Thorax

Endobronchial valves for patients with heterogeneous emphysema and without interlobar collateral ventilation – open label treatment following the BeLieVeR-HIFi study

Journal:	*Thorax*
Manuscript ID	thoraxjnl-2016-208865.R2
Article Type:	Research Letter
Date Submitted by the Author:	n/a
Complete List of Authors:	Zoumot, Zaid; Cleveland Clinic Abu Dhabi, Respiratory and Critical Care Institute Davey, Claire; Royal Brompton and Harefield NHS Foundation Trust and Imperial College, NIHR Respiratory Biomedical Research Unit Jordan, Simon; Royal Brompton and Harefield NHS Foundation Trust and Imperial College, NIHR Respiratory Biomedical Research Unit McNulty, William; Royal Brompton Hospital and National Heart and Lung Institute, NIHR Respiratory BRU Carr, Denis; Royal Brompton and Harefield NHS Foundation Trust and Imperial College, NIHR Respiratory Biomedical Research Unit Hind, Matthew; Royal Brompton Hosital, Respiratory Medicine Polkey, Michael; Royal Brompton Hospital and National Heart and Lung Institute, NIHR Respiratory BRU Shah, Pallav; Royal Brompton and Harefield NHS Foundation and Imperial College, Lung Unit Hopkinson, Nicholas; Royal Brompton and Harefield NHS Foundation Trust and Imperial College, NIHR Respiratory Biomedical Research Unit
Keywords:	Emphysema, Lung Volume Reduction Surgery, Bronchoscopy

SCHOLARONE™
Manuscripts

Confidential: For Review Only

Endobronchial valves for patients with heterogeneous emphysema and without interlobar collateral ventilation – open label treatment following the BeLieVeR-HIFi study

Zaid Zoumot PhD[1,2], Claire Davey MSc[2], Simon Jordan MD[2], William H. McNulty MBBS[2], Dennis H. Carr MD[2], Matthew D. Hind PhD[2], Michael I. Polkey PhD[2], Pallav L. Shah MD[2], *Nicholas S. Hopkinson PhD[2]

[1]NIHR Respiratory Disease, Biomedical Research Unit at the Royal Brompton and Harefield NHS Foundation Trust and Imperial College London, London, UK

[2]Respiratory and Critical Care Institute, Cleveland Clinic Abu Dhabi, UAE

*Corresponding author

Address The Royal Brompton Hospital,

Fulham Road, London, SW3 6NP, UK

Email n.hopkinson@ic.ac.uk

Telephone +44 2073497775

Fax +44 2073497778

Word Count: 933

Key Words: Lung volume reduction, COPD

Confidential: For Review Only

ABSTRACT

Outcomes in early trials of bronchoscopic lung volume reduction using endobronchial valves for the treatment of patients with advanced emphysema were inconsistent. However improvements in patient selection with focus on excluding those with interlobar collateral ventilation and homogeneous emphysema resulted in significant benefits in the BeLieVeR-HIFi study compared to sham treated controls. In this manuscript we present data from the control patients in the BeLieVeR-HIFi study who went on to have open label endobronchial valve treatment after completion of the clinical trial (n=12), combined with data from those in the treatment arm who did not have collateral ventilation (n=19). Three months after treatment the forced expiratory volume in the 1st second increased by 27.3(36.4)%, residual volume reduced by 0.49(0.76)L, the 6 minute walk distance increased by 32.6(68.7) m, and the St George Respiratory Questionnaire for COPD score improved by 8.2(20.2) points. These data extend the evidence for endobronchial valve placement in appropriately selected patients with COPD.

Confidential: For Review Only

INTRODUCTION

Patients with emphysema are breathless because of gas trapping and hyperinflation due to the loss of lung elastic tissue and resultant expiratory airways collapse. Surgical lung volume reduction (LVRS) can improve survival, lung function and quality of life in selected patients with exercise limitation and heterogeneous emphysema[1,2]. The placement of endobronchial valves (BLVR) as a means to reduce lung volume is a potential alternative to LVRS. BLVR has been shown to improve lung function, reduce chest wall asynchrony, and reduce the work of breathing.[3,4] Atelectasis following BLVR is associated with improved survival.[5,6] The BeLieVeR-HIFi study, a double-blind sham-controlled trial,[7,8] found that BLVR led to significant improvements in lung function, exercise capacity and health status at three months when performed in patients with a higher chance of developing atelectasis - those with intact interlobar fissures and heterogeneously distributed emphysema. In this research letter we present data from the control patients in the BeLieVeR-HIFi study who went on to have open label endobronchial valve treatment after completion of the clinical trial. We also combine these data with patients from the original treatment arm who had been found to be collateral ventilation negative (CV-) using the Chartis catheter system and completed trial follow-up.

METHODS

The study protocol, design, randomisation, assessments, procedure, and details of the participants have been previously published[8] and further details of the methods and statistical analyses are in panel S1 of the online supplement.

