Cost-Effectiveness of Endobronchial Valve Therapy for Severe Emphysema: A Model-Based Projection Based on the VENT Study

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Key Words

Chronic obstructive pulmonary disease · Cost-effectiveness · Emphysema · Endobronchial valve therapy · Germany · Lung volume reduction

Abstract

Background: Endobronchial valve (EBV) therapy is an innovative treatment that has been shown to be safe and effective in selected subgroups of patients with severe emphysema. **Objectives:** The objective of our study was to assess the cost-effectiveness of EBV therapy compared to the medical management of patients with high heterogeneity, complete fissures and lobar exclusion in the context of the German health-care system. **Methods:** Clinical data from a subset of VENT (Endobronchial Valve for Emphysema Palliation Trial) provided information about clinical events, health-related quality of life, and disease staging for 12 months. This information was subsequently used to project long-term disease progression, mortality, and health resource utilization. We computed the 5- and 10-year incremental cost-effectiveness ratio (ICER) in euros per quality-adjusted life year (QALY). Costs and effects were discounted at 3% per year. **Results:** EBV therapy led to clinically meaningful disease re-staging at 12 months (37.8% of the cohort improved staging,

compared to 0% in the controls). Over 5 years, EBV therapy was projected to increase survival from 66.4 to 70.7%, and to add 0.22 QALYs. Costs were estimated to increase by EUR 10,299, resulting in an ICER of EUR 46,322 per QALY. Over 10 years, 0.41 QALYs were gained at an additional cost of EUR 10,425, yielding an ICER of EUR 25,142 per QALY. **Conclusions:** Our model-based analysis suggests that EBV therapy leads to clinically meaningful changes in disease staging and progression when compared to medical management, with resulting gains in unadjusted and quality-adjusted life expectancy. Our results indicate that EBV therapy is cost-effective in the German health-care system.

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Introduction

Emphysema is a highly prevalent and debilitating condition that constitutes a substantial subset of chronic obstructive pulmonary disease (COPD). It is associated with a significantly reduced quality of life and life expectancy as well as with increased health-care resource utilization. Medical management of emphysema is well established, but its ability to modify disease progression is limited.

In recent years, endobronchial valve (EBV) therapy has seen increasing adoption as a minimally invasive and reversible treatment approach that can – in selected subsets of patients – provide benefits that are comparable to those previously demonstrated for lung volume reduction surgery (LVRS).

The safety and effectiveness of EBV therapy were evaluated in VENT (Endobronchial Valve for Emphysema Palliation Trial), a multicenter, prospective, randomized, controlled study conducted at 31 clinical sites in the United States and 23 sites in Europe. The study demonstrated that unilateral lobar volume reduction using EBV is safe and clinically superior to optimal medical management [1–3].

The cost-effectiveness of LVRS has been evaluated in several model-based projections that assessed the 5- and 10-year cost-effectiveness of LVRS compared to medical management [4, 5]. Other model-based analyses have been performed to evaluate the cost-effectiveness of pharmaceutical and other interventions for the treatment of COPD, usually taking a lifetime perspective as the basis for their assessments [6–8].

However, no cost-effectiveness analysis of endobronchial lung volume reduction techniques has yet been performed. Our aim, therefore, was to assess the longer-term cost-effectiveness of EBV therapy compared to medical management.

We chose the German health-care system as the setting for this analysis because of its general relevance as the largest health-care system in Europe and the comprehensive experience with EBV therapy in this country.

Materials and Methods

Study Design

For our analysis, we developed a two-tiered approach. The first tier employs VENT study data from valve-treated patients meeting current guideline-recommended inclusion criteria and from matched control patients for the initial 12 months after treatment. The second tier consists of a model-based projection of disease progression through 10 years, based in significant part on a previously published and validated COPD health-economic model for Germany [7]. The model takes into account study-reported clinical events for year 1, and projects clinical events based on disease staging and disease progression for years 2–10. Disease staging, mortality, quality-adjusted life years (QALYs), and costs are computed for each 3-month period.

Therapy-related and clinical event costs for year 1 were obtained from 2014 German diagnosis-related group (G-DRG) reimbursement rates. Cost estimates for years 2–10 were based on the assumptions of the previously published and validated model, plus any EBV-related additional costs [7].

