

Anesthesiology and Respiratory Therapy Devices Panel

Friday, December 5, 2008

**Emphasys Medical, Incorporated
Emphasys Zephyr Endobronchial Valve System
PMA P070025**

FDA Review Summary

Emphasys Medical, Incorporated Emphasys Zephyr Endobronchial Valve System

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Office of Device Evaluation

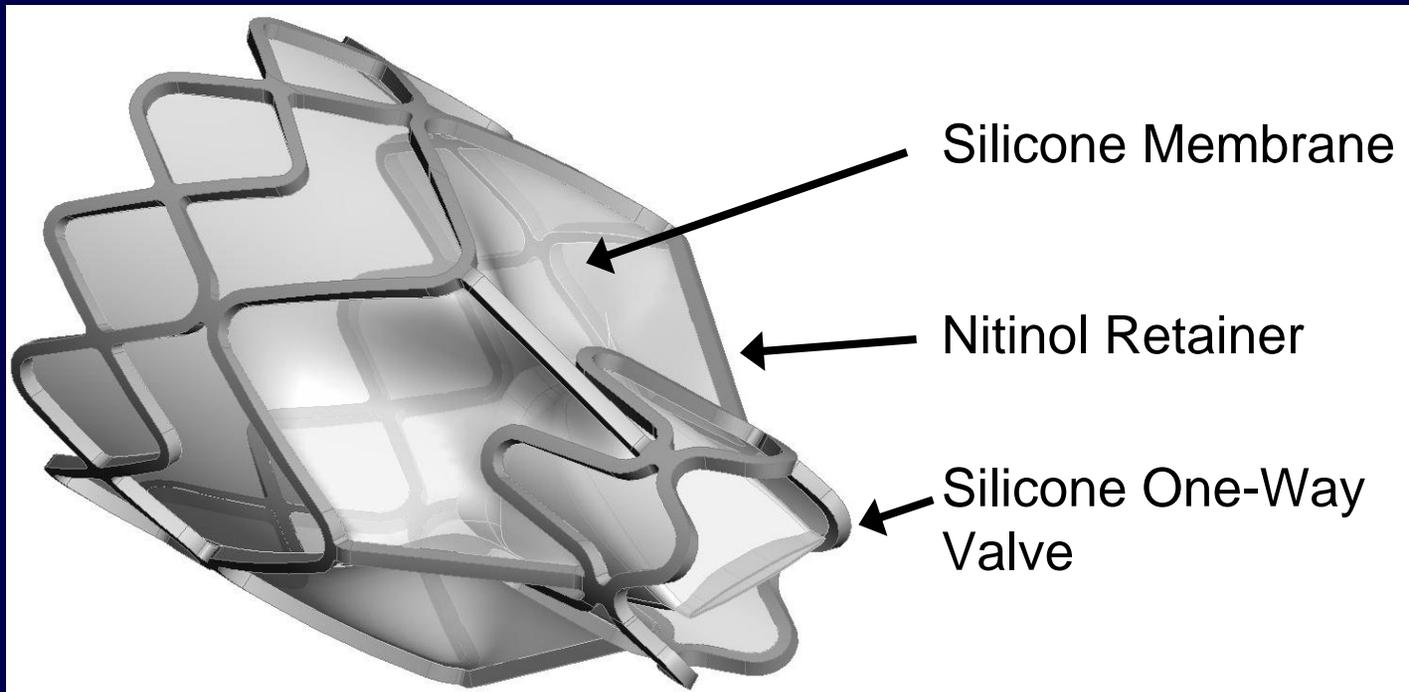


Overview of Presentation

- Device Description
- Clinical and Preclinical Study Introduction
- Statistical Evaluation - Mr. Van Orden
- Clinical Evaluation - Dr. Shure
- Post-Market Study Proposal - Dr. Chen
- Panel Questions (afternoon session)

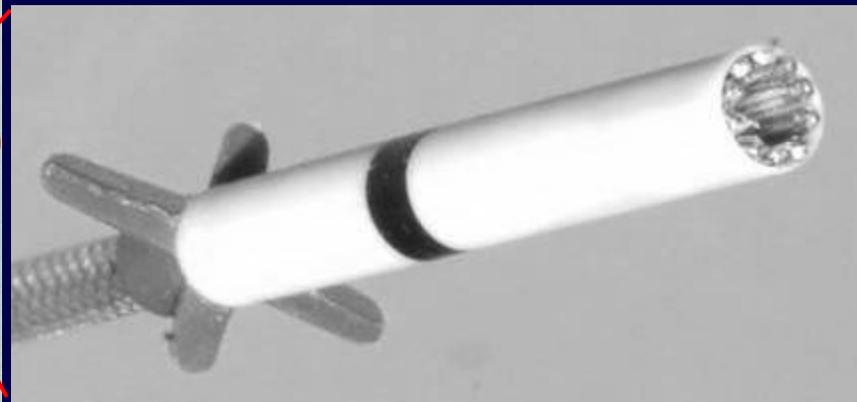
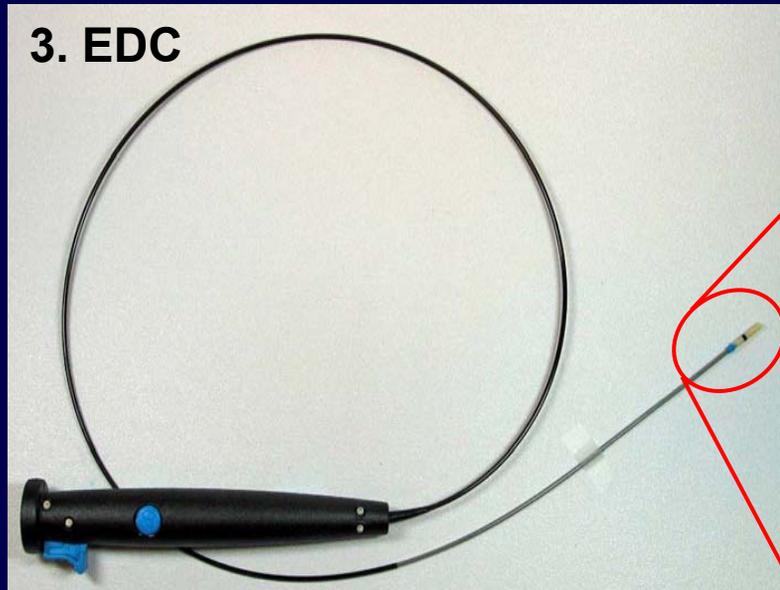
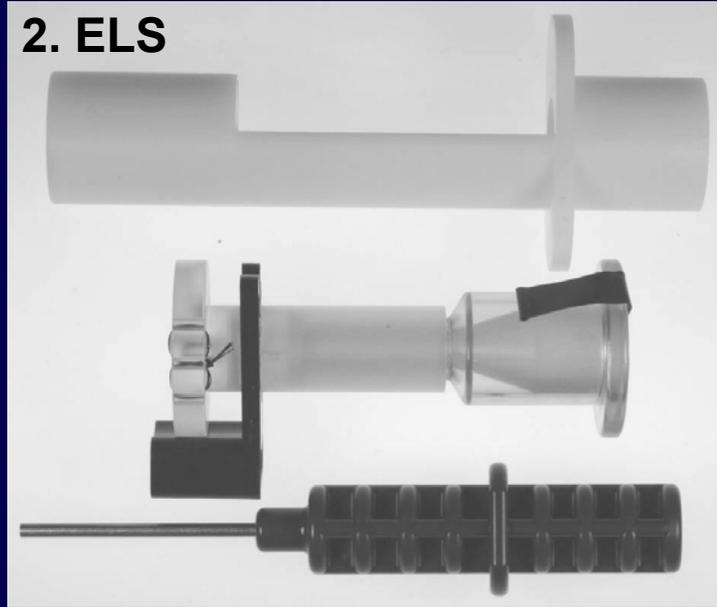
Zephyr Endobronchial Valve System

1. Zephyr Endobronchial Valve (EBV)

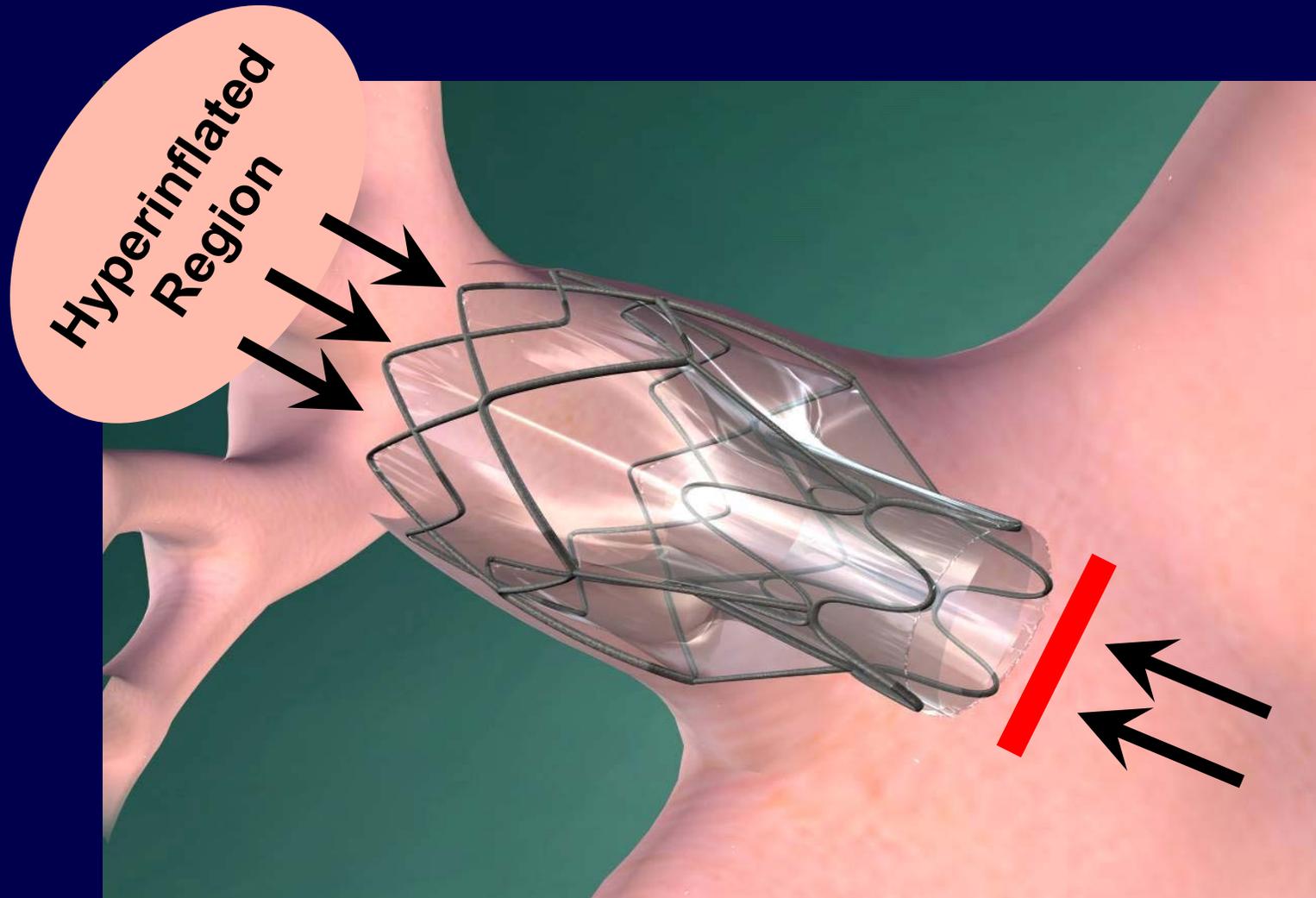


Zephyr EBV System (cont'd)

2. Zephyr Endobronchial Loader System (ELS)
3. Zephyr Endobronchial Delivery Catheter (EDC)



Mechanism of Action



Class III Device

- Provide reasonable assurance of safety and effectiveness (Federal Food, Drug, Cosmetic Act, §513(a)(1)(C))
- Relevant factors (21 CFR 860.7(b))
 - Patient population
 - Conditions of use
 - Probable benefit vs. probable injury
 - Reliability of the device

Proposed Indication for Use

The Zephyr EBV is intended to improve FEV₁ and 6 minute walk test distance in patients with severe heterogeneous emphysema who have received optimal medical management.

