

Zephyr Endobronchial Valve (EBV)

PMA P070025

Anesthesiology and Respiratory Devices
Advisory Panel Presentation

December 5, 2008

Emphasys Medical

John McCutcheon

President and CEO

Emphasys Medical

- Founded in 2000
- Sole product is Zephyr EBV System
- 48 Employees
- Located in Redwood City, CA
- CE Mark



Zephyr Endobronchial Valve



Proposed Indication:

“To improve FEV₁ and six minute walk test distance in patients with severe, heterogeneous emphysema who have received optimal medical management.”

Zephyr EBV FDA Panel Presenters

Clinical Problem,
Device, Trial Design

Gerard Criner, MD
Temple University

Baseline Characteristics,
Conduct of Study and Safety

Armin Ernst, MD
Beth Israel Deaconess Medical Center

Efficacy Results

Frank Scieurba, MD
University of Pittsburgh

Conclusion and
Post Approval Study

Gerard Criner, MD
Temple University

Additional Advisors

Investigators

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University of Iowa
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Imaging Core Lab

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CEC Chair

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Statistician

- Richard Chiacchierini, PhD
RPC Consulting

DSMB Chair

- Robert Wise, MD
Johns Hopkins University

Clinical Problem

Gerard Criner, MD, FCCP

Professor of Medicine

Florence P. Bernheimer Distinguished Service Chair

Director, Pulmonary and Critical Care Medicine

and Temple Lung Center

Temple University School of Medicine

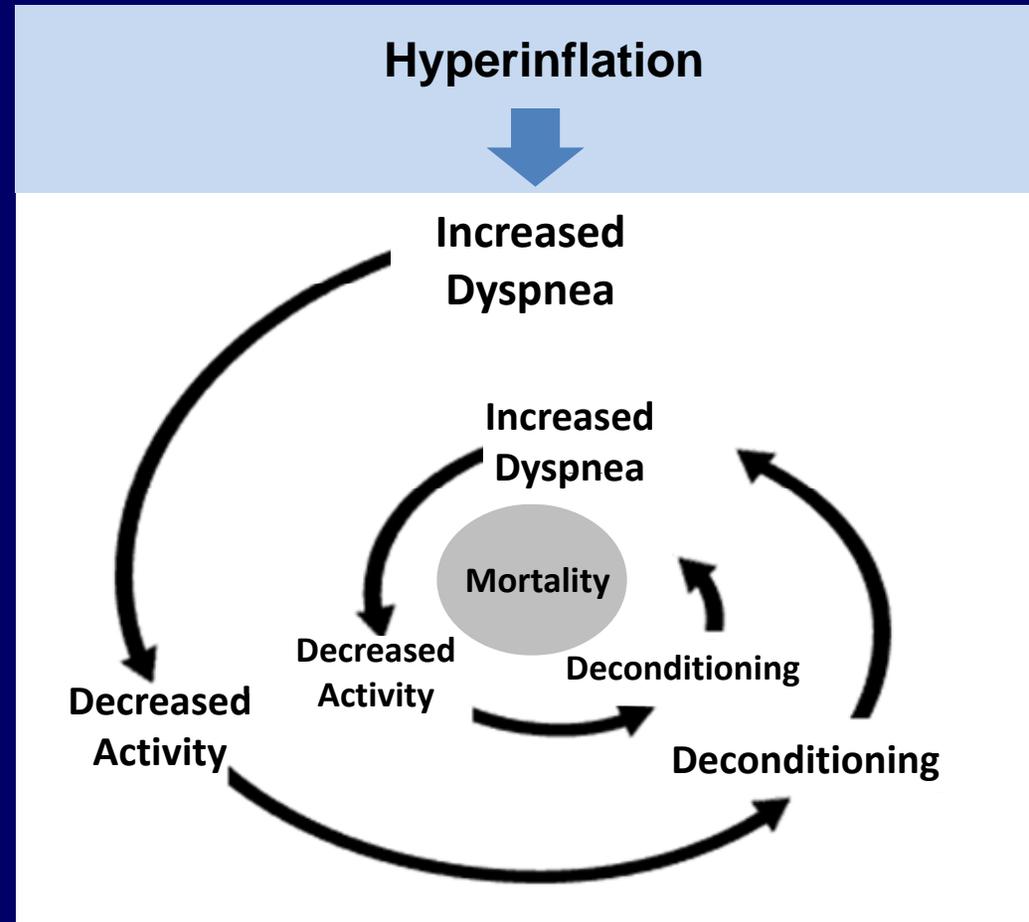
Emphysema

- Emphysema is a progressive, debilitating disorder that markedly impairs quality of life
- Pharmacologic intervention in patients with predominately emphysema is poorly described, but believed to be of limited value
- Only smoking cessation alters the decline in lung function
- Only supplemental oxygen can improve survival. Benefits limited to most severe subset

Pathophysiological Effects of Emphysema

- Irreversible destruction of lung tissue; involves alveolus and small airway
 - Airflow obstruction
 - Impaired gas exchange
 - Gas trapping impairs lung, chest and respiratory muscle mechanics
- Significant patient variability in severity and distribution of extent of emphysema (e.g., heterogeneity)

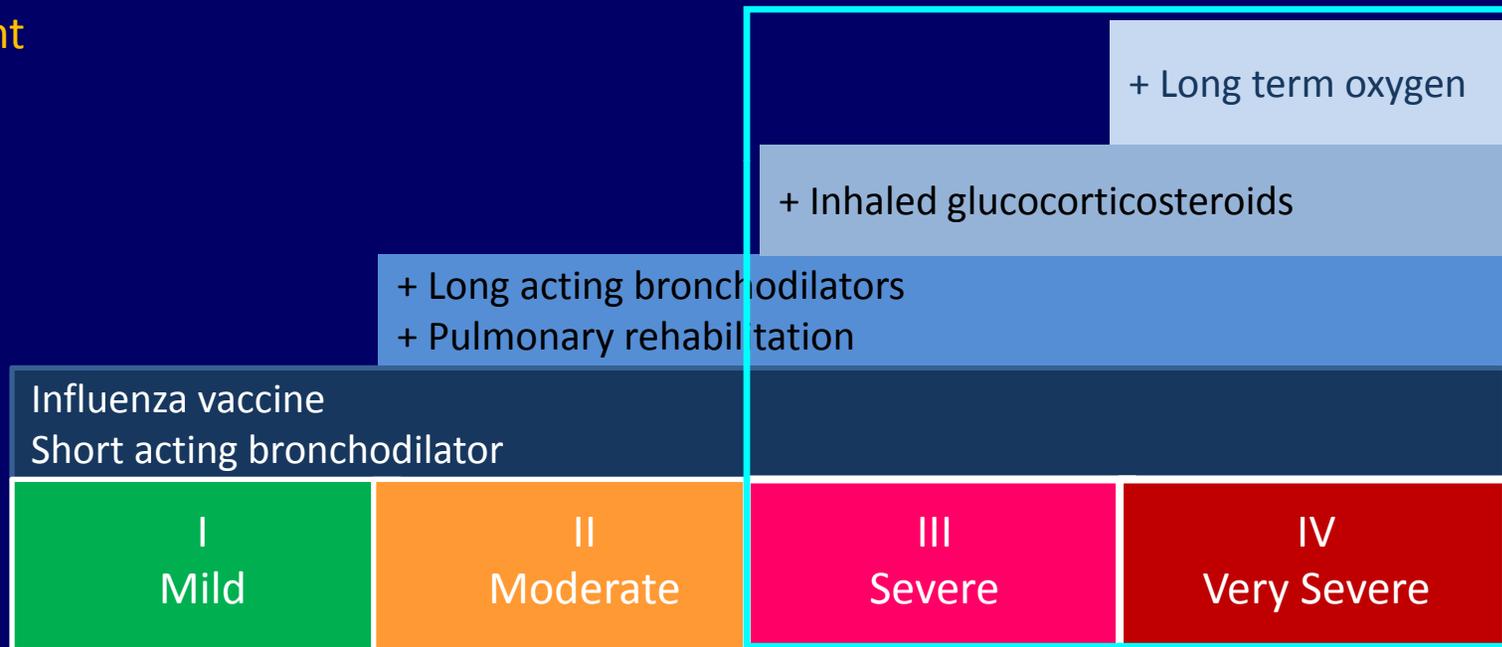
The Inactivity - Dyspnea Spiral



Treatment Options

Treatment Options:

GOLD*
Stage:

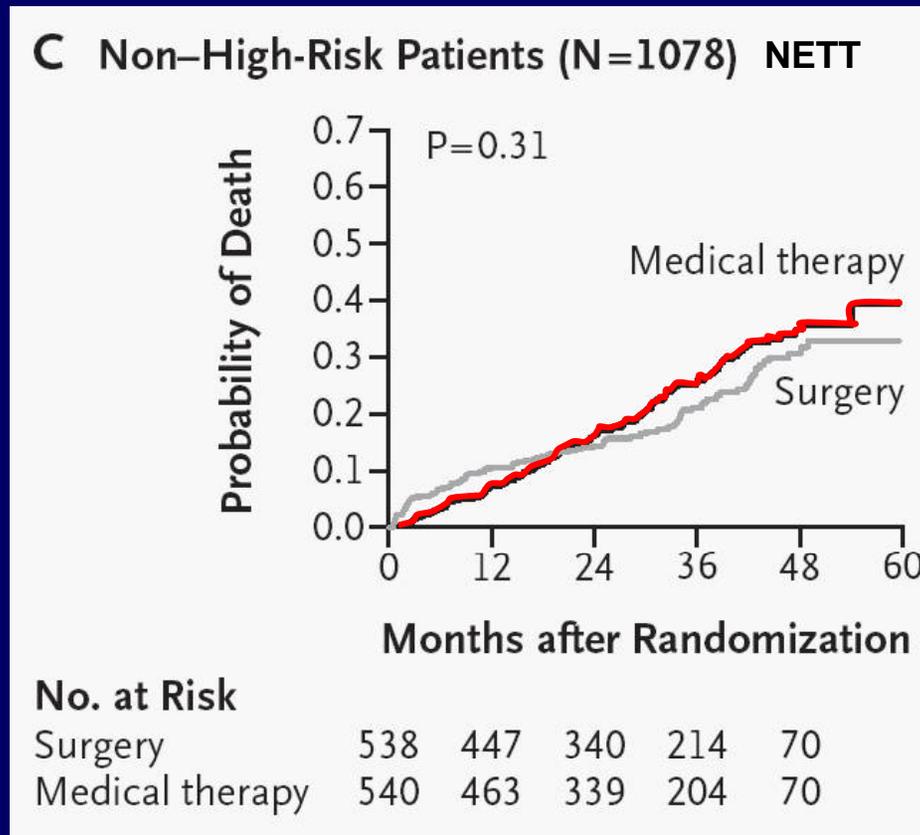


- Typically seek medical attention

- ↑ dyspnea
- ↓ exercise capacity
- repeated exacerbations

- Appreciably impaired
- Exacerbations may be life-threatening

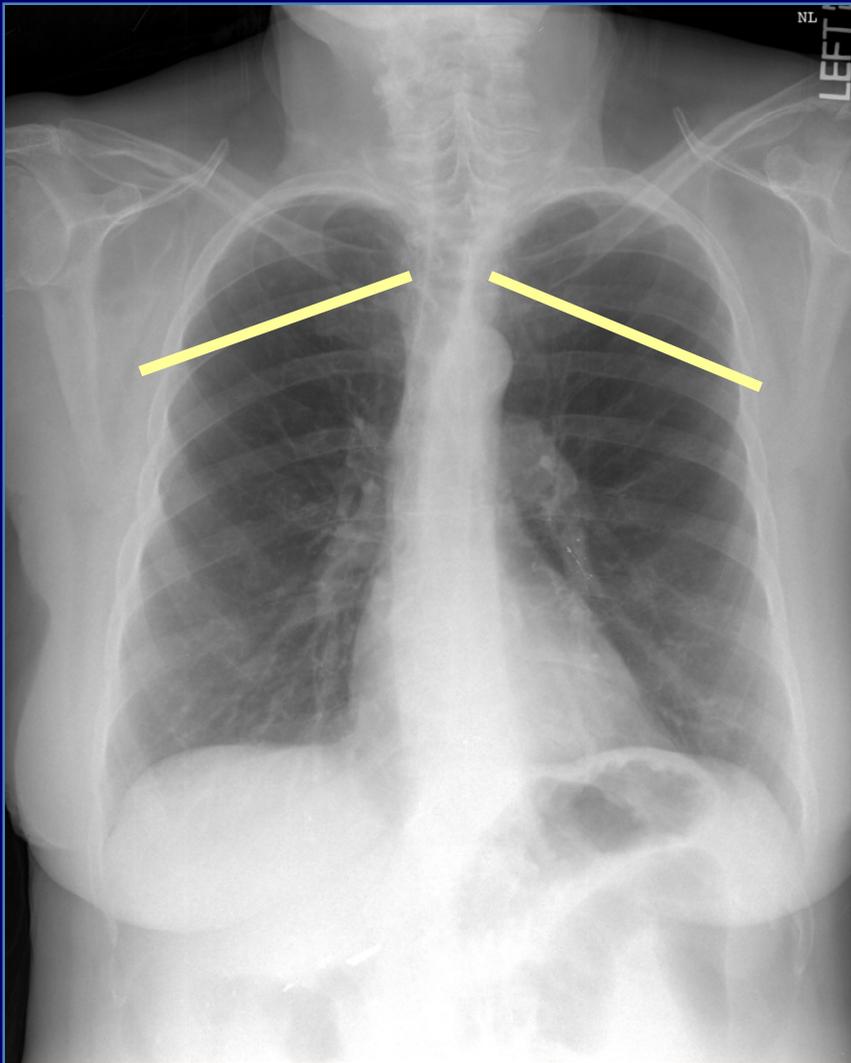
Disease Progresses Despite Maximal Therapy



Mortality: ~40% in 5 years

Exercise (6MWT) : ↓ 63.7 m (-17%) in 2 years

Lung Volume Reduction Surgery: A Surgical Treatment of Hyperinflation



National Emphysema Treatment Trial (NETT)

Unblinded, multicenter, randomized clinical trial comparing medical treatment with lung volume reduction surgery (LVRS) to medical treatment alone in patients with severe emphysema.

Primary endpoints: Survival, Maximum exercise

Secondary endpoints: Lung function, QOL,
6MWT, Cost-effectiveness

NETT Summary

Randomized 1218 patients; identified subgroups



Survival



Exercise capacity



Quality of life

Median follow-up of 29 mos (2.4 yrs) as of Dec 02

Only 60% of patients reached 2 yr testing mark

NETT Subgroup Treatment Effects

- Non High Risk Patients: Mortality RR = 0.89; Exercise OR = 6.78; SGRQ OR = 5.06
 - Upper Lobe/ Low Exercise: Mortality RR = 0.47; exercise OR = ∞ ; SGRQ OR = 8.38
 - Upper Lobe/ High Exercise: Mortality RR = 0.98; Exercise OR = 5.81; SGRQ OR = 5.67
 - Non Upper Lobe/Low Exercise: Mortality RR = 0.81; Exercise OR = 1.77; SGRQ OR = 7.35
 - Non Upper Lobe/High Exercise: Mortality RR = 2.06; Exercise OR = 0.90; SGRQ OR = 1.35

Heterogeneity of Emphysema on HRCT Predicts LVRS Response

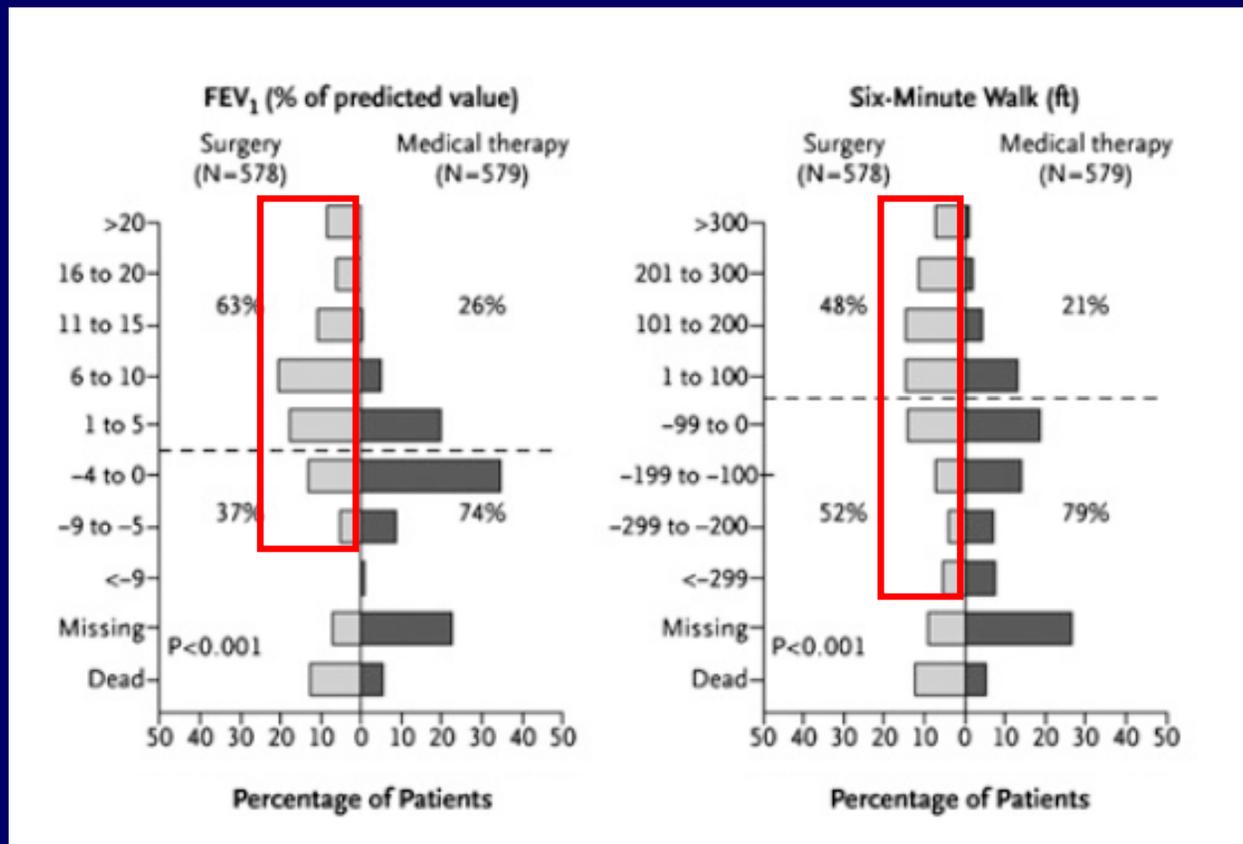
NETT: Complications of LVRS

90 day mortality	5.2%
30 day morbidity	
Air leaks	90% (50% > 7 days)
Major pulmonary (Re-intubation, pneumonia, tracheostomy, ventilator support, failure to wean)	30%
Major cardiovascular (Arrhythmia, MI, pulmonary embolus)	20%

