ERJ Express. Published on November 19, 2009 as doi: 10.1183/09031936.00106009

Biologic Lung Volume Reduction (BioLVR) Therapy for Advanced Homogeneous Emphysema

Y. Refaely[1] MD, M. Dransfield[2] MD, M.R. Kramer[1], M Gotfried[3], W. Leeds[4] MD, G. McLennan[5] MD PhD, S. Tewari[6] MD, M. Krasna[7] MD, G.J. Criner[8] MD

1. Rabin Medical Center, Petah Tiqwa, Israel.
2. University of Alabama Birmingham, Birmingham, AL, USA.
3. Pulmonary Associates, Phoenix, AZ, USA.
4. Veritas Clinical Specialties, Topeka, KS, USA.
5. University of Iowa, Iowa City, Iowa, USA.
6. Akron Medical Center, Akron, Ohio, USA.
7. St. Joseph's Medical Center, Baltimore, Maryland, USA.
8. Temple University, Philadelphia, PA, USA.

Corresponding Author:

Yael Refaely MD
Division of Cardiothoracic Surgery
Rabin Medical Center
Tel Aviv, Israel
Yaelre2@clalit.org.il

Source of support for study: Aeris Therapeutics, Inc., Woburn, MA
Running head: Biologic Lung Volume Reduction (BioLVR)
Number of figures: 2
Number of Tables: 4
Word count – Abstract: 195 Main body: 3253

Abstract:

Objective(s): This report summarizes Phase 2 trial results of Biologic Lung Volume Reduction (BioLVR) for treatment of advanced homogeneous emphysema.

Methods: BioLVR therapy was administered bronchoscopically to 25 patients with homogeneous emphysema in an open-labeled study. Eight patients received Low Dose (LD) treatment with 10 mL/site at 8 subsegments; 17 received High Dose (HD) treatment with 20 mL/site at 8 subsegments. Safety was assessed in terms of medical complications during 6-month follow-up. Efficacy was assessed in terms of change from baseline in gas trapping, spirometry, diffusing capacity, exercise capacity, dyspnea, and health related quality of life.

Results: There were no deaths or serious medical complications during the study. A statistically significant reduction in gas trapping was observed at 3-month follow-up among HD patients, but not LD patients. At 6 months, changes from baseline in FEV_1 (-8.0±13.93% vs. +13.8±20.26%), FVC (-3.9±9.41% vs. +9.0±13.01%), RV/TLC ratio (-1.4±13.82% vs. -5.4±12.14%), dyspnea scores (-0.4±1.27 vs. -0.8±0.73 U) and St. George's Respiratory Questionnaire total domain scores (-4.9±8.3 U vs. -12.2±12.38 U) were better with HD than LD therapy.

Conclusions: BioLVR therapy with 20mL/site at 8 subsegmental sites may be a safe and effective therapy in patients with advanced homogeneous emphysema.

Key words: lung volume reduction surgery, emphysema therapy, bronchoscopic lung volume reduction, interventional pulmonology, homogeneous emphysema.

Introduction:

Surgical lung volume reduction (LVRS) has been performed for patients with advanced upper-lobe-predominant (ULP) and homogeneous emphysema, and both groups have experienced clinical benefit. [1-3] However, larger, more consistent improvements in physiological and functional outcomes, and fewer complications, have been reported in patients with ULP disease. [4, 5] In the National Emphysema Treatment Trial (NETT), only patients with ULP disease experienced a survival benefit following LVRS. [4, 6, 7] Serious post-surgical complications, including cardiac ischemia, arrhythmia, and pulmonary embolus were observed more frequently in patients with homogeneous emphysema. [8] Furthermore, homogeneous patients with an FEV_1 < 20% of predicted were at increased risk of procedural mortality. [4]

Recently, the clinical utility of bronchoscopic methods for achieving lung volume reduction has been evaluated in patents with advanced emphysema because these procedures are uniformly safer than surgical volume reduction. [5, 9] Biologic Lung Volume Reduction (BioLVR) is a novel endobronchial approach that uses a fibrin-based hydrogel to collapse and remodel damaged areas of lung through localized scarring and contraction. The remodeling process is intended to produce therapeutic lung volume reduction more safely than LVRS. [10, 11] BioLVR has been associated with improvements in physiological, functional, and quality of life outcomes in patients with advanced heterogeneous upper lobe predominant emphysema. [12] This article summarizes the results of 2 small dose-ranging Phase 2 studies performed to assess the potential safety and efficacy of BioLVR therapy in severe homogeneous emphysema.

