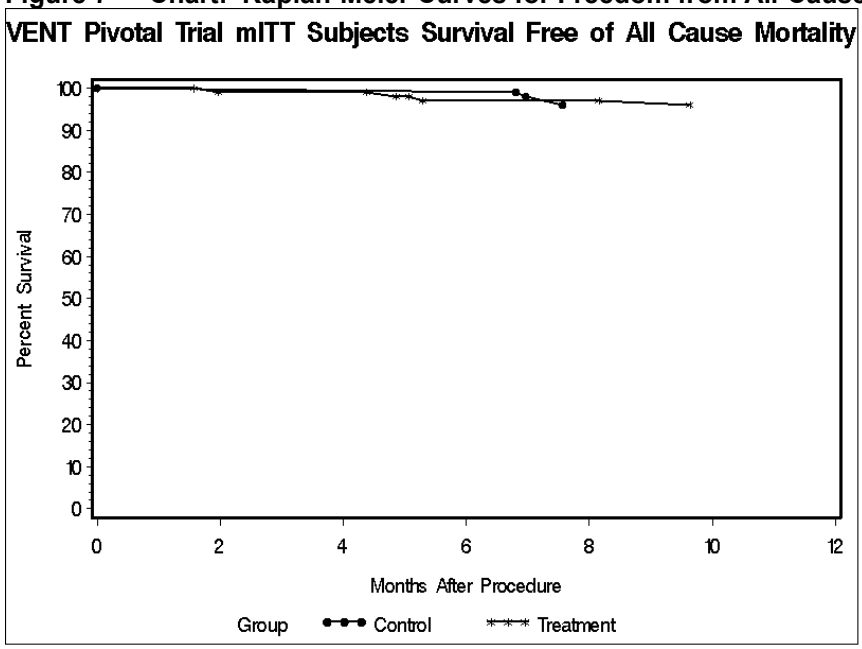
and 3 (3.5% of 87) deaths in the Control Subjects. There was no difference in the survival curves for the Control Subjects and Zephyr EBV Subjects (96.3% and 96.0% freedom from all-cause mortality respectively, p = 0.8763, log rank test).

Table 47 Survival Estimates and 95% Confidence Limits through 1 Year for Zephyr EBV and Control Subjects (M-ITT)

Treatment Group	Month	Subjects Remaining	Proportion Surviving	Lower 95% CL	Upper 95% CL
Control	0	87	1	--	--
	1	87	1	--	--
	3	84	1	--	--
	6	84	1	--	--
	12	42	0.9625	0.9209	1.0000
Zephyr EBV	0	214	1	--	--
	1	212	1	--	--
	3	202	0.9904	0.9772	1.0000
	6	194	0.9706	0.9475	0.9937
	12	115	0.9603	0.9333	0.9873

Source: Attachment 3, Amended Statistical Analysis Report, Table 17:4

Figure 7 Chart: Kaplan-Meier Curves for Freedom from All-Cause Mortality



Source: Attachment 3, Amended Statistical Analysis Report, Figure 17:2

9.3.2 Cox Regression Analysis of MCCs through Six Months

A multivariate Cox regression was performed to evaluate the impact of relevant covariates on the rate of occurrence of at least one MCC through 6 months. While there

was a trend towards a greater likelihood for MCCs at 6 months in the Zephyr EBV Subjects (hazard ratio 3.0, 95% CI = 0.7 to 13.1), this trend was not significant (p = 0.1437).

9.3.3 MCCs by Time Period through 1 Year

The rate of occurrence of MCCs during the second 6 months of follow-up demonstrated an equivalent rate of MCCs in Control Subjects (4.6%) compared with Zephyr EBV Subjects (4.7%). Control Subjects had a 3.5% mortality rate during this period compared with Zephyr EBV Subjects (0.9%). No subjects had empyema or massive hemoptysis. Pneumonia distal to a valve occurred in 2.8% of Zephyr EBV Subjects. One Zephyr EBV Subject had a pneumothorax lasting more than 7 days, and there was an equivalent rate of prolonged respiratory failure, 1.2% in Control Subjects and 0.9% in Zephyr EBV Subjects.

Table 48 Major Complication Composite for First and Second 6-Month Time Periods

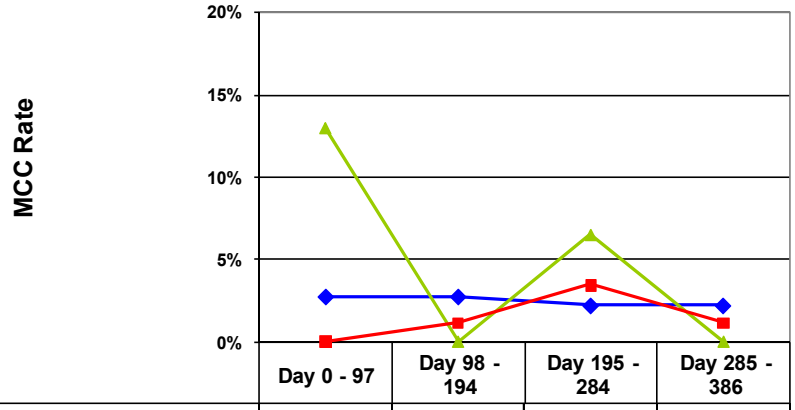
	0 – 194 Days		195 – 386 Days	
MCCs by Time Period	**Control % (n / N)**	**Zephyr EBV % (n / N)**	**Control % (n / N)**	**Zephyr EBV % (n / N)**
MCCs	1.2% (1 / 87)	6.1% (13 / 214)	4.6% (4 / 87)	4.7% (10 / 214)
Death	0.0% (0 / 87)	2.8% (6 / 214)	3.5% (3 / 87)	0.9% (2 / 214)
Empyema	0.0% (0 / 87)	0.0% (0 / 214)	0.0% (0 / 87)	0.0% (0 / 214)
Massive hemoptysis	0.0% (0 / 87)	0.5% (1 / 214)	0.0% (0 / 87)	0.0% (0 / 214)
Distal pneumonia	--	1.4% (3 / 214)	--	2.8% (6 / 214)
Pneumothorax	1.2% (1 / 87)	1.4% (3 / 214)	0% (0 / 87)	0.5% (1 / 214)
Respiratory failure > 24 hours	1.2% (1 / 87)	1.9% (4 / 214)	1.2% (1 / 87)	0.9% (2 / 214)

Source: Attachment 3, Amended Statistical Analysis Report, Tables 16:10 & 16:11

9.3.4 MCCs by Valve Removal Status through One Year

The MCC rates in the Treatment with No Valve Removals group and the Treatment with Valve Removals group decline through the one-year follow-up (see Figure 8). The overall decline in MCC rates appears to be independent of valve removals. The Zephyr EBV Treatment Subjects experienced MCCs at the same rate as Control Subjects in the second, six-month period.

Figure 8 Chart: MCC Rates by Valve Removal by Quarter



	Day 0 - 97	Day 98 - 194	Day 195 - 284	Day 285 - 386
Tx- No Removals, n=183	2.7%	2.7%	2.2%	2.2%
Tx With Removals, n=31	12.9%	0.0%	6.5%	0.0%
Control, n=87	0.0%	1.2%	3.5%	1.2%

Source: Attachment 3, Amended Statistical Analysis Report, Figure 19:3

9.4 Summary: Primary Safety Outcome

At 6 months of follow-up, Control Subjects had a 1.2% (1 / 87) rate of MCCs compared to Zephyr EBV Subjects who had a 6.1% (13 / 214) rate of MCCs, a difference that was not significant (p = 0.0748, Fisher's exact test). This difference was primarily driven by a trend to greater 6 month mortality in the Zephyr EBV Subjects with 6 deaths: 3 from respiratory failure, one from cancer, one from ischemic colitis and 1 from massive hemoptysis, of which only the death from hemoptysis was related to the device.

All-cause mortality over 12 months was equivalent for the two groups: 3.5% for the Control Subjects and 3.7% for the Zephyr EBV Subjects (p = 0.8763, log rank test).

In the second six months of follow-up, the MCC rate in Zephyr EBV Subjects (4.7%) and the MCC rate in Control Subjects (4.6%) were almost identical. Over all 12 months of follow-up, the MCC rate for Control Subjects (4.6%) and for Zephyr EBV Subjects (10.3%) were not significantly different (p = 0.1724, Fisher's exact test).

A Cox regression analysis was done to evaluate the impact of covariates on the occurrence of at least one MCC in the 180 day window. No covariates survived the final model and Zephyr EBV Treatment was not significantly associated with MCC at 6 months (p = 0.1437).

The Primary Safety Outcome—the rate of Major Complication Composite events at 6 months—was higher but not significantly so in the Zephyr EBV Subjects (6.1%) compared with Control Subjects (1.2%, p = 0.0748).

10.0 ADDITIONAL PRE-SPECIFIED ANALYSES

10.1 Introduction

A variety of pre-specified analyses were performed for effectiveness and safety outcome measures, as well as several subgroup analyses. These include:

10.2. Pre-Specified Outcome Analyses
- 10.2.1. Percent Change in Residual Volume
- 10.2.2. Percent Change in Diffusing Capacity
- 10.2.3. Change in Quality of Wellbeing
- 10.2.4. Change in BODE Index
- 10.2.5. Technical Success
- 10.2.6. Rehospitalization

10.3. Pre-Specified, Analysis-Plan-Generated Subgroup Analyses
- 10.3.1. Heterogeneity Score ≥ 15% FEV_1 and 6MWT Outcomes
- 10.3.2. Technical Success and FEV_1
- 10.3.3. Complete Fissure Integrity and FEV_1

10.4. Summary: Additional Pre-Specified Analyses

10.2 Pre-Specified Outcome Analyses

Additional pre-specified analyses on study outcomes included percent change in residual volume and diffusing capacity (DL_{CO}) and change in the BODE Index and the Quality of Well Being Scale using the CC population. The rates of rehospitalization were also analyzed.

10.2.1 Percent Change in Residual Volume

Residual volume was measured at baseline and at 180 day follow-up. There was no significant difference in the percent change in the Zephyr EBV Subjects (–1.3%) and the Control Subjects (+ 0.7%) (p = 0.40).

Table 49 Percent Change in Residual Volume

Residual Volume % Change from Baseline	Control Mean (SD) N Median (Min, Max)	Zephyr EBV Mean (SD) N Median (Min, Max)	Delta[1] (95% CI)	p value [2]
Completed Cases	0.69 (21.95) 74 −2.27 (−44.2, 124.7)	−1.29 (19.83) 176 −1.03 (−63.1, 65.8)	1.25 (−5.1, 3.64)	0.4051

[1] Difference of medians and non-parametric confidence interval
[2] One-sided Wilcoxon rank-sum test
Source: Attachment 3, Amended Statistical Analysis Report, Table 13:38

10.2.2 Percent Change in Diffusing Capacity

Diffusing capacity (DL_{CO}) was measured at baseline and at 180 day follow-up. There was no significant difference in the median percent change in the Zephyr EBV Subjects (+ 2.1%) and the Control Subjects (- 2.1%) (p = 0.14).

Table 50 Percent Change in Diffusing Capacity (DL_{CO})

Diffusing Capacity % Change from Baseline	Control Mean (SD) N Median (Min, Max)	Zephyr EBV Mean (SD) N Median (Min, Max)	Delta [1] (95% CI)	p value [2]
Completed Cases	−2.12 (17.45) 75 −1.69 (−85.6, 30.4)	1.81 (19.07) 178 1.05 (−46.8, 59.4)	2.74 (−2.31, 6.67)	0.1391

[1] Difference of medians and non-parametric confidence interval
[2] One-sided Wilcoxon rank-sum test
Source: Attachment 3, Amended Statistical Analysis Report, Table 13:38

10.2.3 Change in Quality of Wellbeing

The Quality of Wellbeing (QWB) instrument was assessed at baseline and at 180 day follow-up. There was no measurable difference in the QWB scales between the Completed Cases Zephyr EBV Subjects and Control Subjects.

Table 51 Quality of Well Being Scale

QWB Scale Change from Baseline	Control Mean (SD) N Median (Min, Max)	Zephyr EBV Mean (SD) N Median (Min, Max)	Delta [1] (95% CI)	p value [2]
Completed Cases	−0.02 (0.10) 71 −0.01 (−0.3, 0.3)	−0.01 (0.11) 173 0.00 (−0.4, 0.2)	0.01 (−0.01, 0.04)	0.1696

[1] Difference of medians and non-parametric confidence interval
[2] One-sided Wilcoxon rank-sum test
Source: Attachment 3, Amended Statistical Analysis Report, Table 13:38

10.2.4 Change in BODE Index

The BODE Index was assessed at baseline and at 180 day follow-up. The BODE Index significantly improved (0.21 score point reduction) in the Zephyr EBV Subjects compared to the worsened results (0.32 score point increase) in the Control Subjects (p = 0.0024).

Table 52 Change in BODE Index

	Control Mean (SD) N Median (Min, Max)	Zephyr EBV Mean (SD) N Median (Min, Max)	Delta [1] (95% CI)	p value [2]
BODE Index Change from Baseline	0.32 (1.07) 59 0.00 (−3.0, 3.0)	−0.21 (1.25) 160 0.00 (−4.0, 3.0)	−0.0 (−1.00, −0.00)	**0.0024**

[1] Difference of medians and non-parametric confidence interval
[2] One-sided Wilcoxon rank-sum test
Source: Attachment 3, Amended Statistical Analysis Report, Table 13:38

10.2.5 Technical Success

Technical Success, defined for Zephyr EBV Subjects only, required target lobe exclusion confirmed clinically and by HRCT scan at 6 months. Of the 194 imaging-evaluable Zephyr EBV Subjects at 6 months, 56.2% (109 / 194, 95% CI 48.9, 63.3%) demonstrated HRCT-confirmed exclusion of the target lobe by the Zephyr EBV devices at 6 months. The failure modes for the 85 subjects with HRCT-determined Technical Failure are tabulated below.

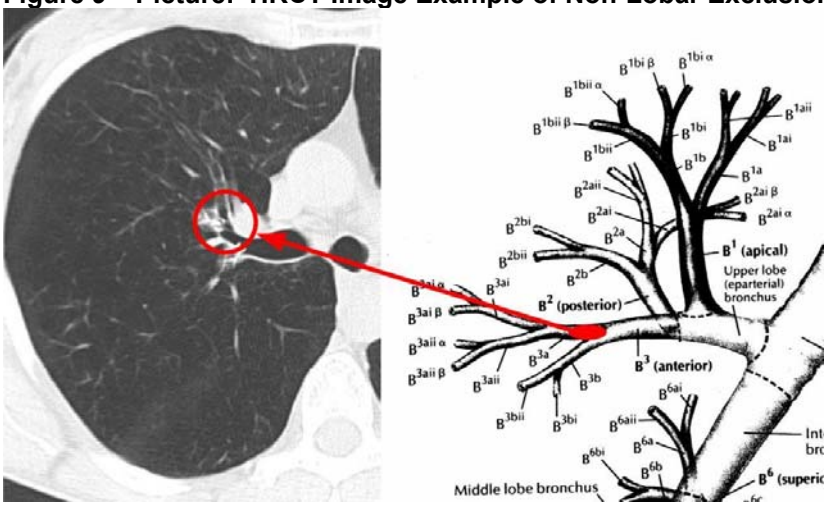
Table 53 Reasons for Incomplete Lobar Exclusion on 180 Day HRCT

Zephyr EBV Group		**% (n)**
HRCT (180 Day) Determined Incomplete Lobar Exclusion		100.0% (85)
Occurring at procedure and determined by site	Segment too small for valve	3.5% (3)
	Unable to place valve	4.7% (4)
	Side branch airway too small	1.2% (1)
	Unable to valve apical segment	2.3% (2)
Occurring at procedure and determined by HRCT	Valve(s) in place but not fully occlusive	78.8% (67)
Occurring post-procedure due to migration, expectoration or removal	Valve(s) removed and not replaced	4.7% (4)
	Valve(s) migrated, removed and not replaced	2.3% (2)
	Valve(s) expectorated and not replaced	2.3% (2)

Source: P070025, September 21, 2007, Volume 011, Page 103

Figure 9 demonstrates the most common reason for Technical Failure, which is a valve which is in place but not fully occlusive. Here, the valve target is RUL B3, but the distal end of valve is in B3a leaving B3b exposed.

Figure 9 Picture: HRCT Image Example of Non-Lobar Exclusion (Technical Failure)



Source: Core Radiology Lab HRCT Images.

10.2.6 Rehospitalization

The rates of rehospitalization for any cause through 6 months of study follow-up were 16.1% (14 / 87) of Control Subjects and 27.1% (58 / 214) of Zephyr EBV Subjects (p = 0.0522). From the 6-month follow up to 1 year, Control Subjects had a 12.6% (11 / 87) rate of rehospitalization versus 19.6% (42 / 214) for Zephyr EBV Subjects (p = 0.1823).

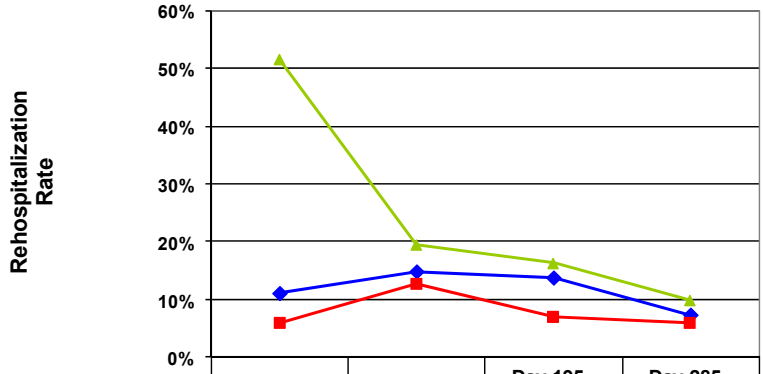
Table 54 Rehospitalization Rates through 6 and 12 Months

Rehospitalization	Control Subjects % (n / N)	Zephyr EBV Subjects	Risk Ratio (95% CI)	p value [1]
Through 6 Months	16.1 (14 / 87)	27.1 (58 / 214)	1.7 (1.0, 2.9)	0.0522
From 6 to 12 Months	12.6 (11 / 87)	19.6 (42 / 214)	1.6 (0.8, 2.9)	0.1823

[1] Two-tailed Fisher's exact test
Source: Attachment 3, Amended Statistical Analysis Report, Table 18:9

Rehospitalization rates were higher in Zephyr EBV Subjects early in the follow-up, declining to a rate similar to Control Subjects in the fourth quarter after randomization. The chart below shows the rate of rehospitalizations by quarter, separating out the potentially confounding effect of valve removals. The higher Rehospitalization Rate in Zephyr EBV Subjects in the first quarter was associated with valve removals.

Figure 10 Chart: Per-Subject Rehospitalization Rates by Quarter



	Day 0 - 97	Day 98 -194	Day 195 - 284	Day 285 - 386
Tx - No Removals, n=183	10.9%	14.8%	13.7%	7.1%
Tx - With Removals, n=31	51.6%	19.4%	16.1%	9.7%
Control, n=87	5.8%	12.6%	6.9%	5.8%

Source: Attachment 3, Amended Statistical Analysis Report, Figure 19:1.

10.3 Pre-Specified, Analysis-Plan-Generated Subgroup Analyses

The VENT Pivotal Trial documents pre-specified a subgroup analysis on Technical Success, and for independent predictor variables which were retained in the multivariate model (see Section 4.5.6). These two remaining significant covariates were Heterogeneity Score and Fissure Integrity. All subgroup analyses are reported using the Completed Cases population.

10.3.1 Technical Success, FEV_1 and 6MWT Outcomes

Zephyr EBV Subjects with Technical Success (HRCT-confirmed target lobe exclusion at 6 months) had a greater mean percent change in FEV_1 at 6 months (9.4%) than those without Technical Success (0.1%) ($\Delta = 9.4\%$, $p = 0.0009$). Technical Success did not have a significant impact on percent change in 6MWT at 6 Months ($p = 0.6746$).

Table 55 FEV_1 and 6MWT: Treatment Group Only—Effect of Lobar Exclusion on % Change in Primary Outcomes 6 Months (CC)

CC Subjects	No Technical Success Mean (SD) N Median (Min, Max)	Technical Success Mean (SD) N Median (Min, Max)	Delta (95% CI)	p value
FEV_1 (%)	0.1 (14.9) 77 −1.3 (−38.3, 40.0)	9.4 (21.9) 100 5.5 (−28.7, 78.9)	9.4 [1] (3.9, 14.8)	**0.0009** [2]
6MWT (%)	3.3 (21.6) 77 3.0 (−53.9, 66.2)	5.2 (23.7) 99 3.9 (−83.3, 108.0)	0.9 [3] (−4.0, 6.9) [4]	0.6746 [5]

[1] Difference of means and unequal variance t-test confidence interval (9.4 - 0.1 = 9.4 due to rounding).
[2] One-sided unequal variance t-test
[3] Difference of medians
[4] Non-parametric confidence interval
[5] One-sided Wilcoxon rank-sum test
Source: Attachment 3, Amended Statistical Analysis Report, Table 13:33

10.3.2 Heterogeneity Score ≥ 15%, FEV_1 and 6MWT Outcomes

The Heterogeneity Score measured the difference in disease severity between ipsilateral lobes of the lung, calculated as the difference in percentage destruction (Density Score) as determined by HRCT. (Please refer to Section 4.6.4 for details). The median baseline value for Heterogeneity Score (15%) was chosen as the threshold for the high heterogeneity subgroup. Higher Heterogeneity as a predictor of Zephyr EBV treatment response is consistent with the hypothesized mechanism of action of lung volume reduction, which reduces non-ventilating space and increases the ventilation of the remaining healthy lung parenchyma. Subjects with High Heterogeneity have less destruction and thus more potentially expandable lung parenchyma in the non-treated lobe compared with subjects with less heterogeneous emphysema, and would tend to respond better.