→ In 2007, only 104 Medicare patients underwent LVRS

NETT Efficacy: 6 Months

NIH/CMS Sponsored Study of LVRS (n = 1218)



Weighing the Clinical Balance: Benefits vs. Complications of LVRS

LVRS Benefits

- ↑ lung function,
- ↑ exercise performance
- ↑ QOL
- ? decreased mortality

LVRS Risks

- peri-procedural mortality
- air leaks
- pain
- respiratory tract infection
- prolonged hospitalization

Symptomatic
patients despite
maximal medical
treatment

Treatment Options

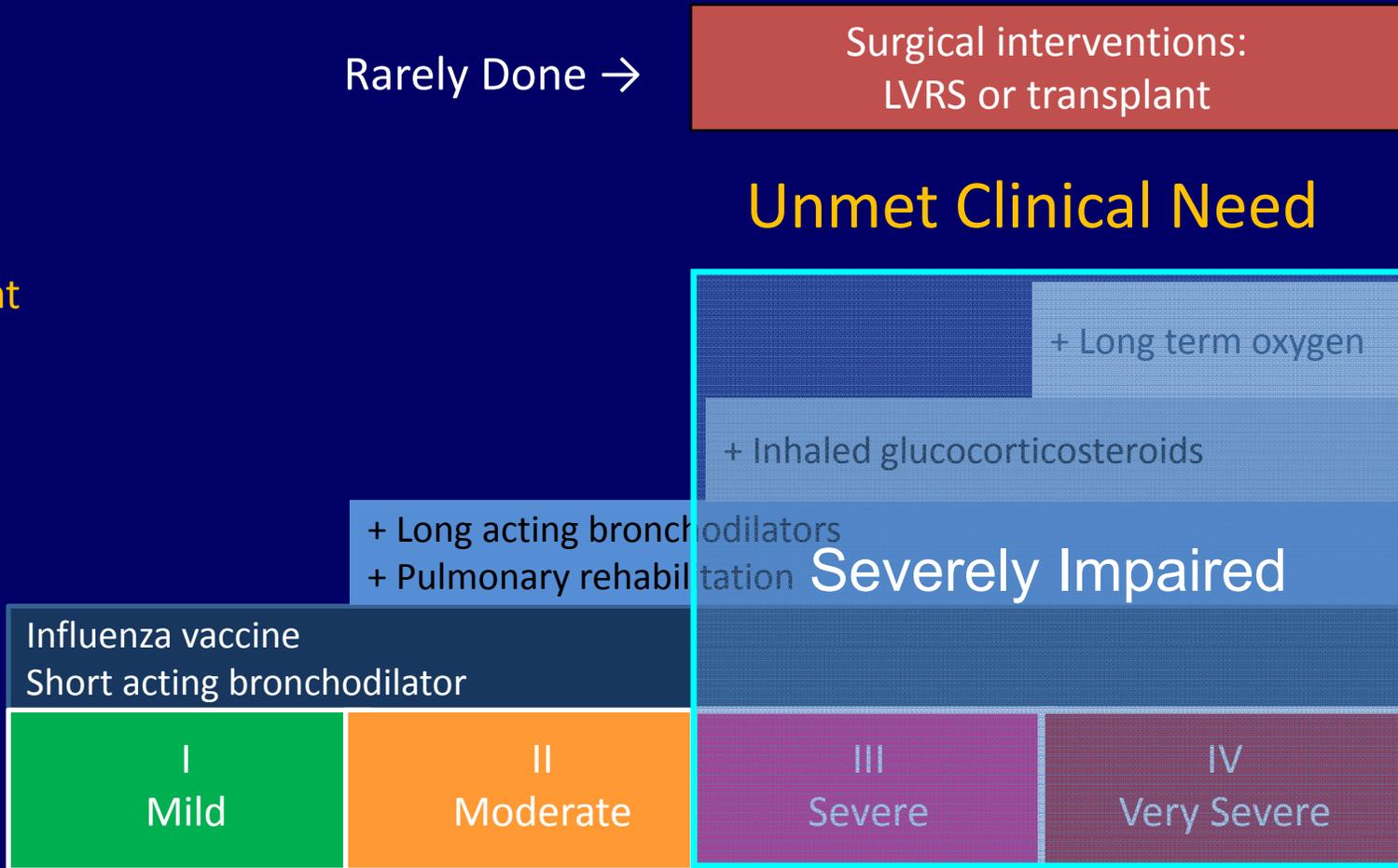
Rarely Done →

Surgical interventions:
LVRS or transplant

Unmet Clinical Need

Treatment
Options:

GOLD*
Stage:



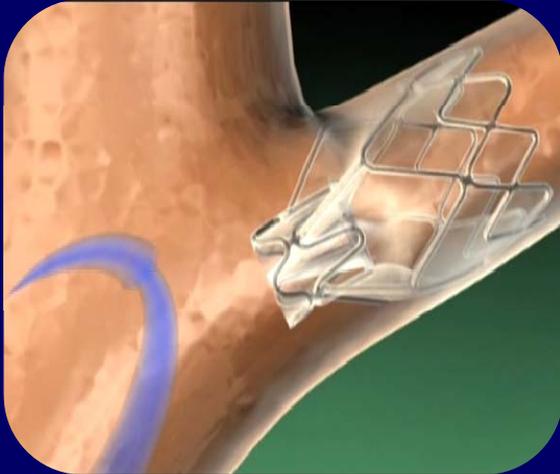
Endobronchial Valve Therapy

Zephyr Endobronchial Valve (EBV)



- Implantable one-way valve
- Modifies airflow in lung
- Bronchoscopic delivery
- Performed under local or general anesthesia
- Removable

Procedure Overview



- Prevents inspiratory inflow
- Allows trapped gas / fluids to escape
- Seals and vents
- Multiple valves placed in segmental bronchi
- Isolates diseased target lobe

EBV Procedure Overview



Delivery

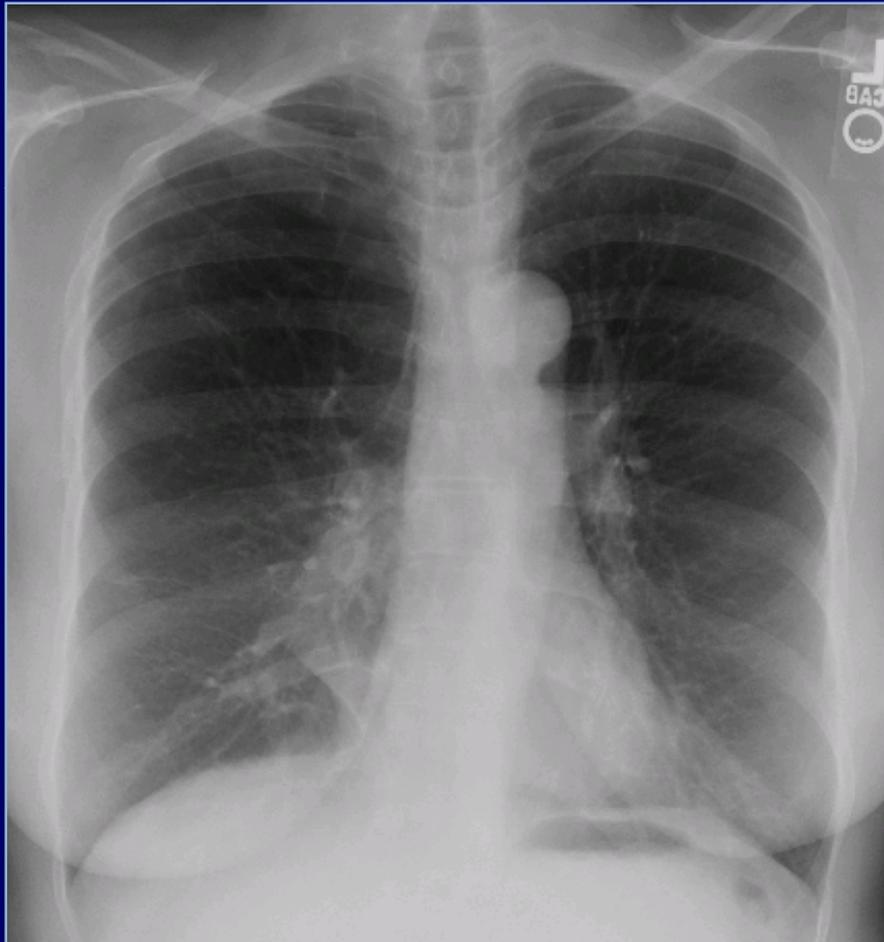
Deployment

Inspiration

Expiration

Before and After EBV Right Upper Lobe Procedure

Before

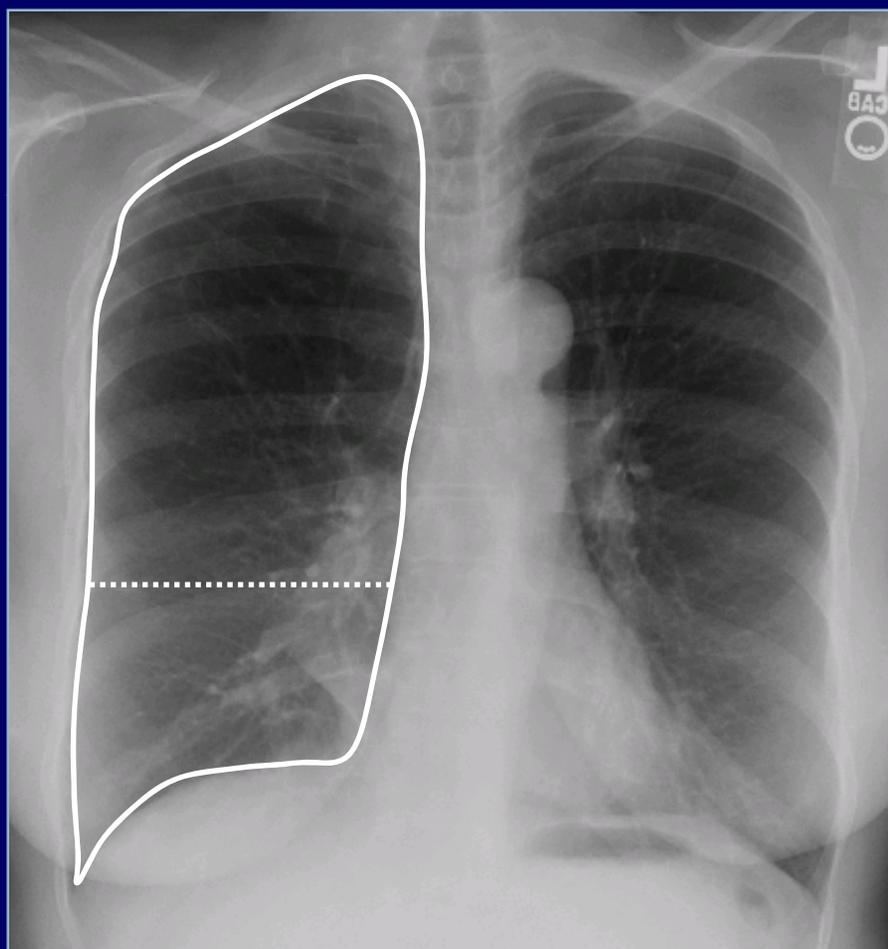


1 Month After

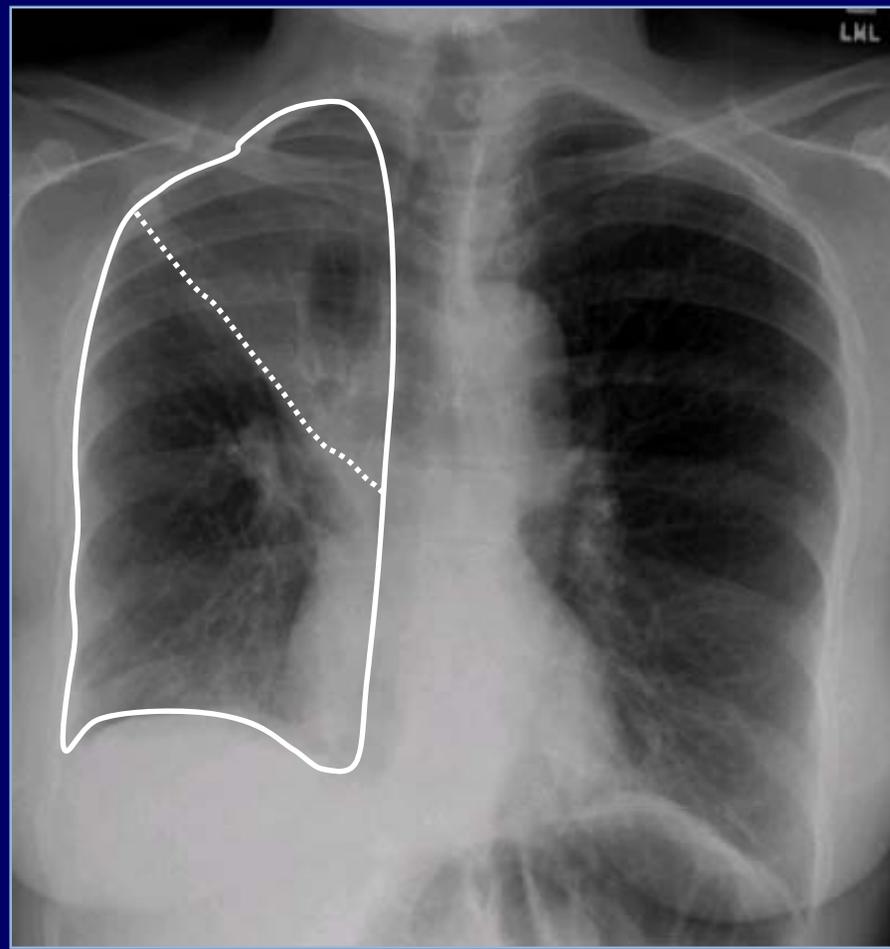


Before and After EBV Right Upper Lobe Procedure

Before



1 Month After



Zephyr EBV Removal



Zephyr Endobronchial Valve (EBV)

IDE Clinical Trial Design – G020230

VENT: Endobronchial Valve for
Emphysema Treatment Trial

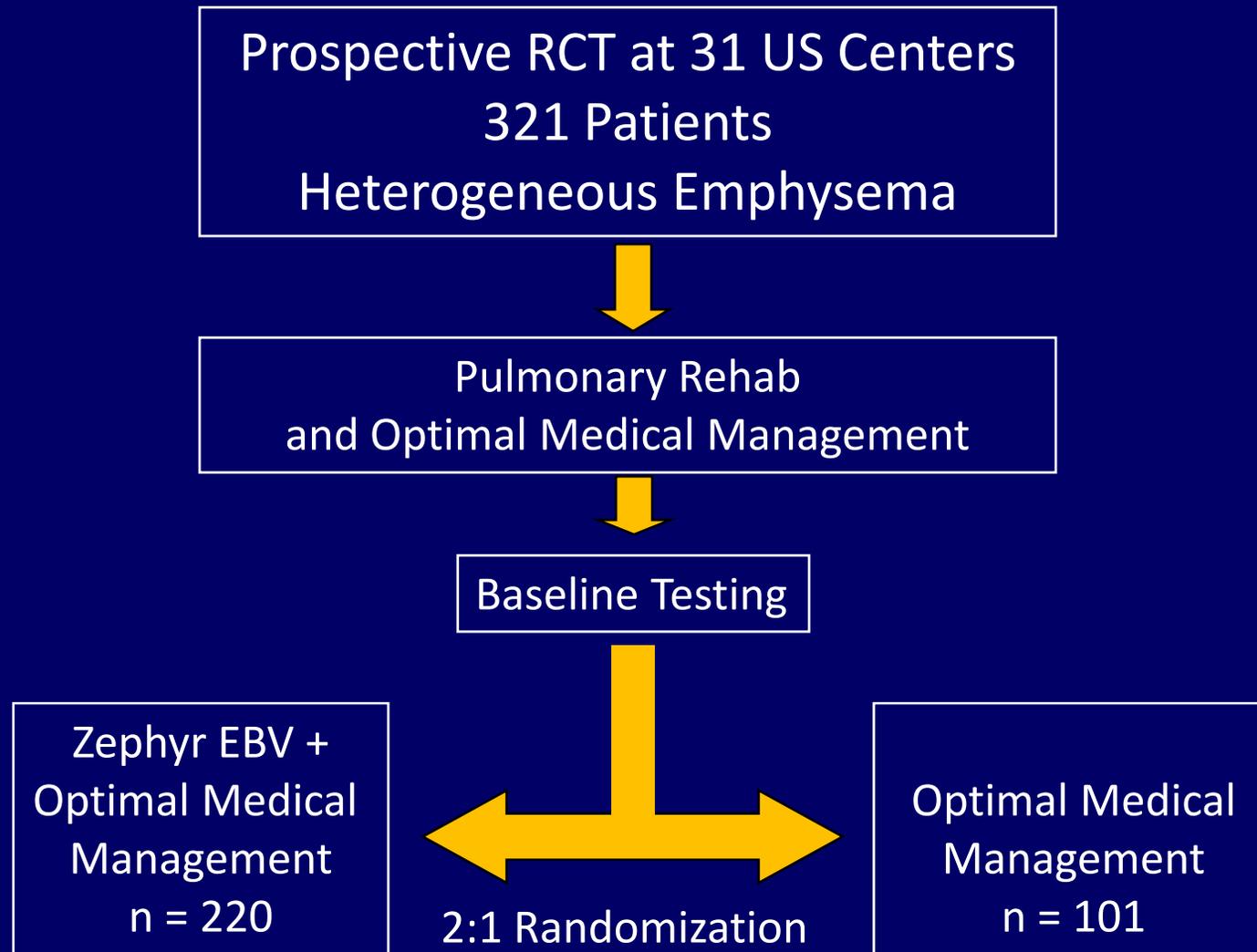
2003 FDA Advisory Panel

Trial Design	Panel Recommendation	VENT
Target patient population	Similar to NETT	✓
Endpoints	Physiologic, exercise tolerance and clinical endpoints	✓
Duration	Efficacy: 6 months Safety: 12 months	✓
Control	Optimal medical management (i.e., no sham) w/pulmonary rehabilitation	✓

Methodology

Heterogeneous Emphysema	- Digital HRCT - Scored by Core Lab - Target lobe — adjacent lobe % emphysema
Pulmonary Rehabilitation	- 6 - 8 weeks - 12 - 18 sessions - Upper and lower limb strength and endurance
Optimal Medical Management	- Smoking cessation - Bronchodilator therapy - Vaccination - Optimized oxygen therapy
Sample Size Calculation	Based on assumption of $15 \pm 33.7\%$ for FEV_1 and $17 \pm 41.5\%$ for 6MWT. Both had very large variance assumptions.