U.S. Clinical Study: IDE G020230

- Endobronchial Valve for Emphysema Palliation N Trial
- Unblinded, prospective, randomized, multi-center trial of the Zephyr EBV compared to optimal medical management controls
- 220 Zephyr EBV and 101 control subjects at 31 sites between December 2004 and April 2006
- Co-Primary Endpoints: (one-sided superiority test)
 - Mean percent change of FEV₁
 - 6MWT from baseline to 6 months
- Primary Safety Endpoint: (evaluation based on risk vs. benefit)
 - Major Complication Composite at 6 and 12 months

Preclinical Evaluation

- **Animal Studies** – assessment of EBV delivery, removal, migration resistance, inversion resistance, and atelectasis in sheep (determined to be satisfactory)
- **Bench Performance Studies** – EBV, ELS, EDC dimensional and functional tests, material assessment tests, fatigue tests (working interactively to resolve)
- **Biocompatibility**
- **Manufacturing**
- **Sterilization, Packaging, Shelf-Life**

FDA Review Team

Melanie Choe, PhD – Lead Review

Lisa Lim, PhD – Mechanical Engineering

Deborah Shure, MD – Clinical / Pulmonary

Julie Swain, MD – Clinical / Cardiothoracic Surgery

Alvin Van Orden, MS – Statistics

Jiping Chen, MD, PhD, MPH – Epidemiology

Ramesh Panguluri, PhD – Biocompatibility/Toxicology/Animal Studies

Steven Turtill, MS – Sterilization and Packaging

Martin Hamilton – Bioresearch and Monitoring

Cliff Patterson – Compliance

Alicia Witters – Patient Labeling

Statistical Review

Emphasys Zephyr Endobronchial Valve System
VENT Pivotal Trial

Alvin Van Orden, MS
Division of Biostatistics
Office of Surveillance and Biometrics

Outline

1. Study Design
2. Subject Accountability and Protocol Violations
3. Primary and Secondary Effectiveness Results
4. Statistical Significance and the Estimation of the Treatment Effect
5. Additional Analyses
6. Safety Results
7. European Data
8. Summary

Study Design

- Unblinded trial with standard of care as the control.
- Randomized 2:1 (Treatment:Control) Stratified by target lobe and exercise capacity.
- Co-primary endpoints:
 - 1) Percent change from baseline FEV1 at 180 days (+/- 14 days) **AND**
 - 2) Percent change from baseline in 6MWT at 180 days (+/- 14 days)
- Primary Safety Endpoint: Major Complications Composite (MCC) at 6 months (<190 days)

Study Design

Effectiveness Analysis Groups

- **Intention to Treat (ITT)** – [Primary effectiveness population]
All randomized patients (101 Control, 220 EBV)
- **Completed Cases (CC)** – All patients that had a visit
(75 Control, 179 EBV)
- **Per Protocol (PP)** – All patients that had a visit except for the major protocol violators (57 control, 141 EBV)

Safety Analysis Group

- **Modified ITT (mITT)** – [Primary safety population]
All patients that had at least one visit post-randomization
(87 Control, 214 EBV)

Study Design

Changes in the Statistical Analysis Plan made after the last patient had been enrolled for 6 months

- European arm of the study was not pooled with the US arm of the study.
- Secondary Endpoints were changed from 9 secondary endpoints to 4 secondary endpoints: SGRQ, mMRC, cycle ergometry, and supplemental oxygen.
- Extended window created for 6 month time point (-30/+45 days).

Subject Accountability at 6 Months

		Control	EBV
	Enrolled	101	220
Not treated as missing	Visit in Window	58.4%	61.4%
	Visit in Post-hoc Extended Window	15.8%	16.8%
Missing	Visit Beyond Extended Window	4.0%	9.5%
	Died	0%	2.7%
	Withdrawn	7.9%	4.1%
	No Visit	13.9%	5.9%

Protocol Violations

- 62 patients (19%) did not meet the inclusion or exclusion criteria
- 9 patients (3%) took medication in violation of the protocol
- Combined, 49 (22%) of the EBV patients and 20 (20%) of the control patients had 'clinically important protocol violations'.

Primary Effectiveness Analysis

EBV-Control (with 95% Confidence Interval)

Primary Endpoints	ITT 6 Months	1-sided p-value*
FEV ₁	6.8% (2.1, 11.5)	0.002
6MWT	5.8% (0.5, 11.2)	0.019

*A one-sided p-value is significant if $p < 0.025$.

Primary Effectiveness Analysis

EBV-Control (with 95% Confidence Interval)

Primary Endpoints	ITT 6 Months	CC 6 Months	PP 6 Months
FEV ₁	6.8%* (2.1, 11.5)	7.2%* (3.2, 11.2)	7.0%* (2.7, 11.3)
6MWT	5.8%* (0.5, 11.2)	5.7%* (1.3, 11.7)	4.1% (-1.0, 10.9)

*The one-sided p-value is less than 0.025.

Effectiveness Results at 12 months

EBV-Control (with 95% Confidence Interval)

Primary Endpoints	ITT 12 Months	CC 12 Months	PP 12 Months
FEV ₁	7.7%* (2.6, 12.7)	8.1%* (4.0, 12.2)	7.0%* (2.6, 11.4)
6MWT	3.8% (-1.4, 9.0)	3.6% (-1.9, 9.1)	2.8% (-2.8, 8.3)

*The one-sided p-value is less than 0.025.

Secondary Effectiveness Results at 6 months

EBV-Control (with 95% Confidence Interval)

Secondary Endpoints	ITT 6 Months	CC 6 Months	PP 6 Months
SGRQ (0-100 points)	-3.4*? (-6.6,-0.3)	-3.4 (-6.6,-0.2)	-3.4 (-7.1, 0.3)
mMRC (0-4 points)	-0.3*? (-0.5,-0.02)	-0.3 (-0.6,-0.05)	-0.2 (-0.5,0.06)
Cycle Ergometry (watts)	3.8*? (0.2, 7.4)	5.0* [0.0, 5.0]	5.0 [0.0, 5.0]
Supplemental O2 (liters/day)	-12*? (-77, 53)	-100 (-319,118)	0.0 (-120, 0]

*The sponsor claims statistical significance after Hochberg's multiplicity adjustment.

Statistical Significance

- Statistical significance was achieved for both primary endpoints in the primary ITT population and in the CC population.
- Statistical significance does not imply clinical significance. Any size difference can be statistically significant with a sufficient sample size.
- The primary endpoints should achieve both statistical and clinical significance

Statistical Significance

- Statistical significance was achieved for the four secondary endpoints after Hochberg's adjustment for multiplicity (if supplemental Oxygen is significant).
- If the same multiplicity adjustment had been made for the nine original secondary endpoints, none of the secondary endpoints would have been statistically significant.
- In the PP population, the 6MWT and all secondary endpoints are not statistically significant.
- The 6MWT and the four secondary endpoints are not statistically significant at 3 or 12 months in any population.

Factors That May Impact the Estimation of the Treatment Effect

1. Lack of Blinding: The patients may be susceptible to the placebo effect, and the investigators may exhibit treatment or assessment bias.
2. Post-hoc Extension of Window:
 - It may not be appropriate to treat the 16% of patients seen in the extended window the same as patients seen within the pre-specified window.
 - The results may be biased due to the post-hoc definition of an extended window.

Factors That May Impact the Estimation of the Treatment Effect

3. Missing data: Over 20% of patients did not have observed 6 month outcomes in the extended window. The underlying assumption that missing patients would have had similar results to those patients whose results were actually observed is unverifiable.
4. Protocol Violations: About 21% of patients had 'clinically important protocol violations'. Inclusion of these patients increases the size of the difference between the treatment and control.

Additional Analyses

Responder Analysis

(At Least 15% Improvement Considered Success)

Population	Variable	Control n/N (%)	EBV n/N (%)	2-sided p-value for the difference
CC	FEV ₁	8/75 (10.7)	42/179 (23.5)	0.02
	6MWT	13/73 (17.8)	45/178 (25.3)	0.25
PP	FEV ₁	6/57 (10.5)	32/141 (22.7)	0.07
	6MWT	9/57 (15.8)	38/140 (25.0)	0.22

FDA Responder Analysis

(15% Improvement in Both Primary Endpoints
Considered Success)

Population	Control n/N (%)	EBV n/N (%)	2-sided p-value
CC	1/73 (1.4)	13/178 (7.3)	0.07
PP	1/56 (1.8)	7/138 (5.1)	0.44

Additional Variables

Change from Baseline to 6 months

CC Population	Control Mean (SD) Median (Min, Max)	EBV Mean (SD) Median (Min, Max)	1-sided p-value*
RV % Change	0.7 (22) -2.3 (-44, 124)	-1.3 (20) -1.0 (-63, 66)	0.40
DL _{CO} % Change	-2.1 (17) -1.7 (-86, 30)	2.1 (19) 1.1 (-47, 59)	0.14
Quality of Well Being	-0.02 (0.1) -0.01 (-0.3,0.3)	-0.01 (0.1) 0.0 (-0.4,0.2)	0.17
BODE	0.32 (1.1) 0.0 (-3, 3)	-.21 (1.3) 0.0 (-4,3)	0.002

*No adjustment for multiplicity has been made

Screening of Covariates to Define a Subgroup

Characteristic	P-Value*
Age (years)	0.2098
Age (years) by EBV Interaction	0.8530
Gender	0.4900
Gender by EBV Interaction	0.6209
Site	0.9842
Site by EBV Interaction	0.9974
BMI (kg/meters ²)	0.9013
BMI by EBV Interaction	0.5448
Target Lobe	0.3319
Target Lobe by EBV Interaction	0.0806
Baseline FEV ₁ (liters)	0.0969
Baseline FEV ₁ (liters) by EBV Interaction	0.7240
Baseline FEV ₁ % Predicted	0.0082
Baseline FEV ₁ % Predicted by EBV Interaction	0.9373
Baseline VC (liters)	0.3473
Baseline VC (liters) by EBV Interaction	0.8505
Baseline FVC (liters)	0.0717
Baseline FVC (liters) by EBV Interaction	0.4890
Baseline FVC % Predicted	0.0041
Baseline FVC % Predicted by EBV Interaction	0.7904
Baseline FEV ₁ /FVC (liters/liters)	0.9258
Baseline FEV ₁ /FVC (liters/liters) by EBV Interaction	0.6185
Baseline RV (liters)	0.6997
Baseline RV (liters) by EBV Interaction	0.9777
Baseline RV % Predicted	0.3268
Baseline RV % Predicted by EBV Interaction	0.9542
Baseline DS of Target Lobe at TLC **	0.3343
Baseline DS of Target Lobe by EBV Interaction at TLC	0.7182
Baseline DS of Target Lobe at RV **	0.1674
Baseline DS of Target Lobe by EBV Interaction at RV	0.8607
Baseline Ipsilateral DS Heterogeneity at TLC **	0.2663
Baseline Ipsilateral DS Heterogeneity by EBV Interaction at TLC	0.0017
Baseline Ipsilateral DS Heterogeneity at RV **	0.2540
Baseline Ipsilateral DS Heterogeneity by EBV Interaction at RV	0.0143
Baseline Thorax DS Heterogeneity at TLC **	0.6536
Baseline Thorax DS Heterogeneity by EBV Interaction at TLC	0.4223
Baseline Thorax DS Heterogeneity at RV **	0.2928
Baseline Thorax DS Heterogeneity by EBV Interaction at RV	0.3280
Baseline Target Lobe Volume % of TLC **	0.6365
Baseline Target Lobe Volume % of TLC by EBV Interaction	0.3870
Baseline Target Lobe Volume % of RV **	0.7266
Baseline Target Lobe Volume % of RV by EBV Interaction	0.2857
Baseline Maximum DS Other than Target at TLC **	0.5598
Baseline Maximum DS Other than Target by EBV Interaction at TLC	0.6849
Baseline Maximum DS Other than Target at RV **	0.5960
Baseline Maximum DS Other than Target by EBV Interaction at RV	0.5021
Baseline Minimum DS Other than Target at TLC **	0.2733
Baseline Minimum DS Other than Target by EBV Interaction at TLC	0.0104
Baseline Minimum DS Other than Target at RV **	0.6355
Baseline Minimum DS Other than Target by EBV Interaction at RV	0.0032
Baseline Target Lobe DS % of Delta at TLC **	0.2165
Baseline Target Lobe DS % of Delta by EBV Interaction at TLC	0.9771

