dNerva™

Targeted Lung Denervation

A one-time bronchoscopic procedure designed to reduce the frequency and severity of COPD exacerbations

NUVAIRA®

Nuvaira® Lung Denervation System is an investigational device in the United States and has CE mark regulatory approval.

Understanding the “Lung Attack”

Chronic obstructive pulmonary disease (COPD) is progressive and leaves patients experiencing symptoms of breathlessness, coughing, sputum production, chest tightness and wheezing driven by the natural release of acetylcholine.

The brain signals the lung, via the vagus nerve, to release acetylcholine in response to toxins, such as tobacco smoke or environment pollution. This generates a repeating cycle of signaling along the nerve pathways between the lung and the brain.

In some COPD patients, this constant cycle of nerve signaling and chronic airway inflammation, creates a state of heightened neural sensitivity called airway hyperresponsiveness. This puts the pulmonary system into a state of permanent high alert which results in an over-exaggerated reaction to normal environmental stimuli. These patients may then suffer from frequent exacerbations, or lung attacks, which medications cannot adequately prevent.[3]

Treatment goals focus on minimizing the impact of lung attacks[19], which can cause:

- **Accelerated decline in lung function**[12,13,14]
- **Increased risk of acute cardiovascular events**[16]
- **Reduced activities of daily living (ADL) and quality of life**[15]
- **Increased risk of future hospital admissions**[6]
- **Increased mortality risk**[17,18]

Lung attacks not only reduce patient quality of life; one severe exacerbation can leave a patient at 14 times greater risk of death within one year.[17,18] COPD is the biggest driver of health care costs related to hospitalization and responsible for $72 billion in annual direct health care expense.[6,7,8,9]

Current Therapies Leave Significant Unmet Needs

Prescribed medications are an integral component of effective disease management, but patients adhering to optimal medical therapy continue to exacerbate in large-scale clinical trials targeting reduction in COPD exacerbation as the primary goal.[10,11]

Disrupting Pulmonary Nerve Input

The goal of **Targeted Lung Denervation (TLD)** is to disrupt parasympathetic pulmonary nerve input to the lung to reduce the clinical consequences of neural hyperactivity[1,2]. Performed during a single bronchoscopic procedure, instead of via inhaled medications, this denervation of the lung permanently disrupts the nerve signaling to and from the lung, which allows airway smooth muscle to relax and mucous secretion to decrease. This moves the pulmonary system to a state of “low alert” to improve symptom tolerance, decrease symptom burden and decrease exacerbations.

This one-time surgical procedure involves passing a specialized catheter through a flexible bronchoscope to complete a full circumferential ablation in the mainstem bronchus of each lung. The bronchoscope is inserted into the mainstem bronchi, and a radio-opaque esophageal balloon is temporarily inserted to facilitate visualization and avoidance of treatment near the esophagus. Performed under general anesthesia, the procedure typically takes 60–90 minutes.

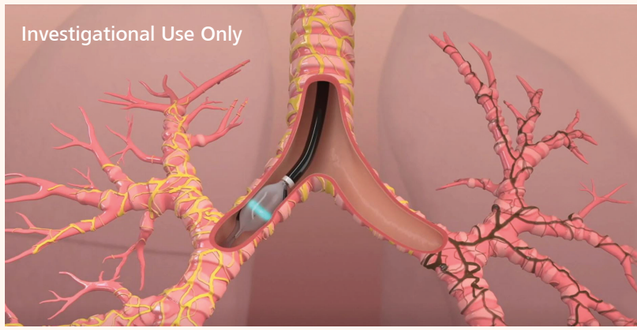
The ablation permanently disrupts pulmonary nerve input to the lung, reducing acetylcholine release. With less acetylcholine, the airway smooth muscle relaxes, and mucous secretion decreases, moving the pulmonary system to a state of “low alert” to improve symptom tolerance, decrease symptom burden and decrease exacerbations.

The Procedure

Step 1: Position
The dNerva catheter threads through the working channel of the bronchoscope and is positioned in the distal aspect of the mainstem bronchi.

Step 2: Inflate
The conduit and balloon are inflated by circulating coolant through the catheter which brings the electrode in contact with the airway wall.

