NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of endobronchial nerve ablation for chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease is the name for a group of lung conditions including emphysema and chronic bronchitis. The airways in the lungs become narrowed and secrete too much mucus, causing breathing difficulties.

In this procedure, a bronchoscope (a tube with a camera on the end) is passed through the mouth or nose and into the lungs. A balloon and an electrode are used to destroy (ablate) the nerves on the outside of the airway (endobronchial nerves) using radiofrequency energy, to widen the airway and reduce mucus production. The aim is to improve breathing.

Contents

Abbreviations

Word or phrase	Abbreviation
Chronic obstructive pulmonary disease	COPD
Chronic obstructive pulmonary disease adverse event	COPDAE
Gastrointestinal	GI
EuroQol 5 dimensions	EQ-5D-5L
EuroQol visual analogue scale	EQ-5D VAS
Forced expiratory volume in 1 second	FEV1
Forced vital capacity	FVC
Pulmonary function tests	PFTs
Randomised controlled trial	RCT
Radiofrequency	RF
Residual volume	RV
Standard deviation	SD
Serious adverse event	SAE
St George's Respiratory Questionnaire – COPD specific version	SGRQ-C
Targeted lung denervation	TLD
Total lung capacity	TLC
Watt	W

Introduction

The National Institute for Health and Care Excellence (NICE) prepared this interventional procedure overview to help members of the interventional procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and professional opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in March 2021.

Procedure name

- Endobronchial nerve ablation for chronic obstructive pulmonary disease

Professional societies

- British Thoracic Society
- Primary Care Respiratory Society UK
- Association of Respiratory Nurse Specialists
- Royal College of Physicians
- Royal College of Physicians and Surgeons of Glasgow
- Royal College of Physicians of Edinburgh.

Description of the procedure

Indications and current treatment

COPD includes emphysema and chronic bronchitis. It's a common condition that mostly affects middle-aged and older adults. Approximately 4.5% of over 40s in the UK have diagnosed COPD. The main cause of COPD is smoking. The main symptoms are breathlessness, a persistent cough and wheezing, and frequent chest infections. COPD gradually gets worse over time and people can have sudden flare-ups (exacerbations).

Although the damage to the lungs caused by COPD is permanent, treatment can help slow disease progression. Treatments include stopping smoking, pulmonary rehabilitation, inhaled beta 2 agonists, antimuscarinic and steroid inhalers, oral medication such as bronchodilators, mucolytics and steroids, and oxygen. In a very small number of people, surgery or lung transplant may be indicated.

What the procedure involves

In COPD, acetylcholine released from parasympathetic airway nerve fibres mediates smooth muscle tone, reflex bronchoconstriction, mucus hyper-secretion and airway inflammation. This procedure disrupts parasympathetic signalling to

the lungs and decreases neuronal release of acetylcholine. The aim is to produce permanent bronchodilation, decrease mucus production and improve breathing.

Endobronchial nerve ablation is a minimally invasive outpatient procedure carried out under general anaesthesia. A bronchoscope is used to visualise the airways and a dual-cooled radiofrequency (RF) catheter, which has a balloon and an electrode on the end, is positioned in the distal mainstem bronchus. Once in position, coolant is passed through the catheter and the balloon inflates, pressing the electrode against the airway wall. RF energy is then delivered from the electrode to ablate the parasympathetic nerves that run along the outside of the mainstem bronchus. The balloon is then deflated and rotated, and the ablation repeated until the whole circumference of the bronchus has been treated. Both main bronchi are treated during a single procedure. Most patients return home on the day of the procedure.

Outcome measures

Pulmonary function tests

Pulmonary function tests (PFTs) measure how well the lungs work and include tests that measure lung size and air flow. Key outcomes include:

- Forced expiratory volume in 1 second (FEV1) – the amount of air a person can blow out in one second.
- Forced vital capacity (FVC) – the total amount of air a person can blow out in 1 complete breath after taking a deep breath in.
- Residual volume (RV) – the volume of air remaining in the lungs after maximum forceful expiration (the volume of air that cannot be expelled from the lungs).

Health-related quality of life (HRQOL)

HRQOL measures used in the studies include:

- COPD-specific St George's Respiratory Questionnaire (SGRQ-C) – scores range from 0 to 100, with lower scores indicating better HRQOL (minimal clinically important difference (MCID) = 4 points).
- EuroQol 5-dimensions (EQ-5D-5L) – scores range from 0 to 1, higher scores indicate better HRQOL (MCID = 0.05 points).
- EuroQol visual analogue scale (EQ-5D VAS) – scores range from 0 to 100, higher scores indicate better HRQOL (MCID = 7 to 10 points).
- COPD Assessment Test (CAT) – scores range from 0 to 40, with lower scores indicating fewer symptoms (MCID = 2 points).

Exercise tolerance and dyspnoea

Exercise tolerance and dyspnoea measures used in the studies include:

- Modified Medical Research Council Scale (mMRC) – scores range from 0 to 4, with lower scores indicating less dyspnoea (MCID = 1 point).
- Baseline Dyspnoea Index and Transitional Dyspnoea IndeTDI) – scores range from -9 to 9, with lower scores indicating a lesser change in dyspnoea (MCID = 1 point).
- Borg scale – used to measure dyspnoea during sub-maximal exercise. Scores 0 to 10 with lower scores indicating less dyspnoea.
- Constant work rate cycle ergometry (CWRE)/cycle endurance – involves performing unloaded pedalling followed by increased work rate and cycling to the point of symptom limitation (measured in minutes).
- 6 minute walk test – involves measurement of the distance walked in 6 minutes (measured in metres).

Gastrointestinal (GI) symptoms

The Patient Assessment of Gastrointestinal Disorders Symptom Severity Index (PAGI-SYM) is used to measure GI symptoms. Scores range from 0 to 100, with higher scores representing more gastrointestinal symptoms.

Efficacy summary

Six studies were carried out by the same research group and used various iterations of the same lung denervation system produced by Nuvaira Inc (previously known as Holaira). The first in-human clinical trial of the procedure consisted of 22 patients receiving targeted lung denervation (TLD) as a staged procedure, 12 of whom received an energy determination of 20 W and 10 of whom received an energy determination of 15 W (Slebos 2015). The second clinical trial delivered TLD as a single procedure at 15 W among 15 participants (Valipour 2018). The third clinical trial comprised a total of 46 participants, 30 of whom were initially recruited as a dose evaluation study to compare 32 W energy (15 participants) with 29 W energy (15 participants) (Valipour 2019). A further 16 participants were later recruited into an open-label confirmation study to confirm GI safety (Valipour 2019). A further paper reported 2 and 3-year outcomes from this dose evaluation and open-label confirmation study (Pison 2021). The final study was a randomised controlled trial (RCT) of 82 participants, 41 of whom received TLD as a single procedure at 32 W and 41 of whom received a sham procedure (Slebos 2019). A further paper reported 2-year outcomes from this trial (Valipour 2020).

Technical success

In the first in-human clinical trial, technical feasibility (the ability to access the target areas of the main bronchus and deliver RF energy to the entire circumference of the bronchus at the target site) was 93% (Slebos 2015).

In the second clinical trial technical feasibility was 93%, with 1 patient receiving treatment in 7 out of 8 quadrants because of poor balloon contact (Valipour 2018). A staged procedure was done in 2 patients because of the airway size being larger than the balloon available at the time of the initial treatment (Valipour 2018).

In the third clinical trial acute procedure success was 97% (29/30) in the dose evaluation study, with 1 report of aphonia post-procedure because of the introduction of a rigid bronchoscope that required speech therapy and a 1-day lipofilling of the vocal cord (Valipour 2019). In the open-label confirmation study, acute procedure success was 94% (15/16), with the catheter unable to be re-inserted after removal for cleaning in 1 patient (Valipour 2019). In the confirmation study, there were more incomplete circumferential treatments in the right lung (45% with <4 activations) than in the dose evaluation study (16.7% with <4 activations) because of the proximity of the RF electrode to the oesophageal balloon (Valipour 2019).

In the RCT, device success (the ability to insert, place and remove the device) was 100% (Slebos 2019). Technical success (the ability to deliver RF energy to each intended location) was 90% (Slebos 2019).

Pulmonary function tests

In the first in-human clinical trial, there was an improvement in FEV1 in the 20 W cohort from 851.0 ml (standard deviation (SD) 277.3) at baseline to 900.0 ml (SD 268.6) at 1 year (Slebos 2015). No improvement was seen in the 15 W cohort (Slebos 2015). Similarly, there was an improvement at 1 year in FVC from 2439.0 ml (SD 538.2) to 2637.0 ml (SD 802.2) in the 20 W cohort (Slebos 2015). There were no statistically significant differences between power cohorts (Slebos 2015). The authors also report that, at the 20 W power level, FVC was statistically significantly improved at 90 days (p=0.016) and 270 days (p=0.036), although numerical values are not provided for this (Slebos 2015).

In the second clinical trial, there were statistically significant improvements in FEV1 compared with baseline at all follow up time periods through to 1 year (+40% improvement [SD 42%] in FEV1 at 1 year). For FVC there were statistically significant improvements at 30, 180 and 365 days (+19%

improvement [SD 24.84%] in FVC at 1 year) (Valipour 2018). Statistical significance was lost at 2 and 3-year follow up (Valipour 2018).

In the third clinical trial there were improvements from baseline at 1 year in FEV1 and FVC in both dosing cohorts and the open-label confirmation group, although statistical significance from baseline was not measured and there were no statistically significant differences between dosing groups (Valipour 2019). At 2 and 3-year follow up there were no statistically significant differences from baseline in FEV1, FVC, RV and TLC (Pison 2021).

In the RCT, there were no statistically significant differences in FEV1, FVC or RV between the treatment and sham arms at 6 months or 1 year (Slebos 2019). Similarly, at 2-year follow up there were no statistically significant differences in FEV1, FVC, TLC, or RV between the control and treatment groups or when comparing 2-year outcomes with 1-year outcomes within groups (Valipour 2020).

Health-related quality of life (HRQOL)

In the first in-human clinical trial, HRQOL (using the SGRQ-C) was statistically significantly improved at 90 days, 270 days and 1 year in the 20 W cohort (Slebos 2015). No improvements were seen in the 15 W group (Slebos 2015).

In the second clinical trial there were no statistically significant findings on HRQOL measures (Valipour 2018).

In the third clinical trial there were improvements in the SGRQ-C and CAT at 1 year, with bigger improvements in the 32 W dosing group and the confirmation group who also received 32 W (Valipour 2019). However, statistical significance from baseline was not presented and there were no statistically significant differences between the 29 W and 32 W dosing groups (Valipour 2019). The authors state that clinically meaningful improvements were observed at 1 year for the SGRQ-C in the 32 W dosing group and the confirmation group, and for the CAT in the confirmation group (Valipour 2019). At 2 and 3-year follow up there were no statistically significant differences from baseline for the SGRQ-C or the CAT (Pison 2021).