Assumptions made in the base case analyses were assessed in deterministic and scenario-based sensitivity analyses. The analysis considered direct medical costs only; it did not include indirect or nonmedical costs associated with lost wages, time spent by patients in traveling and seeking medical care, or time spent by caregivers.

The analyzed subgroup encompassed 37 EBV-treated patients and 36 matched controls. The model-based disease progression from years 1 to 10 was directed by the observed 12-month (re)staging information in the treatment and control subgroups from the VENT study.

Model Structure and Modeling Framework

Our hybrid model relied on actual clinical events and quality-of-life information from the VENT study subgroup for the 1st year and a Markov model for years 2–10. Clinical data about observed restaging of the VENT subgroup at 12 months provided information for the GOLD staging that was used as the input for the Markov model. In turn, the Markov model followed the 2 simulated cohorts – EBV treatment and medical management (control) – from 5 and 10 years. The same model structure was used for both competing strategies, with a cycle length of 3 months.

Clinical events captured during the first 12 months after treatment included those events that were recorded as adverse events in the trial and occurred at least once in the 12-month follow-up period. Such events included COPD exacerbation with hospitalization; COPD exacerbation without hospitalization; respiratory failure requiring more than 24 h of ventilation treatment; pneumonia (excluding distal to implanted EBV); pneumonia distal to implanted EBV; pneumothorax/leak longer than 7 days; stable pneumothorax; migrations, expectorations, aspirations as a composite endpoint, and death.

The Markov model consisted of the following 4 disease states: GOLD stages II, III and IV, and death. In each of the GOLD stages, patients could suffer mild, moderate, or severe exacerbations during the cycle, or die. In GOLD stages II and III, they could also progress to the next higher GOLD stage (fig. 1). In addition, applicable valve removal events for the EBV cohort were considered.

The primary outcome measure was the incremental cost-effectiveness ratio (ICER), which was defined as the incremental direct costs of medical treatment divided by the incremental health benefits expressed as QALYs. Costs and health outcomes were discounted at 3% per year, in line with current guidelines for health-economic analysis [9]. All costs were actual or estimated amounts in EUR in 2014.

Input Parameters

EBV therapy has been demonstrated to induce lobar volume reduction, thus achieving the benefits of lung volume reduction without the associated morbidity and mortality of a surgical procedure. To achieve such a volume reduction, the valves require a closed system (i.e., lobar exclusion), with valves placed in all the segments of the lobe and complete fissures, which are considered a proxy for the lack of collateral ventilation [10]. In addition, heterogeneity – the difference in emphysema percentage between lobes in the treated lung – has been found to have an enhancing effect on clinical endpoints [2].

Clinical data for our analysis were obtained from a subgroup analysis of the VENT study that included patients from both the European and US cohorts of the study. In line with the currently

Fig. 1. Representation of the hybrid model structure. Year 1 is based on clinical data, and years 2–10 are based on the Markov model.

recommended selection algorithm for EBV therapy, the treatment groups used for this analysis were those patients with high heterogeneity (greater than or equal to the median of 15%), complete fissures isolating the target lobe, and lobar exclusion [11].

The combined European/US dataset included a total of 76 patients in the treatment arm who had complete fissures and high heterogeneity $\geq 15\%$. Applying the additional screening for patients who had successful lobar exclusion reduced the number of valve-treated subjects to 37.

The control group was similarly matched to this treatment group except for the lobar exclusion criterion, since these patients did not receive valves. A total of 36 patients met these criteria in the combined dataset, a number that closely correlated to the total number of 76 subjects in the treatment arm given the 2:1 randomization in the VENT study.

Table 1 shows the baseline patient characteristics. All other input parameters were derived from the published literature, including published statistics and databases. Patients selected with the currently used Chartis pulmonary assessment system correspond to these same criteria [12].

Therapy Effectiveness

Therapy effectiveness in year 1 was estimated through differences in mortality and observed changes in health-related quality of life at 6 and 12 months (see section on health-related quality of life, below). In years 2–10, therapy effectiveness was modeled by taking into account disease staging and restaging and consequent disease progression that influenced both survival and health-related quality of life. Of note, differences in therapy effectiveness between EBV patients and controls were based solely on the trial-demonstrated (re)staging at 12 months.

