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# Meta-analysis and Systematic Review of Bronchoscopic Lung Volume Reduction via Endobronchial Valves in Severe Emphysema

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# Abstract

**Introduction**—Pharmacologic therapeutics for advanced emphysema have limited benefit. Bronchoscopic lung volume reduction (BLVR) with endobronchial valves (EBV) have reported improvements in lung function, breathlessness, and quality of life through randomized clinical trials, with less morbidity as comparted to Surgical Lung volume Reduction. We here present a Meta-analysis and systematic review of BLVR in advanced COPD patients

**Methods**—PubMed (NLM), Embase (Elsevier) and Web of Science (Clarivate Analytics) search was conducted using a combination of keywords and subject headings. The search was confined to the last 15 years and was completed on October 23, 2020. Only placebo controlled RCTs of emphysema patients with EBV were included. Quality assessment was done by two independent reviewers.

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**Results**—9 studies were included for the Meta-analysis with a total number of 1383 patients of whom 888 received EBV and 495 standard of care (SOC) medications. Our Metanalysis show statistically significant improvement in FEV1, %FEV1, SGRQ and 6MWD in EBV group compared to SOC. Residual volume (RV) had statistically significant reduction after EBV placement compared with SOC. These differences continued to be present during short term(<=6months) and long-term follow-up (>=6months). These improvements were even higher when the EBV patients' Collateral ventilation was negative/fissure was intact (CV –/FI >9 0%). The rate of hemoptysis and pneumothorax was higher in the EBV group compared to SOC, however, did not lead to increased fatal outcomes.

**Conclusion**—In conclusion, EBV has favorable effects on patients' outcomes in patients who have heterogeneous emphysema particularly with no collateral ventilation

#### Introduction

Chronic Obstructive Lung Disease (COPD) is the third leading cause of death and fourth leading cause of disability in the United States, responsible for six percent of all deaths globally in 2012.<sup>1</sup> The healthcare burden of COPD is projected to increase exponentially in the coming decades. Pulmonary emphysema, a major pathological subtype of COPD, results from abnormal enlargement of the air spaces distal to the terminal bronchioles.<sup>2</sup> Abnormal parenchyma and airway physiology results in excessive gas trapping during the expiratory phase. Patients with advanced emphysema suffer from static and dynamic hyperinflation that leads to dyspnea, exercise intolerance, muscle wasting, reduced physical activity levels and impairments in quality of life. Moreover, these abnormalities predispose to exacerbations of COPD that are associated with increased morbidity and mortality.<sup>3,4</sup>

Pharmacologic therapeutics for COPD patients that have a predominant emphysema phenotype have limited benefit.<sup>1,5</sup> Inhaled therapies such as short and long-acting bronchodilators have been shown to improve  $FEV_1$  and static and dynamic hyperinflation more than placebo, however, the magnitude of the benefit is limited in patients with advanced emphysema. Other guideline-recommended therapies include smoking cessation, influenza, pneumococcal, pertussis and covid-19 vaccines, pulmonary rehabilitation (PR) and continuous oxygen therapy, however no medical therapy provides relief from the progressive disability of severe emphysema as they do not address the structural and physiological disturbances that results from advanced disease.<sup>6</sup>

Lung volume reduction surgery (LVRS), first performed in 1957, served for decades as the only intervention able to relieve severe hyperinflation in emphysema. The National Emphysema Treatment Trial (NETT) demonstrated survival benefit in the subset of patients with upper lobe predominant emphysema and low exercise capacity compared to medical therapy. However, many patients (80%) are ineligible for LVRS, primarily due to associated morbidity and mortality, especially patients with homogeneous emphysema.<sup>7</sup> Minimally invasive techniques, including one-way endobronchial valves (EBV), were developed over the last two decades to reduce hyperinflation and improve clinical outcomes with less associated morbidity and mortality.

Bronchoscopic lung volume reduction (BLVR) has gained popularity over the course of the last decade after reporting improvements in lung function, breathlessness, and quality of life through randomized clinical trials. Along with improvement in pulmonary function tests (PFTs), imaging studies have shown improved ventilation/perfusion mismatch post BLVR. This was especially seen in heterogeneous emphysema, through decreases in treated lobe perfusion and ventilation with compensatory redistribution to the contralateral lung.<sup>8–10</sup> The procedure has the advantage of being minimally invasive with less morbidity and mortality compared to LVRS.<sup>11,12</sup> Currently there are two FDA approved one-way valve systems that reduce hyperinflation in patients with severe COPD. Herein we present a Meta Analysis and a systematic review of the randomized controlled trials using endobronchial valves to perform BLVR.

# Types of Valves

#### **FDA Approved Valves**

The Zephyr Valve is an implantable device that consists of a one-way silicone duckbill valve at the end of a Nitinol self-expanding frame that is covered with a silicone membrane. Zephyr valves are available in 4 sizes to accommodate airway diameters of different ranges (see Figure 1). A Chartis pulmonary assessment system can be used to assess for collateral ventilation and the Stratx Lung Analysis platform, a quantitative CT analysis service, assesses emphysema destruction, fissure completeness and lobar volumes to aid in selecting the best lobe for valve placement. The valves are deployed over endobronchial catheters that also aid airway sizing. The 4.0 catheter is also available in a J-configuration for tortuous airways.<sup>13–15</sup>

The Spiration Valve System is an implantable, umbrella shaped, one-way valve delivery system. The valve is composed of a flexible Nitinol frame that anchors it in place. Spiration valves come in 4 different sizes (5-, 6-, 7-, and 9-mm valves) (see Figure 2). A calibrated balloon catheter determines the appropriate valve size and is passed through a 2.0- or 2.6-mm working channel of the bronchoscope.<sup>16,17</sup> The number of valves implanted can range from two to nine valves. On average most lobes require three to five valves.<sup>11</sup>

#### **Non-FDA Approved Valves**

MedLung EBV and the endobronchial Miyazawa valve are the other valves that are available outside the United States. However, no randomized clinical trials have been published on these valves. Hence, our review excluded these valve systems.

#### **Patient Selection Criteria**

Optimal patient selection is crucial for the successful treatment of hyperinflation utilizing endobronchial valves. Patients should be symptomatic from hyperinflation despite being medically optimized through smoking cessation, bronchodilator therapy, and participation in pulmonary rehabilitation.<sup>18,19</sup> A rigorous work up should be initiated with pulmonary function tests (PFTs), high resolution chest computed tomography (HRCT), and collateral ventilation and fissure analysis.

#### PFTs

Patients with severe hyperinflation from advanced emphysematous destruction as evidenced by a FEV<sub>1</sub> of 45% predicted, RV of  $\geq$ 150% predicted, and a total lung capacity (TLC)  $\geq$ 100% are eligible for endobronchial valves. Patients with a FEV<sub>1</sub> 15% of predicted, DLCO <20% predicted, PaO<sub>2</sub> <45 mmHg, PaCO<sub>2</sub> >50 mmHg, or uncontrolled pulmonary hypertension (including resting systolic pulmonary arterial pressure > 45 mmHg) were excluded in clinical trials. Individuals with a DLCO < 20% had a benefit in a small single center study from 2016 but is a surgical predictor of mortality in patients with homogenous emphysema based on data from NETT.<sup>11,12,20,21</sup> Two other small single center studies reported that EBV can be performed in patients with a FEV<sub>1</sub> < 20% with a success rate of ~50–60%.<sup>22,23</sup> Typically, completion of pulmonary rehabilitation (adapted from the LVRS trials) is recommended prior to undergoing EBV treatment to minimize peri and post-operative complications and maximize post procedural patients exercise tolerance.

#### HRCT

HRCT allows identification of potential targets for intervention as well as post-intervention to confirm EBV placement and assess for target lobe volume reduction.<sup>24</sup> HRCT is performed with a slice thickness of 1 mm. Axial, coronal and sagittal images are acquired during both inspiration and expiration. HRCT allows for quantification of the emphysematous destruction of the peripheral lung tissue along with fissure assessment, a surrogate for collateral ventilation. Quantification can be performed by visual scoring, semiquantitative method using densitometry or by quantification using automated software. Both visual scoring and semi-quantitative methods have high inter-operator variability, hence they are not the preferred methods for determining EBV eligibility.<sup>25</sup> Moreover, the accuracy of CT to predict fissure completeness is not consistent and depends on the specific fissure. CT scans were reported to have a 74% accuracy of predicting fissure completeness for the left lung. However, it overestimates completeness of the right minor fissure, and underestimates completeness of the right major fissure.<sup>26</sup> More accurate automated software programs have been developed to calculate the severity and distribution of emphysema and fissure completeness but require validation.<sup>27</sup>

The reporting systems that are currently available include the Stratx lung analysis system and SeleCT Report. These software programs calculate total and lobar lung volumes and emphysema destruction scores (measured in Hounsfield units, HFU) in the different lobes which can also add the calculation of heterogeneity indexes.<sup>28,29</sup>

The radiologic features associated with good clinical outcomes include presence of heterogeneous emphysema and complete interlobar fissures which can be assessed by quantitative HRCT. Typically, greater than 40–50% area of the targeted lobe should be less than -910 to -920 HU as well as a 10–15% difference in emphysema destruction score between the target lobe and ipsilateral adjacent lobe. It is also recommended to have fissure completeness greater than 90% on Qualitative CT evaluation.

In addition, Quantitative CT assessments(~accuracy ~70–75%) has a correlation with Chartis physiologic assessment (described below) for Collateral ventilation assessment

(agreement ~80%) and is an additional tool to select patients for BLVR.<sup>30–33</sup> Combination of quantitative CT and the Chartis System® Collateral ventilation assessment results in a higher diagnostic pre-procedural assessment for predicting response in patients receiving BLVR.<sup>34</sup> Lastly, the Chartis System® can be used as an additional diagnostic tool to confirm the absence of collateral ventilation in selected patients.<sup>11,12,35,36</sup>

#### **Collateral ventilation and fissure analysis**

Collateral ventilation (CV) is assessed using the Chartis <sup>TM</sup> Pulmonary Assessment System. Both flow and volume are measured distally through a specialized flow catheter while a balloon is inflated proximally, a process that mimics lobar occlusion of the targeted lobe.<sup>37</sup> CV is said to be negative if flow measurements progressively decrease to absence of flow and collateral resistance increases to > 10 cmH<sub>2</sub>0 × s/ml around the catheter.<sup>38,39</sup> Measurements should be taken meticulously as false negative and positive results may occur. A false CV-negative can occur with failure to obstruct all subsegments and incomplete sealing of the bronchus. By contrast a false positive CV- result can occur due to mucous plugging of the distal catheter tip, rapid collapse of the bronchial wall around the catheter, and distal obstruction of the catheter tip by a secondary carina.

In one prospective study, 36 of the 51 CV negative patients showed a significant total lung volume reduction ( 350 mL). This translated into a positive predictive value of 71%. In comparison, 24 out of 29 CV positive patients failed to show significant lung volume reduction for a negative predictive value of 83%.<sup>40</sup>

Chartis<sup>TM</sup> has also been validated for intraoperative assessment of fissure integrity with an accuracy of 71%. The sensitivity and specificity of the Chartis measurement were 86% and 61% and 75% and 79% in HRCT fissure analysis.<sup>32</sup>

#### Nuclear perfusion/ventilation scans

Optimal target lobe selection is dependent on the percentage of perfusion to the target lobe. The 3-dimensional ventilation and perfusion (V/Q) single-photon emission computed tomography (SPECT)/computed tomography (CT) analysis can be used to identify target lobes by quantifying volume, ventilation, and perfusion changes. It can also be used to quantify post-BLVR treatment responses.<sup>41</sup> In BLVR patients, studies have shown robust improvement in exercise capacity (using 6-minute walk test, 6MWT and SGRQ) when target lobe perfusion was <8% of total perfusion in the upper lobes and <13% of total perfusion in the lower lobe targets.<sup>42</sup> In addition, patients with high perfusion in ipsilateral non-target lobes demonstrated greater improvements in 6MWT, while patients with high heterogeneity between target and nontarget lobes are more likely to show greater improvement in FEV<sub>1</sub>.<sup>41,43</sup> 133-Xenon ventilation scintigraphy has shown promise in target lobe selection.<sup>44</sup>

# Methods

# Search Strategy

To identify studies to include or consider for this systematic review, the review team worked with a medical librarian to develop detailed search strategies for each database. The search

was developed for PubMed (NLM) and was translated to Embase (Elsevier) and Web of Science (Clarivate Analytics) using a combination of keywords and subject headings. A grey literature search included bioRxiv and clinicaltrials.gov. The search included no major limits and was confined to the last 15 years. The language was restricted to English without any restrictions to specific populations or geographical areas. The final search was completed on October 23, 2020.

Initial Screen was performed by two independent reviewers using the titles and abstracts to exclude any duplicates, non-COPD trials, COPD trials without lung volume reduction, case reports/series or conference abstracts. After the initial screen, the same two reviewers independently scanned all the articles to identify randomized control trials (RCTs) evaluating the treatment of advanced emphysema patients with EBV. The reviewers independently assessed the full text articles, reviewed them using the inclusion/exclusion criteria below. Any differences were resolved through consensus; with a third reviewer resolving any disagreements.

#### Inclusion and exclusion criteria

Studies fulfilling the following selection criteria were included in this meta-analysis: Randomized placebo-controlled trials (RCTs) of emphysema patients treated with either EBV or standard medications according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines were included. Both experiments and controls should have been available for Odds Ratio (OR), risk differences, weighted mean differences (WMD) and 95% confidence interval (CI). Studies were excluded if one of the following existed: non-EBV treatment of emphysema, not RCTs, reviews, case reports/series and abstracts.

# Quality assessment and data extraction

The quality of studies was also independently assessed by the two reviewers who assessed the studies for biases, appropriate outcomes, duration of follow-up and lack of selective reporting.

Data extraction and critical appraisal were carried out by the two reviewers independently. The results were compared, and any discrepancies were resolved by the third reviewer. Using a standardized data extraction spreadsheet, data on first authors' last name, the publication year, study design, the sample size, study population, inclusion criteria, treatment method, length of follow-up, and outcomes were extracted.

#### **Data Analysis**

The primary outcomes for the review included change in forced expiratory volume in 1 second (FEV<sub>1</sub>), percent predicted FEV<sub>1</sub>(%FEV<sub>1</sub>), 6-minute walk distance (6-MWD), residual volume (RV) and St. George's respiratory questionnaire (SGRQ) after placement of the EBV. Secondary outcomes included mortality, rate of adverse events including acute respiratory failure, pneumonia, and pneumothorax. Continuous outcomes were measured as the mean difference and 95% confidence intervals (CI), and dichotomous outcomes as odds ratio (OR) and 95% CI. We did not impute missing data for any outcome. We assessed heterogeneity between studies by estimation of the  $I^2$  statistic and by a formal statistical

test to indicate statistically significant heterogeneity. We performed subgroup analyses by follow-up time (<6 months vs & >= 6 months) for the primary outcomes. For adverse events, subgroup analysis was performed by short- and long-term follow-up reported in respective studies. Similarly, subgroup analysis was performed by collateral ventilation (CV) and fissure intact (FI > 90% vs < 90%) status for both primary outcomes and adverse events. We conducted meta-analysis using a fixed effects model and conducted statistical tests for subgroup and overall treatment effects between EBV and control. To ensure the generalizability of the results and robustness of the meta-analysis, we also conducted the meta-analysis using a random effects model (see online supplement for results). P values < 0.05 were considered statistically significant. All data analyses were performed using Stata 17.0 (Stat Corp LLC., College Station, TX).

#### Results

Initial screening yielded the following results: PubMed (NLM) from inception to 10/23/20 (413 Results), Embase (Elsevier) from inception to 10/23/20 (902 Results), Web of Science (Clarivate Analytics) from inception to 10/23/20 (419 Results). This search resulted in 1,748 studies (14 from grey literature sources). 619 duplicates were identified, and 5 articles were written in languages other than English. There were 582 studies excluded because they involved COPD without lung volume reduction or other diagnoses. All abstracts, case reports/series, and editorials were excluded (274 in total). 33 articles were excluded because they were unrelated to endobronchial valves. A second screening was performed on the remaining 235 studies. 32 studies were found to be non-endobronchial valve BLVR (i.e., coils, vapor ablation, gels). 100 reviews and 94 trials with other EBV related outcomes were removed (see Figure 3). In the end, 9 studies were included for the Meta-analysis with a total number of 1383 randomized patients, of whom 888 received EBV and 495 received standard medications. All eligible studies were of high quality, and with a follow up duration of minimum 3 months. 7 studies were multicenter, while 2 were single centers. Table 1 summarizes some of the outcomes of these trials.

# Primary Outcomes

# Physiologic parameters (FEV<sub>1</sub>, %FEV<sub>1</sub>, RV)

Our metanalysis revealed that patients who received EBV had an increase in baseline FEV<sub>1</sub> (WMD=102.61 ml; 95% CI: 82.80 to 122.43; p < 0.05;  $\vec{F} = 42.61\%$ , p = 0.08) compared to the standard of care (SOC) group. The percent FEV<sub>1</sub> change (WMD=11.71; 95% CI: 9 to 14.42; p < 0.05;  $\vec{F} = 71.13\%$ , p <0.05) increased in the EBV group compared to the SOC group. RV had a statistically significant reduction in the EBV group compared to the control group (WMD=-533.48 ml; 95% CI, -653.01 to -413.94; p <0.05;  $\vec{F} = 26.90\%$ , p = 0.22). The improvements in FEV<sub>1</sub> (102.55 ml vs 102.84 ml, p=0.99), %FEV<sub>1</sub> (11.41 vs 12.79, p = 0.68) and RV (-537.63 ml vs -520 ml, p=0.90) were similar in both short term (<=6 months) and long-term follow-up (>6 months) (Figure 4).