RESULTS

Baseline characteristics of the open label treated patients (n=14) are detailed in Table S1. Three month follow-up data were available for 12 open-label patients. One died 4 days

Confidential: For Review Only

following treatment due to a pneumothorax occurring at their home; one developed a persistent intractable cough necessitating valve removal and did not return for follow-up evaluation. Clinical outcomes are detailed in Tables 1 and S2, and illustrated in figures 1(A-D) and S1(A-D). FEV_1 increased by 24.2(27.3)% from baseline following endobronchial valve treatment. The patients also experienced statistically significant improvements in TLco and the CAT score as well as measures of exercise capacity. Table 1 also includes data from the 19 CV-ve patients from the original treatment arm of the BeLieVeR-HIFi trial for whom follow up data were available ("original CV- treatment arm patients") and for the two groups combined ("all CV-ve treated patients") (n=31).

Responder rates for achievement of minimal clinically important differences were similar in the open label patients to those in original treatment group of the trial (table S3). Eight of 12 patients treated with valves developed atelectasis or complete lobar collapse on CT, and another two had significant volume loss. Details of adverse events are in Panel S2.

DISCUSSION

These data further support the view that treating patients with heterogeneous emphysema and without interlobar collateral ventilation with endobronchial valves leads to improved lung function, exercise capacity and quality of life. The benefits are more impressive where stricter patient selection criteria are employed, although there is still significant variability in response.. The improvement in gas transfer is of particular interest as this is the lung function measure most strongly associated with survival in people with COPD.[9]

In the original BeLieVeR-HIFi trial, eligibility for valves was based on the results of CT fissure analysis. Collateral ventilation was measured directly using the Chartis system, but by design patients in the intervention arm were still treated even if they were CV positive. In this open label follow up however, patients had had a previous bronchoscopy which confirmed airway anatomy suitable for adequate valve placement and prior Chartis measurements

Confidential: For Review Only

confirming the absence of collateral ventilation. The proportion of open-label treated patients with radiological evidence of volume loss was 83% (10 of 12), higher than the 65% in the original treatment cohort (15 of 23) with rates of responders achieving MCIDs in the various outcomes broadly similar to the original group.

The development of bronchoscopic lung volume reduction techniques has been driven by the desire to offer patients safer and cheaper alternatives to LVRS. As patient selection improves, increasing the likelihood of successful lung volume reduction, there is a significantly higher rate of pneumothorax than the 5% reported in earlier trials. In this series the rate was 10.3%, including one fatal event, though others have reported rates of 20-25%.[10] Although a marker of procedural effectiveness, with eventual clinical benefit in the majority after treatment of the pneumothorax,[11] pneumothorax can be fatal in people with advanced lung disease and little respiratory reserve. Thus, the mortality risk of BLVR may not be lower than that of surgical intervention, especially when compared with unilateral LVRS.[1] Pooled data suggests that 70% of pneumothoraces occur within 72 hours[12] and therefore it may be prudent to observe patients in hospital for 4 days post treatment. Patients who do suffer pneumothoraces are initially managed conservatively and patiently in hospital but may ultimately require valve removal or surgery.[10] This also reduces the advantage of BLVR over LVRS in terms of hospital length of stay, though the level of dependency during this observation period is low.

Our series highlights that fissure completeness, assessed visually on CT thorax (even by dedicated thoracic radiologists) is not a perfect surrogate for the absence of interlobar collateral ventilation. Out of 50 patients enrolled in the original trial and all judged to have intact fissures, eight patients (16%) had positive collateral ventilation on Chartis assessment.

In conclusion, bronchoscopic lung volume reduction using endobronchial valves leads to clinically significant improvements in lung function, exercise capacity and quality of life in the

Confidential: For Review Only

majority of patients when appropriately selected. The risk of pneumothorax needs to be considered and a period of close observation is recommended. Longer follow-up to assess durability of clinical benefits and effect on survival is needed as well as direct comparison of endobronchial valve placement against surgical approaches.

Contributorship

NSH, MIP, SJ, PS developed the study. NSH, MIP, SJ, DHC were involved in patient selection. PS, ZZ and WMcN performed procedures. CD performed assessments. ZZ performed statistical analyses. ZZ and NSH prepared the first draft of this paper which all authors subsequently contributed to and approved. NSH is the guarantor.

Declaration of interests

PS, SJ, MIP, ZZ, WMcN and NSH have been investigators in trials of endobronchial valves, coils, thermal ablation and the airway bypass procedure, and the authors' institution reimbursed for trial expenses by the device manufacturers.

Role of the funding source

This project was awarded by the Efficacy and Mechanism Evaluation (EME) Programme and is funded by the Medical Research Council (MRC) and managed by the National Institute for Health Research (NIHR) on behalf of the MRC-NIHR partnership. The EME Programme is funded by the MRC and NIHR, with contributions from the CSO in Scotland and NISCHR in Wales and the HSC R&D Division, Public Health Agency in Northern Ireland. It is managed by the NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC) based at the University of Southampton.