Therapy-induced benefits to the patient – such as increased survival and improved health-related quality of life in years 2–10 – were therefore conservatively accrued only through differences in overall staging and survival between the EBV and control

Table 1. Baseline characteristics of VENT subgroups (treatment and control)

Variable	EBV therapy (n = 37)	Control (n = 36)
Age, years	62.24 $\pm$ 7.25	62.08 $\pm$ 5.68
Male gender, n (%)	23 (62.2)	19 (52.8)
Body mass index	26.35 $\pm$ 3.18	25.98 $\pm$ 3.38
FEV ₁ , liters	0.84 $\pm$ 0.24	0.88 $\pm$ 0.31
FEV ₁ , % of predicted	28 $\pm$ 6	30 $\pm$ 8
Total SQRQ	51.4	52.7

groups. Meanwhile, disease progression was fully based on the transition probabilities of the previously validated and published COPD model (table 2) [7].

Costs

Costs were considered from the German statutory health insurance perspective, with only direct health-care costs considered. The costs of EBV implantation were based on the 2014 G-DRG reimbursement amount defined by the ICD-10-GM diagnosis code for emphysema, and on the procedure code(s) for EBV placement. In addition, costs included current 2014 add-on payments, which are paid according to the number of valves used. The model assumed an average usage of 3.08 valves per procedure, as determined on the basis of 2012 German nationwide utilization data.

Complications and clinical events during year 1 were assumed to require inpatient treatment, with costs based on the corresponding G-DRG amounts. Costs for stable disease were calculated as the product of stage-dependent costs and the average percentage

Table 2. Model input parameters

Variable	Base case	Reference	
Cohort characteristics			
Age	62	VENT subgroup data	
Male	58%		
Variable	EBV treatment	Control	Reference
<i>Actual clinical events: year 1</i>			
Death	2.7%	2.8%	VENT subgroup data
COPD exacerbation w/ hospitalization	35.1%	24.3%	
COPD exacerbation w/o hospitalization	81.1%	97.2%	
Respiratory failure <24 h on ventilation	2.7%	0%	VENT subgroup data (each event counted towards total percentage)
Respiratory failure >24 h on ventilation	0%	0%	
Pneumonia (excluding distal to EBV)	21.6%	8.3%	
Pneumothorax/leak >7 days	5.4%	0%	
Stable pneumothorax	2.7%	0%	
Valve removal	8.1%	0%	
Pneumonia distal to an implanted valve	5.4%	0%	
Total SGRQ			
Baseline	51.4	52.7	VENT subgroup data
6 months	44.3	54.7	
12 months	42.8	55.3	
GOLD staging at 12 months			
Stage II	13.5%	0%	VENT subgroup data
Stage III	51.4%	44.4%	
Stage IV	35.1%	55.6%	
Variable	Base case (range)	Reference	
<i>Disease progression and events: years 2–10</i>			
Transition probabilities (3 months)			
Stage II to III progression	0.30% (0.26–0.35)	[7], quitters	
Stage III to IV progression	0.69% (0.62–0.76)		
Event probabilities (3 months)			
Valve removal	3.7%	[2], for modeling purposes, assumed to cumulatively occur 2.5 years after procedure	
Mild exacerbation in stage II	8.16% (7.19–9.19)		
Mild exacerbation in stage III	14.51% (13.05–16.04)		
Mild exacerbation in stage IV	14.34% (13.32–15.40)	[7]	
Moderate exacerbation in stage II	18.38% (16.29–20.56)		
Moderate exacerbation in stage III	26.77% (24.05–29.58)		
Moderate exacerbation in stage IV	28.06% (26.20–29.95)		
Severe exacerbation in stage II	3.85% (3.39–4.35)	1.15*RR stage II, according to [14]	
Severe exacerbation in stage III	3.77% (3.35–4.23)		
Severe exacerbation in stage IV	4.86% (4.49–5.23)		
Relative mortality risk in stage II	4.0		
Relative mortality risk in stage III	4.6		
Relative mortality risk in stage IV	9.5		

Table 2 (continued)

