Emphysema

- A severe form of Chronic Obstructive Pulmonary Disease (COPD)
- Progressive disease – destruction of lung tissue
- Air trapping causes persistent breathlessness
Air Trapping and Hyperinflation in Emphysema

- Among the leading causes of death worldwide
- In the US, COPD is expected to be associated with approximately $49 billion in direct medical costs in 2020
- Prognosis and quality of life are worse than patients with lung cancer

Healthy Lung
- Tissue is elastic with large surface area
- Breathing is easy; Lung expands and contracts normally

Lung with Emphysema
- Tissue destruction reduces elasticity and gas exchange
- Air is trapped in the diseased portion of the lung, increasing lung volume and putting pressure on the diaphragm

Hyperinflation is a Key Driver of Symptoms & Mortality

- Higher baseline dyspnea
- Significant intolerance to exercise
- Low peak oxygen uptake
- Lower daily activity levels
- Low BMI and/or muscle strength
- Reduced cardiac and circulatory function

The lungs of a COPD patient are hyperinflated compared to age & height matched healthy individuals

Healthy
- IC ~3.3 L
- TLC 6.45 L
- FRC 4.22 L

COPD
- IC ~1.2 L
- TLC 9.38 L (146%pr)
- FRC 8.22 L (195%pr)

2. Casanova AJRCCM 2001;171:591-597
4. Images used with permission from Prof. Denis O’Donnell, Queen’s University and Kingston General Hospital, December 2016
**Disease Progression**

- Hyperinflation & Shortness of Breath
- Decreased Activity
- Reduced Exercise Capacity & Increased Breathlessness
- Further Decreased Activity
- Further Deconditioning
- High Risk of Mortality

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**Spectrum of Treatment Options**

- Oxygen Therapy, Corticosteroids, Bronchodilator
- Pulmonary Rehabilitation
- Lung Volume Reduction Surgery
- Lung Transplant

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**The Zephyr Endobronchial Valve**

"Breakthrough Technology" Approved by the FDA for Severe Emphysema Patients

- Tiny implantable devices
- Benefits similar to surgery with no cutting
- Precise patient selection
- Proven in clinical trials and included in guidelines
- Fully removable
Spectrum of Treatment Options

Oxygen Therapy, Corticosteroids, Bronchodilators
Pulmonary Rehabilitation
Zephyr® Endobronchial Valves
Long Volume Reduction Surgery
Long Transplant

How Zephyr Valves Work

Zephyr® Valve Patient Benefits

- Improved Health Status (KCOG)
- Improved Quality of Life 
& Exercise (SGI, TSQoL, CAT, WAKI)
- Reduced Breathlessness (mMRC, BORG)
- Improved Lung Function (FEV1, DLCO, FRC)
- Reduced Gas Trapping (RV, IC/TLC)
- Successful Lobar Occlusion (TLVR)

Criner, G et al, AJRCCM. Am J Respir Crit Care Med, 2018; 198 (9): 1151–1164
Emphysema Patients are Eager for New Options

Preference Share Predictions for a Choice Between product like Zephyr® Valve and Medical Management

- Preference study surveyed 294 US patients with severe emphysema
- Found they value access to an interventional treatment that offers benefits above and beyond their current medical management, despite the risks associated with these treatments
- More than 3 in 4 patients would select a treatment with the clinical benefits and risk profile of Zephyr® Valves over current treatment

Spiration Valve System For Emphysema – Indication for Use

- Spiration Valves are one-way endobronchial valves indicated for adult patients with shortness of breath and hyperinflation associated with severe emphysema in regions of the lung that have evidence of low collateral ventilation.

Quantitative CT Analysis

Each lobe (excluding the RML) has a circle that contains values for:

- (E) Emphysema Severity (≥ 40)
- (F) Fissure Completeness (≥ 90)
- (H) Heterogeneity (≥ 10)
Spiration Valve Placement

- The Spiration valve is delivered to the target lobe during a bronchoscopic procedure.
  - During inhalation the valve redirects air to the healthier lobe.
  - Upon exhalation the valve allows trapped air and secretions to escape from the hyperinflated lobe.
  - By allowing air to leave, but not enter diseased areas of the lung, it is possible to reduce hyperinflation in the targeted lobe.
  - Treatment will require placement of multiple valves to achieve complete lobar occlusion in targeted lobe.