In the sham-controlled trial, there were no statistically significant differences in SGRQ-C, CAT, EQ-5D or EQ-5D VAS scores between the treatment and control arms at 6 months or 1 year (Slebos 2019). At 2-year follow up there were no statistically significant differences in the SGRQ-C between the treatment and control groups or when comparing 2-year outcomes with 1-year outcomes within groups (Valipour 2020).

Exercise tolerance and dyspnoea

In the first clinical trial at the 20 W power level cycle endurance was statistically significantly improved from baseline at 180 days, with no other statistically significant changes at other time points or in the 15 W cohort (Slebos 2015).

In the second clinical trial changes in the 6-minute walk test reached statistical significance at 90 days and 1 year post-treatment, although this did not persist at 2 and 3 years (Valipour 2018). There were no statistically significant findings for other exercise or dyspnoea outcomes at any time point (Valipour 2018).

In the third clinical trial there were no improvements seen in exercise tolerance or dyspnoea measures and no statistically significant differences between dosing groups (Valipour 2019).

In the RCT there were no statistically significant differences between treatment and sham groups in TDI, mMRC or constant work rate cycle ergometry (Slebos 2019).

Safety summary

The focus of all included studies was safety, with the primary endpoints being safety outcomes.

Respiratory adverse events

In the first in-human clinical trial, the primary safety endpoint was freedom from documented and sustained worsening of COPD directly attributable to the investigational device or procedure (Slebos 2015). This was achieved in 100% (12/12) of the 20 W cohort and 90% (9/10) of the 15 W cohort (Slebos 2015). The 1 patient who did not meet the endpoint had a decrease in FEV1 from baseline at all time points and a COPD exacerbation 1 day after the second treatment that was reported as related to the procedure (Slebos 2015). Aside from the primary endpoint, respiratory events were the most common serious adverse events (SAEs) (Slebos 2015). Out of a total of 16 SAEs in the year following treatment, 8 were severe COPD exacerbations, 2 were pneumonia and 1 was flu (Slebos 2015). Three of the COPD exacerbations occurred in the 30 days following treatment, and the remainder between 1 and 12 months (Slebos 2015).

In the second clinical trial of 15 patients, the primary safety endpoint was the same and was achieved in 100% of patients (Valipour 2018). In addition, of the 12 SAEs recorded during the 3-year follow up, 5 were severe COPD

exacerbations, 2 of which occurred between 1 and 12 months and 3 between 1 and 2 years of follow up (Valipour 2018). An additional SAE was haemoptysis in a single patient (Valipour 2018).

In the third clinical trial, the primary safety endpoint related to airway events and is described below (Valipour 2019). In this study there were a total of 39 SAEs across the 46 participants (Valipour 2019). Of these, 16 were respiratory in nature and were evenly distributed across the 3 cohorts (5 in the 29 W dose group, 6 in the 32 W dose group and 5 in the confirmation group) (Valipour 2019). There were 8 severe COPD exacerbations and 3 episodes of pneumonia, with individual episodes of bronchitis, cough, aphonia, bronchial fistula and non-small-cell lung cancer (Valipour 2019). At 2-year follow up, there had been a further 1 respiratory SAE in the 29 W dosing group and 6 respiratory SAEs in the confirmation group (Pison 2021). At 3-year follow up, there had been 8 additional respiratory SAEs in the 29 W dosing group, 6 in the 32 W dosing group and 6 in the confirmation group (Pison 2021). Further detail of the respiratory SAEs occurring at 2 and 3 years is not provided (Pison 2021).

In the sham-controlled trial, the primary endpoint was the difference between the treatment and sham groups in the rate of predefined respiratory adverse events 3 to 6.5 months post-treatment (Slebos 2019). These encompassed: respiratory failure, COPD exacerbation, flu, pneumonia, respiratory infection, worsening bronchitis, worsening dyspnoea, tachypnoea, wheezing or local airway effects that required a therapeutic intervention (Slebos 2019). The rate of predefined respiratory adverse events between 3 and 6.5 months post-procedure was 71% in the sham arm and 32% in the treatment arm (p=0.0008) (Slebos 2019). There were no differences in the rate of events between groups 0 to 3 months post-treatment or over the entire 0 to 12.5-month study period (Slebos 2019). By 12.5 months, 90% of the sham group and 83% of the treatment group had experienced a respiratory adverse event, the most common of which were COPD exacerbations and worsening dyspnoea (Slebos 2019). In addition to predefined respiratory adverse events, there were 5 other post-treatment respiratory SAEs (3 in the treatment arm and 2 in the control arm), encompassing episodes of cough, haemoptysis, increased sputum, pharyngitis and sleep apnoea syndrome (Slebos 2019). In terms of hospitalisation for COPD exacerbations, using time to first event analysis the risk of severe COPD exacerbation requiring hospitalisation was significantly lower in the treatment group than in the sham group at 12.5 months (hazard ratio [HR] = 0.35, 95% confidence interval [CI] 80.13 to 0.99, p=0.0390) (Slebos 2019). When considering both severe and moderate COPD exacerbations (those requiring systemic steroids and/or antibiotics with or without hospitalisation) there was no difference between groups at 12.5 months (HR=0.66, 95% CI 0.38 to 1.16, p=0.1498) (Slebos 2019).

At 2-year follow up of the sham-controlled RCT, a further 4 respiratory adverse events had occurred between the 1 and 2-year follow up visits in both the treatment and control arms (8 in total) (Valipour 2020). Using time to first event analysis, at 2 years the risk of a severe COPD exacerbation was statistically significantly lower in the TLD group (HR=0.38, 95% CI 0.15 to 0.99, p=0.04) (Valipour 2020). However, the risk of a moderate and/or severe exacerbation was not statistically significantly different between groups (HR=0.71, 95% CI 0.42 to 1.18, p=0.18) (Valipour 2020). Using the annualised rate of COPD adverse effects (COPDAEs), there were no statistically significant differences in the rate of severe or moderate and/or severe COPDAEs (Valipour 2020).

Airway effects

In the first in-human clinical trial, the RF generally resulted in local asymptomatic blanching to the airway wall, which had resolved at 3 months in 100% of the 15 W cohort and in 73% (n=8/11) of the 20 W patients (Slebos 2015). The remaining 3 had a small granuloma (which was removed) and perforation and a superficial tissue defect that healed spontaneously (Slebos 2015). As a result of these events, the procedure was modified to a more distal electrode placement, more detailed visual assessment of balloon contact before activation and decrease in overall power to 15 W (Slebos 2015).

In the second clinical trial of 15 patients receiving TLD as a single procedure at 15 W, no significant airway wall effects were observed during the study at the 90-day and 365-day follow up bronchoscopies or CT scans (Valipour 2018).

In the third clinical trial, the primary safety endpoint was the rate of TLD-associated adverse airway effects that required a therapeutic intervention through 3 months post-treatment (Valipour 2019). Four patients (1 in the 29 W group and 3 in the 32 W group) met this endpoint (Valipour 2019). 2 patients (1 in the 29 W group and 1 in the 32 W group) were found to have small nodules at treatment sites at the 3-month airway inspection, which spontaneously resolved at 6 months (Valipour 2019). Of the other 2 patients in the 32 W group, 1 received prophylactic steroids and antibiotics immediately post treatment following a larger area of mucosal blanching, which healed by 3 months (Valipour 2019). The final patient developed pneumonia that required intensive care admission and the discovery of a deep ulceration, a mucosal fistula through the thin tissue of the carina and a partial occlusion of the right upper lobe bronchus (Valipour 2019). The patient made a complete recovery (Valipour 2019).

In the sham-controlled trial, there were 2 episodes of medical device site erosion in a single patient in the treatment arm (Slebos 2019).

Gastrointestinal (GI) events

In the first in-human clinical trial of TLD, 1 of the 16 SAEs related to gastroparesis occurred within 30 days post-treatment (Slebos 2015).

In the second clinical trial there were no GI SAEs, although there were 2 episodes of dysphagia and 2 episodes of epigastric pain within 30 days of treatment among the non-serious adverse events (Valipour 2018).

In the third clinical trial, after treatment of the first 13 patients in the randomised dose evaluation phase, reports of gastric adverse events led to a suspension of treatments and detailed investigation (Valipour 2019). The investigation suggested that these events were related to inadvertent injury to oesophageal branches of the vagus nerve during treatment (Valipour 2019). Following this, the study protocol was amended to include fluoroscopic visualisation and active measurement of the distance between the electrode and the outer wall of the oesophagus by an oesophageal balloon to assist in avoiding the thermally sensitive vagus nerve (Valipour 2019). Low power was also used (26W) for treatments close to the main carina (Valipour 2019). After this, 17 patients continued in the randomised dose evaluation study and 16 additional patients were enrolled and treated in an open-label confirmation study (after the dosing phase was completed) to confirm the impact of the protocol amendments on gastric safety (Valipour 2019). Following the protocol amendments, a reduction in the occurrence and severity of gastric events was noted in the remaining subjects treated in the dose evaluation study and the open-label study (Valipour 2019). In total, in the dose evaluation study there were 7 GI events affecting 40% (6/15) of patients in the 29 W group and 4 GI events affecting 20% (3/15) of patients in the 32 W group (Valipour 2019). The most common event was impaired gastric emptying, with 5 reported instances (17% of patients) (Valipour 2019). Four of these patients continued to experience symptoms of gastric emptying 1-year post-procedure (Valipour 2019). At 2-year follow up, there had been 1 additional GI SAE event in the confirmation group, which had resolved and was deemed unrelated to the procedure (Pison 2021). No further GI events were recorded at the 3-year follow up (Pison 2021).

In the sham-controlled trial, the authors report that there was a trend towards increased GI events in the treatment arm, although there were no statistically significant differences between groups (Slebos 2019). In the treatment group there were 7 GI and 3 hepatobiliary post-treatment serious events, and 2 GI events in the sham group (Slebos 2019). In the treatment group these comprised 3 episodes of impaired gastric emptying and individual episodes of abdominal pain, anal abscess, dysphagia and gastro-oesophageal reflux disease (GORD) (Slebos 2019). There were also 2 episodes of cholecystitis and 1 bile duct stone (Slebos 2019). In the control arm, there were single episodes of constipation and

GORD (Slebos 2019). At 1 month there was an increase in PAGI-SYM score in the treatment group from baseline that was significantly different from the sham group (Slebos 2019). However, there were no other statistically significant differences at other time periods (Slebos 2019). At 2-year follow up, a further 1 GI SAE had occurred in the treatment group, with an inconclusive relationship to the procedure (Valipour 2020).