Zephyr EBV VENT Pivotal Trial



Key Study Entrance Criteria

Inclusion

- 40 to 75 years of age
- BMI \leq 31.1 (men)
BMI \leq 32.3 (women)
- Nonsmoking for 4 months
- Heterogeneous emphysema based on HRCT
- $15\% < FEV_1 < 45\%$ predicted
- TLC $>$ 100% predicted
- RV $>$ 150% predicted
- Post rehabilitation 6MWT $>$ 140m

Exclusion

- Alpha-1 antitrypsin deficiency
- Evidence of large bullae
- Sputum production $>$ 60 ml / day
- Significant bronchiectasis
- Recurrent respiratory infections requiring hospitalization
- Unable to complete 3 minutes unloaded pedaling on cycle ergometry
- $DL_{CO} <$ 20% predicted value
- Arrhythmia, recent MI
- Pulmonary hypertension

→ Mirrors NETT Criteria

Primary Endpoint Considerations

Challenges are well recognized:

NIH¹: “No single parameter in patients with COPD is sufficient to be considered the gold standard to assess outcome”

FDA²: “Six Minute Walk test ...may prove difficult in standardizing and garnering consistent results over time. These factors may limit the sensitivity of these measures...since true, but small, clinical benefits may be obscured by measurement noise”

FDA²: “..some [treatments] may have relatively small, but statistically significant, effects on a single measure ... This may be because [of]...the inherent complexity and heterogeneity of COPD. In such a situation, two efficacy endpoints may need to be declared ...to support efficacy.”

Co-primary Efficacy Endpoints

Percent change in FEV₁ from baseline to 6 months

and

Percent change in 6MWT from baseline to 6 months

Analysis Plan Definition of Study Success

“For effectiveness, the differences between arms for the percent change from baseline at 180 days for both FEV₁ and 6MWT reach statistical significance (one-sided test at $p < 0.025$) in favor of the treatment group.”

Secondary Efficacy Endpoints

SGRQ - St. George's Respiratory Questionnaire	Disease-specific QOL
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mMRC - Modified Medical Research Council	Dyspnea
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Cycle Ergometry Maximum Workload	Exercise tolerance
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Supplemental Oxygen Utilization	Daily O ₂ consumption
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→ To control for multiplicity, these four were prospectively chosen from the original nine.

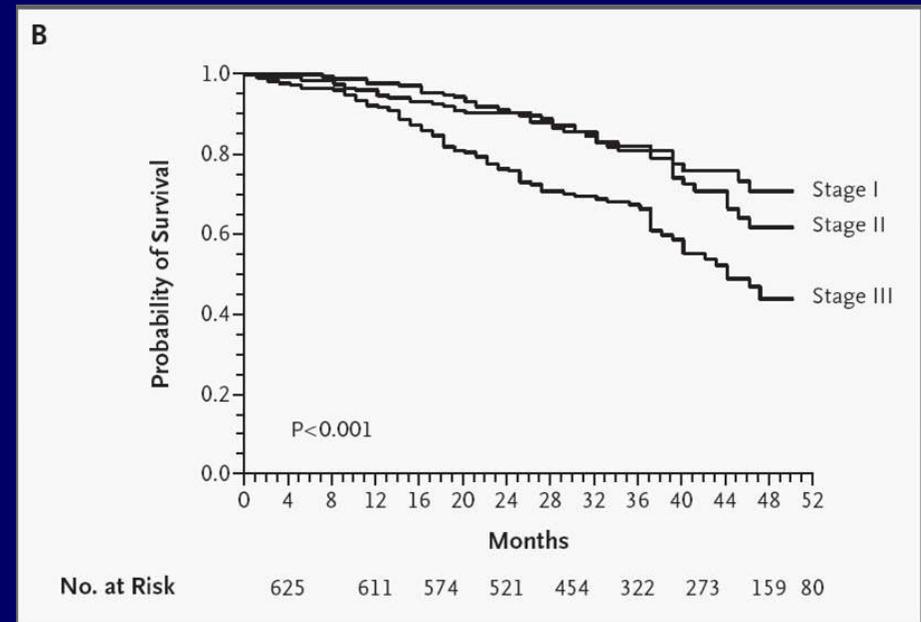
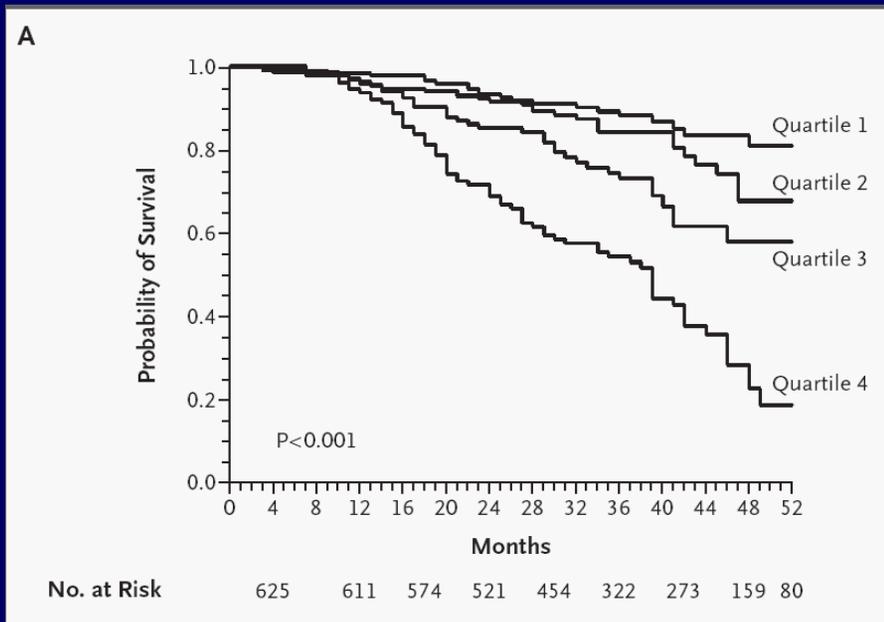
Composite Index: BODE

- Background
 - Developed in response to limitations inherent in using single endpoint to assess a multidimensional disease
 - Calculation
 - 10 point scale based on values to 4 key variables
 - B – Body Mass Index (BMI)
 - O – Obstructive Airway Disease (FEV_1)
 - D – Dyspnea (mMRC)
 - E – Exercise Tolerance (6MWT)
 - Lower score is better
- Integrates both FEV_1 and 6MWT

BODE vs. FEV₁ Predictive of Survival

Baseline BODE

Baseline FEV₁



Primary Safety Endpoint

Major Complications Composite (MCC)

Evaluated at 6 months and 12 months

- Death
 - Pneumonia distal to valve
 - Respiratory failure with ≥ 24 hours ventilation
 - Pneumothorax / air leak > 7 days
 - Massive hemoptysis (> 300 ml)
 - Empyema
- Higher rates were assumed given active intervention vs. non-active control

Study Oversight and Management

- Independent Clinical Events Committee
 - Adjudicated severity and relatedness of all adverse events
- Independent Data Safety Monitoring Board
 - Decisions to halt / continue trial
- Independent Statistical Analysis
- HRCT Core lab (UCLA)
- QOL Core Labs (UCSD)

Study Results: Conduct of Study, BL Characteristics, and Safety

Armin Ernst, MD, FCCP

Chief, Interventional Pulmonology
Beth Israel Deaconess Medical Center
Associate Professor of Medicine and Surgery
Harvard Medical School

VENT: Summary Findings

Positive Trial: Primary Endpoints Met

- Efficacy
 - Demonstrated volume reduction / redistribution
 - Superiority in both co-primary endpoints: FEV₁ and 6MWT at 6 months
 - Superiority in all four secondary endpoints at 6 months
 - Superiority in composite endpoint: BODE
- Safety
 - Higher MCC rate (ns)
 - Equivalent 1 year mortality rate

RESULTS: Baseline Characteristics

Baseline Characteristics Well Matched

	Zephyr EBV	Control	p value
Gender (% male)	60.5%	48.5%	0.052
Age (years)	65.3	64.9	ns
History of smoking (yes)	99.6%	98.0%	ns
Pack Years	63.3	61.7	ns
Continuous O ₂	43.9%	41.7%	ns
Weight (kg)	73.1	71.7	ns
Height (meters)	1.7	1.7	ns
BMI (kg/m ²)	25.1	24.8	ns
Diabetes	7.7%	5.0%	ns
Abnormal ECG	45.9%	42.6%	ns
Blood Pressure			
Systolic (mmHg)	129.1	129.9	ns
Diastolic (mmHg)	73.8	74.6	ns

→ Only gender approaches significance, but not predictive of outcomes in multivariate analysis

Baseline Lung Function Well Matched

	Zephyr EBV Mean	Control Mean	p value
FEV ₁ (liters)	0.87	0.84	ns
FEV ₁ (% Predicted)	30%	30%	ns
FVC (liters)	2.71	2.62	ns
FVC (% Predicted)	70%	70%	ns
FEV ₁ / FVC	0.33	0.33	ns
RV (% Predicted)	216%	212%	ns
TLC (% Predicted)	124%	125%	ns
RV / TLC	0.63	0.63	ns
DL _{CO} (% Predicted)	33%	36 %	ns

→ No significant differences
Consistent with severe emphysema population

Other Baseline Variables Well Matched

	Zephyr EBV Mean	Control Mean	p value
PaO ₂ (mmHg)	69.1	68.4	ns
PaCO ₂ (mmHg)	40.5	41.6	0.044
pH	7.4	7.4	ns
Oxygen Saturation	93%	93%	ns
Six Minute Walk Test (m)	334	351	ns
Cycle Ergometry (max. watts)	45	43	ns
SGRQ	51.5	50.1	ns
mMRC	1.7	1.7	ns
BODE	4.4	4.2	ns

→ Only statistically significant difference = PaCO₂, but not predictive of outcomes in multivariate analysis

VENT Enrolled Patients with Severe and Very Severe Emphysema

VENT Mean
FEV₁ % Predicted = 30%



% of VENT Pts: 46% 54%

GOLD
Stage*:



FEV₁ / FVC ratio: < 70%

< 70%

< 70%

< 70%

FEV₁ % Predicted: ≤ 80%

50% ≤ FEV₁ < 80%

30% ≤ FEV₁ < 50%

FEV₁ ≤ 30%

RESULTS: Conduct of Study

Follow-up Windows & Missing Data

- Protocol window narrowly defined: 6 mo +/- 14 days
 - Completed Cases (extended window): 6 mo -30 / +45 days
 - Benchmark NETT: 6 mo +/- 91 days
 - VENT rates (20%) consistent with other landmark trials in this patient population such as TORCH, UPLIFT, OPTIMAL, etc.
- Sensitivity analysis – primary endpoint results consistent across windows

Eligibility Violations

- Inclusion / Exclusion Violations
 - 23 during initial screening , but eligible at enrollment
 - At baseline: 39 / 321 (12.1% of patients)
- Small, nominal differences between value and eligibility criterion
 - 11 Blood tests (Cotinine, PaCO₂, PaO₂)
 - 24 Plethysmography
 - 5 Spirometry
 - 9 Other (PR, Vaccination, Hypertension, BMI, DLco)
- Co-primary endpoints met with or without eligibility violations

Protocol Deviations

- Protocol deviations in 2,492 of 79,240 (3.1%) monitored fields over course of study
- Typically minor
- Balanced between arms
- Co-primary endpoints met with and without “clinically important” deviations

RESULTS: Safety

Analysis Populations

Study Population and Definition	EBV n (%)	Control n (%)
Intent to Treat (ITT) All randomized subjects	220 (100%)	101 (100%)
Modified Intent to Treat (mITT) Treatment: Patients receiving treatment Control : Patients with ≥ 1 follow-up visit	214 (97.3%)	87 (86.1%)

→ ITT population used for primary efficacy
mITT population used for safety analysis

Safety Data Review Outline

Review four categories of events:

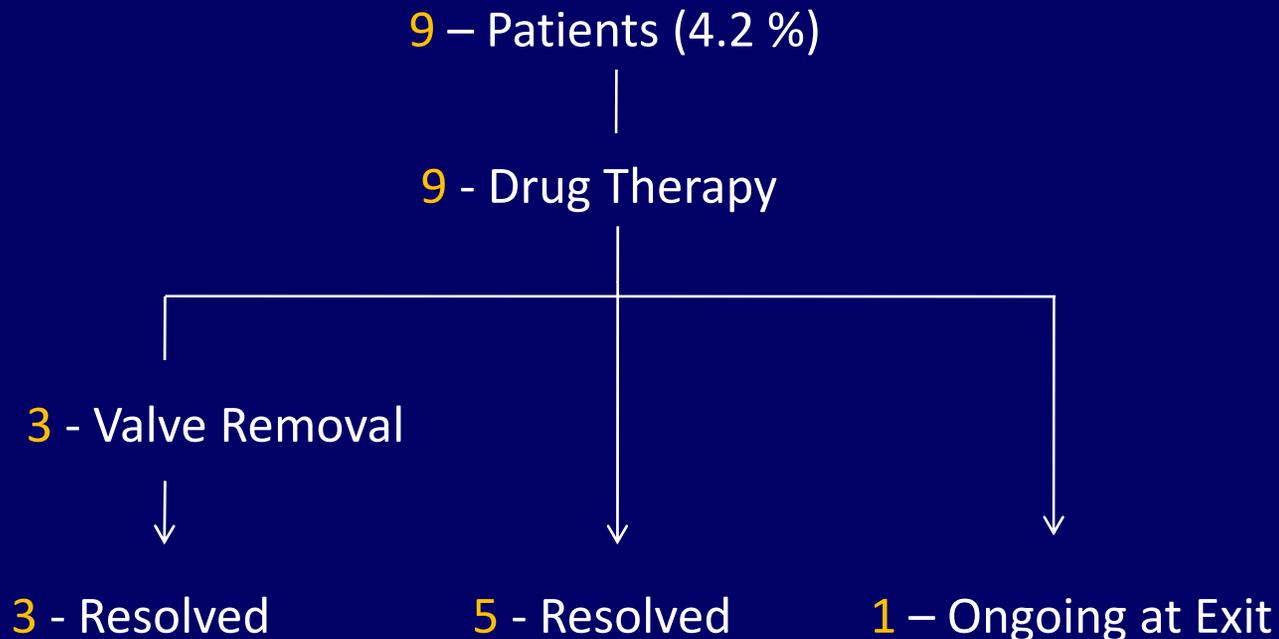
1. Major Complications Composite (MCC) events
2. Non-MCC adverse events
3. Other events unique to treatment arm
4. Rehospitalizations

Primary Safety Endpoint – MCC

	6 months			12 months		
	EBV n = 214	Control n = 87	p value	EBV n = 214	Control n = 87	p value
Major Complication Composite	6.1%	1.2%	0.08	10.3%	4.6%	0.17
Death	2.8%	0.0%	0.19	3.7%	3.5%	1.00
Pneumonia distal to valve	1.4%	NA	----	4.2%	NA	----
Respiratory failure ≥ 24 hours ventilation	1.9%	1.2%	1.00	2.8%	2.3%	1.00
Pneumothorax / air leak > 7 days	1.4%	1.2%	1.00	1.9%	1.2%	1.00
Massive hemoptysis (> 300ml)	0.5%	0.0%	1.00	0.5%	0.0%	1.00
Empyema	0.0%	0.0%	----	0.0%	0.0%	----

→ MCC nominally higher as anticipated (ns)

Distal Pneumonia Details



- Managed effectively with antibiotics and / or valve removal
- None required ventilator support
- One ongoing at study exit
 - Started day 356, discharged on oral antibiotics