In the pre-specified multivariate, mixed model analysis, Heterogeneity Score remained in both FEV_1 and 6MWT models.

Analysis of the co-primary effectiveness outcomes for study subjects with High Heterogeneity Scores (≥ 15%) revealed an improved response for unilateral Zephyr EBV treatment compared with all study subjects, consistent with the physiologic rationale of this treatment. The percent changes in the co-primary outcomes for the Completed-Cases High-Heterogeneity Subgroup were:

FEV_1: Controls: −2.2%: Zephyr EBV: +10.1% (Δ = +12.3%, $p < 0.0001$)
6MWT: Controls: −5.9%: Zephyr EBV: +7.3% (Δ = +14.4%, $p = 0.0003$)

Table 56 Subgroup Analysis: Percent Change in FEV_1 and 6MWT in High Heterogeneity Subgroup at 6 Months (CC)

High Heterogeneity Subgroup Analysis	Control Mean (SD) N Median (Min, Max)	Zephyr EBV Mean (SD) N Median (Min, Max)	Delta (95% CI)	p value
FEV_1 CC	−2.2 (11.3) 40 –4.2 (–21.0, 25.5)	10.1 (22.3) 91 7.5 (–38.3, 78.9)	12.3 [1] (6.5, 18.1)	**<0.0001** [2]
6MWT CC	–5.9 (21.9) 38 –7.6 (–54.9, 66.7)	7.3 (26.6) 90 6.8 (–83.3, 108.0)	14.4 [3] (6.3, 21.0) [4]	**0.0003** [5]

[1] Difference of means and unequal variance t-test confidence interval
[2] One-sided unequal variance t-test
[3] Difference of medians
[4] Non-parametric confidence interval
[5] One-sided Wilcoxon rank-sum test
Source: Attachment 3, Amended Statistical Analysis Report, Table 25:11

10.3.3 Complete Fissure Integrity and FEV_1

Fissure Integrity was assessed by HRCT as a radiological proxy for interlobar collateral airflow. Completeness of the interlobar fissure as a predictor of Zephyr EBV treatment response is consistent with the hypothesized mechanism of action of lung volume reduction, as a complete fissure would result in greater volume reduction in the treated lobe due to isolation from unwanted collateral air movement.

In the pre-specified multivariate, mixed model analysis, Fissure Integrity remained as a significant interaction with Zephyr EBV treatment for % change in FEV_1 at six months.

The percent changes in FEV_1 for the Completed-Cases Complete Interlobar Fissure Subgroup were:

FEV_1: Controls: −2.7%: Zephyr EBV: +13.5% (Δ = +16.2%, $p < 0.0001$)

Table 57 Subgroup Analysis: Percent Change in FEV_1 by Fissure Integrity at 6 Months

% Change in FEV_1	Control Mean (SD) N Median (Min, Max)	Zephyr EBV Mean (SD) N Median (Min, Max)	Delta [1] (95% CI)	p value [2]
Complete Interlobar Fissure (CC)	–2.7 (10.2) 33 –3.7 (–21.0, 25.5)	13.5 (22.9) 68 9.5 (–28.7, 78.9)	16.2 (9.65, 22.76) [1]	**<0.0001**

[1] Difference of means and unequal variance t-test confidence interval
[2] One-sided unequal variance t-test
Source: Appendix 7-5-8, Statistical Analysis of the VENT Trial, Table 25:14

10.4 Summary: Additional Pre-Specified Analyses

Additional effectiveness analyses were performed for residual volume, diffusing capacity, Quality of Wellbeing and the BODE Index. Although Zephyr EBV Subjects trended higher in all these measures, only the BODE Index showed an improvement that was significant ($p = 0.0024$).

Technical Success (complete lobar exclusion by HRCT at 6 months) was achieved in 56.2% of Zephyr EBV Subjects, with the majority of Technical Failures (77.8%) occurring when one or more valves were found to be in place but not fully occlusive.

Rehospitalization rates through 6 months were 16.1% for Control Subjects and 27.1% for Zephyr EBV Subjects, a difference that bordered on significant ($p = 0.0522$). For the period from 6 to 12 months, this difference began to converge, with 12.6% for Control Subjects and 19.6% for Zephyr EBV Subjects. Most of this difference occurred during the first quarter of follow-up in subjects who required removal of one or more Zephyr valves.

Technical Success subjects had an FEV_1 improvement that was 9.4 percentage points higher in subjects with Technical Success compared with subjects with Technical Failure ($p = 0.0009$).

High Heterogeneity subjects demonstrated a substantially larger therapeutic benefit compared with the study population as a whole: FEV_1 improvement at 6 months was 12.3 percentage points higher ($p < 0.0001$), and 6MWT at 6 months was 14.4 percentage points higher ($p = 0.0003$), in High Heterogeneity Zephyr EBV Subjects compared with High Heterogeneity Control Subjects.

Subjects with Complete Fissure Integrity had an FEV_1 improvement that was 16.2 percentage points higher than subjects with Incomplete Fissure Integrity ($p < 0.0001$).

11.0 RESPONDER ANALYSES

11.1 Introduction

Responder analyses were performed on several effectiveness outcome measures to further explore the clinical importance of the observed changes. These further analyses were only performed on those outcome measures that had been found to be statistically significant on pre-specified hypothesis testing.

Responder analyses dichotomize the change in an outcome measure at a level of clinical importance and then compare the proportion of "clinically important" responders in each group. The level of clinical importance—often termed minimal clinically important difference, or MCID—is best established prior to the investigation, either based on empirically determined estimates or clinically accepted values, but when analyzed *post hoc*, MCIDs should be based on independent, empirically determined values whenever possible.

This type of analysis allows the clinician and patient to estimate the treatment effect that an individual is likely to experience. The analysis is quite similar to calculating odds ratios, relative rates and "number needed to treat". All four of these are well-established methods to analyze and convey anticipated clinical treatment effect for individuals for outcome measures that have already been established as statistically significantly improved.[25 - 30]

11.2. Responder Analyses: FEV_1
- 11.2.1. Subjects with Maintained FEV_1
- 11.2.2. High Heterogeneity Subjects with Maintained FEV_1
- 11.2.3. Subjects with ≥ 15% Improvement in FEV_1
- 11.2.4. High Heterogeneity Subjects with ≥ 15% Improvement in FEV_1

11.3. Responder Analyses: 6MWT
- 11.3.1. Subjects with Maintained 6MWT
- 11.3.2. High Heterogeneity Subjects with Maintained 6MWT
- 11.3.3. Subjects with ≥ 15% Improvement in 6MWT
- 11.3.4. High Heterogeneity Subjects with ≥ 15% Improvement in 6MWT

11.4. Responder Analyses: Other Effectiveness Outcome Measures
- 11.4.1. Subjects with ≥ 8 Point Improvement in SGRQ
- 11.4.2. Subjects with ≥ 1 Point Improvement in mMRC
- 11.4.3. Subjects with ≥ 10 Watt Improvement in Maximum Workload during Cycle Ergometry

11.4.4. Subjects with ≥ 1 Point Improvement in the BODE Index
11.5. Summary: Responder Analyses

11.2 Responder Analyses: FEV_1

Two pre-specified responder analyses for FEV_1 were performed using percentage change values: one with subjects who maintained FEV_1 without loss (i.e. change of ≥ 0%) and one with subjects who showed ≥ 15% improvement.

11.2.1 Subjects with Maintained FEV_1

The proportion of Completed-Cases Zephyr EBV Subjects with maintained FEV_1 (change from baseline ≥ 0%) at 6 months was 58.7% (105 / 179) compared with Control Subjects (41.3%, 31 / 75).

Zephyr EBV Subjects were 1.4 times more likely than Control Subjects to maintain their FEV_1 through 6 months of follow-up (95% CI 1.1 – 1.9).

Table 58 Responder Analysis: Subjects with Maintained FEV_1 (Increase ≥ 0%) at 6 Months (CC)

Increase ≥ 0% in FEV_1	Control % (n / N)	Zephyr EBV % (n / N)	Relative Rate (95% CI)
CC Subjects	41.3 (31 / 75)	58.7 (105 / 179)	1.4 (1.1, 1.9)

Source: Attachment 3, Amended Statistical Analysis Report, Table 25:16

11.2.2 High Heterogeneity Subjects with Maintained FEV_1

In the High Heterogeneity Subgroup, the proportion of Completed-Cases Zephyr EBV Subjects with maintained FEV_1 (change from baseline ≥ 0%) at 6 months was 65.9% (60 / 91) compared with Control Subjects (32.5%, 13 / 40).

Zephyr EBV Subjects were 2.0 times more likely than Control Subjects to maintain their FEV_1 through 6 months of follow-up (95% CI 1.3 – 3.2).

Table 59 Responder Analysis: High Heterogeneity Subjects with Maintained FEV_1 at 6 Months (CC)

Increase ≥ 0% in FEV_1	Control % (n / N)	Zephyr EBV % (n / N)	Relative Rate (95% CI)
High Heterogeneity Subjects	32.5 (13 / 40)	65.9 (60 / 91)	2.0 (1.3, 3.2)

Source: Attachment 3, Amended Statistical Analysis Report, Table 25:19

11.2.3 Subjects with ≥ 15% Improvement in FEV_1

The proportion of Completed-Cases Zephyr EBV Subjects with ≥ 15% improvement in FEV_1 from baseline to 6 months was 23.5% (42 / 179) compared with Control Subjects (10.7%, 8 / 75).

Zephyr EBV Subjects were 2.2 times more likely than Control Subjects to improve their FEV_1 by ≥ 15% through 6 months of follow-up (95% CI 1.1 – 4.5).

Table 60 Responder Analysis: Subjects with FEV_1 Improvement ≥ 15% at 6 Months (CC)

Increase ≥ 15% in FEV_1	Control % (n / N)	Zephyr EBV % (n / N)	Relative Rate (95% CI)
CC Subjects	10.7 (8 / 75)	23.5 (42 / 179)	2.2 (1.1, 4.5)

Source: Attachment 3, Amended Statistical Analysis Report, Table 25:16

11.2.4 High Heterogeneity Subjects with ≥ 15% Improvement in FEV_1

In the High Heterogeneity Subgroup, the proportion of Completed-Cases Zephyr EBV Subjects with ≥ 15% improvement in FEV_1 from baseline to 6 months was 35.2% (32 / 91) compared with Control Subjects (12.5%, 5 / 40).

Zephyr EBV Subjects in the High Heterogeneity Subgroup were 2.8 times more likely than Control Subjects to improve their FEV_1 by ≥ 15% through 6 months of follow-up (95% CI 1.2 – 6.7).

Table 61 Responder Analysis: High Heterogeneity Subjects with FEV_1 Improvement ≥ 15% at 6 Months (CC)

Increase ≥ 15% in FEV_1	Control % (n / N)	Zephyr EBV % (n / N)	Relative Rate (95% CI)
High Heterogeneity Subjects	12.5 (5 / 40)	35.2 (32 / 91)	2.8 (1.2, 6.7)

Source: Attachment 3, Amended Statistical Analysis Report, Table 25:19

11.3 Responder Analyses: 6MWT

Two pre-specified responder analyses for 6MWT were performed using percentage change values: one with subjects who maintained 6MWT without loss (i.e. change of ≥ 0%) and one with subjects who showed ≥ 15% improvement.

11.3.1 Subjects with Maintained 6MWT

The proportion of Completed-Cases Zephyr EBV Subjects with maintained 6MWT (change from baseline ≥ 0%) from baseline to 6 months was 60.7% (108 / 178) compared with Control Subjects (46.6%, 34 / 73).

Zephyr EBV Subjects were 1.3 times more likely than Control Subjects to maintain their 6MWT through 6 months of follow-up (95% CI 1.0 – 1.7).

Table 62 Responder Analysis: Subjects with Maintained 6MWT (Increase ≥ 0%) at 6 Months (CC)

Increase ≥ 0% in 6MWT	Control % (n / N)	Zephyr EBV % (n / N)	Relative Rate (95% CI)
CC Subjects	46.6 (34 / 73)	60.7 (108 / 178)	1.3 (1.0, 1.7)

Source: Attachment 3, Amended Statistical Analysis Report, Table 25:16

11.3.2 High Heterogeneity Subjects with Maintained 6MWT

In the High Heterogeneity Subgroup, the proportion of Completed-Cases Zephyr EBV Subjects with maintained 6MWT (change from baseline ≥ 0%) from baseline to 6 months was 65.6% (59 / 90) compared with Control Subjects (36.8%, 14 / 38).

Zephyr EBV Subjects were 1.8 times more likely than Control Subjects to maintain their 6MWT through 6 months of follow-up (95% CI 1.1 – 2.8).

Table 63 Responder Analysis: High Heterogeneity Subjects with Maintained 6MWTat 6 Months (CC)

Increase ≥ 0% in 6MWT	Control % (n / N)	Zephyr EBV % (n / N)	Relative Rate (95% CI)
High Heterogeneity Subjects	36.8 (14 / 38)	65.6 (59 / 90)	1.8 (1.1, 2.8)

Source: Attachment 3, Amended Statistical Analysis Report, Table 25:19

11.3.3 Subjects with ≥ 15% Improvement in 6MWT

The proportion of Completed-Cases Zephyr EBV Subjects with ≥ 15% improvement in 6MWT from baseline to 6 months was 25.3% (45 / 178) compared with Control Subjects.(17.8%, 13 / 73).

Zephyr EBV Subjects were 1.4 times more likely than Control Subjects to improve their 6MWT by ≥ 15% through 6 months of follow-up (95% CI 0.8 – 2.5).

Table 64 Responder Analysis: Subjects with Major Improvement (≥ 15%) in 6MWT at 6 Months (CC)

Increase ≥ 15% in 6MWT	Control % (n / N)	Zephyr EBV % (n / N)	Relative Rate (95% CI)
CC Subjects	17.8 (13 / 73)	25.3 (45 / 178)	1.4 (0.8, 2.5)

Source: Attachment 3, Amended Statistical Analysis Report, Table 25:16

11.3.4 High Heterogeneity Subjects with ≥ 15% Improvement in 6MWT

In the High Heterogeneity Subgroup, the proportion of Completed-Cases Zephyr EBV Subjects with ≥ 15% improvement in 6MWT from baseline to 6 months was 31.1% (28 / 90) compared with Control Subjects (13.2%, 5 / 38).

Zephyr EBV Subjects in the High Heterogeneity Subgroup were 2.4 times more likely than Control Subjects to improve their 6MWT by ≥ 15% through 6 months of follow-up (95% CI 1.0 – 5.7).

Table 65 Responder Analysis: High Heterogeneity Subjects with 6MWT Improvement ≥ 15% at 6 Months (CC)

Increase ≥ 15% in 6MWT	Control % (n / N)	Zephyr EBV % (n / N)	Relative Rate (95% CI)
High Heterogeneity Subjects	13.2 (5 / 38)	31.1 (28 / 90)	2.4 (1.0, 5.7)

Source: Attachment 3, Amended Statistical Analysis Report, Table 25:19

11.4 Responder Analyses: Other Effectiveness Outcome Measures

Four other effectiveness outcome measures were statistically significantly improved in the Zephyr EBV Subjects group: SGRQ, mMRC, maximum workload during cycle ergometry and BODE Index. Each of these outcome measures was subjected to responder analysis using established MCID levels to further assess the clinical importance of the observed treatment effect.

11.4.1 Subjects with ≥ 8 Point Improvement in SGRQ Score

A responder analysis was performed on the proportion of Completed-Cases Subjects with significant improvement in SGRQ from baseline to 6 months. The analysis was performed using ≥ 8 points improvement (≤ –8 point decline) was used based on the MCID value used in the NETT trial for lung volume reduction surgery.[2]

The proportion of Zephyr EBV Subjects with ≥ 8 point improvement in SGRQ was 31.0% (49 / 158) compared with Control Subjects (11.3%, 7 / 62).

Zephyr EBV Subjects were 2.7 times more likely than Control Subjects to improve their SGRQ by ≥ 8 points through 6 months of follow-up (95% CI 1.3 – 5.7).

Table 66 Responder Analysis: Subjects with SGRQ Improvement of ≥ 8 Points at 6 Months (CC)

Improvement ≥ 8 Points in SGRQ	Control % (n / N)	Zephyr EBV % (n / N)	Relative Rate (95% CI)
CC Subjects	11.3 (7 / 62)	31.0 (49 / 158)	2.8 (1.3, 5.7)

Source: Attachment 3, Amended Statistical Analysis Report Table 25:16

11.4.2 Subjects with ≥ 1 Point Improvement in mMRC Dyspnea Scale

A responder analysis was performed on the proportion of Completed-Cases Subjects with significant improvement in mMRC from baseline to 6 months. There is no clear MCID established in the literature based on empirical evidence.[27] An MCID of ≥ 1 point (≤ –1 point decline) was used, for three reasons. First, the mMRC Dyspnea Scale has only 5 categories, scored 0 – 4, and thus the smallest difference a subject can score is 1 point. Secondly, a similar dyspnea scale, the Transition Dyspnea Index, has a recommended MCID of 1 point.[27] Thirdly, the use of ½ the standard deviation of an outcome measure as an estimated MCID has been recommended;[32-35] the VENT Pivotal Study baseline mMRC scores had a ½ standard deviation of 0.42, and the dichotomization of study subjects was the same whether 0.42 or 1 was used because of the integer nature of the scoring.

The proportion of Zephyr EBV Subjects with ≥ 1 point improvement in the mMRC Scale Index was 29.0% (47 / 162) compared with Control Subjects (16.4%, 11 / 67).

Zephyr EBV Subjects were 1.8 times more likely than Control Subjects to improve their mMRC score by ≥ 1 point through 6 months of follow-up (95% CI 1.0 – 3.2).

Table 67 Responder Analysis: Subjects with mMRC Dyspnea Scale Improvement of ≥ 1 Point at 6 Months (CC)

Improved ≥ 1 Point in mMRC	Control % (n / N)	Zephyr EBV % (n / N)	Relative Rate (95% CI)
CC Subjects	16.4 (11 / 67)	29.0 (47 / 162)	1.8 (1.0, 3.2)

Source: Attachment 3, Amended Statistical Analysis Report Table 25:16

11.4.3 Subjects with ≥ 10 Watt Improvement in Maximum Workload during Cycle Ergometry

A responder analysis was performed on the proportion of Completed Cases Subjects with significant improvement in Maximum Workload during Cycle Ergometry from baseline to 6 months. The MCID level used was 10 watts, based on the published assessments of the NETT cohort.[2, 36]

The proportion of Completed Cases Zephyr EBV Subjects with ≥ 10 watt improvement in Maximum Workload during Cycle Ergometry was 24.7% (41 / 166) compared with Control Subjects (13.0%, 9 / 69)

Zephyr EBV Subjects were 1.9 times more likely than Control Subjects to show a ≥ 10 watt improvement in Maximum Workload during Cycle Ergometry through 6 months of follow-up (95% CI 1.0 – 3.7).

Table 68 Responder Analysis: Subjects with Improvement in Maximum Workload during Cycle Ergometry ≥ 10 Watts at 6 Months (CC)

Increase ≥ 10 watts in max workload	Control % (n / N)	Zephyr EBV % (n / N)	Relative Rate (95% CI)
CC Subjects	13.0 (9 / 69)	24.7 (41 / 166)	1.9 (1.0, 3.7)

Source: Attachment 3, Amended Statistical Analysis Report, Table 25:16

11.4.4 Subjects with ≥ 1 Point Improvement in the BODE Index

A responder analysis was performed on the proportion of Completed Cases Subjects with significant improvement in the BODE Index from baseline to 6 months. The MCID level used was 1 unit, based on the studies of Celli and Martinez.[37, 38]

The proportion of Zephyr EBV Subjects with ≥ 1 point improvement (≤ –1 point decline) in the BODE Index was 40.0% (64 / 160) compared with that of Control Subjects (18.6%, 11 / 59).

Zephyr EBV Subjects were 2.2 times more likely than Control Subjects to show a ≥ 1 point improvement (≤ –1 point decline) in the BODE Index through 6 months of follow-up (95% CI 1.2 – 3.8).

Table 69 Responder Analysis: Subjects with ≥ 1 Point Improvement in the BODE Index at 6 Months (CC)

Improvement ≥ 1 Point in BODE	Control % (n / N)	Zephyr EBV % (n / N)	Relative Rate (95% CI)
CC Subjects	18.6 (11 / 59)	40.0 (64 / 160)	2.2 (1.2, 3.8)

Source: Attachment 3, Amended Statistical Analysis Report Table 25:17.

11.5 Summary: Responder Analyses

Responder analyses for the VENT Pivotal Study effectiveness measures of FEV_1 and 6MWT demonstrated that a substantially larger proportion of Zephyr EBV Subjects achieved clinically important levels of improvement than did Control Subjects.

Table 70 Responder Analysis Summary for Maintenance and ≥ 15% Improvement in FEV_1 and 6MWT at 6 Months

Outcome Measure	Relative Rate (95% CI)
FEV_1 ≥ 0%	1.4 (1.1 – 1.9)
FEV_1 – High Heterogeneity Subgroup ≥ 0%	2.0 (1.3 – 3.2)
FEV_1 ≥ 15%	2.2 (1.1 – 4.5)
FEV_1 – High Heterogeneity Subgroup ≥ 15%	2.8 (1.2 – 6.7)
6MWT ≥ 0%	1.3 (1.0 – 1.7)
6MWT – High Heterogeneity Subgroup ≥ 0%	1.8 (1.1 – 2.8)
6MWT ≥ 15%	1.4 (0.8 – 2.5)
6MWT – High Heterogeneity Subgroup ≥ 15%	2.4 (1.0 – 5.7)

Source: Attachment 3, Amended Statistical Analysis Report Tables 25:16 & 25:19.