The study was supported by the NIHR Respiratory Biomedical Research Unit at the Royal Brompton and Harefield NHS Foundation Trust and Imperial College, London who part fund

Confidential: For Review

MIP's salary and wholly funded ZZ's salary. The endobronchial valves were provided free of charge by the manufacturers PulmonX Ltd. PulmonX had no input into the trial design, data analysis or presentation.

The views expressed in this publication are those of the authors and not necessarily those of the MRC, NHS, NIHR or the UK Department of Health

Confidential: For Review Only

REFERENCES

1 Clark SJ, Zoumot Z, Bamsey O, et al. Surgical approaches for lung volume reduction in emphysema. *Clinical Medicine* 2014; **14**:122-127

2 National Emphysema Treatment Trial Research Group. A Randomized Trial Comparing Lung-Volume-Reduction Surgery with Medical Therapy for Severe Emphysema. *N Engl J Med* 2003; **348**:2059-2073

3 Hopkinson NS, Toma TP, Hansell DM, et al. Effect of bronchoscopic lung volume reduction on dynamic hyperinflation and exercise in emphysema. *Am J Respir Crit Care Med* 2005; **171**:453-460

4 Zoumot Z, LoMauro A, Aliverti A, et al. Lung Volume Reduction in Emphysema Improves Chest Wall Asynchrony. *Chest* 2015; **148**:185-195

5 Hopkinson NS, Kemp SV, Toma TP, et al. Atelectasis and survival after bronchoscopic lung volume reduction for COPD. *Eur Respir J* 2011; **37**:1346-1351

6 Garner J, Kemp SV, Toma TP, et al. Survival after Endobronchial Valve Placement for Emphysema: A 10-Year Follow-up Study. *American Journal of Respiratory and Critical Care Medicine* 2016; **194**:519-521

7 Davey C, Zoumot Z, Jordan S, et al. Bronchoscopic lung volume reduction with endobronchial valves for patients with heterogeneous emphysema and intact interlobar fissures (the BeLieVeR-HIFi study): a randomised controlled trial. *Lancet* 2015; **386**:1066-1073

8 Davey C, Zoumot Z, Jordan S, et al. Bronchoscopic lung volume reduction with endobronchial valves for patients with heterogeneous emphysema and intact interlobar fissures (the BeLieVeR-HIFi trial): study design and rationale. *Thorax* 2015; **70**:288-290

9 Boutou AK, Shrikrishna D, Tanner RJ, et al. Lung function indices for predicting mortality in COPD. *European Respiratory Journal* 2013; **42**:616-625

Confidential: For Review Only

10 Valipour A, Slebos DJ, de Oliveira HG, et al. Expert Statement: Pneumothorax Associated with Endoscopic Valve Therapy for Emphysema - Potential Mechanisms, Treatment Algorithm, and Case Examples. *Respiration* 2014; **87**:513-521

11 Kemp SV, Zoumot Z, Mahadeva R, et al. Pneumothorax after endobronchial valve treatment: no drain, no gain? *Respiration* 2014; **87**:452-455

12 Gompelmann D, Herth FJ, Slebos DJ, et al. Pneumothorax following endobronchial valve therapy and its impact on clinical outcomes in severe emphysema. *Respiration* 2014; **87**:485-491

Confidential: For Review Only

Table 1 Change in lung function, health status and exercise tolerance at 90 days

	Open label valve treated patients (n=12)	p value	Original Chartis CV –ve treatment arm patients (n=19)	p value	All CV –ve treated patients (per Chartis) (n=31)	p value
%ΔFEV$_1$	24.2 (27.3)	0.06	28.9 (40.1)	0.001	27.3 (36.4)	0.0002
ΔFEV$_1$ (L)	0.14 (0.20)	0.06	0.23 (0.28)	0.001	0.19 (0.25)	0.0002
%ΔFVC	5.1 (13.0)	0.5	7.51 (16.9)	0.03	6.5 (15.6)	0.02
ΔTLC (L)	-0.23 (0.49)	0.13	-0.37 (0.56)	0.01	-0.33 (0.53)	0.002
ΔRV (L)	-0.42 (0.80)	0.41	-0.54 (0.76)	0.01	-0.49 (0.76)	0.007
ΔRV/TLC %	-3.50 (6.77)	0.10	-4.6 (6.9)	0.03	-4.3 (6.85)	0.004
ΔFRC (L)	-0.28 (0.83)	0.27	-0.42 (0.69)	0.04	-0.38 (0.75)	0.009
ΔTLco (absolute percentage points)	3.5 (6.77)	0.005	3.45 (6.2)	0.02	3.62 (5.16)	0.0007
ΔKco (mmol.min^{-1}.kPa^{-1}.L^{-1})	0.10 (0.07)	0.007	0.05 (0.07)	0.009	0.07 (0.07)	<0.0001
ΔCAT	-3.9 (5.5)	0.05	-4.2 (10.1)	0.20	-4.1 (8.5)	0.03
ΔSGRQc total	-7.5 (14.9)	0.08	-7.5 (20.8)	0.3	-8.5 (20.2)	0.05
Δ6MWD	29 (48)	0.16	33.2 (80.2)	0.02	32.6 (68.7)	0.01
ΔTLim	138 (312)	0.08	165 (260)	0.07	155 (275)	0.01