Treatment Arm Mortality Details

Cause of Death (through 1 Year)	Days Post Treatment	Device Related
Ischemic colitis, sepsis, colectomy, respiratory failure	21	no
Massive hemoptysis, respiratory failure (detailed on next slide)	22	yes
Respiratory failure secondary to COPD	121	no
Emphysema with subpleural bullae	131	no
Stage IV adenocarcinoma : liver, adrenal glands , lymph glands	147	no
Respiratory failure secondary to a COPD exacerbation	161	no
COPD exacerbation, community acquired pneumonia	230	no
Metastatic cancer, liver	284	no

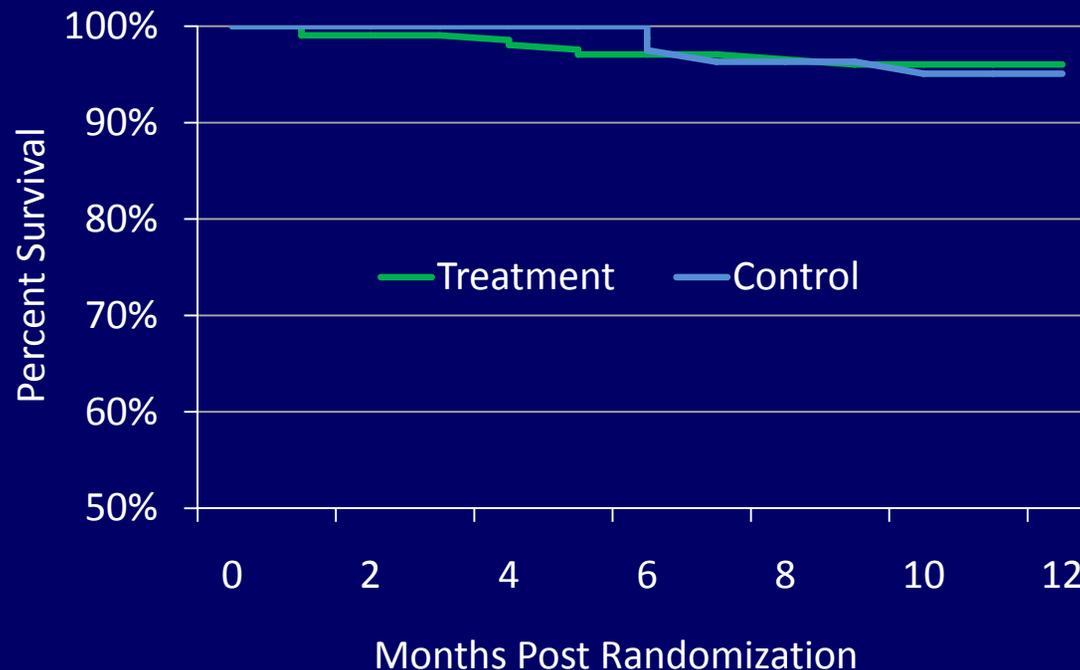
→ Only one event rated possibly or probably device related per CEC

Single Case of Massive Hemoptysis

Timing*	Events
Week 1	- Recurrent hemoptysis, possible vomiting of blood, dyspnea
Day 8	- Increased hemoptysis followed by cardio-respiratory arrest - Resuscitated, intubated and ventilated
Week 3	- Clear evidence of irreversible hypoxic brain injury - Withdrawal of support and subsequent death
Autopsy Findings	- All valves in position, no evidence of perforation, migration, or intrusion into blood vessels - No clear source of bleeding
CEC Conclusions	- No clear link between hemoptysis and device or procedure - Adjudicated Possibly Procedure Related and Probably Device Related
Actions	- Event reported to the DSMB, FDA, IRBs, investigators - Recommendations for careful monitoring of subjects with hemoptysis

Survival Timing

Kaplan-Meier Survival Curve



- Equivalent between arms by Kaplan-Meier analysis ($p = 0.876$, log rank test)
- 12 month rates equivalent: EBV 3.7%, Control 3.5% ($p = 1.000$, Fisher's exact test)
- No difference by multivariate analysis ($p = 0.482$, Cox regression)

Safety Data Review Outline

Review four categories of events:

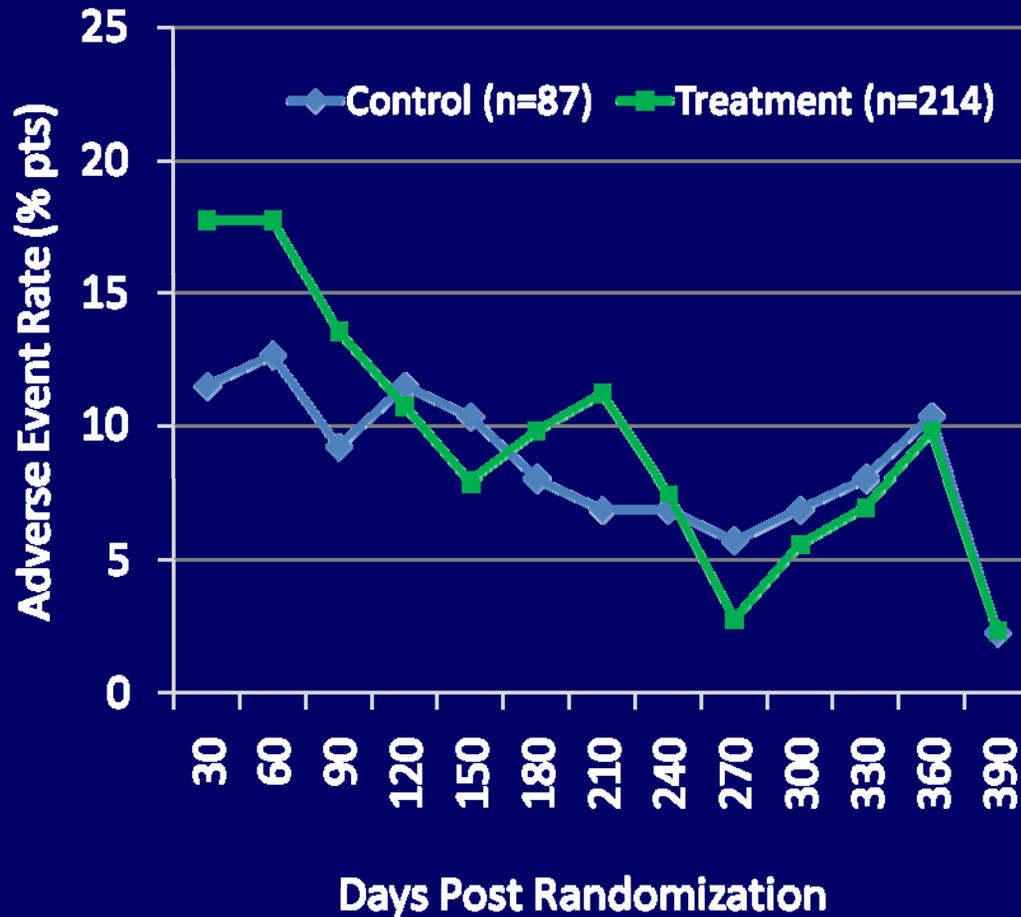
1. Major Complications Composite events
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Non-MCC Adverse Events: 1 Year

Seven AEs significant or trending to significance

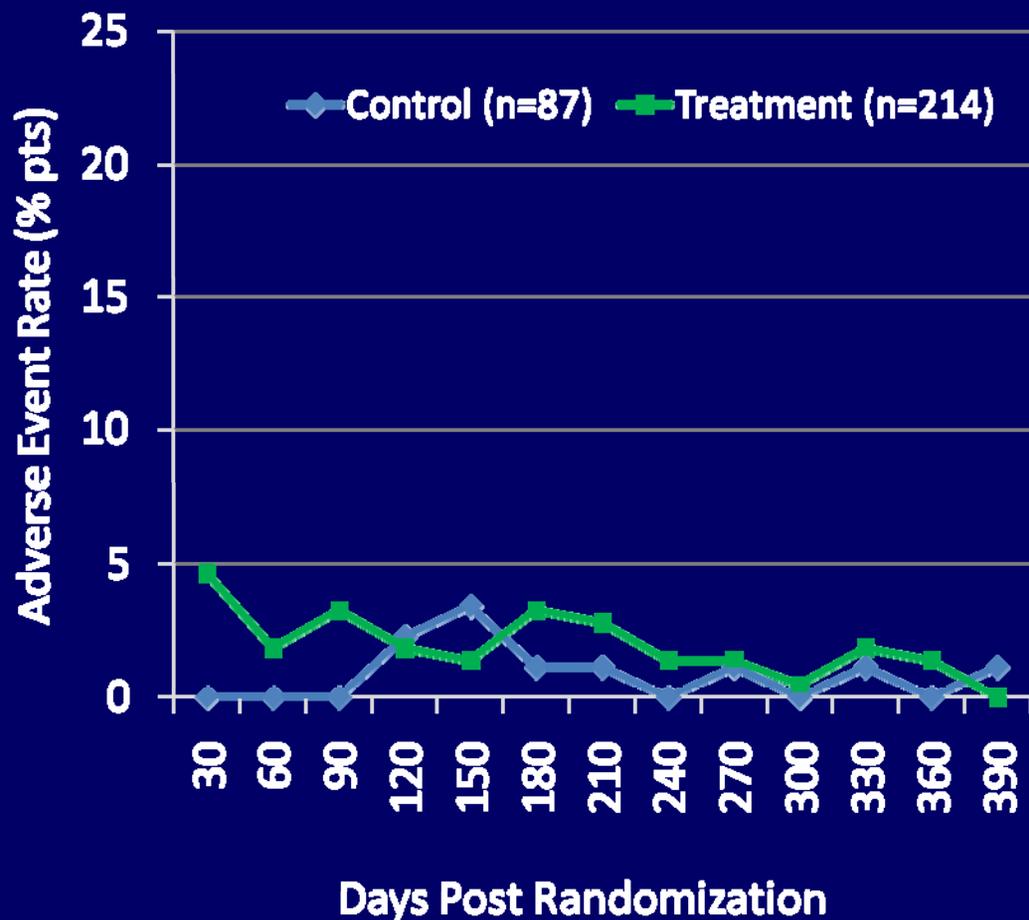
	Zephyr n =214	Control n = 87	p value
COPD Exac (w or w/o hosp)	63.1%	54.0%	0.154
Other Hemoptysis	42.1%	2.3%	<0.001
Non-cardiac Chest Pain	16.4%	3.5%	0.002
Increased SOB	9.8%	2.3%	0.030
Nausea or Vomiting	8.4%	1.2%	0.017
Other Pulmonary Infection	8.4%	1.2%	0.017
Hypoxemia	7.0%	0.0%	0.007

COPD Exacerbations Timing



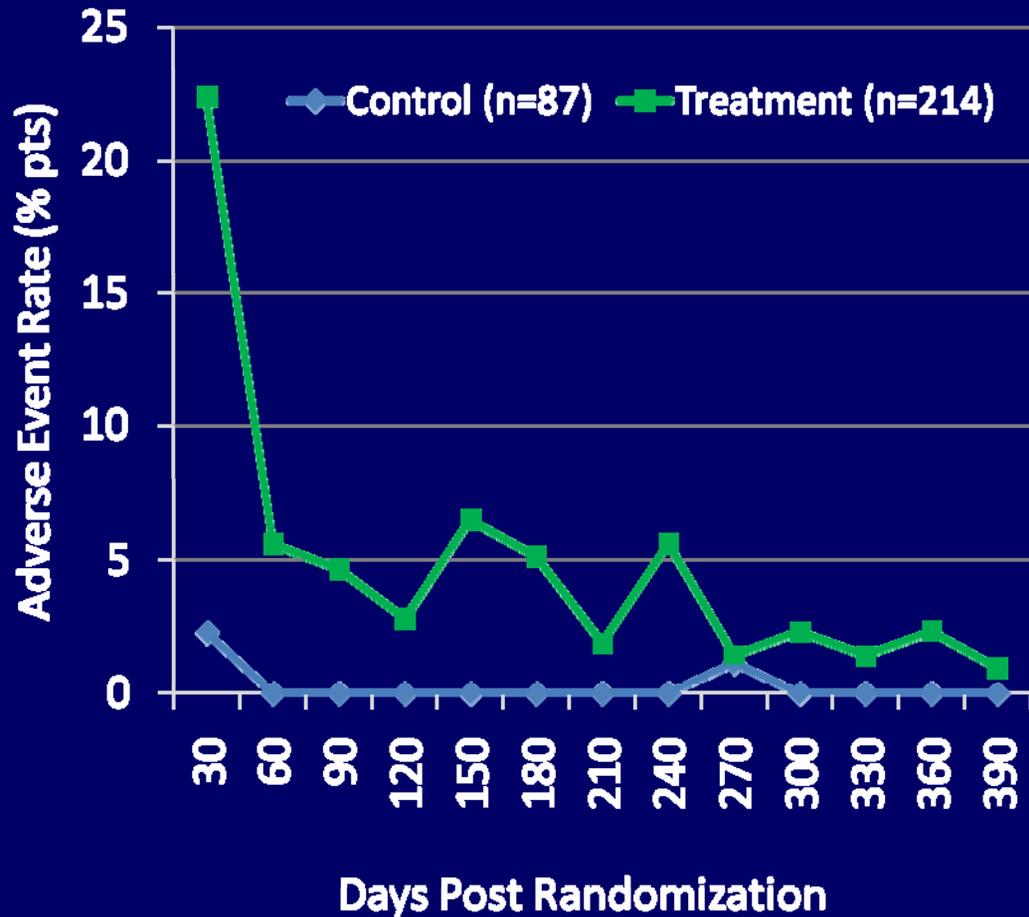
- Anticipated response to intervention
- 40% occur in first 90 days
- Treatment and control equivalent after day 90
- Medically manageable

COPD Exacerbations: SAEs



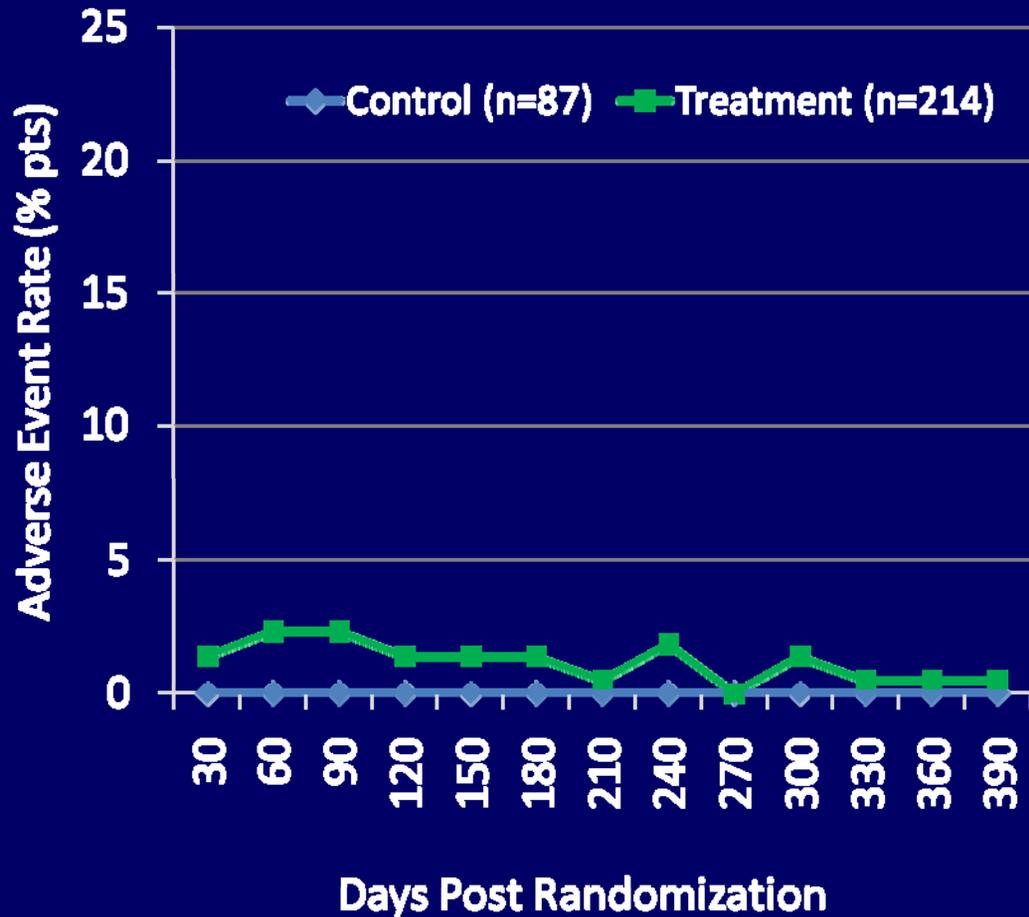
- Greatest difference in first 90 days
- Trends to control rates
- SAE designation due to rehospitalization or bronchoscopic exam