Characteristic	P-Value*
Baseline Target Lobe Volume % of Delta at TLC **	0.4038
Baseline Target Lobe Volume % of Delta by EBV Interaction at TLC	0.4735
Baseline PaCO ₂ (mmHg)	0.5402
Baseline PaCO ₂ (mmHg) by EBV Interaction	0.1266
Baseline PaO ₂ (mmHg)	0.9323
Baseline PaO ₂ (mmHg) by EBV Interaction	0.4267
Baseline DLCO % Predicted	0.8822
Baseline DLCO % Predicted by EBV Interaction	0.3768
Baseline Fissure Score**	0.0236
Baseline Fissure Score by EBV Interaction	0.0028
Baseline 6MWT (meters)	0.7895
Baseline 6MWT (meters) by EBV Interaction	0.8889
Baseline Cycle ergometry (Watts)	0.7819
Baseline Cycle ergometry (Watts) by EBV Interaction	0.4022
RUL Treatment **	0.1404
RUL Treatment by EBV Interaction	0.1398
Baseline TLC (liters)	0.7968
Baseline TLC (liters) by EBV Interaction	0.9666
Baseline TLC % Predicted	0.6571
Baseline TLC % Predicted by EBV Interaction	0.5631
Baseline RV/TLC (liters/liters)	0.3491
Baseline RV/TLC (liters/liters) by EBV Interaction	0.9241
BODE **	0.9575
BODE by EBV Interaction	0.7662
Upper Lobe (versus Lower Lobe)**	0.8501
Upper Lobe (versus Lower Lobe) by EBV Interaction	0.5679
Treatment Side (Right versus Left Side)**	0.0795
Treatment Side (Right versus Left Side) by EBV Interaction	0.0206
NETT Strata **	0.9663
NETT Strata by EBV Interaction	0.7542
NETT Strata by Treatment Side **	0.5024
NETT Strata by Treatment Side by EBV Interaction	0.2607

High Heterogeneity (HH) Subgroup

- Screened over 40 variables and their interactions, including four heterogeneity variables, without a full adjustment for multiplicity.
- The cutoff value defining the subgroup changed throughout the review process.
- May be an increased safety risk in this subgroup. High heterogeneity as a continuous variable is significantly (unadjusted $p=0.0078$) associated with a higher risk of death and LVRS.

FDA Responder Analysis

Comparing the HH Subgroup and the Overall Study Group

(15% Improvement in Both Primary Endpoints Considered Success)

Population	Group	Control n/N (%)	EBV n/N (%)	2-sided p-value
CC	Entire Study	1/73 (1.4)	13/178 (7.3)	0.07
	HH Subgroup	1/38 (2.6)	12/90 (13.3)	0.11
PP	Entire Study	1/56 (1.8)	7/134 (5.1)	0.44
	HH Subgroup	1/28 (3.6)	7/69 (10.1)	0.43

Safety Results

Primary Safety Endpoint at 6 Months

Complication	Control n/N (%)	Zephyr EBV n/N (%)	2-sided p-value
Subjects Experiencing at least One MCC	1/87 (1.2)	13/214 (6.1)	0.075
Death	0/87 (0.0)	6/214 (2.8)	
Empyema	0/87 (0.0)	0/214 (0.0)	
Massive Hemoptysis	0/87 (0.0)	1/214 (0.5)	
Pneumonia Distal to Valve	--	3/214 (1.4)	
Pneumothorax	1/87 (1.2)	3/214 (1.4)	
Respiratory Failure	1/87 (1.2)	4/214 (1.9)	

Adverse Events at 12 Months

Complication	Control n/N (%)	Zephyr EBV n/N (%)	Difference
Hemoptysis	2/87 (2.3)	91/214 (42.5)	40.2%*
Other Pulmonary Infection	1/87 (1.2)	18/214 (8.4)	7.2%*
Increased Shortness of Breath	2/87 (2.3)	21/214 (9.8)	7.5%*
Hypoxemia	0/87 (0.0)	15/214 (7.0)	7.0%*
Non-cardiac Chest Pain	3/87 (3.5)	35/214 (16.4)	12.9%*
Nausea or Vomitting	1/87 (1.2)	18/214 (8.4)	7.2%*
All Valve Implant Related	--	39/214 (18.2)	18.2%*

*The two-sided p-value is less than 0.05.

Serious Adverse Events at 12 months

Complication	Control n/N (%)	Zephyr EBV n/N (%)	Difference
COPD Exacerbation	9/87 (10.3)	50/214 (23.4)	13.1%*
Hemoptysis	0/87 (0.0)	26/214 (12.2)	12.2%*
All Valve Implant Related	--	34/214 (15.9)	15.9%*
Rehospitalization**	22/87 (25.3)	85/214 (39.7)	14.4%*

*The two-sided p-value is less than 0.05.

** Not listed as a SAE but as a separate safety endpoint.

European Data

Population	Endpoint	Control % (N)	EBV % (N)	Difference
Completed Cases (CC)	FEV1	0.8% (55)	6.6% (91)	5.8%
	6MWT	7.7% (55)	9.7% (88)	2.0%
Per Protocol (PP)	FEV1	-2.6% (37)	9.3% (53)	11.9%
	6MWT	7.3% (36)	9.0% (51)	1.7%

Complication	Control n/N (%)	EBV n/N (%)	Two sided P-Value
Patients Experiencing at least One MCC	2/60 (3.3)	15/111 (13.5)	0.035

Summary

- Statistical significance was achieved in the primary effectiveness analysis.
- Estimates of differences between the treatment and control may be impacted by:
 - a) Post-hoc definition of extended window
 - b) Proportion of missing data
 - c) Inclusion of major protocol violators
 - d) Lack of blinding.
- There were higher proportions of adverse events and serious adverse events in the treatment group.

Clinical Review

Emphasys Zephyr Endobronchial Valve System

**Deborah Shure, MD
Pulmonary**

**Julie A. Swain, MD
Cardiothoracic Surgery**

Clinical Overview

- **Procedure**
- **Study design**
- **Study performance**
- **Results**
- **Labeling**

Procedure

- **Single lobe treatment**
- **Number of valves based on physician judgment**
- **Target lobe chosen by an algorithm based on software analysis of HRCT from Core Laboratory**
- **HRCT software is not commercially available or FDA approved**

Study Design

- **Prospective**
- **Unblinded**
- **Multi-center**
- **Randomized**

2:1

Stratified by target lobe and exercise

- **Control = Optimal medical management**

NETT-EBV Issues

- **Sponsor rejected LVRS control suggested by FDA**
- **FDA advised the sponsor that no comparisons could be made to LVRS**
- **Similar entry criteria \neq same population**
- **Unknown covariates
1/2 decade apart; surgery**
- **Equivalent to using historical controls**

Study Design

- Prospective
- **Unblinded**
- Multi-center
- Randomized

2:1

Stratified by target lobe and exercise

- Control = Optimal medical management

Potential Biases Without Blinding

- **Positive placebo effect**
- **Negative placebo effect**
- **Treatment bias**
- **Assessment bias**

Entry Criteria

Major Inclusion

- 40-75 years
- $FEV_1 < 45\%$
- $TLC > 100\%$
- $RV > 150\%$
- Heterogeneous emphysema by Core Lab HRCT

Major Exclusion

- Homogeneous emphysema
- Large bullae (non-target)
- $FEV_1 < 15\%$
- $DLCO < 20\%$

Patient Follow-up

- 1, 3, 6, and 12 months
- Analyses provided are based on *post-hoc* widening of prespecified windows:

<i>Visit</i>	<i>Window</i>	<i>Ext. Window</i>	<i>Added</i>
6 mos	± 14 days	-30/+45 days	47 days
12 mos	± 30 days	± 60 days	2 mos

Co-Primary Effectiveness Endpoint

- % change in FEV₁ at 6 months
- % change in 6MWT at 6 months
- A physiological measurement (FEV₁)
How much you can breath out in one second breathing as fast as you can
- A functional assessment (6MWT)
How far you can walk in six minutes

Co-Primary Effectiveness Endpoint

- **FEV₁** : sample size estimate based on a **15% change** taken from *ATS recommended bronchodilator response of 12%-15% [ref 1]*
 - **6MWT** : sample size estimate based on a **17% change** “because it is between the clinically meaningful threshold (15%) [ref 2] and the 6MWT historical results (20.4%)”
-

References:

1. Lung Function Testing: Selection of Reference Values and Interpretive Strategies, Official Statement of the ATS. *Am Rev Respir Dis* 1991;144:12-2-1218
2. Redelmeier et al. Interpreting Small Differences in Functional Status: The Six Minute Walk Test in Chronic Lung Disease Patients. *Am J Respir Crit Care Med* 1997;155:1278-1282

Co-Primary Effectiveness Endpoint

FDA requested effectiveness data
through 12 months

Statistical significance:
one-sided significance level 0.025
imputation of missing data in ITT

Secondary Effectiveness Endpoints

SGRQ

mMRC

Cycle ergometry

Supplemental O₂

Additional Effectiveness Measures

- A large number of analyses included in the protocol and *post-hoc*, responder analyses:

FEV₁ ≥ 15%

6MWT ≥ 15%

SGRQ ≥ - 8 points

mMRC ≥ - 1 point

Cycle ≥ 10 watts

Based on sponsor identified clinically important differences.

BODE Index

- **A composite**
 - B = body mass index**
 - O = obstruction = FEV1**
 - D = dyspnea = mMRC**
 - E = exercise = 6MWT**
- **2 VENT co-primary endpoint**
- **1 secondary VENT endpoint**

Primary Safety Endpoint

- Major Complications Composite (MCC)
- Components:
 - death*
 - empyema*
 - massive hemoptysis*
 - pneumonia distal to a valve*
 - pneumothorax*
 - respiratory failure*

Primary Safety Endpoint

- **Sponsor proposed 30% delta**
- **FDA did not agree to the 30% delta, stating that it was too high.**
- **No primary safety hypothesis was agreed upon.**
- **FDA stated the data would be evaluated in total for risk/benefit.**

Other Safety Endpoints

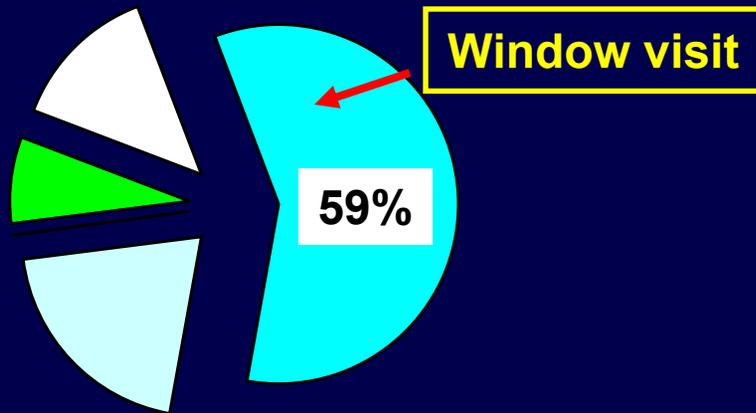
- **Survival**
- **Composite: death, LVRS, transplant**
- **Rehospitalization**
- **Adverse events**