Data are presented as mean (SD). P values are for Wilcoxon signed rank test. FEV$_1$, forced expiratory volume in 1 second; FVC, forced vital capacity; TLC, total lung capacity; RV, residual volume; TLco, carbon monoxide transfer factor; Kco, carbon monoxide transfer coefficient; MRC, Medical Research Council dyspnoea score; CAT, COPD assessment test score; SGRQc, St George's Respiratory Questionnaire for COPD; PYH, pack year smoking history.; 6MWD, six minute walk distance; Tlim, endurance time on cycle ergometry at 70% of peak workload; Chartis CV –ve: No interlobar collateral ventilation on Chartis assessment.

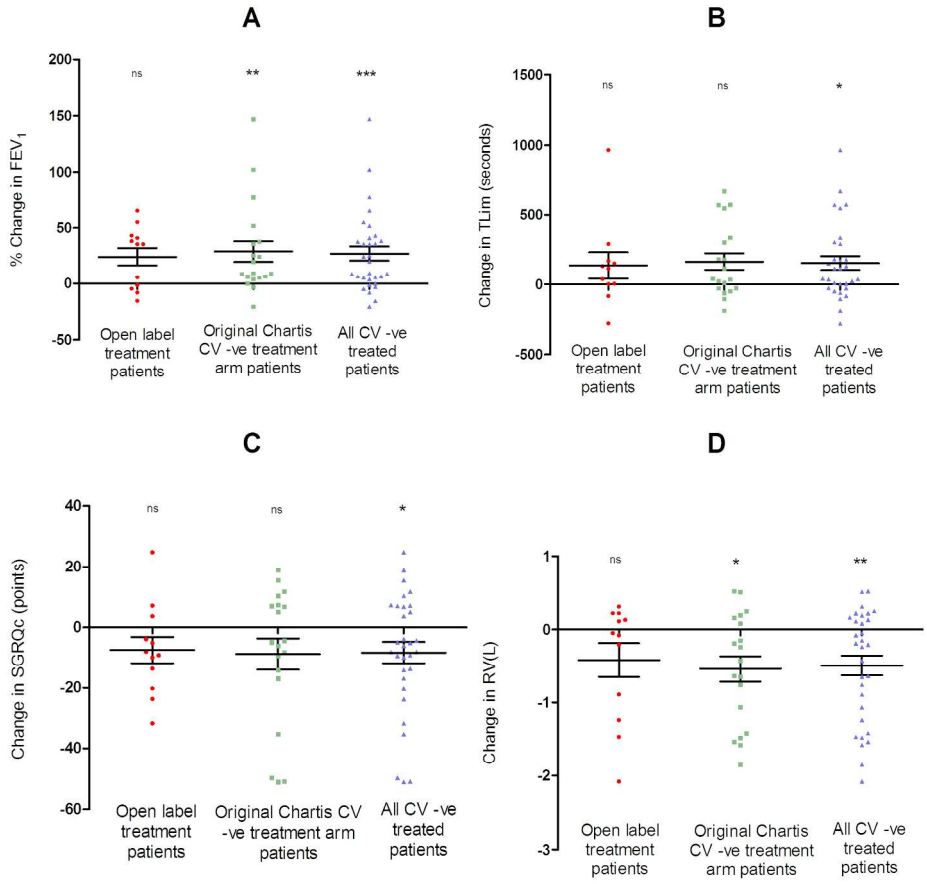
.

Confidential: For Review Only

Figure Legends

Figure 1 Response to bronchoscopic lung volume reduction in open label treated patients, in the original BeLieVeR-HIFi treated patients who were collateral ventilation negative and in both groups combined. Panel A, forced expiratory volume in one second; Panel B, endurance time on cycle ergometry at 70% maximal work rate; Panel C, St George's Respiratory Questionnaire; Panel D, Residual volume assessed by body plethysmography. P values are for Wilcoxon signed rank test. * P<0.05, ** P<0.01, *** P<0.001.