#### Quality of life and activity parameters (SGRQ and 6MWD)

There was a significant improvement in patients' SGRQ scores in the EBV arm compared to SOC (WMD=-7.44; 95% CI: -9.01 to -5.86; p < 0.05;  $\hat{F} = 50.89\%$ ; p=0.03). SGRQ

improvements were similar at short- and long-term follow-up (-7.29 versus -8.07, p=0.70). Our meta-analysis showed a statistically significant improvement in 6MWD among patients who received EBV compared with SOC (WMD=37.45; 95% CI: 27.68 to 47.21, p<0.05;  $\hat{P} = 72.98\%$ ; p <0.05). Improvements in 6MWD were similar at short- and long-term follow-ups (37.10 m versus 39.31 m, p=0.87) (Figure 4). See Supplementary figure 1 for analysis using random effect model

#### Adverse events

Analyzing all nine studies did not reveal any significant difference between mortality rates between the EBV and control group (OR = 1.08, CI: 0.57 to 2.05, p=0.82;  $I^2 = 0.0\%$ , p = 0.95). Deaths were not different at short term and long term follow up between the groups (1.36 versus 0.84, p=0.47). There was a significant increase in incidence of pneumothorax in the EBV group compared to SOC (OR = 10.50, 95% CI = 5.31 to 20.79, p < 0.05,  $l^2$ =32.55%, p=0.10). The incidence of pneumothorax was increased more so in short term follow-up (OR = 18.37, 95% CI = 7.46 to 45.25) compared to long term follow-up (OR = 2.18, 95% CI = 0.69 to 6.87) (p < 0.05). The incidence of respiratory failure (OR = 0.93, 95% CI = 0.49 to 1.76, p = 0.82;  $I^2$  = 0.00%, p = 0.96) was not statistically significant between the two groups. Increased incidence of pneumonia was noted in short term follow-up (OR = 3.12, 95% CI = 1.47 to 6.64, p < 0.05) and overall (OR = 2.18, 95%CI = 1.36 to 3.50, p<0.05;  $\hat{I} = 0.0\%$ , p=0.61), however was not statistically significant at long term follow-up (OR = 1.66, 95% CI = 0.90 to 3.06). (Figure 3). Increased incidence of AECOPD was observed in short term follow-up (OR = 1.48, 95% CI = 1.02 to 2.13, p < 0.05), however was not statistically significant overall (OR=1.11, 95% CI = 0.86 to 1.44, p=0.41:  $I^2 = 31.47\%$ , p = 0.13) and at long term (OR = 0.83, 95% CI 0.57-1.19) follow-up. Hemoptysis was increased in the EBV group compared to the control group (OR = 2.30, 95% CI = 1.31 to 4.03, p<0.05:  $\hat{P}$  = 13.35%, p=0.31). The incidence of hemoptysis was observed more in short term (OR = 3.56, 95% CI = 1.41 to 8.96) compared to long term follow-up (OR = 1.65, 95% CI =0.80 to 3.39) (See Figure 5). See Supplementary figure 2 for analysis using random effect model

# Physiologic, Quality of life parameters and adverse events by Collateral ventilation/fissure intact (FI) status

Our metanalysis revealed that patients who received EBV with no collateral ventilation (CV –) or Fissure intact > 90% (FI) had significantly more improvement in FEV<sub>1</sub> (123.85 ml vs 61.69 ml, p=0.01), %FEV<sub>1</sub> (19.84 vs 7.91, p < 0.05) and RV (-619.87 ml vs -370 ml, p=0.18) than patients with unknown status of CV/FI. SGRQ improvements were also significantly better in the CV –/FI > 90% group compared to CV/FI unknown group (-9.18 vs -3.58, p<0.05). Improvements in 6MWD were also higher in the CV-/FI>90% group, however they were not statistically significant (52.78 vs 33, p = 0.3) (Figure 6)

Patients in the CV -/FI > 90% group had a higher incidence of pneumothorax compared to CV/FI unknown group (OR= 12.54 vs 1.42, p = 0.01). There were no statistically significant differences in rates of pneumonia, AECOPD, respiratory failure and death between the CV -/FI > 90% and CV/FI unknown groups. The rate of hemoptysis however was reduced in the CV - group (OR = 0.77 vs 8.12, p = 0.01) (see Figure 7). See Supplementary figure 3 and 4

for analysis with random effect model. For estimated risk differences for adverse events, see supplementary figure 5 and 6.

# Discussion

Currently, the most widely used lung volume reduction method for the treatment of severe emphysema is EBV. Our meta-analysis shows that EBV therapy for advanced emphysema is associated with a statistically significant improvement in physiologic lung function parameters (FEV<sub>1</sub>, FEV<sub>1</sub>%, RV), functional parameters (6-MWD), and disease specific impact on health parameters (SGRQ) without significant long-term complications. The improvement in lung function parameters and quality of life parameters were even more robust when the patient's CV status was negative.

Although our meta-analysis showed significant improvements in these parameters, it is very important to have a specific selection criterion. VENT, the first RCT, had a statistically significant improvement in FEV<sub>1</sub> by 6.8%, an increase of 20 meters on 6MWT distance, and a reduction of -3.4 in SGRQ scores; however, the magnitude of these mean group changes were not clinically significant balanced against a higher rate of complications in the EBV group.<sup>45</sup> This study emphasized the importance of heterogeneity in emphysema pattern, complete fissure integrity, and complete lobar occlusion during post-hoc analysis. Subsequent studies such as STELVIO, IMPACT, and TRANSFORM utilized these features to improve EBV efficacy to improve lung function and exercise capacity (see table 1).<sup>11,12,36,46–49</sup>. This was followed by landmark trials such as LIBERATE and EMPROVE that led to FDA-approval of the two currently clinically available EBVs in the U.S. The LIBERATE trial used the Zephyr valve system and had 12-month follow-up for safety and efficacy. Besides exercise tolerance and lung function, 12-month follow-up of the LIBERATE also showed meaningful improvements in multidimensional scores (CAT, transitional dyspnea index (TDI)) for breathlessness, activity, and psychosocial parameters, thus improving quality of life.<sup>50</sup> The EMPROVE trial for the Spiration valve system yielded similar clinical improvements. Both trials were performed in patients with heterogeneous emphysema without collateral ventilation. The IMPACT study presented similar results in patients with homogeneous emphysema absent collateral ventilation. STELVIO included homogeneous emphysema, however it was a single center study.<sup>46,48</sup> In addition, different pooled meta-analysis of these RCTs have showed similar statistically significant improvements in FEV<sub>1</sub>, 6-MWD and SGRQ.<sup>51–55</sup> These clinical outcomes are independent of target lobe (upper/lower); if interlobar collateral ventilation is low and complete lobar occlusion is achieved.<sup>56,57</sup> Our meta-analysis also demonstrated significantly more improvement in physiologic and quality of life parameters when the collateral ventilation was negative. Small studies have showed maintenance of improved respiratory function parameters for at least 3 years in patients with persistent lobar collapse.<sup>58,59</sup>

Other than physiologic parameters, CT based assessments have shown decrease in treated lobe volumes that correlate well with clinically meaningful improvements in exercise capacity and pulmonary function.<sup>60,61</sup> Lobar collapse following EBV was associated with long term survival benefit in some small studies, however has not been proven in large studies.<sup>62,63</sup> In addition, EBV treatment has also shown to improve three survival indicators

in severe COPD which include inspiratory capacity/total lung capacity ratio, BODE index and 6MWT.<sup>64,65</sup> Lastly, pulmonary rehabilitation post EBV treatment has an additive effect on improvement in exercise tolerance.<sup>19</sup>

BLVR is associated with multiple respiratory complications, predominantly in the perioperative period. In our meta-analysis, there was an increased incidence of pneumothorax, pneumonia, and hemoptysis in the overall groups, however this increase was most notable in the short-term follow-up groups only. The incidence of AECOPD, respiratory failure and death was not statistically different between the two groups.

Overall, respiratory complications occur in 31–35% of patients.<sup>66</sup> The most common adverse event associated with EBV placement is pneumothorax (~25%).<sup>11,12</sup> Pneumothorax, however, has not been associated with poor clinical outcomes if lobar atelectasis is achieved.<sup>67–69</sup> The majority of pneumothorax (86%) occurred within the first 72 hours of EBV implantation and most required chest tube placement for resolution. In situations where the lung does not fully expand or there is a persistent air leak, removal of one or more valves (about 26–31% of cases) may be necessary.<sup>70</sup> Pneumothorax will most often occur in the ipsilateral lung due to rapid expansion of the ipsilateral nontarget lobe after effective TLVR. Higher emphysematous destruction of the ipsilateral nontarget lobe and high residual volume increases the risk of pneumothorax.<sup>71</sup> Pleural adhesions in the treated lung are associated with an increased risk of pneumothorax.<sup>72</sup> In the early trials in the US and European VENT, pneumothorax was reported at a much lower rate compared to subsequent trials. These studies did not select patients based on lack of CV or intact fissures which led to poorer patient selection for successful BLVR. Pneumothorax appeared to be a positive predictor of successful valve therapy, since patients that developed pneumothorax were better responders to implantation (TLVR 350 ml) compared to non-responders.<sup>66</sup> This was evident from our analysis, which showed majority of the pneumothorax occurred in the CV – group, even though this group had the best clinical outcomes. Although higher rates of microbial colonization and pneumonia have been reported in patients undergoing EBV treatment, there were no differences in acute exacerbations and respiratory failure in patients treated with EBV compared to standard treatments.<sup>66, 73, 74</sup> Although hemoptysis was significant in our analysis, both spiration valve studies did not report any hemoptysis. Of the Zephyr valve system studies, only 3 were reported to be massive, the remaining were mild hemoptysis. Most cases of mild hemoptysis were self-limiting.

Granulation tissue formation is also a long-term complication that occurred in about 40% of EBV patients in our metanalysis. If the granulation is severe, the valve must be removed to allow the airways to heal for 10–12 weeks after which retreatment can be considered.<sup>70</sup> Valve malfunction, incomplete airway occlusion due to use of smaller valves, valve migration are some other complications that can lead to loss of benefit after EBV treatment.

#### Limitations

There were several limitations in our metanalysis. Firstly, the data regarding long-term clinical outcomes and adverse events with BLVR were limited as the trials were restricted to 12 months. The follow-up intervals for primary outcomes and adverse events were different

across and within the trials which made it challenging to define a specific cutoff period for short- and long-term follow ups. Also, the number of trials reporting clinical outcomes at greater than 6-month follow-up were limited. We were also not able to compare the differences in clinical outcomes with homogenous and heterogenous emphysema, as the homogeneous emphysema trials were limited with a small number of patients enrolled and the short duration of follow-up.

#### Conclusions

In conclusion, EBV has favorable effects on patients' outcomes similar to surgical lung volume reduction, but with significantly less adverse outcomes especially in patients who have heterogeneous emphysema with no collateral ventilation. Additional studies of larger numbers of patients with homogeneous emphysema followed for longer periods of time needs to be performed to assess the long-term effectiveness of EBV treatment in this patient population.

# **Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

# Financial Disclosures:

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**Figure 1:** Different sizes of Zephyr endobronchial valves.



**Figure 2:** Different sizes of Spiration Valve system



**Figure 3:** Consort Flow diagram of our screening process

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## Figure 4:

Forest Plots comparing outcomes between the EBV and the control group. A: change in FEV1, B: Change in %FEV1, C: change in Residual Volume (RV), D: Change in 6-minute walk distance(6MWD), E Changes in SGRQ