Methods:

Enrollment Criteria

All study participants had severe airflow obstruction, homogeneous emphysema, respiratory symptoms despite medical therapy, and were either not eligible for, or had refused, surgical lung volume reduction and lung transplantation. Specific study inclusion/exclusion criteria included: 1) homogeneous emphysema determined by high resolution CT imaging; 2) persistent symptoms (i.e. a baseline Medical Research Council Dyspnea [MRCD] score of ≥ 2) despite medical therapy; 3) age > 40 yrs; 4) severe airflow limitation, defined as a ratio of forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC) < 70% and an FEV_1 < 45% predicted; 5) hyperinflation (total lung capacity (TLC) > 110% predicted and residual volume (RV) > 150% predicted); 6) absence of a diagnosis of alpha-1 anti-protease deficiency; 7) absence of clinically significant pulmonary hypertension, defined as a pulmonary systolic pressure > 45 mm Hg (assessed by cardiac echo alone or with right heart catheterization); 8) abstinence from smoking for ≥ 4 months prior to enrollment, and 9) Perfusion of (upper 1/3 right lung + perfusions to upper 1/3 of left lung) < 25% of total lung perfusion by quantitative scintigraphy scanning. [4, 13] Patients determined to be at high risk of mortality for LVRS were also excluded from participation in this trial. [13]

Study Design

Two Phase 2 studies were conducted to define the BioLVR dose required to safely and consistently achieve therapeutic lung volume reduction in patients with advanced homogeneous disease. The studies were identical in design except for dosing

strategy, and were performed at eight hospitals, 7 in the United States and 1 in Israel. The studies were open-label, non-randomized, and non-controlled. The first study evaluated bilateral BioLVR treatment at 8 treatment sites with 10 mL/site (enrollment goal 15 to 20 patients) in patients with advanced homogeneous disease (Low dose, LD). Eight patients enrolled in this study. The second study evaluated bilateral BioLVR treatment at 8 treatment sites with 20 mL/site (enrollment goal 15 to 20 patients) in patients with advanced homogeneous emphysema (High dose, HD). 17 patients enrolled in this study. Both protocols were reviewed and approved by the appropriate national regulatory agencies and local ethics committees. All study participants reviewed and signed informed consent forms before enrollment.

Screening evaluations were completed over the course of three separate visits within a 2-week window. Pulmonary function testing was performed during each screening visit, and representative baseline values for each pulmonary function test were determined as the average of three measurements. Exercise capacity, assessed using 6 Minute Walk Test (6 MWT) distance, was measured on 2 separate occasions during screening and baseline defined as the average of these two measurements. Spirometry, plethysmography, and 6 MWT were performed according to published guidelines. [14-17] Echocardiography, electrocardiography, clinical pathology (hematology, coagulation studies, and serum chemistry measurements) radionucleotide lung perfusion scanning, and chest CT imaging were each performed once during screening. CT images were acquired using a standardized acquisition/reconstruction algorithm (spiral acquisition

using a multi-detector CT scanner with 1 mm collimation, pitch of 1, and 0.5 mm overlap) similar to that used in the National Emphysema Treatment Trial. [18, 19]

BioLVR treatments were administered either in the operating room under general anesthesia (10 mL, 7 patients; 20 mL, 2 patients), in the operating room under conscious sedation (10 mL, 1 patient; 20 mL, 1 patient), or in the bronchoscopy suite under conscious sedation (20 mL, 14 patients) per investigator preference. Conscious sedation regimens included bolus fentanyl and midazolam in 10 patients, low dose propofol infusion in 1 patient, and intravenous remifentanil infusion in 3 patients. All procedures were performed using a flexible bronchoscope. Patients were admitted to the hospital for an observation period of up to 48 hours following treatment.

Outcome Measures

The primary endpoint of the studies was RV/TLC ratio measured at 3 months following treatment. Treatment success was defined as a statistically significant group mean reduction in RV/TLC from baseline. Treatment efficacy was further assessed in terms of the change from baseline at 3 and 6 months in post bronchodilator FEV_1 and FVC, DLco, 6 MWT distance, MRCD score, and St. George's Respiratory Questionnaire (SGRQ) health related quality of life (HRQOL) total domain score, and reduction in RV/TLC at 6 months.

Safety was assessed in terms of the incidence of serious medical complications following BioLVR therapy, and the incidence of post-treatment COPD exacerbations. A

"serious medical complication" was defined as any of the following: 1) death; 2) respiratory failure of > 24 hours duration; 3) pneumothorax; 4) pneumonia; 5) empyema; 6) lung abscess; 7) pulmonary embolus; 8) heart failure; 9) cardiac ischemia or myocardial infarction; 10) cardiac arrhythmia requiring medical treatment; 11) severe COPD exacerbation requiring admission to an intensive care unit; 12) a decline in lung physiology post-treatment resulting in permanent loss of function. This list includes significant pulmonary and cardiovascular morbidity prospectively defined by investigators in the NETT, as well as potential procedure-specific adverse complications prospectively identified by BioLVR investigators. [8, 12]

The BioLVR Procedure

Homogeneous disease was initially assessed by investigators in conjunction with their consulting radiologists. CT dicom images were then forwarded to the sponsor's medical team for computer analysis and confirmation of homogeneous phenotype by demonstrating that the ratio of the percentage of upper to lower lobe voxels < -950 HU was between 0.98 and 1.02 (i.e. 1.0±0.02) using commercially available software (Pulmonary Workstation Plus Software, VIDA Diagnostics, Iowa City, IA). [18] Any patient not meeting this objective computer-based criteria was considered non-homogeneous, and was excluded from this study. All patients received treatment in the upper lobes or superior segments of the lower lobes. The most damaged areas of lung, identified as those with the lowest HU density and least amount of perfusion were selected for dosing. In instances where perfusion scan data and CT data were not entirely

consistent, CT image results received greater consideration in selecting sites for treatment.