Hemoptysis Timing



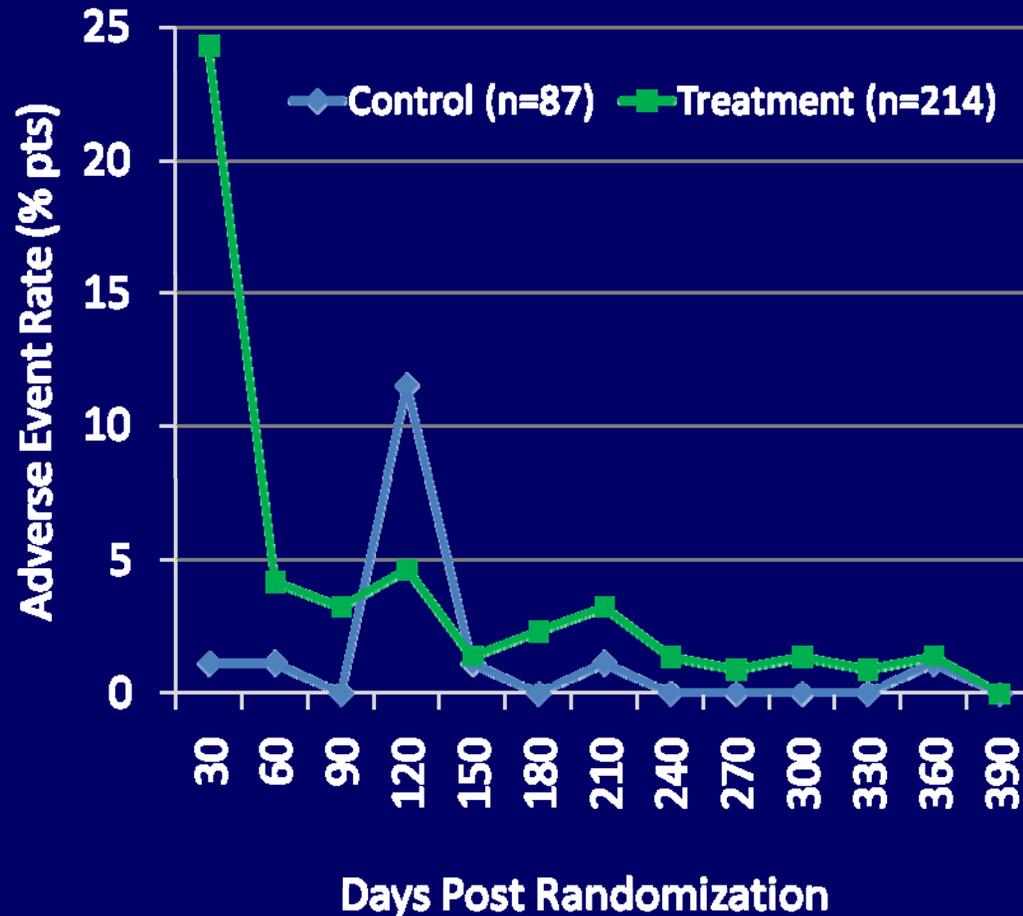
- Expected following bronchoscopic intervention
- Typically blood-tinged sputum
- Most resolve without intervention

Hemoptysis Timing: SAEs



- 11.7% (n = 25) cumulative rate for EBV at 12 months
- 1.4% (n = 3) reported by site as severe
- SAE designation due to rehospitalization or bronchoscopic exam
- Decreases over time

Other Elevated AEs



- Other elevated AEs:
 - Non cardiac chest pain
 - Nausea
 - Hypoxemia
 - Shortness of breath
 - Other pulmonary infection
- Typical following bronchoscopic intervention / anesthesia
- Majority occur within first 30 days

Safety Data Review Outline

Review four categories of events:

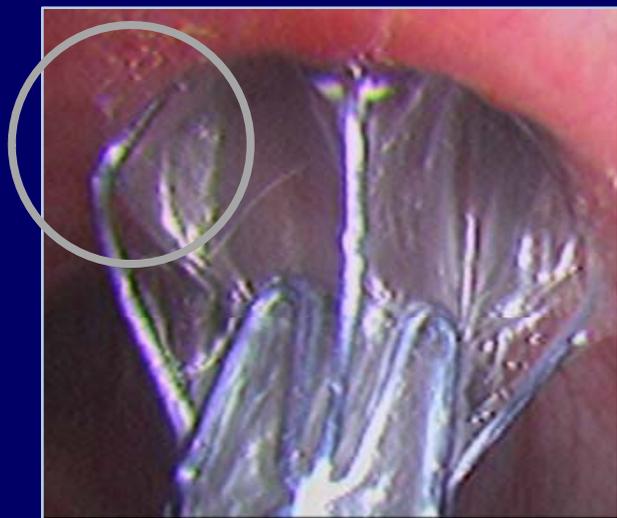
1. Major Complications Composite events
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AEs Unique to Treatment Arm

	0 - 6 Months	7 - 12 Months	12 Months Cumulative*
Overall	13.1%	7.5%	18.2%
Distal pneumonia	1.4%	2.8%	4.2%
Migration / expectoration	6.5%	2.3%	7.9%
Granulation	5.1%	3.3%	7.9%
Catheter-induced bronchial trauma	0.5%	0.0%	0.5%

→ Majority are SAEs due to re-bronch (per CEC convention)

Valve Migration / Expectoration



- **Definition**
 - Migration: Movement of valve from original placement location
 - Expectoration: Migrated valve coughed out
- **Cause**
 - Technique dependent (undersized, too proximal)
- **Clinical Manifestation**
 - Prolonged cough, minor hemoptysis, dyspnea or exacerbation
 - No occult migrations detected by CT

Valve Migration / Expectoration

Frequency (1yr): 7.9% (17 / 214) of patients
2.8% (23 / 820) of valves

Events:

	n (patients)
Migration	9
Expectoration	8

Sequelae: No long term implications

Treatment: All migrations removed successfully

Action: Site communication / retraining mid-trial

Product and Technique Modification

Product modification:

- Depth measurement

Training:

- Modified technique
- Updated instructions for use

International commercial experience:

- Confirms effectiveness of training and product modification



Depth
Marker

Granulation Tissue

Description: - Typical foreign body reaction
- Possibly due to valve misplacement

Frequency (1yr): 7.9% (17 / 214) of patients

Severity: 94% rated mild / moderate by site

Treatment:

Treatment	%
Valve removal	71%
Electrocautery + Mitomycin	6%
Cryotherapy	6%
Exploratory bronchoscopy	6%
Drug therapy	6%
No treatment	6%

Safety Data Review Outline

Review four categories of events:

1. Major Complications Composite events
2. Non-MCC adverse events
3. Other events unique to treatment arm
4. Rehospitalizations

Rehospitalization

- Higher rate at one year in EBV group
 - 39.7% for Treatment vs. 25.3% for Control, (p = 0.024)
 - Expected for active intervention
- Primary causes for rehospitalization (per patient):

COPD Exacerbation: 17.3%	Pneumonia: 8.4%
Valve Replacement: 5.6%	Hemoptysis: 5.6%
- 25% of Treatment rehospitalizations were \leq 1day LOS
- Mean LOS: 5.8 days for EBV vs. 8.6 for Control

Safety Conclusion

- No increased mortality in treatment arm
- Peri-procedural increase in events as expected
 - Typically minor and transient
 - Rates decrease over time
- Only two SAE types statistically significant at 1 year
 - COPD exacerbations, hemoptysis
 - Most peri-procedural
 - Rates equilibrate over time
- Removable

Efficacy Results

Frank Scirba, MD, FCCP

Associate Professor of Medicine

Division of Pulmonary and Critical Care Medicine

Director, Emphysema Research Center

University of Pittsburgh

Efficacy Data Review Outline

1. Primary and Secondary Endpoints
 - 6 month data for key variables
2. Supporting Evidence
 - Confirmation of mechanism of action
 - Responder analysis
3. Predictors of Outcome
4. Durability of Effect: Longitudinal Analysis

Analysis Populations

Study Population and Definition	EBV n (%)	Control n (%)
Intent to Treat (ITT) All randomized subjects	220 (100%)	101 (100%)
Completed Cases (CC) Subjects with evaluable data	179 (81.4%)	75 (74.3%)

→ ITT population used for primary efficacy

→ CC population used for all other analyses

Primary Endpoints

FEV₁

- Volume exhaled in first second (ml)
- Most accepted measure of severity of respiratory mechanics
- Reproducible physiologic measure

6MWT

- Distance walked in 6 minutes
- Global clinical measure of patient exercise capacity
- Performed using ATS standardized instructions and methodology

Study Success Criteria

“For effectiveness, the differences between arms for the percent change from baseline at 180 days for both FEV₁ and 6MWT reach statistical significance (one-sided test at $p < 0.025$) in favor of the treatment group.”

Co-primary Endpoints: Change at 6 Months (ITT)

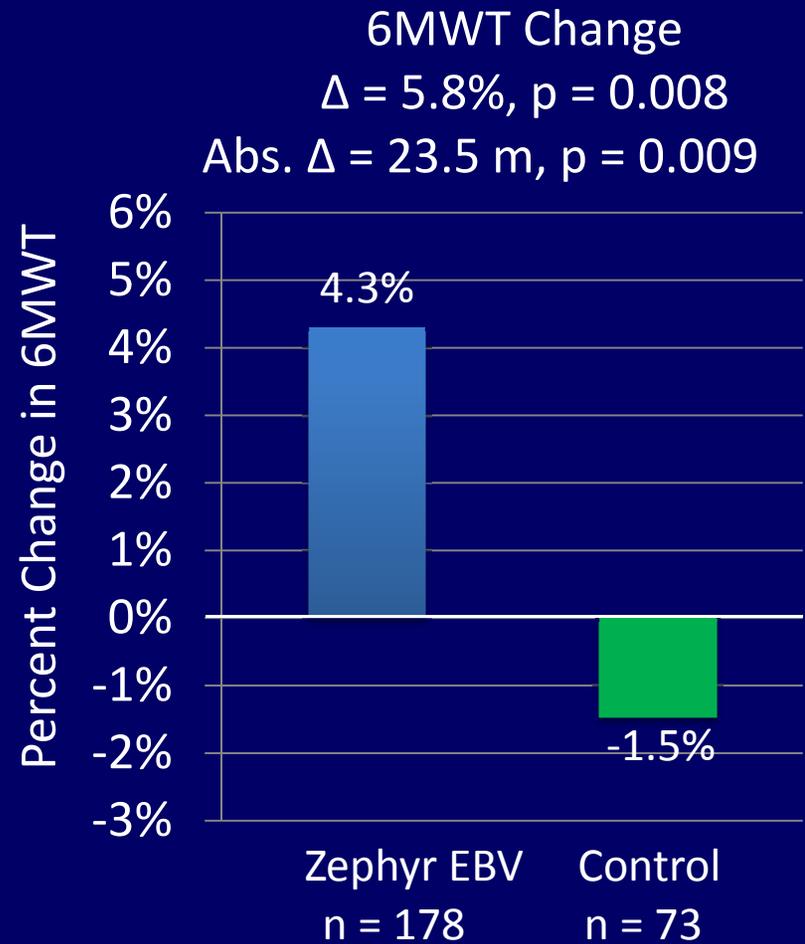
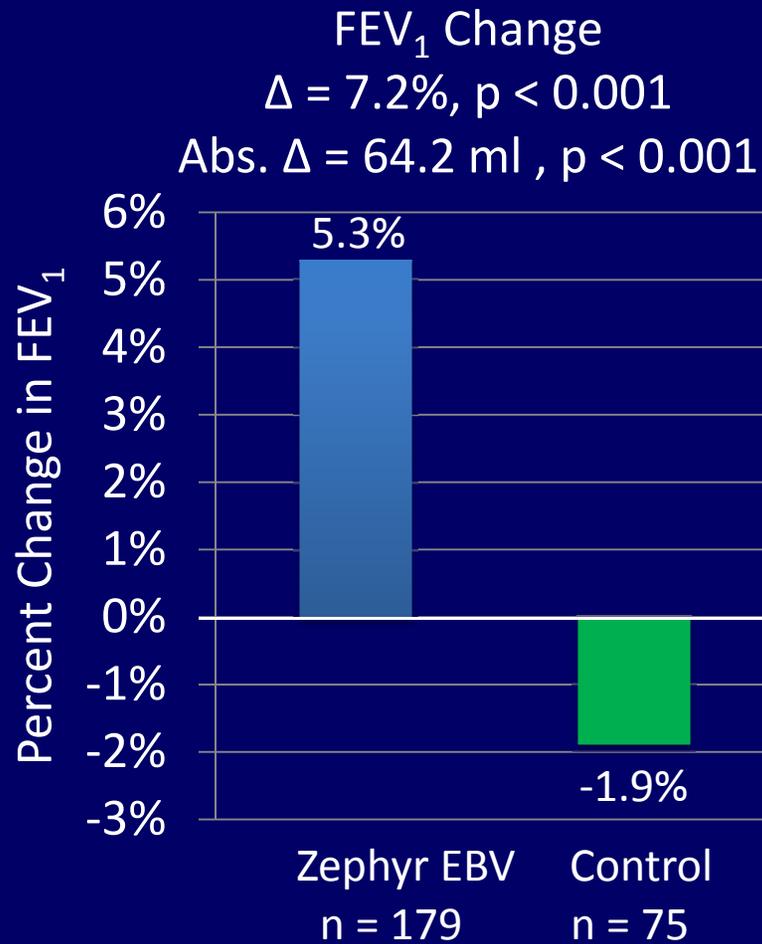
- Multiple imputation of missing values
- Provides point estimate of delta (between group difference of change from baseline to 6 months)

FEV₁ : Delta = 6.8%, p = 0.002

6MWT : Delta = 5.8%, p = 0.019

→ VENT met both co-primary efficacy endpoints

Change in FEV₁ and 6MWT at 6 Months (CC)

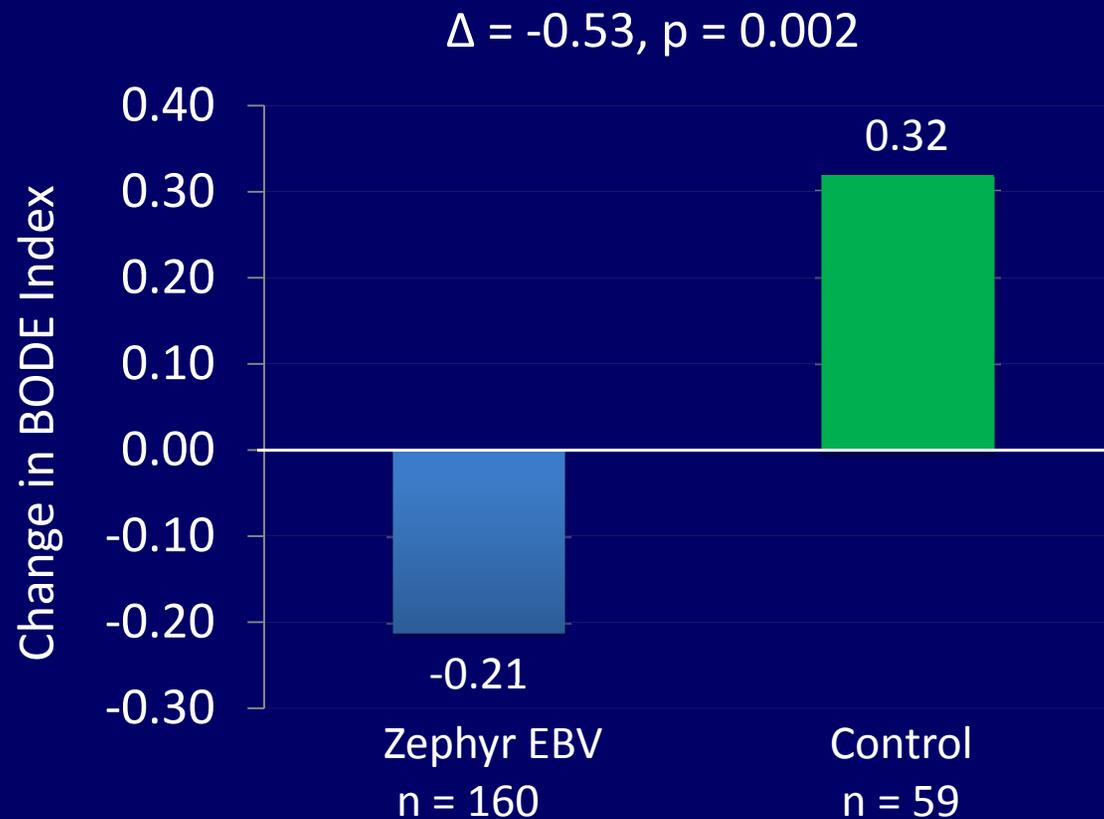


Secondary Endpoints at 6 Months

Endpoint	ITT (Primary Analysis)		CC	
	Delta	p value	Delta	p value
SGRQ (QOL)	-3.4	0.017	-3.4	0.019
mMRC (dyspnea)	-0.26	0.018	-0.30	0.011
Cycle Ergometry (watts)	3.8	0.020	5.0	0.004
Supplemental Oxygen (liters / day)	-12.0	0.020	-100.1	0.184

→ VENT met secondary efficacy endpoints

Change in BODE Index at 6 Months (CC)