Pneumothorax by Follow-up Time	Pneumonia by Follow-up Time	AECOPD by Follow-up Time				
Treatment Control Odds ratio Weigt	Treatment Control Odds ratio Weight	Treatment Control Odds ratio Weight				
Study Yes No Yes No with 95% Cl (%)	Study Yes No Yes No with 95% CI (%)	Study Yes No Yes No with 95% CI (%)				
Short Term	Short Term	Short Term				
LIBERATE 38 90 0 62 53.18 [3.21, 881.77] 4.84	LIBERATE 6 122 0 62 0.03 [0.37, 119.05] 2.33	LIBERATE 13 115 3 59 222 [0.61, 8.11] 3.30				
TRANSFORM 15 50 0 32	TRANSFORM 6 59 1 31	TRANSFORM 7 58 3 29				
IMPACT 12 31 0 50	IMPACT 0 43 1 49 ← 0.3810.02, 9.551 5.02	IMPACT 10 33 6 44 222[073 673] 387				
VENT 9 205 0 87	VENT 7 207 2 85 - 1.44 [0.29, 7.06] 10.06	VENT 20 194 1 86				
EU-VENT 5 106 0 60	EU-VENT 8 103 1 59	EU-VENT 47 64 28 32 ← 0.84 [0.45, 1.58] 19.06				
REACH 5 61 0 33 - 5.99 [0.32, 111.71] 6.25	REACH 1 65 0 33 - 1.53 [0.06, 38.69] 2.37	REACH 5 61 4 29 • 0.59 [ 0.15, 2.38] 4.48				
STELVIO 6 28 0 34 15.74 [0.85, 291.46] 4.18	STELVIO 2 32 1 33 - 2.06 [0.18, 23.88] 3.44	STELVIO 4 30 2 32 - 2.13 [ 0.36, 12.51] 1.60				
BeLiever HiFI 2 23 1 24 ← ■ 2.09 [0.18, 24.61] 9.44	BeLiever HiFI 2 23 0 25 ← 5.43 [0.25, 118.96] 1.65	Bel.inver HiFI 23 2 22 3 ← 1.57 [0.24, 10.30] 1.60				
Heterogeneity: I <sup>2</sup> = 0.00%, H <sup>2</sup> = 1.00	Heterogeneity: I <sup>2</sup> = 0.00%, H <sup>2</sup> = 1.00	Heterogeneity: I <sup>2</sup> = 11.71%, H <sup>2</sup> = 1.13				
Test of 6 = 6; Q(8) = 5.68, p = 0.68	Test of 6, = 6; Q(8) = 4.22, p = 0.84	Test of 6 = 6; Q(8) = 9.06, p = 0.34				
Long Term	Long Term	Long Term				
LIBERATE 8 114 0 62 928 [ 0.53, 163,46] 6.32	LIBERATE 11 111 6 56 - 0.92 [ 0.33, 2.63] 26.48	LIBERATE 37 85 29 33 ← 0.5010.26. 0.931 24.36				
EMPROVE 0 103 0 47 - 0.46 [ 0.01, 23.48] 6.95	EMPROVE 8 95 1 46 - 3.87 [0.47, 31.90] 4.63	EMPROVE 14 89 4 43				
VENT 2 212 2 85 - 0.40 [ 0.06, 2.89] 28.91	VENT 17 197 6 81 ← 1.16 [0.44, 3.06] 28.73	VENT 25 189 8 79 - 1.31 [0.56, 3.02] 9.14				
EU-VENT 4 107 0 60	EU-VENT 12 99 1 59 7.15 [0.91, 56.41] 4.24	EU-VENT 69 42 40 20 <				
Heterogeneity: I <sup>2</sup> = 36.37%, H <sup>2</sup> = 1.57 2.18 [ 0.69, 6.87]	Heterogeneity: I <sup>2</sup> = 29.51%, H <sup>2</sup> = 1.42	Heterogeneity: I <sup>2</sup> = 41.35%, H <sup>2</sup> = 1.70				
Test of 6, = 6; Q(3) = 4.71, p = 0.19	Test of 0, = 0; Q(3) = 4.26, p = 0.24	Test of $\theta_i = \theta_j$ : Q(3) = 5.11, p = 0.16				
0.0016.01.6.01.00.701	0 mm 10 2 2 2 1 2 2 2 2 1 2 2 2 2 2 2 2 2 2	0				
Hateronanaihr I <sup>2</sup> = 35 50%, H <sup>2</sup> = 1 55	Hetermenethr 1 <sup>2</sup> = 0.00% H <sup>2</sup> = 1.00	Overall Heteropenality I <sup>2</sup> = 31.47%, H <sup>2</sup> = 1.46				
Test of 6 = 6: Q(12) = 18.60, p = 0.10 Favors EBV Favors Control	Test of 6 = 6: Q(12) = 10.08. p = 0.61 Favors EBV Favors Control	Test of 8 = 8: O(12) = 17.51, p = 0.13 Favors EBV Favors Control				
Tast of errors differences: 0 /1) = 8 10 n = 0.00	Tast of service differences: O (1) = 1.62, n = 0.20	Test of aroun differences: O (1) = 4.76 p = 0.02				
1/2 4 32 256	1/2 2 8 32 128	12 2 8 12				
Fixed-effects Mantel-Haenazel model	Fixed-effects Mantel-Haenszei model	Fixed-effects Mantel-Haenszei model				
Respiratory Epilure by Follow, up Time	Hemontysis by Follow up Time	Death by Follow up Time				
ryddullaful y r dilufd y'r ullufwruu r llifd		Dedul by Follow-up Tille				
Transformant Control Oride ratio Wainh	Treatment Control Odds ratio Wainht	Transmant Control Odde ratio Waisht				
Treatment Control Odds ratio Weigh Study Yes No Yes No with 95% CI (%)	Treatment Control Odds ratio Weight Study Yes No Yes No with 95% CI (%)	Treatment Control Odds ratio Weight Study Yes No Yes No with 95% Cl (%)				
Treatment         Control         Odds ratio         Weight           Study         Yes         No         with 95% CI         (%)           Short Term	Treatment Control Odds ratio Weight Study Yes No Yes No (%) Short Term	Treatment         Control         Odds ratio         Weight           Study         Yes         No         with 95% CI         (%)           Short Term				
Treatment         Control         Odds ratio         Weight           Study         Yes         No         with 55% CI         (%)           Short Term         LIBERATE         0         128         0         62         0.491 (0.01, 24.80)         3.49	Treatment         Control         Odds ratio         Weight           Study         Yes         No         with (95% CI         (%)           ShortTerm         UBERATE         11         17         1         5.74 [0.72, 45.47]         6.41	Treatment         Control         Odds ratio         Weight           Study         Yes         No         with 55% CI         (%)           Short Term         LIBERATE         4         124         0         62         4.52 (0.24, 85.25)         3.59				
Treatment         Control         Odds ratio         Weight           Study         Yes         No         with 95% CI         (%)           Short Term         LIBERATE         0         128         0         62         0.49 (0.01), 24.80)         3.49           EMPROVE         3         110         0         59         →         3.377 (0.19, 74.20)         3.31	Treatment Control         Odds ratio         Weight           Study         Yes         No         with 55% CI         (%)           Short Term         UBERATE         11         17         1         61         574 (0.72, 45.47)         6.41           EMPROVE         0         113         0         59         0.52 (0.01, 26.76)         3.39	Treatment         Control         Odds ratio         Weight           Study         Yes         No         with 55% CI         (%)           Short Term         LEBRATE         4         124         0         62         4.52 (0.24, 85.26)         3.59           EMPROVE         0         113         0         59         ■         0.52 (0.01, 26.75)         3.61				
Treatment         Control         Odda nalo         Weight           Study         Yes         No         with 59°C (C)         10°           Stort Term         B         0.62         -         -0.49(0.01, 24.00)         340           LIBERATE         0.128         0.62         -         -         -0.49(0.01, 24.00)         342           FINANSORING         0.50         9.2         -         -         0.50(0.12, 25.71)         345	Treatment Control         Odds ratio         Weight           Study         Yer No Yes No         win 50% Cl         Ni           Bibort Term         Image: Study         Study         Study         Study           LIBERATE         11 117         1 61         Study         Study         Study           TRNASFCRM         113         0 52         Odds ratio         Stall 3.39         Tanuary Stall 3.39	Buty         Treatment Control         Odds ratio         Weight           Buch Term         uith 6% 5C1         (%)           Buch Term         uith 6% 5C1         (%)           LBERATE         4 124         0 62         452(0.24, 6526)         359           LMERAVE         0 52         -         -         0.52(0.01, 8578)         361           TANASFORM         1 64         0 52         -         1.51(0.66, 38.15)         300				
Treatment         Control         Dods ratio         Weight           Study         Yes         No         with 59% CI         (%)           Short Term         LIBERATE         0         128         0         62         0.491(0.01, 24.80)         3.49           LIBERATE         0         128         0         62         0.491(0.01, 24.80)         3.49           FUNRYSCIONU         65         0.52         0.051(0.01, 24.80)         3.49           IMPACT         0         43         1         49         0.381(0.02, 0.55)         7.17	Treatment Caritol         Odds ratio         Weight           Sludy         Yes No         with 5% Cl         (%)           Boart Tem	Treatment Control         Odds ratio         Weight           Study         Yes         No         with 5% CI         (%)           Bont Term				
Treatment         Control         Odds ratio         Weight           Study         Yes         No         with 55% CI         (%)           Short Term         UBERATE         0         128         0         62         0.481 [0.01, 24.80]         3.49           EMPROVE         3         110         0         59         →         3.377 [0.16, 74.20]         3.37           TRANSFORM         0.65         0.32         ↔         0.59 [0.01, 25.57]         3.55           MPACT         0.43         1.49         ↔         0.283 [0.03, 26.59]         7.17           VENT         3         2.11         0.87         ↔         2.291 [0.15, 56.65]         3.64	Treatment         Control         Odds ratio         Weight           Study         Yes         No         with 50% CI         (%)           Short Term         UBERATE         11 117 1         61         574 [0.72, 45.47]         6.41           EMERATE         11 117 1         61         574 [0.72, 45.47]         6.41         574 [0.72, 45.47]         6.41           EMERATE         11 117 1         61         574 [0.72, 45.47]         6.41         5.74 [0.72, 45.47]         6.41           EMERATE         11 40 0.22          151 [0.06, 38.15]         3.39           TRANSFORM         1 64 0.32          151 [0.06, 25.74]         2.81           VENT         13 201 0         87          1172 [0.06, 192.44]         3.46	Study         Yes         No         Ves         No         With 56% CI         (%)           Boot Term         LBERATE         4         124         0         62         452         128         359           LBERATE         4         124         0         62         62         62         62         128         359           TRANSFORM         1         64         9.2         151         106         0.38         369           MPACT         0         31         1.49         0.03         0.02         957         024         957         2268         10.43         1.28         388				
Treatment         Control         Odda rafio         Weight with 5% CI         Weight with 5% CI	Treatment         Control         Odds ratio         Weight           Study         Yer         No fts No         win (5% Cl         N)           Bond Term                LIBERATE         11 117         1 61               TRANSFORM         113 0         59                  33         M/ACT          43 0         52	Treatment Control         Odds salo         Weight           Study         Yes         No         Yes         Weight           Bort Term         LBERNE         4         124         0         62           LARROPC         0         131         0         90         0.52				
Treatment         Control         Odds ratio         Weight           Study         Yes         No         with 5% CI         (N)           Bond Term         UBERATE         0.128         0.62         0.49 [0.01, 24.60]         3.49           EMPROVE         3.10         0.59         →         3.377 [0.15, 72.40]         3.37           FINANSFORM         0.65         0.32         ←         0.05 [0.01, 24.60]         3.49           IMPACT         0.43         1.49         ←         0.38 [0.02, 955]         7.17           VENT         3.211         0.87         ←         2.21 [0.02, 056]         3.49           EUVERT         4.107         1.59         ←         2.21 [0.02, 019]         5.55           EEAPROV         0.66 [0.03.3         ●         ●         0.50 [0.01, 2.69]         2.47	Treatment Control         Odds ratio         Weight           Sludy         Yes No Yes No         with 0% Cl         (%)           Bloot term	Treatment Control         Odds ratio         Weight           Study         Yes         No         with 5% CI         %b)           Bont Tem         LIBERATE         4         124         0         422         0.24           LIBERATE         4         124         0         62         4.52         3.59           EAMPROVE         0         113         0.59         ■         0.52         0.58         5.83         3.60           TRANSFORM         0         13         1.40          0.38         1.60         0.83         3.60         NPACT         0         4.31         4.42         0.08         1.61         0.62         ↓				
Treatment Control         Odds ndo         Weight with 29% CI         Weight with 29% C	Treatment Cartici         Odds ratio         Weight           Study         Yes         No         ss.         with 0% Cc         N/           Bibot Term	Treatment Control         Octa ratio         Wright           Study         Yes         No         Yes         With 50% CI         %1           LBERATE         4         124         0         62         452 [024, 8526]         359           LBERATE         4         124         0         62         452 [024, 8526]         359           TRANSFORM         1         64         0         32         9         0.38 [012, 956]         760           VENT         0         43         1         49         0         238 [012, 955]         760           VENT         2         0         6         0.32         0.432         388         300           ENVENT         1         10         9         0.54 [013, 432]         388         246 [010, 432]         388           ENVENT         1         10         9         0.54 [013, 432]         388         300 [012, 788]         246 [010, 432]         388           STELVO         1         33         0.34				
Treatment         Control         Odda rafio         Weight           Study         Yes         No         with 59°C (C)         10° <t< td=""><td>Treatment Carbin         Odds ratio         Weight           Study         Yen No Yes No         win 50% CI         Ni           Band Tam        </td><td>Treatment Control         Odds salo         Weight           Study         Yes         No         Yes         Weight           Budy         Yes         No         Yes         Weight           LBERNT EM         LBEANT AT         1123         0.9         452(0.24, 6528)         39           LBERNTOPE         0.82 (0.14, 5279)         31         1.95         0.52 (0.14, 5279)         31           TRANSFORM         1.64         0.32         +         0.33 (0.02, 955)         7.60           VENT         2.12 2.0         87         -         0.26 (0.01, 432)         38           EUVENT         1.10         1.99         0.64 (0.03, 8.78)         7.12 (0.43, 38)           STELVO         1.30         0.34         -         -         3.09 (0.12, 7.58)         2.65           Bel.werk HF         2.23         0.25         -</td></t<>	Treatment Carbin         Odds ratio         Weight           Study         Yen No Yes No         win 50% CI         Ni           Band Tam	Treatment Control         Odds salo         Weight           Study         Yes         No         Yes         Weight           Budy         Yes         No         Yes         Weight           LBERNT EM         LBEANT AT         1123         0.9         452(0.24, 6528)         39           LBERNTOPE         0.82 (0.14, 5279)         31         1.95         0.52 (0.14, 5279)         31           TRANSFORM         1.64         0.32         +         0.33 (0.02, 955)         7.60           VENT         2.12 2.0         87         -         0.26 (0.01, 432)         38           EUVENT         1.10         1.99         0.64 (0.03, 8.78)         7.12 (0.43, 38)           STELVO         1.30         0.34         -         -         3.09 (0.12, 7.58)         2.65           Bel.werk HF         2.23         0.25         -				
Treatment         Control         Odda ratio         Weight           Study         Yes         No         with 59% CI         (%)           Stort Term         B         128         0         62         0.491 (0.01, 24.69)         34.90           EMPROVE         3         110         0         59         3.777 (0.19, 7.420)         331           TRANSFORM         0.65         0.32         0.050 (0.01, 24.59)         34.93         4.94         0.038 (0.02, .959)         7.17         VENT         3.211         0         67         2.22 (0.02, .019)         6.53         EELVENT         2.21 (0.02, .019)         6.53         EELVENT         3.20 (0.15, .66.66)         3.44         1.00 (0.02, .549)         2.74         EDL .94         2.75         BeLiver HIF1         1.24         0.25	Treatment Carbin         Odds ratio         Weight           Study         Yes No Yes No         win 0% Cl         Ni           Boart tem          win 0% Cl         Ni           LIBERATE         11         117         1         61         574 (1072, 4547)         64.1           EMPROFE         0         113         0         99         CO2(107), 45/19         339           TRANSFORM         164         0.22         151 (106, 3549)         338         38           IPANSFORM         153         0.5         156 (106, 3549)         349         448         436           EVENT         13         0.48         59         537 (106, 2186)         248         59         106 (107, 258)         248         59           FELVO         13         0.31         0.34	Treatment Control         Odds ratio         Weight           Study         Yet         No         Yet         Winh C% CI         No           Bohn Tem         LBERATE         4         124         0         62         452[0.24, 65.26]         36]           LBERATE         4         124         0         62         452[0.24, 65.26]         36]           LMPROVE         0         133         0         59         0.52[0.01, 26.75]         36]           TRANSFORM         144         0         0.52[0.01, 26.75]         36]         151[0.06, 38.15]         30]           MPACT         0         4.1         4         0.33[0.02, 95.5]         7.60]           VENT         2         2.12         0         87         -2.26[0.10, 43.21]         3.88]           EVANT         110         1.99         0.64[0.03, 7.17]         2.788]         2.65]           BeLivert MFI         2         2.30         2.5         -5.43[0.25, 118.86]         2.50]           Heitrogenety 1 <sup>+1</sup> 0.00%, H <sup>+1</sup> 1.00         1.36[0.54, .3.39]         1.36[0.54, .3.39]         1.36[0.54, .3.39]				
Treatment Control         Odds niko         Weight win 89% CI         Weight win 89% CI <thw< td=""><td>Treatment Carbol         Odds ratio         Weight           Study         Yes No         with f0% C         fN/           Bibort Yem         with f0% C         fN/         with f0% C         fN/           UBRATE         11 177         161         574 (10.72, 45.47)         641           DMPROVE         0.133         0.92         45.71 (0.72, 45.47)         641           VENT         1.43         0.52         45.71 (0.72, 45.47)         641           VENT         0.43         0.52         45.71 (0.72, 45.47)         641           VENT         1.43         0.52         45.71 (0.72, 45.47)         641           RIPACH         0.66         0.33         45.71 (0.72, 45.47)         641           EUVENT         1.51         1.59         45.71 (0.72, 45.47)         641           FRACH         0.66         0.33         45.91 (0.42, 558)         343           STELVO         1.31         0.34         3.06 (1.41, 8.96)         255           Homogenetity         6.25         0.55         3.56 (1.41, 8.96)         3.56 (1.41, 8.96)           Test of a.=6, O(0)         3.72, p.= 0.88         57.61         3.56 (1.41, 8.96)         3.56 (1.41, 8.96)  <td>Treatment Connol         Octa ratio         Wright With 50% CI         Wright With 50% CI           Study         Yes         No         Yes         No         With 50% CI         %1           LBERATE         4         124         0         62         452 [0.24, 85.26]         359           LBERATE         4         124         0         62         452 [0.24, 85.26]         369           MPACT         0         43         1.49         0         36 [0.02, 955]         760           VENT         2.10         0.7         2.26 [0.01, 0.32]         388         2.06 [0.01, 0.32]         388           EUVENT         1.10         1.9         0.54 [0.03, 873]         7.02         2.06 [0.01, 0.32]         388           EUVENT         1.10         1.9         0.54 [0.03, 873]         7.02         2.06 [0.01, 4.32]         3.88           BeLiver IMF1         2.30         0.55         -         5.43 [0.25, 11.86]         2.50           Hettrogenetpt: /* 0.076, I** 10.07         1.36 [0.54, 3.36]         1.36 [0.54, 3.36]         1.36 [0.54, 3.36]</td></td></thw<>	Treatment Carbol         Odds ratio         Weight           Study         Yes No         with f0% C         fN/           Bibort Yem         with f0% C         fN/         with f0% C         fN/           UBRATE         11 177         161         574 (10.72, 45.47)         641           DMPROVE         0.133         0.92         45.71 (0.72, 45.47)         641           VENT         1.43         0.52         45.71 (0.72, 45.47)         641           VENT         0.43         0.52         45.71 (0.72, 45.47)         641           VENT         1.43         0.52         45.71 (0.72, 45.47)         641           RIPACH         0.66         0.33         45.71 (0.72, 45.47)         641           EUVENT         1.51         1.59         45.71 (0.72, 45.47)         641           FRACH         0.66         0.33         45.91 (0.42, 558)         343           STELVO         1.31         0.34         3.06 (1.41, 8.96)         255           Homogenetity         6.25         0.55         3.56 (1.41, 8.96)         3.56 (1.41, 8.96)           Test of a.=6, O(0)         3.72, p.= 0.88         57.61         3.56 (1.41, 8.96)         3.56 (1.41, 8.96) <td>Treatment Connol         Octa ratio         Wright With 50% CI         Wright With 50% CI           Study         Yes         No         Yes         No         With 50% CI         %1           LBERATE         4         124         0         62         452 [0.24, 85.26]         359           LBERATE         4         124         0         62         452 [0.24, 85.26]         369           MPACT         0         43         1.49         0         36 [0.02, 955]         760           VENT         2.10         0.7         2.26 [0.01, 0.32]         388         2.06 [0.01, 0.32]         388           EUVENT         1.10         1.9         0.54 [0.03, 873]         7.02         2.06 [0.01, 0.32]         388           EUVENT         1.10         1.9         0.54 [0.03, 873]         7.02         2.06 [0.01, 4.32]         3.88           BeLiver IMF1         2.30         0.55         -         5.43 [0.25, 11.86]         2.50           Hettrogenetpt: /* 0.076, I** 10.07         1.36 [0.54, 3.36]         1.36 [0.54, 3.36]         1.36 [0.54, 3.36]</td>	Treatment Connol         Octa ratio         Wright With 50% CI         Wright With 50% CI           Study         Yes         No         Yes         No         With 50% CI         %1           LBERATE         4         124         0         62         452 [0.24, 85.26]         359           LBERATE         4         124         0         62         452 [0.24, 85.26]         369           MPACT         0         43         1.49         0         36 [0.02, 955]         760           VENT         2.10         0.7         2.26 [0.01, 0.32]         388         2.06 [0.01, 0.32]         388           EUVENT         1.10         1.9         0.54 [0.03, 873]         7.02         2.06 [0.01, 0.32]         388           EUVENT         1.10         1.9         0.54 [0.03, 873]         7.02         2.06 [0.01, 4.32]         3.88           BeLiver IMF1         2.30         0.55         -         5.43 [0.25, 11.86]         2.50           Hettrogenetpt: /* 0.076, I** 10.07         1.36 [0.54, 3.36]         1.36 [0.54, 3.36]         1.36 [0.54, 3.36]				
Treatment         Control         Odda rafio         Weight           Study         Yee No         win 59°C CI         (%)           Study         Yee No         win 59°C CI         (%)           Boot Term           0.62         0.64 (0.01, 24.60)         34           LUBERATE         0.128         0.62          0.63 (0.01, 24.60)         34           LUBRATE         0.128         0.52         0.50 (0.01, 25.57)         3.65           IMPACT         0.43         1.49          0.38 (0.02, 9587)         7.17 (0.17, 8266)         3.64           EUVENT         2.11<0	Treatment Carbin         Odds ratio         Weight           Study         Yer No Yes No         win 50% CI         Ni           Bisont Term	Treatment Control         Odds salo         Weight with 50% CI         %           Study         Yes         No         Yes         No         Yes         Weight           Budy         Yes         No         Yes         No         Yes         Weight           LBERATIC         4         124         0         62         452 [0.24, 65:29]         39           LBERATIC         0         43         1         69         0.52 [0.16, 257]         361           TRANSFORM         1         64         0.32         ←         0.38 [0.02, 955]         760           VENT         2.12 2         8         7         62.63 [0.10, 432]         38         EU-KONT         1.03 [0.32, 955]         760           SELVICH         1.10 1         59         0.54 [0.03, 67.01]         0.43 [0.02, 758]         260         0.54 [0.03, 67.01]         1.03 [0.22, 758]         265           SELVICH         1.30 [0.25, H <sup>2</sup> 0.25         +         5.54 [0.25, 118.80]         2.50         Hetrogenety H <sup>2</sup> 2.80 [0.00, K <sup>2</sup> + 1.00         1.36 [0.54, .338]         Test of a. #, Q(8) = 4.65, p = 0.79           Long Term         Long Term         Long Term         Long Term         Long Term         Long Term         L				
Treatment         Control         Odda ratio         Weight with 5% C2	Treatment         Control         Odds ratio         Weight           Study         Yer         No Yes         No         win (0%C)         N)           Board term         Image: Control         Image: Control         Image: Control         Image: Control         Image: Control           LIBERATE         11         117         1         61         574 (10.72, 45.47)         64.1           FINASFORM         1         61         59         COS (10.01, 257)         339         155 (10.66, 38.51)         339           IMPACT         0         43         0         50         116 (10.02, 39.74)         348         6.89           VENT         13         201         0         F	Treatment Control         Odds ratio         Weight				
Treatment         Control         Odds ndo         Weight           Study         Yes         No         No         Weight         Weight           Study         Yes         No         No         No         No         No         No           LIBERATE         0         128         0         62         0.48 (0.01, 24.60)         3.49           LIBERATE         0         128         0         62         0.50 (10.01, 25.97)         3.45           IMPACT         0         4.3         1.49         0.38 (10.02, 0.59)         7.17 (10.74.66)         3.44           VENT         1.11         9.9         2.20 (10.25.66)         3.44         1.00 (10.2, 558)         3.44           SELVID         0         3.44         1.00 (10.2, 558)         3.44         1.00 (10.2, 558)         3.44           Intercogneting:         1.00 (10.2, 558)         3.44         1.00 (10.02, 558)         2.45           Intercogneting:         1.00 (10.2, 558)         3.44         1.00 (10.2, 558)         3.45           Intercogneting:         1.00 (10.2, 558)         3.44         1.00 (10.02, 558)         3.45           Intercogneting:         1.00 (10.2, 2.78)         3.45         1.00 (10.02, 2.78)	Treatment Carbol         Odds ratio         Weight           Study         Yen No Yes No         with 0% Ci         Ni           Bibot Term	Treatment Cond         Octa ratio         Wright           Study         Yes         No         Yes         With 65% CI         %1           LUERATE         4         124         0         62         452 [024, 8528]         359           LUERATE         4         124         0         62         452 [024, 8528]         359           TRANSFORM         1         64         0         52         053 [012, 8578]         361           MPACT         0         43         1         49         0         03 [012, 956]         760           VENT         2         2         0         7         268 [010, 432]         38         268         054 [013, 873]         371           EU-VENT         1         10         19         0         0.54 [013, 471]         103         34         309 [012, 758]         265           BcLWer MFI         2         0.31         0.34         309 [012, 758]         265         543 [025, 118.69]         206           Test of a = % U(8) = 465, p=0.79         1.36 [024, 3.28]         728         264         1.32 [026, 3.28]         728           LEBRATE         1         121         61         0.50 [003, 8.20]         728				
Treatment Control         Odda rafo         Weight           Study         Yes No         win 59°C (2) (4)         Weight           Sont Tem         III 0         50         410 (20) (24,80) (34)         344           LIBEROLE         0.128 0 (62         0.62 (20) (20) (25,71) (34)         344           LIBEROLE         0.128 0 (62         0.50 (20) (25,71) (34)         344           LIBEROLE         0.43 1 49         0.38 (102, 0.95) (7) (7,74,20) (33)         344           MIRACT         0.43 1 49         0.38 (102, 0.95) (7) (7,74,20) (33)         556 (34) (25) (25) (24, 02) (95) (25) (24) (25) (25) (24) (25) (25) (24) (25) (25) (24) (25) (25) (24) (25) (25) (24) (25) (25) (26) (26) (26) (26) (26) (26) (26) (26	Treatment         Control         Odds ratio         Weight           Study         Yer         No         Yes         Weight           Study         Yes         No         Yes         Weight           UBRATE         11         117         1 61         574 (0.72, 45.47)         641           LIRPROYE         0 131         0 59         ●         0.52 (0.17, 278)         329           MPACT         0 43         0 50         ●         0.52 (0.17, 278, 139)         337 (1040, 35.57)         339           MPACT         0 43         0 50         ●         1172 (069, 199.44)         348         EUVENT         61 (05 1 59         337 (1040, 28.68)         338         0.50 (0.01, 25.68)         343           REACH         0 66         0 33         ●         0.30 (0.02, 32.88)         2.55         100 (0.02, 32.88)         2.55           Belkwer HF         0 25 0 25         ●         0.35 (11.41, 8.96)         2.56         1.56 (11.41, 8.96)           Treat of a + 0, CR) = 3.72, p = 0.88         ■         ■         0.64 (0.05, 1.52) (5.59)         3.56           LingTerm         ■         0.64 (0.05, 1.22, 48) 3.54         9.54         9.54         9.54         9.54	Treatment Control         Odds safe         Weight           Study         Yes         No         Yes         No         Yes         No         Weight         Staft         S				
Treatment         Control         Odda ratio         Weight           Study         Yes No         with 59'C (2) (4)         Weight         Weight           Short Term         III 0         59         Transformer         0.049 (0.01, 24.00) 34.00         34.00           EMPROVE         3 110         0         59	Treatment         Control         Odds rabo         Weight           Study         Yer         No Yan         No         Win (DK.C)         No           Board term         Min (DK.C)         No         No         Win (DK.C)         No           LIGERATE         11         117         1         61         574 (10.22, 45.47)         64.1           FINASSIGNE         113         0         59         C.523 (10.17, 257)         333         155 (10.66, 38.15)         339           MPACT         0.43         0.50         THE (10.22, 93.74)         238         116 (10.22, 93.74)         238         116 (10.22, 93.74)         238         126 (10.17, 258)         248         559         537 (10.40, 2586)         330 (10.17, 258)         248         551 (10.17, 258)         249         551 (10.17, 258)         249         356 (11.41, 858)         126 (12.5, 15.21, 25.29)         255         100 (10.02, 53.89)         255         100 (10.02, 53.89)         255         100 (10.22, 53.89)         255         100 (10.22, 53.89)         255         100 (10.22, 53.89)         255         100 (10.22, 53.89)         255         100 (10.22, 53.89)         255         100 (10.22, 53.89)         255         100 (10.22, 53.89)         255         100 (10.02, 53.89)         356 (11.41, 858) <td>Study         Yes         No         Yes         Octor non         With (5%) CI         (%)           Buch Term         LBERATE         4         124         0         62         452 (0.24, 65.26)         3.59           LBERATE         4         124         0         62         452 (0.24, 65.26)         3.99           LBERATE         4         124         0         62         652 (0.16, 7879, 3.81         3.00           MARCT         0         3.1         49        </td>	Study         Yes         No         Yes         Octor non         With (5%) CI         (%)           Buch Term         LBERATE         4         124         0         62         452 (0.24, 65.26)         3.59           LBERATE         4         124         0         62         452 (0.24, 65.26)         3.99           LBERATE         4         124         0         62         652 (0.16, 7879, 3.81         3.00           MARCT         0         3.1         49				
Treatment Control         Odds ratio         Weight with 595 CI         Weight with 595	Treatment Carbol         Odds ratio         Weight           Study         Yen No Yes No         win f0% Ci         Ni           Band Tam         win f0% Ci         Ni         win f0% Ci         Ni           LIBERATE         11 117         1 61         574 (0.72, 45.47)         44.1           LIBERATE         11 117         1 61         574 (0.72, 45.47)         43.1           LIPROVE         0 43         0 50         151 (0.66, 38.15)         3.9           MPACT         0 43         0 50         1172 (0.69, 19.44)         3.4           EU-VENT         1 103         0 34	Treatment Connol         Odds ratio         Wright Win 50% CI         Win Win 50% CI         Win Win Win 50% CI         Win Win Win Win 50% CI         Win Win Win Win Win Win Win Win Win Win				
Treatment Control         Odda rafo         Weight           Study         Yes No         win 55°C (2) (4)         Weight           Short Tem         III 600 (2) (2) (2) (2) (2) (2) (2) (2) (2) (2)	Treatment         Control         Odds ratio         Weight           Study         Yer No Yes No         with 05% Cl         N/h           Bont Term         UBRAVE         11 117 1 61         574 (10.72, 45.47) 641           LIBRAVE 01 013 0 59	Treatment Control         Odds safe         Weight           Study         Yes         No         Yes         No         Yes         No           But         With 50% CI         %         Min         With 50% CI         %         No           LUERATIC         4         124         0         62         452 [0:34, 527]         36           LUERATIC         0         43         1         49         0         038 [0:02, 955]         7.60           MIPACT         0         43         1         49         0         0.83 [0:02, 955]         7.60           VENT         2:10         1         59         0.54 [0:03, 0:32]         38         0.44 [0:03, 0:33]         0.84           BULWENT         1         10         59         0.54 [0:03, 6:37]         7.28         26           BULWENT HFI         2         23         0.25         +5.41 [0:25, 118.86]         2.50           Heargement, *1 cot, *1         102         0         4         0.81 [0:24, 3:36]         7.28           LUERATIC         1<121				
Treatment Curitod         Odds ratio         Weight with 25°C (11, 01, 02, 02, 02, 02, 02, 02, 02, 02, 02, 02	Treatment Carbol         Odds ratio         Weight with 5% C	Treatment Connol         Octa ratio         Wight Silv           Study         Yes         No         Yes         Yes <t< td=""></t<>				
Treatment Control         Odda ratio         Weight with 595 CE         Weight with 595	Treatment Carbol         Odds ratio         Weight           Study         Yen No Yes No         with 05% Cl         N/h           Bisont Tem         with 05% Cl         N/h         with 05% Cl         N/h           LIBERATE         11 117         1 61         574 (0.72, 45.47)         44.1           LIBERATE         11 117         1 61         574 (0.72, 45.47)         44.1           LIBERATE         11 117         1 61         574 (0.72, 45.47)         44.1           LIBERATE         1 117         1 63         32         1 51 (0.66, 38.15)         339           MPACT         0 43         0 50         1172 (0.69, 1984)         348         129, 129, 129, 129, 129, 112, 120, 128, 128, 133           BEACH         0 66         0 33         0 34         0 50 (10.01, 258, 92, 34)         306 (10.12, 528, 92, 34)           BEACH         0 25 0 25         100 (10.02, 92, 82, 82, 256         100 (10.02, 92, 82, 82, 256)         100 (10.02, 92, 82, 82, 256)           LIBERATE         1 13 0 0 47         4 + 6, Q(8) - 375, p = 0.88         464 (0.51, 162, 1562)         554 (10.01, 62, 1562)         356 (10.01, 52, 92, 31)           LIBERATE         1 13 0 0 47         4 + 6, Q(8, 13, 24, 83, 34)         404 (0.01, 22, 84, 34)         44 + 45, Q(8, 13, 24, 93, 34)         464	Treatment Connol         Odds ratio         Wright with 50% CI         Wright with 50%				
Treatment Control         Odds ratio         Weight with 5% CE         Weight with 5% CE <th< td=""><td>Treatment         Control         Odds ratio         Weight           Study         Yer No Yes No         with 05% CI         N/h           Bont Tem         UBRAYE         11 117 1         1         574 (10.72, 45.47)         64.1           TRANSFORM         113 0         69         0.512 (10.72, 245.47)         64.1         574 (10.72, 45.47)         64.1           TRANSFORM         113 0         69         0.523 (10.1, 25.79)         339         151 (10.8, 35.19)         339           MPACT         0.43 0         59         151 (10.8, 35.19)         339         1172 (10.97, 94.49)         34           EUVENT         6.105 1         59         337 (10.42, 25.69)         333         0.50 (10.17, 25.69)         343           REACH         0.66 0         0.33         3.03 (0.12, 7.58)         2.40         3.60 (12.7, 15.8)         2.40           REMOVEM FF         0.25 0         2.55         10.01 (0.02, 32.38)         2.55         10.01 (0.02, 32.38)         2.55           Hemogrouphy f = 10.03, N f = 2.06         3.56 (1.41, 5.96)         3.56 (1.41, 3.96)         3.56 (1.41, 3.96)         3.56 (1.41, 3.96)         3.56 (1.41, 3.96)         3.56 (1.41, 3.96)         3.56 (1.41, 3.96)         3.56 (1.41, 3.96)         3.56 (1.41, 3.96)         3.56 (1.41,</td><td>Treatment Control         Odds safe         Weight with 50% CCI         Weight S0% CONT         Weight S0% CONT</td></th<>	Treatment         Control         Odds ratio         Weight           Study         Yer No Yes No         with 05% CI         N/h           Bont Tem         UBRAYE         11 117 1         1         574 (10.72, 45.47)         64.1           TRANSFORM         113 0         69         0.512 (10.72, 245.47)         64.1         574 (10.72, 45.47)         64.1           TRANSFORM         113 0         69         0.523 (10.1, 25.79)         339         151 (10.8, 35.19)         339           MPACT         0.43 0         59         151 (10.8, 35.19)         339         1172 (10.97, 94.49)         34           EUVENT         6.105 1         59         337 (10.42, 25.69)         333         0.50 (10.17, 25.69)         343           REACH         0.66 0         0.33         3.03 (0.12, 7.58)         2.40         3.60 (12.7, 15.8)         2.40           REMOVEM FF         0.25 0         2.55         10.01 (0.02, 32.38)         2.55         10.01 (0.02, 32.38)         2.55           Hemogrouphy f = 10.03, N f = 2.06         3.56 (1.41, 5.96)         3.56 (1.41, 3.96)         3.56 (1.41, 3.96)         3.56 (1.41, 3.96)         3.56 (1.41, 3.96)         3.56 (1.41, 3.96)         3.56 (1.41, 3.96)         3.56 (1.41, 3.96)         3.56 (1.41, 3.96)         3.56 (1.41,	Treatment Control         Odds safe         Weight with 50% CCI         Weight S0% CONT				
Treatment Control         Odds ratio         Weight with 05% CI         Weight (N)           Short Tem LIBERATE         0 128         0 62         0.48 (0.01, 24.00)         34.00           LURPOVE         110         0.59         0.317 (0.17, 42.00)         33.17 (0.17, 42.00)         33.17 (0.17, 42.00)           TRANSFORU         0 65         0.32         0.35 (0.01, 25.57)         7.17           MPACT         0.43         1.49         0.38 (0.02, 55.67)         7.41           VENT         3.11         0.59         -2.21 (0.24, 20.19)         65.66           REACH         0.60         0.33         0.00 (0.01, 25.69)         3.44           Hetrogenety, fr = 0.005, fr = 1.00         1.54 (0.25, 584)         3.44         1.00 (0.02, 51.64)           Luerg Tem LUBERATE         1.21 (2.02, 2.01)         6.55         0.00 (0.01, 2.50)         3.12           LUBERATE         1.24 (2.25         3.12 (0.12, 2.07)         1.32 (0.22, 2.79)         1.32           LUBERATE         1.21 (2.02, 0.47         1.54 (0.32, 2.79)         1.54 (0.32, 2.79)         1.54           LUPROVE         1.92 (2.0, 4.7)         1.39 (0.06, 3.76)         3.52         0.00 (0.10, 3.80)         1.62           LUPROVE         1.92 (2.0, 4.7)         1.55 <td< td=""><td>Treatment Carbol         Odds rate         Weight           Study         Yen No Yes No         with 05% C         Yes           Bond Term         with 05% C         Yes         Yes           LIBERATE         11 177         161         574 (10.72, 45.47)         641           LIBERATE         11 177         161         574 (10.72, 45.47)         641           LIBERATE         11 177         108, 2378         339         Treatment Carbol         523 (10.87)         337           WHACT         0.43         0.50         ↓         1161 (10.22, 931, 238)         338         317 (10.47, 258)         348           REACH         0.66         0.33         ↓         ↓         310 (10.22, 558)         248           Belwert FF         0.25         0.25         ↓         100 (10.22, 52.80)         255           Heimogenetry, fr = 0.00%, fr = 1.00         0.47         ↓         0.44 (10.01, 22.48)         354           Long Term         LIBERATE         12 10         9         53         0.64 (10.25, 1.82)         555           Long Term         LIBERATE         12 10.08         87         40.41 (10.75, 221, 311         116 (10.02, 32.81)         156 (10.08, 3.38)           Livet at at = 4, 0.2(1) = 7</td><td>Treatment Connol         Octa ratio         Wright with 65% CI         Wright with 65%</td></td<>	Treatment Carbol         Odds rate         Weight           Study         Yen No Yes No         with 05% C         Yes           Bond Term         with 05% C         Yes         Yes           LIBERATE         11 177         161         574 (10.72, 45.47)         641           LIBERATE         11 177         161         574 (10.72, 45.47)         641           LIBERATE         11 177         108, 2378         339         Treatment Carbol         523 (10.87)         337           WHACT         0.43         0.50         ↓         1161 (10.22, 931, 238)         338         317 (10.47, 258)         348           REACH         0.66         0.33         ↓         ↓         310 (10.22, 558)         248           Belwert FF         0.25         0.25         ↓         100 (10.22, 52.80)         255           Heimogenetry, fr = 0.00%, fr = 1.00         0.47         ↓         0.44 (10.01, 22.48)         354           Long Term         LIBERATE         12 10         9         53         0.64 (10.25, 1.82)         555           Long Term         LIBERATE         12 10.08         87         40.41 (10.75, 221, 311         116 (10.02, 32.81)         156 (10.08, 3.38)           Livet at at = 4, 0.2(1) = 7	Treatment Connol         Octa ratio         Wright with 65% CI         Wright with 65%				
Treatment Control         Odds ratio         Weight with 65° CL         Weight with 65° CL         Weight with 65°	Treatment         Control         Odds ratio         Weight           Study         Yen No Yes No         with 05% Cl         N/h           Bond Tem         with 05% Cl         N/h         Study         with 05% Cl         N/h           LIBEROYE         11 117         1 61         Study	Treatment Connol         Odds ratio         Weight with 55% CI           Study         Yes No         Yes No         with 55% CI         %1           LUERATE         4         124         0         62         452         39           LUERATE         4         124         0         62         452         39           LUERATE         4         124         0         62         452         39           MARCT         0         43         1.49         0.33         102         633         151         1006         38.19         300           VENT         2.12         0.87         0.01         0.41         10.32         338         10.12         333         10.41         10.32         339         10.12         2.85         7.80         10.41         10.32         336         10.12         7.858         2.86         10.41         10.32         330         10.12         7.858         2.86         10.02         1.36         0.54         10.25         1.36         0.54         10.25         1.36         0.54         10.32         2.82         1.36         0.54         1.38         2.30         1.38         2.30         1.44         1.32				
Treatment         Control         Odds ratio         Weight with 55°C         Weight (N)           Study         Yes         No         with 55°C         (N)         (N)           Short Term         Weight         with 55°C         (N)         (N)         (N)           LIBERATE         0         28         0.62         0.49 (0.01, 24.60]         34           LIBERATE         0         28         0.50 (0.01, 25.77]         3.65           IMPACT         0         43         1.49         0.038 (0.02, 25.97]         3.65           MAPACT         0         43         1.49         0.038 (0.02, 25.97]         3.65           VENT         3.211<0	$\begin{tabular}{ c c c c c c c c c c c c c c c c c c c$	Treatment Control         Odds safe         Weight           Study         Yes         No         Yes         No         Yes         No         Weight         Staff         <				