Confidential: For Review Only



Response to bronchoscopic lung volume reduction in open label treated patients, in the original BeLieVeR-HIFi treated patients who were collateral ventilation negative and in both groups combined. Panel A, forced expiratory volume in one second; Panel B, endurance time on cycle ergometry at 70% maximal work rate; Panel C, St George's Respiratory Questionnaire; Panel D, Residual volume assessed by body plethysmography. P values are for Wilcoxon signed rank test. * P<0.05, ** P<0.01, *** P<0.001.
figures 1
208x202mm (300 x 300 DPI)

For Peer Review Only

Online Supplement:

Endobronchial valves for patients with heterogeneous emphysema and without interlobar collateral ventilation – open label treatment following the BeLieVeR-HIFi study

Zaid Zoumot PhD[1,2], Claire Davey MSc[2], Simon Jordan MD[2], William H. McNulty MBBS[2], Dennis H. Carr MD[2], Matthew D. Hind PhD[2], Michael I. Polkey PhD[2], Pallav L. Shah MD[2], *Nicholas S. Hopkinson PhD[2]

[1]NIHR Respiratory Disease, Biomedical Research Unit at the Royal Brompton and Harefield NHS Foundation Trust and Imperial College London, London, UK

[2]Respiratory and Critical Care Institute, Cleveland Clinic Abu Dhabi, UAE

*Corresponding author

Address The Royal Brompton Hospital,

Fulham Road, London, SW3 6NP, UK

Email n.hopkinson@ic.ac.uk

Telephone +44 2073497775

Fax +44 2073497778

Confidential: For Review Only

Panel S1: METHODS

The BeLieVeR-HIFi study was a 1:1 randomised, parallel group, double-blind sham bronchoscopy controlled trial of unilateral, endobronchial valve placement (Zephyr valves, PulmonX, California) in patients with heterogeneous emphysema and intact interlobar fissures. The study was approved by the London – Bentham Research Ethics Committee (REC No. 11/LO/1608), the sponsor was Imperial College, London. There was a trial steering group and an independent data monitoring committee. All patients provided written informed consent and were recruited between March 2012 and September 2013. The procedures were performed using moderate sedation with Midazolam and Alfentanyl in the bronchoscopy suite at the Royal Brompton Hospital. Endobronchial valves were placed to occlude all segmental bronchi leading to the target lobe

Patients with optimally medically managed and stable severe or very severe COPD were included (forced expiratory volume in one second (FEV_1) <50% predicted, residual volume (RV) >150% predicted, 6 minute walk distance (6MWD) <450m, and significant breathlessness (MRC dyspnoea score $\geq$3)). Their CT scans demonstrated heterogeneous emphysema with a defined target lobe, and intact adjacent interlobar fissures. Assessments were performed at baseline and 3 months after bronchoscopy, by an assessment team blind to treatment allocation. Assessments included complete lung function testing, endurance cycle ergometry with metabolic measurements at 70% of their maximal workload determined on an initial incremental test, a 6MWD test, and quality of life questionnaires (SGRQc[1] and CAT[2 3]).

Confidential: For Review Only

Target lobe volume change was assessed by a thoracic radiologist (DC) and scored as follows:

0 – No change,

1 - Some volume loss (Fissures shift)

2- Segmental atelectasis (Band of collapsed lung)

3 – Complete atelectasis (Complete collapse).

Open Label group

Measurements of collateral ventilation using the Chartis™ (PulmonX, California) balloon catheter system were made in all participants during the initial sham bronchoscopy. At the 3 months end of study visit, all treatment options available to the control group patients were discussed. Only patients where collateral ventilation was not detected (CV –ve) were offered open label valve placement. Treatment was performed within 2 weeks of the end of study visit. Of 25 control patients, 14 had BLVR treatment and of the remaining 11, two had died, four had positive collateral ventilation during Chartis assessment (of these two had no further treatment, one had LVRS and one was enrolled into another bronchoscopic LVR trial), and of the five without collateral ventilation on Chartis assessment two preferred LVRS, one had recurrent infections and much airway secretions on initial bronchoscopy and thus valves were avoided in favour of LVRS, one was felt to have a very high risk of pneumothorax due to the presence of ipsilateral paraseptal bullae in the non-target lobe, and one was found to have airway anatomy which did not support endobronchial valve placement.

Statistical Analysis

The primary endpoint in this follow-up study is the difference in the percentage change in FEV_1 measured 3 months post procedure. Secondary endpoints included: (1) change in the

Confidential. For Review Only

Residual Volume (RV), (2) change in endurance time (Tlim) on cycle ergometry at 70% of maximum achieved workload, (3) change in six minute walk distance, and (4) changes in health status (CAT, SGRQc).

Statistical analysis performed by ZZ using PASW (Predictive Analytics Software; IBM) version 20 for Windows. Categorical data are presented as percentages and comparisons done using the Pearson chi-squared test. Normally distributed numeric data are presented as mean (SD). Non-normally distributed numeric data are presented as median (IQR). Statistical analysis for differences between baseline values (at the final control visit) and 3 months following endobronchial valve treatment was assessed by Wilcoxon signed rank tests. A p value <0·05 was taken to indicate statistical significance. For responder analyses minimum clinically important differences (MCID) were pre-specified as a 15% increase for FEV_1, 350mls reduction for the residual volume[4], 4 points decrease for the SGRQc[1 5], 2 points decrease for the CAT[3 6] an increase of 105 seconds for endurance cycle Tlim[7] and an increase of 26m for the 6MWD[8].