BioLVR treatments were delivered at the subsegmental airway level as previously reported. [12] The bronchoscope was advanced into the subsegmental orifice of the treatment site and wedged in position to prevent backflow of reagents. A dual lumen catheter was advanced into the airways with the tip positioned 3-4 cm beyond the end of the bronchoscope. BioLVR Fibrinogen and Thrombin Solutions were then prepared and delivered through the catheter over 10-15 seconds. Following administration, the catheter was removed. The bronchoscope was kept in wedge position for 30 seconds following instillation of the reagents and then repositioned at the next treatment site.

Data Presentation and Statistical Analysis

Safety and efficacy results are available for all patients in both treatment groups. Efficacy outcomes at 6 weeks, and 3 and 6 months post treatment were compared to baseline values and reported as change from baseline. Percentage change from baseline is reported for pulmonary function measures including FEV_1, FVC, DLco and RV/TLC ratio. Absolute change from baseline is reported for MRCD, 6 MWT distance, and SGRQ. Statistical significance of the post-treatment change in the primary endpoint (RV/TLC ratio at 12 weeks) was assessed by nonparametric testing (Mann-Whitney test). A significant change was defined as $P < 0.05$. Comparisons for all the secondary endpoints were performed by nonparametric testing (Kruskal-Wallis one-way analysis of variance comparing results at 6, 12 and 24 weeks), and statistical significance was based

upon P values subject to correction for multiple comparisons using the method of Bonferroni. Correlations between continuous variables were performed using the method of Pearson. Safety outcome measures are summarized using descriptive statistics.

Results

Patient enrollment and demographic information

Demographics of patients in the LD and HD treatment groups at the time of enrollment are summarized in Table 1. The two groups were similar with respect to age, gender distribution, smoking history, and medication usage. Oxygen use at rest, with activity, and during sleep, and the fraction of patients using any supplemental oxygen, was significantly higher in HD compared to LD patients. Furthermore, a significantly larger fraction of HD patients than LD patients had participated in pulmonary rehabilitation within 6 months of study enrollment.

Baseline physiological and functional parameters for the two groups are summarized in Table 2. There were no significant differences in baseline characteristics between the groups, although HD patients had a lower mean 6 MWT distance than LD patients prior to therapy (293 ± 68.1 vs. 355 ± 108.7 m, $p = 0.10$).

The HD arm of the study was fully enrolled. Enrollment in the LD arm of the study was terminated after only 8 patients because of lack of response to therapy.

Safety Results

All patients in LD and HD groups tolerated full dose therapy at 8 subsegmental sites. There were no procedural complications. Specifically, there were no episodes of bleeding, spillage of hydrogel material, pneumothorax, respiratory failure, or instances in which conscious sedation had to be converted to general anesthesia because of clinical instability.

Analysis of adverse medical events following BioLVR treatment demonstrated that LD and HD dosing were equally safe. There were no deaths or serious medical complications reported in either treatment group. However, treatment in both groups was associated with significant side effects. Consistent with its mechanism of action, BioLVR therapy caused a transient inflammatory reaction characterized by leukocytosis, fever, and malaise within 8 to 24 hours of treatment. Seven of 8 LD patients, and 16 of 17 HD patients, manifested at least one of these symptoms. In a smaller subset of patients, transient symptoms of pleuritic chest pain, shortness of breath, nausea, and headache were reported. In most cases, this reaction was self limited and resolved within 24-48 hours. Hospital length of stay was primarily dictated by the recovery time associated with this reaction. Hospital length of stay was 1.75±0.71 days (Range 1-3 days) for LD patients and 1.47±1.00 days (Range 1-5 days) for HD patients.

Post treatment COPD exacerbations were observed in 2 of 8 LD patients (incidence = 25%; 0.5 exacerbations/patient/year), one of which occurred within the first 30 days following treatment and was deemed related to treatment. Post treatment COPD

exacerbations were observed in 3 of 17 HD patients (incidence = 18%; 0.35 exacerbations/patient/year), 2 of which occurred within the first 30 days following treatment and were deemed related to treatment. All events were of mild or moderate severity, but 4 required hospitalization and intensification of medical treatment.

Efficacy Results

Efficacy responses out to 6 months are summarized in Table 3. HD BioLVR therapy produced a statistically significant reduction in the study primary endpoint, RV/TLC ratio at 3 month follow-up (-6.9±9.6%, p=0.008). Improvements following HD therapy at 12 and 24 weeks were also observed in FEV_1, FVC, MRCD and SGRQ although only improvements in FEV_1, MRCD, and SGRQ were statistically significant. No significant improvements were observed following LD therapy in any outcome measures. Response patterns of the major physiological and patient reported outcomes at 6 months post treatment are summarized in Figure 1.