# Figure 5:

Forest Plots comparing adverse events between the EBV and the control group. A: pneumothorax, B: Pneumonia, C: Acute exacerbation of COPD (AECOPD) D: Respiratory failure, E: Hemoptysis, F: Death

Change from Baseline EEV/1 by CV//Elb=90% vs CV//El unknown	Change from Bageline % EEV/1 by CV /EI>=00% vs CV/ELupknown
Treatment Control Mean diff Weight	Change from Baseline %PEV1 by CV-/FI>=90% Vs CV/FI unknown
Study N Mean SD N Mean SD with 95% CI (%)	Study N Mean SD N Mean SD with 95% CI (%)
CV-/FI>=90%	CV-/FI>=90%
LIBERATE 128 104 200 62 -3 194 - 107.00 [ 46.93, 167.07] 13.27	LIBERATE 128 17.16 27.93 62 -8 26.94 - 17.96 [ 9.59, 26.33] 12.85
EMPROVE 86 67 167 39 -32 114 - 99.00 [ 41.26, 156.74] 14.37	TRANSFORM 65 20.7 29.6 32 -8.6 1329.30 [ 18.55, 40.05] 7.79
TRANSFORM 65 140 240 32 -90 140 - 230.00 [ 140.01, 319.99] 5.91	IMPACT 43 13.75 28.1 50 -3.48 12.89 17.23 [ 8.55, 25.91] 11.94
IMPACI 43 100 180 50 -20 100	STELVIO 34 20.9 28.09 34 3.1 10 - 17.80 [ 7.78, 27.82] 8.97
STELVIO 34 161 232 34 21 87 - 140.00 [ 56.71, 223.29] 6.90	Heterogeneity: I <sup>2</sup> = 18.32%, H <sup>2</sup> = 1.22
Heterogeneity: I <sup>2</sup> = 24.18%, H <sup>2</sup> = 1.32	Test of $\theta_i = \theta_i$ : $Q(3) = 3.67$ , $p = 0.30$
Test of $\theta_i = \theta_j$ : Q(5) = 6.59, p = 0.25	CV/FI unknown
	VENT 220 4.3 21.83 101 -2.5 14.69 - 6.80 [ 2.12, 11.48] 41.12
VENT 220 34.5 170 101 .25.4 116	EU-VENT 92 6 26 54 -2 20 -8.00 [-0.05, 16.05] 13.89
BeLiever HiFI 25 180 266 25 30 630	BeLiever HiFI 25 24.77 40.57 25 3.87 7.78 - 20.90 [ 4.71, 37.09] 3.44
Heterogeneity: I <sup>2</sup> = 0.00%, H <sup>2</sup> = 1.00	Heterogeneity: I <sup>2</sup> = 25.61%, H <sup>2</sup> = 1.34
Test of $\theta_i = \theta_j$ : Q(1) = 0.43, p = 0.51	Test of $\theta_i = \theta_j$ : Q(2) = 2.69, p = 0.26
	Querall 12.87 ( 0.87, 15.97)
Overall • 102.97 [ 81.09, 124.85]	Heterogeneity: 1 <sup>2</sup> = 71.56%. H <sup>2</sup> = 3.52
Test of B = B: Q(7) = 13.93, p = 0.05 Eavors Control Favors EBV	Test of 0, = 0; Q(6) = 21.10, p = 0.00 Favors Control Favors EBV
Test of aroun differences: 0.(1) = 6.01 n = 0.01	Test of oroug differences: Q.(1) = 14.73 g = 0.00
-200 0 200 400	0 10 20 30 40 <b>Q</b>
Fixed-effects inverse-variance model	Fixed-effects inverse-variance model
Change from Baseline RV by CV-/FI>=90% vs CV/FL unknown	Change from Baseline 6MWD by CV-/FI>=90% vs CV/FI unknown
Treatment Control Mean diff Weinht	Treatment Control Mean diff Weight
Study N Mean SD N Mean SD with 95% CI (%)	Study N Mean SD N Mean SD with 95% CI (%)
CV-/FI>=90%	CV-/FI>=90%
LIBERATE 112 -490 830 58 30 660 -520.00 [ -766.20, -273.80] 29.85	LIBERATE 128 12.98 81.54 62 -26.33 81.5
TRANSFORM 65 -660 1040 32 10 790	TRANSFORM 65 36.2 76.9 32 -42.5 68.2 -78.70 [47.31, 110.09] 13.73
IMPACT 43 -420 900 50 50 870 - 470.00 [-830.34, -109.66] 13.94	MPACT 40 22.6 66.6 50 -17.3 52.8
STELVIO 24 -865 714 33 -34 267	STELVIO 34 60 71.65 34 -14 31.53 -74.00 [47.69, 100.31] 19.55
Heterogeneity: I <sup>2</sup> = 6.18%, H <sup>2</sup> = 1.07 -619.87 [-766.71, -473.03]	Heterogeneity: I <sup>2</sup> = 51.04%, H <sup>2</sup> = 2.04
Test of 0, = 0; Q(4) = 4.26, p = 0.37	Test of 0, = 0;: Q(4) = 8.17, p = 0.09
CV/FIURKNOWN Relinver HIEL 25 -500 775 25 -110 363	Reliever HIEL 25 29 70 26 25 4 55 72 33 00 L 2 15 68 151 10 95
Heterogeneity 1 <sup>2</sup> = 0.00% H <sup>2</sup> = 1.00	Heterogeneity: I <sup>2</sup> = 0.00%, H <sup>2</sup> = 1.00 33.00 [ -2.15, 68.15]
Test of 0, = 0; Q(0) = 0.00, p = .	Test of $\theta_i = \theta_i$ : Q(0) = 0.00, p = .
Overall -579.70 [ -714.21, -445.18]	Overall 50.61 [ 38.98, 62.24]
Heterogeneity: I* = 17.38%, H* = 1.21	Heterogeneity: I' = 45.97%, H' = 1.85
rest or e, = e, G(5) = 6.05, p = 0.30 Pavors EBV Pavors Control	Test of e, = e; Q(5) = 9.25, p = 0.10 Pavors Control Pavors EBV
Test of group differences: $Q_b(1) = 1.79$ , p = 0.18	Test of group differences: $Q_{0}(1) = 1.08$ , $p = 0.30$
-1000 -300 0 500	EiverLefferts inverse variance model
Oberes for Deally DODO LOD	
Change from Baseline SGRQ by CV	V-/FT2=9U70 VS GV/FT UNKNOWN Maga diff Weight
Study N Mean SD N Mean SD	with 95% CI (%)
CV-/FI>=90%	
LIBERATE 128 -7.55 15.71 625 15.5	-7.05 [ -11.79, -2.31] 14.33
EMPROVE 95 -5.8 16.8 41 3.7 10.9	-9.50 [-15.10, -3.90] 10.30
IKANSFORM 65 -7.2 15.1 32 -7 10.4 IMPACT 37 .8.63 11.2 48 101 9.3	-0.30 [-12.32, -0.68] 9.53
REACH 63 -8.39 17.43 32 2.11 17.24 -	-10.50 [-17.89, -3.11] 5.91
STELVIO 24 -17.39 17.44 33 -2.68 8.93	-14.71 [-21.64, -7.78] 6.72
Heterogeneity: $l^2 = 0.00\%$ , $H^2 = 1.00$	<ul> <li>-9.18 [ -11.43, -6.93]</li> </ul>
Test of $\theta_i = \theta_j$ : Q(5) = 4.22, p = 0.52	
CV/FLunknown	
VENT 220 -2.8 13.93 101 .6 12.16	-3.40 [ -6.56, -0.24] 32.36
BeLiever HiFI 25 -8.72 20.6 25 -3.66 10.8	-5.06 [-14.18, 4.06] 3.88
Heterogeneity: I <sup>2</sup> = 0.00%, H <sup>2</sup> = 1.00	-3.58 [ -6.56, -0.59]
Test of $\theta_i = \theta_j$ ; Q(1) = 0.11, p = 0.74	
Overall	-7 15 (
Heterogeneity: $l^2 = 46.02\%$ . $H^2 = 1.85$	
Test of 6, = 6; Q(7) = 12.97, p = 0.07	Favors EBV Favors Control
Test of group differences: Q <sub>b</sub> (1) = 8.64, p = 0.00	
-20	-10 0 10
Final effects inverse uniques model	<b>—</b>
Pixed-enecis inverse-variance model	

# Figure 6:

Forest Plots comparing outcomes between CV + and CV – group. A: change in FEV1, B: Change in %FEV1, C: change in Residual Volume (RV), D: Change in 6-minute walk distance(6MWD), E Changes in SGRQ