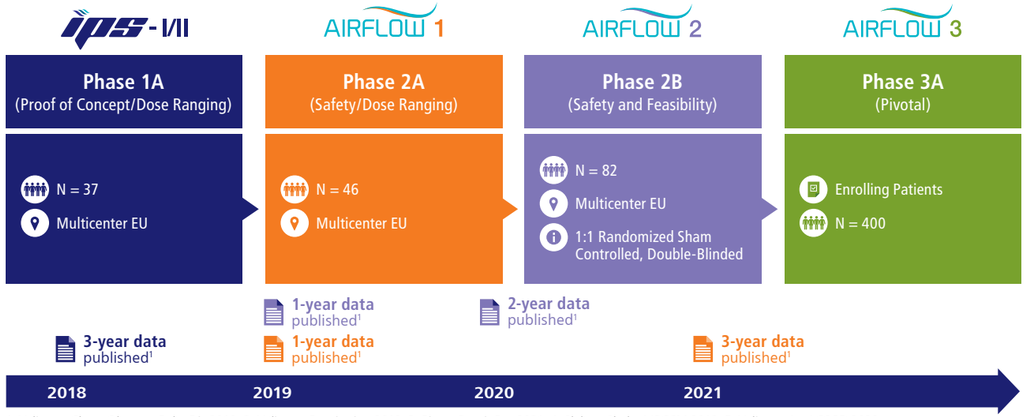
Step 3: Confirm
Visual confirmation of good contact of the electrode with the airway wall and adequate distance from the esophagus (confirmed under fluoroscopy).



Step 4: Active
Radio-frequency energy activation. After completion of the activation, the physician will rotate the catheter 90 degrees and then repeat. Each mainstream bronchus is treated four times to complete circumferential ablation and thus deliver a full treatment.

Post-Procedure
The patient can expect to go home the same day as the procedure. The patient will be provided with a card explaining their participation in a clinical trial and are advised to present that should they become ill for any reason and seek medical care.

Nuvaira Clinical Development Program



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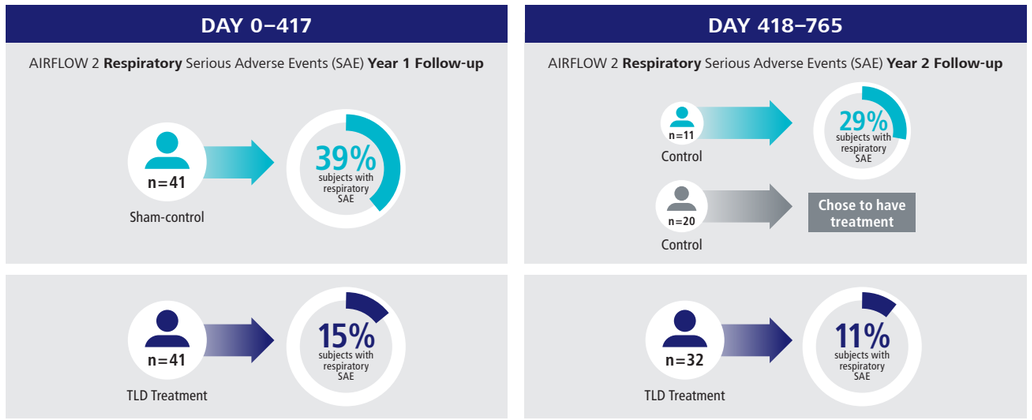
AIRFLOW 2 Trial Results to Date

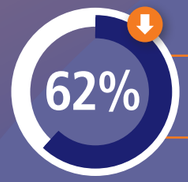
AIRFLOW 2 was a multicenter, 1:1 randomized, sham-controlled, double-blinded, prospective study. Unblinded after 12.5 months, sham patients were invited to cross-over to TLD treatment in a separate protocol. Intended to evaluate the safety and impact of TLD in moderate-to-severe symptomatic patients on optimal medical therapy, it was offered at 16 study sites in 5 countries.

Primary Endpoint



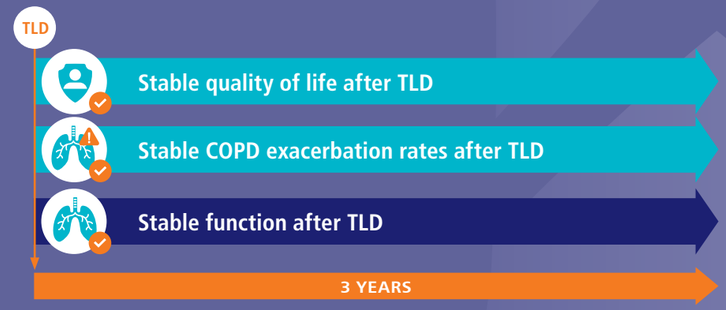
The Nuvaira Lung Denervation System is the first pulmonary product to successfully apply to France's National Authority for Health (HAS) Forfait Innovation program. The program grants temporary funding to evaluate CE marked devices that are deemed to be truly innovative in a rigorous clinical trial to confirm a significant clinical benefit, filling an unmet medical need and leading to a simplified market access pathway.