Other

In the first in-human clinical trial, aside from respiratory and GI events, the remaining SAEs related to 1 case of anaphylaxis post-procedure and others that were deemed unrelated to the procedure (coronary artery bypass surgery, chest pain resulting in hospitalisation and stomach cancer) (Slebos 2015).

In the second clinical trial, there were 6 non-respiratory SAEs, encompassing heart arrythmia, prostatic hypertrophy, stroke (n=2), urinary retention and a motorcycle accident (Valipour 2018). None was deemed to be device-related (Valipour 2018).

In the third clinical trial, aside from respiratory and GI events, there were 2 serious cardiac events (Valipour 2019). One patient had an aortic dissection and died and another had an acute myocardial infarction (Valipour 2019). Both events were investigated and concluded to be unrelated to the procedure (Valipour 2019). At 2-year follow up, there had been a further 13 SAEs that were not respiratory or GI, of which 2 were cardiac and the remainder were not described (Pison 2021). At 3-year follow up, there had been an additional 29 SAEs (Pison 2021). Of these, 3 were cardiac, with 1 patient dying from acute cardiac death that was investigated and deemed unrelated to the procedure (Pison 2021).

In the sham-controlled trial, several other SAEs occurred, which were unlikely to be related to the procedure (Slebos 2019). In the treatment arm these encompassed single episodes of: osteoarthritis, osteoporosis, radiculopathy, haematuria, a road traffic accident, coronary artery disease, supra-ventricular tachycardia and retinal degeneration (Slebos 2019). In the control arm there were single episodes of: musculoskeletal discomfort, hip arthroplasty, rehabilitation therapy, a therapeutic procedure, urinary tract infection, femoral neck fracture, peripheral artery stenosis, acute myocardial infarction and sepsis (Slebos 2019). At 2-year follow up, between the 1 and 2-year follow up visits there had been 3 further non-respiratory and non-GI SAEs in the treatment arm (Valipour 2020). These consisted of SAEs relating to the musculoskeletal system, the reproductive system and skin and subcutaneous tissue disorders (Valipour 2020). In the control arm, there had been 1 cardiac SAE and 1 psychiatric SAE (Valipour 2020).

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to endobronchial nerve ablation for the therapy of COPD. The following databases were searched, covering the period from their start to 24 September 2020. MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see the literature search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The inclusion criteria were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with COPD.
Intervention/test	Endobronchial nerve ablation.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on 165 patients from 2 non-randomised clinical trials, 1 randomised clinical trial (including a dose evaluation study and an open label

confirmation study), 1 randomised-controlled clinical trial, and 2 additional papers which reported longer-term outcomes from the 2 randomised clinical trials.

Other studies that were considered to be relevant to the procedure but were not included in the main summary of the key evidence are listed in the appendix.

Summary of key evidence on endobronchial nerve ablation for the therapy of COPD

Study 1 Slebos D-J (2015)

Study details

Study type	Non-randomised clinical trial (safety and technical feasibility study)
Country	South Africa (2 sites) and the Netherlands (1 site)
Recruitment period	Study carried out between 31 October 2011 and 21 November 2013
Study population and number	n=22 (n=12 in 20W cohort, n=10 in 15W cohort)
Age and sex	20W cohort: 63 years, 58% (n=7) males 15W cohort: 64 years, 40% (n=4) males
Patient selection criteria	Inclusion criteria: • FEV1 30%–60% • FEV1/ FVC <70% • Patient is diagnosed with COPD (FEV1/ FVC <70%) • Positive relative change in FEV1 >15% following administration of ipratropium • ≥40 years of age or older • Smoking history of at least 10 pack years • Non-smoking for a minimum of 6 months before consent and agreed to continue not smoking for the duration of the study • Patient has provided written informed consent • The patient is willing, able and agrees to complete all protocol-required baseline and follow up assessments including taking and abstaining from medications • The patient has no child-bearing potential or a negative pregnancy test • Patient is a candidate for bronchoscopy in the opinion of the physician or per hospital guidelines • Current influenza vaccination and/or pneumococcus vaccination consistent with local recommendations and/or policy Exclusion criteria: • Pulmonary hypertension, peripheral oedema suggesting CHF or polycythaemia • Patient has an $SaO_2 \leq 88\%$ or a $PaO_2 \leq 7.3$ kPa (55 mm Hg) • Patient has a $PaCO_2 > 8.0$ kPa (60 mm Hg) • Previous lung transplant, LVRS, median sternotomy, bullectomy or lobectomy • Pulmonary nodule requiring surgery

	• History of recurrent respiratory infections (>3 hospitalisations within 1 year of consent) • Presence of a pacemaker, internal defibrillator or other implantable electronic devices • Active respiratory infection within the past 4 weeks • COPD exacerbation within the past 4 weeks • Myocardial infarction within the last 6 months • Unstable or life-threatening arrhythmia within the last year • Malignancy treated with radiation or chemotherapy within the last 2 years • Presence of other respiratory diseases (cystic fibrosis, tuberculosis, vocal cord • dysfunction, Churg-Strauss syndrome, allergic bronchopulmonary aspergillosis) • Known hypersensitivity to anticholinergic drugs or components • Known allergy to medications required for bronchoscopy (such as lidocaine, atropine) that cannot be medically controlled • Clinical diagnosis of sleep apnoea • Clinical diagnosis of asthma or other respiratory disease other than COPD • Known coagulopathy • Patient is taking clopidogrel, coumadin or other blood-thinning medication • The patient has any disease or condition that might interfere with completion of this study (for example, life expectancy less than 1 year) • Patient is currently enrolled in another clinical trial
Technique	Prior to the intervention, patients underwent a period of washout of bronchodilators, after which baseline testing was carried out. Patients then underwent a minimum 8-day run-in period while on tiotropium bromide. The procedure was performed using rigid bronchoscopy and a flexible bronchoscope placed beside it for visualisation. The initial subjects were treated with 20W in all positions, except for the posterior-medial aspects of the left bronchus where the power was reduced to 15W due to the proximity of the oesophagus. Due to local airway events, a protocol amendment was made and additional patients underwent treatment with a more distal placement of the electrode along the medial wall to avoid the thin tissue of the carina, and 15W in all positions. Bronchoscopic and fluoroscopic visualisation were used to guide the electrode positioning. The procedure was delivered as a 2-stage intervention, with the second bronchus treated 30 days after the first. No special post-procedure medications were required, and tiotropium was stopped.
Follow-up	1 year
Conflict of interest/source of funding	The study was funded by Holaira, Inc. (the company who produced the lung denervation system). One of the study authors is the founder and chief technology officer of the study sponsor.

Analysis

Follow-up issues: Follow up to 1 year:
20W cohort - 83% (10/12). 1 patient was withdrawn prior to their second treatment after a coronary-artery bypass graft, and another missed their 1 year visit.
15W cohort - 100% (although 1 patient refused the second treatment).

Study design issues: This was a non-randomised, non-blinded safety and feasibility study. There was no control group, with all participants receiving the intervention plus tiotropium. Although the inclusion and exclusion criteria are presented, the methods for recruiting participants are not described.

The primary safety endpoint of the study was freedom from documented and sustained worsening of COPD directly attributable to the investigational device or procedure 365-days post-procedure. This was defined as a decrease in the individual patient's FEV1 by any amount at all follow up time points, along with a report of an adverse event that was reported to have a probable or definite relation to the device. Secondary endpoints included technical feasibility of the device and change from baseline in pulmonary function tests, exercise capacity assessments and HRQOL. Technical feasibility was defined as the ability to access the target treatment area of the main bronchus and deliver RF energy to the entire circumference of the bronchus at the target treatment site. Outcomes were assessed using validated measures. Pulmonary function was assessed using spirometry and body plethysmography. Exercise capacity was assessed using cycle ergonometry, the 6 Minute Walk Test and the common Borg and mMRC scales. HRQOL was assessed using the SGRQ-C and the Clinical COPD Questionnaire, with higher score on both tools indicating worse HRQOL. In addition to washout baseline and tiotropium trough baseline, outcomes were assessed at 30, 90, 180, 270 and 365-days post-treatment. All follow up tests were performed whilst washed out of any bronchodilators taken.

Numerical follow up data is only provided for the 1 year follow up. For FEV1, FVC, cycle ergometry endurance and SGRQ-C, the results of interim visits are presented as a graphical figure, but with no numerical values.

P values are presented for comparison of energy cohorts, however there is no table presenting p values for comparison of findings from baseline and at different time points. These are only reported for the time points where there were significant differences. No detail is provided of the statistical tests used to generate p values.

Study population issues: This was a very small study with no control group.

Key efficacy findings

Number of patients analysed: 22

Pulmonary function tests

Results from 1 year follow up are displayed in the table below. In addition, the authors report that, at the 20W power level, FVC was statistically significantly improved at 90 days (p=0.016) and 270 days (p=0.036) although numerical values are not provided.

Clinical outcome	20 watt cohort – mean (standard deviation (SD))	15 watt cohort – mean (SD)	Overall – mean (SD)	P value*
FEV1 (mL):				
Baseline	851.0 (277.3)	836.0 (148.0)	843.5 (216.5)	0.882
1 year	900.0 (268.6)	835.0 (185.5)	867.5 (227.1)	0.537
% change	11.6 (32.3)	0.02 (151)	5.8 (25.3)	0.324
FVC (mL):				
Baseline	2439.0 (538.2)	2448.0 (602.9)	2443.5 (556.3)	0.972
1 year	2637.0 (802.2)	2509.0 (665.6)	2573.0 (720.4)	0.702
% change	7.6 (21.9)	39 (19.1)	5.7 (20.1)	0.690
Total lung capacity:				
Baseline	7.2 (1.2)	6.8 (1.2)	7.0 (1.2)	0.501
1 year	7.3 (1.8)	7.2 (1.2)	7.2 (1.5)	0.824
% change	1.0 (11.8)	5.2 (9.6)	3.2 (10.6)	0.405
Residual volume:				
Baseline	4.6 (0.7)	4.1 (0.7)	4.4 (0.7)	0.164
1 year	4.6 (1.2)	4.4 (0.9)	4.5 (1.0)	0.696
% change	0.5 (21.2)	7.9 (20.6)	4.4 (20.6)	0.451
Inspiratory capacity:				
Baseline	1.8 (0.5)	1.7 (0.6)	1.8 (0.5)	0.885
1 year	1.7 (0.78)	1.8 (0.6)	1.8 (0.7)	0.743
% change	-2.0 (31.6)	7.3 (22.0)	2.9 (26.6)	0.462
Pulmonary resistance (kPaxs/L):				
Baseline	0.8 (0.3)	1.0 (0.2)	0.9 (0.2)	0.233
1 year	0.8 (0.2)	0.8 (0.1)	0.8 (0.2)	0.695
% change	-4.6 (13.8)	-19.1 (18.8)	-12.2 (17.8)	0.074