Pneumothorax by CV-/FI>=90% vs CV/FI unknown					Pneumonia by CV-/FI>=90% vs CV/FI unknown				AECOPD by CV-/FI>=90% vs CV/FI unknown					
	Treatment Control		Odds ratio We	aht	Treatment Control		Odds ratio	Weight	1	Treatment (	Control		Odds ratio Weigh	
Study	Yes No Yes No		with 95% CI (*	() Study	Yes No Yes No		with 95% CI	(%)	Study	Yes No Y	Yes No		with 95% Cl (%)	
CV-/FI>=90%				CV-/FI>=90%					CV-/FI>=90%					
LIBERATE	8 114 0 62		9.28 [ 0.53, 163.46] 8	19 LIBERATE	11 111 6 56	- <b>-</b>	0.92 [ 0.33, 2.63	32.68	LIBERATE	37 85 2	29 33	·	0.50 [ 0.26, 0.93] 34.56	
EMPROVE	0 103 0 47		0.46[0.01, 23.48] 9	06 EMPROVE	8 95 1 46	· · · · · · · · · · · · · · · · · · ·	3.87 [ 0.47, 31.90	5.72	EMPROVE	14 89	4 43		1.69 [ 0.53. 5.44] 6.12	
TRANSFORM	15 50 0 32		19.95 [ 1.15, 345.05] 6	79 TRANSFORM	6 59 1 31	· · · · · · · · · · · · · · · · · · ·	3.15[0.36, 27.37	5.49	TRANSFORM	7 58	3 29	· · · · · · · · · · · · · · · · · · ·	1.17 [ 0.28, 4.85] 4.63	
IMPACT	12 31 0 50		-40.08 [ 2.29, 700.91] 4	41 IMPACT	0 43 1 49	«	0.38[0.02, 9.55	6.20	IMPACT	10 33	6 44		- 2.22[0.73, 6.73] 5.49	
REACH	5 61 0 33	· · · · · · · · · · · · · · · · · · ·	5.99 [0.32, 111.71] 8	10 REACH	1 65 0 33	· · ·	1.53 [ 0.06, 38.69	2.93	REACH	5 61	4 29		0.59 [ 0.15, 2.38] 6.36	
STELVIO	6 28 0 34		15.74 [ 0.85, 291.46] 5	42 STELVIO	2 32 1 33	· · · · · · · · · · · · · · · · · · ·	2.06 [ 0.18, 23.88	4.25	STELVIO	4 30	2 32	· ·	2.13 [ 0.36, 12.51] 2.28	
Heterogeneity: I <sup>2</sup> = 0.00%, H <sup>2</sup> = 1.00				Heterogeneity	r: I <sup>2</sup> = 0.00%, H <sup>2</sup> = 1.00	-	1.49[0.72, 3.08	1	Heterogeneity: I	<sup>2</sup> = 41.22%, H <sup>2</sup> =	= 1.70	-	0.90 [ 0.60, 1.37]	
Test of 0, = 0; Q(5) = 3.76, p = 0.58					Test of 6 = 6, Q(5) = 2.81, p = 0.73					Test of 0; = 0; Q(5) = 8.51, p = 0.13				
CVIFI Linknown				CV/FI Unkno	with				CV/FI Unknown					
VENT	2 212 2 85	-	0.4010.06 2.801.37	NO VENT	17 197 6 81	-	1.1610.44 3.06	35.46	VENT	25 189	8 79	_	1.3110.56 3.021 12.96	
FILVENT	4 107 0 60		5.0710.27 95.681 8	27 EU-VENT	12 99 1 59	-	7.1510.91. 56.41	523	EU-VENT	60 42 4	40 20	-	0.8210.42 1.501 25.34	
Bel lever HIFI	2 23 1 24		2 09 [ 0 18 24 61] 12	25 BeLiever HIFI	2 23 0 25			2.04	BeLiever HIFI	23 2 2	22 3	· · · · · · · · · · · · · · · · · · ·	- 15710.24 10.301 2.27	
Hatarmanaity 12	= 16 22% H <sup>2</sup> = 1 10		1.42 [ 0.41 . 4.07]	Heteropeneity	1 <sup>2</sup> = 36.42% H <sup>2</sup> = 1.57	-	2 10 1 0 94 4 72	1	Heteropeneity I	= 0.00% H <sup>2</sup> = 1	1.00	-	10210.62 1.671	
Test of 0, = 0: Q(2	() = 2.39, p = 0.30		the form, send	Test of 0, = 0;	Q(2) = 3.15, p = 0.21		and the set		Test of 8 = 8; Q	(2) = 0.95, p = 0.	.62		conferent conf	
						1								
Overall		+	6.09 [ 2.74, 13.51]	Overall		*	1.75 [ 1.02, 3.00		Overall			+	0.95 [ 0.60, 1.31]	
Heterogeneity: I <sup>2</sup> =	= 35.99%, H <sup>2</sup> = 1.56			Heterogeneity	c I <sup>2</sup> = 0.00%, H <sup>2</sup> = 1.00				Heterogeneity: I	<sup>2</sup> = 16.87%, H <sup>2</sup> =	1.20			
Test of 6 = 6; Q(8) = 12.50, p = 0.13 Favors Control Favors EBV					Test of 6, = 8; Q(8) = 6.13, p = 0.63 Favors Control Favors EBV				Test of $\theta_i = \theta_j$ : Q	(8) = 9.62, p = 0.	1.29	Favors Control Favors EBV		
Test of group differences: Q <sub>4</sub> (1) = 6.26, p = 0.01					differences: Q <sub>a</sub> (1) = 0.38, p = 0	0.54		D	Test of group dif	ferences: Q <sub>2</sub> (1)	= 0.13, p = 0.1	72	-	
		1/2 4 32 256				1/2 2 8 32		к				1/2 1 2 4	8	
Fixed-effects Mantel-Haenzel model Respiratory Failure by CV-/FI>=90% vs CV/FI unknown				Fixed-effects N	Fixed-effects Mantei-Haenszel model					ntel-Haenszel m	nodel		C	
					Hemoptysis by CV-/FI>=90% vs CV/FI unknown					Death by CV-/FI>=90% vs CV/FI unknown				
	Respiratory Failure D	V CV-/FI>=90% VS CV/FI	unknown		Hemoptysis b	y CV-/FI>=90% VS CV/FI UN	nown			D	leath by CV	/-/FI>=90% vs CV/FI unkn	IOWIT	
	Treatment Control	y CV-/FI>=90% vs CV/FI	Odds ratio We	aht	Treatment Control	y Cv-/FI>=90% vs CV/FI uni	Odds ratio	Weight		Treatment (	leath by CV Control	/-/FI>=90% vs CV/FI unkn	IOWN Odds ratio Weigh	
Study	Treatment Control Yes No Yes No	y CV-/FI>=90% vs CV/FI	Odds ratio We with 95% CI (1	ght i) Study	Treatment Control Yes No Yes No	y CV-/FI>=90% V\$ CV/FI UN	Odds ratio with 95% CI	Weight (%)	Study	Di Treatment O Yes No Y	leath by CV Control Yes No	/-/FI>=90% vs CV/FI unkn	IOWI1 Odds ratio Weigh with 95% CI (%)	
Study CV-(FI>=90%	Respiratory Pailure D Treatment Control Yes No Yes No	y CV-/FI>=90% vs CV/FI	Unknown Odds ratio We with 95% CI (1	ght i) Study CV-/FI>=90%	Treatment Control Yes No Yes No	y CV-iFI>=90% VS CVIFI Uni	Odds ratio with 95% Cl	Weight (%)	Study CV-/FI>=90%	Di Treatment ( Yes No Y	leath by CV Control Yes No	/-/FI>=90% vs CV/FI unkn	Odds ratio Weigh with 95% CI (%)	
Study CV-/FI>=90% LIBERATE	Treatment Control Yes No Yes No	y CV-/FI>=90% vs CV/FI	Unknown Odds ratio We with 95% CI (1 0.25 [ 0.02, 2.79] 16	ght j) Study CV-/FI>=90% 54 LIBERATE	Treatment Control Yes No Yes No 12 110 9 53	y CV-IFI>=90% VS CV/FI UN	Odds ratio With 95% Cl 0.64 [ 0.25, 1.62	Weight (%)	Study CV-(FI>=90% LIBERATE	Treatment O Yes No Y	leath by CV Control res No 1 61	-//FI>=90% vs CV/FI unkn	OWT Odds ratio Weigh with 95% CI (%) 0.50 [ 0.03. 8.20] 8.90	
Study CV-/FI>=90% LIBERATE EMPROVE	respiratory Failure b       Treatment Control       Yes No       1     121       2     60       1     102     0	<	Unknown Odds ratio We with 95% CI (1 0.25 [ 0.02, 2.79] 16 1.39 [ 0.06, 34.76] 4	ght i) Study CV-/FI>=90% 54 LIBERATE 24 EMPROVE	Treatment Control Yes No Yes No 12 110 9 53 0 103 0 47	y cv-rri>≊90% vs cViri une	Odds ratio with 95% Cl 0.64 [0.25, 1.62 0.46 [0.01, 23.48	Weight (%)	Study CV-IFI>=90% LIBERATE EMPROVE	Di Treatment C Yes No Y 1 121 1 1 102 0	leath by CV Control (es No 1 61 0 47	-/FI>=90% vs CV/FI unkn	OWN Odds ratio Weigh with 95% CI (%) 0.50 [ 0.03, 8.20] 8.90 1.39 [ 0.06, 34.76] 4.56	
Study CV-/FD=90% LIBERATE EMPROVE TRANSFORM	Treatment         Control           Yes         No         Yes         No           1         121         2         60           1         102         0         47           0         65         0         32	↓ CV-/FI>=90% VS CV/FI	URKNOWN Odds ratio We with 95% Cl (1 0.25 [ 0.02, 2.79] 16 1.39 [ 0.06, 34.76] 4 0.50 [ 0.01, 25.57] 4	ght i) Study CV-FI>=90% 54 LIBERATE 24 EMPROVE 16 TRANSFORM	Hermoptysis b           Treatment         Control           Yes         No           12         110         9         53           0         103         0         47           1         64         0         32	y cv-rri>≊90% vs cvirt une	Odds ratio With 95% CI 0.64 [0.25, 1.62 0.46 [0.01, 23.48 1.51 [0.06, 38.15	Weight (%)	Study CV.FI>=90% LIBERATE EMPROVE TRANSFORM	Di Treatment C Yes No Y 1 121 1 1 102 0 1 64 0	leath by CV Control res No 1 61 0 47 0 32	I I I I I I I I I I I I I I	OWN Odds ratio Weigh with 95% CI (%) 0.50 [ 0.03, 8.20] 8.90 1.39 [ 0.06, 34.76] 4.56 1.51 [ 0.06, 38.15] 4.41	
Study CV-/FÞ=90% LIBERATE EMPROVE TRANSFORM IMPACT	Treatment         Control           Yes         No         Yes         No           1         121         2         60           1         102         0         47           0         65         0         32           0         43         1         49	<	URKNOWN Odds ratio We with 95% CI (1 0.25 [0.02, 2.79] 16 1.39 [0.06, 34.76] 4 0.50 [0.01, 25.57] 4 0.38 [0.02, 9.55] 8	ght         Study           CV-/FI>=80%         LIBERATE           24         EMPROVE           16         TRANSFORM           54         IMPACT	Hemoptysis b           Treatment         Control           Yes         No         Yes           12         110         9         53           0         103         0         47           1         64         0         32           0         43         0         50		Odds ratio with 95% Cl 0.64 [ 0.25, 1.62 0.46 [ 0.01, 23.48 1.51 [ 0.06, 38.15 1.16 [ 0.02, 59.74	Weight (%)   69.69   4.41   4.22   2.97	Study CV.FI>=90% LIBERATE EMPROVE TRANSFORM IMPACT	Di Treatment ( Yes No Y 1 121 1 1 102 ( 1 64 ( 0 43 1	leath by CV Control (res No 1 61 0 47 0 32 1 49	-/FI>=90% vs CV/FI unkn	Odds ratio Weigh with 95% Cl (%) 0.50[0.03, 8.20] 8.90 1.39[0.06, 34.76] 4.56 1.51[0.06, 38.15] 4.41 0.38[0.02, 9.55] 9.29	
Study CV-/Fb=90% LIBERATE EMPROVE TRANSFORM IMPACT REACH	Treatment         Control           Yes         No         Yes         No           1         121         2         60           1         102         0         47           0         65         0         32           0         43         1         49           0         66         0         33	<	Ocds ratio         We with 95% CI           0.25 [ 0.02, 2.79]         16           1.39 [ 0.06, 34.76]         4           0.50 [ 0.01, 25.57]         4           0.38 [ 0.02, 9.55]         8           0.50 [ 0.01, 25.95]         8	ght         Study           CV-/FI>=90%         CV-/FI>=90%           54         LIBERATE           24         EMPROVE           16         TRANSFORM           54         IMPACT           14         REACH	Hemoptysis b           Treatment         Control           Yes         No         Yes           12         110         9         53           0         103         0         47           1         64         0         32           0         43         0         50           0         66         0         33		Odds ratio 0dds ratio with 95% Cl 0.64 [0.25, 1.62 0.46 [0.01, 23.48 1.51 [0.06, 38.15 1.16 [0.02, 59.74 0.50 [0.01, 25.95	Weight (%)   69.69   4.41   4.22   2.97   4.26	Study CV./FI>=90% LIBERATE EMPROVE TRANSFORM IMPACT REACH	Di Treatment ( Yes No Y 1 121 1 1 102 ( 1 64 ( 0 43 1 0 66 1	leath by CV Control (res No 1 61 0 47 0 32 1 49 1 32	I./FI>=90% vs CV/FI unkn	Odds ratio         Weight	
Study CV-/Fb=90% LIBERATE EMPROVE TRANSFORM IMPACT REACH STELVIO	Treatment         Control           Treatment         Control           1         121         2         60           1         102         0         47           0         65         0         32           0         66         0         33           0         34         0         34	<	Odds ratio         We           0dds ratio         We           with 95% CI         (1           0.25 [0.02, 2.79]         16           1.39 [0.06, 34.76]         4           0.50 [0.01, 25.57]         4           0.50 [0.01, 25.57]         4           0.50 [0.01, 25.56]         4	ght Study CV-#D>=90% 54 LIBERATE 24 EMPROVE 16 TRANSFORM 54 IMPACT 14 REACH 10 STELVIO	Hemophysis D           Treatment         Control           Yes         No           12         110         9           53         0         103         0           1         164         0         32           0         43         0         50           0         66         0         33           1         33         0         30		Odds ratio with 95% Cl 0.64 [0.25, 1.62 0.46 [0.01, 23.48 1.51 [0.06, 38.15 1.16 [0.02, 59.74 0.50 [0.01, 25.95 3.09 [0.12, 78.55	Weight (%)   69.69   4.41   4.22   2.97   4.26   3.10	Study CV-/FI>=90% LIBERATE EMPROVE TRANSFORM IMPACT REACH STELVIO	Di           Treatment         C           Yes         No         Y           1         121         1           1         102         C           1         64         C           0         65         1           1         33         C	Peath by CV Control (res No 1 61 0 47 0 32 1 49 1 32 0 34	./FI>=90% vs CV/FI unkn	Odds ratio         Weigh with 95% CI         Weigh (%)           0.50 [0.03, 8:20]         8:90         1.39 [0.06, 34.76]         4.56           1.51 [0.06, 38.15]         4.41         0.38 [0.02, 9:55]         9:29           0.16 [0.01, 4.11]         13.36	
Study CV-FF>=90% LIBERATE EMPROVE TRANSFORM IMPACT REACH STELVIO Heterogenetity: I <sup>2</sup>	No         Pailure b           Treatment Control         Control           1         121         2         60           1         102         0         47           0         65         0         32           0         43         1         49           0         66         0         33           0         34         0         34	<	Odds ratio         Wet           0dds ratio         Wet           with 95% Cl         (1           0.25 [0.02, 2.79]         16           1.39 [0.06, 34.76]         4           0.50 [0.01, 25.57]         4           0.38 [0.02, 9.55]         8           0.50 [0.01, 25.95]         4           1.00 [0.02, 5184]         3           0.50 [0.01, 4, 181]         3	ght         Study           CV-FI>=90%         CV-FI>=90%           54         LIBERATE           16         TRANSFORM           54         IMPACT           14         REACH           10         STELVIO           Heterogeneity	Hemophysis D           Treatment Control           Yes         No           12         110         9         53           0         103         0         47           1         64         0         32           0         43         0         50           0         66         0         33           1         33         0         34           c         r = 0.00%, if = 1.00         100         100		Chowin Odds ratio with 95% Cl 0.64 [0.25, 1.62 0.46 [0.01, 23.48 1.51 [0.06, 38.15 1.16 [0.02, 59.74 0.50 [0.01, 25.96 3.09 [0.12, 78.55 0.77 [0.35, 1.70	Weight (%)   69.69   4.41   4.22   2.97   4.26   3.10	Study CV-/FI>=90% LIBERATE EMPROVE TRANSFORM IMPACT REACH STELVIO Heterogeneity: I <sup>*</sup>	Di Treatment ( Yes No Y 1 121 1 1 102 ( 1 64 ( 0 43 1 0 66 1 1 33 ( 1 33 ( 1 33 (	leath by CV Control fes No 1 61 0 47 0 32 1 49 1 32 0 34 1.00	//FI>=90% vs CV/FI unkn	Odds ratio         Weigh (%)           0.50 [0.03, 8.20]         8.20]           1.50 [0.06, 34.76]         4.56           1.51 [0.06, 84.56]         4.56           0.30 [0.02, 9.55]         9.29           0.60 [0.01, 47.16]         3.36	
Study CV-/FI>=90% LIBERATE EMPROVE TRANSFORM IMPACT REACH STELVIO Heterogeneity: I <sup>2</sup> Test of 0, = 6; O(5	Non-spiratory Pailure D           Treatment Control           1         121         2         60           1         102         0         47           0         65         0         32           0         43         1         49           0         66         0         33           0         34         0         34           0.00%, H <sup>2</sup> = 1.00             0         0.86         p.037	<	Odds ratio         Web           0.255 [ 0.02, 2.79]         16           1.39 [ 0.06, 34.76]         4           0.50 [ 0.01, 25.57]         4           0.38 [ 0.02, 9.55]         8           0.50 [ 0.01, 25.57]         4           0.30 [ 0.02, 51.84]         3           0.50 [ 0.01, 4, 1.81]         1	Study         Study           CV-FI>->90%         CV-FI>->90%           54         LIBERATE           24         EMPROVE           16         TRANSFORM           54         IMPACT           14         REACH           10         STELVIO           Heterogeneity         Test of 6, = 6;	Hemophysis D           Treatment Control           Yes         No           12         110         9         53           0         103         0         47           1         64         0         32           0         43         0         50           0         66         0         33           1         33         0         34           ct <sup>2</sup> -0.05%, tf <sup>2</sup> 100         Q(5)           Q(5)         -1.18, p.0.95         55		0649 ratio 0645 ratio with 95% C1 0.64 [0.25, 1.62 0.46 [0.01, 23.48 1.51 [0.06, 38.15 1.16 [0.02, 59.74 0.50 [0.01, 25.95 3.06 [0.12, 78.55 0.77 [0.35, 1.70	Weight (%)   69.69   4.41   4.22   2.97   4.26   3.10 	Study CV-/FD=90% LIBERATE EMPROVE TRANSFORM IMPACT REACH STELVIO Heterogeneity: I <sup>1</sup> Test of θ, = θ; QI	Di Treatment ( Yes No Y 1 121 1 1 102 ( 1 64 ( 0 43 1 0 66 1 1 33 ( <sup>2</sup> =0.00%, H <sup>2</sup> =1 (5)=2.17, p=0.)	reath by CV Control res No 1 61 0 47 0 32 1 49 1 32 0 34 1.00 .83	//FI>=90% vs CV/FI unkn	Odds ratio with 95% C1         Weigh (%)           0.50 [0.03, 8.20]         8.20]           1.39 [0.06, 34.76]         4.56           1.51 [0.06, 38.15]         4.41           0.36 [0.02, 9.55]         9.29           0.16 [0.01, 4.11]         13.36           0.30 [0.12, 78.58]         3.24           0.76 [0.24, 2.41]         1.36	
Study CV/FD=90% LIBERATE EMPROVE TRANSFORM IMPACT REACH STELVIO Heterogeneity: I <sup>*</sup> Test of 9, = 6; Q(5	No Yes         No         Yes         No           1         121         2         60           1         102         0         47           0         65         0         32           0         43         1         49           0         66         0         33         0           0         34         0         34         =           0         04         34         =         =           0         05         0.34         =         =           0         05         0.05         p         =	<	Unknown         Wei           Oddi rafio         Wei           with 95% Cl         (*)           0.25 [0.02, 2.79]         16           1.38 [0.06, 34.76]         4           0.50 [0.01, 25.57]         4           0.58 [0.02, 9.55]         8           0.59 [0.01, 25.96]         4           —         1.00 [0.02, 51.84]         3           0.50 [0.14, 1.81]         1	ght ) Study CV-FI>=90% 54 LIBERATE 24 EMPROVE 16 TRANSFORM 54 IMPACT 14 REACH 10 STELVIO Heterogeneity Test of 6, = 6; 010 Util Liberation 15 CM	Hemophysis D           Treatment Cortol           Yes         No           12         10         9           13         0         47           1         64         0         32           0         43         0         50           0         66         0         33           1         33         0         34           c1 <sup>2</sup> 0.00%, H <sup>2</sup> 1.00         Q(5)           Q(5)         1.18, p = 0.95         50		0dds ratio with 95% Cl 0.64 [0.25, 1.62 0.46 [0.1, 23.46 1.51 [0.06, 38.15 1.16 [0.02, 59.74 0.50 [0.01, 25.95 3.09 [0.12, 78.55 0.77 [0.35, 1.70	Weight (%)   69.69   4.41   4.22   2.97   4.26   3.10 	$\label{eq:study} \begin{split} \hline & Study \\ \hline & CV.FID=90\% \\ LIBERATE \\ EMPROVE \\ TRANSFORM \\ IMPACT \\ REACH \\ STELVIO \\ Helerogeneity: I' \\ Test of e_i = e_i; Oi \\ \hline \end{array}$	Di Treatment ( Yes No Y 1 121 1 1 102 ( 1 64 ( 0 43 1 0 66 1 1 33 ( 1 33 ( 1 33 ( 5) = 2.17, p = 0.)	Control (res No 1 61 0 47 0 32 1 49 1 32 0 34 1.00 .83	//FI>=90% vs CV/FI unkn	Odds ratio with 95% C1         Weigh (%)           0.50 [0.03, 8.20]         8.20]           1.39 [0.06, 34.76]         4.56           1.51 [0.06, 38.15]         4.45           0.60 [0.02, 955]         9.29           0.60 [0.01, 111]         13.6           0.76 [0.02, 4.241]         3.09	