→ Highly significant improvement

Protocol Violations and Missing Data Effect on 6 Month Outcomes

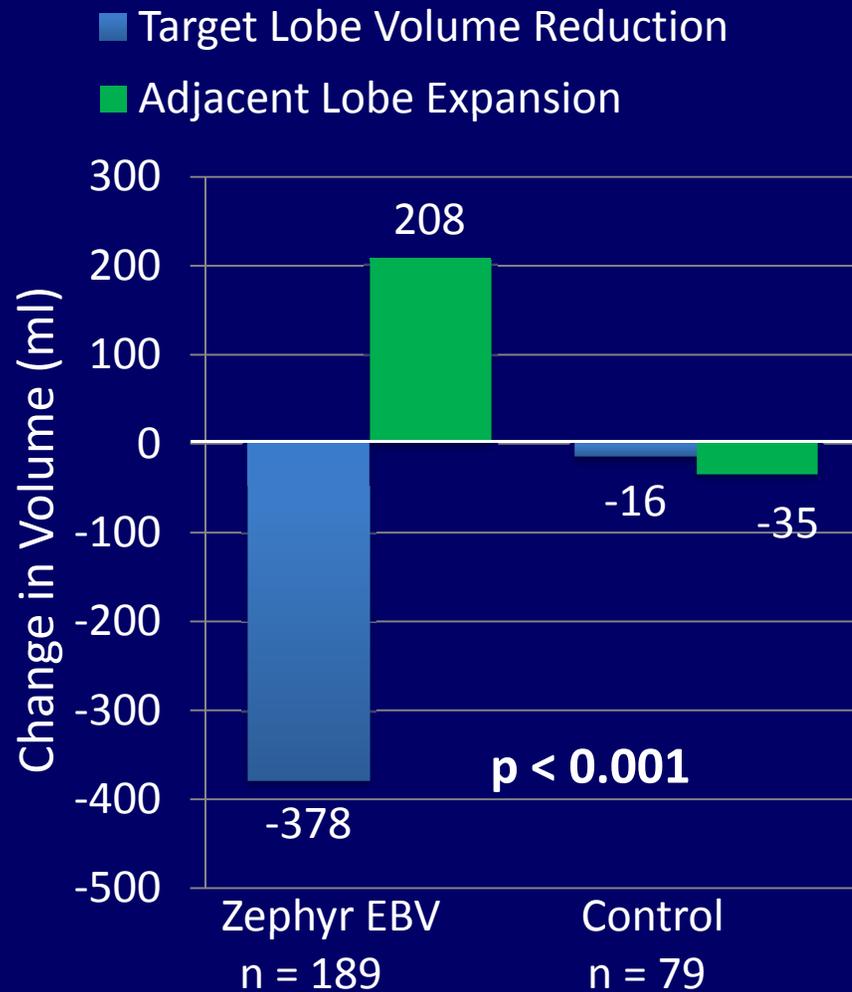
	Δ % FEV ₁ (n)	p value	Δ % 6MWT (n)	p value
ITT	6.8 (321)	0.002	5.8 (321)	0.019
CC	7.2 (254)	< 0.001	5.8 (251)	0.008
In protocol window (\pm 14 days)	7.6 (200)	< 0.001	5.5 (195)	0.025
Without Inc./Exc. violations	7.6 (210)	< 0.001	7.8 (208)	0.018
Without protocol violations*	8.6 (185)	< 0.001	10.9 (183)	< 0.001

→ Significant improvements regardless of visit window, eligibility violations, or protocol violations

Efficacy Data Review Outline

1. Primary and Secondary Endpoints
 - 6 month data for key variables
2. Corroborating Analyses
 - Mechanism of action
 - Responder analysis
3. Predictors of Outcome
4. Durability of Effect: Longitudinal Analysis

Demonstrated Target Lobe Volume Reduction at 6 Months



- Independently assessed by HRCT Core Lab
- Significant reduction in target lobe volume
- Significant expansion of adjacent lobe volume
- Achieved intended effect
- High correlation with change in FEV₁, p < 0.001

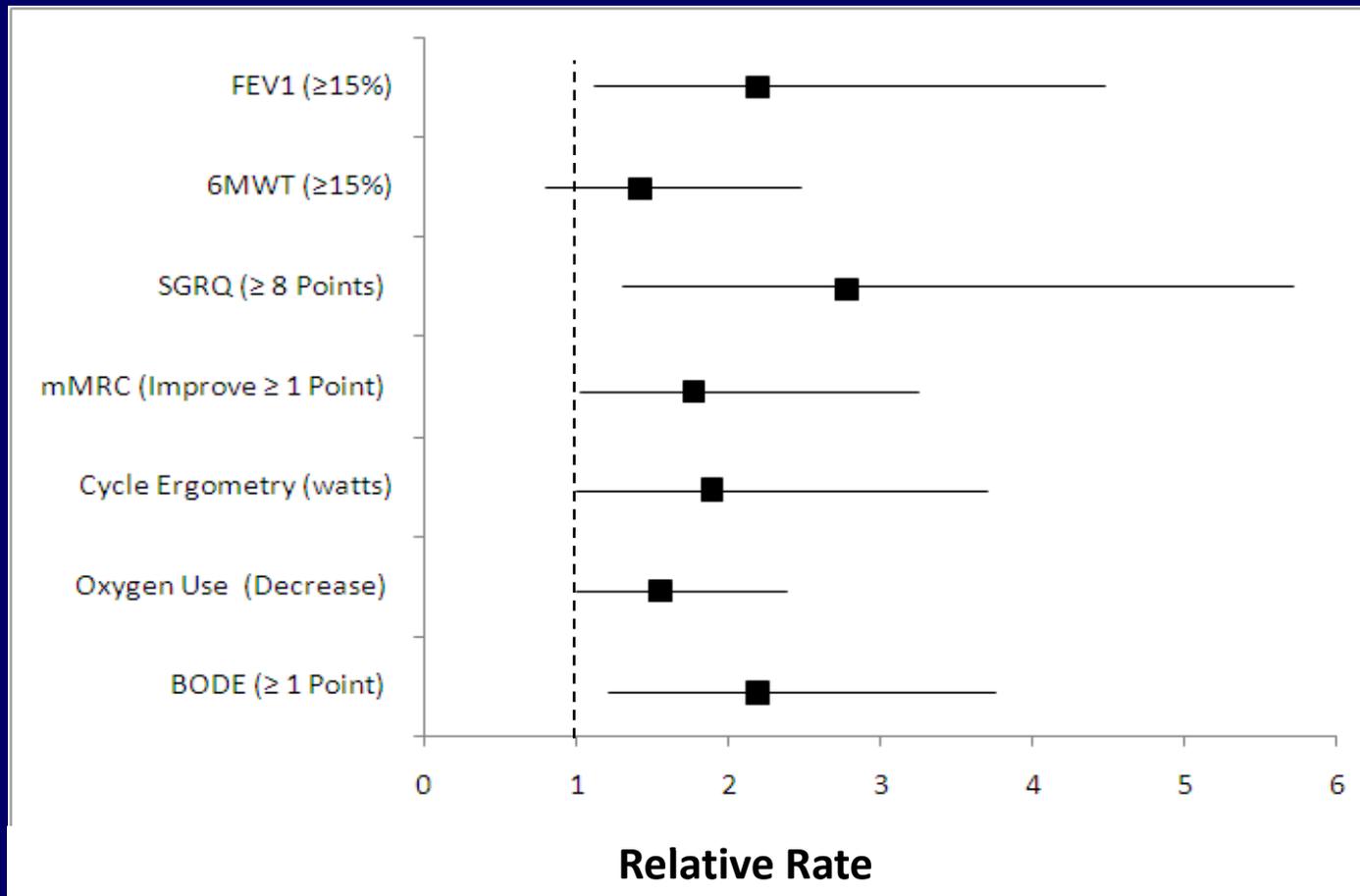
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Responder Analysis Thresholds

Variable	Threshold	Rationale
FEV ₁	≥ 15% improvement	- Pre-specified in protocol
6MWT	≥ 15% improvement	- Pre-specified in protocol
SGRQ	≥ 8 point score reduction	- NETT
mMRC	≥ 1 point score reduction	- 1 point on 0-4 pt integer scale
Cycle	≥ 10 watt increase	- NETT
O ₂	Increase/decrease	- Pre-specified in protocol
BODE	≥ 1 point score reduction	- NETT

Responder Analysis at 6 Months



Responder Analysis at 6 Months

	EBV n / N (%)	Control n / N (%)	RR	95% CI	p value
FEV ₁ ≥ 15%	42 / 179 (23.5)	8 / 75 (10.7)	2.2	(1.1, 4.5)	0.013
6MWT ≥ 15%	45 / 178 (25.3)	13 / 73 (17.8)	1.4	(0.8, 2.5)	0.133
SGRQ	49 / 158 (31.0)	7 / 61 (11.3)	2.8	(1.3, 5.7)	0.001
mMRC	47 / 162 (29.0)	11 / 67 (16.4)	1.8	(1.0, 3.2)	0.031
Cycle Ergometry	41 / 166 (24.7)	9 / 69 (13.0)	1.9	(1.0, 3.7)	0.032
Oxygen Decrease	56 / 95 (59.0)	15 / 40 (37.5)	1.6	(1.0, 2.4)	0.012
BODE	64 / 160 (40.0)	11 / 59 (18.6)	2.2	(1.2, 3.8)	0.002

→ Proportion of responders higher in treatment arm for all measures

Responder Analysis Clinical Significance

Threshold	Clinical Significance
+ 15% Δ FEV ₁ = 131 ml	<ul style="list-style-type: none">• Equal to 2-3 years of typical decline due to emphysema¹• Equals 4 years smoking cessation
1 point BODE	<ul style="list-style-type: none">• Data from NETT study (Martinez et. al²)• Decrease > 1 point at 6 months associated with 43% decrease in mortality risk
4 point SGRQ	<ul style="list-style-type: none">• All of the following relative to baseline:³<ul style="list-style-type: none">- Can wash / dress more quickly- Can now walk up stairs without having to stop- Can now go out for shopping / entertainment

¹Am J Respir Crit Care Med Vol 166. pp 675–679, 2002

²Am J Respir Crit Care Med Vol 178. pp 491–499, 2008

³COPD: Journal of Chronic Obstructive Pulmonary Disease, 2:75–79

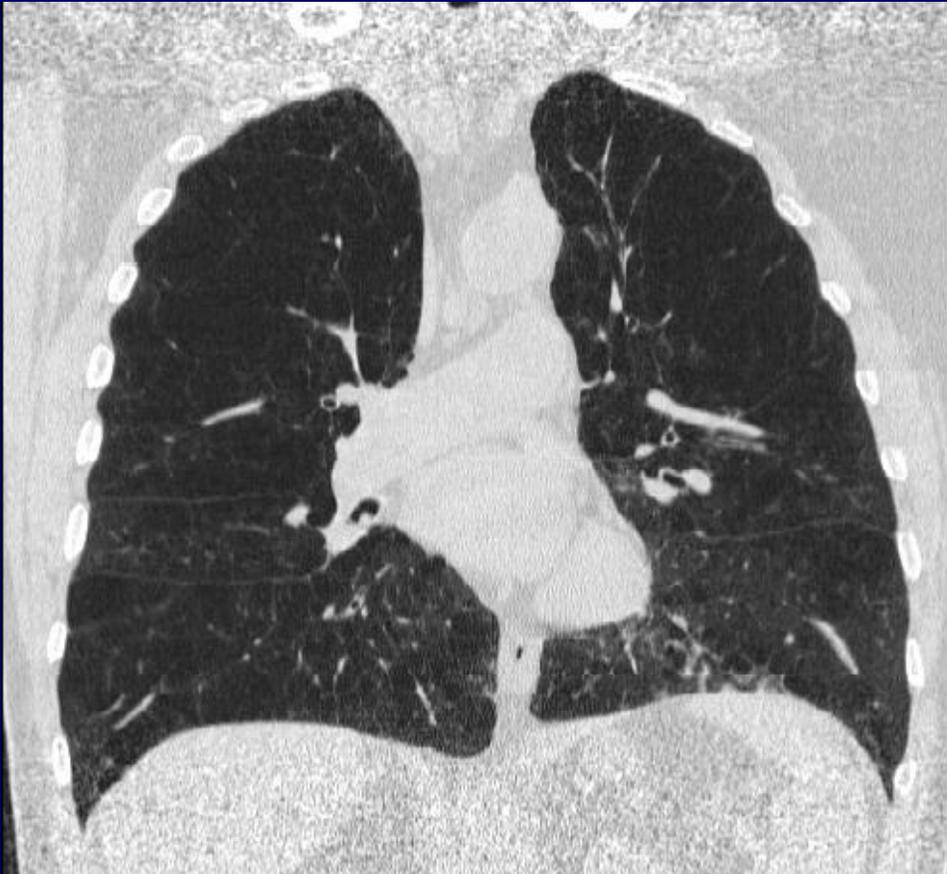
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Predictors of Outcome

- Multivariate, mixed model analysis to identify predictors, pre-specified in statistical analysis plan
- Further analysis (dichotomization) dictated by statistical analysis plan
- Designed to identify important predictors of clinical outcomes from pre-specified set of variables
- Two key predictors identified based on this analysis
 - Heterogeneity
 - Fissure Integrity

Heterogeneity



- Independently assessed by HRCT Core lab
- Based on continuous measure of quantitative emphysema score (-910HU)
- Heterogeneity: difference between target and adjacent lobe
- Consistent with proposed mechanism of action and surgical literature

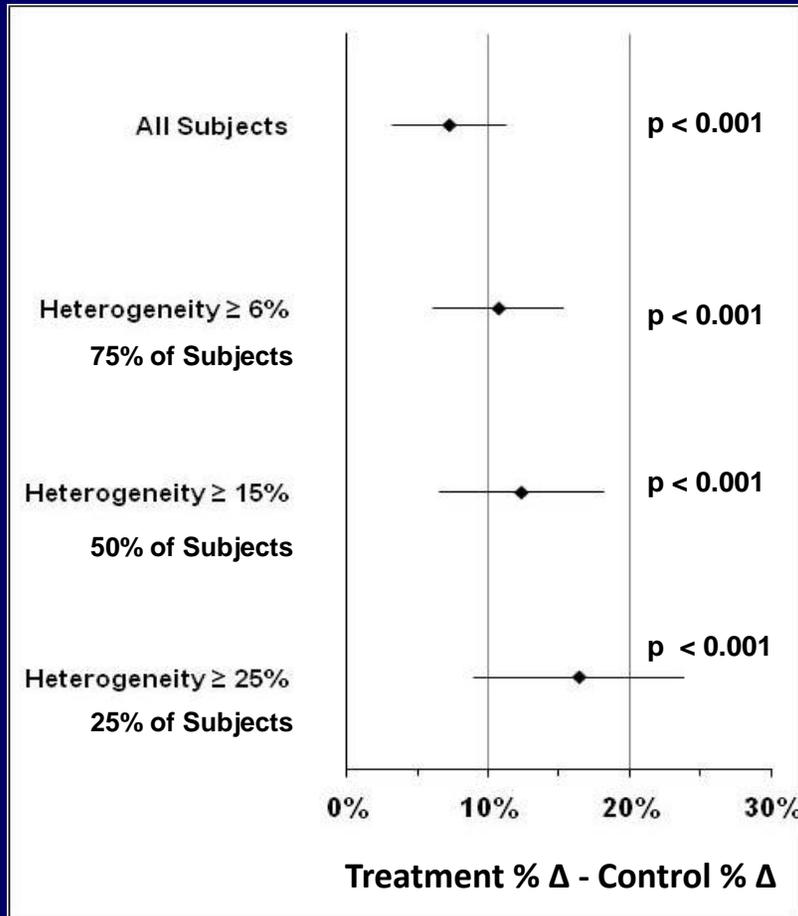
Heterogeneity



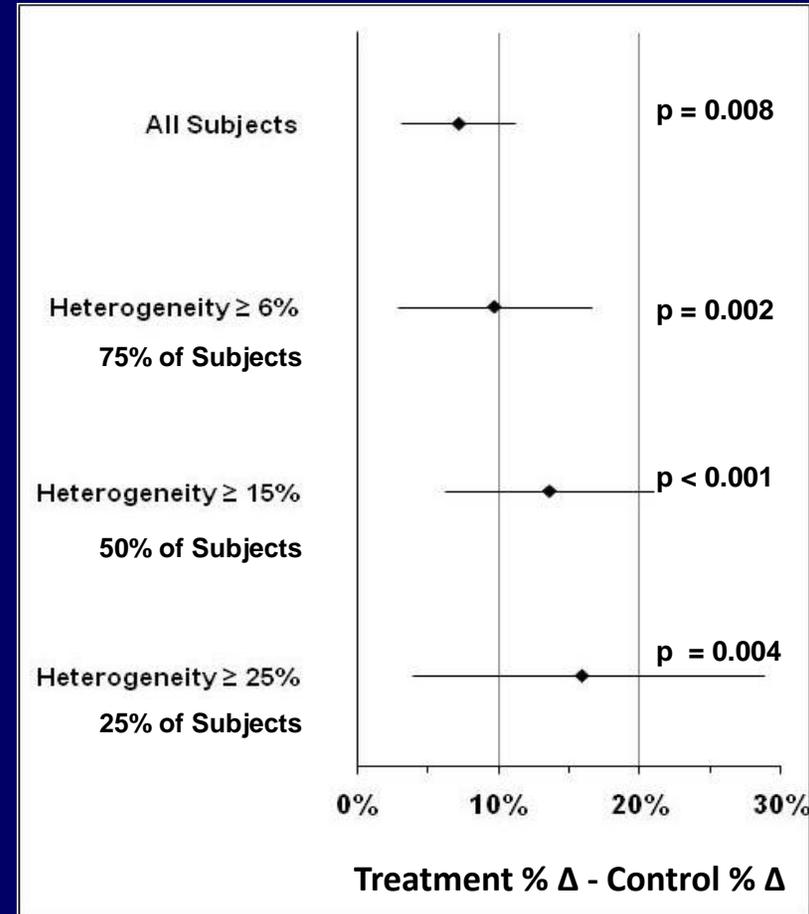
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Co-Primary Endpoints Heterogeneity Sensitivity

