A pRospective, multicenter, single-arm study EvaLuating the safety and feasIbility of Targeted Lung Denervation (TLD) for the trEatment of severe asthma.

Published: 13-04-2017
Last updated: 11-04-2024

Evaluate safety and technical feasibility of TLD Therapy in the treatment of patients with severe asthma.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Respiratory disorders NEC
Study type	Interventional

Summary

ID

NL-OMON45521

Source
ToetsingOnline

Brief title
RELIEF 1

Condition

- Respiratory disorders NEC

Synonym
Asthma, lung disease

Research involving
Human

Sponsors and support

Primary sponsor: NUVAIRA, Inc
Source(s) of monetary or material Support: Door industrie zie hieronder (NUVAIRA Inc.)

Intervention

Keyword: Asthma, Bronchoscopy, RF ablation, Vagal nerve

Outcome measures

Primary outcome

Primary Safety Outcome:

Freedom from device related therapeutic interventions at 7 days and 1, 3, 6 and 12 months. Therapeutic interventions are defined as administration of non-protocol required antibiotics or steroids, an endoscopic procedure or surgery to treat findings and/or conduction of another diagnostic test to assess the treatment area due to safety concerns.

Secondary outcome

Secondary Outcome Measures:

1. Device success

2. Technical success

3. Change in Asthma Quality of Life Questionnaire (AQLQ) score (absolute and symptom score)

4. Change in Asthma Control Questionnaire (ACQ)

5. Change in Leicester Cough Questionnaire (LCQ)

6. Rate of respiratory and non-respiratory adverse events

7. Change in morning and evening peak expiratory flow (PEF)

8. Change in pre-and post-bronchodilator FEV1

9. Change in methacholine PC20

10. Change in rescue medication usage

11. Number and level of asthma exacerbations

12. Respiratory-related unscheduled physician office visits

13. Emergency department visits and hospitalizations

14. Change in inflammatory markers and bronchoscopic specimens

15. Change in CT scan measurements

Study description

Background summary

Acetylcholine release from parasympathetic nerves activates muscarinic receptors present on airway smooth muscle, submucosal glands, and blood vessels to cause bronchoconstriction, mucus production and vasodilation, respectively. In asthma and chronic obstructive pulmonary disease (COPD), bronchoconstriction and mucus secretion is increased and the airways are hyperresponsive to acetylcholine. Previous COPD studies, IPS-I (NCT01483534), IPS-II (NCT01716598) and AIRFLOW-1 (NCT02058459) have established feasibility and safety of TLD therapy in the COPD population as well as establish the optimal energy level. A fourth clinical study, AIRFLOW-2 (NCT02058459) which began enrollment in 2016, is enrolling COPD patients in a randomized vs. sham control study design. RELIEF-1 is the first study aimed at establishing safety and feasibility of TLD in the severe asthma population and is expected to support future larger population trials with this disease. This study is not statistically powered to assess efficacy outcomes.

Hypotesis:TLD Therapy will be a safe and feasible method to ablate the airway nerve trunks that travel parallel to and outside of the main bronchi and into the lungs to achieve TLD and potentially improve breathing and reduce acute attacks (exacerbations) for patients suffering from severe asthma.

Study objective

Evaluate safety and technical feasibility of TLD Therapy in the treatment of patients with severe asthma.

Study design

Prospective, multicenter, single-arm (non-randomized) study. All patients will undergo a run in period on optimal medical therapy as part of eligibility testing. After additional baseline screening but prior to the procedure all patients will take a course of steroids prior to the procedure. Final determination to initiate treatment will be made after initial airway inspection. A total of 30 patients will be treated. Inflammatory biomarkers (washes and brushings) will be collected in all patients and bronchial biopsies will be collected from the last 15 patients. Matching samples will be collected during a required bronchoscopic follow up. All patients will be prescribed peri-procedural antibiotics and/or steroids to minimize procedural risks. All patients will be provided a mobile handheld spirometer to measure and record daily peak expiratory flow values both before and after treatment to monitor lung function. Patient follow-up will be conducted out to 3 years.

Intervention

Bronchoscopically guided Targeted Lung Denervation (TLD) Therapy with the Nuvaira-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. Adult; age *21 to *65;
2. Patient has provided written informed consent using a form that has been reviewed and approved by the Ethics Committee;
3. Diagnosis of severe asthma as defined by the 2017 GINA Report, and are taking regular maintenance medication that includes: a) Inhaled corticosteroid (ICS) at a dosage >1000*g beclomethasone per day or equivalent, AND b) Long-acting *-agonist (LABA) at a dosage of *100*g Salmeterol per day or equivalent (MDI prn); -or- a) Inhaled corticosteroid (ICS) at a dosage >1000*g beclomethasone per day or equivalent, AND b) Leukotriene receptor antagonist (LTRA) or theophylline; And may be taking other add-on medications including (but not limited to): * Tiotropium; *Oral corticosteroids (OCS) at a dosage of *10mg per day. Note: Subjects on a dosage regimen of 20mg OCS every other day may be included as this averages to a daily dose of 10mg.
4. Pre-bronchodilator FEV1 *60% predicted on stable therapy after a 4-week medication run-in of an inhaled corticosteroid (>1000*g beclomethasone per day or equivalent) and a long-acting *-agonist (*100 *g Salmeterol per day or equivalent MDI prn);
5. Subject has at least two days of asthma symptoms during the 4-weeks of the Baseline Diary Period;
6. Women of child bearing potential must have a negative pregnancy test (serum or urine) at screening and agree not to become pregnant for the duration of the study;
7. Non-smoker for at least 6 months (if former smoker, less than 10 pack years total smoking history) and agree to continue not smoking for duration of the study;
8. Patient is a candidate for bronchoscopy in the opinion of the physician or per hospital