Study CV/FD=90% LIBERATE EMPROVE TRANSFORM IMPACT REACH STELVO Heterogeneity: I <sup>2</sup> Test of 8 = 6; Q(5 CV/FI Unknown	No Yes         No         Yes         No           1         121         2         60           1         121         2         60           1         122         0         43           0         65         0         32           0         43         1         49           0         66         0         33           0         34         0         34           =0.00%, H <sup>+</sup> =1.00		Unknown Odds ratio with 55% CL (1 0.25 [ 0.02, 2.79] 16 1.39 [ 0.06, 54.78] 4 0.55 [ 0.01, 25.57] 4 0.38 [ 0.02, 9.58] 8 0.55 [ 0.01, 25.58] 4 0.55 [ 0.14, 1.81]	ght ) Study CV-FI≫90% CV-FI≫90% 54 LIBERATE 24 EMPROVE 16 TRANSFORM 14 REACH 15 STELVIO Heterogeneity Test of θ, = θ; CVIFI Unkno	Telemopysis b         D           Yes         No         Yes           12         110         9         53           0         103         0         47           1         64         0         32           0         42         0         60           0         66         0         33           1         30         0         34           c1 <sup>2</sup> -0.00%, if # = 100         Q(5) = 1.18, p = 0.95		Odds ratio with 95% Cl 0.64 [0.25, 1.62 0.44 [0.01, 23.48 1.51 [0.06, 38:15] 1.16 [0.02, 59.74 0.50 [0.01, 25.95 3.00 [0.12, 78.55 0.77 [0.35, 1.70	Weight (%)   69.69   4.41   4.22   2.97   4.26   3.10 	Study CV.FED=90% LIBERATE EMPROVE TRANSFORM IMPACT REACH STELVIO Helterogeneity: I <sup>1</sup> Tost of 0 = 0; Q/ CV/FEUnknown	Di Treatment ( Yes No Y 1 121 1 1 102 ( 1 64 ( 0 43 1 1 33 ( 1 33 ( 1 33 ( 1 33 ( 1 33 ( 1 5) = 2.17, p = 0.)	Control (res No 1 61 0 47 0 32 1 49 1 32 0 34 1.00 .83	/FI>=90% vs CV/FI unkn	Odds ratio         Weigh with 95% C1         Weigh (%)           0.50 [0.03, 8.20]         8.20         8.50           1.30 [0.06, 34.76]         4.51         4.41           0.30 [0.01, 2.78,55]         3.24         0.76 [0.24, 2.41]	
Study CV-/FD>90% LIBERATE EMPROVE TRANSFORM IMPACT REACH STELVIO Helerogeneity: I <sup>2</sup> Test of 0, = 0; Q(5 CV/FI Unknown VENT	Testigneric Control           Yes         No           1         121         2         60           1         102         0         47           0         66         0         33           0         43         1         49           0         66         0         33           0         34         0         34           0         66         0         33           0         34         0         34           0         68         0         33           0         34         0         34           1         200%         #*100            1         201         2         85		Unknow 056 ratio 056 ratio 025 [002, 2.79] 16 1.38 [006, 54.78] 4 0.38 [002, 558] 4 0.38 [002, 558] 4 1.00 [002, 5184] 3 0.59 [0.14, 1.81] 0.66 [0.10, 3.68] 17	ght         Study           (V-FF)=90%         CV-FF)=90%           54         LIBERATE           16         TRANSFORM           16         TRANSFORM           16         TRANSFORM           17         REACH           10         STELVIO           Heterogeneity         Test of 6, = 6;           53         VENT	Herropcysis b         Second Seco		Odds ratio           0.dds ratio           0.84 (0.25, 1.62)           0.84 (0.25, 1.62)           0.44 (0.01, 23.46)           1.51 (0.06, 38.15)           1.14 (0.02, 56.74)           0.50 (0.01, 25.96)           0.07 (0.35, 1.70)           — 11.72 (0.66, 199.44)	Weight (%)   69.69   4.41   4.22   2.97   4.26   3.10   	Study CV-/FI>=90% LIBERATE EMPROVE TRANSFORM IMPACT REACH STELVIO Heterogeneity: I <sup>*</sup> Test of $\theta_i = \theta_i$ : QI CV/FI Unknown VENT	Di Treatment ( Yes No Y 1 121 1 1 102 ( 1 64 ( 0 43 1 1 33 ( 1 33 ( 1 33 ( 1 33 ( 1 33 ( 1 5)) 2 .17, p = 0.1 6 208 3	1         61           1         61           0         47           0         32           1         49           1         32           0         34           1.00         83           3         84		Odds ratio         Weigh with 95% CI         Weigh (%)           0.50 [ 0.03, 8.20]         8.20]         8.30           1.39 [ 0.06, 34.76]         4.56         8.50           1.51 [ 0.06, 8.815]         4.41         0.34 [ 0.02, 9.55]         9.24           0.30 [ 0.02, 9.55]         9.24         0.76 [ 0.24, 2.41]         13.36           0.81 [ 0.20, 3.30]         28.04         10.21         10.21	
Study CV-FP-90% LIBERATE EMPROVE TRANSFORM IMPACT REACH STELVIO Heterogeneity: I <sup>*</sup> T Test of 8 = 6; Q( CV/FI Unknown VENT EU-VENT	Testigneric         Control           Yes         No           1         121         2         60           1         102         0         47           0         66         0         32           0         43         1         49           0         64         0         33           9         0         64         0         34           9         0         64         0         34           9         0         64         0         34           9         0         64         0         34           9         0         64         0         34           9         0         64         0         34           9         0         64         0         34           9         0         8         0         34           9         0         5         55         5		Unknown Odds ratio with 95% CI (7 0.25 ( 0.02, 2.79) 16 1.39 ( 0.06, 34.78) 4 0.50 ( 0.01, 25.56) 8 0.30 ( 0.02, 9.55) 8 0.30 ( 0.01, 25.56) 4 1.00 ( 0.02, 19.56) 4 1.00 ( 0.02, 19.56) 4 0.55 ( 0.14, 181) 0.55 ( 0.14, 181) 0.55 ( 0.16, 2.15) 38	Study         Study           CV-/FD-90%         CV-/FD-90%           24         LBERATE           24         EMPROVE           16         TRANSFORM           54         IMPACT           10         STELVIO           Heterogenety         Test of 0,= 0;           CVIFI Unknoo         S3           50         EU-VENT	$\begin{tabular}{ c c c c c c c c c c c c c c c c c c c$		Odds ratio     web 95% C1     Odds ratio     web 95% C1     Odds ratio     web 95% C1     Odds ratio     odd [0.07, 23.48     1.51 [0.06, 38.15     1.16 [0.02, 50.47     0.50 [0.07, 25.96     3.00 [0.12, 78.55     0.77 [0.35, 1.70	Weight (%)   69.69   4.41   4.22   2.97   4.26   3.10       4.31   3.87	Study CV-FID-980% LIBERATE EMPROVE TRANSFORM IMPACT REACH STELVIO Heterogeneity, I' Test of 6: -9; QI CV/FI Unknown VENT EU-VENT	Di Treatment ( Yes No Y 1 121 1 1 102 ( 1 64 ( 0 43 1 1 33 ( 1 3)	leath by CV Control (res No 1 61 0 47 0 32 1 49 1 32 0 34 1.00 .83 3 84 3 57	AFP=80% vs CV/F Lunkn	Odds ratio         Weight with 95% CI         Weight with 95%	
Study CV-FD=50% LBERATE EMPROVE TRANSFORM IMPACT REACH STEL/O Helerogeneity: I <sup>*</sup> Test of its = 6; Q(t CV/FI Unknown VENT EuLyENT BeLiever HFI	No         Teachant         Control           1         1/21         2.60           1         1/21         2.60           0         4.3         1.40           0         64         0.47           0         64         0.42           0         4.3         1.40           0         64         0.33           0         34         0.40           9=0.60, p=0.87         7           3         211         2           4         1.26         5.55           1         24         0.25		Unstrown Ods ratio with 95% CI (? 0.25 ( 0.02, 2.79) 16 1.39 ( 0.06, 34.78) 4 0.50 ( 0.01, 25.57) 4 0.50 ( 0.01, 25.57) 4 0.50 ( 0.01, 25.58) 4 - 1.00 ( 0.02, 51.84) 3 0.50 ( 0.10, 368) 17 0.60 ( 0.10, 368) 17 	ght         Study           CV/FI>-90%         UBERATE           54         LIBERATE           16         TRANSFORM           16         TRANSFORM           10         STELVIO           Heterogeneity         Test of 0, = 0;           CVIFI Unknop         EU-VENT           33         VENT           36         Bulleven HFI           36         Bulleven HFI	Herroropole         Solution           Yes         No         Yes           12         110         9         53           0         102         0         47           1         64         0         52           0         66         0         33           1         34         0         50           cf         6.00%, H' = 100         34         cf           10         9         9.58         58		Odds ratio           Odds ratio           with 95% CI           0.64 [0.25, 1.62           0.44 [0.01, 23.48           1.51 [0.06, 38.15           1.51 [0.06, 38.15           1.61 [0.02, 50.24           0.50 [0.01, 23.48           0.50 [0.01, 23.48           0.50 [0.01, 23.5           0.77 [0.35, 1.70	Weight (%)   69.69   4.41   4.22   2.97   4.26   3.10     4.31   3.87   3.18	Study CV-FI>=80% LUBERATE EMPROVE TRANSFORM MPACT REACH STELVIO Test of e. = e, QI CV/FI Unknown VENT EU-VENT BeLiever HFI	Di Treatment ( Yes No Y 1 121 1 102 ( 1 64 ( 0 66 1 1 33 ( <sup>1</sup> = 0.00%, H <sup>2</sup> = 1 (5) = 2.17, p = 0.1 6 208 3 5 106 3 2 23 (	leath by CV Control (res No 1 61 0 47 0 32 1 49 1 32 0 34 1.00 .83 3 84 3 57 0 25	AFI>=80% vs CV/F Lunk	Odds notio         Weight with 95% CI         Weight (%)           0.50 [ 0.03, 8.20]         4.00         5.01         5.01           1.50 [ 0.03, 8.20]         4.03         1.03         5.01         5.01           0.61 [ 0.20, 8.20]         4.01         1.30         0.01         5.01         2.01           0.61 [ 0.20, 8.20]         2.04         0.01         1.03         2.01         0.01	
Study CV-RP-s99% LIBERATE EMPROVE TRANSFORM IMPACT REACH STELVIO Heterogeneity: I <sup>*</sup> - Test of the sty Ott CV/RI Unknown VENT EU-VENT Beclaver HPI Heterogeneity: I <sup>*</sup>	Testigneric         Control           Yes         No           1         121         2         60           1         120         0         47           0         66         0         32           0         43         1         49           0         64         0         33         0           0         34         0         40         34           0,005, H <sup>4</sup> = 100         34		Unknown Odd-rafio with 99% CI (7 0.25 [ 0.02, 2.79] 16 1.39 [ 0.06, 34.78] 17 0.50 [ 0.17, 257] 4 0.36 [ 0.02, 2.55] 8 0.50 [ 0.17, 257] 4 0.35 [ 0.11, 257] 4 0.55 [ 0.14, 1.81] 0.60 [ 0.10, 3.68] 17 0.63 [ 0.18, 2.15] 38 -3.12 [ 0.12, 0.39] 17	Study         Study           CV-FD-#0Y, CV-FD-#0Y, EURPATE         EURPATE           4         EURPATE           16         TRANSFORM           16         TRANSFORM           14         REACH           10         STELVIO           13         VENT           16         Bulaverth           17         Bellaverth	$\label{eq:restriction} \begin{array}{c c c c c c c c c c c c c c c c c c c $		Chown Deds ratio with 95% C1 0.64 (0.25, 1.62 0.44 (0.01, 23.48 1.57) (0.66, 38) (0.50, 23.47) (0.50, 20.50) (0.01, 25.96 3.00) (0.12, 78.55 0.77) (0.35, 1.70) (0.72, 78.55 0.77) (0.35, 1.70) (0.75, 22 1.00) (0.02, 75.22 1	Weight (%)   69.69   4.41   4.22   2.97   4.26   3.10       4.31   3.87   3.18	Study CV-FID=80% LUBERATE EMPROVE EMPROVE EMPROVE TRANSFORM MMACT REACH STELVIO Heterogeneity: r <sup>1</sup> Test of 6 = 6; QI CV/FI Unknown VENT EU-VENT Belaver HFI Heterogeneity: r <sup>2</sup>	Di Treatment ( Yes No Y 1 121 1 1 102 ( 1 64 ( 0 43 1 5 0.00%, H <sup>2</sup> 1 5 100 2 5 100 2 2 23 ( <sup>2</sup> = 0.00%, H <sup>2</sup> 1	leath by CV Control res No 1 61 0 47 0 32 1 49 1 32 0 34 1 00 .83 3 84 3 57 0 25 1.00	AFP=80% vs CV/F Lunk	Odds notic         Weights           Odds notic         Weights           0.50         0.00         8.70           0.50         0.00         8.70           0.50         0.00         8.70           0.50         0.00         8.70           0.50         0.00         8.76           0.51         0.00         8.75           0.51         0.00         8.75           0.51         0.00         8.75           0.51         0.00         8.75           0.51         0.00         9.75           0.51         0.20         3.00           0.51         0.20         3.00           0.51         0.20         3.00           0.54         0.21         2.81           0.54         0.21         1.89           0.54         0.21         1.89           1.50         2.81         1.50	
Study CV-RP-s69% LIBERATE EMPROVE TRANSFORM IMPACT REACH STELVIO STELVIO Helerogeneity: F Test of & = 8; O(2 CV/FI Unknown VENT EL-VENT BeLaver HIFI F Helerogeneity F Test of & = 8; O(2	Testigneric         Control           Yes         No           1         121         2           0         65         0         32           0         43         1         40           0         66         0         32         0           0         64         0         33         0         34         0         34           0         66         0.5         55         1         2.4         0.5         55           1         12         85         5         5         1         2.4         0.25           0         26, p = 0.057         7         0.056, cf = 10.0         -         -         -		Unktrown Odds radge with 96% CI (1) 0.25 (0.02, 2.79) 16 1.36 (0.00, 34.76) 4 0.50 (0.01, 25.57) 4 0.50 (0.01, 25.59) 4 - 1.00 (0.02, 51.58) 4 - 1.00 (0.02, 51.58) 4 - 0.50 (0.14, 1.81) 0.60 (0.10, 3.68) 17 0.63 (0.18, 2.19) 38 	ght         Study           CV/FD-80%         CV/FD-80%           LIBERAT         LIBERAT           4         EMPROVE           6         TRMARFUR           10         STELVIO           H010         Test of 4 = 6;           H010         Test of 4 = 6;	Internorphysics         Pretroing/Section           12         110         9         5.0           12         100         0         4.0         50           1         14         0         0.2         0         4.0         50           0         100         0         3.2         0         4.0         50         0         6.0         0.33         1         3         0         3.4         r.6         0.00(5)         -1.16, p.e<0.55		Odds:ratio           0.645 ratio           with 95% CI           0.64 [0.25, 1.62           0.46 [0.01, 2.46           1.51 [0.06, 38:15]           1.61 [0.02, 50:74           0.50 [0.01, 25:65           0.07 [0.35, 1.70]	Weight (%) 1 69.69 1 4.41 2 4.22 1 2.97 4 26 1 3.10 1 4.31 1 3.87 3 .18 1	Study CV-FID=90% LUBERATE EMPROVE TRANSFORM MPACT REACH STELVIO Heterogeneity: (1 Test of 6 = 6; Q) CV/FI Unknown VENT EU-VENT Bediwer Higt Test of 6 = 6; Q)	Di Treatment ( Yes No Y 1 121 1 1 102 ( 1 64 ( 0 43 1 5 0.05%, h <sup>2</sup> = 1 5 106 1 2 23 ( <sup>2</sup> = 0.00%, h <sup>2</sup> = 1 2 2 ( <sup>2</sup> = 0.00%, h <sup>2</sup> = 1 2 ( <sup>2</sup> = 0.00%, h <sup></sup>	leath by CV Control fees No 1 61 0 47 0 32 1 49 1 32 0 34 1.00 .83 3 84 3 57 0 25 1.00 .53	AFP=80% vs CV/F Luke	Odds ratio         Weight with 95% CI         Weight with 95%	
Study CV-XP-99%, LIBERATE EMPROVE EMPROVE TRANSFORM MIPACT REACH STELVIO Helerogeneity, I <sup>2</sup> T est of a = 6; O(2) CV/FI Unknown VENT BoLkever HFI Helerogeneity, I <sup>2</sup> T aut of a = 6; O(2) Overall	Non-Stratter         Call           1         1/21         2.60           1         1/21         2.60           0         64         0.47           0         65         0.32           0         43         1.40           0         66         0.33           0         34         0.40           9 = 0.66, p = 0.37         -           3         211         2.65           1         24         0.25           0.00%, H <sup>4</sup> = 1.00         -           1         24         0.25           0.00%, H <sup>4</sup> = 1.00         25           0.00%, H <sup>4</sup> = 1.00         25           0.00%, H <sup>4</sup> = 1.00         25		URATIONI Odds radio with 90% CI (1) 0.25[0.02, 2.79] 16 1.38[0.06, 34.78] 4 0.30[0.01, 35.87] 4 0.30[0.01, 35.87] 4 0.30[0.10, 35.88] 4 0.50[0.10, 3.68] 17 0.50[0.10, 3.58] 17 0.50[0.10, 3.58] 17 0.50[0.10, 3.58] 17 0.50[0.10, 3.58] 17 0.50[0.10, 3.58] 17 0.50[0.10, 3	ght         Sludy           i)         Skudy           CV-475-40%         LiteRAT           k4         LiteRAT           k6         TRANSCRN           k4         MARCH           k4         MARCH           k4         MARCH           k6         TRANSCRN           k6         TRANSCRN           k6         TRANSCRN           k6         TRANSCRN           k6         TRANSCRN           k6         K6           k7         K6           k8         K6           k9         K6           k9         K6           k9         K6           k9         K6           k9         K6           k9 <td><math display="block">\label{eq:restriction} \begin{split} &amp; \text{Hermorphysics} \\ \hline \text{Treatment: Costs of } \\ \hline \text{Treatment: Costs of } \\ \text{Treatment: Costs of } \\ \text{Treatment: Costs of } \\ \text{Treatment } \\ </math></td> <td></td> <td>0494 ratio 0494 (0.25. 1.62 0.44 (0.25. 1.62 0.44 (0.25. 1.62 0.46 (0.07. 22.46 1.16 (0.05. 38.15 1.16 (0.05. 38.15 1.16 (0.05. 38.15 1.16 (0.05. 38.15 1.16 (0.05. 38.15 1.17 (0.35. 1.17 1.17 (0.05. 1.17) 1.17 (0.0</td> <td>Weight (%)   60.69   4.41   4.22   2.97   4.26   3.10     3.87   3.18</td> <td>Study CV.4FD=80% LIBERATE EMPROVE TRANSFORM MPACT REACH STELVIO Heterogeneity, f Test of e. e, o CVFF Unknown VENT EU-VENT Ballwer HFI Heterogeneity, f Test of e. e, o</td> <td>Di Treatment ( Yes No Y 1 121 - 1 102 ( 1 64 ( 0 43 - 1 33 ( 1 33 ( 5 106 - 2 23 ( - 2 23 ( - - - - - - - - - - - - - - - - - - -</td> <td>leath by CV Control (res No 1 61 0 47 0 32 1 49 1 32 0 34 1.00 .83 3 84 3 57 0 25 1.00 .53</td> <td>AFP=80% vs CV/F Lunk</td> <td>Odds ratio         Weight with 95% CI         Weight (%)           0.55(10.0.         8.20         8.50           1.39(10.0.         3.124         4.11           0.35(10.0.         9.52         9.53           0.46(10.0.         4.11         1.36           0.46(10.0.         4.11         1.36           0.46(10.0.         3.124         2.41           0.86(10.2.         2.41         1.38           0.86(10.2.         3.302         2.04           0.86(10.2.         3.302         2.04           0.86(10.2.         3.302         2.04           0.86(10.2.         3.302         2.04           0.86(10.2.         3.302         2.04           0.86(10.2.         3.302         2.05           0.86(10.2.         3.302         2.04           0.96(10.2.         3.302         2.05</td>	$\label{eq:restriction} \begin{split} & \text{Hermorphysics} \\ \hline \text{Treatment: Costs of } \\ \hline \text{Treatment: Costs of } \\ \text{Treatment: Costs of } \\ \text{Treatment: Costs of } \\ \text{Treatment } \\ $		0494 ratio 0494 (0.25. 1.62 0.44 (0.25. 1.62 0.44 (0.25. 1.62 0.46 (0.07. 22.46 1.16 (0.05. 38.15 1.16 (0.05. 38.15 1.16 (0.05. 38.15 1.16 (0.05. 38.15 1.16 (0.05. 38.15 1.17 (0.35. 1.17 1.17 (0.05. 1.17) 1.17 (0.0	Weight (%)   60.69   4.41   4.22   2.97   4.26   3.10     3.87   3.18	Study CV.4FD=80% LIBERATE EMPROVE TRANSFORM MPACT REACH STELVIO Heterogeneity, f Test of e. e, o CVFF Unknown VENT EU-VENT Ballwer HFI Heterogeneity, f Test of e. e, o	Di Treatment ( Yes No Y 1 121 - 1 102 ( 1 64 ( 0 43 - 1 33 ( 1 33 ( 5 106 - 2 23 ( - 2 23 ( - - - - - - - - - - - - - - - - - - -	leath by CV Control (res No 1 61 0 47 0 32 1 49 1 32 0 34 1.00 .83 3 84 3 57 0 25 1.00 .53	AFP=80% vs CV/F Lunk	Odds ratio         Weight with 95% CI         Weight (%)           0.55(10.0.         8.20         8.50           1.39(10.0.         3.124         4.11           0.35(10.0.         9.52         9.53           0.46(10.0.         4.11         1.36           0.46(10.0.         4.11         1.36           0.46(10.0.         3.124         2.41           0.86(10.2.         2.41         1.38           0.86(10.2.         3.302         2.04           0.86(10.2.         3.302         2.04           0.86(10.2.         3.302         2.04           0.86(10.2.         3.302         2.04           0.86(10.2.         3.302         2.04           0.86(10.2.         3.302         2.05           0.86(10.2.         3.302         2.04           0.96(10.2.         3.302         2.05	