1-year follow-up

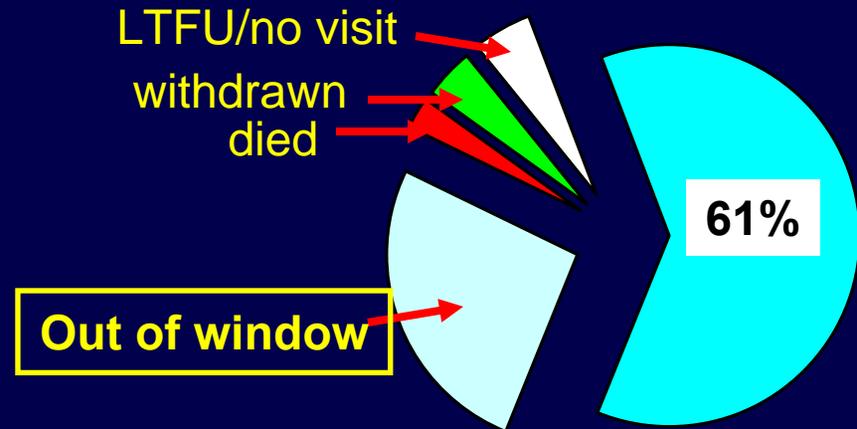
RESULTS

Data Accountability – Missing Data

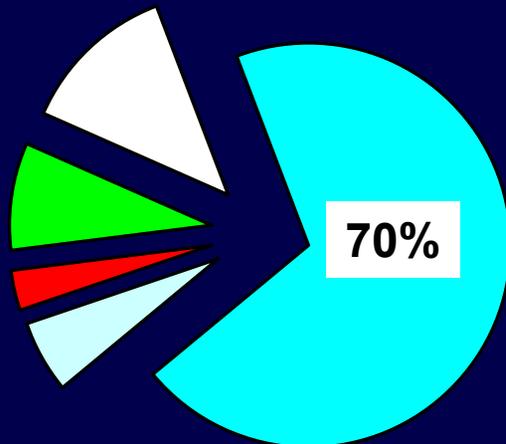
Control - 6 Month Visit



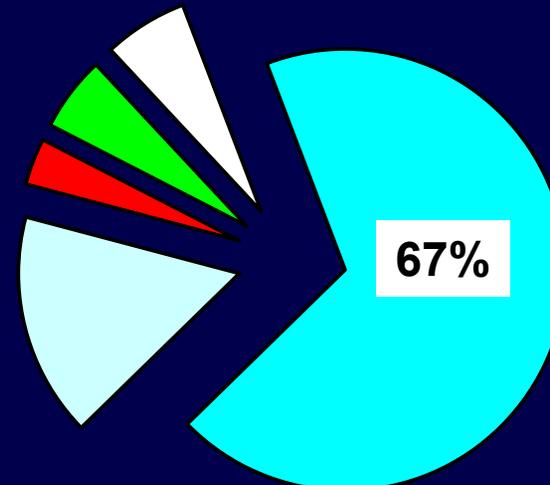
EBV - 6 Month Visit



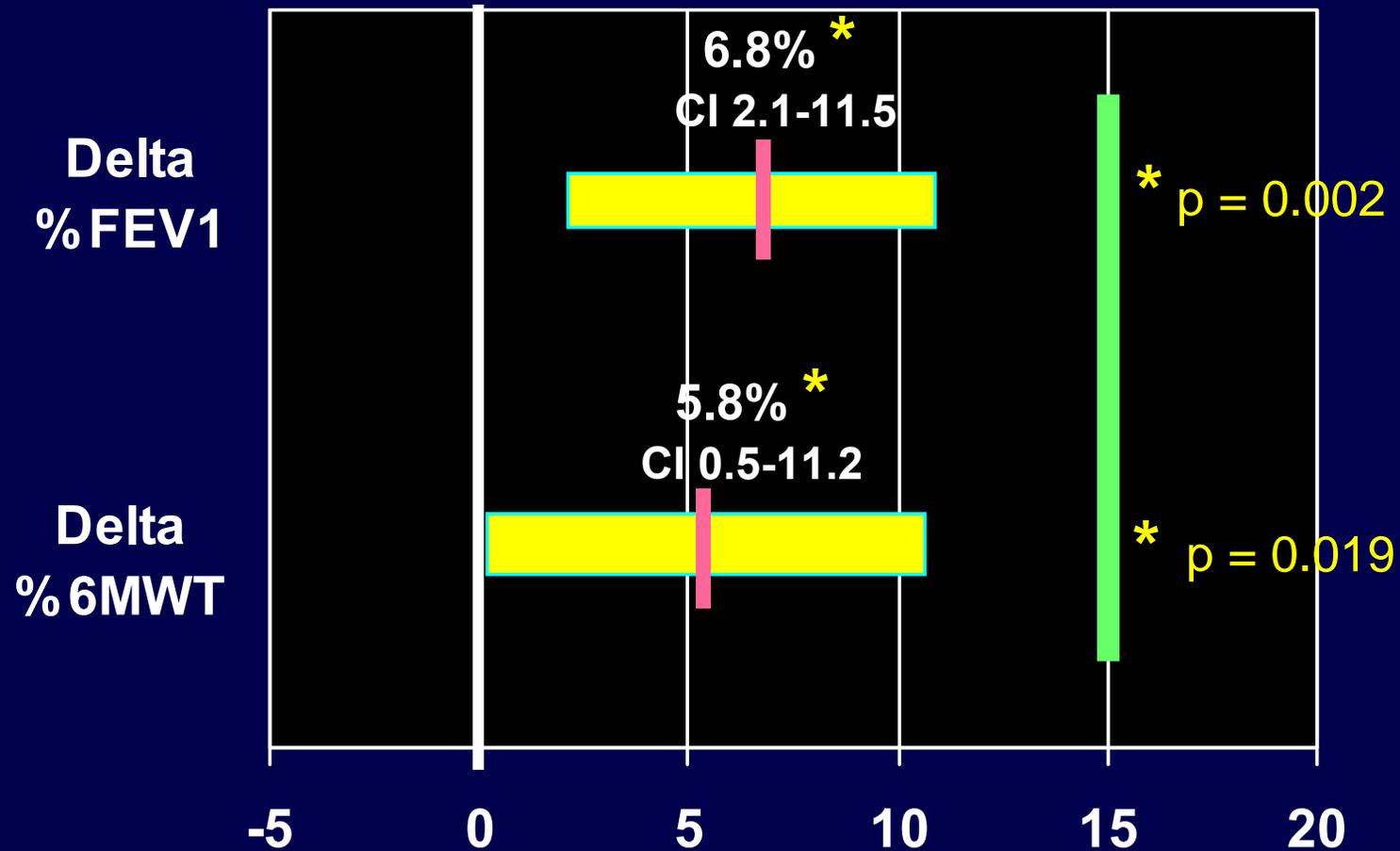
Control – 1 Year Visit



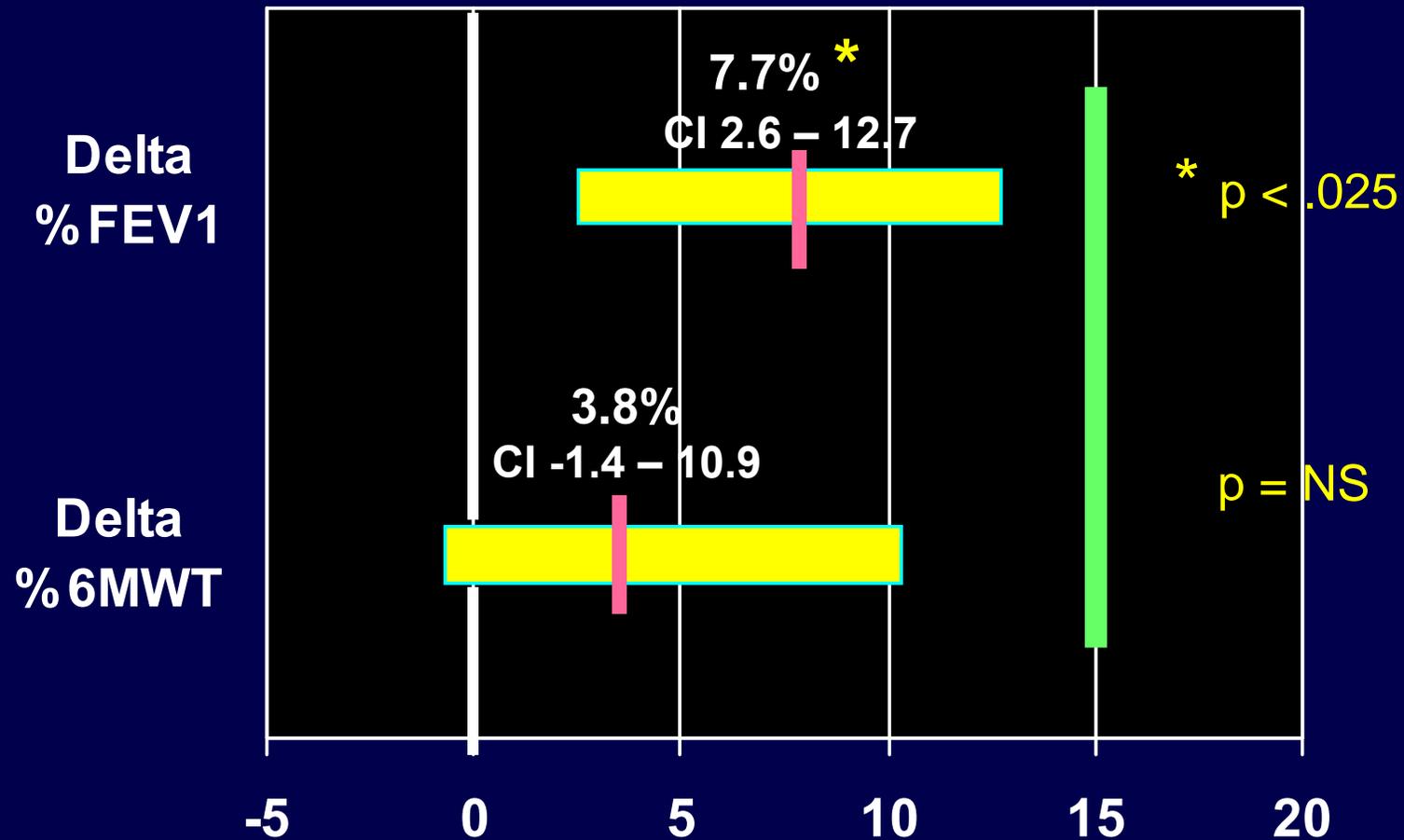
EBV - 12 Month visit



Primary Effectiveness at 6 Months (Multiple Imputation, ITT)

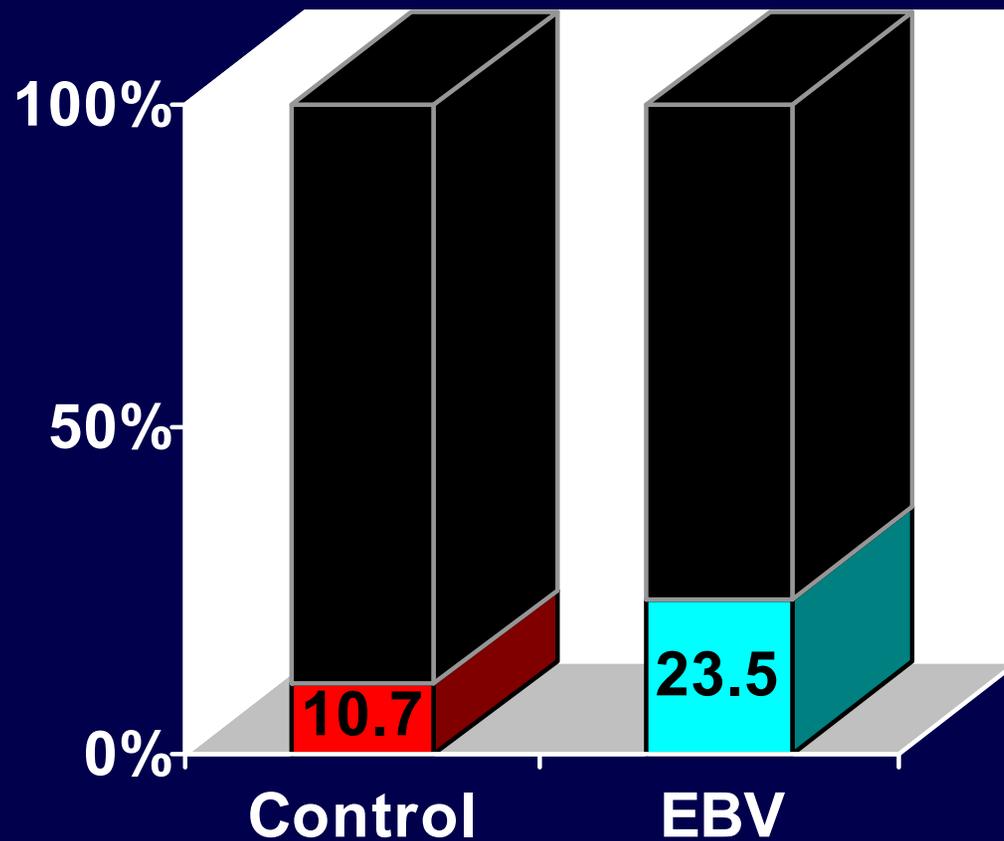


Effectiveness at 12 Months (Multiple Imputation, ITT)