EMPROVE Study Overview

- EMPROVE evaluated the safety and effectiveness of the Spiration Valve System in 172 patients with severe emphysema.
- 2:1 randomization into SVS treatment arm (n=113), and standard of care control arm (n=59).
- Alpha-1 antitrypsin deficiency non-randomized SVS treatment arm (n=20).
- Primary and secondary effectiveness endpoints measured 6 months following randomization.
- Longer term durability of effectiveness measured at 12 months following randomization.
- The EMPROVE clinical trial demonstrated that patients treated with the SVS benefitted from significant clinical and statistical improvements in lung function and quality of life, compared to standard of care medical management.

*A negative change in SGRQ represents an improvement in disease specific health status. A 4-point reduction is considered clinically meaningful.

Agenda

- The Problem of Severe Emphysema & Hyperinflation
- A New Treatment Option: The Zephyr® Valve
- Review of Key Clinical Data from Multiple Trials
- Which Patients are Eligible?
Clinical Benefits for a Diverse Patient Profile

- Upper and Lower Lobe Treatment
- Heterogeneous and Homogeneous emphysema
- Collateral ventilation status indicated by CT and confirmed by Chartis®

VENT and BeLieVeR Trials

Key Learning:
- Patients without collateral ventilation have greater improvement.
- Total lobar occlusion is required for improvement.
Collateral Ventilation Screening

- Collateral ventilation is airflow between lobes "through channels that bypass the normal airways."
- Only lobes WITHOUT collateral ventilation should be treated with Zephyr® Valves


Pulmonx Tools Enable Precise Patient Selection

- Noninvasive: StratX® Analysis Platform
  - Quantitative analysis of CT scan
  - Cloud-based system
  - Identify one or more potential lobes for treatment

Procedure: Chartis® Pulmonary Assessment System

- Simulate treatment
- Measure airflow and pressure

Assessing Collateral Ventilation — Chartis® System

- No collaterals, higher likelihood of good treatment response
- Collaterals, lower likelihood of good treatment response
STELVIO

- 84 patients identified with severe (homogeneous and heterogeneous) emphysema on CT, likely with complete fissures
- 68 patients confirmed as collateral ventilation negative with Chartis® System, and likely responders to Zephyr® Valves

Key Learning:
- Confirmation CV patients have improvement in lung function, exercise capacity, and quality of life
- Excellent outcomes in heterogeneous and homogeneous disease

IMPACT

- 93 subjects with homogeneous emphysema randomized 1:1 Zephyr® Valve and SoC

Key Learning:
- Confirmation of efficacy across primary and secondary outcome measures in homogeneous emphysema patients

TRANSFORM

- 97 patients with severe heterogeneous emphysema on CT and CV on Chartis® were randomized 2:1 to Zephyr® Valve and SoC

Key Learning:
- Confirmation of efficacy across primary and secondary outcome measures in heterogeneous emphysema patients
The LIBERATE Study

- Multicenter, international randomized controlled study IDE approval trial
  - 100 severe heterogeneous emphysema subjects with little to no collateral ventilation, randomized 2:1 Zephyr® Valve to Standard of Care
  - First and only valve RCT with 12-month follow-up in both treatment and control arms

Baseline Demographics

<table>
<thead>
<tr>
<th></th>
<th>Zephyr Valve (n=128)</th>
<th>SoC (n=62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, Female</td>
<td>72 (56.3%)</td>
<td>29 (46.8%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>64.0 ± 6.85</td>
<td>62.5 ± 7.12</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.67 ± 3.90</td>
<td>24.32 ± 4.38</td>
</tr>
<tr>
<td>Smoking history (pack years)</td>
<td>50.78 ± 26.88</td>
<td>48.59 ± 28.48</td>
</tr>
<tr>
<td>Emphysema score of the target lobe at -910 HU</td>
<td>70.9 ± 8.52</td>
<td>70.9 ± 8.77</td>
</tr>
<tr>
<td>Heterogeneity Index between target and ipsilateral lobes</td>
<td>25.5 ± 9.85</td>
<td>26.1 ± 9.81</td>
</tr>
</tbody>
</table>