Delta % FEV₁

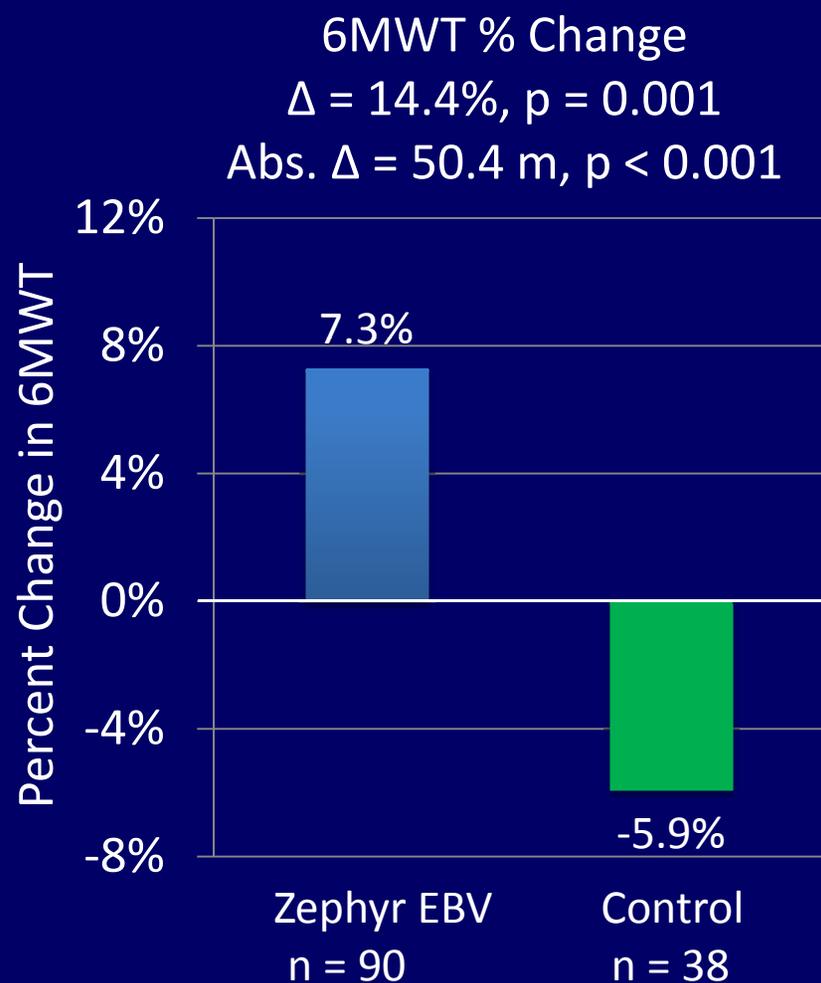
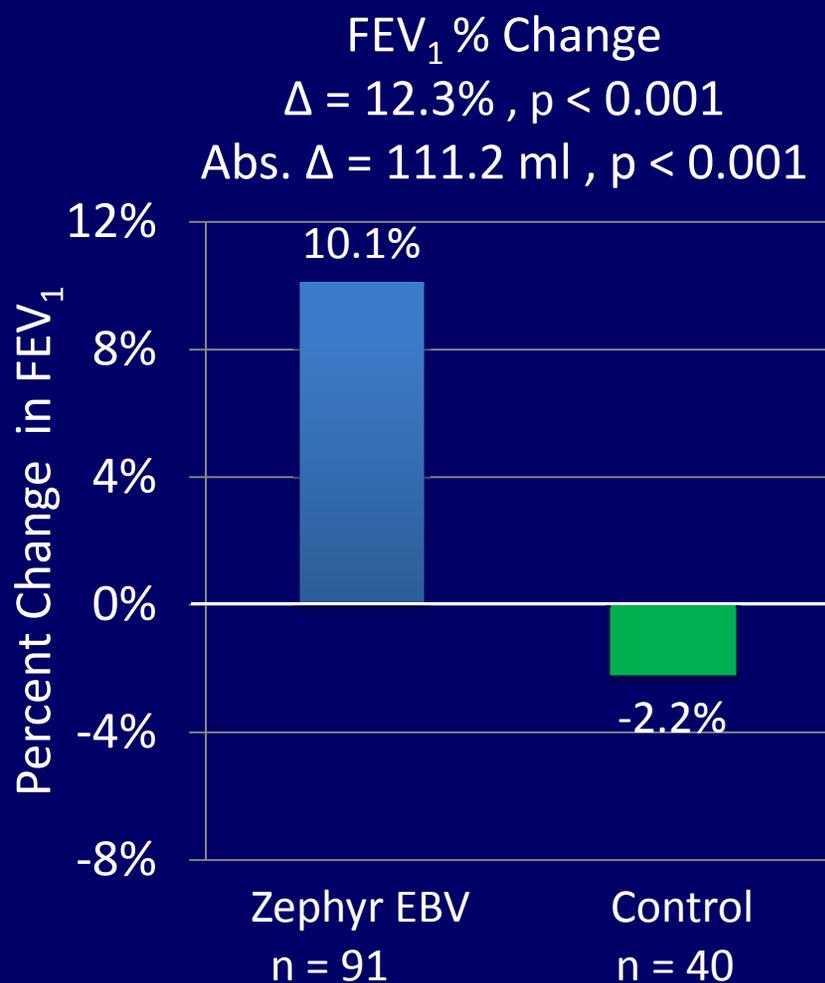


Delta % 6MWT



96 → FEV₁ and 6MWT responses increase with increasing heterogeneity

Percent Change in FEV₁ and 6MWT in High Heterogeneity Subgroup* at 6 Months (CC)

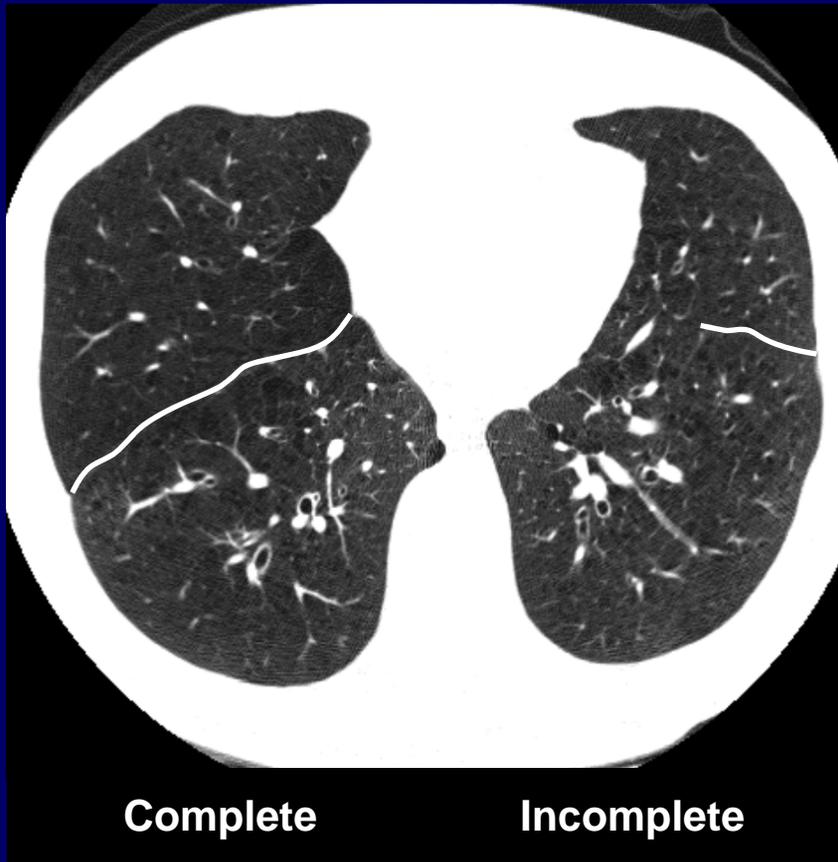


High Heterogeneity

6 Month Responder Analysis (CC)

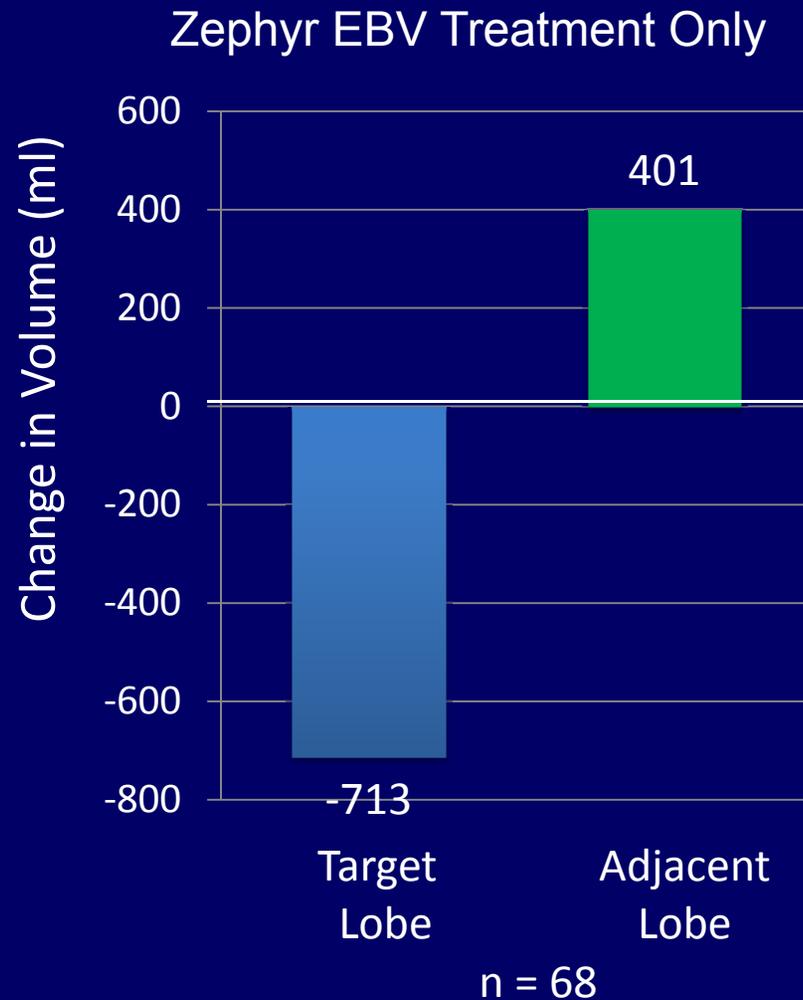
	EBV n / N (%)	Control n / N (%)	Relative Rate	95% CI	p value
FEV ₁ ≥ 15%	32 / 91 (35.2)	5 / 40 (12.5)	2.8	(1.2, 6.7)	0.006
6MWT ≥ 15%	28 / 90 (31.1)	5 / 38 (13.2)	2.4	(1.0, 5.7)	0.025

Fissure Integrity



- Independently assessed by HRCT Core lab
- Categorized as:
 - Complete
 - Incomplete
- Incomplete fissures
 - Proxy for inter-lobar airflow
 - Attenuates volume reduction

Greater Target Lobe Volume Reduction Complete Fissure Subgroup at 6 Months (CC)

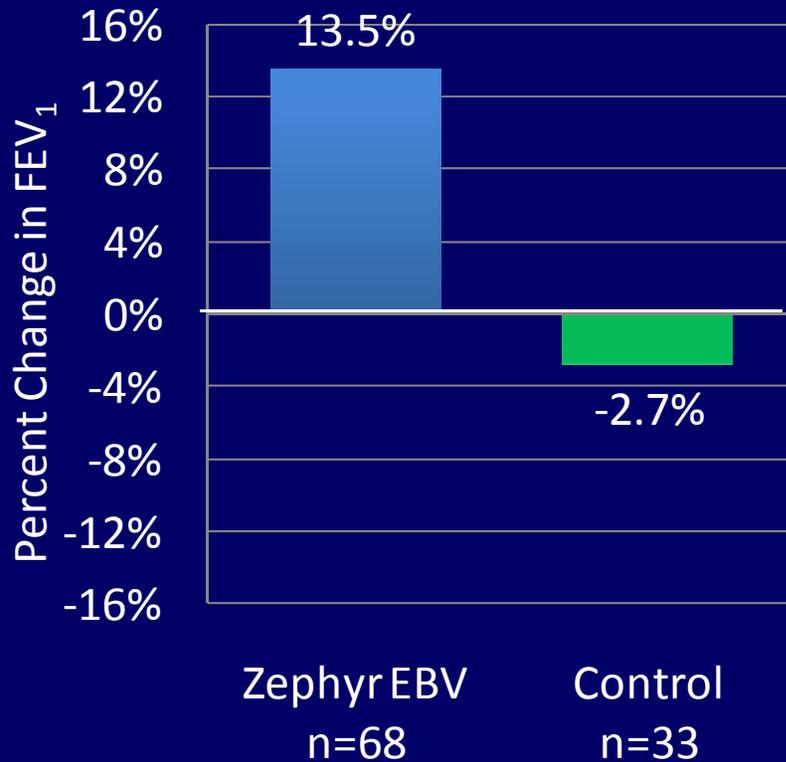


- Proxy for collateral ventilation
- Creates closed system
- Rates of Complete Fissure
 - Right Oblique = 54%
 - Right Horizontal = 39%
 - Left Oblique = 62%

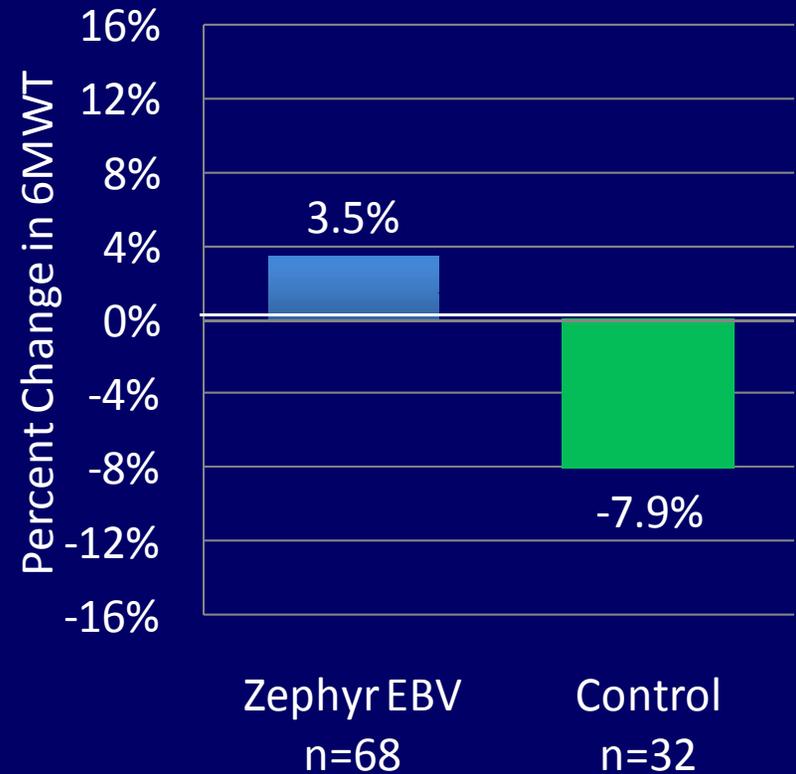
Change in FEV₁ and 6MWT

Complete Fissure Subgroup at 6 Months (CC)

FEV₁ Change
 Δ 16.2%, p = 0.001
 Δ 136.2 ml, p < 0.001



6MWT Change
 Δ 11.4%, p = 0.075
 Δ 44.5 m, p = 0.085



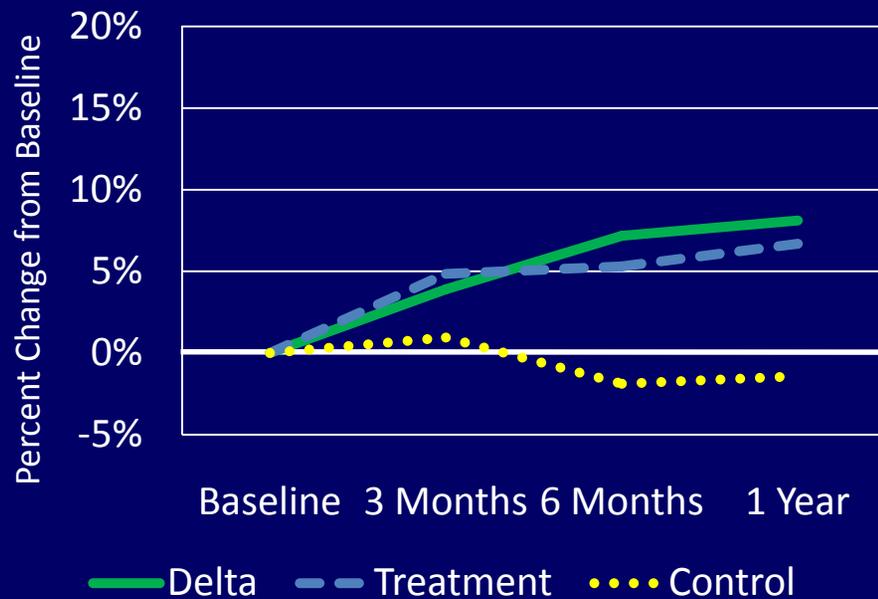
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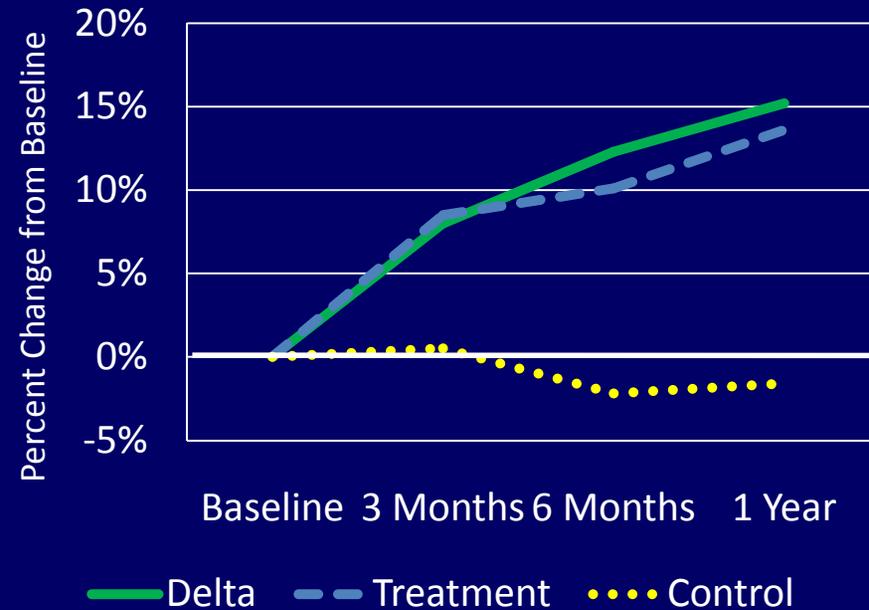
FEV₁ Longitudinal Results

→ Treatment does not erode over time per multivariate, longitudinal analysis, $p < 0.001$