Study CV-FP>=90%, LIBERATE EMPROVE TRANSFORM MIPACT TRANSFORM MIPACT TRANSFORM MIPACT TRANSFORM MIPACT TRANSFORM MIPACT REACH STELVIO Heterogeneith: I <sup>®</sup> - Test of 8, = 8; O(2) Overall	Testignettic Control         Yes         No           1         121         2         60           1         120         0         47           0         66         0         32           0         43         1         49           0         66         0         33           0         54         0         34         0           10         0.65         5         5         1         24         25           0.00%, H <sup>4</sup> = 1.00         72         25         20.00%, H <sup>4</sup> = 1.00         1         24         25		Unknown Odds ndb Ve with 90% CI (1 0.25 ( 0.02, 2.79) 16 1.39 ( 0.6, 34.78) 4 0.30 ( 0.01, 25.89) 4 0.30 ( 0.12, 558) 4 0.05 ( 0.11, 518) 4 0.05 ( 0.21, 518) 4 0.05 ( 0.11, 518) 4 0.05 ( 0	ght         Sudy           CV-47b-80%         CV-47b-80%           LIBERATE         EMPROVE           LIBERATE         EMPROVE           H         INASFORM           H         MPACH           Test of 6, = 6,         Bulkerer HF1           Heterogramming         Test of 6, = 6,           VENT         Bulkerer HF1           Heterogramming         Test of 6, = 6,           Overall         Heterogramming	$\begin{tabular}{ c c c c c } \hline Herroropoly (Control $C$) & $V$ extreme to $V$ e$		Odds ratio           0.64 (0.25, 1.62)           0.64 (0.25, 1.62)           0.64 (0.25, 1.62)           0.64 (0.25, 1.62)           0.65 (0.05, 0.25, 0.05)           0.50 (0.05, 0.25, 0.05)           0.50 (0.05, 0.25, 0.05)           0.50 (0.05, 0.25, 0.05)           0.50 (0.05, 0.25, 0.17)	Weight (%)   69.69   4.41   4.22   2.97   4.26   3.10     4.31   3.87   3.18	Study CV .FP=80% USERATE EMPROVE TRANSFORM MPACT REACH STELVON FT test of 0;= 0; 0; CV/FI Unknown VENT Belaiver HFI Heterogenet; f' Test of 0;= 0; 0; Overall	Di Treatment ( Ves No V 1 121 - 1 102 ( 1 64 ( 0 43 - 1 33 ( - 0.00%, H <sup>2</sup> = 1 (5) = 2.17, p = 0.1 - - - - - - - - - - - - -	leath by CV Control (res No 1 61 0 47 0 32 1 49 1 32 0 34 1 52 0 34 1 00 83 3 84 3 57 0 25 1.00 53	AFP=30% vs CV/F Lunk	Odds ratio         Weights           Odds ratio         Weights           0.50         0.00         8.20           1.59         0.00         8.27           1.51         0.00         8.27           0.50         0.00         8.27           0.51         0.00         8.29           0.87         0.26         9.29           0.87         0.26         1.27           0.87         0.24         2.41           0.87         0.24         2.41           0.87         0.24         2.41           0.87         0.24         2.41           0.87         0.24         2.41           0.87         0.24         2.41           0.87         0.24         2.41           0.87         0.24         2.41           0.87         0.24         2.41           0.87         0.24         2.83           0.86         0.46         1.87	
Sludy CV-(Fb=96%), LBERATE EMPROVE TRANSFORM MIPACT REACH STELVIO Heterogeneity, F <sup>1</sup> , Test of 8 = 6, QZ CV/FI Unknown VENT BeLiver HFI Beliver HFI Heterogeneity, F <sup>1</sup> Test of 8 = 6, QZ Overall Heterogeneity, F <sup>1</sup> Test of 8 = 6, QZ	Totaginarity - Faultory           Yes         No           1         121         2.60           1         102         0.47           0         43         1.40           0         66         0.32           0         43         1.40           0         66         0.33           0         34         0.34           0         65         55           1         2.40         2.5           0.000, H <sup>2</sup> = 1.00		UINTOWN Odds radge UINTOWN Odds radge UINTOWN	pht         Study           i)         Study           CV-47b-400X         CV-47b-400X           4         LIBERATE           4         LIBERATE           4         BMPACH           54         MPACH           64         MPACH           7         Text of 6 = 6,           7         Text of 6 = 6,           10         STELVO           50         EU-VENT           50         EU-VENT           100         VENT           101         VENT           102         VENT           103         VENT           104         REACH           105         EU-VENT           106         Studower HF1           Heterosgneth         Text of 6, = 6,           104         Text of 6, = 7,	$\label{eq:restriction} \begin{split} & \text{HerropCyses} \\ \hline \text{Test No:} & \text{Costs} & \text{Costs} \\ \hline \text{Test No:} & \text{Costs} & \text{O} \\ \hline 12 & 103 & 0 & 47 \\ 1 & 1 & 64 & 0 & 50 \\ 0 & 66 & 0 & 33 \\ 1 & 33 & 0 & 34 \\ \text{F} & -62005, \text{F}^{-1} & 0 & 50 \\ \text{Costs} & -135, \text{p} & 0.95 \\ \hline \text{m} \\ \hline 13 & 201 & 0 & 87 \\ \text{m} & 13 & 201 & 0 & 10 \\ \text{m} & 13 & 201 & 0 & 10 \\ \text{m} & 13 & 201 & 0 & 10 \\ \text{m} & 13 & 201 & 0 & 10 \\ \text{m} & 13 & 201 & 0 & 10 \\ \text{m} & 13 & 201 & 0 & 10 \\ \text{m} & 13 & 201 & 0 & 10 \\ \text{m} & 13 & 201 & 0 & $	V CV-PPARIX VS CVPF UN	Odds ratio           With 55% CI           0.44 (10.7), 22.44           0.46 (10.7), 22.44           1.55 (10.6), 33.7           1.55 (10.6), 33.7           0.56 (10.7), 25.44           0.56 (10.7), 25.44           0.56 (10.7), 25.44           0.56 (10.7), 25.45           0.67 (10.35, 170)	Weight (%)   69.69   4.41   4.22   2.97   4.26   3.10       4.31   3.87   3.18	Study CV 476-80% LIBERATE LIBERATE LIBERATE LIBERATE LIBERATE REACH STELVO NELACH STELVO NELACH STELVO CVIFI Unknown VENT ELV-VENT Bellwere Hit Heterogeneity: f Test of &= 0; Q Overall Heterogeneity: f Heterogeneity: f	Di Treatment ( Yes No Y 1 121 1 102 ( 1 64 ( 0 43 1 0 66 1 3 3 ( = 0.00%, h <sup>2</sup> = 1 5 106 2 2 23 ( = 0.00%, h <sup>2</sup> = 1 (2) = 128, p = 0 (2) = 128, p = 0	leath by CV Control (res No 1 61 0 47 0 32 1 49 1 32 0 34 1.00 83 3 84 3 57 0 25 1.00 53 1.00 53 88 9 Fav	AFI>=80% vs CV/F Luke	Odds ratio um 95% CI         Weigh (%)           0.55 (10.0.         8.20 (10.0.         8.20 (10.0.           1.59 (10.0.         8.20 (10.0.         8.20 (10.0.         8.20 (10.0.           1.51 (10.0.         8.31 (14.0.         8.10 (14.0.         8.10 (14.0.           0.61 (12.0.         8.20 (10.0.         8.50 (14.0.         8.50 (14.0.           0.61 (12.0.         8.50 (14.0.         8.50 (14.0.         8.50 (14.0.           0.61 (12.0.         3.30 (10.2.         7.55 (12.4.         8.50 (14.0.           0.61 (12.0.         3.30 (10.2.         11.58 (14.0.         10.0.           0.61 (12.0.         3.30 (10.2.         11.58 (14.0.         10.0.           0.61 (12.0.         3.30 (10.2.         11.58 (14.0.         10.0.           0.61 (12.0.         3.30 (10.2.         11.58 (14.0.         10.0.           0.56 (10.4.         1.197 (14.0.)         11.0.         11.0.	
Study CV-Fb-98% LBERATE EMPROVE TRANSFORM MPACT REACH STELVIO Heterogeneity, FT Test of e. e. 9, Qt CV/FI Unknown VENT BoLIwer HFI Heterogeneity, FT Test of e. e. 9, Qt Overeil Heterogeneity, FT Test of e. e. 9, Qt	Non-Final Control         Yes         No           1         1/21         2.60           1         1/21         2.60           0         64         0.47           0         66         0.32           0         43         1.40           0         66         0.33           0         34         0.40           9=0.66, p=0.37         7           3         211         2.65           0.00%, H <sup>4</sup> = 1.00         25           0.00%, H <sup>4</sup> = 1.00         25           0.00%, H <sup>4</sup> = 1.00         9=0.55           0.00%, H <sup>4</sup> = 1.00         9=0.55	Corter Favos EBV	Unktrown Odds rady with 96% CI (1) 0.25[0.02, 2.79] 16 1.38[0.06, 34.78] 4 0.30[0.01, 35.87] 4 0.30[0.02, 55.81] 3 0.50[0.10, 3.68] 17 0.50[0.10, 3.58] 18 0.50[0.10, 3.68] 17 0.50[0.10, 3.58] 18 0.50[0.10, 3.	ph1         Sudy           CV-F3-e975         CV-F3-e975           54         LIBERATE           24         ENFROVE           16         TRANSFCHAR           16         TRANSFCHAR           10         STELVIO           Heterogravity         Text of e + 0;           10         EU-FNT           11         EU-FNT           11         EU-FNT           12         EU-FNT           13         EU-FNT           14         EU-FNT           14         EU-FNT           14         EU-FNT </td <td><math display="block">\begin{tabular}{ c c c c c } \hline Treatment Coded &amp; the treatment C</math></td> <td>vos Control Paros EBV 01</td> <td>Odds ratio           0.64 (0.25, 1.62)           0.64 (0.25, 1.62)           0.64 (0.25, 1.62)           0.64 (0.25, 1.62)           0.65 (0.01, 22.44)           0.65 (0.01, 22.44)           0.60 (0.01, 22.44)           1.61 (0.83)           0.60 (0.01, 22.44)</td> <td>Weight (%)   69.69   4.41   4.22   2.97   4.26   3.10     4.31   3.87   3.18</td> <td>Study CV-FP-980% LUBERATE ENRROVE TRANSFORM MMACT REACH STELVIO Test of 0: -0; -0; CV/FI Unknown VENT EsLiv/ENT Beliares HRI Heterogeneity; // Test of 0: -0; -0; Oversil Heterogeneity; // Test of 0: -0; -0; CV/FI Unknown</td> <td>Di Treatment ( Yeas No Y 1 1221 - 1 1022 ( 1 64 ( 0 43 - 1 64 ( 0 43 - 1 64 ( 0 43 - 1 64 ( 0 43 - 1 64 ( 0 66 - 1 33 ( = 0.00%, H<sup>2</sup> = 1 (2) = 1.28, p = 0.1 - - - = 0.00%, H<sup>2</sup> = 1 (2) = 1.28, p = 0.1 - - - = 0.00%, H<sup>2</sup> = 1 (3) = 3.58, p = 0.1 - - - - - - - - - - - - -</td> <td>leath by CV Control (res No 1 61 0 47 0 32 1 49 1 32 0 34 1 00 83 3 84 3 57 0 25 1.00 5.53 1.00 5.53</td> <td>AFI&gt;=80% vs CV/F Lunka e</td> <td>Odds noto         Weight with 95% CI         Weight (%)           0.55(10.0.         8.20         8.50           1.39(10.0.         3.12         4.61           0.51(10.0.         8.20         8.50           0.51(10.0.         8.20         8.50           0.61(10.2.         3.24         4.61           0.61(10.2.         3.02         8.54           0.61(10.2.         3.02         2.64           0.61(10.2.         3.02         2.64           0.61(10.2.         3.02         2.64           0.50(10.1.         1.66         2.83           0.50(10.4.         2.83         1.00(10.4.</td>	$\begin{tabular}{ c c c c c } \hline Treatment Coded & the treatment C$	vos Control Paros EBV 01	Odds ratio           0.64 (0.25, 1.62)           0.64 (0.25, 1.62)           0.64 (0.25, 1.62)           0.64 (0.25, 1.62)           0.65 (0.01, 22.44)           0.65 (0.01, 22.44)           0.60 (0.01, 22.44)           1.61 (0.83)           0.60 (0.01, 22.44)	Weight (%)   69.69   4.41   4.22   2.97   4.26   3.10     4.31   3.87   3.18	Study CV-FP-980% LUBERATE ENRROVE TRANSFORM MMACT REACH STELVIO Test of 0: -0; -0; CV/FI Unknown VENT EsLiv/ENT Beliares HRI Heterogeneity; // Test of 0: -0; -0; Oversil Heterogeneity; // Test of 0: -0; -0; CV/FI Unknown	Di Treatment ( Yeas No Y 1 1221 - 1 1022 ( 1 64 ( 0 43 - 1 64 ( 0 43 - 1 64 ( 0 43 - 1 64 ( 0 43 - 1 64 ( 0 66 - 1 33 ( = 0.00%, H <sup>2</sup> = 1 (2) = 1.28, p = 0.1 - - - = 0.00%, H <sup>2</sup> = 1 (2) = 1.28, p = 0.1 - - - = 0.00%, H <sup>2</sup> = 1 (3) = 3.58, p = 0.1 - - - - - - - - - - - - -	leath by CV Control (res No 1 61 0 47 0 32 1 49 1 32 0 34 1 00 83 3 84 3 57 0 25 1.00 5.53 1.00 5.53	AFI>=80% vs CV/F Lunka e	Odds noto         Weight with 95% CI         Weight (%)           0.55(10.0.         8.20         8.50           1.39(10.0.         3.12         4.61           0.51(10.0.         8.20         8.50           0.51(10.0.         8.20         8.50           0.61(10.2.         3.24         4.61           0.61(10.2.         3.02         8.54           0.61(10.2.         3.02         2.64           0.61(10.2.         3.02         2.64           0.61(10.2.         3.02         2.64           0.50(10.1.         1.66         2.83           0.50(10.4.         2.83         1.00(10.4.	
Study CV-4FD-980% LBERATE EMPROVE TRANSFORM MIPACT REACH STELVIO Heterogeneity: F <sup>1</sup> Test of 8 = 6; Og Overall Heterogeneity: F <sup>1</sup> Test of 8 = 6; Og Overall Test of 8 = 6; Og Test of 8 = 6; Og Test of 9 = 6; Og Test of 9 = 0; Og	Testigneric Control         Testigneric Control           1         121         2         60           1         120         0         47           0         66         0         32           0         43         1         49           0         66         0         33           0         5         5         5           0         241         2         25           0.00%, H <sup>4</sup> = 1.00	S Cottor Favors EBV	URKTOWN 005 r010 025 [0.02, 2.79] 16 1.39 [0.6, 34.78] 4 0.30 [0.01, 25.89] 4 0.30 [0.10, 35.89] 4 0.30 [0.10, 35.89] 4 0.50 [0.10, 35.89] 4 0.50 [0.10, 35.89] 4 0.50 [0.10, 36.8] 17 0.53 [0.18, 2.19] 38 -3.12 [0.12, 0.01, 35.89] 4 0.65 [0.30, 1.39] 0.65 [0.30, 1.39]	ph1         Study           CV-FP3-90%         CV-FP3-90%           54         LIBERATE           LIBERATE         LIBERATE           14         REARTS           14         REACH           15         TRANSFORM           14         REACH           15         VENT           16         Bulleverth           17         VENT           18         VUNT           19         Bulleverth           19         Bulleverth           19         Bulleverth           11         Test of 4 = 6;           11         Test of 4 = 6;           11         Test of 4 = 6;	$\begin{tabular}{ c c c c c } \hline Herroropoly Control $$ $$ $$ $$ $$ $$ $$ $$ $$ $$ $$ $$ $$$	VIC V-PIPERUTS VS CVIPIUM	Odds ratio           0.64 (0.25, 1.62)           0.64 (0.25, 1.62)           0.64 (0.25, 1.62)           0.64 (0.25, 1.62)           0.65 (0.05, 0.25, 0.05)           0.50 (0.05, 0.25, 0.05)           0.50 (0.05, 0.25, 0.05)           0.50 (0.05, 0.25, 0.05)           0.50 (0.05, 0.25, 0.05)           0.50 (0.05, 0.25, 0.05)           0.50 (0.05, 0.25, 0.05)           0.50 (0.05, 0.25, 0.05)           0.50 (0.05, 0.25, 0.05)           0.50 (0.05, 0.25, 0.05)           0.50 (0.05, 0.25, 0.05)           0.50 (0.05, 0.25, 0.05)           0.50 (0.05, 0.25, 0.05)           0.50 (0.05, 0.25, 0.05)           0.50 (0.05, 0.25, 0.05)           0.50 (0.05, 0.05)           0.50 (0.05, 0.05)           0.50 (0.05, 0.05)           0.50 (0.05, 0.05)           0.50 (0.05, 0.05)           0.50 (0.05, 0.05)           0.50 (0.05, 0.05)           0.50 (0.05, 0.05)           0.50 (0.05, 0.05)           0.50 (0.05, 0.05)           0.50 (0.05, 0.05)           0.50 (0.05, 0.05)           0.50 (0.05, 0.05)           0.50 (0.05, 0.05)           0.50 (0.05, 0.05)           0.50 (0.05, 0.05)	Weight (%) 1 60.69 1 4.41 1 4.22 1 2.97 4.26 1 3.10 1 4.28 1 3.10 1 3.87 1 3.18	Shudy CV-FD-90% LBERATE EMPROVE TRANSFORM MPACT REACH STELVIO Heterogenetity of EU-VENT Bell-were Hill Heterogenetity of Test of 6 = 6, 00 Oversil Heterogenetity of Test of 6 = 6, 00 Test of 6 = 6, 00	Di Treatment ( Yes No Y 1 121 - 1 102 ( 1 64 ( 0 43 - 1 33 ( 1 0 66 - 1 33 ( 1 33 ( 1 0 00%, H <sup>2</sup> - 1 ( 5 100 3; 2 2 3 ( 2 0 00%, H <sup>2</sup> - 1 ( 2 0 0.0%, H <sup>2</sup> - 1 ( 2 0 0.0%, H <sup>2</sup> - 1 ( 2 0 0.0%, H <sup>2</sup> - 1 ( 8) = 3.58, p = 0. ( 1 ences: Q, (1) =	leath by CV Control res No 1 61 0 32 1 49 1 32 1 49 1 32 1 49 1 32 1 49 1 32 1 3 4 1 00 .83 3 84 3 57 0 0 53 1.00 .53 1.00 .53	AFP=80% vs CV/F Lunkn	Oddin nolo Weigh with 95% CI (%) 0.50 [0.03, 8.20 8.90 1.39 [0.03, 3.476 4.41 0.39 [0.02, 8.53] 8.29 0.36 [0.04, 4.11] 3.24 0.76 [0.34, 2.41] 0.36 [0.24, 2.41] 0.36 [0.24, 2.41] 0.36 [0.24, 1.97] 0.36 [0.44, 1.97]	
Study CV-4Fb+80% LBERATE EMPROVE TRANSFORM IMPACT REACH STELVIO Heterogeneity: F Test of e, e; QQ Overstil Heterogeneity: F Test of e; QQ Overstil Heterogeneity: F Test of e; QQ	Teachard         Control           Yes         No           1         121         2.60           1         122         2.60           0         43         1.40           0         66         0.32           0         43         1.40           0         66         0.33           0.3         211         2.85           6         105         5.55           1         24         0.25           0.00%, H <sup>2</sup> = 1.00         1)         9.40.55           0.00%, H <sup>2</sup> = 1.00         1)         9.10.85           0.00%, H <sup>2</sup> = 1.00         1)         9.28, p = 0.35           0.00%, H <sup>2</sup> = 1.00         1)         9.28, p = 0.35	S Cottel Faires EBV	UINTION Odd rafio with 95% CI (1) 0.55 (0.02, 2.79) 16 1.38 (0.06, 34.76) 4 0.30 (0.01, 55.75) 4 0.30 (0.01, 55.75) 4 0.30 (0.01, 55.85) 4 - 1.00 (0.02, 51.86) 4 - 1.00 (0.02, 51.86) 4 - 0.50 (0.10, 3.06) 17 0.50 (0.10, 3.06) 17 0.50 (0.10, 3.06) 17 0.50 (0.10, 3.06) 17 0.50 (0.10, 3.06) 17 0.55 (0.30, 1.39) 2 2	ph/l         Sudy           OV-FD-90%         CV-FD-90%           54         LIBERATE           24         EMPOVE           16         TRANSFORM           44         IMPACT           14         REACH           10         STELVIO           14         REACH           10         STELVIO           10         STELVIO           10         EU-VENT           10         EU-VENT           10         EU-VENT           10         EU-VENT           10         EU-VENT           11         Heterogravity           11         Text of e,=0,           12         Text of e,=0,           12         Text of e,=0,           12         Text of e,=0,	$\label{eq:restriction} \begin{split} & \text{HerritoryOsted} \\ \hline & \text{Test Nov.} & \text{Costed} \\ \hline & \text{Test Nov.} & \text{Test Nov.} \\ \hline & 12 & 110 & 9 & 53 \\ 0 & 43 & 0 & 50 \\ 0 & 66 & 0 & 33 \\ 1 & 33 & 0 & 34 \\ 1 & 1 & 64 & 0 & 52 \\ 0 & 66 & 0 & 33 \\ 1 & 33 & 0 & 34 \\ 0 & 66 & 0 & 33 \\ 1 & 133 & 0 & 34 \\ 0 & 66 & 0 & 33 \\ 1 & 133 & 0 & 34 \\ 0 & 61 & 0 & 60 \\ 0 & 25 & 0 & 25 \\ 0 & 25 & 0 &$	V CV-PP-240% V8 CVP+ Un	Odom         Ods ratio           0.44 (12.5)         1.62           0.44 (12.5)         1.62           0.44 (12.5)         1.62           0.45 (10.6)         3.64           0.55 (10.6)         3.64           0.56 (10.7)         2.44           0.57 (10.3)         1.70	Weight (%)   60.69   4.41   4.22   2.27   4.26   3.10     4.31   3.87   3.18   	Shudy CV-FD-380% LUBERATE EMPROVE TRANSFORM MMACT REACH STELVIO Heterogeneity, I <sup>*</sup> Test of 0: - 9, 0( CV/FI Unknown VENT EU-VENT Belaiver VENT Heterogeneity, I <sup>*</sup> Test of 0: - 9, 0( Overall Heterogeneity, I <sup>*</sup> Test of 0: - 9, 0( CVENT	Di Di Constanti de la constant	leath by CV Control (res No 1 61 0 47 0 32 1 49 1 32 0 34 1 40 83 3 84 3 57 0 25 1.00 .53 1.00 .53 Fave = 0.24, p = 0.6 cold	√FD=80% vs CV/FLuike	Oddin ratio Oddin ratio 0 0 0 ratio 0 0 rati	