Responder analyses for the VENT Pivotal Study effectiveness measures of SGRQ, mMRC, maximum workload and the BODE Index all demonstrated that a substantially larger proportion of Zephyr EBV Subjects achieved clinically important levels of improvement than did Control Subjects (see Table 71).

Table 71 Responder Analysis Summary for Secondary Effectiveness Outcomes and BODE at 6 Months

Outcome Measure	MCID	Relative Rate (95% CI)
SGRQ	8 points	2.8 (1.3 – 5.7)
mMRC	1 point	1.8 (1.0 – 3.2)
Ergometry	10 watts	1.9 (1.0 – 3.7)
BODE Index	1 point	2.2 (1.2 – 3.8)

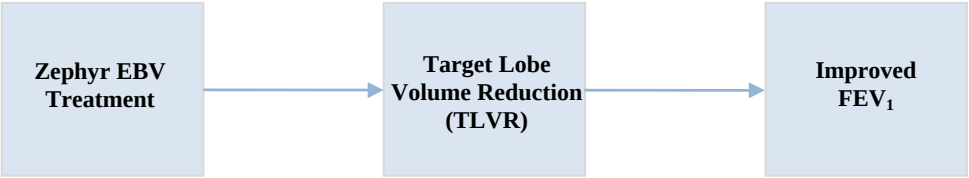
Source: Attachment 3, Amended Statistical Analysis Report Tables 25:16.

12.0 TREATMENT, VOLUME REDUCTION AND FEV_1

12.1 Introduction

Several analyses of study variables were performed in Zephyr EBV Subjects only to explore the primary rationale of Zephyr EBV treatment: that Zephyr EBV treatment leads to reduction in target lobe volume reduction (TLVR) as measured by Target Lobe Atelectasis Score (TLAS), and that this is associated with measurable therapeutic benefit as assessed by improvement in FEV_1.

Figure 11 Chart: Zephyr EBV Treatment, TLVR and FEV_1



These pre-specified analyses of factors affecting change in FEV_1 at 6 months—already demonstrated to be a significant effectiveness outcome measure—are an important exploration of Zephyr EBV performance, and help to elucidate and confirm hypothesized therapeutic mechanisms. The relationships that are examined in this section are as follows:

12.2. Treatment, Volume Reduction and Improved FEV_1
- 12.2.1. Zephyr EBV Treatment Leads to TLVR
- 12.2.2. TLVR is Significantly Associated with Improved FEV_1 at 6 Months

12.3. Factors Associated with Target Lobe Volume Reduction
- 12.3.1. Technical Success and Target Lobe Volume Reduction
- 12.3.2. Fissure Integrity and Target Lobe Volume Reduction
- 12.3.3. Technical Success, Fissure Integrity and Target Lobe Volume Reduction

12.4. Other Volume Changes Assessed by HRCT

12.5. Factors Associated with Improved FEV_1
- 12.5.1. Technical Success, Fissure Integrity and FEV_1

12.6. Discussion: Treatment, Volume Reduction and FEV_1

12.2 Treatment, Volume Reduction and Improved FEV_1

12.2.1 Zephyr EBV Treatment Leads to TLVR

Target Lobe Volume Reduction (TLVR) was assessed by Target Lobe Atelectasis Score at total lung capacity ($TLAS_{TLC}$). TLAS is a direct measure of target lobar volume change over time, calculated as the percentage difference in HRCT-assessed volume from baseline to 6 months (see Section 4.6.7).

Implantation of the Zephyr EBV in study subjects was associated with a large and highly significant difference in the $TLAS_{TLC}$ ($p < 0.0001$) at 6 months between Zephyr EBV Subjects (−20.6%) and Control Subjects (−1.7%). Thus, Zephyr EBV treatment results in dramatic volume reduction in the target lobe over time.

Table 72 Effect of EBV Treatment on $TLAS_{TLC}$

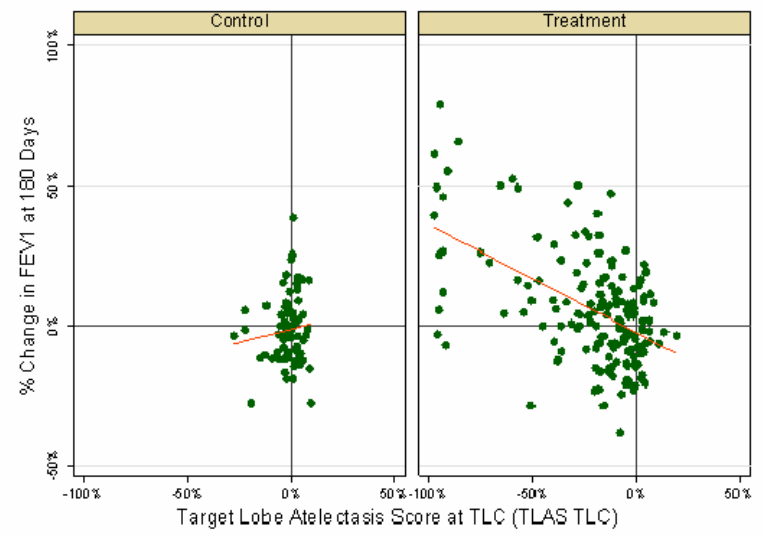
	Control Mean (SD) N Median (Min, Max)	Zephyr EBV Mean (SD) N Median (Min, Max)	Delta (95% CI)
$TLAS_{TLC}$	−1.7% (7.0%) 73 −1.1% (−27.5%, 9.8%)	−20.6% (27.3%) 172 −12.2% (−97.7%, 19.3%)	−18.9 (−23.3, −14.5)

[1] Difference of means and unequal variance t-test confidence interval
Source: Attachment 3, Amended Statistical Analysis Report, Table 13:25

12.2.2 TLVR is Significantly Associated with Improved FEV_1 at 6 Months

Analysis of the relationship between TLVR measured by $TLAS_{TLC}$ and therapeutic benefit measured by percent change in FEV_1 at 6 months reveals a dramatic difference between Control Subjects and Zephyr EBV Subjects. Control Subjects have no significant relationship between these two variables, whereas Zephyr EBV Subjects demonstrate much more substantial reductions in $TLAS_{TLC}$ and a significant association between $TLAS_{TLC}$ and Percent Change in FEV_1 in the Zephyr EBV Subjects ($r^2 = 0.2785$, $p = 0.0000$, $n = 179$). This is dramatically demonstrated in the following chart:

Figure 12 Chart: $TLAS_{TLC}$ vs. % Change in FEV_1 (CC)



Source: Attachment 3, Amended Statistical Report Figure 13.9

12.3 Factors Associated with Target Lobe Volume Reduction

Zephyr EBV treatment is intentionally designed to produce Target Lobe Volume Reduction (TLVR). Two factors were significantly associated with TLVR, Technical Success and Fissure Integrity, both of which are clinically and physiologically expected and relevant.

12.3.1 Technical Success and Target Lobe Volume Reduction

Zephyr EBV Subjects with Technical Success (complete lobar exclusion at 6 months) as determined by HRCT had a 17.0% larger reduction in $TLAS_{TLC}$ than those with Technical Failure (incomplete lobar exclusion), respectively −28.1% vs. −11.1% (p = 0.0001).

Table 73 Technical Success (Complete Lobar Exclusion) and $TLAS_{TLC}$

	Technical Failure (Incomplete Lobar Exclusion) Mean (SD) N Median (Min, Max)	Technical Success (Complete Lobar Exclusion) Mean (SD) N Median (Min, Max)	Delta (95% CI) [1]
$TLAS_{TLC}$	−11.1% (14.6%) 76 −7.4% (−54.1%, 6.7%)	−28.1% (32.3%) 96 −17.6% (−97.7, 19.3%)	−17.0% (−24.3, −9.7)

[1] Unequal variance t-test confidence interval
Source: Attachment 3, Amended Statistical Analysis Report, Table 13:29

12.3.2 Fissure Integrity and Target Lobe Volume Reduction

Zephyr EBV Subjects with Fissure Integrity in the target lobe as determined by HRCT had significantly larger reductions in $TLAS_{TLC}$ compared to those with Incomplete Fissures.

For the left lung, subjects with a complete left oblique fissure had a 19.4% greater reduction in $TLAS_{TLC}$ of −40.1% compared with −20.7% for subjects with an incomplete left oblique fissure (p = 0.0111).

Table 74 Left Target Lung, Fissure Integrity and $TLAS_{TLC}$ (CC)

	Incomplete Left Oblique Fissure Mean (SD) N Median (Min, Max)	Complete Left Oblique Fissure Mean (SD) N Median (Min, Max)	Delta 95% CI [1]
$TLAS_{TLC}$	−20.7% (22.8%) 25 −11.7% (−71.0, 19.3%)	−40.1% (36.9%) 40 −27.9% (−96.1, 4.0%)	−19.4% (−34.2, −4.6)

[1] Unequal variance t-test confidence interval
Source: Attachment 3, Amended Statistical Analysis Report, Table 13:28

The right lung, with two fissures, is more complicated, but the same positive effect of HRCT-determined fissure integrity on the magnitude of $TLAS_{TLC}$ response is present. Subjects with both fissures complete have a significantly greater change in $TLAS_{TLC}$ of −33.0% compared to −13.3% or less if any or both of the fissures are incomplete.

Table 75 Right Target Lung, Fissure Integrity and $TLAS_{TLC}$

	$TLAS_{TLC}$ Mean (SD) N Median (Min, Max)
Both Fissures Complete	−33.0% (27.9%) 23 −25.4% (−97.7, 3.3%)
Right Horizontal-Only Complete	−13.3% (12.0%) 13 −12.6% (−36.4, 3.7%)
Right Oblique-Only Complete	−10.1% (10.1%) 24 −10.7% (−36.3, 8.6%)
Neither Fissure Complete	−4.4% (10.9%) 39 −2.6% (−37.9, 13.8%)

Source: Attachment 3, Amended Statistical Analysis Report, Table 13:27

12.3.3 Technical Success, Fissure Integrity and Target Lobe Volume Reduction

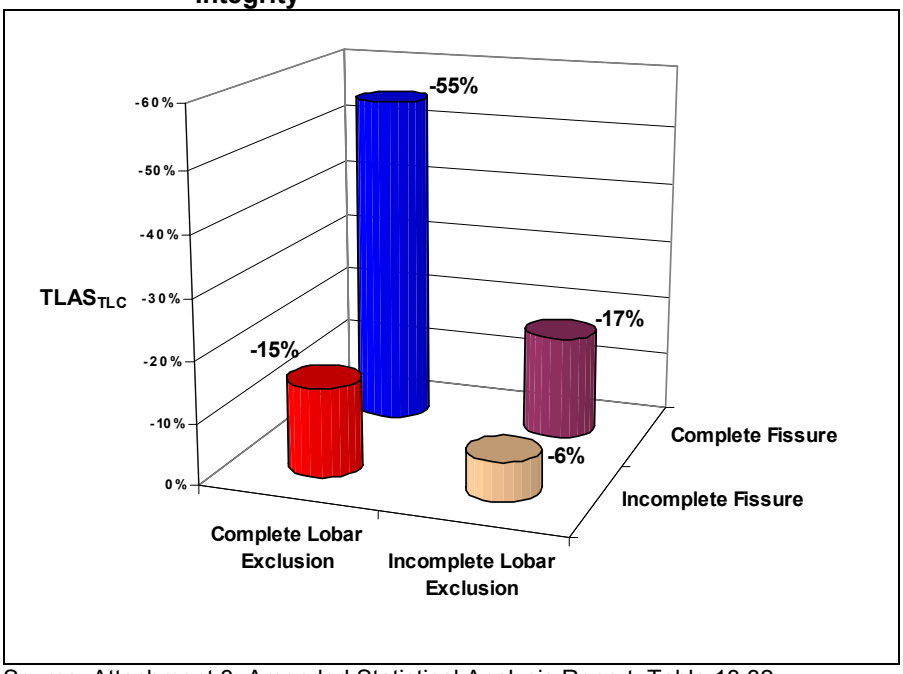
When both Technical Success and Fissure Integrity are jointly compared with change in $TLAS_{TLC}$ there is an additive effect, with Zephyr EBV Subjects with both Technical Success and Fissure Integrity having a reduction of −54.8%.

Table 76 $TLAS_{TLC}$ in Zephyr EBV Subjects by Lobar Exclusion and Fissure Integrity

	Incomplete Lobar Exclusion Mean (SD) N Median (Min, Max)	Complete Lobar Exclusion Mean (SD) N Median (Min, Max)
Both Fissures Complete	−17.2% (15.3%) 29 −14.1% (−50.8, 4.0%)	−54.8% (35.8%) 34 −52.4% (−97.7, 3.9%)
One or Both Fissures Incomplete	−6.4% (10.9%) 46 −4.3% (−37.9, 6.7%)	−14.7% (18.3%) 55 −11.7% (−71.0, 19.3%)

Source: Attachment 3, Amended Statistical Analysis Report Table 13:32

Figure 13 Chart: $TLAS_{TLC}$ in Zephyr EBV Subjects by Lobar Exclusion and Fissure Integrity



Source: Attachment 3, Amended Statistical Analysis Report, Table 13:32

12.4 Factors Associated with Improved FEV_1

Zephyr EBV treatment, Technical Success and Fissure Integrity were shown above to be associated with TLVR. All three of these factors were also associated with significant improvements in FEV_1 at 6 months.

Zephyr EBV Treatment: This was demonstrated as one of the two co-Primary Outcome Measures (See Section 8.2.1) where the Zephyr EBV Subjects had a 6.8% greater change in FEV_1 compared with the Control Subjects.

Technical Success: This was demonstrated as a pre-specified subgroup analysis (See Section 10.3.1) where the Zephyr EBV Subjects with Technical Success had a 9.4% greater change in FEV_1 compared with Zephyr EBV Subjects without Technical Success.

Fissure Integrity: This was demonstrated as a pre-specified subgroup analysis (See Section 10.3.3) where the Zephyr EBV Subjects with Complete Fissure Integrity had a 16.2% greater change in FEV_1 compared with Control Subjects.

12.4.1 Technical Success, Fissure Integrity and FEV_1

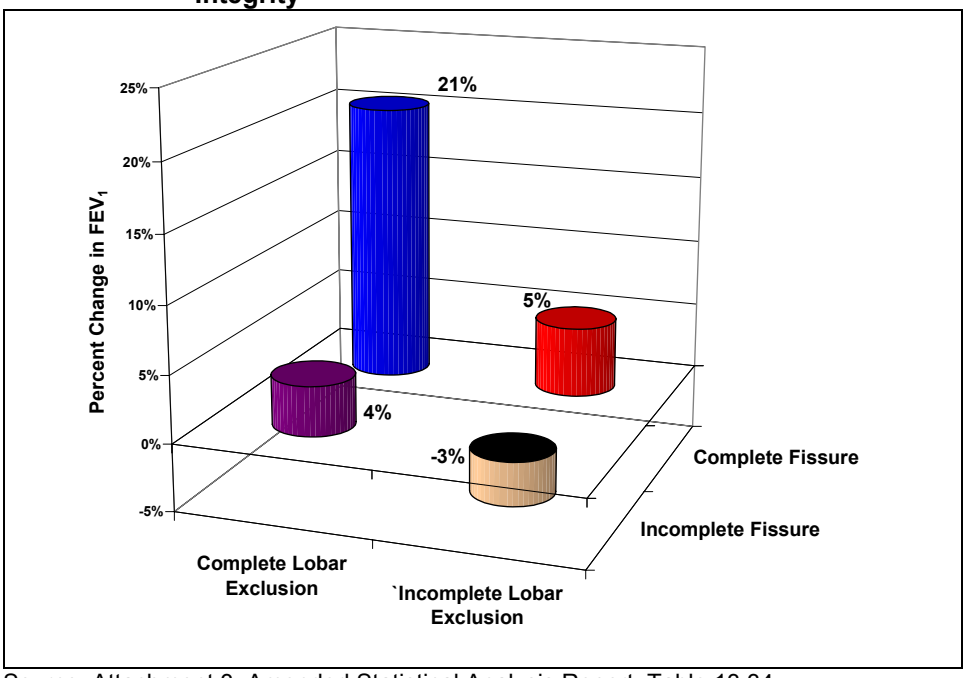
Zephyr EBV subjects with Technical Success (Complete Lobar Exclusion) and Complete Fissures have a much greater improvement in FEV_1 (+20.6%) compared to those Zephyr EBV Subjects with neither factor (−3.2%, range −38.3% to +21.4%).

Table 77 Percent Change in FEV_1 at 6 Months in Zephyr EBV Subjects by Lobar Exclusion and Fissure Integrity

	Incomplete Lobar Exclusion Mean (SD) N Median (Min, Max)	Complete Lobar Exclusion Mean (SD) N Median (Min, Max)
Complete Fissures	5.2% (17.4%) 29 6.5% (−28.6, 40.0%)	20.6% (25.1%) 37 19.3% (−28.7, 78.9%)
Incomplete	−3.2% (12.4%) 47 −4.2% (−38.3, 21.4%)	3.7% (16.9%) 56 2.2% (−21.0, 52.3%)

Source: Attachment 3, Amended Statistical Analysis Report, Table 13:34

Figure 14 Chart: FEV_1 in Zephyr EBV Subjects by Lobar Exclusion and Fissure Integrity



Source: Attachment 3, Amended Statistical Analysis Report, Table 13:34

12.5 Summary: Treatment, Volume Reduction and FEV_1

The VENT Pivotal Trial prospectively assessed the hypothesized mechanism of treatment effect, which was to cause volume loss in non-ventilating lung with resulting improved ventilation in healthier lung parenchyma.

Study results strongly suggest this to be the case. Unilateral treatment of subjects with heterogeneous emphysema with Zephyr EBVs elicited substantial target lobe volume reduction (TLVR) as measured by target lobe atelectasis score ($TLAS_{TLC}$). Zephyr EBV Subjects showed a 20.6% reduction in lobar volume compared with 1.7% loss in Control Subjects ($p < 0.0001$).

Furthermore, the TLVR resulting from Zephyr EBV treatment was highly associated with improved FEV_1 in Zephyr EBV Subjects at 6 months of follow-up ($r^2 = 0.2785$, $p = 0.0000$).

Relevant clinical factors that would be associated with a closed system (exclusion of all lobar bronchi with Zephyr EBV devices and completeness of interlobar fissures to prevent collateral air flow) were highly associated with the degree of TLVR as measured by $TLAS_{TLC}$. Zephyr EBV Subjects with Technical Success (complete lobar exclusion) had a mean $TLAS_{TLC}$ of −28.1% compared with −11.1% for Zephyr EBV Subjects without Technical Success. Zephyr EBV Subjects with complete interlobar fissures had mean $TLAS_{TLC}$ of −40.1% (left lung) and −33.0% (right lung) compared with −20.7% and −4.4% respectively for incomplete fissures. The combination of Technical Success and Complete Fissure Integrity resulted in a mean $TLAS_{TLC}$ of −54.8% compared with −6.4% when both factors were absent.

Zephyr EBV treatment (Section 8.2), Technical Success (Section 10.3.1) and Fissure Integrity (Section 10.3.3) were also significantly associated with greater change in FEV_1 in Zephyr EBV Subjects when these factors were present.

13.0 SAFETY PROFILE AT ONE YEAR

13.1 Introduction

Adverse events were categorized and aggregated to allow characterization of the safety profile of Zephyr EBV Subjects compared with Control Subjects. In addition, several specific categories of adverse events specific to Zephyr EBV Subjects were analyzed. These safety evaluations are presented as follows:

13.2. Review of Adverse Events
- 13.2.1. Adverse Events
- 13.2.2. Adverse Events by Quarter
- 13.2.3. Serious Adverse Events
- 13.2.4. Serious Adverse Events by Quarter
- 13.2.5. Device-Related Adverse Events
- 13.2.6. Procedure-Related Adverse Events

13.3. Zephyr EBV Subjects with Specific Adverse Events
- 13.3.1. Granulation Tissue
- 13.3.2. Valve Expectoration or Migration
- 13.3.3. Pneumonia Distal to Valves
- 13.3.4. Massive Hemoptysis
- 13.3.5. Valve Treatment for Persistent Air Leak

13.4. Valve Removal During Study Follow-Up

13.5. Discussion: Adverse Events through One Year

13.2 Review of Adverse Events

13.2.1 Adverse Events

Adverse events through 1 year of follow-up are summarized in the following table.