Table 4 shows the fraction of patients in HD and LD treatment groups with improvements in physiological, functional, and quality of life measures meeting established minimal clinically important difference (MCID) criteria. HD therapy produced clinically meaningful improvements in FEV_1 and FVC (> 12% improvements) in 29% to 47% of patients. The fraction of patients demonstrating improvements in spirometry remained stable between 3 and 6 months, confirming durability of response. Clinically significant improvements in dyspnea (i.e., ≥ 1 unit decline in MRCD score) and HRQoL (> than 4 unit reduction in SGRQ total domain score) were observed in 2/3

to 3/4 of patients out to 6 months following HD therapy. The fraction of patients demonstrating clinically significant improvements in 6 MWD (i.e., ≥ 50 m increase in 6 MWT distance) following HD therapy was substantially smaller.

Clinically significant responses following LD treatment were observed only in MRCD and SGRQ scores post treatment.

Radiologic Responses to BioLVR

CT imaging was performed at baseline and 6 weeks post treatment. Both HD and LD groups displayed baseline radiography consistent with severe emphysema assessed in terms of overall tissue density and fraction of lung with tissue density < -950 HU (HD: -901±34 HU, 31±12% < -950 HU; LD: -892±46 HU, 26±18% < -950 HU). Therapy was not associated with radiologic evidence of BioLVR responses outside of pre-selected treatment sites. There was no radiologic evidence of treatment-related mediastinal or pleural pathology. Scarring responses were observed at 47±19% of LD and at 60 ± 20% of HD treatment sites. Among the combined cohort of 25 patients, the number of treatment sites demonstrating radiologic evidence of remodeling correlated significantly with percentage improvements in FEV_1 at 3 ($r = 0.49$, $p=0.01$, $n=25$) and 6 ($r = 0.56$, $p=0.004$, $n=25$) month follow-up.

CT images from selected patients are presented in Figure 2. These images show the peripheral subsegmental upper lobe atelectasis characteristic of BioLVR responses.

On a per-site basis, scarring reactions were more extensive following 20 mL/site treatment than 10 mL/site treatment.

Discussion

Biologic Lung Volume Reduction is a novel bronchoscopic therapy for reducing lung hyperinflation in advanced emphysema. BioLVR treatment involves endobronchial administration of a hydrogel that flows into the alveolar compartment and polymerizes, collapsing enlarged airspaces and triggering a localized inflammatory reaction that remodels and contracts diseased emphysematous lung tissue. Prior results have demonstrated the safety and potential efficacy of BioLVR in patients with advanced upper lobe predominant (ULP) emphysema. [9, 12, 20] In a cohort of 22 patients, BioLVR therapy with 20 mL of hydrogel at 8 subsegmental sites was associated with improvements in FEV_1, FVC, RV/TLC ratio, dyspnea scores, and health related quality of life out to 6 months following treatment. The present study shows that treatment can be performed safely with physiological and functional benefits in patients with advanced homogeneous emphysema, although responses reported here are smaller than those observed in patients with upper lobe heterogeneous disease.

Theoretical considerations suggest that volume reduction therapy could benefit patients with advanced emphysema independent of whether the distribution of disease is homogeneous or heterogeneous. [21] Resection of hyperinflated lung tissue and normalization of the mechanical relationship between the over-sized lung and chest wall increases lung recoil, vital capacity, and expiratory flows, and restores the respiratory

muscles to a more normal configuration. In practice, LVRS has been associated with reduced efficacy and a higher incidence of complications in homogeneous compared to heterogeneous ULP emphysema and is generally avoided in patients with homogeneous emphysema. [8]

Results presented here suggest that BioLVR may represent a safer, potentially effective alternative to LVRS in patients with advanced homogeneous emphysema. Although encouraging, these results must be considered preliminary, and interpreted with caution. Selection bias exists in this study as enrollment was limited specifically to patients not eligible for, or refusing surgical volume reduction and transplantation. Furthermore, confirmation of these initial findings in a larger, randomized controlled trial with longer follow-up is needed to fully assess the utility of BioLVR therapy in patients with advanced homogeneous emphysema. It is also important to note that patients identified by NETT investigators as being at high risk of death following LVRS (homogeneous disease with $FEV_1 < 20\%$ predicted) were specifically excluded from this study. Thus, the potential for BioLVR to address this important unmet need was not addressed in this study.