*P values are for comparisons between cohorts, not for comparison from baseline

Exercise tolerance and dyspnoea

Clinical outcome	20 watt cohort – mean (SD)	15 watt cohort – mean (SD)	Overall – mean (SD)	P value*
Cycle ergometry endurance (min):				
Baseline	5.8 (2.3)	4.2 (2.1)	5.1 (2.3)	0.139
1 year	12.7 (13.5)	6.9 (8.3)	10.1 (11.5)	0.301
% change	6.8 (12.8)	2.6 (8.7)	5.0 (11.1)	0.441
Borg scale: post-testing dyspnoea				
Baseline	4.4 (1.6)	6.1 (1.3)	5.2 (1.7)	0.023
1 year	4.1 (2.0)	5.3 (1.8)	4.6 (1.9)	0.223
% change	-0.3 (2.0)	-0.9 (2.0)	-0.6 (2.0)	0.556
mMRC scale:				
Baseline	1.0 (1.3)	1.2 (1.1)	1.1 (1.1)	0.788
1 year	0.3 (0.5)	1.8 (1.3)	1.0 (1.2)	0.031
% change	-0.7 (0.8)	0.6 (1.3)	-0.1 (1.2)	0.085
6 minute walk test (metres):				
Baseline	388.1 (92.8)	425.4 (74.7)	406.8 (79.1)	0.304
1 year	412.3 (51.7)	416.1 (120.0)	414.2 (89.9)	0.928
% change	24.2 (45.6)	-9.3 (70.6)	7.5 (60.4)	0.224

*P values are for comparisons between cohorts, not for comparison from baseline

Health-related quality of life (HRQOL)

Clinical outcome	20 watt cohort – mean (SD)	15 watt cohort – mean (SD)	Overall – mean (SD)	P value*
St George's Respiratory questionnaire:				
Baseline	53.2 (14.1)	57.9 (17.9)	55.4 (15.6)	0.575
1 year	42.1 (12.0)	57.1 (21.8)	49.1 (18.4)	0.120
% change	-11.1 (9.1)	-0.9 (8.6)	-6.3 (10.1)	0.045
Clinical COPD questionnaire:				
Baseline	2.8 (1.0)	2.63 (1.0)	2.7 (1.0)	0.732
1 year	2.2 (1.0)	2.77 (1.0)	2.4 (1.0)	0.230
% change	-0.6 (0.8)	0.14 (0.7)	-0.3 (0.8)	0.051

*P values are for comparisons between cohorts

Technical feasibility

Technical feasibility was 93% (39/42 procedures delivered full circumferential treatment).

Key safety findings

Primary safety endpoint

Clinical outcome	20 watt cohort (n=12)	15 watt cohort (n=10)
Primary safety endpoint* achieved – n (%)	12 (100)	90 (9)

Airway events

The RF generally resulted in local asymptomatic blanching to the airway wall, which had resolved at 3 months in 100% of the 15W cohort and in 73% (n=8/11) of the 20W patients. The remaining 3 had a small granuloma (which was removed) and perforation and a superficial tissue defect that healed spontaneously. As a result of these events, the procedure was modified to a more distal electrode placement, more detailed visual assessment of balloon contact before activation and decrease in overall power to 15W.

All adverse events

Adverse events during 1 year follow up	20 watt cohort (n=12)		15 watt cohort (n=10)		All (n=22)	
	Adverse event frequency n=60 (%)	Subject frequency (%)	Adverse event frequency n=39 (%)	Subject frequency (%)	Adverse event frequency n=99 (%)	Subject frequency (%)
Serious						
Device-related:						
Gastroparesis	-	-	1 (3)	1 (10)	1 (1)	1 (5)
Procedural-related:						
Anaphylactic reaction	1 (2)	1 (8)	-	-	-	-
COPD exacerbation	-	-	1 (3)	1 (10)	1 (1)	1 (5)
Other:						
Chest pain	-	-	1 (3)	1 (10)	1 (1)	1 (5)
COPD exacerbation	2 (3)	2 (17)	5 (13)	3 (30)	7 (7)	5 (23)
Coronary artery disease	1 (2)	-	-	-	1 (1)	1 (5)
Influenza	-	-	-	-	-	-
Lung infection	-	-	1 (3)	1 (10)	1 (1)	1 (5)
Stomach cancer	2 (3)	2 (17)	-	-	2 (2)	2 (9)
	-	-	1 (3)	1 (10)	1 (1)	1 (5)
Non-serious						
Device-related:						
Bronchial perforation	2 (3)	2 (17)	-	-	2 (2)	2 (9)
Bronchial stenosis	1 (2)	1 (8)	-	-	1 (1)	1 (5)
Bronchial ulceration	1 (2)	1 (8)	1 (3)	1 (10)	1 (1)	1 (5)
COPD exacerbation	-	-	-	-	1 (1)	1 (5)
Granulomas	1 (2)	1 (8)	-	-	1 (1)	1 (5)
Worsening of FEV1	-	-	1 (3)	1 (10)	1 (1)	1 (5)
Procedural-related:						
Broken tooth	1 (2)	1 (8)	-	-	1 (1)	1 (5)
Cough	2 (3)	2 (17)	-	-	2 (2)	2 (9)
Dyspnoea	2 (3)	2 (17)	1 (3)	1 (10)	3 (3)	3 (14)

Eczema	-	-	1 (3)	1 (10)	1 (1)	1 (5)
Headache	2 (3)	2 (17)	-	-	2 (2)	2 (9)
Mucus	3 (5)	3 (25)	-	-	3 (3)	3 (14)
Sore throat	3 (5)	3 (25)	1 (3)	1 (10)	4 (4)	4 (4)
Tracheal injury	1 (2)	1 (8)	-	-	1 (1)	1 (1)
Other:						
Abscess	-	-	1 (3)	1 (10)	1 (1)	1 (5)
Back ache	1 (2)	1 (8)	-	-	1 (1)	1 (5)
Bronchitis	-	-	5 (13)	2 (20)	5 (5)	2 (9)
Candida	-	-	1 (3)	1 (10)	1 (1)	1 (5)
Chest pain	1 (2)	1 (8)	-	-	1 (1)	1 (5)
Common cold	2 (3)	2 (17)	-	-	2 (2)	2 (9)
COPD exacerbation	12 (20)	7 (58)	13 (33)	6 (60)	25 (25)	13 (59)
Cough	1 (2)	1 (8)	-	-	1 (1)	1 (5)
Diarrhoea	1 (2)	1 (8)	-	-	1 (1)	1 (5)
Difficulty swallowing	1 (2)	1 (8)	-	-	1 (1)	1 (5)
Dizziness	2 (3)	2 (17)	1 (3)	1 (10)	3 (3)	3 (14)
Dyspnoea	3 (5)	2 (17)	1 (3)	1 (10)	4 (4)	3 (14)
Influenza	3 (5)	3 (25)	1 (3)	1 (10)	4 (4)	4 (18)
Gastritis	2 (3)	2 (17)	1 (3)	1 (10)	3 (3)	3 (14)
Gastroparesis	1 (2)	1 (8)	-	-	1 (1)	1 (5)
Pneumonia	1 (1)	1 (8)	-	-	1 (1)	1 (5)
Respiratory inflammation	4 (7)	4 (33)	-	-	4 (4)	4 (18)
Sinusitis	-	-	1 (3)	1 (10)	1 (1)	1 (5)

Study 2 Valipour A 2018

Study details

Study type	Non-randomised, prospective single-dose registry study
Country	Austria (1 site) and France (3 sites)
Recruitment period	Study conducted between September 2012 and May 2015
Study population and number	15
Age and sex	63.2 years, male = 47% (n=7)
Patient selection criteria	Identical as to Study 1
Technique	This study followed the pilot study described as Study 1 and replicated the design to understand the safety profile of the intervention when performed as a single dose procedure. Washout and tiotropium run-in were conducted as described for Study 1. Targeted lung denervation was performed via rigid bronchoscopy using an energy level determination of 15W. Bronchoscopic and fluoroscopic visualisation were used to guide electrode positioning. A staged procedure was performed in 2 patients due to the airway size being unexpectedly larger than the balloon available at the time of the initial treatment. Subjects stopped taking tiotropium after completion of the procedure.
Follow-up	3 years
Conflict of interest/source of funding	Study funded by Nuvaira Inc (formerly Holaira). One of the authors is a founder and stockholder of Nuvaira Inc and the inventor of the device used in the study.

Analysis

Follow-up issues: 100% of patients were followed up to 1 year, 67% (10/15) to 2 years and 60% (9/15) to 3 years.

Study design issues: As per Study 1. This study was carried out by the same research group and its design was nearly identical to Study 1, with a few exceptions: 1) the intervention being delivered as a single procedure; 2) all patients receiving an energy determination of 15W; 3) different research sites; 4) follow up continuing to 3 years.

The primary safety endpoint was freedom from documented and sustained worsening of COPD directly attributable directly attributable to the investigational device or procedure 365-days post-procedure. This was defined as a decrease in the individual patient's FEV1 by any amount at all follow up time points, along with a report of an adverse event that was reported to have a probable or definite relation to the device. Secondary endpoints included technical feasibility of the device and change from baseline in pulmonary function tests, exercise capacity assessments and HRQOL. Technical feasibility was defined as the ability to access the target treatment area of the main bronchus and deliver RF energy to the entire circumference of the bronchus at the target treatment site. Outcomes were assessed using validated measures as described for Study 1.

Numerical follow up data is only presented for the 1 year follow up. Data for the 30, 90, 180, 730 and 1,095-day follow up is presented as a graphical figure for FEV1 and FVC, with no numerical data. For the remaining outcomes, data from the other follow up visits is not presented. Details of the statistical tests to generate p values is not provided.

Study population issues: 100% of patients were of White ethnicity.

Key efficacy findings

Number of patients analysed: 15

Technical feasibility

Technical feasibility: 93% (n=14/15). One patient received treatment in 7 out of 8 quadrants due to poor balloon contact. A staged procedure was performed in 2 patients due to the airway size being larger than the balloon available at time of the initial treatment.

Pulmonary function tests

The results of 1 year follow up are displayed in the table below. Statistical significance was lost at 2 and 3 year follow up.