Variable	Base case (range)	Reference
Utilities (years 2–10)		
Stage II, cycle w/o exacerbation	0.790 (0.770–0.809)	
Stage II, cycle w/ mild exacerbation	0.787	
Stage II, cycle w/ moderate exacerbation	0.770	
Stage II, cycle w/ severe exacerbation	0.759	
Stage III, cycle w/o exacerbation	0.750 (0.730–0.769)	
Stage III, cycle w/ mild exacerbation	0.747	[7]
Stage III, cycle w/ moderate exacerbation	0.731	
Stage III, cycle w/ severe exacerbation	0.721	
Stage IV, cycle w/o exacerbation	0.650 (0.590–0.708)	
Stage IV, cycle w/ mild exacerbation	0.647	
Stage IV, cycle w/ moderate exacerbation	0.634	
Stage IV, cycle w/ severe exacerbation	0.615	
<i>Costs, EUR (2014)</i>		
EBV placement		
DRG payment for valve placement	4,337.47	DRG E02C
Add-on payment/valve	1,702.60	Add-on payment
Average number of valves	3.08 (alternative scenario: 4.0)	German national utilization data, based on 2012 procedure codes
Year-1 event costs		
Respiratory failure >24 h on ventilation	2,507	DRG E64C
Pneumonia (excluding distal to EBV)	1,471	DRG E69E
Pneumothorax/leak >7 days	3,005	DRG E76C
Stable pneumothorax	3,005	DRG E76C
Pneumonia distal to implanted valve	3,454	DRG E77F
Direct medical costs per 3-month cycle		
Direct costs in stable stage II	209 (157–267)	based on [7], includes [18–22]
Add. cost in cycle w/ mild exacerbation	10 (2–24)	based on [7], includes [18]
Add. cost in cycle w/ moderate exacerbation	45 (26–70)	based on [7], includes [19]
Add. cost in cycle w/ severe exacerbation	3,299 (2,287–4,493)	based on [7], includes [19, 23]
Direct costs in stable stage III	414 (350–483)	based on [7], includes [18–22]
Add. cost in cycle w/ mild exacerbation	25 (15–37)	based on [7], includes [18]
Add. cost in cycle w/ moderate exacerbation	60 (39–83)	based on [7], includes [19]
Add. cost in cycle w/ severe exacerbation	3,508 (2,490–4,697)	based on [7], includes [19, 23]
Direct costs in stable stage IV	486 (412–568)	based on [7], includes [18–22]
Add. cost in cycle w/ mild exacerbation	23 (14–35)	based on [7], includes [18]
Add. cost in cycle w/ moderate exacerbation	59 (38–82)	based on [7], includes [19]
Add. cost in cycle w/ severe exacerbation	3,750 (2,726–4,933)	based on [7], includes [19, 23]
w/ = With; w/o = without. *Relative risk.		

of patients in each stage, where the latter was computed as the average percentage of the cohort in each stage, based on baseline and 12-month data from the trial cohorts [7].

For years 2–10, costs for each 3-month cycle were computed according to the respective staging at that time point and stage-dependent direct medical costs, plus additional direct medical costs incurred for each mild, moderate, or severe exacerbation. In addition, information reported about the posttrial period of the VENT study was used to estimate and include any costs that may be associated with valve removal in the period beyond 12 months [2].

Mortality and Health-Related Quality of Life

Age- and gender-specific baseline mortality rates were based on the 2007/2009 life tables for Germany [13]. GOLD-stage-specific relative mortality risks were applied to the baseline mortality rates to obtain stage-specific mortality rates for use in the model (table 2). Because the previously published model assumed the same relative mortality risk for stage III and IV patients, which does not reflect latest clinical evidence, we adjusted the stage III relative mortality risk to a lower value while maintaining the previously used stage II and stage IV relative risks [14].