FEV₁ Responder Analysis (≥15%) CC - 6 Months

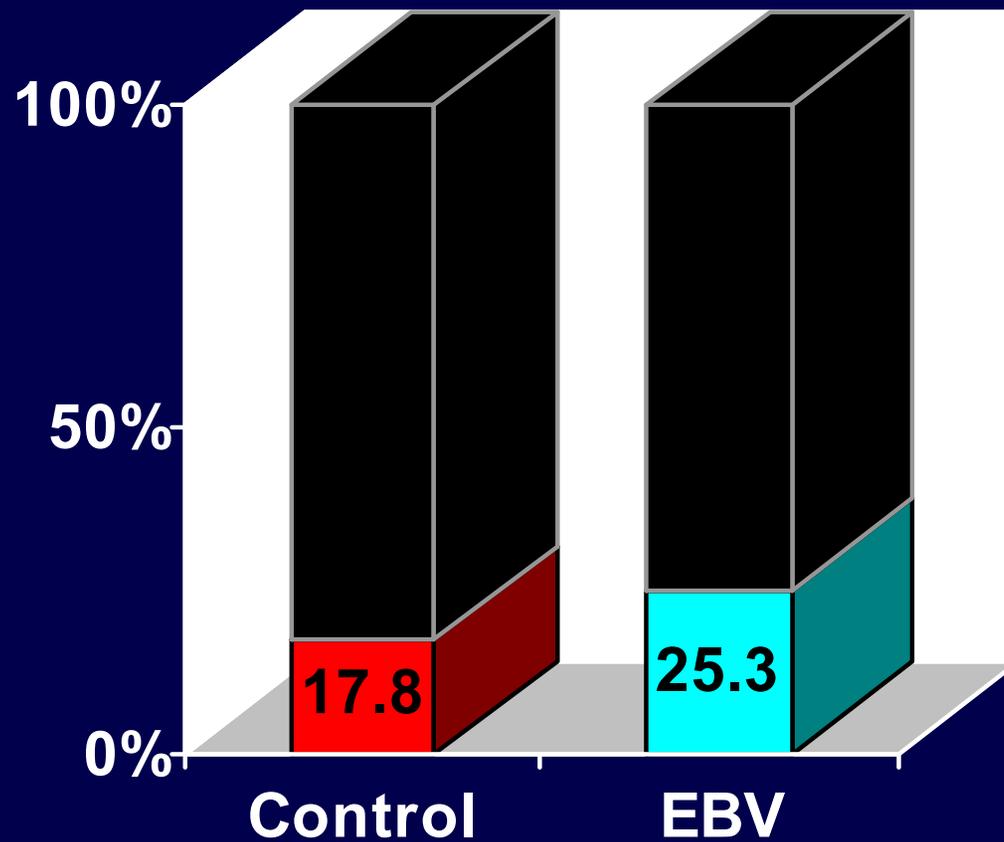
■ Non-Responder
■ Responder



p < 0.025

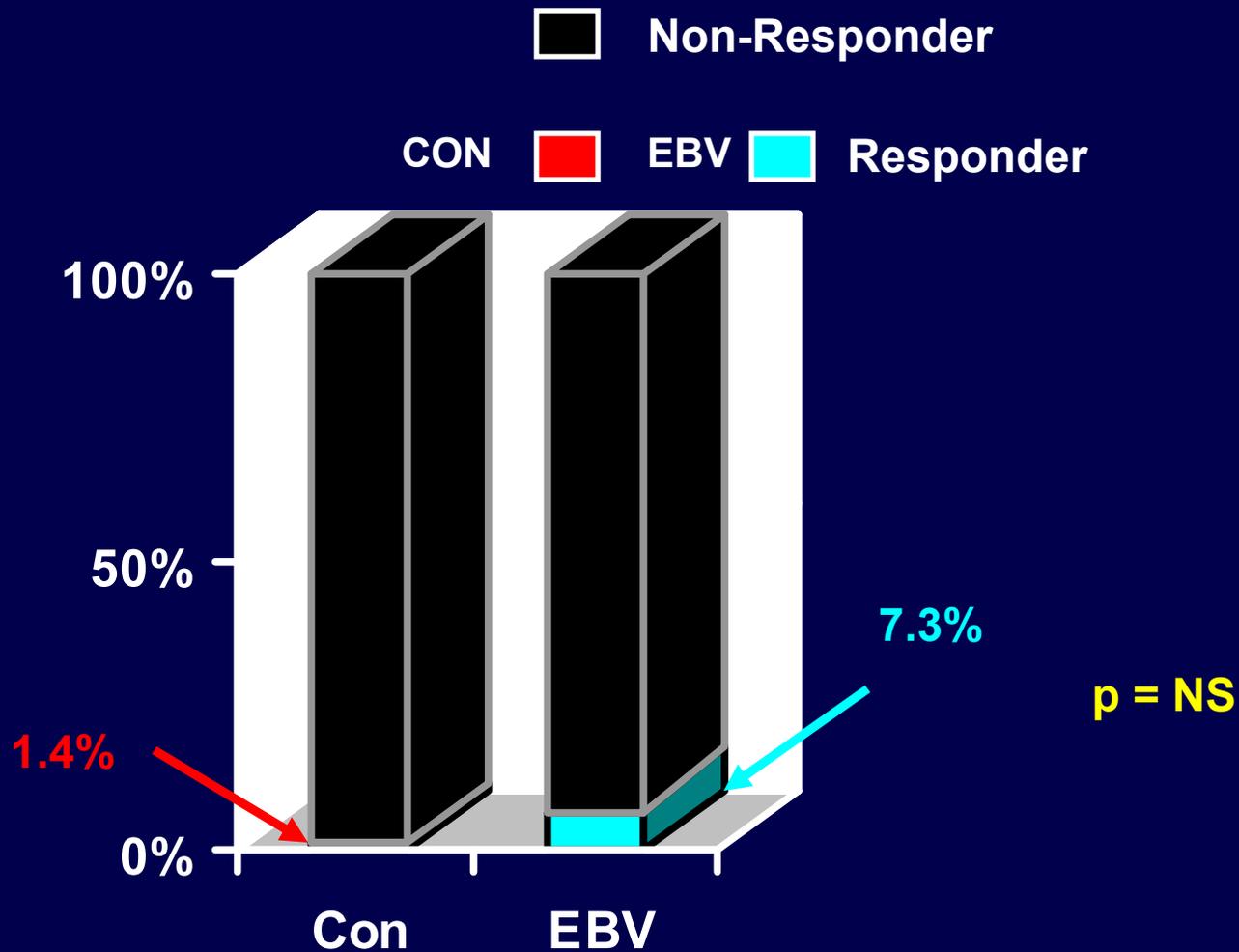
6-MWT Responder Analysis ($\geq 15\%$) CC - 6 Months