Respiratory Function

<table>
<thead>
<tr>
<th></th>
<th>Zephyr Valve (n=128)</th>
<th>SoC (n=62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-BD (FEV₁) (L)</td>
<td>0.76 ± 0.25</td>
<td>0.75 ± 0.22</td>
</tr>
<tr>
<td>Post-BD (FEV₁) (% predicted)</td>
<td>28.0 ± 7.45</td>
<td>26.2 ± 6.28</td>
</tr>
<tr>
<td>DLCO (% predicted)</td>
<td>34.6 ± 11.34</td>
<td>33.1 ± 9.84</td>
</tr>
<tr>
<td>Residual Volume (% predicted)</td>
<td>224.5 ± 42.45</td>
<td>224.6 ± 38.86</td>
</tr>
<tr>
<td>6 Minute Walk Distance (m)</td>
<td>311 ± 81</td>
<td>302 ± 79</td>
</tr>
<tr>
<td>SGRQ Total Score</td>
<td>55.15 ± 14.08</td>
<td>53.10 ± 14.14</td>
</tr>
<tr>
<td>mMRC Score</td>
<td>2.4 ± 0.97</td>
<td>2.2 ± 0.83</td>
</tr>
<tr>
<td>BODE Index</td>
<td>5.34 ± 1.52</td>
<td>5.32 ± 1.56</td>
</tr>
</tbody>
</table>

Responders on Continuous Oxygen Usage | 46 (35.9%) | 17 (27.4%) |

LIBERATE Primary and Secondary Outcomes

- Primary Endpoint: Percent of Subjects with FEV₁ Change from Baseline to 12 months of ≥15%
- Secondary Endpoints: Change from Baseline to 12 months FEV₁, RV, BODE, SGRQ, 6MWD, and mMRC

Responder Rates for Key Outcomes

- FEV₁: ≥15% and ≥12% improvement
- SGRQ Score: ≥4 points improvement
- mMRC: ≥1 point improvement
- BODE Index: ≥1 point improvement
- RV: ≥310 mL improvement
- 6MWD: ≥25-meter improvement
- TLVR: ≥350 mL improvement
Patient Reported Outcome – LIBERATE

Multiple measures of activity levels in Zephyr® treated patients showed statistically significant improvements compared to SoC at 12-months, notably TDI measures of effort, task, and functional impairment. These changes in activity levels can be very meaningful for patients. For example, a 3-point change in TDI focal score implies a return to most work/leisure activities previously impacted, and 54.9% of Zephyr Value-treated patients achieved this in LIBERATE.

Emphysema Symptoms from Daily Diary

Patients reported their daily symptoms in a Daily Diary by responding to the question, “Mark the scale to show the intensity of the emphysema symptoms you had today (scale of 0=none to 10=intolerable; instrument not validated).” Over the year following randomization, control patients perceived worsening of their symptoms, while Zephyr®-treated patients on average perceived an improvement of symptoms within two weeks after the procedure, which persisted out to at least 12 months.

At the individual level, “Zephyr Valve experienced significantly more days that were ‘better’ and fewer days that were ‘worse’ over 12 months.”

LIBERATE Safety

<table>
<thead>
<tr>
<th>Event</th>
<th>Zephyr® Valve (N=128)</th>
<th>SoC (N=62)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>4 (3.1%)</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>34 (26.6%)*</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Severe COPD exacerbation</td>
<td>10 (7.8%)</td>
<td>3 (4.8%)</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1 (0.8%)</td>
<td>7 (5.7%)</td>
<td></td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>2 (1.6%)</td>
<td>1 (0.8%)</td>
<td></td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>0</td>
<td>1 (0.8%)</td>
<td></td>
</tr>
<tr>
<td>Diverticulitis</td>
<td>0</td>
<td>1 (0.8%)</td>
<td></td>
</tr>
</tbody>
</table>

SAEs Occurring in at Least 3% of Subjects, as Defined by Investigators

SAEs as Adjudicated by CEC
76% of Pneumothoraces within 3 Days of Procedure

- All Zephyr Valve procedures are done as in-patient procedures with a 3-night stay
- Zephyr Valve Treating Centers are trained to handle pneumothorax
- Patients are advised of the signs and symptoms of pneumothorax at discharge