Table 3. Health outcomes and incremental cost-effectiveness results at 5 and 10 years

	Costs, EUR			Effects, QALYs			ICER, EUR/ QALY
	EBV	control	difference	EBV	control	difference	
Base case, 5 years	20,734	10,435	10,299	2.88	2.66	0.22	46,322
Base case, 10 years	25,857	15,432	10,425	4.43	4.02	0.41	25,142

Utility estimates were derived as follows. During the first 12 months, trial-collected St. George Respiratory Questionnaire (SGRQ) scores were used to estimate utility scores. Baseline, and 6- and 12-month SGRQ scores were converted to EQ-5D utility weights using an established mapping algorithm [15]. In line with documented clinical experience in this population, we assumed no quality-of-life benefit between the EBV and control groups for the 1st month, and then for months 2–6 the difference observed at 6 months, and for months 6–12 the average of the differences recorded at 6 and 12 months [12]. For projections from years 2–10, GOLD-stage-dependent utility weights were used that were further differentiated depending on whether patients experienced an exacerbation during the corresponding 3-month cycle.

Analysis of Uncertainty

Comprehensive one- and multi-way sensitivity analyses were conducted to evaluate the effects of parameter uncertainty, including variations in the EBV therapy-related inputs. The parameter ranges were derived from prior published data, from the previously published COPD model used in this analysis, and from expert opinion where applicable (table 2).

Results

Base Case Results

Analysis of the 12-month data from the VENT subgroup showed a higher incidence of events in the EBV cohort than in the medically managed cohort (table 3). However, these differences related primarily to the 6-month period immediately following treatment. One year after treatment, mortality was similar between the treatment and control groups.

Substantial differences were observed between the GOLD staging of the two cohorts. While patients in the control group either remained at their baseline stage or progressed to the next higher GOLD stage, 37.9% of patients in the EBV group improved by one stage (13.5% from GOLD III to II; 24.4% from GOLD IV to III). Correspondingly, SGRQ scores in the control group worsened from 52.65 at baseline to 55.34 at 12 months – indicating a decline in quality of life – whereas the scores for the treatment group improved from 51.44 at baseline to

44.26 at 6 months, and 42.79 at 12 months. Using the SGRQ to EQ-5D mapping algorithm, and considering mortality, the year-1 gain associated with EBV treatment totaled 0.11 QALYs.

Using the 12-month staging and survival information for each cohort as input to the model projections for years 2–10, the 5-year survival rate for the EBV cohort was 70.7%, while the rate for the control cohort was 66.4%. Over 10 years, projected survival for the EBV cohort was 39.9%, compared to 33.7% in the control cohort.

In addition to improved survival, the GOLD staging at 5 years for the EBV cohort was projected to be markedly lower than for the control cohort, with 10.2% at stage II (vs. 0% in the control group), 35.8% at stage III (vs. 28.6%), and 24.7% at stage IV (vs. 37.8%). Figure 2 shows the projected disease progression for both cohorts over the full 10-year time horizon by GOLD stage.

At 5 years, the undiscounted QALYs totaled 3.09 for the EBV cohort and 2.85 for the control cohort, resulting in a total incremental gain of 0.24 QALYs for the treatment cohort. At 10 years, the undiscounted QALY gains were 5.02 for the treatment cohort and 4.55 for the control cohort, for a gain of 0.47 (table 3 shows the discounted QALYs for both time frames).

Based on the average use of 3.08 valves per procedure, the initial costs of EBV placement were EUR 9,581 per patient. Over the 5-year horizon, the total undiscounted costs for the EBV cohort were EUR 21,478 per patient, and for the control cohort they were EUR 11,180, for a difference of EUR 10,298. The resulting 5-year discounted ICER was EUR 46,322 per QALY gained (EUR 43,647 per QALY undiscounted). Over 10 years, total undiscounted costs were EUR 27,841 for the EBV cohort and EUR 17,383 for the controls, for a difference of EUR 10,458. The 10-year discounted ICER was EUR 25,142 per QALY gained (EUR 21,920 per QALY undiscounted).

Uncertainty Analyses

The cost-effectiveness projections were found to be robust across a wide range of assumptions, including varia-

Fig. 2. Percent of patients in GOLD stages II, III, and IV, or dead for the EBV and control cohorts. Year 1 is based on actual VENT data; the following years are based on model projection.