BioLVR treatment was associated with a predictable, acute, self-limited mild-to-moderate inflammatory reaction in all patients. This "flu-like" reaction resolves within 24-48 hours, responds to general supportive medical care, and is reasonably well tolerated. Side effects were similar to those previously reported in patients who received BioLVR at 8 subsegmental sites for treatment of ULP emphysema. [12]

The safety profile of BioLVR reported here in advanced homogeneous emphysema compares favorably to LVRS and other endobronchial lung volume reduction techniques. LVRS is associated with a 5 to 20% 90 day mortality and endobronchial valve therapy (n=98) and airway bypass (n=36) with an approximately 1 to 3% 90 day mortality. [8, 22, 23] By comparison, no deaths were observed among the 25 patients treated with BioLVR in this study. Serious pulmonary and cardiovascular complications within 30 days of treatment have been reported in up to 49% of LVRS patients and 27% of airway bypass patients. [12], 17] In the current study none of 25 patients treated with BioLVR experienced serious medical complications out to 6-months.

Improvements in physiology post BioLVR therapy follow a pattern consistent with the mechanism proposed by Fessler et al [20] to explain physiological responses to surgical volume reduction. Among LD and HD patients combined, percentage change in both FEV_1 ($n=25$, $r = -0.614$, $p<0.001$) and FVC ($n=25$, $r=-0.744$, $p<0.001$) at 6 months correlated with percentage reduction in gas trapping (RV/TLC ratio) suggesting that the basis for improvement following BioLVR therapy in patients with advanced homogeneous emphysema is lung-chest wall re-sizing. This physiological mechanism of action is further supported by CT imaging, which shows a statistically significant although limited correlation between the number of treatment sites that demonstrate atelectasis and the improvements in pulmonary function.

Imaging studies confirm the ability to target BioLVR therapy to specific anatomic locations via the endobronchial route. Neither LD nor HD therapy was associated with radiographic evidence of mediastinal, pleural or parenchymal changes beyond those associated with treatment-site remodeling. Radiographic responses were observed more consistently, and were larger following HD therapy compared to LD therapy (Figure 2).

Although this Phase 2 study was open labeled and uncontrolled, results support the potential efficacy and safety of BioLVR therapy in patients with advanced homogeneous emphysema and persistent respiratory symptoms. Improvements at follow-up time points in objective, largely effort independent, physiological outcomes including FEV_1 and RV/TLC cannot be explained by a placebo effect. Potential therapeutic effectiveness is further supported by evidence of a dose-response relationship across LD and HD patients in physiological and patient reported outcomes.

In summary, BioLVR therapy is one of several endobronchial approaches being developed to treat lung hyperinflation in advanced emphysema. In this small study, safety and efficacy responses following HD therapy in patients with homogeneous emphysema compared favorably to LVRS and endobronchial airway bypass, and the responses appeared durable out to 6 months of follow-up. Additional, randomized controlled studies in a larger number of patients are required to confirm the preliminary findings presented here, but initial results suggest that BioLVR therapy may represent a new treatment for patients with advanced homogeneous emphysema.

TABLES

Table 1. Patient Demographics

Parameter	Low Dose (N=8)	High Dose (N=17)	P-Value[1]
Age (yrs) Mean (SD)	63.1 (5.06)	66.0 (6.75)	0.30[1]
Gender [n, (%)] Male	5 (62.5)	11 (64.7)	>0.99[2]
BMI (kg/m^2) Mean (SD)	25.6 (6.24)	26.6 (5.08)	0.69[1]
Smoking History (pack yrs) Mean (SD)	58.5 (32.67)	63.9 (28.93)	0.68[1]
Oxygen Use at Rest (L) Mean (SD)	0.4 (1.06)	1.4 (1.05)	0.034[1]
Oxygen Use with Activity (L) Mean (SD)	0.4 (1.06)	2.8 (1.43)	<0.001[1]
Oxygen Use during Sleep (L) Mean (SD)	0.2 (0.71)	1.9 (0.95)	<0.001[1]
Using Any Oxygen [n, (%)]	1 (12.5)	15 (93.8)	<0.001[2]
Pulmonary Rehabilitation Prior 6 Months [n, (%)]	2 (25.0)	14 (82.3)	0.022[2]
Medication Use			
Short acting β-agonist	87.5%	93.7%	NS
Short anticholinergic	25%	31.3%	NS
Long acting β-agonist	100%	81.3%	NS
Long acting anticholinergic	75%	62.5%	NS
Inhaled corticosteroid	87.5%	87.5%	NS
Theophylline preparation	37.5%	25%	NS
Systemic corticosteroid	37.5%	12.5%	NS

[1] t-test
[2] Fisher's exact test

Definition of abbreviations: BMI = body mass index

Table 2. Baseline Physiology

Parameter	Low Dose (N=8)	High Dose (N=17)	P-Value
FEV_1 Post Bronchodilator (L) Mean (SD)	0.80 (0.194)	0.79 (0.197)	0.89[1]
% Predicted FEV_1 Post Bronchodilator Mean (SD)	29.3 (6.89)	29.6 (8.59)	0.94[1]
FEV_1/FVC Mean (SD)	0.31 (0.043)	0.31 (0.101)	0.84[2]
RV (L) Mean (SD)	4.4 (0.70)	4.4 (1.17)	0.89[1]
% Predicted RV Mean (SD)	197.4 (32.48)	195.3 (40.94)	0.90[1]
TLC (L) Mean (SD)	6.8 (1.16)	7.4 (1.66)	0.39[1]
% Predicted TLC Mean (SD)	113.4 (5.10)	125.9 (14.35)	0.009[2]
RV/TLC Mean (SD)	0.65 (0.104)	0.60 (0.071)	0.18[1]
6 MWT Distance (m) Mean (SD)	355.0 (108.71)	293.1 (68.09)	0.100[1]
MRCD Score Mean (SD)	2.9 (0.83)	2.7 (0.48)	0.49[1]

[1] t-test based on equal variances
[2] t-test based on unequal variances
Definition of abbreviations: FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; RV = residual volume; TLC = total lung capacity; 6 MWT = 6 minute walk test distance; MRCD = Medical Research Council Dyspnea.

