# A Multicenter, Randomized, Sham-controlled Study to Evaluate Safety and Efficacy After Treatment with the Nuvaira* Lung Denervation System in Subjects with Chronic Obstructive Pulmonary Disease (COPD)

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Primary objective: To evaluate the efficacy of targeted lung denervation (TLD) in addition to optimal medical care to reduce moderate or severe exacerbations and related hospitalizations, compared with optimal medical care alone, in subjects with...

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| **Ethical review** | Approved WMO |
| **Status** | Recruiting |
| **Health condition type** | Respiratory disorders NEC |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON55508

**Source**
ToetsingOnline

**Brief title**
AIRFLOW 3

### Condition

- Respiratory disorders NEC

**Synonym**
chronic bronchitis, COPD

**Research involving**

Human

## Sponsors and support

**Primary sponsor:** NUVAIRA inc.
**Source(s) of monetary or material Support:** Door industrie;zie hieronder

## Intervention

**Keyword:** Bronchoscopy, COPD, RF ablation, Vagal nerve

## Outcome measures

**Primary outcome**

Moderate or severe COPD exacerbations through 12 months;

For the purpose of this study a COPD exacerbation will be defined as a complex

of respiratory events/symptoms (increase or new onset) of more

than one of the following: cough, sputum, wheezing, dyspnea or chest tightness

with at least one symptom lasting at least three days requiring treatment with

antibiotics and/or systemic steroids (moderate exacerbation) and/or

hospitalization (severe exacerbation). (Vogelmeier, 2011)

The primary analysis of the primary endpoint is defined as a comparison of the

probability of subjects having a moderate or severe COPD exacerbation (primary

endpoint event) between the Active Treatment arm and the Sham Control arm based

on a log-rank test, and will be based on the time from the date of

randomization to the date of a subject*s first primary endpoint event, or to

the close date of the 12-month visit window for subjects who do not experience

a primary endpoint event. Subjects who have not experienced a primary endpoint

event and are lost-to-follow-up or

withdrawn prior to the close of the 12-month visit window will be censored at

the date of their last known status.

**Secondary outcome**

1. Time to first severe COPD exacerbation (defined as a comparison between study arms of the survival distributions for events based on log-rank tests). Time frame: randomization to 12 months.

2. Time to first severe COPD exacerbation (defined as a comparison between study arms of the survival distributions for events based on log-rank tests), only for the subgroup of subjects who had a severe COPD exacerbation in the year prior to randomization. Time frame: randomization to 12 months.

3. Change in SGRQ-C (defined as a comparison between study arms of the mean change in SGRQ-C based on a linear model for change in SGRQ-C, adjusted for baseline SGRQ-C). Time frame: randomization to 12 months.

4. Change in FVC (defined as a comparison between study arms of the mean change in FVC based on a linear model for change in FVC, adjusted for baseline FVC). Time frame: randomization to 12 months.

5. Change in FEV1 (defined as a comparison between study arms of the mean change in FEV1 based on a linear model for change in FEV1, adjusted for baseline FEV1). Time frame: randomization to 12 months.

6. Transition Dyspnea Index (TDI) (defined as a comparison between study arms of the TDI based on a linear model for change in TDI). Time frame: randomization to 12 months.

7. Change in RV (defined as a comparison between study arms of the mean change in RV based on a linear model for change in RV, adjusted for baseline RV). Time frame: randomization to 12 months.

8. Time to first respiratory-related hospitalization (defined as a comparison between study arms of the survival distributions for events based on log-rank tests). Time frame: randomization to 12 months.

9. Change in SF-36 total score (defined as a comparison between study arms of the mean change in SF-36 total score based on a linear model for change in SF-36 total score, adjusted for baseline SF-36 total score). Time frame: randomization to 12 months.

10. CAT responders (defined as a comparison between study arms of the proportion of subjects with a >=2 point decrease in CAT). Time frame: randomization to 12 months.

## Study description

**Background summary**

It is well known that increased smooth muscle tone in patients with Chronic Obstructive Pulmonary Disease (COPD) is due in part to increased parasympathetic drive. Pharmacologic blockade of vagus nerve input to airway smooth muscle in the human lung leads to improvements in lung function and overall health status. Once daily-inhaled tiotropium improves peak flow by 25% and causes a 9% sustained improvement in the forced expiratory volume in one second (FEV1) in patients with COPD with a baseline FEV1 <= 65% of predicted. It is also known that mechanical disruption of the vagus nerve as it passes between the brain and the lung can also lead to improvements in pulmonary function. Intrathoracic bi-lateral vagotomy was investigated as a treatment for COPD and asthma as early as the 1940s, and most recently in the 1980s. In patients with severe COPD, surgical resection of the vagus nerve led to a 30% improvement in FEV1 in one patient with severe COPD. In severe asthma, vital capacity (VC) has also been shown to improve from 2.36 L to 2.79 L (18%) and maximal voluntary ventilation (a parameter linearly related to FEV1) increased from 43 L/min to 50 L/min (16%). Prior to vagotomy, histamine caused a 25% reduction in VC compared to only 9% after vagotomy. Sputum production was essentially stopped in 8/11 patients with heavy sputum. However, due to a high risk of procedure related mortality (as high as 28%) following bilateral thoracotomies, surgical resection of the vagus nerve in the lung has never been