Completed Cases



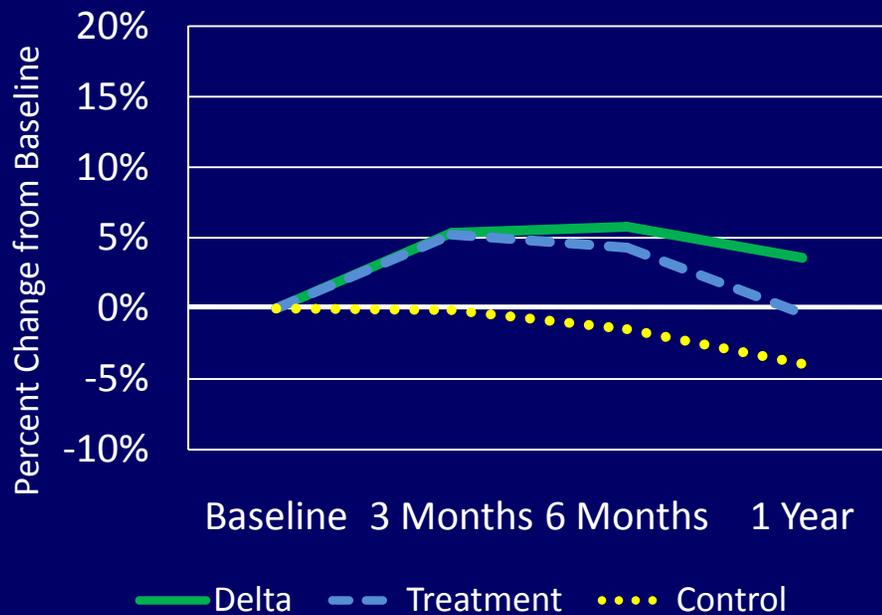
High Heterogeneity



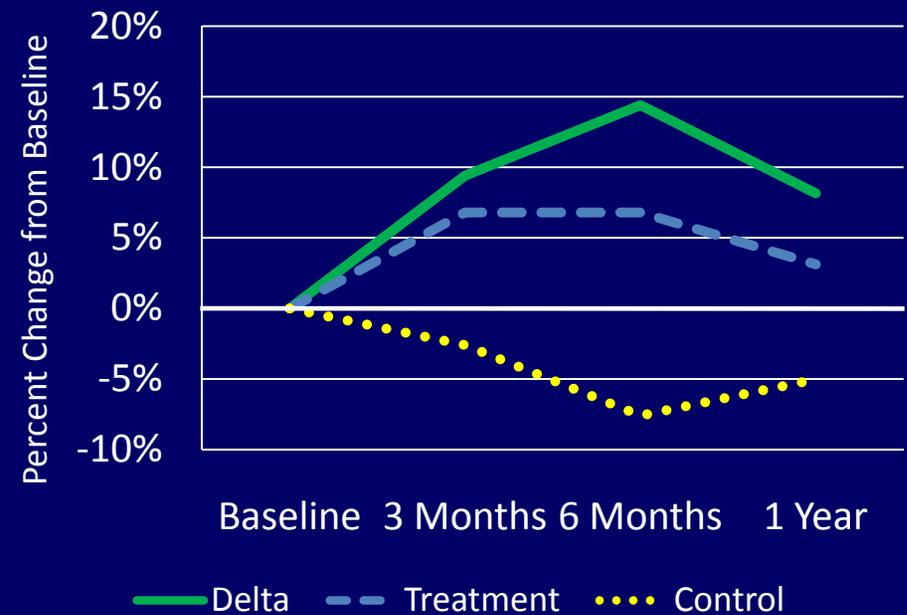
6MWT Longitudinal Results

→ Treatment does not erode over time per multivariate, longitudinal analysis, $p = 0.014$

Completed Cases

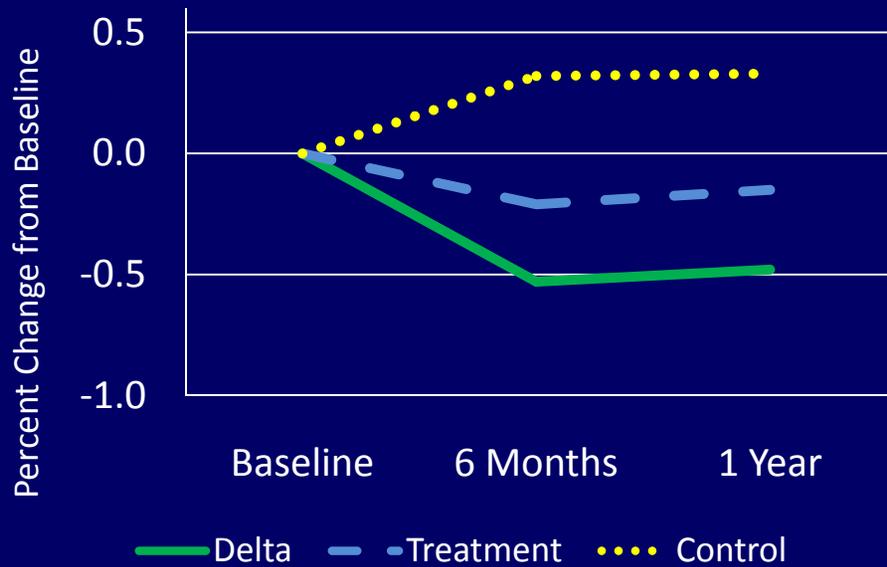


High Heterogeneity

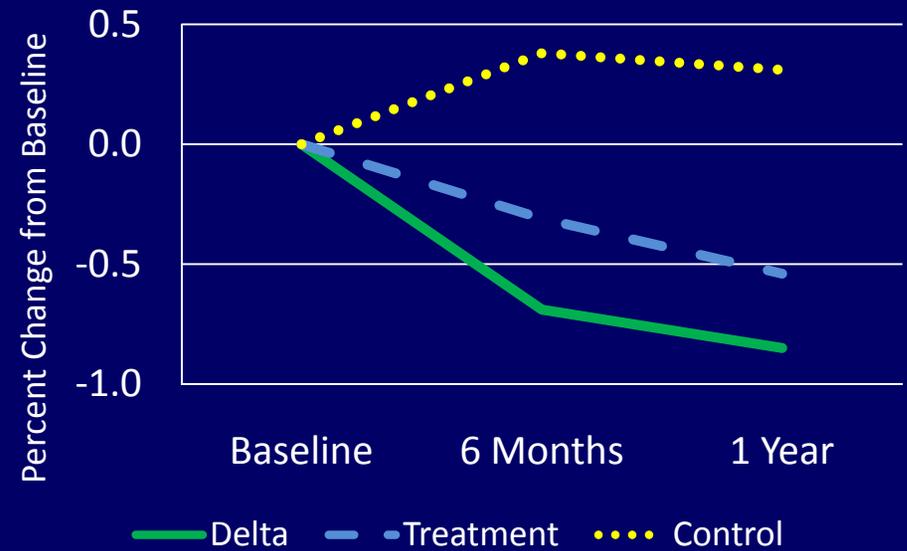


BODE Longitudinal Analysis

Completed Cases



High Heterogeneity



Efficacy Conclusions

- Met primary and secondary endpoints
 - Lung function, exercise tolerance, and QOL
- Achieved target lobe volume reduction
- BODE (integrative parameter) corroborates treatment effect
- Favorable responder analysis across numerous measures
- Enhanced efficacy in subjects with High Heterogeneity and Complete Fissures
- Sustained benefit at 12 months

Training, Post Approval Study Proposal, and Conclusion

Gerard Criner, MD, FCCP

Professor of Medicine

Florence P. Bernheimer Distinguished Service Chair

Director, Pulmonary and Critical Care Medicine

and Temple Lung Center

Temple University School of Medicine

Training and Post Approval Studies

Physician Training

- Goal is controlled introduction
- Didactic:
 - Labeling
 - Pivotal trial results
 - Bronchoscopy video of implant procedure
 - HRCT assessment of destruction, heterogeneity
- Hands-on
 - Device preparation and loading
 - Valve implants and removals in simulated lung anatomy
 - Proctoring of initial cases

Zephyr EBV

Proposed Post Approval Studies

- PAS I - VENT Long Term Follow-up
 - Primary Objective: Collect and report long-term safety and efficacy data at three and four years post enrollment in the VENT study
- PAS II – Post Market Assessment
 - Primary Objective: Evaluate the training effectiveness and longer-term safety of the Zephyr EBV during commercial use by various physicians with a range of experience .

Zephyr EBV

PAS I - VENT Long Term Follow-up

- Design: Multi-center, observational
 - Up to 284 patients and 29 institutions
 - Follow-up treatment and control groups
- Follow-Up :
 - 3 and 4 years post VENT enrollment
- Subject Population
 - VENT mITT population
- Study Objective: Assess Long-term Safety
 - Safety: Adverse Events
 - Physiologic: FEV₁, FVC
 - Exercise: 6MWT
 - Clinical: BODE, Survival

Zephyr EBV

PAS II - Post Market Assessment

- Design: Prospective, observational, open-label study
 - 200 patients and 30 institutions
- Follow-up:
 - 30 and 180 Days, 1, 2 and 3 years post procedure
- Subject Population
 - In compliance with the indications for use and restrictions of the approved labeling
- Study Objectives:
 - Safety: Serious adverse events
 - Training Effectiveness: Migration and expectoration rates

VENT Study Summary

- VENT is a landmark study
 - After NETT it is the largest interventional trial ever conducted in severe emphysema
 - Largest interventional study in severe emphysema ever conducted by industry
 - First ever prospective randomized controlled trial to evaluate lung volume reduction via endobronchial treatment
 - First to evaluate regional effects of lobar treatment
 - HRCT data provides novel paradigm for subject selection, mechanistic effect and outcome assessment that is impervious to placebo effect

Study Conduct

- Visit windows employed for analysis reasonable for this patient population and narrower than NETT
- Missing data rates are similar to other landmark studies in severe COPD populations
- No impact on study outcomes due to protocol or eligibility deviations
 - Primary endpoints met regardless of whether protocol or eligibility deviations are included in the analysis

Study Summary: Safety

- Equivalent mortality to control
- Complications
 - Peri-procedural increase in events as expected
 - Typically minor and transient
 - Rates decrease over time
 - Medically-manageable, no surgical interventions
- Removable device

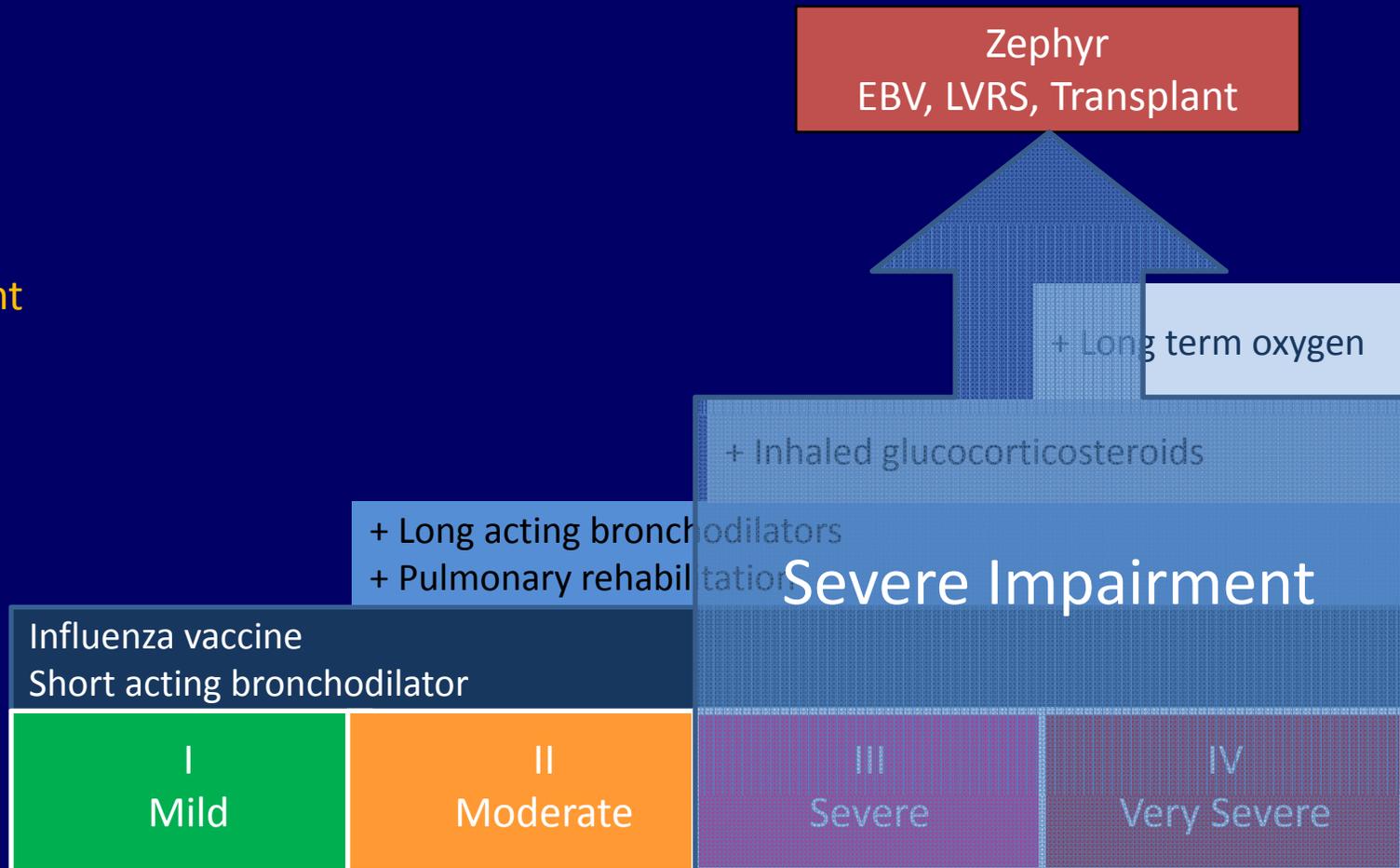
Established Clinically Significant Efficacy

- Met primary and secondary efficacy endpoints
- Responder analysis shows clinically meaningful changes in significant % of treated cohort with minimal morbidity and mortality
- Changes in BODE signify disease modifying therapy

Zephyr EBV in Practice

Treatment Options:

GOLD* Stage:



- Typically seek medical attention

- ↑ dyspnea
- ↓ exercise capacity
- repeated exacerbations

- Appreciably impaired
- Exacerbations may be life-threatening

Assessing the Risks and Benefits of Treatments in Severe Emphysema

Factors

- Clinical benefit
- Morbidity
- Mortality
- Patient preference

Options

- Medical Management
- EBV
- LVRS
- Transplant

Zephyr EBV Risk / Benefit

- Severe emphysematous patients with limited options
- Reasonable, anticipated, manageable risks
- Clinically important benefits in substantial number of patients
- Benefits outweigh risks
- Study results demonstrated reasonable assurance of safety and effectiveness

Zephyr EBV

Reasonable Assurance of
Safety and Effectiveness

AFTERNOON SLIDES

Primary Safety Endpoint – MCC

	6 months				12 months			
	EBV n = 214	Control n = 87	Delta (95% CI)	p value	EBV n = 214	Control n = 87	Delta (95% CI)	p value
Major Complication Composite	6.1%	1.2%	4.93% (1.02, 8.83)	0.08	10.3%	4.6%	5.68 (0.31, 11.68)	0.17
Death	2.8%	0.0%	2.80% (0.59, 5.02)	0.19	3.7%	3.5%	0.29 (-4.31, 4.89)	1.00
Pneumonia distal to valve	1.4%	NA	----	----	4.2%	NA	----	----
Respiratory failure ≥ 24 hours ventilation	1.9%	1.2%	0.72% (-2.16, 3.60)	1.00	2.8%	2.3%	0.50 (-3.34, 4.35)	1.00
Pneumothorax / air leak > 7 days	1.4%	1.2%	0.25% (-2.5, 3.0)	1.00	1.9%	1.2%	0.72 (-2.16, 3.60)	1.00
Massive hemoptysis (> 300ml)	0.5%	0.0%	0.47% (-0.45, 1.38)	1.00	0.5%	0.0%	0.47 (-0.45, 1.38)	1.00
Empyema	0.0%	0.0%	----	----	0.0%	0.0%	----	----

→ MCC nominally higher as anticipated (ns)

Baseline Characteristics

	Remained Mean	Withdrew Mean	p value
Gender (% male)	42.75%	54.05	ns
Age (years)	65.09	65.35	ns
History of smoking (yes)	99.28%	97.30%	ns
Pack Years	60.0	65.8	ns
BMI (kg/m ²)	25.00	24.83	ns
Diabetes	6.88%	2.70%	ns
Abnormal ECG	44.57%	54.05%	ns

→ No significant differences

Baseline Lung Function

	Remained Mean	Withdrew Mean	p value
FEV ₁ (liters)	0.87	0.83	ns
FEV ₁ (% Predicted)	30%	30%	ns
FVC (liters)	2.68	2.62	ns
FVC (% Predicted)	70%	71%	ns
FEV ₁ / FVC	0.33	0.32	ns
RV (% Predicted)	214%	214%	ns
TLC (% Predicted)	125%	124%	ns
RV / TLC	0.63	0.64	ns
DL _{CO} (% Predicted)	34%	37%	ns

→ No significant differences

Other Baseline Variables Well Matched

	Remained Mean	Withdrew Mean	p value
PaO ₂ (mmHg)	68.88	69.06	ns
PaCO ₂ (mmHg)	40.68	41.91	ns
pH	7.43	7.42	ns
Oxygen Saturation	93%	94%	ns
Six Minute Walk Test (m)	341.71	325.2	ns
Cycle Ergometry (max. watts)	45.3	39.2	ns

→ No significant differences