Table 3. Summary of Efficacy Response to BioLVR Treatment

Outcome	6 Weeks		3 Months		6 Months	
	LD (N=8)	**HD (N=17)**	**LD**	**HD**	**LD**	**HD**
% ΔFEV$_1$ (post-BD)	**-1.7±5.89** NS	**+7.3±14.92** NS	**+5.6±5.49** NS	**+11.6±16.36** (p=0.007)*	**-8.0±13.93** NS	**+13.8±20.26** (p=0.007)*
%ΔFVC (post-BD)	**-1.7±9.77** NS	**+3.8±11.97** NS	**+2.4±8.89** NS	**+7.6±13.00** NS	**-3.9±9.41** NS	**+9.0±13.01** NS
%ΔRV/TLC	**-3.9±8.26** NS	**-5.0±6.54** NS	**-5.5±11.23** NS	**-6.9±9.60** (p=0.008)**	**-1.4±13.82** NS	**-5.4±12.14** NS
%ΔDLco	**-2.8±10.6** NS	**+1.1±19.8** NS	**-3.4±13.6** NS	**+10.1±24.0** NS	**-1.4±10.8** NS	**+4.8±20.7** NS
Δ6MWD (m)	**-15.1±39.7** NS	**-15.4±71.9** NS	**-28.5±49.0** NS	**+7.3±54.6** NS	**-35.9±60.45** NS	**+2.6±38.25** NS
ΔMRCD	**-0.5±0.76** NS	**-0.6±0.61** NS	**-0.5±0.76** NS	**-0.9±0.93** (p=0.001)**	**-0.4±1.27** NS	**-0.8±0.73** (P=0.001)*
ΔSGRQ (total domain score)	**-9.4±9.62** NS	**-9.9±12.06** (p=0.0001)*	**-4.9±8.39** NS	**-13.0±14.59** (p=0.,0001)*	**-4.6±7.92** NS	**-12.2±12.38** (p=0.0001)*

The values presented are mean ± standard deviation and median, P values were determined from a Kruskal-Wallis test comparing outcomes across the three timepoints for each treatment group separately

*Statistical significance for all secondary outcome measures requires a $P < 0.007$ based upon Bonferroni correction for multiple comparisons

**Comparison for RV/TLC at 12 weeks vs baseline, the primary outcome measure, was performed by Mann-Whitney test

Definition of abbreviations: Δ=change, BD=bronchodilator, LD=low dose, HD=high dose, FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; RV/TLC = residual volume to total lung capacity ratio; DLco = diffusing capacity; 6MWD = 6 minute walk test distance; MRCD = Medical Research Council Dyspnea Score; SGRQ = St. George Respiratory Questionnaire

Table 4. Responder Analysis

Number & Percentage of Patients with MCID Responses to BioLVR Treatment Patients with Homogeneous Disease (N=25)

	Low Dose (N=8)		High Dose (N=17)	
Evaluation	**n/N**	**%**	**n/N**	**%**
Post FEV_1				
Week 6	0/8	0.0%	6/17	35.2%
Week 12	1/8	12.5%	6/17	35.2%
Week 24	0/8*	0.0%	5/17	29.4%
Post FVC				
Week 6	0/8	0.0%	5/17	29.4%
Week 12	0/8	0.0%	6/17	35.3%
Week 24	0/8*	0.0%	8/17	47.1%
MRC Dyspnea				
Week 6	3/8	37.5%	10/17	58.8%
Week 12	3/8	37.5%	11/17	64.7%
Week 24	2/8*	14.3%	11/17	64.7%
6MWT, distance				
Week 6	0/8	0.0%	2/17	11.8%
Week 12	0/8	0.0%	5/17	29.4%
Week 24	0/8*	0.0%	2/17*	12.5%
SGRQ Total Domain[1]				
Week 6	6/8	75.0%	14/17	82.4%
Week 12	5/8	62.5%	13/17	76.5%
Week 24	5/8	62.5%	12/17	76.5%

Note: FEV_1 and FVC response based on a 12% improvement (increase) from baseline. Response for functional assessments defined as increase of 50 meters for the 6MWT distance, a decrease of 1 for MRC dyspnea, and a decrease of 4 for SGRQ

* Data imputed for 1 patient from 12 week time point

Definition of abbreviations: Post = post-bronchodilator; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; RV = residual volume; TLC = total lung capacity; 6 MWT = 6 minute walk test; MRC Dyspnea = Medical Research Council Dyspnea; SGRQ = St. George's Respiratory Questionnaire.