routinely practiced. More recently, knowledge of the long-term effects of lung denervation has been demonstrated in two patient populations: 1) lung transplant patients; and, 2) patients who received sleeve resections (removal of the mainstem bronchus and associated airway nerve trunks) as treatments for lung cancer. Lung transplant recipients have both vagus nerve fibers and bronchial arteries severed during surgery. In the early days of lung transplantation, there was a concern that lung denervation would lead to worsened physiologic function (i.e. decrease of Hering-Breuer reflex, decrease of cough reflex). These issues have not been observed did not come to bear, and lung transplant patients have not been found to have to have any clinical issues due to their lung denervation. In lung cancer patients, it has been shown that there is no difference in outcomes, stage by stage, for patients who received a sleeve resection versus a traditional pneumonectomy for treatment. It is generally believed that airway nerve trunk branches of the vagus nerves that influence airway smooth muscle constriction do not re-grow following transplantation, though there is some evidence that afferent sensory pathways may regenerate over time. Four previous studies, IPS-I (NCT01483534), IPS-II (NCT01716598) and AIRFLOW 1 and 2 (NCT02058459) have established feasibility and safety of targeted lung denervation (TLD) therapy in the COPD population utilizing the TLD-system. In the AIRFLOW 1 also the optimal dose was established. This AIRFLOW-3 study is FDA trial that will investigate the efficacy and safety of the treatment.

**Study objective**

Primary objective: To evaluate the efficacy of targeted lung denervation (TLD) in addition to optimal medical care to reduce moderate or severe exacerbations and related hospitalizations, compared with optimal medical care alone, in subjects with chronic obstructive pulmonary disease (COPD).
Secondary objective: To evaluate the long-term safety and other efficacy assessments of targeted lung denervation (TLD) in addition to optimal medical care compared with optimal medical care alone.

**Study design**

This is a prospective, multi-center, randomized, sham-controlled, double-blind (subject and follow-up assessor(s)), safety and efficacy study.

**Intervention**

Bronchoscopic targeted lung denervation (TLD) treatment with the Nuvaira* Lung Denervation System.

**Study burden and risks**

Risks associated with the Nuvaira-system are minimized by design. Risks are

minimized under this protocol due to: - Operators with a high degree of experience in interventional bronchoscopy - Extensive non-clinical evaluation of the device and therapy (animal and bench top testing) - The use of standard medical grade materials in the manufacture of the device - The well-established nature of the bronchoscopic procedure and technique used to perform this procedure - Use of RF energy which is well understood in medical applications based upon literature review and pre-clinical evaluations performed to date, it is expected that TLD therapy may provide some benefit to the subject; however, there may be no direct benefits of study participation. However, subject participants will undergo an enhanced level of clinical scrutiny of pulmonary health compared to routine clinical care, which may provide some indirect health benefits.

## Contacts

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## Trial sites

### Listed location countries

Netherlands

## Eligibility criteria

**Age**
Adults (18-64 years)
Elderly (65 years and older)

## Inclusion criteria

1) Subject >=40 years of age at the time of consent;
2) Women of child bearing potential must not be pregnant, evidenced by a negative pregnancy test (blood or urine) pre-treatment, or lactating and agree not to become pregnant for the duration of the study;
3) Smoking history of at least 10 pack years;
4) Not smoking or using any other inhaled substance (e.g., cigarettes, vaping, cannabis, pipes) for a minimum of 2 months prior to consent and agrees to not start for the duration of the study;
5)Subject has received a flu vaccination within the 12 months prior to the procedure or agrees to obtain vaccination once it becomes available and agrees to annual vaccinations for the duration of the study;
6) SpO2 >=89% on room air at the time of screening;
7) CAT score >=10 at the time of screening;
8) Diagnosis of COPD with 25% <= FEV1 <=80% of predicted, PaCO2 < 50 (if FEV1 <30%) and FEV1/FVC <70% (post-bronchodilator);
9) Documented history of >= 2 moderate COPD exacerbations or >= 1 severe COPD exacerbation leading to hospitalization in the 12 months prior to consent with at least one exacerbation occurring
while the subject was on optimal medical care (taking a LAMA and a LABA, or scheduled SABA or SAMA instead of either a LAMA or a LABA, not both, as regular respiratory maintenance
medication);
10)Subject is on optimal medical care at the time of consent;
11) If subject has participated in a formal pulmonary rehabilitation program recently, program completion must have occurred >=3 months prior to consent; if in a maintenance program, subject agrees to continue their current program through their 12-month follow-up visit;
NOTE: Prior participation in a pulmonary rehabilitation program is not required for inclusion in the study.
12) Subject is a candidate for bronchoscopy in the opinion of the physician investigator or per hospital guidelines and is able to discontinue blood thinning medication peri-procedurally;
13) The subject is able and agrees to complete all protocol required baseline and follow up tests and assessments including taking certain medications (e.g., azithromycin, prednisolone / prednisone);
14) Subject has provided written informed consent using a form that has been reviewed and approved by the Institutional Review Board (IRB) / Ethics Committee (EC).