Clinical outcome	Baseline – mean (SD)	1 year – mean (SD)	Percent change from baseline – mean (SD)
FEV1 (mL)	765.33 (257.45)	1,012.14 (272.99)	40.29 (42.12)*
FVC (mL)	2,248.00 (614.05)	2,605.00 (634.59)	19.25 (24.84)*

*P<0.05

Exercise tolerance and dyspnoea

The results of 1 year follow up are displayed in the table below. The authors also report that the 6 minute walk test was statistically significantly improved at 90 day follow up. Statistically significant improvements did not persist at the 2 and 3 year follow up.

Clinical outcome	Baseline – mean (SD)	1 year – mean (SD)	Absolute change from baseline – mean (SD)
Cycle ergometry endurance (min)	7.36 (2.96)	9.81 (4.92)	2.68 (6.06)
Borg scale: post-testing dyspnoea	5.4 (2.35)	4.64 (1.21)	-0.82 (1.83)
mMRC scale	2.27 (1.03)	1.60 (1.06)	-0.67 (1.05)
6 minute walk test (metres)	361.8 (125.62)	415.47 (112.76)	53.67 (74.40)*

*P<0.05

Health-related quality of life (HRQOL)

The result of the 1 year follow up are displayed in the table below. In addition, the authors report that HRQOL (as measured using the SGRQ-C) was statistically significantly improved at 90 day and 270 day follow up.

Clinical outcome	Baseline – mean (SD)	1 year – mean (SD)	Absolute change from baseline – mean (SD)
St George's Respiratory questionnaire	47.95 (16.97)	49.37 (20.93)	-1.85 (20.77)
Clinical COPD questionnaire	2.71 (1.17)	2.63 (1.41)	0.00 (1.29)

Key safety findings

Primary safety endpoint

Clinical outcome	Patient cohort (n=15) – n (%)
Primary safety endpoint* achieved – n (%)	15 (100)

Adverse events

Adverse event	≤30 day (n=15), n (%)	≥30 days to 1 year (n=15), n (%)	1-2 years (n=10), n (%)	2-3 years (n=9), n (%)
Serious adverse events:				
COPD exacerbation	-	2 (13)	3 (30)	-
Heart arrythmia	-	1 (7)	-	-
Haemoptysis	-	-	1 (10)	-
Prostatic hypertrophy	1 (7)	-	-	-
Motorcycle accident	-	-	-	1 (11)
Stroke	-	-	-	2 (22)
Urinary retention	1 (7)	-	-	-
Non-serious adverse events:				
Common cold	1 (7)	-	-	-
COPD exacerbation	2 (13)	2 (13)	11 (110)	3 (33)
Cough	-	1 (7)	-	-
Dislodged teeth	1 (7)	-	-	-
Dysphagia	2 (13)	-	-	-
Epigastric pain	2 (13)	-	-	-
Headache	-	-	-	1 (11)
Haemoptysis	-	1 (7)	1 (10)	-
Herpes zoster	-	-	1 (10)	-
Hoarseness	-	-	-	1 (11)
Hypoxaemia	1 (7)	-	-	-
Lower respiratory infection	-	5 (33)	1 (10)	-
Nausea/vomiting	-	1 (7)	-	-
Paraesthesia (left hand)	-	-	1 (10)	-
Tachycardia	-	-	-	2 (22)
Tingling in left upper lobe	1 (7)	-	-	-
Thoracic pain	1 (7)	-	-	-
Sigmoiditis	-	1 (7)	-	-
Syncope	-	-	-	1 (11)

Airway events

No significant airway wall effects were observed during the study at the 90-day and 365-day follow up bronchoscopies or CT scans.

Study 3 Valipour 2019

Study type	Randomised, double-blind safety and feasibility study
Country	Austria, Belgium, France, Germany, the Netherlands and the United Kingdom
Recruitment period	Study conducted between August 2014 and July 2016
Study population and number	**46 participants:** Dose evaluation study: n=30 (15 participants in 32W group, 15 in 29W group) Open-label confirmation study: n=16
Age and sex	29W group: 61 years, 60% (n=9) males 32W group: 64 years, 27% (n=4) males Open-label confirmation group: 63 years, 38% (n=6) males
Patient selection criteria	Inclusion criteria: • COPD (defined as a post-bronchodilator FEV1/FVC ratio of ≤0.70, and post-bronchodilator FEV1 30-60% of predicted normal values) • Age ≥40 and ≤75 years • Persistent symptoms (indicated by either Modified Medical Research Council (mMRC) grade ≥2 and/or COPD assessment test (CAT) score ≥10) • Reversibility to anticholinergic medications as demonstrated by a positive relative change in FEV1 and/or FVC of >12% and >200mL following inhalation of 80µg ipratropium bromide Additional exclusion criteria for participants in the open-label confirmation group: • History of prior abdominal surgical procedures • Baseline gastroparesis cardinal symptom index score ≥18, as part of the patient assessment of gastrointestinal disorders symptom severity index prior to treatment • Recent (<3 months ago) narcotic use
Technique	The AIRFLOW-1 study was initiated to assess airway safety and to evaluate targeted lung denervation (TLD) energy dose by randomising 30 patients to 2 selected doses (29 versus 32W). Major enhancements had been made to the TLD system and device compared to earlier studies. These included compatibility of the catheter with flexible bronchoscopy and a larger electrode to decrease procedure time. Therefore, the aim of the study was to evaluate 2 higher dose power levels that were intended to maximise efficacy whilst maintaining safety. Patients underwent TLD to both lungs in a single procedure under general anaesthesia. After randomisation, the treatment catheter was advanced through the bronchoscope and circumferential treatment achieved by activating the electrode in up to 4 positions per bronchi.

	Bronchoscopic and fluoroscopic visualisation was used to guide electrode placement before and during energy delivery. All patients were prescribed 25-30mg prednisolone and 500mg azithromycin daily for 1 day before and 2 days after the procedure. All participants received tiotropium bromide for a minimum of 90 days. After treatment of the first 13 patients in the randomised dose evaluation phase, reports of gastric adverse events led to a suspension of treatments and a detailed investigation. Following this, the study protocol was amended to include fluoroscopic visualisation and active measurement of the distance between the electrode and the outer wall of the oesophagus by an oesophageal balloon to assist in avoiding the thermally sensitive vagus nerve. Low power was also used (26W) for treatments close to the main carina. At this point, 17 patients continued enrolment in the randomisation dose study and 16 additional patients were enrolled and treated in an open-label confirmation study (after the dosing phase was completed) to confirm the impact of protocol, procedural, and training enhancements on gastric safety. 32W was used for the open-label study.
Follow-up	1 year
Conflict of interest/source of funding	The study was funded by Nuvaira Inc.

Analysis

Follow-up issues: Follow-up to 1 year

- 29W group: 87%, n=13/15 (1 subject withdrew and 1 missed 1 year visit)
- 32W group: 73%, n=11/15, (1 subject withdrew, 1 subject died and 2 missed the 1 year visit)
- Open-label confirmation group: 88%, n=14/16 (1 subject withdrew, 1 missed the 1 year visit)

Study design issues: The methods used to recruit patients are not described. In the randomised dose evaluation phase, after confirmation of airway compatibility at the time of the procedure, randomisation was performed using tamper-resistant sealed envelopes that contained the letter codes that were entered into the console to deliver the appropriate radiofrequency power level for treatment. This allowed for triple blinding of the treating physician, participant and follow up physician.

The primary safety endpoint for the randomised dose evaluation phase was the rate of TLD-associated adverse airway effects that required a therapeutic intervention (defined as the administration of antibiotics, conduction of another diagnostic test to assess the treatment area or an endoscopic procedure or surgery to treat findings) through 3 months post-treatment. Secondary endpoints included: procedural success (defined as the ability to insert and place the catheter to intended locations and intact removal without the report of an in-hospital serious adverse event); overall adverse events; change from baseline to 1 year for PFTs, HRQOL, dyspnoea and exercise capacity assessments.

The primary safety endpoint for the open-label confirmation phase was the rate and frequency of adverse events through 1-month post-treatment compared to the randomised dose evaluation phase. Secondary endpoints were the same.

Validated outcome measures were used. Health-related quality of life (HRQOL) was measured using the: SGRQ-C, CAT, EQ-5D and EQ-5D VAS. Dyspnoea was assessed using the TDI and mMRC scales. Exercise

tolerance was assessed using cycle ergometry training. Baseline chest CT scans were used to assess bronchial anatomy and the level of disease to rule out other pulmonary abnormalities. These tests were all carried out at baseline and again at 12 months, both after bronchodilator washout. In addition, follow up bronchoscopy was performed to evaluate airway wall effects.

P values are presented in comparison of dosing groups. However, the statistical tests used to generate these are not described. No p values are presented to compare baseline outcomes with outcomes at 1 year. This was a small study, with no control, and was not powered to assess noninferiority of safety outcomes or superiority of efficacy outcomes between dosing groups.

Study population issues: 98% of patients were of White ethnicity.

Key efficacy findings

Number of patients analysed: 46

Clinical outcomes

Outcome – change at 1 year from baseline washout off bronchodilators	Dosing group			Confirmation group, 32W (n=16) – mean (±SD)
	32W (n=15) – mean (±SD)	29W (n=15) – mean (±SD)	P value (32 vs. 29W)	
Pulmonary function tests				
FEV1 (mL)	94 (228)	57 (82)	0.6050	34 (174)
FVC (mL)	212 (497)	238 (316)	0.8761	208 (528)
TLC (L)	0.04 (0.21)	0.01 (0.30)	0.8173	0.19 (0.7)
RV (L)	-0.12 (0.52)	-0.23 (0.55)	0.6311	-0.01 (1.0)
IC (L)	-0.04 (0.28)	-0.07 (0.44)	0.8374	0.06 (0.3)
Health-related quality of life measures				
SGRQ-C	-7.5 (10)	-1.9 (12)	0.2534	-6.1 (21)
CAT	-2.9 (6.1)	0.3 (7.8)	0.2800	-6.2 (9.6)
EQ-5D	0.1 (0.2)	0.0 (0.2)	0.6930	0.1 (0.2)
EQ-5D VAS	9.1 (2.1)	3.2 (14)	0.4229	0 (22)
Exercise tolerance/dyspnoea measures				
mMRC	0.1 (0.9)	0.0 (0.7)	0.7900	-0.2 (0.7)
TDI	0.5 (2.7)	-0.7 (4.3)	0.4516	1.3 (3.8)
Exercise endurance (min)	-2.7 (8)	-0.3 (4.7)	0.7969	-2.1 (9.3)

Technical feasibility

Procedure characteristics	Dosing group		Open label confirmation study (n=16)
	29W group (n=15)	32W group (n=15)	
Acute procedure success, n (%)	14 (93)	15 (100)	15 (94)
Left lung treatment, n (%):			
≥4 activations	13 (87)	15 (100)	15 (94)
<4 activations	2 (13)	0	1 (6)
Right lung treatment, n (%):			
≥4 activations	13 (87)	12 (80)	9 (56)
<4 activations	2 (13)	3 (20)	7 (45)