■ Non-Responder
■ Responder

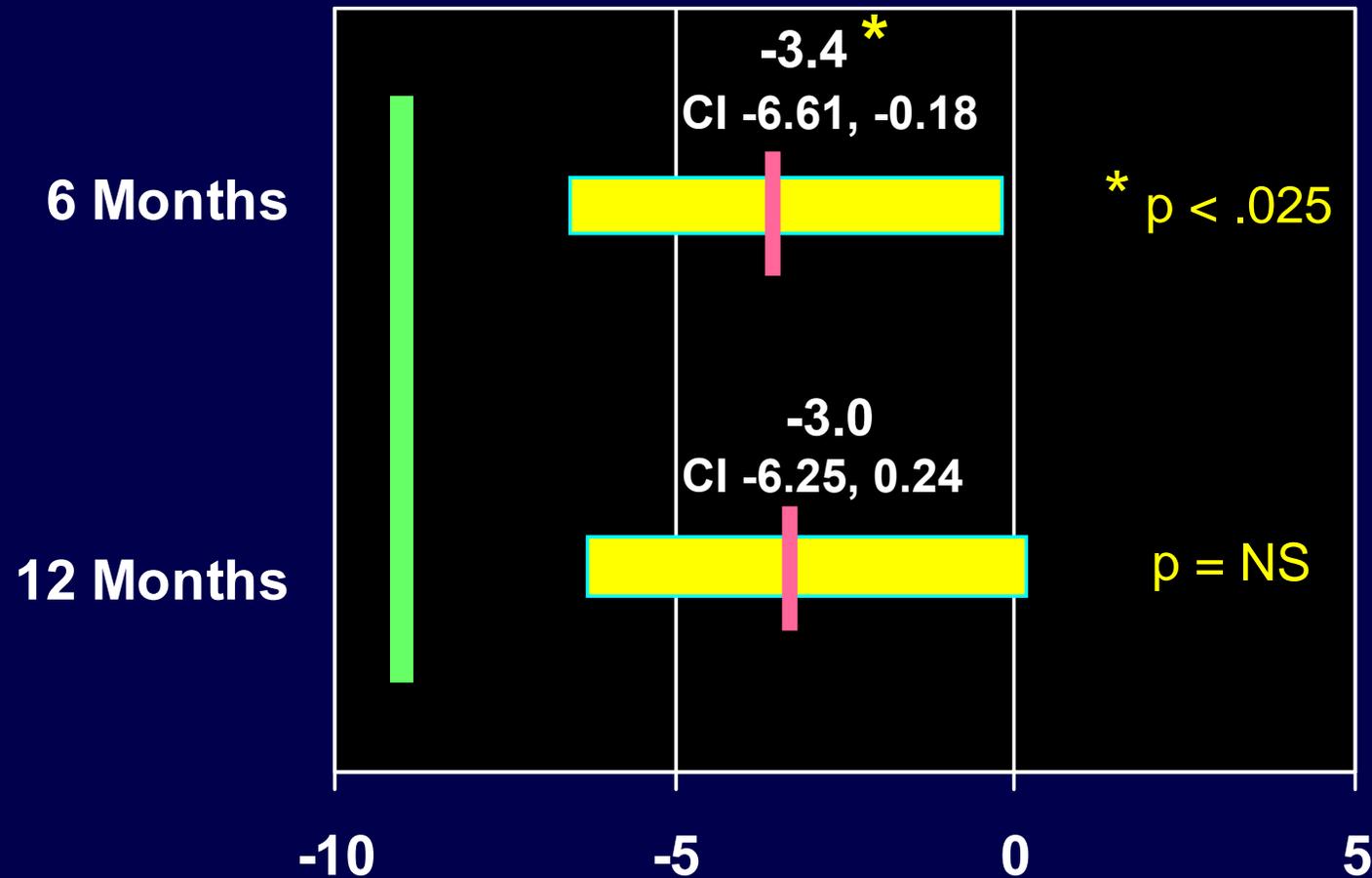


$p = NS$

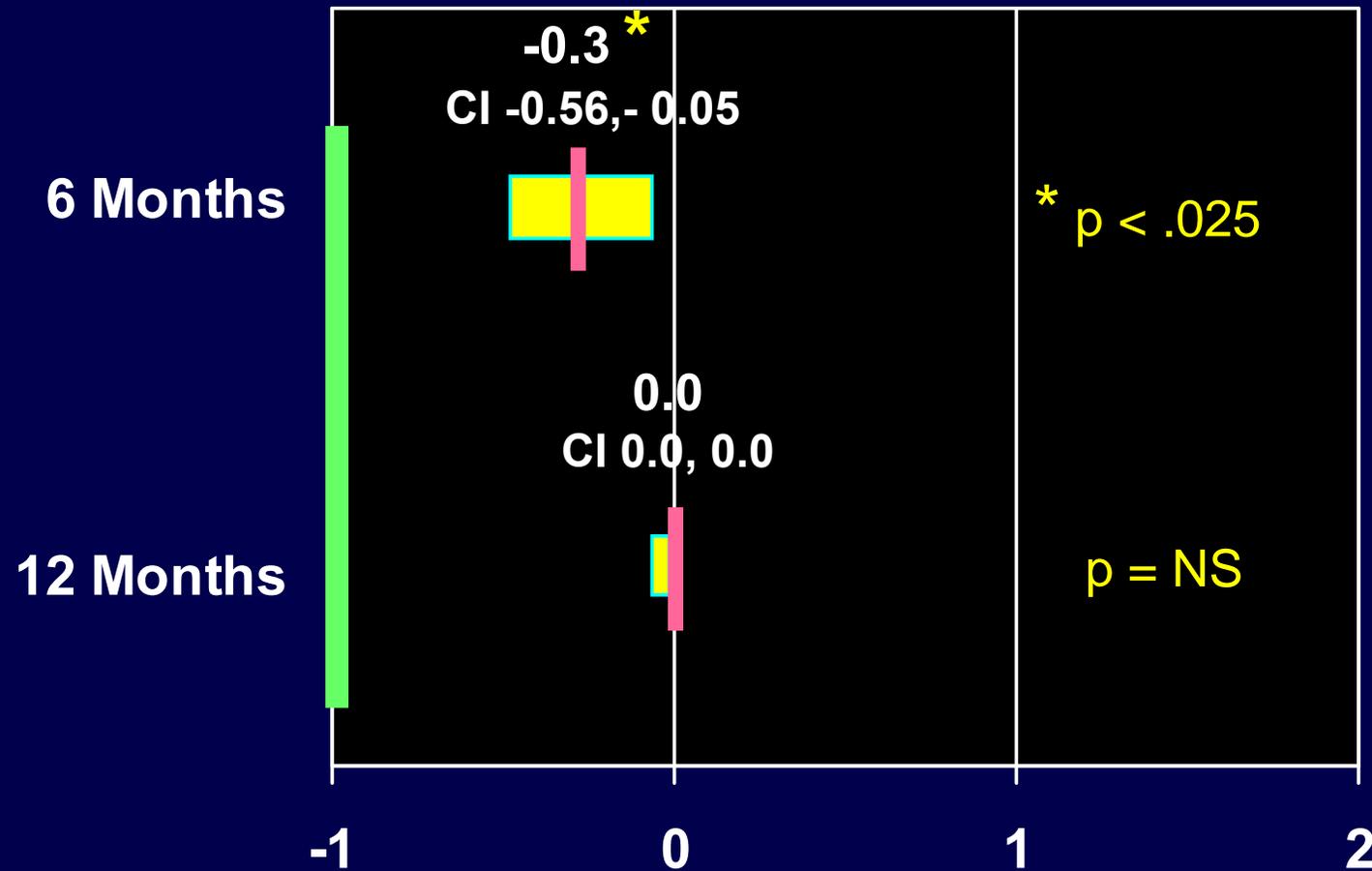
Responders ($\geq 15\%$) Co-Primary Endpoint 6 Months (CC)



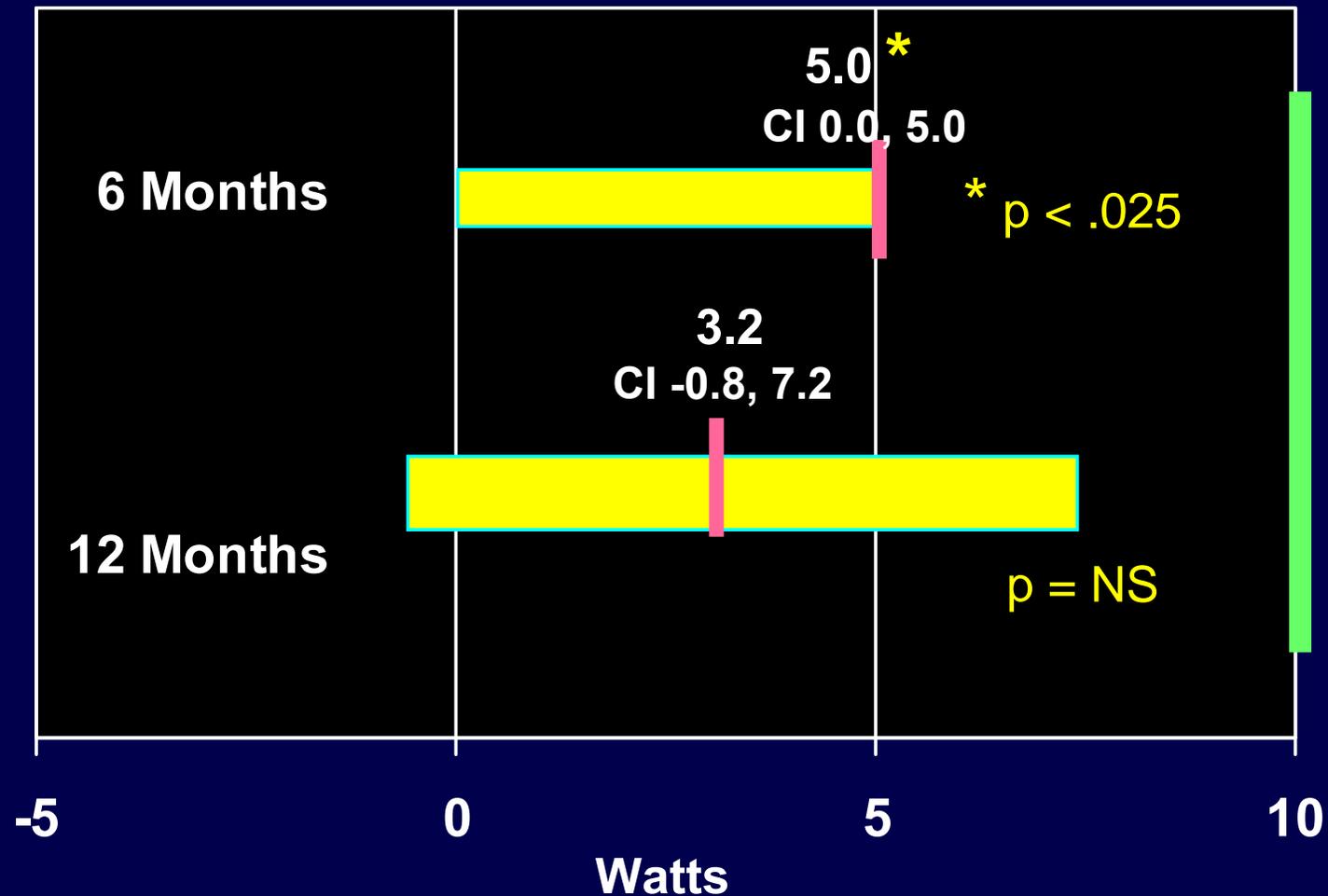
Secondary Effectiveness Endpoint SGRQ (CC)



Secondary Effectiveness Endpoint mMRC (CC)



Secondary Effectiveness Endpoint Cycle Ergometry (CC)



High Heterogeneity Issue

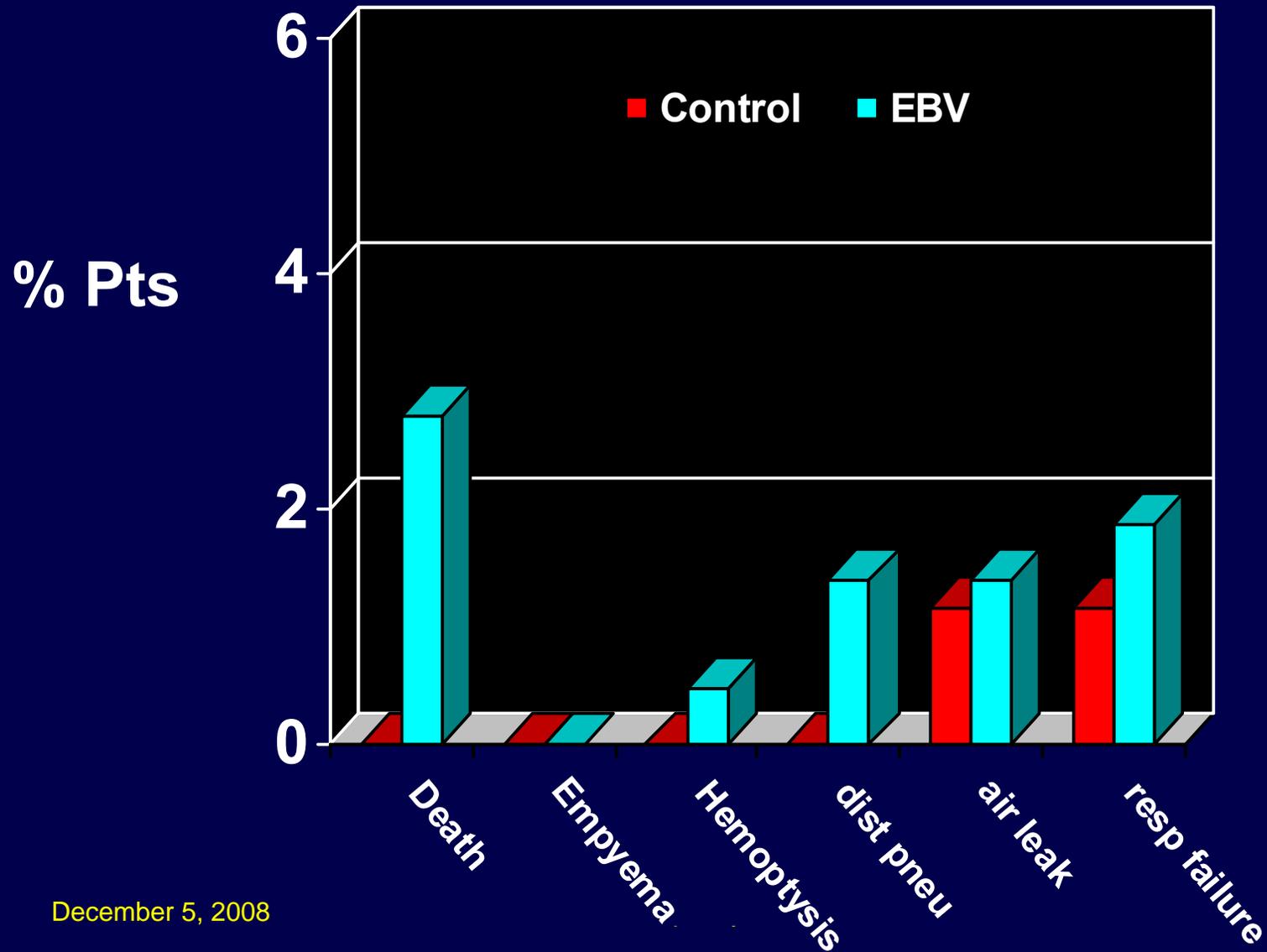
- **Post hoc**
- **Not uniquely defined**
- **Statistical issues re multiplicity**
- **Associated with higher incidence of death / LVRS ($p = 0.0078$)**

Primary Safety

Major Complications Composite

- EBV 6.07%
 Control 1.15%
- Not statistically significant

MCC Components – 6 months



Control Deaths (0-6 Months)

- None
- $n = 0$ (0%)

EBV Deaths (0-6 Months)

n = 6 (2.8%)

Lobe	Age	Time	Cause of Death / Adverse Events
LLL	62	21 days	Respiratory Failure post surgery, 2 days after EBV procedure
RUL	73	23 days	Hemoptysis (valve) with Respiratory Failure 8 days post
RUL	69	4 mos	EBV Respiratory Failure from COPD Exacerbation Prior hospitalizations for COPD Exacerbation

EBV Deaths (0-6 Months)

(continued)

Lobe	Age	Time	Cause of Death/Adverse Events
RUL	69	4.4 mos	Respiratory Failure from COPD Exacerbation with non-valve pneumonia
RUL	67	5 mos	Metastatic cancer; Unknown primary
RUL	68	5.3 mos	Respiratory Failure from COPD Exacerbation Prior hospitalizations for COPD Exacerbation and hemoptysis

Control Deaths (6-12 Months)

n = 3 (3.4%)