Table 78 Adverse Events through 1 year

Adverse Events through 1 year	Control % (95% CI)	Zephyr EBV % (95% CI)	p value [1]
All-Cause Mortality [2]	3.5% (0.7 – 9.8%)	3.7% (1.6 – 7.2%)	1.0000
All Cardiovascular	6.9% (2.6 – 14.4%)	7.9% (4.7 – 12.4%)	1.0000
Arrhythmia	4.6% (1.3 – 11.4%)	6.1% (3.3 – 10.2%)	0.7856
CHF	1.2% (0.0 – 6.2%)	0.5% (0.0 – 2.6%)	0.4952
CAD	1.2% (0.0 – 6.2%)	1.9% (0.5 – 4.7%)	1.0000
Other Cardiac	0.0% (0.0 – 4.2%)	0.0% (0.0 – 1.7%)	--
Cerebrovascular Disease	0.0% (0.0 – 4.2%)	0.5% (0.0 – 2.6%)	1.0000
TIA	0.0% (0.0 – 4.2%)	0.0% (0.0 – 1.7%)	--
Stroke	0.0% (0.0 – 4.2%)	0.5% (0.0 – 2.6%)	1.0000
Thromboembolic Disease	0.0% (0.0 – 4.2%)	0.5% (0.0 – 2.6%)	1.0000
Deep Vein Thrombosis	0.0% (0.0 – 4.2%)	0.5% (0.0 – 2.6%)	1.0000
Pulmonary Embolism	0.0% (0.0 – 4.2%)	0.0% (0.0 – 1.7%)	--
All COPD/Emphysema	62.1% (51.0 – 72.3%)	77.6% (71.4 – 83.0%)	**0.0095**
COPD Exacerbation	57.5% (46.4 – 68.0%)	72.4% (65.9 – 78.3%)	**0.0141**
COPD with hospitalization	10.3% (4.8 – 18.7%)	18.2% (13.3 – 24.1%)	0.1174
COPD w/o hospitalization	50.6% (39.6 – 61.5%)	57.5% (50.6 – 64.2%)	0.3069
Other Pulmonary Infection	1.2% (0.0 – 6.2%)	8.4% (5.1 – 13.0%)	**0.0174**
Increased SOB	2.3% (0.3 – 8.1%)	9.8% (6.2 – 14.6%)	**0.0295**
Cough	1.2% (0.0 – 6.2%)	6.1% (3.3 – 10.2%)	0.0748
Bronchospasm	0.0% (0.0 – 4.2%)	1.9% (0.5 – 4.7%)	0.3277
Any Respiratory Failure	3.5% (0.7 – 9.8%)	3.3% (1.3 – 6.6%)	1.0000
≥ 24 hours ventilation [2]	2.3% (0.3 – 8.1%)	2.8% (1.0 – 6.0%)	1.0000
< 24 hours ventilation	0.0% (0.0 – 4.2%)	0.0% (0.0 – 1.7%)	--
No ventilation	1.2% (0.0 – 6.2%)	0.5% (0.0 – 2.6%)	0.4952
Pneumonia Not Distal to Valve	10.3% (4.8 – 18.7%)	11.2% (7.3 – 16.2%)	1.0000
RV Increase from BL>15%	1.2% (0.0 – 6.2%)	0.5% (0.0 – 2.6%)	0.4952
Altered ABGs	1.2% (0.0 – 6.2%)	8.4% (5.1 – 13.0%)	**0.0174**
New/worse hypercapnia	1.2% (0.0 – 6.2%)	2.3% (0.8 – 5.4%)	0.6765
Hypoxemia	0.0% (0.0 – 4.2%)	7.0% (4.0 – 11.3%)	**0.0073**
All Pulmonary/Thoracic	9.2% (4.1 – 17.3%)	52.8% (45.9 – 59.7%)	**<0.0001**
Hemoptysis	2.3% (0.3 – 8.1%)	42.5% (35.8 – 49.5%)	**<0.0001**
Massive Hemoptysis [2]	0.0% (0.0 – 4.2%)	0.5% (0.0 – 2.6%)	1.0000
Other Hemoptysis	2.3% (0.3 – 8.1%)	42.1% (35.4 – 49.0%)	**<0.0001**
Pneumothorax	2.3% (0.3 – 8.1%)	5.1% (2.6 – 9.0%)	0.3602
Air leak > 7 days [2]	1.2% (0.0 – 6.2%)	1.9% (0.5 – 4.7%)	1.0000
Expanding Pneumothorax	2.3% (0.3 – 8.1%)	1.9% (0.5 – 4.7%)	1.0000
Stable Pneumothorax	1.2% (0.0 – 6.2%)	1.4% (0.3 – 4.0%)	1.0000
Empyema [2]	0.0% (0.0 – 4.2%)	0.0% (0.0 – 1.7%)	--
Pleural Effusion	0.0% (0.0 – 4.2%)	0.5% (0.0 – 2.6%)	1.0000
Other Pulmonary/Thoracic AEs	6.9% (2.6 – 14.4%)	21.0% (15.8 – 27.1%)	**0.0022**
Non–cardiac Chest Pain	3.5% (0.7 – 9.8%)	16.4% (11.7 – 22.0%)	**0.0018**
Lung Mass/Cancer	2.3% (0.3 – 8.1%)	0.9% (0.1 – 3.3%)	0.5820
ARDS	0.0% (0.0 – 4.2%)	0.0% (0.0 – 1.7%)	--
Fractured Rib	0.0% (0.0 – 4.2%)	0.9% (0.1 – 3.3%)	1.0000
Wheezing Non–valve Related	1.2% (0.0 – 6.2%)	4.7% (2.3 – 8.4%)	0.1865

Adverse Events through 1 year	Control % (95% CI)	Zephyr EBV % (95% CI)	p value [1]
All Valve / Implant Related		18.2% (13.3 – 24.1%)	
Expectoration/Aspiration/Migration		7.9% (4.7 – 12.4%)	
Pneumonia Distal to Valve [2]		4.2% (1.9 – 7.8%)	
Adverse tracheobronchial effect		8.4% (5.1 – 13.0%)	
Bronchial granulation tissue		7.9% (4.7 – 12.4%)	
Bronchial ulceration		0.0% (0.0 – 1.7%)	
Bronchial trauma		0.5% (0.0 – 2.6%)	
Dysphonia		1.4% (0.3 – 4.0%)	
All General AEs	33.3% (23.6 – 44.3%)	49.1% (42.2 – 56.0%)	**0.0150**
Non–pulmonary infections	18.4% (10.9 – 28.1%)	19.2% (14.1 – 25.1%)	1.0000
Upper respiratory infections	13.8% (7.3 – 22.9%)	15.4% (10.9 – 21.0%)	0.8588
Other non–pulmonary infections	5.8% (1.9 – 12.9%)	4.7% (2.3 – 8.4%)	0.7712
Fever	1.2% (0.0 – 6.2%)	3.3% (1.3 – 6.6%)	0.4458
Other Pain	4.6% (1.3 – 11.4%)	7.0% (4.0 – 11.3%)	0.6028
Gastrointestinal Adverse Events	4.6% (1.3 – 11.4%)	7.9% (4.7 – 12.4%)	0.4540
Nausea or Vomiting	1.2% (0.0 – 6.2%)	8.4% (5.1 – 13.0%)	**0.0174**
Other General	12.6% (6.5 – 21.5%)	22.9% (17.5 – 29.1%)	0.0554

[1] Two-sided Fisher's exact test
[2] A component of the Major Complications Composite (MCC) as defined in Section 4.5.5
Source: Attachment 3, Amended Statistical Analysis Report, Table 16:12

Over 1 year of follow-up, subjects in the two groups had equivalent all-cause mortality rates; 3.5% in Control Subjects and 3.7% in Zephyr EBV Subjects (p = 1.0000). Cardiovascular events were 6.9% in Control Subjects and 7.9% in Zephyr EBV Subjects (p = 1.000).

The VENT Pivotal Study revealed the high degree of pulmonary morbidity present in subjects with severe heterogeneous emphysema, with 77.6% of Zephyr EBV Subjects and 62.1% of Control Subjects having one or more COPD / emphysema category adverse events; this difference was significant (p = 0.0095). This difference was driven by the following subcategories of adverse events: COPD exacerbation (72.4% Zephyr EBV Subjects and 57.5% Control Subjects, p = 0.0141, Other Pulmonary Infection (8.4% compared with 1.2% respectively, p = 0.0174), Increased SOB (9.8% compared with 2.3% respectively, p = 0.0295) and Altered ABGs (8.4% compared with 1.2% respectively, p = 0.0174).

The rate of pulmonary / thoracic adverse events was higher in Zephyr EBV Subjects, 52.8%, compared with Control Subjects, 9.2% (p < 0.0001). This difference was driven by the following subcategories of adverse events: hemoptysis (42.1% Zephyr EBV Subjects compared with 2.3% in Control Subjects, p < 0.0001), and Noncardiac Chest Pain (16.4% compared with 3.5%, p = 0.0018).

Specific adverse events were associated with the Zephyr EBV. Granulation tissue narrowing the airways adjacent to the valves was observed in 7.9% (17 of 214) of implanted Zephyr EBV Subjects. Eight (8) of 214 Zephyr EBV Subjects (3.7%) expectorated one or more valves and 4.2% (9 of 214) of implanted Zephyr EBV Subjects experienced valve migrations without expectoration during study follow-up. Nine (9) Zephyr EBV Subjects (4.2%) had pneumonia distal to the valves during study follow-up.

General AEs occurred more frequently in Zephyr EBV Subjects (49.1%) compared with Control Subjects (33.3%, p = 0.0150); this appeared to be driven by procedure-related nausea or vomiting (8.4% vs. 1.2%, p = 0.0174) and a range of infrequent events (22.9% vs. 12.6%, p = 0.0554) including headache, sore throat, nose bleed, rhinitis, and lower leg / ankle edema. This may have been driven in part by detection bias in the more intently observed treatment group.

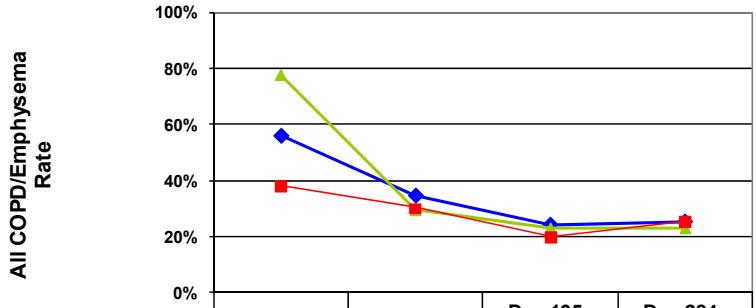
13.2.2 Adverse Events by Quarter

Events that were significantly higher at 1 year in Zephyr EBV Subjects than in Control Subjects included COPD Exacerbations, Other Pulmonary Infections, Increased Shortness of Breath, Hypoxemia, Hemoptysis, Non-cardiac Chest Pain, and General Adverse Events. The Figures below examine these events by quarter of follow-up in order to understand which events are short term and potentially triggered by the intervention and which are longer term and more likely due to the presence of the implant. This is further illustrated by separating Zephyr EBV Treatment event rates by those Subjects with one or more valves removed post-procedure and those Subjects with no valve removals post-procedure.

COPD Exacerbations adverse event rates were aggregated with other emphysema-related and pulmonary adverse events in All COPD/Emphysema Rates.

The All COPD/Emphysema rate declines in the Treatment with No Valve Removals group and the Treatment with Valve Removals group (see Figure 15) over the follow-up period. The overall decline in the All COPD/Emphysema rates appears to be independent of valve removals and the adverse event rate for the Treatment with No Valve Removals group approaches the adverse event rate for the Control group by the fourth quarter of follow-up.

Figure 15 Chart: All COPD/Emphysema Rates by Valve Removal by Quarter

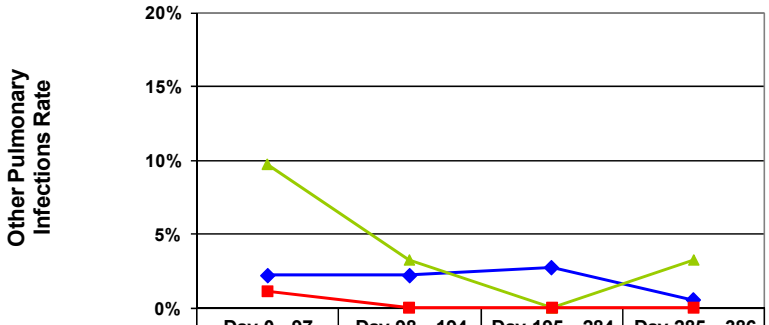


	Day 0 - 97	Day 98-194	Day 195 - 284	Day 284 - 386
Tx -No Removals, n=183	55.7%	34.4%	24.0%	25.1%
Tx -With Removals, n=31	77.4%	29.0%	22.6%	22.6%
Control, n=87	37.9%	29.9%	19.5%	25.3%

Source: Attachment 3, Amended Statistical Analysis Report, Figure 19:4

The Other Pulmonary Infections rate declines in the Treatment with No Valve Removals group in the fourth quarter and the rate in the Treatment with Valve Removals group declines after the second quarter (see Figure 16). The rates are low for both groups and it is unclear whether the overall decline in the Other Pulmonary Infections rate is related to valve removals.

Figure 16 Chart: Other Pulmonary Infection Rates by Valve Removal by Quarter

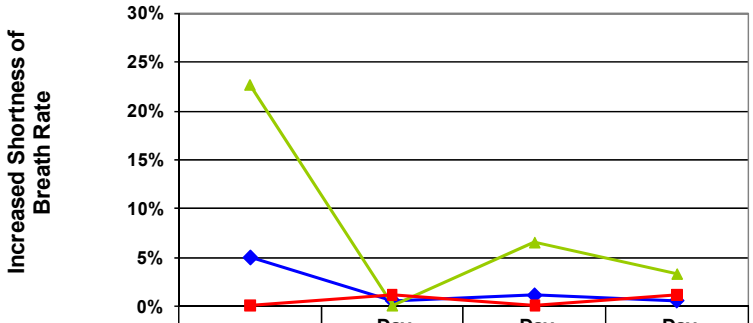


	Day 0 - 97	Day 98 - 194	Day 195 - 284	Day 285 - 386
Tx - No Removals, n=183	2.2%	2.2%	2.7%	0.6%
Tx - With Removals, n=31	9.7%	3.2%	0.0%	3.2%
Control, n=87	1.2%	0.0%	0.0%	0.0%

Source: Attachment 3, Amended Statistical Analysis Report, Figure 19:11

The occurrence of shortness of breath was nominally higher in the first 3 quarters for Zephyr EBV Subjects relative to Control Subjects, and then dropped in the fourth quarter. This decline in Shortness of Breath rates occurred in Zephyr EBV Subjects with valve removals as well as independent of valve removals.

Figure 17 Chart: Increased Shortness of Breath Rates by Valve Removal by Quarter

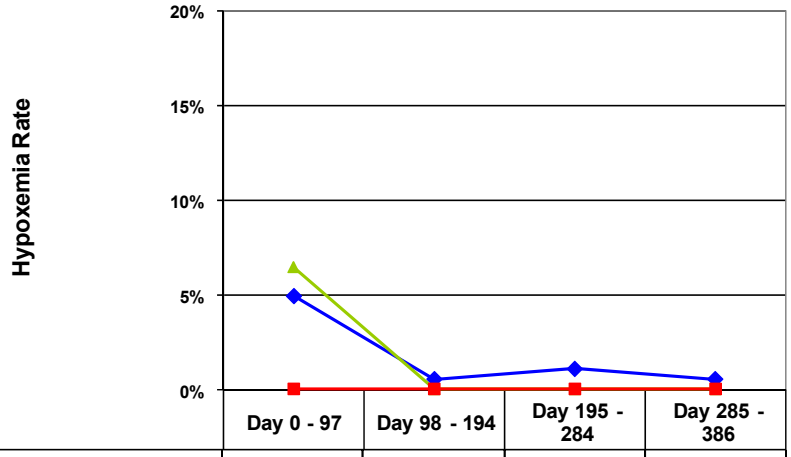


	Day 0 - 97	Day 98 - 194	Day 195 - 284	Day 285 - 386
Tx - No Removals, n=183	4.9%	0.6%	1.1%	0.6%
Tx - With Removals, n=31	22.6%	0.0%	6.5%	3.2%
Control, n=87	0.0%	1.2%	0.0%	1.2%

Source: Attachment 3, Amended Statistical Analysis Report, Figure 19:5

Zephyr EBV Treatment Subjects and Control Subjects had similar rates of Hypoxemia after the first three months of the follow-up interval regardless if the Subject had valves removed or not.

Figure 18 Chart: Hypoxemia Rates by Valve Removal by Quarter

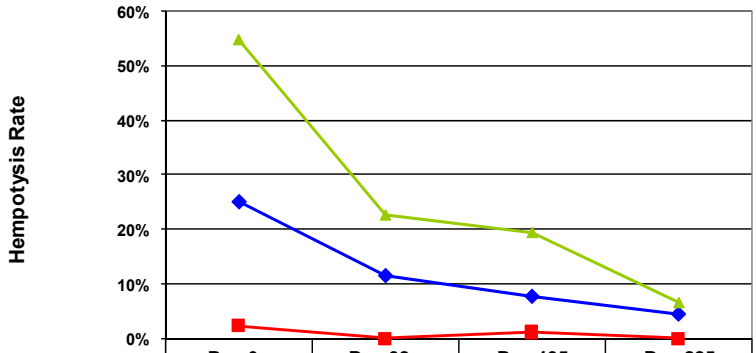


	Day 0 - 97	Day 98 - 194	Day 195 - 284	Day 285 - 386
Tx - No Removals, n =183	4.9%	0.6%	1.1%	0.6%
Tx - With Removals, n=31	6.5%	0.0%	0.0%	0.0%
Control, n=87	0.0%	0.0%	0.0%	0.0%

Source: Attachment 3, Amended Statistical Analysis Report, Figure 19:8

Hemoptysis occurred at higher rates in Zephyr EBV Subjects, and although this did not fall to the same level as Control Subjects, it decreased substantially every quarter of study follow-up. This decline in Hemoptysis rates occurred in both the Treatment with Valve Removals and the Treatment with No Valve Removal groups.

Figure 19 Chart: Hemoptysis Rates by Valve Removal by Quarter

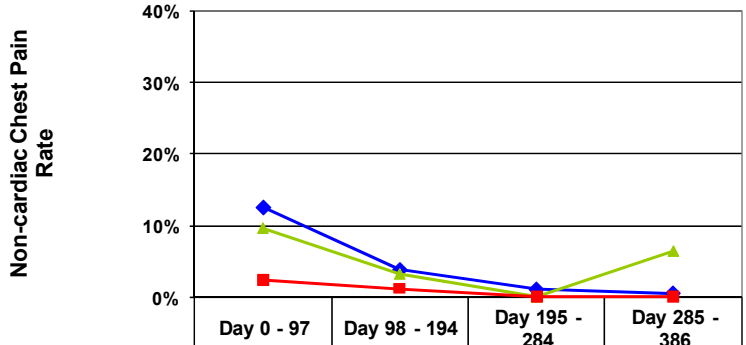


	Day 0 - 97	Day 98 - 194	Day 195 - 284	Day 285 - 386
Tx - No Removals, n=183	25.1%	11.5%	7.7%	4.4%
Tx - With Removals, n=31	54.8%	22.6%	19.4%	6.5%
Control, n=87	2.3%	0.0%	1.2%	0.0%

Source: Attachment 3, Amended Statistical Analysis Report, Figure 19:9

Non-cardiac Chest Pain was significantly higher in Zephyr EBV Subjects than in Control Subjects in the first quarter of follow up. These events appear to be transient and resolve independent of valve removal.

Figure 20 Chart: Non-cardiac Chest Pain Rates by Quarter

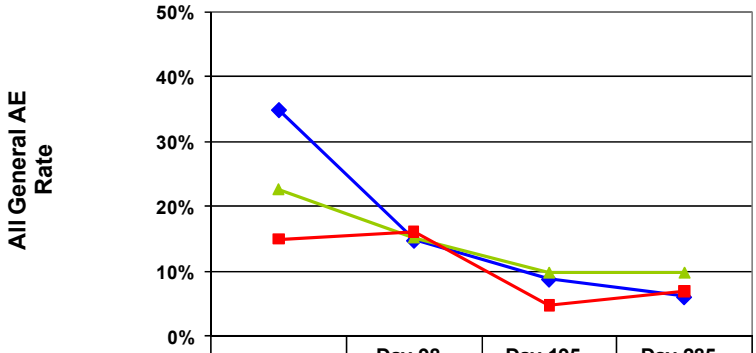


	Day 0 - 97	Day 98 - 194	Day 195 - 284	Day 285 - 386
Tx - No Removals, n=183	12.6%	3.8%	1.1%	0.6%
Tx - With Removals, n=31	9.7%	3.2%	0.0%	6.5%
Control, n=87	2.3%	1.2%	0.0%	0.0%

Source: Attachment 3, Amended Statistical Analysis Report, Figure 19:12

General Adverse Events, which included post-procedural Nausea or Vomiting, occurred at a higher rate in Zephyr EBV Treatment Subjects in the first quarter after randomization, but declined steadily throughout the study follow up period to rates similar to Control Subjects. These declines in the Treatment group appear to be independent of valve removals.

Figure 21 Chart: General Adverse Event Rates by Quarter



	Day 0 - 97	Day 98 - 194	Day 195 - 284	Day 285 - 386
Tx - No Removals, n=183	35.0%	14.8%	8.7%	6.0%
Tx - With Removals, n=31	22.6%	15.1%	9.7%	9.7%
Control, n=87	14.9%	16.1%	4.6%	6.9%

Source: Attachment 3, Amended Statistical Analysis Report, Figure 19:15

13.2.3 Serious Adverse Events

Serious adverse events (SAEs) through 1 year of follow-up are summarized in the following table.