Confidential: For Review Only

Table S1 Baseline characteristics of study participants

	Open label valve treated patients (n=14)	Original treatment Arm (n=25)	All valve treated patients (n=39)
Age	63.9 (7.2)	62.3 (7.0)	62.7 (6.9)
Gender (M/F)	7/7	17/8	24/15
BMI	24.1 (5.0)	24.5 (5.1)	24.4 (4.9)
PYH	55.6 (27.0)	56 (26)	55.5 (25.4)
Exacerbation rate/yr	2.79 (2.36)	3 (3)	3.24 (2.74)
FEV_1 (L)	0.83 (0.34)	0.93 (0.35)	0.89 (0.33)
FEV_1%pred	31.1 (9.7)	31.6 (10.2)	32.0 (10.3)
TLC %pred	141.0 (15.5)	132 (12)	135.1 (13.6)
RV %pred	241 (47)	219 (39)	226.5 (41.8)
RV%TLC	64.1 (8.1)	60.23 (8.06)	61.7 (8.0)
TL_{CO} %pred	33.5 (11.5)	33.8 (10.8)	34.1 (10.9)
Kco %pred	43.7 (13.9)	45.8 (12.8)	45.9 (13.5)
$PaCO_2$ (kPa)	4.99 (0.69)	4.81 (0.86)	4.85 (0.79)
PaO_2 (kPa)	9.32 (0.61)	9.74 (1.45)	9.56 (1.20)
MRC	3.64 (0.50)	4 (1)	3.59 (0.50)
CAT	25.7 (5.2)	24 (5)	24.7 (5.5)
SGRQc - total	69.7 (12.4)	67.8 (13.2)	69.0 (12.8)
6MWD (m)	335.3 (80.4)	342.3 (94.6)	337.2 (89.8)
Tlim (s)	286.4 (200.3)	306.1 (166.7)	299.3 (176.4)

Data are presented as mean (SD). BMI, body mass index; PYH, tobacco pack year history; FEV_1, forced expiratory volume in 1 second; TLC, total lung capacity; RV, residual volume, TLco, carbon monoxide transfer factor; MRC, Medical Research Council dyspnoea score; CAT, COPD assessment test score; SGRQc, St George's Respiratory Questionnaire for COPD; PYH, pack year smoking history.; 6MWD, six minute walk distance; Tlim, endurance time on cycle ergometry at 70% of peak workload.

Confidential: For Review Only

Table S2 Change in lung function, health status and exercise tolerance at 90 days

	Open label valve treated patients (n=12)	p value	Original Chartis CV –ve treatment arm patients (n=19)	p value	All CV –ve treated patients (per Chartis) (n=31)	p value
%ΔFEV$_1$	35.6 (-2.2 to 41.6)	0.06	9.4 (6.0 to 36.8)	0.001	19.8 (4.8 to 39.7)	0.0002
ΔFEV$_1$ (L)	0.21 (-0.18 to 0.29)	0.06	0.13 (0.05 to 0.38)	0.001	0.18 (0.04 to 0.32)	0.0002
%ΔFVC	0.46 (-5.4 to 16.6)	0.5	4.8 (1.4 to 11.3)	0.03	3.1 (-4.0 to 13.8)	0.02
ΔTLC (L)	-0.05 (-0.26 to 0.01)	0.13	-0.32 (-0.65 to 0.05)	0.01	-0.16 (-0.60 to 0.03)	0.002
ΔRV (L)	-0.06 (-0.98 to 0.15)	0.41	-0.43 (-1.25 to 0.12)	0.01	-0.21 (-1.16 to 0.15)	0.007
ΔRV/TLC %	-2.9 (-7.9 to 2.5)	0.10	-4.7 (-8.4 to 0.3)	0.03	-3.4 (-8.4 to 1.2)	0.004
ΔFRC (L)	-0.02 (-0.66 to 0.16)	0.27	-0.24 (-1.25 to 0.04)	0.04	-0.22 (-0.94 to 0.09)	0.009
ΔTLco (absolute percentage points)	3.3 (1.8 to 5.5)	0.005	2.9 (-0.5 to 5.5)	0.02	3.3 (0.9 to 5.6)	0.0007
ΔKco (mmol.min^{-1}.kPa^{-1}.L^{-1})	0.11 (0.07 to 0.15)	0.007	0.06 (0.01 to 0.10)	0.009	0.08 (0.01 to 0.13)	<0.0001
ΔCAT	-2.5 (-8.5 to -0.5)	0.05	-5.0 (-8.5 to 1.0)	0.20	-4.0 (-8.5 to 1.0)	0.03
ΔSGRQc total	-8.6 (-15.3 to -2.0)	0.08	-4.9 (-15.5 to 7.1)	0.3	-6.1 (-15.5 to 6.9)	0.05
Δ6MWD	16.5 (-6.75 to 70.5)	0.16	30.0 (12.0 to 76.5)	0.02	30.0 (-2.5 to 75.0)	0.01
ΔTLim	116.0 (4.0 to 161.5)	0.08	42.0 (-26.5 to 321.0)	0.07	79.0 (-18.8 to 264.5)	0.01