guidelines;
NOTE: Examples of suitability of patients for bronchoscopy include, but are not limited to:
* Cardiovascular fitness
* Ability of patient to be intubated
* Ability to oxygenate patient
* Absence of previously diagnosed high-grade tracheal obstruction
* Absence of uncorrectable coagulopathy
9. Patient is a candidate to undergo methacholine challenge testing in the opinion of the physician;(e.g., does not have uncontrolled hypertension, history of MI or stroke within 3 months prior to the test, aortic or cerebral aneurysm);
10. The patient is willing, able and agrees to complete all protocol required baseline and follow up testing assessments and comply with medication requirements.

Exclusion criteria

1. In the 24 months prior to enrollment, the subject has:
* Been intubated for asthma
* Had intensive Care Unit admission(s) for asthma
* Been treated with immunosuppressant therapy for any reason (steroids excluded)
2. In the 12 months prior to enrollment, the subject has had:
* * 3 lower respiratory tract infections requiring antibiotics
* * 3 hospitalizations for asthma exacerbations
3. In the 3 months prior to enrollment, the subject has taken/used an opioid(s)
4. In the 6 weeks prior to enrollment the subject had a lower respiratory tract infection or asthma exacerbation that required:
* antibiotics
* unscheduled physician visits for asthma care
* changes in use of asthma maintenance medication
* taking of rescue medication over normal dose in a 24-hour period for asthma symptoms
* a steroid burst (pulse)
NOTE: Prophylactic use of rescue medication for exercise is not counted in daily totals.
5. Current use of oral steroids >10mg at the time of enrollment;
6. History of poor medication compliance;
7. Prior lung or chest procedure (i.e. bronchial thermoplasty, metal stent, median sternotomy, etc.);
8. Other chronic pulmonary disorders associated with asthma-like symptoms, including (but not limited to) cystic fibrosis, chronic obstructive pulmonary disease, chronic bronchitis, vocal cord dysfunction eosinophilic granulomatosis with polyangiitis (EGPA), previously called the Churg-Strauss syndrome (CSS), or interstitial lung disease that is the sole cause of asthma symptoms, severe scoliosis or chest wall deformities that affect lung function, or congenital disorders of the lungs or airways;
9. Pre-existing diagnosis of pulmonary hypertension, defined as a sustained elevation of the mean pulmonary artery pressure greater than or equal to 25 mm Hg at rest by right heart catheterization or estimated by echocardiogram to be greater than 40 mm Hg;
10. Uncontrolled diabetes as evidenced by an HbA1c >7%;

11. Patient has an implantable electronic device;
12. Known contraindication or allergy to anticholinergic drugs or components;
13. Known contraindication or allergy to medications required for bronchoscopy or general anesthesia (such as lidocaine, atropine, propofol, sevoflurane, etc.) or peri-procedural therapy (i.e. prednisone, azithromycin) that cannot be medically controlled;
14. Based on investigator judgment, the patient is unable to stop taking blood thinning medication (with the exception of aspirin) 7 days before and not re-start until 7 days after the study procedure;
15. Documented history of untreated severe (AHI index >30/hr) obstructive sleep apnea;
16. The patient has any disease or condition that might interfere with completion of a procedure or this study or patient safety (e.g., structural esophageal disorder, bronchiectasis, pneumothorax, pleural effusion, life expectancy <3 years);
17. Screening Chest CT Scan reveals bronchi anatomy cannot be fully treated with the available catheter sizes or discovery of a pulmonary nodule requiring follow-up or intervention unless proven benign;
18. Patients who had abdominal surgical procedures on stomach, esophagus or pancreas (esophagectomy, gastrostomy, gastrectomy, bariatric surgery, fundoplication, vagotomy, etc.);
19. Patients with a GCSI score *18.0 prior to treatment;
20. Patient is currently enrolled in another clinical trial that has not completed follow-up.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	09-01-2018
Enrollment:	10
Type:	Actual

Ethics review

Approved WMO Date:	13-04-2017
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	13-09-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	06-03-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	31-10-2018
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	NCT02872298
CCMO	NL59938.042.16