduced during a single procedure. Average duration of hospital stay was substantially shorter than what has been reported for previous trials investigating vapour ablation. The pneumothorax rate in patients in the treatment group was low and the one patient who had a pneumothorax more than 30 days after treatment did not need chest tube insertion or surgery. Conversely, the low incidence of pneumothorax in the STEP-UP trial might be attributed to the gradual nature of lung volume reduction with thermal vapour ablation. Volume reduction following thermal vapour ablation is a natural process that typically occurs gradually over a 4–6-week period. This gradual reduction might reduce the tension on the lung to the extent that pneumothorax incidence is much lower.

A strength of our study was the randomised controlled approach for investigating thermal vapour ablation and segmental bronchoscopic lung volume reduction. The investigator, patients, and sponsor were masked to any compiled summary statistics for each trial group during the entire treatment phase of the study. For a double-blinded effort, a sham procedure would be needed for the control group. However, patients in the control group were not subjected to sham procedures because of ethical concerns related to complications associated with bronchoscopy and anaesthesia in this highly compromised patient population. Because patients and hospital staff were aware of treatment status, subjective measures might have been reported with an unintentional bias. Likewise, a larger adverse event profile for the treatment group could perhaps be partly attributable to the same cause.

Emphysema is a progressive disease with no known cure. Lung volume reduction therapies offer clinically meaningful improvement in pulmonary function, quality of life, and exercise capacity, but these results tend to diminish with time as the disease progresses. Vapour ablation therapy in a targeted manner leads to clinically meaningful improvements, and the potential to administer additional treatments in the future is an exciting aspect of thermal ablation therapy.

Contributors
All authors contributed to the recruitment of patients, collection of data, and data interpretation. FJFH and PLS wrote the first draft of the report. All authors contributed to data interpretation and subsequent revisions and approved the final submitted version.

Table 6: Serious adverse events and hospital admissions

<table>
<thead>
<tr>
<th>Event</th>
<th>Treatment group (n=45)</th>
<th>Control group (n=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>After treatment session 1</td>
<td>After treatment session 2</td>
</tr>
<tr>
<td>COPD exacerbation</td>
<td>6 (13%)</td>
<td>6 (13%)</td>
</tr>
<tr>
<td>Pneumonia or pneumonitis</td>
<td>6 (13%)</td>
<td>3 (8%)</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>0</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Requiring surgery</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Requiring chest tube(s)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>0</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Death</td>
<td>1 (2%)</td>
<td>0</td>
</tr>
<tr>
<td>Any serious respiratory adverse event</td>
<td>10 (22%)</td>
<td>9 (22%)</td>
</tr>
</tbody>
</table>

Data are n (%). *180 days after treatment session 1 or 90 days after treatment session 2.

Figure 3: Endpoints for pulmonary function, quality of life, and exercise tolerance in each trial group
FEV1=forced expiratory volume in 1 s. SGRQ=St George’s Respiratory Questionnaire. 6MWT=6-min walk test.

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Treatment group from baseline</th>
<th>Control group from baseline</th>
<th>Between-group difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1 improvement (%)</td>
<td>10·1% (p=0·0047)</td>
<td>14·7% (p&lt;0·0001)</td>
<td>-4·6% (p=0·0143)</td>
</tr>
<tr>
<td>SGRQ-C improvement (points)</td>
<td>9·7 (p=0·0021)</td>
<td>-6·6 (p=0·0243)</td>
<td>-3·1 (p=0·0004)</td>
</tr>
<tr>
<td>6MWT improvement (m)</td>
<td>29·4 (p=0·0748)</td>
<td>30·5 (p=0·054)</td>
<td>-1·1 (p=0·002)</td>
</tr>
</tbody>
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Declaration of interests
We declare no competing interests.

Acknowledgments
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References