Key safety findings

Primary safety endpoint

	Dosing group		Confirmation group
	29W (n=15)	32W (n=15)	32W (n=16)
Primary safety endpoint - n (% of patients)	1 (6.6)	3 (20)	0

Serious adverse events

	Dosing group		Confirmation group
Serious adverse event (SAEs) at 12 months	**29W (n=15)**	**32W (n=15)**	**32W (n=16)**
Total SAEs - event frequency (patient frequency)	**16 (9)**	**14 (5)**	**9 (5)**
Pulmonary – event frequency (patient frequency):	5 (3)	6 (3)	5 (4)
COPD exacerbation	3	3	2
Pneumonia	1	1	1
Bronchitis	-	-	1
Cough	-	-	1
Aphonia	1	-	-
Bronchial fistula	-	1	-
Non-small cell lung cancer	-	1	-
Gastrointestinal – event frequency (patient frequency):	7 (6)	4 (3)	0
Impaired gastric emptying	3	2	-
Epigastric discomfort	-	1	-
Nausea	1	-	-
Duodenal ulcer haemorrhage	1	-	-
Cholecystitis acute	-	1	-
Colitis	1	-	-
Diverticulitis	1	-	-
Cardiac – event frequency (patient frequency):	0	2 (2)	0 (0)
Aortic dissection, death	-	1	-
Acute myocardial infarction	-	1	-
Other – event frequency (patient frequency)*	4 (3)	2 (2)	3 (2)

*Other events included: 29W group = urine retention, iron deficiency anaemia, depression, bursitis; 32W group = non-cardiac chest pain, arthritis; Confirmation group = non-cardiac chest pain, tendonitis, hypoglycaemia

Study 4 Slebos D-J 2019

Study details

Study type	Multi-centre, sham-controlled, double-blind randomised controlled trial
Country	Austria, Belgium, France, Germany, the Netherlands and the United Kingdom
Recruitment period	July 2016 – May 2017
Study population and number	82 patients (41 in treatment group, 41 in sham group)
Age and sex	Sham group: Age = 63.68 years, male = 46.3% Treatment group: Age = 63.71 years, male = 53.7%

Patient selection criteria	Inclusion criteria:
	• Aged 40-75 years
	• Diagnoses of moderate to severe COPD. This was defined as:
	  ○ A post-bronchodilator FEV1/FVC ratio of 0.70 and FEV1 30–60% of predicted AND
	  ○ A modified Medical Research Council dyspnoea scale (mMRC) score ≥2 OR
	  ○ A COPD Assessment Test score ≥10
	Exclusion criteria:
	• More than 2 respiratory system-related hospitalisations within the past year
	• Gastroparesis Cardinal Symptom Index ≥18
	• Previous lung or chest procedure

Technique	Patients were randomly assigned 1:1 to a sham procedure or targeted lung denervation (TLD). After a 7-day washout period of bronchodilators, patients underwent baseline testing. This was followed by a minimum 7-day run-in period whilst receiving inhaled tiotropium. Bronchoscopy was performed under general anaesthetic. Patients allocated to the treatment arm received Nuvaira lung denervation therapy. The sham group underwent a mock procedure. Treatments were carried out as outpatient procedures unless the specific hospital protocol required an overnight stay. All patients received standard prophylaxis related to interventional bronchoscopy consisting of steroids and antibiotics (exact details not provided) on the day of and for 2 days after the procedure.
Follow-up	12.5 months
Conflict of interest/source of funding	The study was supported by Nuvaira Inc.

Analysis

Follow-up issues: Follow up to 1 year: treatment group = 92.7% (n=39/41), sham group = 90.2% (37/41)

IP overview: Endobronchial nerve ablation for chronic obstructive pulmonary disease

Study design issues: The process by which patients were recruited is not described. Double blinding was achieved by 2 separate study teams: an unblinded team not involved in any of the follow up and a separate blinded assessment team that performed all follow up assessments and was not involved in or present for the procedure. On the day of the procedure, patients were randomised after administration of anaesthesia. Randomisation schemes were generated by the independent statistical group in tamper-resistant randomisation envelopes. For the sham group, blinding was ensured by performing an entire mock procedure with a taped recording of the functional console procedure sounds.

Validated outcome measures were used in the study. This consisted of spirometry, body plethysmography, and constant work rate cycle ergometry. Health-related quality of life (HRQOL) questionnaires were used: SGRQ-C, EQ-5D-5L, EQ-5D VAS and CAT. mMRC and TDI were used for assessment of dyspnoea and the PAGI-SYM was used to assess GI symptoms.

The focus of the study was safety and the primary endpoint was the difference between the treatment and sham groups in the rate (percentage) of respiratory adverse events 3-6.5 months after treatment. These were predefined as respiratory failure, COPD exacerbation, influenza, pneumonia, respiratory infection, worsening bronchitis, worsening dyspnoea, tachypnoea, wheezing, or local airway effects that required a therapeutic intervention. Secondary safety measures included overall rates and severity of adverse events and acute procedure success (device success without the occurrence of an in-hospital serious adverse event before discharge). Primary performance endpoints included device success (the ability to insert, place and remove the device) and technical success (the ability to deliver RF energy to each intended location). HRQOL, dyspnoea scores, lung function measures and exercise tolerance were evaluated as exploratory secondary endpoints.

Hypothesis tests were carried out to compare outcomes for the treatment and sham groups, with t tests or non-parametric equivalents used for continuous data. Fisher's exact test was used to compare categorical data. Comparisons of time to event data, such as time to first COPD exacerbation, were accomplished using a standard log-rank statistic. The sample size was not based on a power calculation and the authors state that the p values are presented for exploratory endpoints to help quantify and frame the results.

Key efficacy findings

Number of patients analysed: 12.5-month follow up: Treatment group = 36 (88%), sham group = 38 (93%)

Primary performance outcomes

Measure of procedural success	**Percentage success - %**	
Device success	100	
Technical success	90 (n=38/42*)	
Incomplete circumferential treatment:	**Left main bronchi**	**Right main bronchi**
<4 activations	16	46
Average percentage of mainstem treated	94	83

*Paper states here that 42 treatments were performed, despite only 41 patients in the treatment group

Clinical outcomes

Outcome – on drug compared with baseline off drug	Sham group – mean (±SD)	Treatment group – mean (±SD)	P value for sham vs treatment (t test)
Pulmonary function			
FEV1 (mL):			
6 months	86.4 (179.5)	127.6 (201.0)	0.3453
12 months	103.5 (192.7)	74.32 (213.1)	0.5386
FVC (mL):			
6 months	147.2 (360.8)	240.0 (389.7)	0.2815
12 months	211.4 (411.8)	235.4 (471.1)	0.8158
RV (L):			
6 months	-0.09 (0.9)	-0.32 (0.8)	0.2431
12 months	-0.23 (0.8)	-0.35 (0.6)	0.4770
Health-related quality of life			
SGRQ-C:			
6 months	-3.76 (13.8)	-8.31 (12.6)	0.1382
12 months	-2.46 (14.5)	-5.05 (14.4)	0.4414
CAT:			
6 months	-3.18 (8.0)	-1.97 (6.5)	0.4720
12 months	-3.24 (8.3)	-0.89 (6.4)	0.1754
EQ-5D:			
6 months	0.03 (0.2)	0.06 (0.1)	0.2868
12 months	-0.01 (0.2)	0.02 (0.2)	0.4374
EQ-5D VAS:			
6 months	3.11 (21.5)	9.11 (22.5)	0.2415
12 months	6.03 (23.1)	6.68 (20.9)	0.8988
Dyspnoea/exercise tolerance			
TDI:			
6 months	-1.51 (3.7)	0.25 (3.2)	0.2431
12 months	-1.24 (3.4)	-1.17 (3.1)	0.4770
mMRC:			
6 months	-0.26 (1.0)	-0.47 (1.0)	0.3368
12 months	-0.21 (1.0)	-0.44 (0.8)	0.2790
CWRE (minutes):			
6 months	1.24 (4.49)	1.25 (6.31)	0.9935
12 months	0.77 (7.6)	0.85 (7.4)	0.9649

Key safety findings

Primary safety endpoint

Respiratory adverse event 3-6.5 months post-treatment (patients may have multiple events)	Sham group - % (n)	Treatment group - % (n)	P value
Worsening bronchitis	4.9 (2)	-	0.4938
COPD exacerbation	43.9 (18)	26.8 (11)	0.1731
Discovered airway effects requiring a therapeutic intervention	-	2.4 (1)	1.0000
Worsening dyspnoea	22.0 (9)	4.9 (2)	0.0496
Influenza	2.4 (1)	-	1.0000
Pneumonia	4.9 (2)	2.4 (1)	1.0000
Respiratory infection	-	-	-
Respiratory failure	-	-	-
Tachypnoea	-	-	-
Wheezing	2.4 (1)	-	1.0000
Total	**70.7 (29)**	**31.7 (13)**	**0.0008**

Non-serious respiratory adverse events 3-6.5 months post-procedure

Respiratory adverse event 3-6.5 months post-treatment (patients may have multiple events)	Sham group - % (n)	Treatment group - % (n)	P value
Worsening bronchitis	4.9 (2)	-	0.4938
Common cold	4.9 (2)	4.9 (2)	1.0000
Congestion	-	-	-
COPD exacerbation	36.6 (15)	17.1 (7)	0.0797
Cough	14.6 (6)	2.4 (1)	0.1088
Worsening dyspnoea	17.1 (7)	4.9 (2)	0.1549
Haemoptysis	-	-	-
Hoarseness	4.9 (2)	2.4 (1)	1.0000
Increased mucus	2.4 (1)	2.4 (1)	1.0000
Influenza	2.4 (1)	-	1.0000
Mucosal candidiasis	-	-	-
Pneumonia	2.4 (1)	-	1.0000
Pulmonary infection	-	-	-
Rhinitis/pollinosis	-	-	-
Sore throat	-	2.4 (1)	1.0000
Thoracic pain	-	-	-
Wheezing	2.4 (1)	-	1.0000
Total	**65.9 (27)**	**34.1 (14)**	**0.0077**