Table 4. Sensitivity analyses: key scenarios and corresponding ICERs at 5 and 10 years

Scenario	ICER, EUR/QALY	
	5 years	10 years
Base case (discounted)	46,322	25,142
Base case (undiscounted)	43,647	21,920
High number of valves (4/procedure)	53,367	28,920
High pneumothorax rate year 1 (25%)	48,549	26,337
High number of valve migrations/expectorations/aspirations year 1 (14.1%)	45,944	24,940
100% male	44,702	24,582
100% female	49,290	26,873

tions in cost-relevant adverse event rates, gender, and the number of valves used. Use of an average of 4 valves per procedure, as opposed to the German national average of 3.08, increased the 5- and 10-year ICERs to EUR 53,367 and 28,920 per QALY gained, respectively. Table 4 provides an overview of the most relevant scenario results, including the discounted ICERs at 5 and 10 years. The full range of scenario analyses is provided in online supplementary table 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000368088).

Discussion

Our results indicate that EBV placement – when used in the recommended patient population presenting with high heterogeneity and complete fissure (absence of col-

lateral ventilation) [11] as well as procedurally accomplished lobar exclusion – may be a cost-effective strategy when compared to other, well-accepted medical treatments with an ICER below the commonly accepted threshold of EUR 50,000 per QALY over a wide range of assumptions and follow-up time frames. EBV placement seems to offer substantive value over time, despite the upfront costs of valves and valve placement.

This value results from gains in health-related quality of life, documented by the trial-reported SGRQ scores during the first 12 months, and evidenced by clinically meaningful restaging observed at 12 months. In turn, this restaging at 12 months resulted in projected gains in quality of life and increased survival in subsequent years. Higher upfront costs for the EBV cohort – related to the costs of valve implantation and treatment of postprocedural events – are partly compensated by savings in the

subsequent years that result from lower annual treatment costs than for the control cohort.

The projected 5-year survival rates for the EBV and control cohorts of around 63–68% are in line with the findings of a recent cohort study that investigated GOLD-stage-dependent survival over periods of up to 5 years [14] and with the findings of the National Emphysema Treatment Trial (NETT) [16], confirming the overarching validity of our model-based projections.

While the results of cost-effectiveness analyses commonly cannot be compared directly between studies for a variety of reasons – including differences in the characteristics of the studied cohorts as well as differences in the comparators and health-care systems studied – it is nevertheless worthwhile to place the obtained results in perspective with findings of other recent cost-effectiveness analyses of COPD treatments.

The projected EBV-associated 5-year gain of 0.24 QALYs (undiscounted) obtained in this study is higher than the QALY gains estimated in recent analyses of pharmaceutical interventions, but lower than the gains projected for continuous oxygen therapy and lung transplantation. Specifically, the multinational economic analysis of the TORCH (Towards a Revolution in COPD Health) study showed a 3-year gain of 0.081 QALYs for combination treatment with salmeterol/fluticasone propionate compared to placebo [17]. Over a 4-year time horizon, tiotropium – when compared to usual care – was found to add 0.052 QALYs [18]. Use of the once-daily maintenance bronchodilator indacaterol, when compared to tiotropium and salmeterol regimens, was found to add 0.008 QALYs over a 3-year time horizon [19]. Continuous oxygen therapy, in a US-based analysis, was found to add 0.59 QALYs over a 5-year horizon compared to nocturnal oxygen therapy [20]. Lung transplantation, when compared to conventional therapy, was estimated to add 0.51 QALYs in a time frame of approximately 4 years [21], and 2.95 QALYs over the patients' lifetime [22].

The ICERs in these assessments ranged from dominating in the indacaterol analysis (a projected QALY gain at overall reduction in treatment cost), to being cost-effective with regard to the country-specific willingness-to-pay thresholds for the other studied pharmaceutical interventions and for continuous oxygen therapy and to being conditionally cost-effective in the lung transplantation analyses (transplantation considered cost-effective only in a subset of the studied populations, but not cost-effective in the remainder of the populations). The ICER obtained in our EBV analysis therefore falls within the same general range as the ICERs of re-

cently studied advanced pharmaceutical treatments for COPD, and compares favorably to cost-effectiveness projections of lung transplantation.