Table 79 Per-Subject Serious Adverse Events through 1 Year

Serious Adverse Events through 1 year	Control n = 87 % (95% CI)	Zephyr EBV n = 214 % (95% CI)	p value [1]
All-Cause Mortality [2]	3.5% (0.7 - 9.8%)	3.7% (1.6 - 7.2%)	1.0000
All Cardiovascular	4.6% (1.3 - 11.4%)	4.2% (1.9 - 7.8%)	1.0000
Arrhythmia	2.3% (0.3 - 8.1%)	2.3% (0.8 - 5.4%)	1.0000
CHF	1.2% (0.0 - 6.2%)	0.5% (0.0 - 2.6%)	0.4952
CAD	1.2% (0.0 - 6.2%)	1.9% (0.5 - 4.7%)	1.0000
Other Cardiac	0.0% (0.0 - 4.2%)	0.0% (0.0 - 1.7%)	--
Cerebrovascular Disease	0.0% (0.0 - 4.2%)	0.5% (0.0 - 2.6%)	1.0000
TIA	0.0% (0.0 - 4.2%)	0.0% (0.0 - 1.7%)	--
Stroke	0.0% (0.0 - 4.2%)	0.5% (0.0 - 2.6%)	1.0000
Thromboembolic Disease	0.0% (0.0 - 4.2%)	0.0% (0.0 - 1.7%)	--
Deep Vein Thrombosis	0.0% (0.0 - 4.2%)	0.0% (0.0 - 1.7%)	--
Pulmonary Embolism	0.0% (0.0 - 4.2%)	0.0% (0.0 - 1.7%)	--

Serious Adverse Events through 1 year	Control n = 87 % (95% CI)	Zephyr EBV n = 214 % (95% CI)	p value [1]
All COPD/Emphysema	18.4% (10.9 - 28.1%)	28.5% (22.6 - 35.1%)	0.0805
COPD Exacerbation	10.3% (4.8 - 18.7%)	23.4% (17.9 - 29.6%)	**0.0101**
COPD with hospitalization	10.3% (4.8 - 18.7%)	18.2% (13.3 - 24.1%)	0.1174
COPD w/o hospitalization	0.0% (0.0 - 4.2%)	2.8% (1.0 - 6.0%)	0.1867
Other Pulmonary Infection	0.0% (0. 0 - 4.2%)	3.3% (1.3 - 6.6%)	0.1989
Increased SOB	0.0% (0.0 - 4.2%)	0.0% (0.0 - 1.7%)	--
Cough	0.0% (0.0 - 4.2%)	0.0% (0.0 - 1.7%)	--
Bronchospasm	0.0% (0.0 - 4.2%)	0.0% (0.0 - 1.7%)	--
Any Respiratory Failure	3.5% (0.7 - 9.8%)	3.3% (1.3 - 6.6%)	1.0000
≥ 24 hours ventilation [2]	2.3% (0.3 - 8.1%)	2.8% (1.0 - 6.0%)	1.0000
< 24 hours ventilation	0.0% (0.0 - 4.2%)	0.0% (0.0 - 1.7%)	--
No ventilation	1.2% (0.0 - 6.2%)	0.5% (0.0 - 2.6%)	0.4952
Pneumonia Not Distal to Valve	9.2% (4.1 - 17.3%)	7.0% (4.0 - 11.3%)	0.4847
RV Increase from BL>15%	0.0% (0.0 - 4.2%)	0.0% (0.0 - 1.7%)	--
Altered ABGs	0.0% (0.0 - 4.2%)	2.8% (1.0 - 6.0%)	0.1867
New/worse hypercapnia	0.0% (0.0 - 4.2%)	1.4% (0.3 - 4.0%)	0.5594
Hypoxemia	0.0% (0.0 - 4.2%)	1.9% (0.5 - 4.7%)	0.3277
All Pulmonary/Thoracic	3.5% (0.7 - 9.8%)	17.3% (12.5 - 23.0%)	**0.0007**
Hemoptysis	0.0% (0.0 - 4.2%)	12.2% (8.1 - 17.3%)	**<0.0001**
Massive Hemoptysis [2]	0.0% (0.0 - 4.2%)	0.5% (0.0 - 2.6%)	1.0000
Other Hemoptysis	0.0% (0.0 - 4.2%)	11.7% (7.7 - 16.8%)	**0.0003**
Pneumothorax	2.3% (0.3 - 8.1%)	4.7% (2.3 - 8.4%)	0.5192
Air leak > 7 days [2]	1.2% (0.0 - 6.2%)	1.9% (0.5 - 4.7%)	1.0000
Expanding Pneumothorax	2.3% (0.3 - 8.1%)	1.9% (0.5 - 4.7%)	1.0000
Stable Pneumothorax	0.0% (0.0 - 4.2%)	0.9% (0.1 - 3.3%)	1.0000
Empyema [2]	0.0% (0.0 - 4.2%)	0.0% (0.0 - 1.7%)	--
Pleural Effusion	0.0% (0.0 - 4.2%)	0.0% (0.0 - 1.7%)	--
Other Pulmonary/Thoracic AEs	1.2% (0.0 - 6.2%)	1.4% (0.3 - 4.0%)	1.0000
Non-cardiac Chest Pain	0.0% (0.0 - 4.2%)	0.9% (0.1 - 3.3%)	1.0000
Lung Mass/Cancer	1.2% (0.0 - 6.2%)	0.0% (0.0 - 1.7%)	0.2890
ARDS	0.0% (0.0 - 4.2%)	0.0% (0.0 - 1.7%)	--
Fractured Rib	0.0% (0.0 - 4.2%)	0.5% (0.0 - 2.6%)	1.0000
Wheezing Non-valve Related	0.0% (0.0 - 4.2%)	0.0% (0.0 - 1.7%)	--
All Valve / Implant Related		15.9% (11.3 - 21.5%)	
Expectoration/Aspiration/Migration		7.5% (4.3 - 11.9%)	
Pneumonia Distal to Valve [2]		4.2% (1.9 - 7.8%)	
Adverse tracheobronchial effect		7.0% (4.0 - 11.3%)	
Bronchial granulation tissue		6.5% (3.6 - 10.7%)	
Bronchial ulceration		0.0% (0.0 - 1.7%)	
Bronchial trauma		0.5% (0.0 - 2.6%)	
Dysphonia		0.0% (0.0 - 1.7%)	

Serious Adverse Events through 1 year	Control n = 87 % (95% CI)	Zephyr EBV n = 214 % (95% CI)	p value [1]
All General AEs	5.8% (1.9 - 12.9%)	8.9% (5.4 - 13.5%)	0.4833
Non-pulmonary infections	1.2% (0.0 - 6.2%)	1.4% (0.3 - 4.0%)	1.0000
Upper respiratory infections	0.0% (0.0 - 4.2%)	0.0% (0.0 - 1.7%)	--
Other non-pulm. infections	1.2% (0.0 - 6.2%)	1.4% (0.3 - 4.0%)	1.0000
Fever	0.0% (0.0 - 4.2%)	0.0% (0.0 - 1.7%)	--
Other Pain	0.0% (0.0 - 4.2%)	0.5% (0.0 - 2.6%)	1.0000
Gastrointestinal Adverse Events	1.2% (0.0 - 6.2%)	3.7% (1.6 - 7.2%)	0.4551
Nausea or Vomiting	0.0% (0.0 - 4.2%)	0.0% (0.0 - 1.7%)	--
Other General	3.5% (0.7 - 9.8%)	5.1% (2.6 - 9.0%)	0.7640

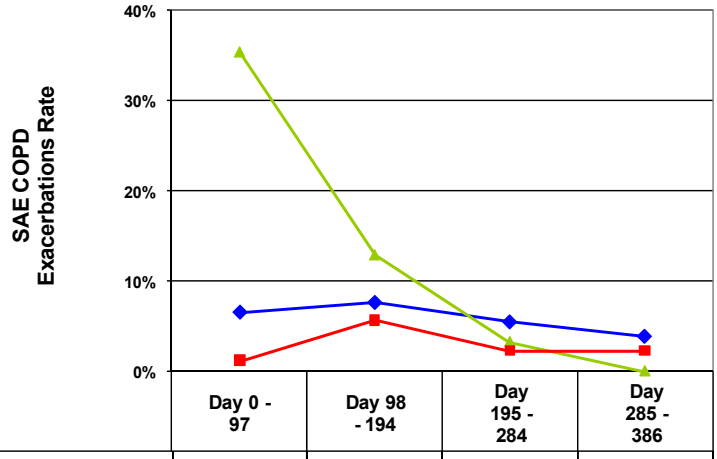
[1] Two-sided Fisher's exact test
[2] A component of the Major Complications Composite (MCC) as defined in Section 4.5.5
Source: Attachment 3, Amended Statistical Analysis Report, Figure 16:19

The significant differences between treatment groups included COPD / Emphysema SAEs, which were higher in Zephyr EBV Subjects (23.4%) compared with Control Subjects (10.3%, p = 0.0101); driven predominantly by those exacerbations requiring hospitalization. The occurrence of Pulmonary / Thoracic SAEs was higher in Zephyr EBV Subjects (17.3%) compared with Control Subjects (3.5%, p = 0.0007); this was driven by the rate of hemoptysis (12.2% vs. 0.0%, p < 0.0001). The remaining rates of SAEs were not significantly different between the Zephyr EBV Subjects and Control Subjects.

13.2.4 Serious Adverse Events by Quarter

The disproportion of SAEs occurring in relation to use of the Zephyr EBV was more pronounced during the first 3 to 6 months after valve placement, following the trend of the adverse events overall. SAE COPD Exacerbation rates for Zephyr EBV Subjects approached the rates for Control Subjects in the fourth quarter of study follow-up. SAE COPD Exacerbations in the first quarter were often treated with valve removal. Zephyr EBV Treatment Subjects experienced SAE COPD Exacerbations at a declining rate after the first six months of follow-up independent of valve removal.

Figure 22 Chart: SAEs – COPD Exacerbations Rates by Valve Removal by Quarter

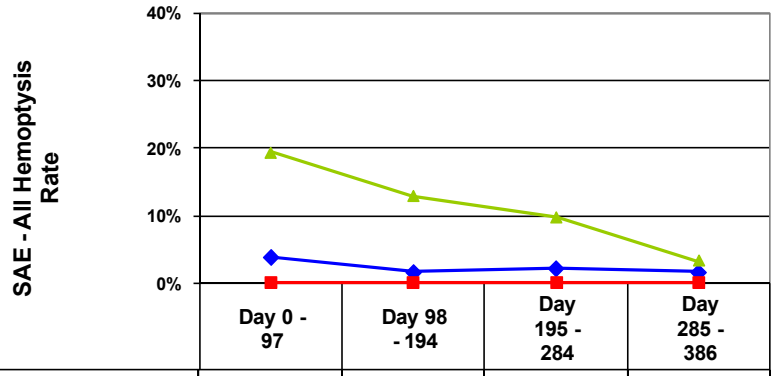


	Day 0 - 97	Day 98 - 194	Day 195 - 284	Day 285 - 386
Tx - No Removals, n=183	6.6%	7.7%	5.5%	3.8%
Tx - With Removals, n=31	35.5%	12.9%	3.2%	0.0%
Control, n=87	1.2%	5.8%	2.3%	2.3%

Source: Attachment 3, Amended Statistical Analysis Report, Figure 19:13

The rate of Zephyr EBV Treatment Subjects with SAE Hemoptysis declined over the 1-year study follow-up period.

Figure 23 Chart: SAEs – All Hemoptysis Rates by Quarter



	Day 0 - 97	Day 98 - 194	Day 195 - 284	Day 285 - 386
Tx - No removals, n=183	3.8%	1.6%	2.2%	1.6%
Tx - With removals, n=31	19.4%	12.9%	9.7%	3.2%
Control , n=87	0.0%	0.0%	0.0%	0.0%

Source: Attachment 3, Amended Statistical Analysis Report, Figure 19:14

13.2.5 Device-Related Adverse Events

All adverse events were adjudicated by the CEC, which categorized each event as Not Related, Remote, Possible, or Probable with respect to the Zephyr EBV Device-relatedness or Procedural relatedness. The tables below summarize the CEC findings for events during the procedure hospitalization and for events occurring after discharge for the procedure.

Of the 118 adverse events reported in Zephyr EBV Subjects during the initial procedure hospitalization, 40.7% were not related, 5.9% were remote, 40.7% were possible, and 12.7% were probable with respect to device-relatedness. The 15 "probable" device-related adverse events during the initial hospitalization included hypoxemia (2), prolonged air leak (2), stable pneumothorax (2), pleural effusion (1), non-cardiac chest pain (6), wheezing not related to the valve (1) and pneumonia distal to valve (1).

Please refer to Attachment 3, Amended Statistical Analysis Report, Table 18:1 for detailed tabulation.

Of the 734 adverse events reported in Zephyr EBV Subjects after the initial procedure hospitalization, 28.5% were not related, 36.0% were remote, 27.7% were possible, and 7.9% were probable with respect to device-relatedness. The 58 "probable" device-related adverse events after the initial hospitalization included death (1), hypoxemia (1), massive hemoptysis (1), other hemoptysis (18), expanding pneumothorax (2), wheezing not related to the valve (7), pneumonia distal to valve (8) and bronchial granulation tissue (20).

Please refer to Attachment 3, Amended Statistical Analysis Report, Table 18:2 for detailed tabulation.

13.2.6 Procedure-Related Adverse Events

Of the 118 adverse events reported in Zephyr EBV Subjects during the initial procedure hospitalization, 12.7% were not related, none were remote, 2.5% were possible, and 84.7% were probable with respect to procedure-relatedness. The 100 "probable" procedure-related adverse events during the initial hospitalization included general cardiovascular (1), arrhythmia (1), COPD exacerbation with hospitalization (1), COPD exacerbation without hospitalization (2), increased SOB (4), cough (4), bronchospasm (3), new or worsening hypercapnia (4), hypoxemia (8), hemoptysis (22), prolonged pneumothorax (2), expanding pneumothorax (1), stable pneumothorax (3), pleural effusion (1), non-cardiac chest pain (12), valve expectoration (2), bronchial trauma (1), dysphonia (3), and other general adverse events (26).

Please refer to Appendix 7-5-8, Statistical Analysis of the VENT Pivotal Trial, Table 18:5 for detailed tabulation.

Of the 734 adverse events reported in Zephyr EBV Subjects after the initial procedure hospitalization, 78.7% were not related, 8.4% were remote, 8.3% were possible, and 4.5% were probable with respect to procedure-relatedness. The 33 "probable" procedure-related adverse events after the initial hospitalization included COPD exacerbation with hospitalization (1), COPD exacerbation without hospitalization (1), increased SOB (2), cough (4), bronchospasm (1), hypoxemia (1), other hemoptysis (10), wheezing not related to valve (1), valve expectoration/migration (3) and other general adverse events (9).

Please refer to Attachment 3, Amended Statistical Analysis Report, Table 18:6 for detailed tabulation.

13.3 Zephyr EBV Subjects with Specific Adverse Events

13.3.1 Granulation Tissue

During symptom-driven bronchoscopy, 17 Zephyr EBV Subjects (7.9% of 214 subjects) were found to have granulation tissue narrowing the airways adjacent to valves during the course of study follow-up. These subjects developed moderate tissue formation adjacent to one or more valves. The observed granulation tissue was felt to be typical reactive tissue that can form adjacent to any foreign body present in the airways, such as that which forms at the distal end of an indwelling metal tracheostomy.

Table 80 Zephyr EBV Subjects with Granulation Tissue

Subject ID	Action Taken	Days Post-Procedure
	Valve Removal	86[1]
	Electrocautery & Topical Mitomycin Electrocautery & Topical Mitomycin Electrocautery & Topical Mitomycin	124 231 351
	Valve Removal	166
	Valve Removal	194
	Valve Removal	25
	Valve Removal	327
	Exploratory Bronchoscopy	198
	None	146
	Drug Therapy	34
	Valve Removal	275
	Valve Removal	19

Action Taken	Days Post-Procedure
Valve Removal	288
Valve Removal	244
Valve Removal	211
Valve Removal	88
Valve Removal	84
Exploratory Bronchoscopy	83
Cryotherapy	113

ranulation tissue was diagnosed during Valve Removal procedure. Valve Removal ot a result of diagnosis of Granulation Tissue.
Source: P070025, September 21, 2007, Volume 011, Page 122

13.3.2 Valve Expectoration or Migration*

Valve migration occurred when the valve was not retained in the original position within the target bronchus. Valve migration outside the target bronchus occurred when the valve migrated to a non-target bronchus, and valve expectoration occurred when the valve migrated out of the target bronchus and was subsequently coughed out by the subject. Seventeen (17) Zephyr EBV Subjects (7.9% of 214) experienced valve migration. Of these, 9 subjects (4.2%) had 1 or more valves that migrated, but were not expectorated, 6 subjects (2.8%) expectorated 1 or more valves, and 2 subjects (0.9%) had at least one migration without expectoration and at least one expectoration during the course of study follow-up.

* Effort was made to obtain bronchoscopic video of the placement procedure when valve migration was reported. Of the 23 instances of Zephyr EBV migration, procedural video was obtained for 14. A qualitative assessment was made by Emphasys technical personnel. They identified 3 probable root-causes for the migration (see bullet points below). Based on these findings, additional training was initiated. Additionally, a visual "marker band" (original PMA Vol. 001, Page 80) has been added to the distal end of the delivery catheter in order to aid physicians in calibrating the depth of the bronchial target and the longitudinal position of the valve relative to the carina of the target bronchus. This marker band was not implemented during the conduct of the study.

- Bronchial target too short for Zephyr EBV placement (2/14)
- Zephyr EBV placed too proximal within target bronchus (6/14)
- Bronchial target too large in diameter for Zephyr EBV placement (5/14)
- Zephyr EBV did not migrate – compared follow-up video to procedural video (1/14)

Table 81 Zephyr EBV Subjects with Valve Migrations or Expectorations

Zephyr EBV Group	% (n)
Subjects with Valve Migrations or Expectorations	7.9% (17 / 214)
Migration Only	4.2% (9 / 214)
One valve migrated within target bronchus	1.4% (3 / 214)
One valve migrated outside target bronchus	2.3% (5 / 214)
One valve migrated within, and 3 valves migrated outside target bronchus	0.5% (1 / 214)
Expectorated	3.7% (8 / 214)
One valve expectorated	2.3% (5 / 214)
Two valve expectorated	0.5% (1 / 214)
One valve expectorated and one valve migrated within target bronchus	0.5% (1 / 214)
One valve expectorated and one valve migrated outside target bronchus	0.5% (1 / 214)

Source: P070025, September 21, 2007, Volume 011, Page 123

There were 820 valves implanted and not removed procedurally in the 214 subjects with one or more valves implanted. Of these 820 valves, 23 valves (2.8%) in 17 subjects migrated or were expectorated. Of these, 4 valves (0.5%) migrated within the target bronchus, 10 migrated outside the target bronchus (1.2%), and 9 valves (1.1%) were expectorated. Fourteen (14) of these 17 Zephyr EBV Subjects had at least 1 migrated or expectorated valve replaced.

Table 82 Summary: Zephyr EBV Subjects with Valve Expectoration or Migration

Subject ID	Expectoration/Migration Description	Number of Valves	Action Taken	Days Post Procedure
	Contralateral migration	1	Valve removed - not replaced	274
	Expectoration from lungs	1	Valve replaced	20
	Migration within target bronchus	1	Valve removed - not replaced	244
	Expectoration from lungs	1	Valve replaced	3
	Contralateral migration	1	Valve removed and replaced	19
	Expectoration from lungs	1	Valve replaced	0
	Ipsilateral migration	1	Valve removed and replaced	66
	Contralateral migration	1	Valve removed and replaced	186
	Migration within target lobe	1	Valve removed and replaced	192
	Proximal Migration within target bronchus	1	Valve removed and replaced	224
	Contralateral migration	1	Valve removed and replaced	25
	Ipsilateral migration	1	Valve removed and replaced	38

Subject ID	Expectoration/Migration Description	Number of Valves	Action Taken	Days Post Procedure
	Expectoration from lungs	1	Valve not replaced	200
	Expectoration from lungs	1	Valve replaced	0
	Expectoration from lungs	1	Valve not replaced	16
	Distal Migration within target bronchus	1	Valve left in place - additional valve placed adjacent to existing valve	100
	Expectoration from lungs	1	Valve replaced	2
	Proximal Migration within target bronchus	1	Valve removed and replaced	12
	Ipsilateral migration	1	Valve removed and replaced	160
	Expectoration from lungs	1	Valve replaced	273
	Expectoration from lungs	1	Valve replaced	21
	Ipsilateral migration	1	All implanted valves removed - not replaced	0
	Proximal Migration within target bronchus	1	Valve removed and replaced	0
Total		**23**		

Source: P070025, September 21, 2007, Volume 011, Page 123-124.

13.3.3 Pneumonia Distal to Valves

Nine (9) Zephyr EBV Subjects (4.2%) had pneumonia distal to valves during the 1 year follow-up period. All subjects received drug therapy and valves were removed from 3 of the 9 subjects (33.3%). Eight (8) of the 9 resolved during the study follow-up period and one was ongoing at the end of the 1-year study follow-up period. The subject with an unresolved pneumonia distal to valves at study exit had been admitted for treatment (drug therapy and bronchoscopy) during the trial and was discharged on oral antibiotics three days post study exit. The valves in this subject were not removed during bronchoscopy.

Table 83 Zephyr EBV Subjects with Pneumonia Distal to Valves

	Actions Taken	Days Post Procedure	Resolved
	Drug Therapy, Valve Removal	0[1]	Yes
	Drug Therapy, Bronchoscopy	356	Ongoing
	Drug Therapy, Hospitalization	163	Yes
	Drug Therapy	275	Yes
	Drug Therapy, Bronchoscopy, Hospitalization	230	Yes
	Drug Therapy	208	Yes
	Drug Therapy, Valve Removal	258	Yes
	Drug Therapy, Valve Removal	208	Yes
	Drug Therapy, Hospitalization	15	Yes

[1] Date of onset was reported by site as Unknown. Earliest possible onset date was the date of the EBV procedure.
Source: P070025, September 21, 2007, Volume 011, Page 125

13.3.4 Massive Hemoptysis

Subject complained of recurrent hemoptysis, possible vomiting of blood, and dyspnea between the original procedure and Day 8 of follow-up. On Day 8, the subject experienced increased hemoptysis followed by cardiorespiratory arrest. He was intubated and ventilated, but after two weeks clear evidence of irreversible hypoxic brain led to withdrawal of support and subsequent death. Autopsy revealed advanced bullous emphysema with all 4 stents in position without perforation, migration or intrusion into blood vessels, and without any clear source of bleeding. This event was reviewed by the DSMB and promptly communicated to the FDA, IRBs and participating Investigators with recommendations for close monitoring of subjects with recurrent hemoptysis. No other case of massive hemoptysis occurred during study follow-up.