Respiratory adverse events 0-3 and 0-12.5 months post-treatment

Diagnosis	Sham group - % (n)	Treatment group - % (n)	P value
Worsening bronchitis:			
0-3 months	4.9 (2)	2.4 (1)	1.0
0-12.5 months	9.8 (4)	9.8 (4)	1
COPD exacerbation:			
0-3 months	22.0 (9)	22.0 (9)	1.0
0-12.5 months	68.3 (28)	53.7 (22)	0.5641
Discovered airway effects that require a therapeutic intervention:			
0-3 months	-	-	-
0-12.5 months	-	2.4 (1)	1.0000
Worsening dyspnoea:			
0-3 months	9.8 (4)	12.2 (5)	1.0
0-12.5 months	36.6 (15)	22.0 (9)	0.3526
Influenza:			
0-3 months	-	4.9 (2)	0.4938
0-12.5 months	2.4 (1)	9.8 (4)	0.3597
Pneumonia:			
0-3 months	4.9 (2)	4.9 (2)	1.0
0-12.5 months	17.1 (7)	12.2 (5)	0.7578
Respiratory infection:			
0-3 months	-	-	-
0-12.5 months	-	-	-
Respiratory failure:			
0-3 months	-	-	-
0-12.5 months	-	-	-
Tachypnoea:			
0-3 months	-	-	-
0-12.5 months	-	-	-
Wheezing:			
0-3 months	-	4.9 (2)	0.4942
0-12.5 months	2.4 (1)	4.9 (2)	1
Total:			
0-3 months	**36.6 (15)**	**46.3 (19)**	**0.3766**
0-12.5 months	**90.2 (37)**	**82.9 (34)**	**0.5187**

Risk of COPD exacerbation requiring hospitalisation

Using time to first event analysis, the risk of severe COPD exacerbation requiring hospitalisation was significantly lower in the treatment group than in the sham group at 12.5 months (hazard ratio (HR) = 0.35, 95% confidence interval (CI) 80.13-0.99, p=0.0390). When considering both severe and moderate COPD exacerbations (those requiring systemic steroids and/or antibiotics with or without hospitalisation) there was no difference between groups at 12.5 months (HR=0.66, 95% CI 0.38-1.16, p=0.1498).

Gastrointestinal serious adverse events

Gastrointestinal event	**Sham group – n total events (% patients with events)**	**Treatment group – n total events (% patients with events)**
Impaired gastric emptying	3 (7.32)	-
Abdominal pain	1 (2.44)	-
Anal abscess	1 (2.44)	-
Constipation	-	1 (2.44)
Dysphagia	1 (2.44)	-
Epigastric discomfort	-	1 (2.44)
Gastro-oesophageal reflux disease	1 (2.44)	-
Total	**7 (14.63)**	**2 (4.88)**

Other serious adverse events

Serious adverse event	Sham group – n total events (% patients with events)	Treatment group – n total events (% patients with events)
General disorders and administration site conditions:		
Medical device site erosion	-	2 (2.44)
Musculoskeletal and connective tissue disorders:		
Musculoskeletal discomfort	1 (2.44)	-
Osteoarthritis	-	1 (2.44)
Osteoporosis	-	1 (2.44)
Nervous system disorders:		
Radiculopathy		1 (2.44)
Surgical and medical procedures:		
Hip arthroplasty	1 (2.44)	1 (2.44)
Rehabilitation therapy	1 (2.44)	-
Therapeutic procedure	1 (2.44)	-
Renal and urinary disorders:		
Haematuria	-	1 (2.44)
Urinary tract infection	1 (2.44)	-
Injury, poisoning and procedural complications:		
Femoral neck fracture	1 (2.44)	-
Road traffic accident	-	1 (2.44)
Cardiac disorders:		
Acute myocardial infarction	1 (2.44)	-
Coronary artery disease	-	1 (2.44)
Supraventricular tachycardia	-	1 (2.44)
Infections and infestations:		
Sepsis	1 (2.44)	-
Eye disorders:		
Retinal degeneration	-	1 (2.44)
Hepatobiliary disorders:		
Cholecystitis	-	2 (4.88)
Bile duct stone	-	1 (2.44)

Study 5 Valipour A 2020

Study details

Study type	Multi-centre, sham-controlled, double-blind randomised controlled trial
Country	Austria, Belgium, France, Germany, the Netherlands and the United Kingdom
Recruitment period	July 2016 – May 2017
Study population and number	82 patients (41 in treatment group, 41 in sham group)
Age and sex	Sham group: Age = 63.68 years, male = 46.3% Treatment group: Age = 63.71 years, male = 53.7%
Patient selection criteria	As for Study 4 Slebos 2019
Technique	As for Study 4 Slebos 2019.
Follow-up	2 years
Conflict of interest/source of funding	The study was supported by Nuvaira Inc.

Analysis

Follow-up issues: Follow up to 2 years:
Treatment group = 88% (n=36/41) – 2 subjects withdrew consent, 1 subject became unable to travel, 1 subject was removed due to a treatment change, 1 subject was removed due to a thyroid goitre
Sham group = 34% (16/41) – 2 subjects withdrew consent, 1 subject became unable to travel, 1 subject was removed due to a treatment change, 20 subjects crossed over to the treatment arm after unblinding at 1 year, 2 subjects withdrew because they were ineligible for crossover.

Study design issues: The paper reports 2 year outcomes from the AIRFLOW-2 trial, which has been reported in more detail as Study 4 Slebos 2019. Subjects were unblinded after the 1 year follow up, after which 20 subjects in the sham arm crossed over to the treatment arm and received TLD between the 1 and 2 year follow up visits.

The outcome measures presented for efficacy are measures of pulmonary function (FEV1, FVC, TLC and RV) and HRQOL (SGRQ-C). For safety, the number, timing and rate of COPD exacerbations are presented, along with the number and category of all SAEs.

In terms of statistical analysis, t-tests were used for normally distributed continuous data and non-parametric equivalents were used where the data was not normally distributed. Fisher's exact test was used for categorical data. Negative binomial regression was used for annualised rate comparisons. A standard Log rank statistic was used for comparisons between groups of time to event data, such as time to first COPD exacerbation.

Key efficacy findings

Number of patients analysed: 2 year follow up - Treatment group = 36, sham group = 16

Pulmonary function and HRQOL

Absolute difference between year 1 and year 2 run-in tiotropium measurements*	Control – mean ± standard deviation (SD), (n)	TLD – mean ± SD, (n)
FEV1 – litres (L)	-0.05 ± 0.21 (11)	-0.02 ± 0.14 (30)
FVC – L	0.11 ± 0.54 (11)	-0.14 ± 0.29 (30)
TLC – L	-0.24 ± 0.52 (11)	0.04 ± 0.44 (30)
RV – L	-0.31 ± 0.45 (11)	0.21 ± 0.53 (30)
SGRQ-C	-0.03 ± 15.02 (12)	1.81 ± 12.66 (34)

*All p values were non-significant when comparing year 2 and year 1 outcomes within groups, and when comparing outcomes between the control and TLD groups

Key safety findings

All serious adverse events at 2 year follow up

	Event frequency - n	
Serious adverse events between 1 and 2 year follow up	**TLD group**	**Control group**
Respiratory	4	4
Gastrointestinal	1*	-
Cardiac	-	1
Musculoskeletal and connective tissue disorders	1	-
Reproductive system	1	-
Skin and subcutaneous tissue disorder	1	-
Psychiatric	-	1
Total	8	6
P-value		0.72

*1 severe GI event was reported 507 days post-TLD, with an inconclusive relationship to the TLD procedure

COPD adverse events

Time to event analysis

The risk of a severe COPD exacerbation requiring hospitalisation was significantly lower in the TLD group than the control group at 2 years, as assessed in a time-to-first event analysis (HR=0.38, 95% CI=0.15-0.99, p=0.04). However, there was no statistical difference in risk of moderate or severe COPD exacerbation from baseline to 2 years (HR=0.71, 95% CI=0.42-1.18, p=0.18).

Annualised rate of COPD adverse events

		Year 1		Year 2	
		Control	**TLD**	**Control**	**TLD**
Moderate and severe COPD adverse events (AECOPDs)	Annual rate	1.16	1.09	0.81	0.64
	Number of AECOPDs	54	50	20	23
	Follow up years	54	50	20	23
	P-value		0.90		0.54
Severe AECOPDs	Annual rate	0.39	0.24	0.16	0.11
	Number of AECOPDs	18	11	4	4
	Follow up years	46.6	45.7	24.8	35.8
	P-value		0.43		0.71

Study 6 Pison C 2021

Study type	Randomised, double-blind safety and feasibility study
Country	Austria, Belgium, France, Germany, the Netherlands and the United Kingdom
Recruitment period	Study conducted between August 2014 and July 2016
Study population and number	**46 participants:** Dose evaluation study: n=30 (15 participants in 32W group, 15 in 29W group) Open-label confirmation study: n=16
Age and sex	29W group: 61 years, 60% (n=9) males 32W group: 64 years, 27% (n=4) males Open-label confirmation group: 63 years, 38% (n=6) males
Patient selection criteria	As for Study 3 Valipour 2019
Technique	As for Study 3 Valipour 2019
Follow-up	3 years
Conflict of interest/source of funding	The study was supported by Nuvaira Inc.

Analysis

Follow-up issues: Follow up to 3 years

- **29W group:** 73%, n=11/15 (1 subject lost to follow up, 1 subject received another intervention, 2 subjects withdrew)
- **32W group:** 80%, n=12/15, (2 subjects withdrew, 1 subject died)
- **Open-label confirmation group:** 69%, n=11/16 (1 subject lost to follow up, 1 subject withdrew, 2 subjects received another intervention, 1 subject died)

Study design issues: This paper reports 3 year outcomes from the AIRFLOW-1 trial, which is reported in more detail as Study 3 Valipour 2019.

For efficacy, the outcomes presented measure pulmonary function and HRQOL. Washout measures of pulmonary functions evaluated were FEV1, FVC, RV and TLC. HRQOL measures evaluated were the SGRQ-C and the CAT. All were measured at 1, 2 and 3 years post-TLD and compared with baseline. For safety, the number of COPD exacerbations are presented along with the number and category of all serious adverse events.

Statistical hypothesis tests were used and data from 1, 2 and 3 year time-points compared with baseline. Where data were normally distributed, paired t-tests were used. Non-parametric equivalents were used where the data was not normally distributed.

Key efficacy findings

Number of patients analysed: 44 at 1 year, 38 at 2 years, 35 at 3 years

Pulmonary function

Pulmonary function was not statistically significantly different from baseline at the 2 and 3 year follow up visits. Overall lung function was stable during the 3 years of follow up.

HRQOL

HRQOL was not statistically significantly different from baseline at the 2 and 3 year follow up timepoints. Overall HRQOL was stable over the 3 years of follow up.