## Exclusion criteria

1) Body Mass Index <18 or >35;

2) Subject has an implantable electronic device and has not received appropriate medical clearance;;
3) Uncontrolled diabetes in the opinion of the investigator;
4) Malignancy treated with radiation or chemotherapy within 1 years of consent;
5) Asthma as defined by the current Global Initiative for Asthma (GINA) guidelines;
6)Subject diagnosed with a dominant non-COPD lung disease or condition affecting the lungs which is the main driver of the subjects clinical symptoms (e.g., cystic fibrosis, paradoxical vocal cord motion, eosinophilic granulomatosis with polyangiitis (EGPA), allergic bronchopulmonary aspergillosis, interstitial lung disease or active tuberculosis) or has a documented medical history of pneumothorax within 1 years of consent;
7) Clinically relevant bronchiectasis, defined as severe single lobe or multilobar bronchial wall thickening associated with airway dilation on CT scan leading to cough and tenacious sputum on most days;
8) Pre-existing diagnosis of pulmonary hypertension, clinical evidence of pulmonary hypertension,
(cardiovascular function impairment including peripheral edema) and mPAP >=25 mmHg at rest by right heart catheterization (or estimated right ventricular systolic pressure >50 mmHg by
echocardiogram if no previous right heart catheterization)
9) Myocardial infarction within last 6 months, EKG with evidence of life threatening arrhythmias or acute ischemia, pre-existing documented evidence of a LVEF <40%, stage C or D (ACC/AHA) or Class III or IV (NYHA) congestive heart failure, or any other past or present cardiac findings that make the subject an unacceptable candidate for a bronchoscopic procedure utilizing general anesthesia;
10) Surgical procedures(s) on the stomach, esophagus or pancreas performed <=2 years prior to consent or ongoing related symptoms within the past year;
11)Symptomatic gastric motility disorder(s) (e.g. gastroparesis) as evidenced by GCSI score >=18.0, severe uncontrolled GERD (e.g., refractory heartburn, endoscopic esophagitis) or severe dysphagia (e.g., esophageal stricture, achalasia, esophageal spasm); NOTE: Subjects with a hiatal hernia are allowed if subject meets all other enrollment criteria.
12) Any disease or condition that might interfere with completion of a procedure or this study (e.g., structural esophageal disorder, life expectancy <3 years);
13) Prior lung or chest procedure (e.g., lung transplant, LVRS, BLVR, lung implant, metal stent, valves, median sternotomy, bullectomy, lobectomy, segmentectomy or other interventional lung or chest procedure) performed <=1 year of consent);
14) Daily use of >10 mg of prednisone or its equivalent at the time of consent;
15) Chronic use of *40 mg MEDD opioid only medication per day;
16) Known contraindication or allergy to medications required for bronchoscopy or general anesthesia (e.g., lidocaine, atropine, propofol, sevoflurane) that cannot be medically controlled;
17) Baseline chest CT scan reveals bronchi anatomy cannot be fully treated with

available catheter sizes, presence of severe emphysema >50% lobar attenuation area or severe bullous disease (>1/3 hemithorax) (as determined by the CT core lab using a single density mask threshold of -950 HU) or discovery of a mass that requires treatment;
18) Subject is currently enrolled in another interventional clinical trial that has not completed follow-up.

# Study design

## Design

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| Study type: | Interventional |
| Intervention model: | Crossover |
| Allocation: | Randomized controlled trial |
| Masking: | Double blinded (masking used) |
| Control: | Placebo |
| Primary purpose: | Treatment |

## Recruitment

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| Recruitment status: | Recruiting |
| Start date (anticipated): | 04-07-2019 |
| Enrollment: | 65 |
| Type: | Actual |

# Ethics review

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| Approved WMO Date: | 24-06-2019 |
| Application type: | First submission |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 23-08-2019 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |

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| Approved WMO Date: | 01-04-2020 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 24-08-2020 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 06-10-2021 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 05-07-2022 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 31-10-2022 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 08-03-2023 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |

# Study registrations

## Followed up by the following (possibly more current) registration

No registrations found.

## Other (possibly less up-to-date) registrations in this register

No registrations found.

## In other registers

| Register | ID |
| --- | --- |
| ClinicalTrials.gov | NCT03639051 |
| CCMO | NL68937.042.19 |