Data are presented as median (IQR). P values are for Wilcoxon signed rank test. FEV$_1$, forced expiratory volume in 1 second; FVC, forced vital capacity; TLC, total lung capacity; RV, residual volume; TLco, carbon monoxide transfer factor; Kco, carbon monoxide transfer coefficient; MRC, Medical Research Council dyspnoea score; CAT, COPD assessment test score; SGRQc, St George's Respiratory Questionnaire for COPD; PYH, pack year smoking history.; 6MWD, six minute walk distance; Tlim, endurance time on cycle ergometry at 70% of peak workload; Chartis CV –ve: No interlobar collateral ventilation on Chartis assessment.

Confidential: For Review Only

Table S3 Responder rates according to lung function, health status and exercise criteria

	Cross-over valve treated patients (n=12)	Original treatment arm Chartis CV –ve patients (n=19)	AllChartis CV –ve valve treated patients (n=31)
FEV_1 ≥15% improvement	7 (58%)	9 (47%)	16 (53%)
RV ≥0.35L reduction	4 (33%)	10 (53%)	14 (45%)
6MWD ≥26m improvement	6 (50%)	11 (58%)	17 (55%)
Endurance cycle time ≥105 secs improvement	6 (50%)	9 (47%)	15 (48%)
SGRQc ≥4 points reduction	8 (67%)	11 (58%)	19 (61%)
CAT ≥2 points reduction	6 (50%)	12 (63%)	18 (58%)

FEV_1 forced expiratory volume in one second, RV residual volume, 6MWD six minute walk distance, SGRQc St George's respiratory questionnaire, CAT COPD assessment test score, Chartis CV –ve: No interlobar collateral ventilation on Chartis assessment.