Our study is subject to a number of limitations. First, as in any model-based health-economic projection, long-term clinical effectiveness and cost-effectiveness were estimated based on short-term clinical data; actual long-term effectiveness of EBV therapy may vary. However, model-based projections are common practice in the health-economic evaluation of chronic conditions. Our projected time frames of 5 and 10 years are shorter than the lifetime horizons assumed in most cost-effectiveness analyses of COPD interventions [7, 8] and are in line with the time frames evaluated in the NETT cost-effectiveness analysis [5]. As is documented by the reduction in EBV-related ICERs between the 5- and 10-year time horizons, the use of even longer time frames would have further improved the health-economic profile for EBV therapy, but would not have changed the finding that EBV therapy is a cost-effective treatment strategy.

Second, our assumption that a difference in GOLD staging at 12 months is the only factor influencing disease progression in the remainder of the model – and therefore a measure of treatment effectiveness – might not fully reflect the spectrum of actual disease progression that may be observed. On the one hand, the assumption is probably overly conservative. Specifically, the differences in modelled EQ-5D utility weights (health-related quality of life) between the EBV and control cohorts is consistently less than 0.02 during years 2–10, as compared to a substantially more pronounced difference in health-related quality of life observed at 6 and 12 months in the VENT study subgroup.

Further, evidence from the NETT study suggests that the 12-month difference in quality of life between LVRS patients and controls was maintained or only gradually declined through year 5 [23]. This suggestion is supported by the reported 5-year discounted QALY gain of 0.26 between the overall LVRS and control cohorts in the NETT study cost-effectiveness analysis [5], which is higher than the QALY gain of 0.22 found in our study. The higher QALY gains found in the NETT study appear in spite of the comparatively lower gain in SGRQ scores at 12 months in that study compared to the VENT subgroup. Higher QALY gains over the 5-year period for the EBV cohort would have resulted in a lower ICER and thus a more favorable health-economic profile. The same holds true for our 10-year projections.

On the other hand, our assumption about disease progression might be optimistic. Disease progression in

EBV-treated patients might differ from the progression that has been documented in patients with 'native' disease staging. For example, it is unknown how valve-induced tensions might affect emphysematous tissue in neighboring lobes, and whether there is a possibility they could in some patients contribute to accelerated loss of lung function in the longer term. Further, there are insufficient long-term clinical data to demonstrate that downstaging confers a long-term survival benefit to valve-treated patients.

Third, our model is a simplified representation of actual disease progression that may not always reflect the full spectrum of possible disease pathways. Specifically, for year 2 and the following years, any disease-related complication is subsumed under either mild, moderate, or severe exacerbation – with the exception of considered valve removals – assuming that treatment of these exacerbations is similar for EBV-treated and medically managed patients. Late pneumothorax, infection requiring valve removal, or loss of atelectasis are not considered in the model as there is currently little evidence documenting the occurrence of these events.

Fourth, our analysis considers direct medical costs only. Inclusion of indirect costs – which are included in some policy models evaluating COPD strategies – would only make the incremental cost-effectiveness of EBV therapy more favorable. Similarly, our analysis does not take into account potential productivity gains that may be associated with the EBV treatment-related improvement in disease severity.

Fifth, our model does not take into account costs of potential screening, diagnostic procedures, or pulmonary rehabilitation. While these costs would increase overall treatment costs, they would not influence the incremental analysis as they would apply to both the EBV cohort and the control cohort.

Finally, our model is subject to a number of additional limitations stated by the authors of the underlying projection model [7]. Specifically, some of the disease progression probabilities are based on international data as opposed to German data only. Further, the transition probabilities do not account for different phenotypes of patients, but rather use general probabilities estimated for COPD patients that meet the respective GOLD stage criteria.

In summary, our findings suggest that EBV treatment in patients selected by current treatment algorithms is associated with clinically meaningful gains in health-related quality of life and survival, and offers a cost-effective treatment strategy in the German health-care system compared to medical management.

Financial Disclosure and Conflicts of Interest

Dr. Pietzsch is president, CEO, and shareholder of Wing Tech Inc., a technology consulting firm focusing on early-stage assessment of medical technologies. Wing Tech Inc. received consulting fees from Pulmonx Inc. to develop the health-economic model used in this analysis. Abigail Garner worked as a consultant for Wing Tech Inc. on this project. Felix J.F. Herth received lecture fees from Pulmonx Inc.

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