13.3.5 Valve Treatment for Persistent Air Leak

Subject was a Zephyr EBV Subject who developed a complete left pneumothorax on the day after valve implantation. A chest tube was inserted and the pneumothorax significantly cleared. However, he continued to have a large, persistent air leak and subcutaneous emphysema. A Compassionate Use request to the FDA to utilize Zephyr EBVs to resolve this air leak was approved (G020230 / S39) and on the 9th day after implantation 2 additional Zephyr EBVs were placed in the superior segment of the left lower lobe after isolating the air leak by balloon occlusion. After the procedure, the air leak was significantly reduced, but a small air leak still remained. The chest tube was left in place after the procedure. The suction used on the chest tube was reduced after the procedure and the subject's air leak completely sealed eight days post Zephyr EBV Treatment. The chest tube was removed three days later and the subject was discharged

from the hospital the following day. The subject was evaluated 2 – 3 weeks from discharge and was reported as returning to normal activities.

13.4 Valve Removal during Study Follow-Up

Thirty-one (31, 14.5%) of Zephyr EBV Subjects underwent the removal of one or more Zephyr EBV valves during the course of study follow-up. Eighty seven (87) valves underwent one or more remova h 85 of the 87 valves (97.7%) being successfully removed. Subject had a total of 4 valves removed in 4 separate procedures: 2 valves successfully removed in two procedures, followed by a third procedure in which 2 additional valves could not be removed, followed two days later by removal of those 2 valves. Subject had 4 of 5 valves removed successfully in a first procedure and the 5th valve successfully removed 50 days later. The only 2 valves which were not successfully retrieved were in Subjec who had 2 of 4 attempted valves removed in a single procedure and no subsequent procedure to attempt removal of the remaining 2 valves.

Table 84 Per-Subject Reasons for Attempted Valve Removal during Study Follow-up

Zephyr EBV Group (per subject)	% (n) [1]
Migration	25.8% (8 / 31)
Post Obstructive Pneumonia	3.2% (1 / 31)
Pneumonia, Hemoptysis	3.2% (1 / 31)
Hemoptysis	3.2% (1 / 31)
Hemoptysis & Granulation Tissue	3.2% (1 / 31)
Granulation	3.2% (1 / 31)
Granulation and Migration	3.2% (1 / 31)
Subject's Request	22.6% (7 / 31)
Placed in Incorrect Airway	9.7% (3 / 31)
Increased Dyspnea	3.2% (1 / 31)
Continuing COPD Exacerbation	6.5% (2 / 31)
To Access Distal Airway for Biopsy	3.2% (1 / 31)
Other	9.7% (3 / 31)

[1] Denominator = 31 subjects with valve removal attempted
Source: P070025, September 21, 2007, Volume 011, Page 126

Twelve (12) valves were removed due to migration, 3 due to post-obstructive pneumonia, 5 due to hemoptysis, 8 due to granulation, 28 at the subject's request, 7 placed in incorrect airways, 3 due to increased dyspnea, and 7 due to continuing COPD exacerbations. Other reasons for valve removal included removal prior to LVRS, endobronchial erosion with suppuration, and to allow distal biopsy.

Of the 44 specific instances of valve removal, 33 resulted in resolution of the reason for that intervention in 25 of these 31 Zephyr EBV Subjects (80.6% resolution rate). The

unresolved adverse events in the 6 subjects without resolution despite valve removal were COPD exacerbation (1), pneumonia and hemoptysis (1), granulation tissue (1), hemoptysis (1), hemoptysis and granulation tissue (1) and endobronchial erosion and suppuration (1).

Table 85 Summary: Valve Removal during Study Follow-Up

Day [1]	Removal S / A [2]	Reason(s) for Removal	Status / Day [3]
160	1 / 1	Valve Migrated	Resolved / 160
70	4 / 4	Subject Request (Not feeling better)	Resolved / 71
134	5 / 5	Continuing COPD Exacerbation	Ongoing at study exit [4]
242	7 / 7	Subject Request (Worsened breathing)	Resolved / 243
296	1 / 1	Post-obstructive Pneumonia	Resolved / 301
132	4 / 4	Subject Request (Shortness of breath)	Resolved / 132
86 113 239 241	1 / 1 1 / 1 0 / 2 2 / *	Non-functioning Valve B2b Removed B2a to Place Large Valve in B2 Pneumonia and Continued Hemoptysis Pneumonia and Continued Hemoptysis	Resolved / 86 Resolved /113 Pneumonia: Resolved / 268; Hemoptysis: Ongoing at study exit; Pneumonia: Resolved / 268; Hemoptysis: Ongoing at study exit
38	2 / 2	Planned Removal [5]	Resolved / 38
166 263	1 / 1 3 / 3	Granulation Tissue Granulation Tissue	Ongoing at study exit Ongoing at study exit
111 188 194 224	1 / 1 1 / 1 1 / 1 1 / 1	Valve Migration Valve Migration Valve Migration Valve Migration	Resolved / 111 Resolved / 188 Resolved / 194 Resolved / 224
25 84	1 / 1 3 / 3	Valve Migration Granulation Tissue	Resolved / 25 Resolved / 84
29	1 / 1	Valve Migration	Resolved / 29
7	2 / 2	Placed in Incorrect Lobe	Resolved / 7
327 377	4 / 5 1 / *	Hemoptysis Hemoptysis	Ongoing at study exit [6] Ongoing at study exit [6]
25	3 / 3	Increased Dyspnea	Resolved / 39
85	4 / 4	Subject Request (No details)	Resolved / 85
78	1 / 1	Hemoptysis Granulation Tissue	Hemoptysis: Ongoing at study exit; Granulation Tissue: Ongoing at study exit
275	1 / 1	Valve Migration	Resolved / 275
294	3 / 3	Pre-LVRS	Resolved / 294
74	1 / 1	Valve Migration	Resolved / 74
25	1 / 1	Valve Migration	Resolved / 25
288	2 / 4	Subject Request (No details)	Resolved / 288
244	1 / 1	Valve Migration	Resolved / 244
120	3 / 3	Subject Request, Worsened PFTs (Not feeling better and worsened PFTs)	Resolved / 120

Subject ID	Day [1]	Removal S / A [2]	Reason(s) for Removal	Status / Day [3]
	19	2 / 2	Continuing COPD Exacerbation	Resolved / 29
	1	5 / 5	Placed in Incorrect Lobe	Resolved / 1
	211	4 / 4	Subject Request (No details)	Resolved / 211
	88	1 / 1	Valve Migration	Resolved / 88
	38	1 / 1	Valve Migration	Resolved / 38
	99	3 / 3	To Biopsy Mass Distal to Valves	Resolved / 99
	210	1 / 1	Endobronchial Erosion and Suppuration	Ongoing at study exit

[1] Day of removal procedure(s), based on Start Date(s) reported on Event Log
[2] S / A = successful / attempted removals
[3] Status / Day = Post-EBV Removal, status and resolution day of event that triggered valve removal attempt(s). Event was noted as "Resolved" if Stop Date was provided and "Ongoing" if Stop Date was not provided. If EBV removal was per subject's request, then status and resolution day of EBV Removal was reported.
[4] Subject prematurely discontinued study at Day 284 post-randomization.
[5] Tempo or air leak (compassionate use in Zephyr EBV study subject)
[6] Subject prematurely exited study; last visit was made on Day 183 post-randomization.
* Same valve(s) reattempted
Source: P070025, September 21, 2007, Volume 011, Page 127-128

13.5 Summary: Adverse Event Profile through One Year

Mortality: all-cause mortality was similar in the two groups through one year of follow-up, with 3.5% (95% CI 0.7 – 9.8%) of Control Subjects and 3.7% (95% CI 1.6 – 7.2%) of Zephyr EBV Subjects dying of any cause during the year. This difference was not significant.

COPD / Emphysema Adverse Events: The VENT Pivotal Study revealed the high degree of pulmonary morbidity present in subjects with severe heterogeneous emphysema, with 77.6% of Zephyr EBV Subjects and 62.1% of Control Subjects having one or more COPD / emphysema category adverse events; this difference was significant ($p = 0.0095$). This difference was driven by the following subcategories of adverse events: COPD exacerbation (72.4% Zephyr EBV Subjects and 57.5% Control Subjects, $p = 0.0141$, Other Pulmonary Infection (8.4% compared with 1.2% respectively, $p = 0.0174$), Increased SOB (9.8% compared with 2.3% respectively, $p = 0.0295$) and Altered ABGs (8.4% compared with 1.2% respectively, $p = 0.0174$).

When serious adverse events are examined only COPD Exacerbation is significantly different, with an 23.4% rate for Zephyr EBV Subjects and a 10.3% rate for Control Subjects ($p = 0.0101$).

Pulmonary / Thoracic Adverse Events: The rate of these adverse events was much higher in Zephyr EBV Subjects, 52.8%, compared with Control Subjects, 9.2% ($p < 0.0001$). This difference was driven by the following subcategories of adverse events:

hemoptysis (42.1% Zephyr EBV Subjects compared with 2.3% in Control Subjects, $p < 0.0001$), and Noncardiac Chest Pain (16.4% compared with 3.5%, $p = 0.0018$).

When serious adverse events are examined, only other hemoptysis remains significantly more frequent in Zephyr EBV Subjects, 11.7%, compared with 0.0% in Control Subjects ($p = 0.0003$).

General / Other Adverse Events: The remaining categories of adverse events occurred somewhat more frequently in Zephyr EBV Subjects, 49.1%, compared with Control Subjects, 33.3% ($p = 0.015$). Rates that were higher in Zephyr EBV Subjects included nausea and vomiting (often related to procedure sedation), headaches, sore throat and similar minor complaints.

There are no significant differences in the rate of serious adverse events for General / Other adverse events.

Resolution of Adverse Events: Most of these adverse event and serious adverse event rates decline after the first three months of follow-up, suggesting that the passage of time and when indicated removal of one or more valves are effective responses to these events.

Valve Expectoration or Migration: Of 820 implanted valves at the completion of the initial procedure, 23 (2.8%) migrated or were expectorated in 17 subjects between Days 0 and 274 without significant sequelae, and 14 subjects had at least one of these valves replaced during study follow-up.

Pneumonia Distal to Valves: 9 Zephyr EBV Subjects (4.2%) had pneumonia distal to valves and received drug therapy (9) and valve removal (3). Eight (8) of the 9 resolved during the study follow-up period and one subject, with onset on Day 356, was still under treatment at the end of the 1-year study follow-up period.

Massive Hemoptysis: One Zephyr EBV Subject experienced dyspnea and, hemoptysis between Days 0 and 8, and then presented in cardiorespiratory arrest on Day 8 and died thereafter of hypoxic brain damage. Autopsy revealed bullous emphysema, 4 intact and well-positioned valves, and no obvious source of bleeding.

Valve Treatment for Persistent Air Leak: One Zephyr EBV Subject developed complete left pneumothorax on Day 1, with only partial resolution after chest tube placement. Compassionate Use treatment with 2 additional valves in the superior segment of the left lower lobe significantly reduced but did not eliminate the air leak until 8 days later.

Valve Removal During Study Follow-Up: Thirty one (31, 14.5%) Zephyr EBV Subjects had one or more valves removed after the initial procedure. Eighty five (85) of 87 valves attempted were successfully removed (97.7%). Of these 31 subjects, 25 (80.6%) had resolution of the reason for the intervention following valve removal.

14.0 OUTCOME MEASURES AT ONE YEAR

14.1 Introduction

Although the VENT Pivotal Study was not designed to assess effectiveness outcomes past 6 months, *post hoc* assessments of effectiveness outcome measures were made for Completed Cases subjects with one year follow-up data. These analyses included:

14.2. Effectiveness Outcome Measures at 1 Year
- 14.2.1. Percent Change in FEV_1 at 1 Year
- 14.2.2. High Heterogeneity Percent Change in FEV_1 at 1 Year
- 14.2.3. Percent Change in 6MWT at 1 Year
- 14.2.4. High Heterogeneity Percent Change in 6MWT at 1 Year
- 14.2.5. Change in SGRQ at 1 Year
- 14.2.6. Change in mMRC Dyspnea Scale at 1 Year
- 14.2.7. Change in Maximum Workload during Cycle Ergometry at 1 Year
- 14.2.8. Change in Use of Supplemental Oxygen at 1 Year

14.3. Matched 6 Month and 1 Year FEV1 and 6MWT Data
- 14.3.1. Matched 6 Month and 1 Year FEV_1 Outcomes
- 14.3.2. High Heterogeneity Matched 3, 6, and 12 Month FEV_1 Outcomes
- 14.3.3. Matched 6-Month and 1-Year 6MWT Outcomes
- 14.3.4. High Heterogeneity Matched 3, 6, and 12 Month 6MWT Outcomes

14.4. Summary: Effectiveness Outcome Measures at 1 Year

14.2 Effectiveness Outcome Measures at 1 Year

14.2.1 Percent Change in FEV_1 at 1 Year

At the end of 1 year of follow-up, Completed-Cases Zephyr EBV Subjects demonstrated a 6.7% higher FEV_1 and Control Subjects a 1.4% lower FEV_1, for an 8.1% net difference between the two groups (95% CI 4.0, 12.2%). This persistent Zephyr EBV treatment benefit was slightly larger than the 7.2% net difference observed at 6 months.

Table 86 Percent Change in FEV_1 at 1 Year (CC)

FEV_1 – % Change from Baseline	Control Mean (SD) N Median (Min, Max)	Zephyr EBV Mean (SD) N Median (Min, Max)	Delta [1] (95% CI)
CC Subjects	–1.4 (10.8) 74 –1.7 (–29.1, 31.6)	6.7 (22.1) 175 2.0 (–34.2, 88.4)	8.1 (4.0, 12.2)

[1] Difference in means and unequal variance t-test confidence interval
Source: Attachment 3, Amended Statistical Analysis Report, Table 15:1

14.2.2 High Heterogeneity Subgroup: Percent Change in FEV_1 at 1 Year

In the High Heterogeneity Subgroup at the end of 1 year of follow-up, Zephyr EBV Subjects demonstrated a 13.6% higher FEV_1 and Control Subjects a 1.6% lower FEV_1, for a 15.2% net difference between the two groups (95% CI 9.1, 21.2%). This persistent Zephyr EBV treatment benefit was greater than the 8.1% net difference observed in the entire CC cohort at 1 year.

Table 87 High Heterogeneity Subgroup: Percent Change in FEV_1 at 1 Year (CC)

FEV_1 – % Change from Baseline	Control Mean (SD) N Median (Min, Max)	Zephyr EBV Mean (SD) N Median (Min, Max)	Delta [1] (95% CI)
CC Subjects	-1.6 (10.4) 41 0.0 (-29.1, 21.8)	13.6 (24.2) 87 10.2 (-32.5, 88.4)	15.2 (9.1, 21.2)

[1] Difference in means and unequal variance t-test confidence interval
Source: Attachment 3, Amended Statistical Analysis Report, Table 25:11

14.2.3 Percent Change in 6MWT at 1 Year

At the end of 1 year of follow-up, Zephyr EBV Subjects in the Completed-Cases analysis of 6MWT demonstrated a 0.4% reduction and Control Subjects a 3.9% reduction, for a 3.7% net Zephyr EBV treatment benefit (95% CI 1.8, 9.2%).

Table 88 Percent Change in 6MWT at 1 Year (CC)

6MWT – % Change from Baseline	Control Mean (SD) N Median (Min, Max)	Zephyr EBV Mean (SD) N Median (Min, Max)	Delta [1] (95% CI)
CC Subjects	–3.9 (16.9) 75 -3.2 (-63.1, 31.6)	–0.4 (26.3) 173 1.1(-98.3, 108.0)	3.6 (–1.8, 9.2)

[1] Difference in means and unequal variance t-test confidence interval (-3.9)- (-0.4) = 3.6 due to rounding)
Source: Attachment 3, Amended Statistical Analysis Report, Table 15:2

14.2.4 High Heterogeneity Subgroup: Percent Change in 6MWT at 1 Year

In the High Heterogeneity Subgroup at the end of 1 year of follow-up, Zephyr EBV Subjects demonstrated a 3.1% higher 6MWT and Control Subjects a 5.0% reduction, for an 8.2% net Zephyr EBV treatment benefit (95% CI −0.4, 16.7%).

Table 89 High Heterogeneity Subgroup: Percent Change in 6MWT at 1 Year (CC)

FEV_1 – % Change from Baseline	Control Mean (SD) N Median (Min, Max)	Zephyr EBV Mean (SD) N Median (Min, Max)	Delta (95% CI) [1]
CC Subjects	-5.0 (19.2) 41 -3.5 (-63.1, 29.5)	3.1 (29.2) 87 3.2 (-75.6, 108.0)	8.2 (-0.4, 16.7)

[1] Difference in means and unequal variance t-test confidence interval (3.1)- (-5.0) = 8.2 due to rounding)
Source: Attachment 3, Amended Statistical Analysis Report, Table 25:11

14.2.5 Change in SGRQ at 1 Year

At the end of 1 year of follow-up, Zephyr EBV Subjects in the Completed-Cases analysis of SGRQ demonstrated a mean 1.7 point improvement (score reduction) and the Control Subjects had a mean 1.2 point deterioration (score increase), a net Zephyr EBV treatment benefit of −2.8 (95% CI −6.2, 0.6).

Table 90 Change in SGRQ at 1 Year (CC)

SGRQ – Change from Baseline	Control Mean (SD) N Median (Min, Max)	Zephyr EBV Mean (SD) N Median (Min, Max)	Delta [1] (95% CI)
CC Subjects	1.3 (9.0) 61 0.9 (-19.7, 28.7)	-1.7 (14.4) 149 -2.1 (-39.3, 46.6)	-3.0 (-6.3, 0.2) [1]

[1] Difference in means and unequal variance t-test confidence interval
Source: Attachment 3, Amended Statistical Analysis Report, Table 25.1

14.2.6 Change in mMRC Dyspnea Scale at 1 Year

At the end of 1 year of follow-up, Zephyr EBV Subjects in the Completed-Cases analysis of the mMRC Dyspnea Scale demonstrated a mean 0.03 point deterioration (score increase) and the Control Subjects had a mean 0.14 point deterioration (score increase), no difference of –0.0 (95% CI −0.0, 0.0).

Table 91 Change in mMRC Dyspnea Scale at 1 Year

mMRC – Change from Baseline	Control Mean (SD) N Median (Min, Max)	Zephyr EBV Mean (SD) N Median (Min, Max)	Delta [1] (95% CI)[2]
Subjects	0.14 (1.09) 66 0.00 (-3.00, 4.00)	0.03 (1.10) 159 0.00 (-4.00, 3.00)	0.00 [3] (0.00, 0.00) [4]

[1] Difference in medians
[2] Non-parametric confidence interval
Source: Attachment 3, Amended Statistical Analysis Report, Table 25.1

14.2.7 Change in Maximum Workload during Cycle Ergometry at 1 Year

At the end of 1 year of follow-up, Zephyr EBV Subjects in the Completed-Cases analysis of maximum workload during cycle ergometry had a mean 2.0 watt deterioration and the Control Subjects had a mean 5.1 watt deterioration, a net Zephyr EBV treatment benefit of 3.2 watts (95% CI −0.8, 7.2).

Table 92 Change in Maximum Workload during Cycle Ergometry at 1 Year (CC)

Cycle Ergometry – Change from Baseline	Control Mean (SD) N Median (Min, Max)	Zephyr EBV Mean (SD) N Median (Min, Max)	Delta [1] (95% CI)
CC Subjects	-5.1 (12.3) 69 0.0 (-50.0, 20.0)	-2.0 (17.3) 154 0.00 (-120.0, 50.0)	3.2 (-0.8, 7.2) [1]

[1] Difference of means and unequal variance t-test confidence interval (-2.0)- (-5.1) = 3.2 due to rounding)
Source: Attachment 3, Amended Statistical Analysis Report, Table 25.1

14.2.8 Change in Use of Supplemental Oxygen at 1 Year

At the end of 1 year of follow-up, Zephyr EBV Subjects in the Completed-Cases analysis of supplemental oxygen use showed an increased use of 109.5 liters / day and the Control Subjects showed an increased use of 172.3 liters / day, a net Zephyr EBV treatment benefit of −62.8liters a day (95% CI −302.5, 176.9).

Table 93 Change in Use of Supplemental Oxygen at 1 Year (CC)

Supplemental O_2 – Change from Baseline	Control Mean (SD) N Median (Min, Max)	Zephyr EBV Mean (SD) N Median (Min, Max)	Delta [1] (95% CI)
CC Subjects (liters / day)	172.3 (744.05) 72 0.0 (-1680.0, 3150.0)	109.5 (1100.61) 171 0.0 (-3840.0, 4965.0)	-62.8 (-302.5, 176.9)[1]

[1] Difference of means and unequal variance t-test confidence interval
Source: Attachment 3, Amended Statistical Analysis Report, Table 25.1

14.3 Matched 3, 6, and 12 Month FEV_1 and 6MWT Data

A matched-groups data analysis was performed for FEV_1 and 6MWT for Completed Cases subjects with relevant data at baseline, three months, six months and one year to investigate the timing and durability of treatment response in comparable subjects. There were 133 Zephyr EBV Subjects and 57 Control Subjects with FEV_1 data at baseline, three months, six months, and one year. There were 129 Zephyr EBV Subjects and 56 Control Subjects with 6MWT data at baseline, three months, six months, and one year.