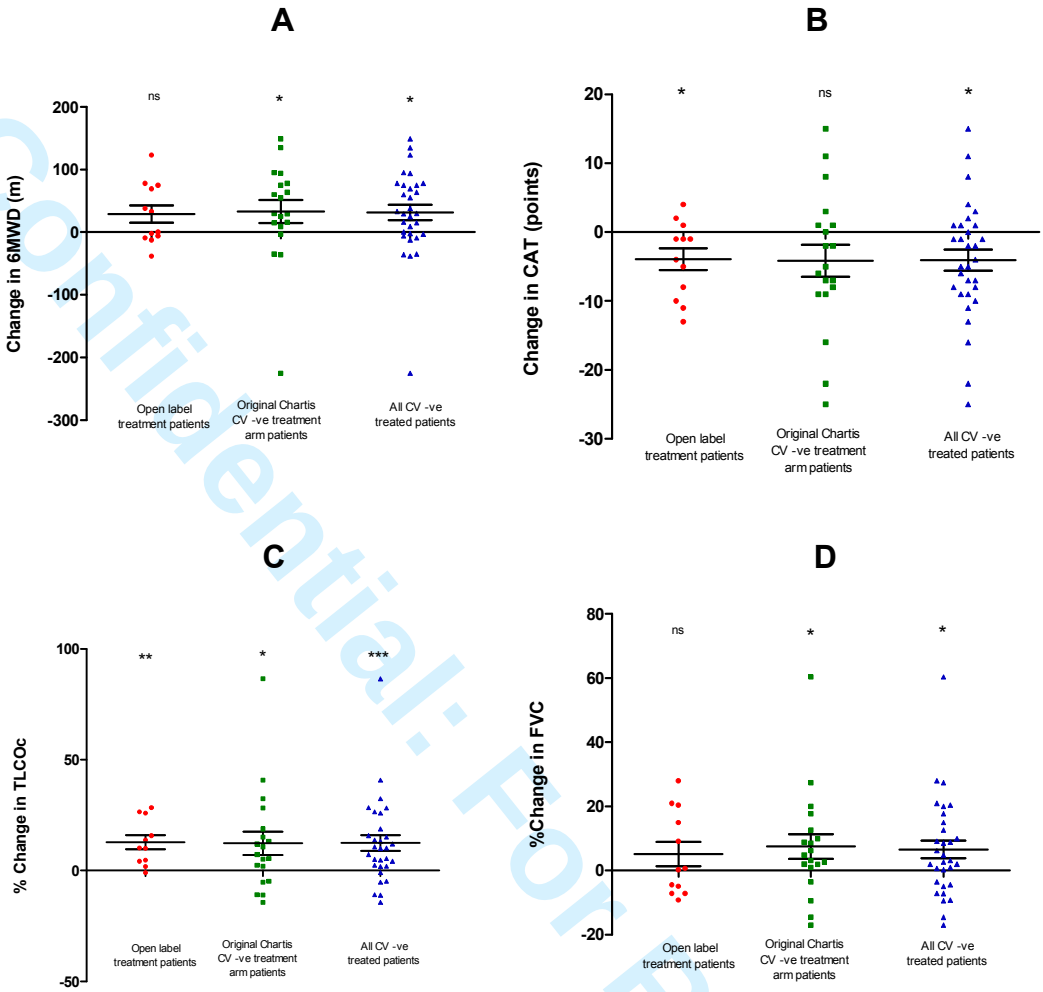
Panel S2: Adverse events

Confidential: For Review Only

There was one death secondary to a pneumothorax directly attributable to treatment with endobronchial valves. Changes to our admission and follow-up protocols were subsequently implemented as described above. There was one other pneumothorax in an open label patient. This occurred 5 days post treatment (one day after discharge), and the patient was treated conservatively with intercostal chest tube drainage. He had excellent clinical outcomes at his 3 months follow-up visit. One patient developed a persistent cough necessitating bronchoscopy and valve removal. Two other patients required repeat bronchoscopy to investigate clinical deteriorations, and in one case valves were repositioned and the other mucus plugs cleared with good outcomes in both cases.

Confidential: For Review Only

Figure S1 (A-D): Response to valve placement CV –ve patients.



Response to bronchoscopic lung volume reduction in open label treated patients, in the original BeLieVeR-HIFi treated patients who were collateral ventilation negative and in both groups combined. Panel A, six minute walk distance; B COPD assessmsent test score; C TLco carbon monoxide transfer factor; D forced vital capacity. * P<0.05, ** P<0.01, *** P<0.001.

Confidential: For Review Only

Panel S3: Limitations of the study

Limitations of this extension study include the small sample size and open-label and unblinded nature of the treatment and follow-up. Furthermore, analysis does not account for missing data from patient who died. However the primary and most secondary outcomes were objective rather than subjective. All treatments were undertaken at a single highly specialised centre with extensive experience of treating patients with end stage emphysema using LVRS and a variety of bronchoscopic lung volume reduction techniques, as part of clinical trials and in routine clinical care. The set-up at our centre includes a pre-existing multidisciplinary team that meets on a weekly basis involving dedicated thoracic radiologists, thoracic surgeons, pulmonologists and physiotherapists. It may not be possible to achieve similar outcomes at other centres without this infrastructure or clinical experience

Confidential: For Review Only

REFERENCES

1. Meguro M, Barley EA, Spencer S, et al. Development and validation of an improved, COPD-specific version of the St George's respiratory questionnaire*. CHEST Journal 2007;**132**(2):456-63 doi: 10.1378/chest.06-0702[published Online First: Epub Date]|.

2. Jones PW, Harding G, Berry P, et al. Development and first validation of the COPD Assessment Test. Eur Respir J 2009;**34**(3):648-54 doi: 10.1183/09031936.00102509[published Online First: Epub Date]|.

3. Dodd JW, Hogg L, Nolan J, et al. The COPD assessment test (CAT): response to pulmonary rehabilitation. A multicentre, prospective study. Thorax 2011;**66**(5):425-29 doi: 10.1136/thx.2010.156372[published Online First: Epub Date]|.

4. Hartman JE, ten Hacken NHT, Klooster K, et al. The minimal important difference for residual volume in patients with severe emphysema. European Respiratory Journal 2012;**40**(5):1137-41 doi: 10.1183/09031936.00219111[published Online First: Epub Date]|.

5. Schünemann HJ, Griffith L, Jaeschke R, et al. Evaluation of the minimal important difference for the feeling thermometer and the St. George's Respiratory Questionnaire in patients with chronic airflow obstruction. Journal of Clinical Epidemiology 2003;**56**(12):1170-76 doi: 10.1016/s0895-4356(03)00115-x[published Online First: Epub Date]|.

6. Kon SSC, Canavan JL, Jones SE, et al. Minimum clinically important difference for the COPD Assessment Test: a prospective analysis. The Lancet Respiratory Medicine 2014;**2**(3):195-203 doi: http://dx.doi.org/10.1016/S2213-2600(14)70001-3[published Online First: Epub Date]|.

7. Casaburi R. Factors Determining Constant Work Rate Exercise Tolerance in COPD and their Role in Dictating the Minimal Clinically Important Difference in Response to Interventions. COPD: Journal of Chronic Obstructive Pulmonary Disease

Confidential: For Review Only

2005;**2**(1):131-36 doi: doi:10.1081/COPD-200050576[published Online First: Epub Date]|.

8. Puhan MA, Chandra D, Mosenifar Z, et al. The minimal important difference of exercise tests in severe COPD. European Respiratory Journal 2011;**37**(4):784-90 doi: 10.1183/09031936.00063810[published Online First: Epub Date]|.

Confidential: For Review Only