Figure Legends

Figure 1. Summary of Responses to LD and HD BioLVR Therapy at 3 and 6 months Post-treatment

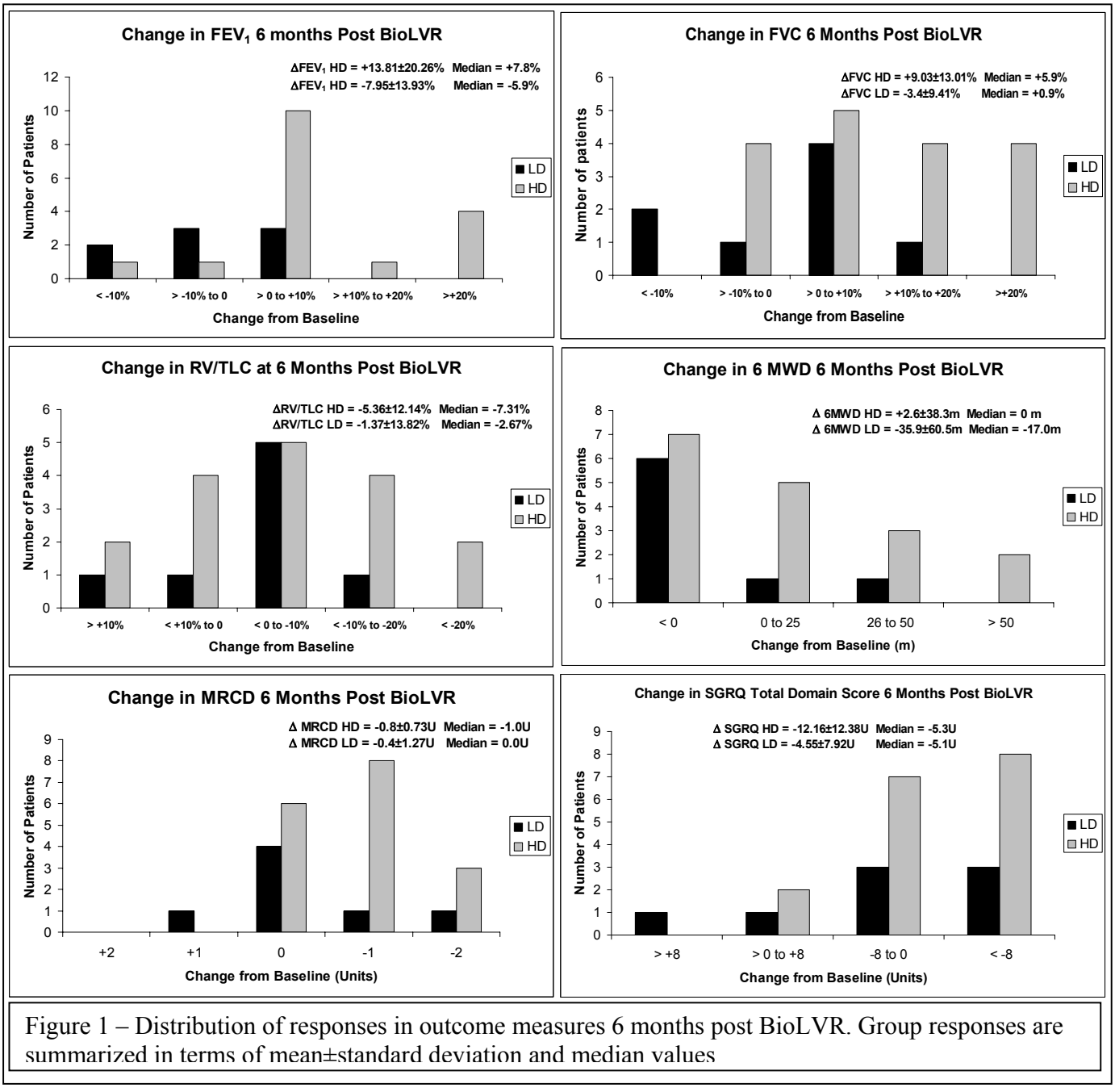


Figure 1 – Distribution of responses in outcome measures 6 months post BioLVR. Group responses are summarized in terms of mean±standard deviation and median values