14.3.1 Matched 3, 6, and 12 Month FEV_1 Outcomes

Matched-group Zephyr EBV Subjects had a net increase in FEV_1 of 3.9% compared with the matched-groups Control Subjects at three months (95% CI, -0.7 – 8.5%). This improvement increased to a net increase in FEV_1 of 7.1% compared with the matched-pairs Control Subjects at six months (95% CI, 2.7 – 11.5%) and to 8.8% at one year (95% CI, 4.1 – 13.5%).

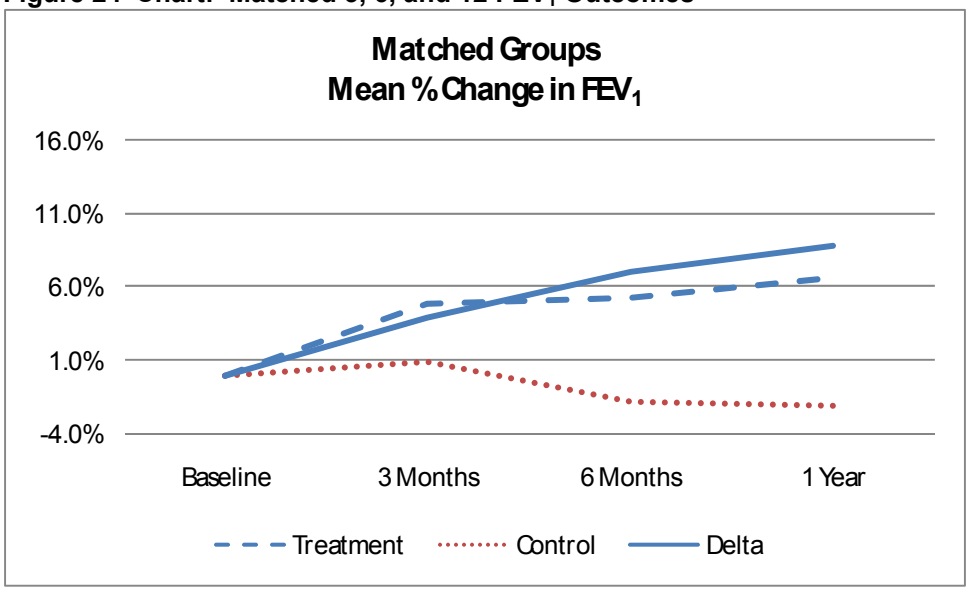
Table 94 Matched 3, 6, and 12 Month % Change in FEV_1

Percent Change in FEV_1	Control Mean (SD) N Median (Min, Max)	Zephyr EBV Mean (SD) N Median (Min, Max)	Delta [1] (95% CI)
3 Months	0.9 (11.8) 57 -1.2 (-26.4, 39.2)	4.9 (19.8) 133 1.2 (-33.7, 88.3)	3.9 (-0.7, 8.5)
6 Months	-1.8 (11.3) 57 -3.4 (-27.7, 25.5)	5.3 (19.0) 133 3.8 (-38.3, 65.7)	7.1 (2.7, 11.5)
1 Year	-2.1 (11.0) 57 -2.0 (-29.1, 23.0)	6.7 (21.6) 133 2.0 (-33.9, 88.4)	8.8 (4.1, 13.5)

[1] Difference of means and unequal variance t-test confidence interval (4.9)- (0.9) = 3.9 due to rounding)
Source: Attachment 3, Amended Statistical Analysis Report, Table 25:9

This continued benefit on disease progression throughout 1 year of follow-up as measured by FEV_1 is demonstrated in the following chart.

Figure 24 Chart: Matched 3, 6, and 12 FEV_1 Outcomes



Source: Attachment 3, Amended Statistical Analysis Report, Table 25:9

14.3.2 High Heterogeneity Subgroup Matched 3, 6, and 12 Month FEV_1 Outcomes

Matched-group Zephyr EBV Subjects in the High Heterogeneity Subgroup had a net increase in FEV_1 of 7.6% compared with the matched-groups Control Subjects at three months (95% CI, 0.8 – 14.3%). This improvement increased to a net increase in FEV_1 of 11.9% compared with the matched-pairs Control Subjects at six months (95% CI, 4.9 – 18.5%) and to 13.7% at one year (95% CI, 6.6 – 20.8%).

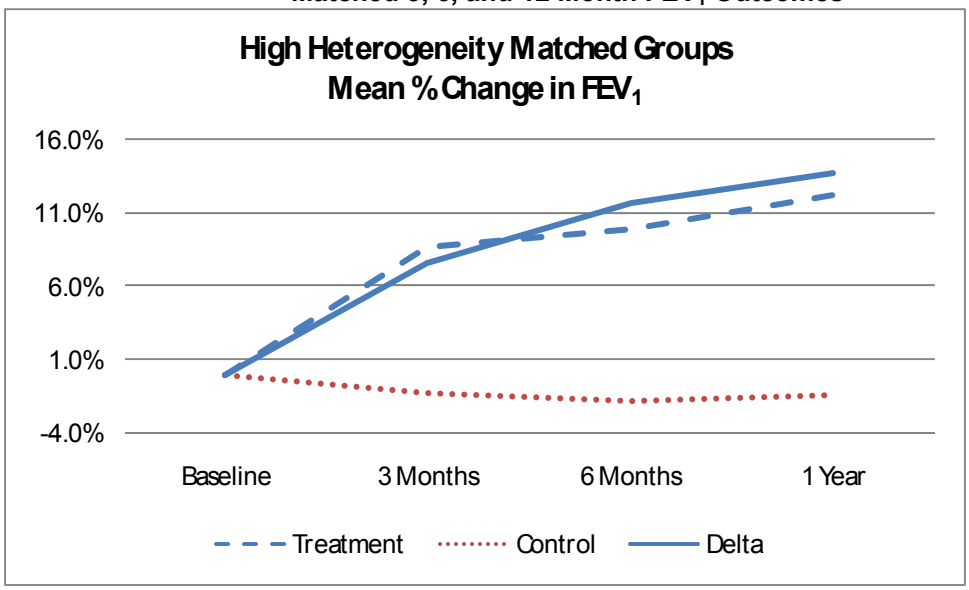
Table 95 High Heterogeneity Subgroup: Matched 3, 6, and 12 Month % Change in FEV_1

Percent Change in FEV_1	Control Mean (SD) N Median (Min, Max)	Zephyr EBV Mean (SD) N Median (Min, Max)	Delta [1] (95% CI)
3 Months	0.9 (11.4) 30 -1.3 (-26.4, 32.7)	8.5 (21.9) 66 3.5 (-26.1, 88.3)	7.6 (0.8, 14.3)
6 Months	-1.8 (11.5) 30 -4.2 (-19.2, 25.5)	10.0 (22.0) 66 7.7 (-38.3, 65.7)	11.9 (5.1, 18.6)
1 Year	-1.4 (11.4) 30 0.7 (-29.1, 21.8)	12.3 (23.6) 66 9.6 (-32.5, 88.4)	13.7 (6.6, 20.8)

[1] Difference of the means and unequal variance t-test confidence interval (10.0)- (-1.8) = 11.9 due to rounding)
Source: Attachment 3, Amended Statistical Analysis Report, Table 25:13

This continued benefit on disease progression in the High Heterogeneity Subgroup throughout 1 year of follow-up as measured by FEV_1 is demonstrated in the following chart.

Figure 25 Chart: High Heterogeneity Subgroup Matched 3, 6, and 12 Month FEV_1 Outcomes



Source: Attachment 3, Amended Statistical Analysis Report, Table 25:13

14.3.3 Matched 3, 6, and 12 Month 6MWT Outcomes

Matched-pairs Zephyr EBV Subjects had a net increase in 6MWT of 7.4% compared with the matched-pairs Control Subjects at three months (95% CI, 1.2 – 11.5%). At six months, Zephyr EBV Subjects had a net increase in 6MWT of 6.8% compared with the matched-pairs Control Subjects (95% CI, 0.5– 13.1%), and a net increase of 5.5% at 12 months (95% CI, -0.7 – 11.7%).

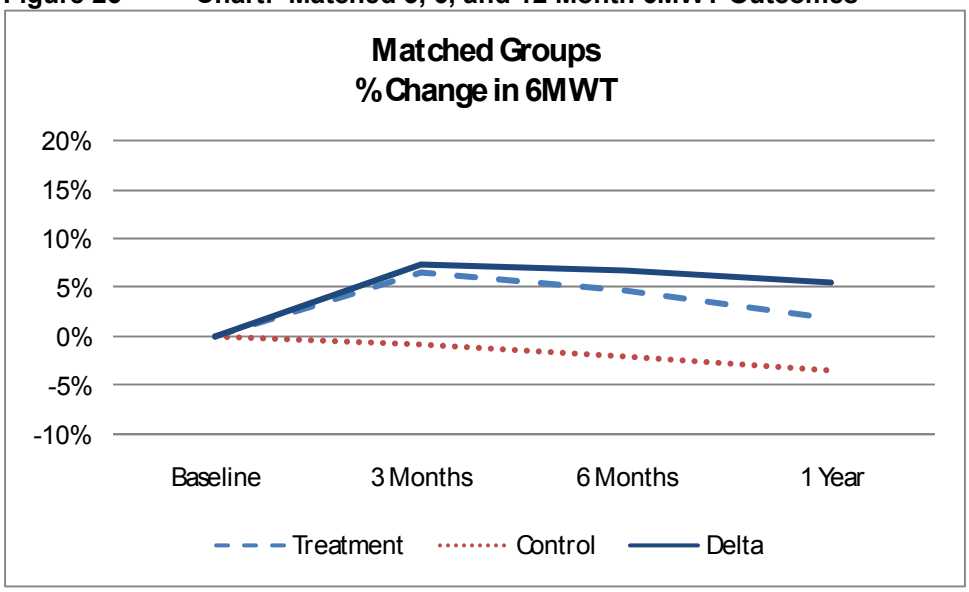
Table 96 Matched 3, 6, and 12 Month Data for Percent Change in 6MWT

Percent Change in 6MWT	Control Mean (SD) N Median (Min, Max)	Zephyr EBV Mean (SD) N Median (Min, Max)	Delta (95% CI)
3 Months	0.3 (19.2) 56 -0.8 (-55.4, 50.0)	6.9 (18.3) 129 6.6 (-43.7, 83.2)	7.4 [2] (1.2, 11.5)[3]
6 Months	-1.2 (24.5) 56 -2.1 (-54.9, 71.4)	4.9 (22.3) 129 4.7 (-53.9, 108.0)	6.8 [2] (0.5, 13.1)[3]
1 Year	-3.5 (16.7) 56 -3.3 (-63.1, 31.6)	1.9 (24.8) 129 2.5 (-72.3, 108.0)	5.5 [1] (-0.7, 11.7)

[1] Difference of means and unequal variance t-test confidence interval (1.9 – (-3.5) = 5.5 due to rounding)
[2] Difference of medians
[3] Non-parametric confidence interval
Source: Attachment 3, Amended Statistical Analysis Report, Table 25:9

The chart below demonstrates that the 6MWT benefit in the Zephyr EBV Treatment group peaks early and then declines at a rate similar to that of the Control group. Thus, the separation at one year is approximately the same as at 3 and 6 months.

Figure 26 Chart: Matched 3, 6, and 12 Month 6MWT Outcomes



Source: Attachment 3, Amended Statistical Analysis Report, Table 25:9

14.3.4 High Heterogeneity Matched 3, 6, and 12 Month 6MWT Outcomes

Matched-pairs Zephyr EBV Subjects in the High Heterogeneity Subgroup had a net increase in 6MWT of 9.4% compared with the matched-pairs Control Subjects at three months (95% CI, 2.1 – 17.7%). At six months, High Heterogeneity Zephyr EBV Subjects had a net increase in 6MWT of 14.7% compared with the matched-pairs Control Subjects (95% CI, 7.6 – 25.2%), and a net increase of 11.0% at 12 months (95% CI, 1.0 – 21.0%).

Table 97 High Heterogeneity Subgroup: Matched 3, 6, and 12 Month Data for Percent Change in 6MWT

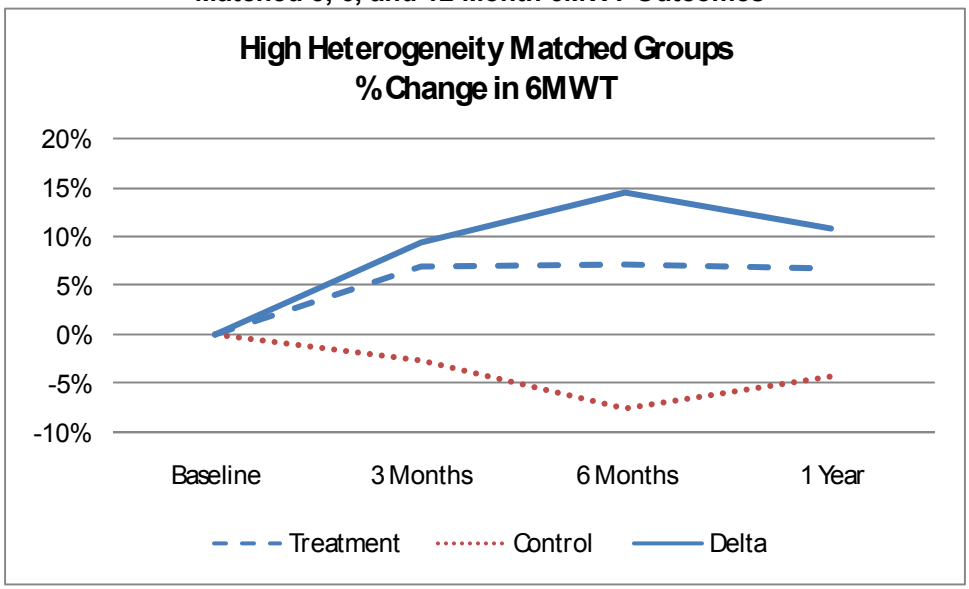
Percent Change in 6MWT	Control Mean (SD) N Median (Min, Max)	Zephyr EBV Mean (SD) N Median (Min, Max)	Delta (95% CI)
3 Months	-3.1 (20.9) 29 -2.6 (-55.4, 50.0)	7.8 (21.5) 65 6.9 (-43.7, 83.2)	9.4 [2] (2.1, 17.7)[3]
6 Months	-7.4 (23.3) 29 -7.5 (-54.9, 66.7)	9.2 (25.4) 65 7.1 (-53.8, 108.0)	14.7 [2] (7.6, 25.2)[3]
1 Year	-4.3 (18.8) 29 -3.4 (-63.1, 25.0)	6.7 (29.2) 65 6.3 (-72.3, 108.0)	11.0 [1] (1.0, 21.0)

[1] Difference of means and unequal variance t-test confidence interval
[2] Difference of medians (6.9) - (-2.6) = 9.4 and (7.1) - (-7.5) =14.7 due to rounding)
[3] Non-parametric confidence interval
Source: Attachment 3, Amended Statistical Analysis Report, Table 25:13

The chart below demonstrates that the 6MWT benefit in the High Heterogeneity Zephyr EBV Treatment group seems to peak at 6 months.

Thus, the separation at one year is approximately the same as at 3 months.

Figure 27 Chart: High Heterogeneity Subgroup Matched 3, 6, and 12 Month 6MWT Outcomes

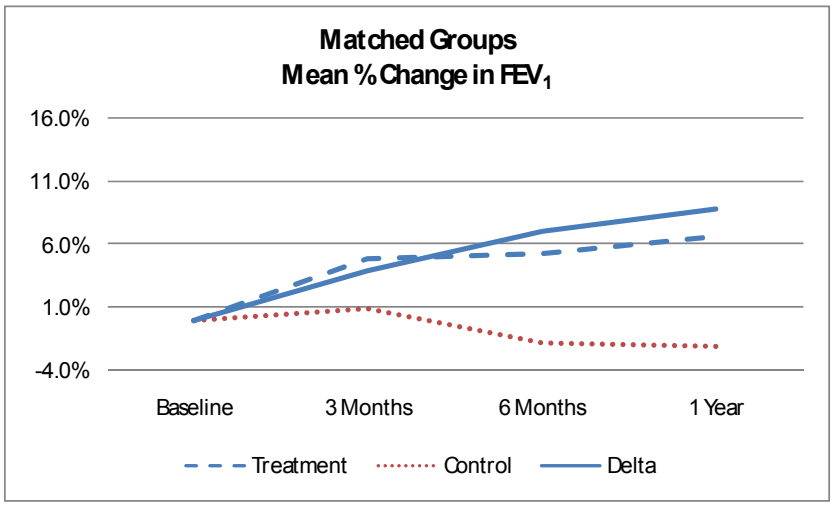


Source: Attachment 3, Amended Statistical Analysis Report, Table 25:13

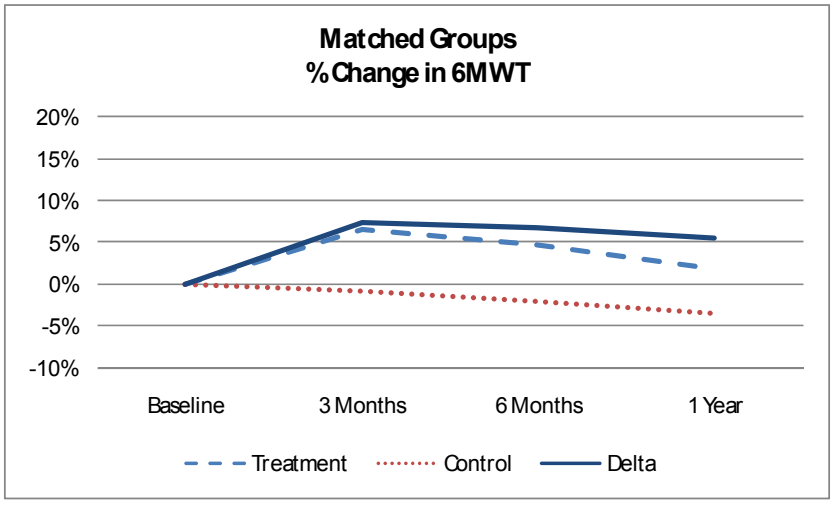
14.4 Summary: Effectiveness Outcome Measures at 1 Year

Although the VENT Pivotal Study was not designed or sized to test significance of effectiveness measures at 1 year of follow-up, outcome measurements continued to favor Zephyr EBV Treatment over the Control through this time point.

From matched grouped comparisons of results at 3 months, 6 months, and 1 year FEV1 appears to continue to improve in the Zephyr EBV Treatment Group through the entire 1 year follow-up. The treatment effect remained statistically-significant at 1 year.



Zephyr EBV Treatment Group benefit in 6MWT appears to peak at 3 months while retaining most of the net benefit through 1 year for those Subjects with matched data. However, the treatment effect was not statistically-significant at 1 year.



15.0 CONCLUSIONS

Overview: The VENT Pivotal Trial was a randomized, controlled, multi-center trial that enrolled subjects with severe heterogeneous emphysema to assess the safety and effectiveness of the Emphasys Endobronchial Valve (Zephyr EBV) and procedure compared to optimal medical management. Zephyr EBV Subjects underwent bronchoscopic Zephyr EBV implantation and both Zephyr EBV Subjects and Control Subjects received optimal medical management. Six month follow-up for all subjects included assessment of a variety of relevant pulmonary and general outcome measures as evaluated by specific spirometry, body plethysmography, diffusing capacity, QoL and exercise tests; a 12 month follow-up visit was also performed. The co-primary effectiveness outcomes were the percent change in both FEV_1 and 6MWT in Zephyr EBV Subjects compared to Control Subjects determined at the 6 month follow-up visit; superiority had to be demonstrated in both measures to meet the outcome. The primary safety outcome was the Major Complication Composite at 6 months.

Validity of Results: The VENT Pivotal Trial enrolled 321 subjects and randomization resulted in highly comparable treatment groups with severe, heterogeneous emphysema (101 Control Subjects, 220 Zephyr EBV Subjects). Study subjects were assessed, treated and followed under the provisions of the approved study protocol, with a high degree of subject, device and imaging accountability. Monitoring procedures, data handling and statistical practice ensured that the results reported in this Clinical Study Report are valid scientific evidence.

Procedure: The bronchoscopic initial implantation procedure was quick (33.8 minutes) with 71.5% of subjects treated with conscious sedation only. A mean of 3.8 valves were implanted per Zephyr EBV Subject, with Acute Technical Success in 94.9%. Valves were frequently removed and replaced without difficulty during implantation procedures, allowing the operator to achieve optimal positioning.

Primary Effectiveness Outcome: The VENT Pivotal Trial met its co-primary outcomes, with a significant percent improvement in both FEV_1 and 6MWT in Zephyr EBV Subjects when compared with Control Subjects at 6 months of follow-up. These significant differences existed whether the analysis was performed with multiple imputation for missing values or with completed cases only, and were confirmed by pre-specified multivariate analysis.

Intent-to-treat: 1° Effectiveness Outcomes	Delta	p value
Percent Change in FEV_1	6.8 (2.1, 11.5)	**0.002**
Percent Change in 6MWT	5.8 (0.5, 11.2)	**0.019**

Secondary Effectiveness Outcomes: The four secondary effectiveness outcomes were met, with the changes in the St. Georges Respiratory Questionnaire, the Modified Medical Research Council Dyspnea Scale, the maximum workload measured by cycle ergometry, and the use of supplemental oxygen all significantly better in the Zephyr EBV Subjects when compared with the Control Subjects.