Summary of Key Measures Across Studies in CV- Patients

<table>
<thead>
<tr>
<th>ACT</th>
<th>Design</th>
<th>Intervention: Comparison</th>
<th>Procedural Success</th>
<th>Long Duration FEV1%</th>
<th>Exercise Capacity 6MWD</th>
<th>Quality of Life SGRQ</th>
<th>Difference Zephyr Valve vs. Control Groups (ITT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIBERATE</td>
<td>2:1 Randomization</td>
<td>Heterogeneous only</td>
<td>Multicenter</td>
<td>84%</td>
<td>18.0%</td>
<td>-7.1 pts</td>
<td>14.0% (p=0.01) 38 m (p=0.001) -1.1 pts (p=0.001)</td>
</tr>
<tr>
<td>TRANSFORM</td>
<td>2:1 Randomization</td>
<td>Heterogeneous only</td>
<td>Multicenter</td>
<td>90%</td>
<td>29.3%</td>
<td>-6.5 pts</td>
<td>20.3% (p=0.01) 79 m (p=0.01) -0.5 pts (p=0.03)</td>
</tr>
<tr>
<td>IMPACT</td>
<td>1:1 Randomization</td>
<td>Homogeneous only</td>
<td>Multicenter</td>
<td>89%</td>
<td>16.3%</td>
<td>-7.5 pts</td>
<td>16.3% (p=0.0001) 28 m (p=0.016) -1.3 pts (p=0.001)</td>
</tr>
<tr>
<td>STELvio</td>
<td>1:1 Randomization</td>
<td>Heterogeneous &amp; Homogeneous</td>
<td>Single Center</td>
<td>88%</td>
<td>17.8%</td>
<td>-14.7 pts**</td>
<td>17.8% (p=0.0001) 74 m (p=0.001) -14.7 pts** (p=0.001)</td>
</tr>
</tbody>
</table>

*Data on file at PMX (not in publication) **Completed cases, all other values listed are ITT population

Criner, G et al, AJRCCM. 2018; 198 (9): 1151–1164
Clinically Accepted Globally

Zephyr® Valve treatment of severe emphysema is included in global and national guidance documents, such as those sponsored by:

- Global Initiative for Chronic Obstructive Lung Disease (GOLD) Evidence Level A
- The UK’s National Institute for Care and Excellence (NICE)
- German Respiratory Society (DGP)
- National Health Care Institute of the Netherlands (Zorginstituut Nederland)

>20,000 Patients Treated Globally

Agenda

The Problem of Severe Emphysema & Hyperinflation

A New Treatment Option: The Zephyr® Valve

Review of Key Clinical Data from Multiple Trials

Which Patients are Eligible?

Zephyr® Valve Indication for Use – United States

The Pulmonx Zephyr Endobronchial Valves are implantable bronchial valves indicated for the bronchoscopic treatment of adult patients with hyperinflation associated with severe emphysema in regions of the lung that have little to no collateral ventilation.
Minimum Criteria for Referral

1. Confirmed diagnosis of COPD
2. Non-smoking or willing to quit smoking
3. FEV₁ < 50% predicted
4. Breathless despite optimal medical management (mMRC≥2)

Modified MRC Dyspnea Scores

0. I only get breathless with strenuous exercise
1. I get short of breath when hurrying up stairs or walking up a slight hill
2. I walk slower than people of the same age on the level because of breathlessness, or I have to stop for breath when walking at my own pace on the level
3. I have to stop for breath after walking about 100meters or after a few minutes on the level
4. I am too breathless to leave the house, or I am breathless when dressing or undressing

How to Send a Referral

Identify Potential Candidates

- Explore Existing Database
  - PFT Software (FEV₁ < 50%, RV > 150%, TLC > 100%)
  - Possible ICD-10-CM Diagnosis Codes (J42, J44)

Make a Connection with Local Treating Center

- Locate on MyLungsMyLife.com website
- Reach out to treating center and schedule a meeting to discuss referrals
- Set up an easy referral process for your patients – use referral form

Follow up with Referral Once Treated

- The treating center will communicate with the patient
- Patient to report back once seen by physician
- When you get your patient back
- Report all outcomes back to the treating center

* These are only suggested broad search terms, and as such, not all patients will ultimately qualify for Zephyr® Valves.

