A Sequential Two Phase Multicenter, Randomized Study to Optimize Dose Selection and Evaluate Safety After Treatment with the Holaira* Lung Denervation System in Patients with Moderate to Severe COPD.

Published: 06-08-2014
Last updated: 21-04-2024

Phase A: To evaluate the safety and feasibility of the Holaira System at two energy levels in order to establish the optimal energy dose.Phase 2: To compare the safety and feasibility outcomes between the Holaira System vs. a Sham-control group...

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

Summary

ID

NL-OMON44168

Source
ToetsingOnline

Brief title
AIRFLOW

Condition

- Respiratory disorders NEC

Synonym
chronic bronchitis, COPD

Research involving

Human

Sponsors and support

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

Intervention

Keyword: Bronchoscopy, COPD, RF ablation, Vagal nerve

Outcome measures

Primary outcome

Phase A: Rate of bronchoscopic airway effects that require a therapeutic

intervention through 3 months

Phase 2: Rate of respiratory related adverse events between 3 and 6.5 months

Secondary outcome

Change in:

* Spirometry Measures (FEV1, FVC, FEV1/FVC)

* Plethysmography measures (ex. Raw, sGaw, TLC, IC, etc.)

* Exercise testing: Cycle Ergometery & 6MWT

* Heath-related Quality of Life (SGRQ-C, CAT, EQ-5D)

* Chest CT assessment

* Number of adverse events through 3 years

* Acute Procedure Success

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. We hypothesize that Targeted Lung Denervation Therapy will be a safe method to ablate the nerve trunks that travel parallel to and outside of the main bronchi and into the lungs to achieve Targeted Lung Denervation.

Two previous studies, IPS-I (NCT01483534) and IPS-II (NCT01716598) have established feasibility of targeted lung denervation (TLD) therapy in the COPD population utilizing the Holaira System. Two separate energy doses were utilized in these studies and a lower limit of efficacy was established with the lower dose. Further clinical investigation is indicated to confirm safety

and performance at an optimal energy level.

Study objective

Phase A: To evaluate the safety and feasibility of the Holaira System at two energy levels in order to establish the optimal energy dose.
Phase 2: To compare the safety and feasibility outcomes between the Holaira System vs. a Sham-control group utilizing the optimal energy dose.

Study design

A prospective, sequential two phase multicenter, randomized double-blind (subject and follow-up team), safety and feasibility study with unblinding at the 6 month follow up interval. The goal of Phase A will be to compare two energy doses and select the optimal energy dose to be utilized in Phase 2. The goal of Phase 2 is to compare the optimal energy dose to a Sham-control. All subjects will be followed for a minimum of 3 years.

Intervention

Bronchoscopically guided Targeted Lung Denervation (TLD) Therapy with the Holaira-System.

Study burden and risks

Risks associated with the Holaira-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. Diagnosis of COPD with FEV1 30% to 60% and FEV1/FVC <70% (post-bronchodilator);
2. mMRC grade * 2 or CAT score * 10 at the time of enrollment
3 Positive relative change in FEV1 and/or FVC of >12% and >200 mL following administration of ipratropium bromide during reversibility testing (only phase A);
4. Patient *40 and *75 years of age at the time of consent;
5. 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;
6. Smoking history of at least 10 pack years;
7. Non-smoking for a minimum of 2 months prior to consent and agrees to not smoke for the duration of the study;(Negative nicotine test required, unless subject is currently taking smoking cessation medication, patch, gum, etc.)
8. Participated in a pulmonary rehabilitation program and/or confirmed to have been engaged or attempted regular physical activity under professional supervision in the past 12 months and agrees to continue or restart regular physical activity for duration of study;
9. Current influenza vaccination and/or pneumococcus vaccination consistent with local recommendations and/or policy;
10. Patient is a candidate for bronchoscopy in the opinion of the physician or per hospital guidelines;

11.The patient is willing, able and agrees to complete all protocol required baseline and follow up testing assessments including taking and abstaining from certain medications (e.g., tiotropium bromide capsules);
12.Patient has provided written informed consent using a form that has been reviewed and approved by the Ethics Committee (EC).

Exclusion criteria

1. Has been <6 weeks (from start of testing) following the resolution of a COPD exacerbation or active lower respiratory infection (e.g. pneumonia); (NOTE: The start of testing may be delayed in order to accommodate this requirement.)
2. History of recurrent respiratory infections and/or COPD exacerbations (more than 2 hospitalizations within 1 year of enrollment);
3. Prior lung or chest procedure (e.g. lung transplant, LVRS, BLVR, lung implant, metal stent, valves, coils, median sternotomy, bullectomy, segmentectomy or lobectomy, etc);
4. Documented history of asthma diagnosed with onset <30 years of age, cystic fibrosis, tuberculosis, paradoxical vocal cord motion, Churg-Strauss syndrome, allergic bronchopulmonary aspergillosis or severe interstitial lung disease or active tuberculosis;
5.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;
6. Pulmonary nodule requiring follow-up or intervention unless proven benign;
7. Inability to perform exercise tolerance testing without physical assistance; (Note: normal walking aids allowed (e.g. cane, walker))
8. Malignancy treated with radiation or chemotherapy within the last 2 years;
9. Failed Cardiac Clearance: defined as myocardial infarction within last 6 months, EKG with evidence of life threatening arrhythmias or acute ischemia, pre-existing documented evidence of an LVEF <45%, 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 patient not an acceptable candidate for a bronchoscopic procedure utilizing general anesthesia;
10. Patient has an implantable electronic device;
11. Patient has a PaO2 *7.3 kPa (55 mm Hg) and/or a PaCO2 >8.0 kPa (60 mm Hg) on room air;
12. Uncontrolled diabetes as evidenced by an HbA1C >7%;
13. Known coagulopathy;
14. Known hypersensitivity to anticholinergic drugs or components;
15. Known allergy to medications required for bronchoscopy or general anesthesia (such as lidocaine, atropine, propofol, sevoflurane) that cannot be medically controlled;
16. 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;
17. Daily use of >10 mg of prednisone or its equivalent at the time of enrollment;
18. Documented history of untreated severe (AHI index >30/hr) obstructive sleep apnea;
19. Body Mass Index <18 or >33 male/34 female
20. The patient has any disease or condition that might interfere with completion of this

study (e.g., life expectancy <3 years);
21. Patient is currently enrolled in another clinical trial that has not completed follow-up;
22. Screening Chest CT Scan reveals bronchi anatomy cannot be fully treated with available catheter sizes, presence of severe emphysema (as determined by the CT core lab).
23. In the opinion of the treating investigator, use of the Holaira System is not technically feasible due to patient anatomy or other clinical finding;
24. Previous diagnosis of Alpha 1-antitrypsin deficiency (defined as <0.8 g/l) (Phase A only);
25. Clinically relevant bronchiectasis;
26. Patients who had abdominal surgical procedures on stomach, esophagus or pancreas (e.g. Esophagectomy, Gastrostomy, Gastrectomy, Bariatric surgery, fundoplication, vagotomy);
27. Patients with a GCSI score *>18.0 prior to treatment;
28. Recent (<3 months ago) or narcotic use

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	13-08-2014
Enrollment:	25
Type:	Actual

Ethics review

Approved WMO

Date:	06-08-2014
Application type:	First submission

Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	16-10-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	30-10-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-03-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	26-11-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	20-01-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	23-06-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	25-07-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	22-09-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	18-05-2018
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	NCT02058459
CCMO	NL48849.042.14