Intent-to-treat: 2° Effectiveness Outcomes	Delta	p value
SGRQ (points)	–3.4 (–6.6, –0.3)	**0.0167**
mMRC (points)	–0.26 (–0.49, –0.02)	**0.0183**
Maximum workload (watts)	3.8 (0.2, 7.4)	**0.0203**
Supplemental O_2 (L / day)	–12.0 (–76.7, 52.7)	**0.0198**

Primary Safety Outcome: At 6 months of follow-up, Control Subjects had a 1.2% rate of Major Complication Composite events (MCCs) compared with 6.1% for Zephyr EBV Subjects, a trend that was not significant (p = 0.0748). This difference was primarily driven by a trend to greater 6 month mortality in the Zephyr EBV Subjects with 6 deaths: 3 from respiratory failure, one from cancer, one from ischemic colitis and 1 from massive hemoptysis, of which only the death from hemoptysis was related to the device.

All-cause mortality over 12 months was equivalent for the two groups: 3.5% for the Control Subjects and 3.7% for the Zephyr EBV Subjects (p = 0.8763, log rank test). The MCC rate in the second 6 months of follow-up was almost identical: 4.6% for Control Subjects and 4.7% for Zephyr EBV Subjects. Zephyr EBV treatment was not significantly associated with the occurrence of MCCs through 6 months.

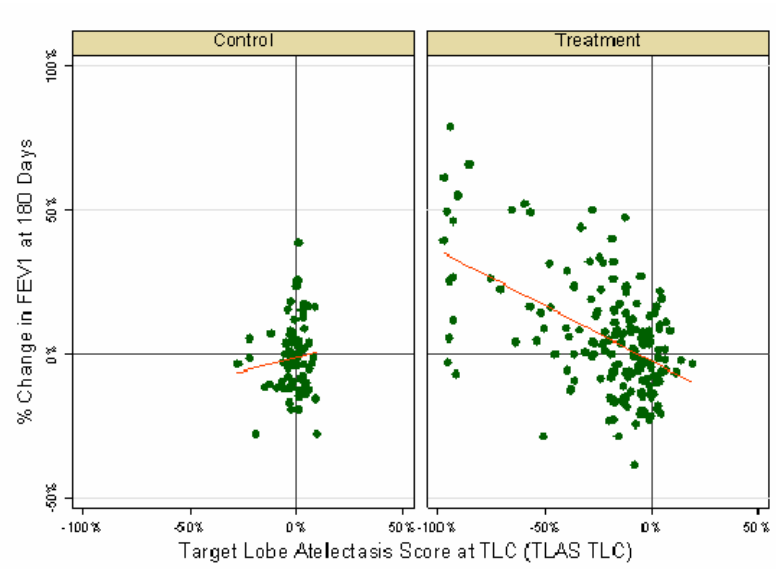
Additional Pre-Specified Analyses: The change in BODE Index was significantly better in the Zephyr EBV Subjects than Control Subjects (p.0.0024). Percent changes in residual volume and diffusing capacity were slightly but not significantly better in Zephyr EBV Subjects, and the Quality of Wellbeing instrument revealed no difference between the groups. Technical success (complete lobar exclusion) was found in 56.2% of Zephyr EBV Subjects on HRCT at 6 months. There was a trend towards higher hospitalization

rates for Zephyr EBV Subjects (27.1%) compared with Control Subjects (16.1%) through 6 months, which was borderline significant (p = 0.0522); this difference appeared to be driven largely by study-related valve removal procedures and diminished during the last 6 months of follow-up.

Clinical Importance of Zephyr EBV Treatment Response:

Responder analyses performed at generally accepted levels of minimal clinically important differences (MCIDs) on key outcome measures revealed that single lobe Zephyr EBV treatment confers a consistent pattern of clinical benefit for FEV_1, 6MWT, SGRQ, mMRC, maximum workload by cycle ergometry and the BODE Index, all key clinical indicators of disease status.

Treatment, Volume Reduction and FEV_1: Analyses of relevant study variables supported the primary rationale of Zephyr EBV treatment, which was that Zephyr EBV treatment led to reduction in target lobe volume reduction (TLVR), which in turn led to improvement in changes in pulmonary function at 6 months.



The VENT Pivotal Trial prospectively assessed the hypothesized mechanism of treatment effect, which was to cause volume loss in non-ventilating lung with resulting improved ventilation in healthier lung parenchyma. Study results strongly suggest this to be the case. Unilateral treatment of subjects with heterogeneous emphysema with Zephyr EBVs elicited substantial target lobe volume reduction (TLVR) as measured by target lobe atelectasis score ($TLAS_{TLC}$). Zephyr EBV Subjects showed a 20.6% reduction in lobar volume compared with 1.7% loss in Control Subjects.

Furthermore, the TLVR resulting from Zephyr EBV treatment was highly associated with improved FEV_1 in Zephyr EBV Subjects at 6 months of follow-up ($r^2 = 0.2785$, $p = 0.0000$).

Relevant clinical factors that would be associated with a closed system (exclusion of all lobar bronchi with Zephyr EBV devices and completeness of interlobar fissures to prevent collateral air flow) were highly associated with the degree of TLVR as measured by $TLAS_{TLC}$. Zephyr EBV Subjects with Technical Success (complete lobar exclusion) had a mean $TLAS_{TLC}$ of −28.1% compared with −11.1% for Zephyr EBV Subjects without Technical Success. Zephyr EBV Subjects with complete interlobar fissures had mean $TLAS_{TLC}$ of −40.1% (left lung) and −33.0% (right lung) compared with −20.7% and −4.4% respectively for incomplete fissures. The combination of Technical Success and Complete Fissure Integrity resulted in a mean $TLAS_{TLC}$ of −54.8% compared with −6.4% when both factors were absent.

Safety Profile: A review of the adverse event (AE) profile of the Zephyr EBV reveals that implanted subjects had higher rates of emphysema related conditions, including such manifestations as COPD exacerbations, other pulmonary infections, increase shortness of breath and hypoxemia. Use of the Zephyr EBV was associated with higher rates of hemoptysis and atypical chest pain. When considering serious adverse events (SAEs) only COPD exacerbations requiring hospitalization and hemoptysis emerged as significantly more frequent events. For both AEs and SAEs, event rates in the Zephyr EBV Subjects tended to decline during study follow-up and approach the rates of the Control Subjects. These declines in adverse event rates appeared to be independent of valve removals.

Key aspects of the Zephyr EBV safety profile that have emerged from the VENT Pivotal Trial include the following characteristics:

- Use of the Zephyr EBV was associated with increased rates of COPD related adverse events, hemoptysis, atypical chest pain and perhaps rehospitalization through 1 year of follow-up.
- Granulation tissue, valve migration, and pneumonia distal to the valve are adverse events that are specifically related to the use of this device.
- These phenomena diminish with time.
- The device can be safely removed with a high degree of success, and when valve removal is performed as a result of an adverse event, the adverse event generally resolves.
- There was no difference in all-cause mortality between the Control Subjects and Zephyr EBV Subjects over the 1-year study follow-up.

Outcome Measures at One Year: Although the VENT Pivotal Study was not designed or sized to test significance of effectiveness measures at 1 year of follow-up, outcome measurements continued to favor Zephyr EBV Treatment over the Control through this time point. These results were confirmed by responder analysis and matched-pairs analysis.

Conclusion: The VENT Pivotal Trial results demonstrate that unilateral treatment of severe heterogeneous emphysema in medically optimized subjects achieved substantial additional improvement in a variety of outcomes including FEV_1 and 6MWT over that achieved by approved medical treatments alone. This level of additional improvement in maximally treated, severely ill subjects is clinically important. Such findings constitute valid scientific evidence demonstrating the effectiveness of the Zephyr EBV device in improving important subjective and objective measures of health in a population of subjects with severe heterogeneous emphysema. While there are several clear risks of the use of the Zephyr EBV device, these are generally minor, tend to diminish over time, and usually resolve after device removal. Use of the Zephyr EBV in patients with severe heterogeneous emphysema provides an important palliative benefit that exceeds the attendant risks.

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17.0 CHANGE TRACKER

Note: Section, Table and other numbering is for the version contained in that column.

Reference	CSR Version dated March 18, 2008	CSR Version dated August 8, 2008	Rationale
Terminology throughout	"endpoint"	"outcome" and "outcome measure"	To clarify the difference between study measures and specifically defined primary and secondary outcomes for those measures
Terminology throughout	"Emphysema Score"	"Density Score"	The terms are synonymous, Density Score is the currently preferred usage
Convention throughout	Mean differences reported universally	Median differences reported for non-parametric distributions with equal variances. Mean difference reported when a parametric inference test is or would be used.	Medians are a more appropriate estimate of the differences between distributions when the distribution is non-parametric.
Synopsis	Revised to reflect changes in Clinical Study Report overall		Revised to reflect changes in body of document
Section 1.0	No changes		No changes
Section 2.0	Section 2.1, Study Responsibilities	Section 2.1, Study Responsibilities	Reduced roles of consultants. Minor changes clarifying responsibilities
Section 3.0	Section 3.2 Zephyr Delivery Catheter and Zephyr Loader System	Section 3.2 Zephyr Delivery Catheter and Zephyr Loader System	Added footnote to delivery catheter photo (figure 3) to clarify change made post enrollment

Reference	CSR Version dated March 18, 2008	CSR Version dated August 8, 2008	Rationale
Section 4.5, SAP	Section 4.5.2 Error and Bias Control Section 4.5.3: Analytic Methods .	Section 4.5.2 Error and Bias Control Section 4.5.3: Analytic Methods	Removed "maximally blinded" qualifier for CEC due to ambiguity of term Language regarding populations and windows for analysis was edited for clarity Modified "intent-to-treat (ITT)" to "multiple-imputation intent-to-treat (ITT)" Added "results combined for analysis"
Section 4.5, SAP	Section 4.5.5, Safety Endpoints Section 4.5.6, Effectiveness Endpoints Section 4.5.7, Additional Analyses	Section 4.5.5, Safety Measures and Outcomes Section 4.5.6, Effectiveness Measures and Outcomes	Composite of Death/LVRS/transplant as an outcome measure not included in revised CSR (but still in Statistical Analysis Report (SAR)) To clarify which outcomes measures were pre-specified and which were *post hoc* To add and justify certain analyses performed in response to FDA queries: • *Post hoc* responder analyses • *Post hoc* analyses of treatment, target lobe volume reduction and FEV_1 response • *Post hoc* 1 year effectiveness outcome measures
Section 4.6, Imaging Procedures	Section 4.6 Imaging Procedures Section 4.6.3, Quantitative Image Analysis	Section 4.6 Imaging Procedures Section 4.6.3, Quantitative Image Analysis	More specificity added to role of core lab Revised for clarity
Section 4.6, Imaging Procedures	[none]	Section 4.6.4, Density (Emphysema) and Heterogeneity Scoring	Added to clarify procedures

Reference	CSR Version dated March 18, 2008	CSR Version dated August 8, 2008	Rationale
Section 4.6, Imaging Procedures	Section 4.6.4 Fissure Integrity Assessment	Section 4.6.5 Fissure Integrity Assessment	Added clarification and image.
Section 4.6, Imaging Procedures	[none]	Section 4.6.7, Target Lobe Atelectasis Score (TLAS) Methodology	Added to clarify procedures
Section 4.7, Changes in the Conduct of the Study	[none]	Section 4.7.3, Additional Analyses Resulting from FDA Communications	Added to clarify additional analyses
4.8, Protocol Deviations	4.8, Protocol Deviations	4.8 Protocol Deviations	Minor corrections in text treatment of Table 4, no change in Table 4.
4.9, Study Definitions	4.9, Study Definitions	4.9, Study Definitions	Corrections and additions to definitions for clarity and completeness
Section 5.0, Study Accountability and Population	Section 5.5, Distribution of Subjects by Study Site and Strata including Table	Section 5.1 includes statement that stratification was successful and refers reader to SAR for details	Section 5.5 and Table deleted as unnecessary for Clinical Study Report (all data still in SAR)
Section 6.0 Baseline Subject Characteristics	[none]	Section 6.7, BODE Indices Section 6.8, SGRQ Scores Section 6.9, mMRC Dyspnea Scale Scores Section 6.12 HRCT Characteristics	Correct an inadvertent omission by including important baseline data regarding secondary effectiveness outcome measures Correct an inadvertent omission and provide more clarity regarding heterogeneity in response to FDAs deficiency questions
Section 7.0	Minor changes		Minor changes

Reference	CSR Version dated March 18, 2008	CSR Version dated August 8, 2008	Rationale
Primary Effectiveness Outcome	Section 8.1, Primary Effectiveness Endpoint 8.1.1 – Mean Percent Changes in FEV1 and 6MWT- Univariate Tests Table 33 Primary Effectiveness Endpoint… 8.1.2 – Multivariate 8.1.3.1 – Completed Cases	Section 8.2, Primary Effectiveness Outcomes 8.2.1 – Percent Change in FEV1 and 6MWT – Multiple Imputation Table 38 Primary Effectiveness Outcome… [none] 8.2.2 – Completed Cases	Reorganized for clarity. Removed multivariate ITT as a component of the Primary Effectiveness Outcome per FDA statistician. Removed table 32 for same reason. Modified and updated per direction from FDA statistician. ITT multivariate no longer done per FDA statistician.
Secondary Effectiveness Outcomes	Section 8.2, Secondary Effectiveness Endpoints 8.2.1 – SGRQ 8.2.2 – mMRC 8.2.3 – Maximum workload 8.2.4 – Supplemental oxygen	Section 8.3, Secondary Effectiveness Outcomes 8.3.1 – SGRQ 8.3.2 – mMRC 8.3.3 – Maximum workload 8.3.4 – Supplemental oxygen	Reorganized for clarity. Change from ITT to multiple imputation
Primary Safety Outcome	Section 9.2, Primary Safety Endpoint: Major Complications Composite	Section 9.2, Primary Safety Outcome: Major Complications Composite	Reorganized for clarity. No change in data or conclusions presented
Primary Safety Outcome – Related Analyses	Section 9.3.1, All-Cause Mortality Section 9.2.1, Cox Regression Analysis of MCCs Section 9.2.2, MCC by Time Period Section 9.4.8, MCC Rates by Calendar Quarter of Follow-up	Section 9.3.1, All-Cause Mortality Section 9.3.2, Cox Regression Analysis of MCCs Section 9.3.3, MCC by Time Period Section 9.3.4, MCCs by Valve Removal Status through One Year	Reorganized for clarity. No change in data or conclusions presented Brief cause of death added to Table 45, Summary: Subjects with One or More MCCs

Reference	CSR Version dated March 18, 2008	CSR Version dated August 8, 2008	Rationale
Additional Pre-Specified Analyses	Section 10.2.3, Mean % Change in RV Section 10.2.4, Mean % Change in Diffusing Capacity Section 10.2.2, Mean Change in QWB Section 10.2.1, Mean Change in BODE Index Section 10.3, Technical Success Section 9.3.1, Rehospitalization	Section 10.2.1, Mean % Changes in RV Section 10.2.2, Mean % Changes in Diffusing Capacity Section 10.2.3, Mean Change in QWB Section 10.2.4, Mean Change in BODE Index Section 10.2.5, Technical Success Section 10.2.6, Rehospitalization	Reorganized for clarity. No change in data or conclusions presented
Pre-Specified Subgroup Analyses	Section 10.4, FEV_1 and 6MWT: Effect of Lobar Exclusion Section 8.1.3.2, Subgroup Analysis: Heterogeneity Score ≥ 15%	Section 10.3.1, Technical Success, FEV_1 and 6MWT Outcomes Section 10.3.2, Heterogeneity Score ≥ 15%, FEV_1 and 6MWT Outcomes	Reorganized for clarity. No change in data or conclusions presented
Pre-Specified Subgroup Analyses	[none]	Section 10.3.3, Complete Fissure Integrity and FEV_1	Correct an inadvertent omission by including this important pre-specified subgroup analysis
Responder Analyses – Pre-Specified	8.1.3.3, ≥ 15% Improvement in FEV_1 8.1.3.4, ≥ 15% Improvement in 6MWT	11.2.3, ≥ 15% Improvement in FEV_1 11.3.3, ≥ 15% Improvement in 6MWT	Reorganized for clarity. No change in data or conclusions presented
Responder Analyses – Pre-Specified	[none]	11.2.1, Maintained (≥ 0% improvement) in FEV_1 11.3.1, Maintained (≥ 0% improvement) in 6MWT	Correct an inadvertent omission by including these important pre-specified responder analyses

Reference	CSR Version dated March 18, 2008	CSR Version dated August 8, 2008	Rationale
Responder Analyses – From Analysis Plan	[none]	All By High Heterogeneity Subgroup: 11.2.2 Maintained (≥ 0% improvement) in FEV_1 11.2.4 Maintained (≥ 0% improvement) in 6MWT 11.3.2 ≥ 15% Improvement in FEV_1 11.3.4, ≥ 15% Improvement in 6MWT	Analyses performed in response to FDA query regarding clinical importance of demonstrated statistical effects
Responder Analyses – *Post hoc*	[none]	11.4.1, ≥ 4 and ≥ 8 Point Improvement in SGRQ 11.4.2, ≥ 1 Point Improvement in mMRC 11.4.3, ≥ 10 Watt Improvement in Maximum Workload during Cycle Ergometry 11.4.4, ≥ 1 Point Improvement in BODE Index	Analyses performed in response to FDA query regarding clinical importance of demonstrated statistical effects

Reference	CSR Version dated March 18, 2008	CSR Version dated August 8, 2008	Rationale
Post hoc investigation of mechanism of treatment effect	10.6.1, Zephyr EBV Treatment Leads to TLVR 10.5.2, Effect of TLVR on FEV_1 and 6MWT 10.6.5, Complete Lobar Exclusion (Technical Success) and $TLAS_{TLC}$ 10.6.4, Fissure Completeness and $TLAS_{TLC}$ 10.6.6, EBV Subjects with Complete Lobar Exclusion (Technical Success) and Complete Fissures by Target Lung	12.2.1, Zephyr EBV Treatment Leads to TLVR 12.2.2, TLVR is Significantly Associated with Improved FEV_1 at 6 Months 12.3.1, Technical Success and TLVR 12.3.2, Fissure Integrity and TLVR 12.3.3, Technical Success, Fissure Integrity and TLVR 12.4.1, Technical Success, Fissure Integrity and FEV_1	Reorganized for clarity. No change in data or conclusions presented except: • 6MWT results not included in revised CSR (but still in SAR) • Left and right lung sub-analyses in March 18 CSR Section 10.6.6 not included in revised CSR (but still in SAR)
Safety Profile	9.4.1, Adverse Events 9.4.9, Adverse Events with Higher Rates in Zephyr EBV Subjects by Quarter of F/U 9.4.10, Serious Adverse Events 9.4.11, Serious Adverse Events by Calendar Quarter of F/U through 1 Year 9.4.12, Device-Related Adverse Events 9.4.12, Procedure-Related Adverse Events	13.2.1, Adverse Events 13.2.2, Adverse Events by Quarter 13.2.3, Serious Adverse Events 13.2.4, Serious Adverse Events by Quarter 13.2.5, Device-Related Adverse Events 13.2.6, Procedure-Related Adverse Events	Reorganized for clarity. No change in data or conclusions presented except: • Tables listing device- and procedure-related adverse events not included in revised CSR (but still in SAR)
Safety Profile	9.4.2, Granulation Tissue 9.4.3, Valve Expectoration or Migration 9.4.4, Pneumonia Distal to Valves 9.4.7, Massive Hemoptysis 9.4.6, Valve Tx for Persistent Air Leak 9.4.5, Valve Removal During Study F/U	13.3.1, Granulation Tissue 13.3.2, Valve Expectoration or Migration 13.3.3, Pneumonia Distal to Valves 13.3.4, Massive Hemoptysis 13.3.5, Valve Tx for Persistent Air Leak 13.4, Valve Removal During Study F/U	Reorganized for clarity. Addition of footnote to 13.3.2 to clarify potential root causes of valve migrations No change in data or conclusions presented

Reference	CSR Version dated March 18, 2008	CSR Version dated August 8, 2008	Rationale
Post hoc Outcome Measures at One Year	8.3.1, Mean % Changes in FEV_1 at 1 Year 8.3.2, Mean % Changes in 6MWT at 1 Yr. 8.3.3, Mean Changes in SGRQ at 1 Year 8.3.4, Mean Changes in mMRC at 1 Year 8.3.5, Mean Changes in Maximum Workload at 1 Year 8.3.6, Mean Changes in Supplemental Oxygen at 1 Year	14.2.1, Percent Change in FEV_1 at 1 Year 14.2.2, High Heterogeneity Percent Change in FEV_1 at 1 Year 14.2.3, Percent Change in 6MWT at 1 Yr. 14.2.4, High Heterogeneity Percent Change in FEV_1 at 1 Year 14.2.3, Change in SGRQ at 1 Year 14.2.4, Change in mMRC at 1 Year 14.2.5, Change in Maximum Workload at 1 Year 14.2.6, Changes in Supplemental Oxygen at 1 Year	Reorganized for clarity. Analyses performed in response to FDA query regarding durability of treatment effect at one year
Post hoc Outcome Measures at One Year	[none]	14.3 Matched 3, 6, and 12 Month FEV_1 and 6MWT Data 14.3.1, Matched 3, 6, and 12 Month FEV_1 Outcomes 14.3.2, High Heterogeneity Subgroup Matched 3, 6, and 12 Month FEV_1 Outcomes 14.3.3, Matched 3, 6, and 12 Month 6MWT Outcomes 14.3.4, High Heterogeneity Subgroup Matched 3, 6, and 12 Month 6MWT Outcomes	Additional analyses performed in response to FDA query regarding durability of treatment effect at one year

Reference	CSR Version dated March 18, 2008	CSR Version dated August 8, 2008	Rationale
Conclusions	11.0, Discussion and Conclusions	15.0, Conclusions	Revised to reflect changes in body of document
References	12.0, References	16.0, References	Additional references regarding responder analyses and MCIDs included