**Refer to ICD International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) list here: https://www.cdc.gov/nchs/icd/icd10cm.htm

Typical Work Up for Zephyr® Valve Eligibility

- Medical History
  - Diagnosis of emphysema
  - BMI < 35 kg/m²
  - Stable with ≤ 20mg prednisone (or equivalent) daily
  - Non-smoking
  - Collect any available imaging and lung function studies
  - 6MWD (100m-500m)

- Pulmonary Function Tests (post-Bronchodilator)
  - Spirometry (FEV₁, 15-45% predicted)
  - Body Plethysmography (RV < 115%, TLC < 102% for Heterogeneous emphysema and RV > 300% predicted, TLC < 102% predicted for Homogeneous emphysema)
  - Arterial Blood Gas Levels collected on room air
  - Rule out severe hypercapnia PaCO₂ ≥ 45 mmHg
  - Rule out severe hypoxemia PaO₂ ≤ 65 mmHg

- Imaging
  - High-Resolution CT (≤ 1.5mm slice thickness, TLC view)
  - PET/CT Scan (Highly Recommended)

- Echocardiogram
  - Rule out congestive heart failure, LVEF < 45%
  - Rule out uncontrolled pulmonary hypertension, sPAP > 45mm Hg
Patient Screening & Treatment Process

Clinical Work Up

Step 1:
- Medical history
- Lung function tests
- CT Scan

Step 2:
- StratX report to support target lobe selection:
  - Lobar volume
  - Emphysema destruction score
  - Fissure completeness

Step 3:
- Chartis procedure:
  - Confirm target lobe has no collateral ventilation

Step 4:
- Zephyr Valves placed to completely occlude the target lobe

Step 5:
- The patient should remain in the hospital for 3 nights following the procedure for observation

Reimbursement for Zephyr® Valves

- Most patients who qualify for the procedure are able to secure insurance coverage for their Zephyr Valve treatment when the medical criteria are met.
- Many plans cover the Zephyr Valve treatment and most plans that do not yet have a policy are approving prior-authorization requests on a case-by-case basis.
- It is recommended that a patient seek prior-authorization approval before the procedure.
- For patients whose doctor has recommended the Zephyr Valve procedure, the Pulmonx Patient Reimbursement Support Program is available to patients and their caregivers as they navigate the insurance process for the Zephyr Valve procedure.

Summary

1. Zephyr® Valves have been extensively studied clinically (4 Randomized Controlled Trials)
2. Patients treated with Zephyr Valve had clinically significant improvement in lung function, exercise capacity, and quality of life.
3. Endobronchial Valve treatment is an established therapy for patients with emphysema included in global guidance of the treatment of COPD. GOLD (Evidence Level A)
4. Most patients who qualify for the Zephyr Valve procedure are able to secure insurance coverage for their treatment.
5. Severe emphysema patients are searching for additional therapies.
Complications of the Zephyr® Endobronchial Valve treatment can include but are not limited to pneumothorax, worsening of COPD symptoms, hemoptysis, pneumonitis, dyspnea and, in rare cases, death.

**Brief Statement**

United States

Brief Statement: The Pulmonx Zephyr® Endobronchial Valves are implantable bronchial valves indicated for the bronchoscopic treatment of adult patients with hyperinflation associated with severe emphysema in regions of the lung that have little to no collateral ventilation. The Zephyr Valve is contraindicated for: Patients for whom bronchoscopic procedures are contraindicated; those with evidence of active pulmonary infection; known allergies to Nitinol (nickel-titanium) or its constituent metals (nickel or titanium); known allergies to silicone; or with large bullae encompassing greater than 30% of either lung; Patients who have not quit smoking. The Zephyr Valve should be used with caution and only after careful consideration in treating patients with: Prior lung transplant, LVRS, median sternotomy, or lobectomy; Congestive heart failure or recent myocardial infarction; FEV1 <15% of predicted value. Use is restricted to a trained physician. Prior to use, please reference the Zephyr Endobronchial Valve System Instructions for more information on indications, contraindications, warnings, all precautions, and adverse events.

**Brief Statement**

Chartis® System is indicated for use by bronchoscopists during a bronchoscopy in adult patients with emphysema, a form of Chronic Obstructive Pulmonary Disease (COPD), in a bronchoscopy suite. The system, composed of the Chartis® Catheter and Chartis® Console, is designed to measure pressure and flow in order to calculate resistance to airflow and quantify collateral ventilation in isolated lung compartments. The Chartis® Catheter is used through the working channel of a bronchoscope and connects to the Chartis® Console. The Chartis® Console is capital equipment that is reusable and displays the patient information. The Chartis® System is contraindicated in the presence of active infection or major bleeding diathesis. There are no known interfering substances. Use is restricted to a trained physician. Prior to use, please reference the Chartis System Instructions for Use/User Manual for more information on indications, contraindications, warnings, all precautions, and adverse events.

Caution: Federal law restricts this device to sale by or on the order of a physician.

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