Group	Age	Time	Cause of Death/Adverse Events
CON	66	7 mos	Non Small Cell Lung Cancer
CON	70	6.5 mos	COPD – gradual worsening
CON	69	6 mos	Pneumothorax complications after wedge resection for pulm nodule

EBV Deaths (6-12 Months)

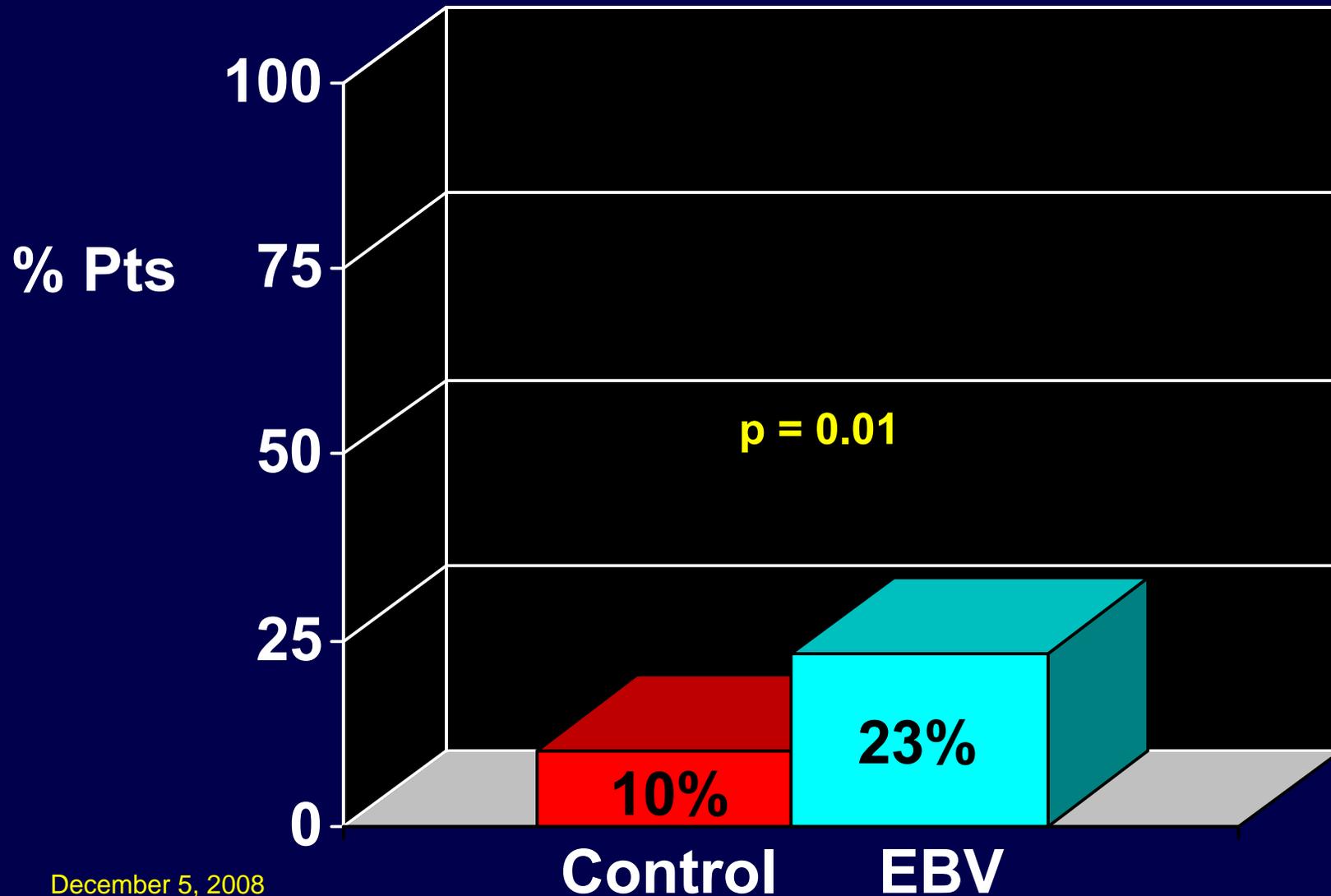
n = 2 (0.93%)

Group	Age	Time	Cause of Death/Adverse Events
LUL	66	7.5 mos	COPD Exacerbation and RUL pneumonia
RUL	50	9.3 mos	COPD Exacerbation with MVent 2.5 mos post EBV; Died of metastatic cancer

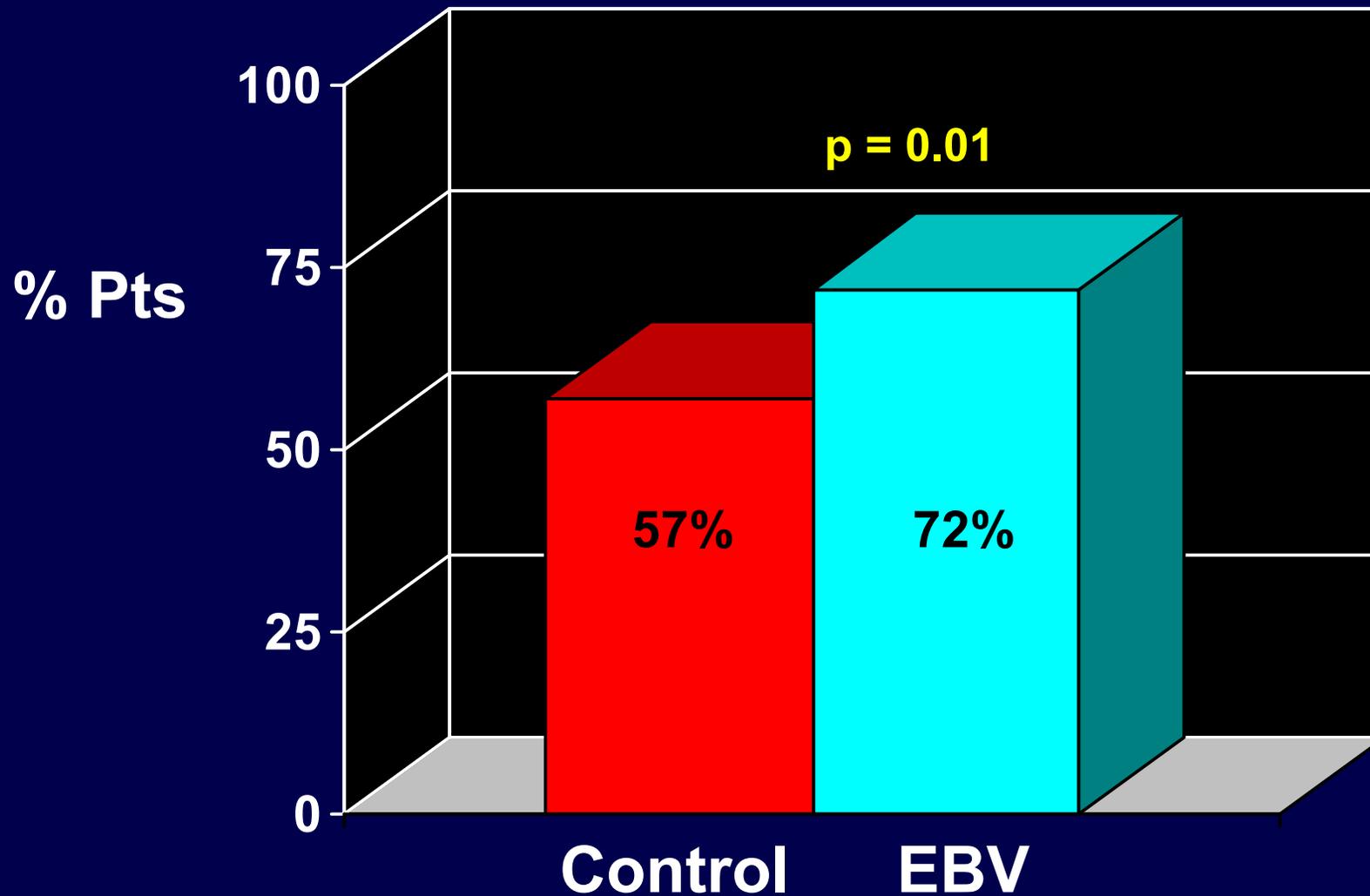
Deaths - Summary

- **12 month totals comparable**
3.4% Control 3.7% EBV
- **Control deaths later**
1/3 COPD related
- **EBV death 6/8 earlier**
6/8 COPD related
- **Prior COPD hospitalizations 3/8 EBV**

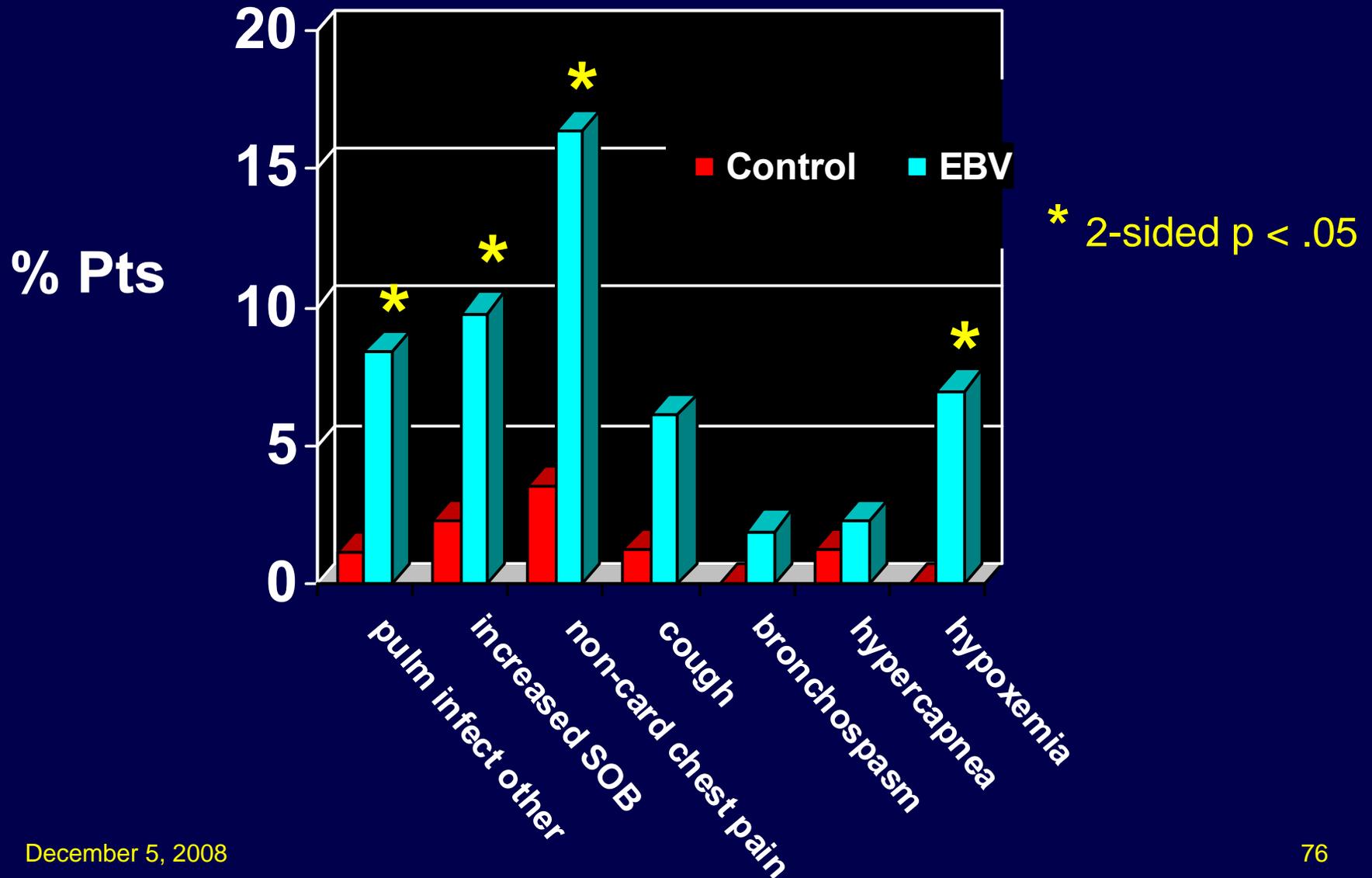
Serious Adverse Events – 12 months COPD Exacerbations