# Figure 7:

Forest Plots comparing ADR between CV + and CV – group. A: pneumothorax, B: Pneumonia, C: Acute exacerbation of COPD (AECOPD) D: Respiratory failure, E: Hemoptysis, F: Death

# Table 1:

#### Summary of Clinical outcomes for EBV in Trials (Intention to treat analysis)

		Physiologic parameters (presented as difference between groups, except TLC)				ted as ept TLC)	Functional parameters					
Trials	HE/ HO & CV-/ CV+	Year	Follow- up in months	N	Trial Type	Post-BD FEV1 percent improvement	RV improvement in milliliters (ml)	TLC reduction in EBV patients in ml	6MWD improvement in meters	SGRQ	BODE index	
Zephyr valves												
LIBERATE	HE/C V-	2018	12	190	Multicenter Randomized Control trial (RCT)	17.6%	522	1142	39.31	-7.05	-1.2	
TRANSFORM	HE/C V-	2017	3	97	Multicenter RCT	29.3%	670	1090	78.7	-6.5	-1.75	
IMPACT	HO/ CV-	2016	3	93	Multicenter RCT	16.9	480	NA	40	-7.6	-1.16	
STELVIO	HO/ HE/C V-	2015	6	68	Single Center Prospective RCT	17.8%	NA	1366	74	-14.7	NA	
BeLiever-HiFi	HE	2015	3	50	Single center, double blind RCT	5.89 %	180	NA	22	-0.83	NA	
EU-VENT ^	HE	2012	6	171	Multicenter RCT	20%	NA	50%	24%	-5.3 NS	NA	
VENT^	HE	2010	6	321	Multicenter RCT	6.8%	NA	NA	20	-3.4	NA	
Spiration Valve	s											
EMPROVE	HE	2019	6	172	Multicenter RCT	NA 101 ml	361	974	6.9 NS	-13	NA	
REACH	HE	2019	6	107	Multicenter unblinded RCT	15.2%	370	757	36.4	-10.5	NA	

HE- heterogenous emphysema distribution, HO- homogenous emphysema distribution, CV- Collateral ventilation, FEV<sub>1</sub>- Forced expiratory volume in 1 second, RV = residual volume, TLC- total lung capacity, 6MWD- 6-minute walk distance, SGRQ- St. George's respiratory Questionnaire, NS = not significant.