Figure 2a. Baseline and Week-6 Post BioLVR HD Therapy CT Responses

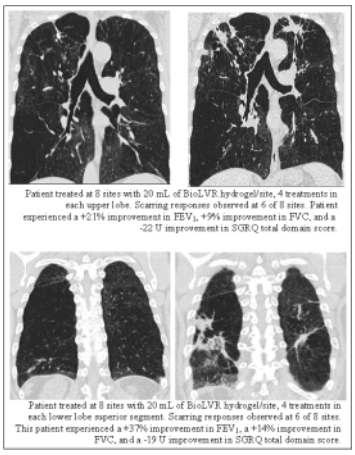
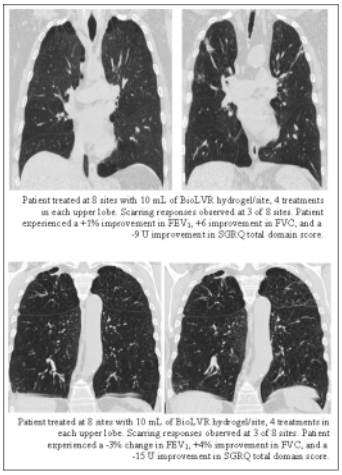


Figure 2b. Baseline and Week-6 Post BioLVR LD Therapy CT Responses



Bibliography

1. **Date, H., et al., *Predictors of improvement in FEV1 (forced expiratory volume in 1s) after lung volume reduction surgery.* Surg Today, 2000. 30(4): p. 328-32.**
2. **DeCamp, M.M., Jr., et al., *The evaluation and preparation of the patient for lung volume reduction surgery.* Proc Am Thorac Soc, 2008. 5(4): p. 427-31.**
3. **McKenna, R.J., Jr., A. Gelb, and M. Brenner, *Lung volume reduction surgery for chronic obstructive pulmonary disease: where do we stand?* World J Surg, 2001. 25(2): p. 231-7.**
4. **Fishman, A., et al., *A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema.* N Engl J Med, 2003. 348(21): p. 2059-73.**
5. **Wood, D.E., *Results of lung volume reduction surgery for emphysema.* Chest Surg Clin N Am, 2003. 13(4): p. 709-26.**
6. **Martinez, F.J. and A. Chang, *Surgical therapy for chronic obstructive pulmonary disease.* Semin Respir Crit Care Med, 2005. 26(2): p. 167-91.**
7. **Ramsey, S.D., et al., *Cost effectiveness of lung-volume-reduction surgery for patients with severe emphysema.* N Engl J Med, 2003. 348(21): p. 2092-102.**
8. **Criner, G.J. and A.L. Sternberg, *National Emphysema Treatment Trial: the major outcomes of lung volume reduction surgery in severe emphysema.* Proc Am Thorac Soc, 2008. 5(4): p. 393-405.**
9. **Criner, G.J., et al., *Biologic Lung Volume Reduction (BioLVR) in Advanced Upper Lobe Emphysema: Phase 2 Results.* Am J Respir Crit Care Med, 2009.**
10. **Ingenito, E.P., et al., *Bronchoscopic lung volume reduction using tissue engineering principles.* Am J Respir Crit Care Med, 2003. 167(5): p. 771-8.**
11. **Ingenito, E.P., D.E. Wood, and J.P. Utz, *Bronchoscopic lung volume reduction in severe emphysema.* Proc Am Thorac Soc, 2008. 5(4): p. 454-60.**
12. **Criner, G.J., et al., *Biologic lung volume reduction in advanced upper lobe emphysema: phase 2 results.* Am J Respir Crit Care Med, 2009. 179(9): p. 791-8.**
13. ***Patients at high risk of death after lung-volume-reduction surgery.* N Engl J Med, 2001. 345(15): p. 1075-83.**
14. **Wanger, J., et al., *Standardisation of the measurement of lung volumes.* Eur Respir J, 2005. 26(3): p. 511-22.**
15. **Aggarwal, A.N. and R. Agarwal, *The new ATS/ERS guidelines for assessing the spirometric severity of restrictive lung disease differ from previous standards.* Respirology, 2007. 12(5): p. 759-62.**
16. ***ATS statement: guidelines for the six-minute walk test.* Am J Respir Crit Care Med, 2002. 166(1): p. 111-7.**
17. **Brooks, D., S. Solway, and W.J. Gibbons, *ATS statement on six-minute walk test.* Am J Respir Crit Care Med, 2003. 167(9): p. 1287.**
18. **Washko, G.R., et al., *Computed tomographic-based quantification of emphysema and correlation to pulmonary function and mechanics.* Copd, 2008. 5(3): p. 177-86.**
19. **Kohl, G., *The evolution and state-of-the-art principles of multislice computed tomography.* Proc Am Thorac Soc, 2005. 2(6): p. 470-6, 499-500.**

20. **Reilly, J., et al., *Biological lung volume reduction: a new bronchoscopic therapy for advanced emphysema.* Chest, 2007. 131(4): p. 1108-13.**
21. **Fessler, H.E., et al., *Physiologic basis for improved pulmonary function after lung volume reduction.* Proc Am Thorac Soc, 2008. 5(4): p. 416-20.**
22. **Yim, A.P., et al., *Early results of endoscopic lung volume reduction for emphysema.* J Thorac Cardiovasc Surg, 2004. 127(6): p. 1564-73.**
23. **Cardoso, P.F., et al., *Clinical application of airway bypass with paclitaxel-eluting stents: early results.* J Thorac Cardiovasc Surg, 2007. 134(4): p. 974-81.**