TLD Impact on Two Year Outcomes[20]



Lower Risk of Severe Exacerbation in COPD Patients with TLD

Observed Clinical Stability after Three Years[21,22]



AIRFLOW 2 Results Provided Solid Basis for AIRFLOW 3

The Nuvaira Lung Denervation System has been designated as a Breakthrough Device by the US Food and Drug Administration (FDA). This program creates an expedited pathway for prioritized FDA review of devices that have potential to provide more effective treatment or diagnosis of life-threatening or irreversibly debilitating diseases or conditions. In March 2021, the FDA's review of safety data on the first 50 patients enrolled in Nuvaira's AIRFLOW 3 pivotal trial resulted in full IDE approval for completion of the 400-patient study, and in April, the Centers for Medicare & Medicaid Services (CMS) approved the AIRFLOW 3 trial for the purposes of Medicare coverage (42 CFR 405 Subpart B).

AIRFLOW 3 Is Now Enrolling

The AIRFLOW 3 trial will be comprised of up to 400 patients across sites in the United States and Europe with the primary endpoint being a comparison of the probability of subjects having a moderate or severe exacerbation between the treatment arm and the sham-control group at one year post procedure.

INCLUSION CRITERIA
40+ years old
BMI 18–35
25–80% FEV_1 predicted and FEV_1 / FVC < 70% post-bronchodilator
2+ moderate (OCS and/or antibiotics treatment) or 1+ severe (ER or hospitalization) COPD exacerbations in the past year
CAT ≥ 10
Non-smoking / Non-vaping for 2+ months
Candidate for bronchoscopy and general anesthesia
Current flu vaccine (or willingness to be vaccinated when available)
Resting SpO_2 ≥ 89% on room air

EXCLUSION CRITERIA
Ongoing GI-related symptoms (severe uncontrolled GERD or severe dysphagia, gastroparesis, or recent major GI surgery)
Diagnosis of active non-COPD lung disease
Clinically relevant bronchiectasis
Current diagnosis of active asthma
MI < 6 months, EKG evidence of life-threatening arrythmias or acute ischemia
Pre-existing documented LVEF < 40%, stage C or D ACC/AHA or Class III or IV (NYHA) CHF
Diagnosed pulmonary hypertension with clinical evidence of CV function impairment (peripheral edema, sustained mPAP > 25 mmHg at rest (right hearth cath), or estimated RVSP > 50 mmHg echo)
Radiation or chemo treatment within 1 year of consent
> 10 mg daily prednisone or equivalent

Pulmonary Rehab: Not required for this trial. If patient is currently in rehab, wait 3 months after completion before consenting.

Endobronchial Valves: Patients may be eligible if EBV implant > 1 year. Or EBV explant > 3 months and implant > 1 year.

Opioids: Low dose use allowed for valid medical condition.

Trial Locations Include

TREATMENT LOCATIONS IN THE UNITED STATES

FirstHealth of the Carolinas
Pinehurst, NC

University of Michigan Health
Ann Arbor, MI

Washington University Medical Center
St. Louis, MO

Medical University of South Carolina
Charleston, SC

Beth Israel Lahey Health
Burlington, MA

Suburban Lung Associates
Elk Grove Village, IL

The Ohio State University Wexner Medical Center
Columbus, OH

Temple Health Lung Center
Philadelphia, PA

Ascension St. Vincent's
Jacksonville, FL

University of Louisville Health
Louisville, KY

Houston Methodist Hospital
Houston, TX

University of Pittsburgh Medical Center
Pittsburgh, PA

Spectrum Health
Grand Rapids, MI

Duke University Medical Center
Durham, NC

Harbor-UCLA Medical Center
Torrance, CA

UC Davis Health
Sacramento, CA

University of Alabama Lung Health Center
Birmingham, Alabama

St. David's Medical Center
Georgetown, TX

The University of Chicago Medicine
Chicago, IL

Honor Health
Phoenix, AZ

TREATMENT LOCATIONS IN EUROPE

Klinik Floridsdorf
Vienna, Austria

Thoraxklinik Universitatsklinikum Heidelberg
Heidelberg, Germany

CHU de Grenoble
Grenoble, France

CHU de Reims
Reims, France

Nouvel Hôpital Civil
Strasbourg, France

Claude-Bernard - Hôpital Bichat
Paris, France

Hôpital Larrey
Toulouse, France

Hôpital Arnaud de Villeneuve
Montpellier, France

Hôpital Pasteur
Nice, France

Hôpital de la Cavale Blanche
Brest, France

Royal Brompton Hospital
London, UK

University Medical Center Groningen
Groningen, Netherlands

Amsterdam UMC
Amsterdam, Netherlands

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Common potential risks associated with the TLD procedure include, but are not limited to, worsening of COPD symptoms (shortness of breath, increased cough, COPD exacerbations), coughing up blood tinged mucous, difficulty swallowing, chest pain, upset stomach or feeling of fullness, trouble processing food, and fever.

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