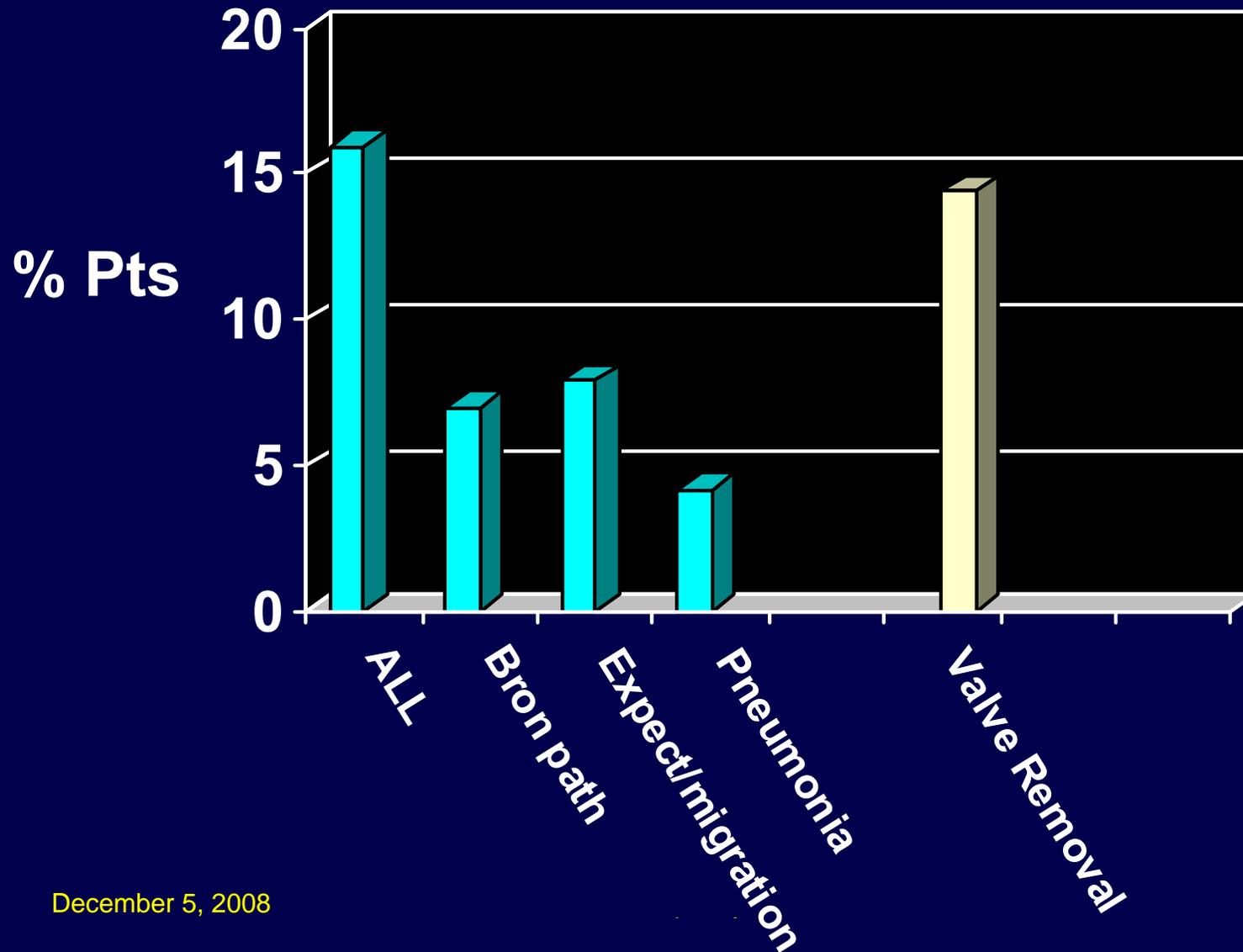
COPD Exacerbations (AE) – 12 months



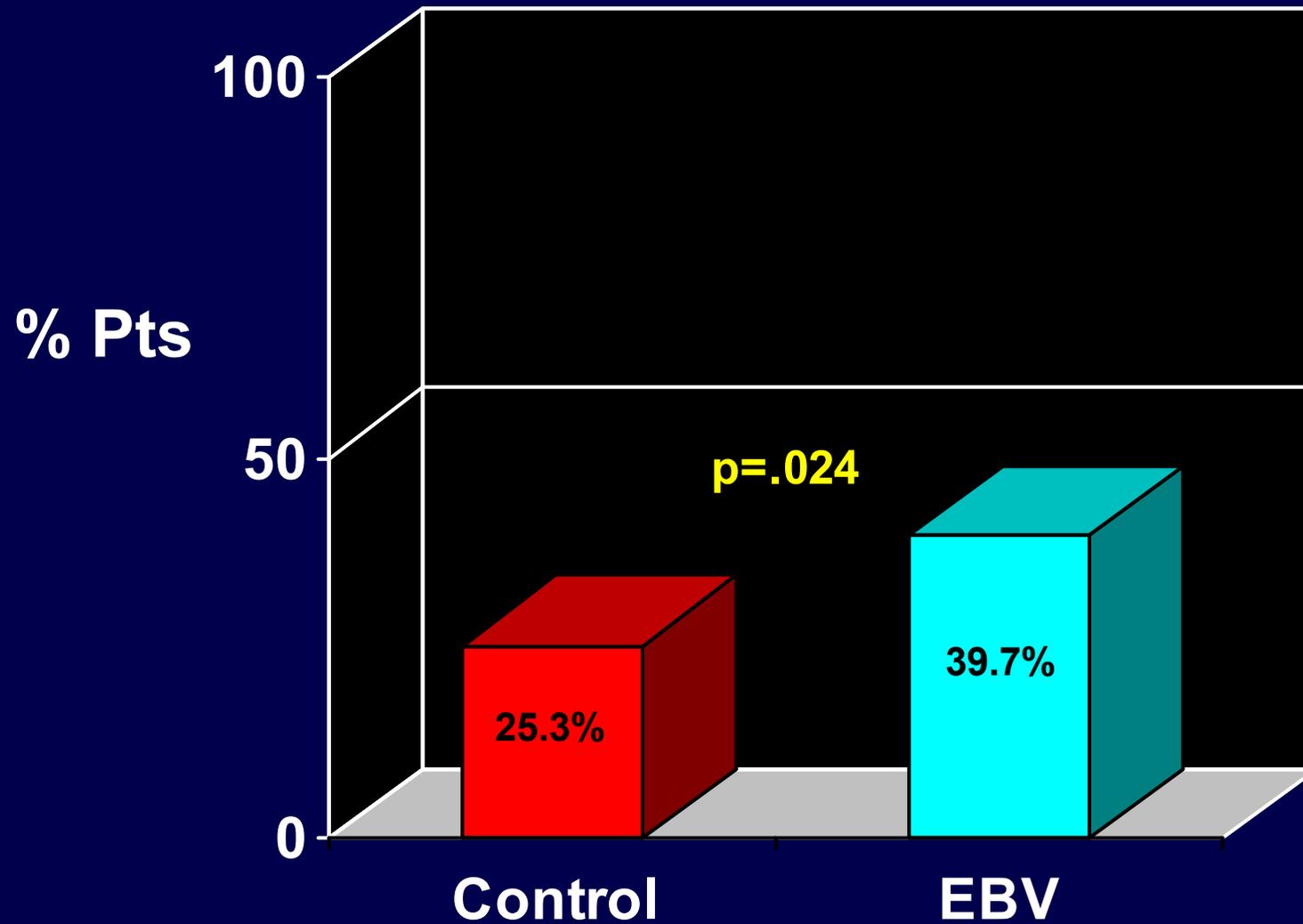
COPD/Pulmonary Adverse Events – 1 yr



Unique EBV Serious Adverse Events 12 months



All Hospitalizations – 12 months



EBV Europe

- Effectiveness - not significant

FEV1 Δ 5.8% 6MWT Δ 1.9%
CC Population

- MCC significantly worse in the treated group

13.5% EBV
3.3% Control
p= 0.0348

Proposed Instructions for Use

- Different method of target lobe selection
 - radiographic assessment**
 - not tested in VENT trial**
- Number of lobes to be treated not specified
- Training is not specified

Clinical Issues Summary

- Interpretation with respect to missing data
- Clinical significance of the endpoints
- Significance of the safety data in a risk/benefit analysis
- Instructions for Use indications, target lobe selection, and training are not the same as the VENT trial and have not been tested

P070025
Emphasys Zephyr[®]
Endobronchial Valve (EBV)
Post-Approval Study (PAS)

Jiping Chen, MD, PhD, MPH
Epidemiology Branch
Division of Postmarket Surveillance
Office of Surveillance and Biometrics

Anesthesiology and Respiratory Therapy Devices Panel Meeting
December 5, 2008

Outline

- General principles
- Rationale for postmarket questions
- Assessment of the PAS protocol /outline
- PAS issues for panel discussion

Reminder

- The discussion of a Post-Approval Study (PAS) prior to a formal recommendation on the approvability of this PMA should not be interpreted to mean FDA is suggesting the Panel find the device approvable.
- The plan to conduct a PAS does not decrease the threshold of evidence required to find the device approvable.
- The premarket data submitted to the Agency and discussed today must stand on its own in demonstrating a reasonable assurance of safety and effectiveness in order for the device to be found approvable.

General Principles for Post-Approval Studies

- Objective is to evaluate device performance and potential device-related problems in a broader population over an extended period of time after premarket establishment of reasonable evidence of device safety and effectiveness.
- Post-approval studies **should not** be used to evaluate unresolved issues from the premarket phase that are important to the initial establishment of device safety and effectiveness.

Need for Post-Approval Studies

- Gather postmarket information
 - Longer-term performance
 - Real world community performance
 - Effectiveness of training programs
 - Sub-group performance
 - Rare adverse events

- Account for Panel recommendations

Important Postmarket Questions

- What will the real world performance of the device be in the more general population of patients and providers?
- What is the long-term safety and effectiveness of the device postmarket?
- Is there need of a postmarket failure analysis for removed / expectorated valves?

FDA Assessment

Sponsor's Proposed PAS Outline - New Patients

Study Design

Prospective, single-arm, open-label, observational study

- Need for an appropriate control to address device durability
- Controls:
 - EBV vs. Lung Volume Reduction Surgery (LVRS)
 - EBV vs. Standard of Care Controls
 - Patient comparability (EBV: unilaterally; LVRS: bilaterally)

FDA Assessment (cont'd)

Sponsor's Proposed PAS Outline - New Patients

Effectiveness Endpoint

The post-bronchodilator spirometry at 1, 2, and 3 years post-procedure

- Appropriateness for not considering 6MWT as an effectiveness endpoint

FDA Assessment (cont'd)

Sponsor's Proposed PAS Outline - New Patients

Safety Endpoints

SAEs at 1, 2, and 3 years post - procedure

- An underestimation of AEs
- Not sufficient for evaluating device long-term safety profile
- Device safety remains a concern in the VENT study

FDA Assessment (cont'd)

Sponsor's Proposed PAS Outline - New Patients

Duration of follow-up

Subjects will be followed for 3 years post -
procedure

- Appropriateness of the duration of follow-up

FDA Assessment (cont'd)

Sponsor's Proposed PAS Outline – New Patients

Study Sample Size

Up to 200 EBV subjects

- Observed rate of valve expectoration / migration in **VENT: 7.9%**

Assumptions:

- Expected rate of valve expectoration / migration: 4 - 6% in PAS
- Upper one-sided 95% CI < 10% (**expected postmarket 6% + 4%** width)
- Sample size is not hypothesis-driven and maybe underestimated
- Valve expectoration /migration rate: postmarket **6%(?)**

PAS Issues for Panel Discussion

(1) PAS study with new subjects

- Study Design
- Control Selection
- Sample Size
 - Appropriateness of the assumption that postmarket valve expektoration/migration rate $<$ in premarket
- Effectiveness Endpoint
 - Need for evaluating 6MWT as an effectiveness endpoint
- Safety Endpoint
- Duration of Follow-up

(2) Additional issues / questions that can be addressed in a PAS

Questions?