Key safety findings

Serious adverse events at 2 and 3 years

	Serious adverse events – n patients (n events)							
Group	**All-cause**		**Respiratory**		**Gastrointestinal**		**Cardiac**	
	Year 2	**Year 3**	**Year 2**	**Year 3**	**Year 2**	**Year 3**	**Year 2**	**Year 3**
Dosing group - 29W	1 (1)	5 (9)	1 (1)	5 (8)	0	0	0	0
Dosing group - 32W	1 (1)	5 (9)	0	4 (6)	0	0	1 (1)	1 (1)
Confirmation group	6 (9)	6 (8)	6 (6)	5 (6)	1 (1)*	0	1 (1)	2 (2)**

*A patient in the confirmation group experienced increased dysphagia at 650 days post-procedure, which fully resolved and was determined not to be related to the procedure or device.
**One of these patients died due to acute cardiac death that was determined to be unrelated to TLD.

COPD exacerbations

Across the entire patient cohort, the percentage of patients having at least one moderate or severe COPD exacerbation was 70% (31/44), 61% (23/38) and 46% (16/35) at the 1, 2 and 3 year follow up respectively.

Validity and generalisability of the studies

- All included studies were prospective in design.
- All studies were conducted by the same research group and used progressive iterations of the same lung denervation system produced by the same company.
- Small numbers of patients were included and only 1 involved a control group.
- The primary focus of all included studies was safety and there is limited analysis of efficacy. A study protocol (Slebos 2020) was identified in the evidence review for a further RCT by the same research group that conducted the included studies where the primary outcome will be reduction in COPD exacerbations. Secondary outcomes will also relate to efficacy. Therefore, it is likely that further evaluation of the efficacy will be available when this RCT is published.
- With the exception of the first in-human clinical trial of the procedure where 2 study sites were in South Africa, all studies were conducted in Western Europe (the Netherlands, Austria, France, Belgium, Germany and the UK).
- The mean age of study participants ranged from 61-64 years and the proportion of male participants ranged from 27-60%.
- The vast majority of participants were of White ethnicity.
- Follow up periods ranged from 1-3 years and losses to follow up ranged from 7% at 1 year to 66% at 2 years due to unblinding of an RCT and several participants crossing over to the treatment arm (Valipour 2020).
- Extensive exclusion criteria, especially for Slebos (2015) and Valipour (2018), may limit the generalisability of results to the general population of patients with COPD who are likely to have considerable comorbidities.

Existing assessments of this procedure

There were no published assessments from other organisations identified at the time of the literature search.

Related NICE guidance

Below is a list of NICE guidance related to this procedure.

Interventional procedures

- Bronchoscopic thermal vapour ablation for upper-lobe emphysema. NICE Interventional Procedures Guidance 652 (2019). Available from: https://www.nice.org.uk/guidance/ipg652.
- Endobronchial valve insertion to reduce lung volume in emphysema. NICE Interventional Procedures Guidance 600 (2017). Available from: https://www.nice.org.uk/guidance/ipg600.
- Insertion of endobronchial nitinol coils to improve lung function in emphysema. NICE Interventional Procedures Guidance 517 (2015). Available from: https://www.nice.org.uk/guidance/ipg517.
- Lung volume reduction surgery for advanced emphysema. NICE Interventional Procedures Guidance 114 (2005). Available from: https://www.nice.org.uk/guidance/ipg114.

NICE guidelines

- Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2018). NICE guideline 115. Available from: https://www.nice.org.uk/guidance/NG115.

Additional information considered by IPAC

Professional experts' opinions

Expert advice was sought from consultants who have been nominated or ratified by their professional Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by professional experts, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not

limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. No Professional expert questionnaires for endobronchial nerve ablation for the therapy of COPD were submitted.

Patient commentators' opinions

NICE's Public Involvement Programme will send questionnaires to NHS trusts for distribution to patients who had the procedure (or their carers). When NICE has received the completed questionnaires, these will be discussed by the committee.

Company engagement

A structured information request was sent to 1 company who manufacture a potentially relevant device for use in this procedure. NICE received 1 completed submission. This was considered by the IP team and any relevant points have been taken into consideration when preparing this overview.

References

1. Slebos D-J, Klooster K, Koegelenberg CFN et al. (2015) Targeted lung denervation for moderate to severe COPD: A pilot study. Thorax 70(5):411–9.
2. Valipour A, Asadi S, Pison C et al. (2018) Long-term safety of bilateral targeted lung denervation in patients with COPD. International Journal of COPD 13:2163–72.
3. Valipour A, Shah P, Pison C et al. (2019) Safety and dose study of targeted lung denervation in moderate/severe COPD patients. Respiration 98:329–39.
4. Slebos D-J, Shah PL, Herth FJF et al (2019). Safety and adverse events after targeted lung denervation for symptomatic moderate to severe chronic obstructive pulmonary disease (AIRFLOW) a multicenter randomized controlled clinical trial. American Journal of Respiratory and Critical Care Medicine 200(12):1477–86.
5. Valipour A, Shah PL, Herth FJ et al. (2020) Two-year outcomes for the double-blind, randomized, sham-controlled study of targeted lung denervation in patients with moderate to severe COPD: AIRFLOW-2. Internation Journal of Chronic Obstructive Disease 15:2807-2816.
6. Pison C, Shah PL, Slebos D-J et al. (2021). Safety of denervation following targeted lung denervation therapy for COPD: AIRFLOW-1 3-year outcomes. Respiratory Research 22(1):62.

Literature search strategy

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane)	24/09/2020	Issue 9 of 12, September 2020
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane)	24/09/2020	Issue 9 of 12, September 2020
International HTA database (INAHTA)	24/09/2020	n/a
MEDLINE (Ovid)	24/09/2020	1946 to September 22, 2020
MEDLINE In-Process (Ovid)	24/09/2020	1946 to September 22, 2020
MEDLINE Epubs ahead of print (Ovid)	24/09/2020	September 22, 2020
EMBASE (Ovid)	24/09/2020	1974 to 2020 Week 38

Trial sources searched

- Clinicaltrials.gov
- ISRCTN
- WHO International Clinical Trials Registry

Websites searched

- National Institute for Health and Care Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- General internet search

MEDLINE search strategy

The MEDLINE search strategy was translated for use in the other sources.

1	Denervation/
2	Catheter Ablation/
3	Catheterization/
4	Vagotomy/
5	or/1-4
6	Lung/
7	Vagus Nerve/
8	(lung* or 'vagus nerve*' or 'vagal nerve*' or bronchi*).tw.

9	or/6-8
10	5 and 9
11	((lung* or vagus or vagal) adj4 (denervat* or ablat* or neurectom* or neurotom*)).tw.
12	TLD.tw.
13	(Lung* adj4 (parasympathe* or catheter*)).tw.
14	or/11-13
15	10 or 14
16	exp chronic obstructive lung disease/
17	(copd or coad or cobd or aecb).tw.
18	emphysema*.tw.
19	(chronic* adj4 bronch*).tw.
20	(chronic* adj3 (airflow* or airway* or bronch* or lung* or respirat* or pulmonary) adj3 obstruct*).tw.
21	(pulmonum adj4 (volumen or pneumatosis)).tw.
22	pneumonectasia.tw.
23	*Dyspnea/
24	(chronic* adj3 (breath* or respirat*) adj3 (difficult* or labor* or labour* or problem* or short*)).tw.
25	(chronic* adj3 (dyspnea* or dyspnoea* or dyspneic or breathless*)).tw.
26	or/16-25
27	15 and 26
28	(Holaira or Nuvaira).tw.
29	27 or 28
30	nonhuman/ not human/
31	29 not 30

Appendix

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the summary of the key evidence. It is by no means an exhaustive list of potentially relevant studies.

Additional papers identified

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in summary of key evidence section
Aaron S, Mahler D. (2020) Calming nervous airways: targeted lung denervation for chronic obstructive pulmonary disease. American Journal of Respiratory and Critical Care Medicine 200(12):1455-1456.	Editorial article	Provides commentary on targeted lung denervation including existing research in this area.	Editorial article
Bilaçeroğlu S. (2019) Interventional Bronchoscopy in the Management of Chronic Obstructive Lung Disease. Respiratory Medicine 15(2):133-139.	Review article	Provides an overview of interventional bronchoscopy options for the management of COPD.	Review article
Garner J, Kemp S. (2017) Interventional bronchoscopy for COPD. Clinical Pulmonary Medicine 24(2):79-86.	Review article	Provides an overview and summary of existing research for interventional bronchoscopy options for COPD.	Review article

Gompelmann D, Eberhardt R, Herth F. (2015) Novel endoscopic approaches to treating chronic obstructive pulmonary disease and emphysema. Seminars in Respiratory and Critical Care Medicine 36(4):609-615.	Review article	Provides a summary of different endoscopic treatment approaches for COPD, their mechanisms of action, and the results of available clinical trials.	Review article
Gompelmann D, Sarmand N, Herth F. (2017) Interventional pulmonology in chronic obstructive pulmonary disease. Current Opinion in Pulmonary Medicine 23(3):261-268.	Review article	Provides an update on existing interventional treatment options for COPD.	Review article
Gülşen A. (2018) Bronchoscopic lung volume reduction: A 2018 review and update. Turkish Thoracic Journal 19(3):141-149.	Review article	Provides an overview and summary of existing research for lung volume reduction options, including targeted lung denervation.	Review article
Herth F. (2016) Emphysema: Valves, coils, steam and lung denervation. Respirology 21(3):20.	Conference presentation	Provides broad guidance regarding patient selection and the current position of the available techniques for patients with advanced emphysema.	Conference presentation

Kemp S, Shah P. (2016) An update on bronchoscopic treatments for chronic pulmonary disease. Interventional Pulmonology 22(3):265-270.	Review article	Provides an update on existing bronchoscopic treatment options for COPD.	Review article
Koegelenberg C, Theron J, Slebos D-J et al. (2015) Additive effect of targeted lung denervation plus drug in patients with COPD. European Respiratory Journal 46(59):PA3963	22 patients followed for 1 year	Conference abstract reporting on the first in-human trial of the procedure (Slebos 2015). 1 year outcomes provided as in paper. No new safety concerns are reported.	Conference abstract reporting on the Slebos 2015 paper.
Koegelenberg C, Theron J, Slebos D-J et al. (2016) Antimuscarinic bronchodilator response retained after bronchoscopic vagal denervation in chronic obstructive pulmonary disease patients. Respiration; International Review of Thoracic Diseases 92(1):58-60.	Letter to the editor	Provides an overview of the Slebos 2015 paper.	Letter to the editor summarising the Slebos 2015 paper.
Kontogianni K, Eberhardt R. (2018) Endoscopic approaches for treating emphysema. Expert Review of Respiratory Medicine 12(8):641-650.	Review article	Provides an overview and commentary on different endoscopic techniques for treating emphysema.	Review article

Pison C, Shah P, Slebos D-J et al. (2020) Safety of denervation following targeted lung denervation (TLD) therapy for COPD: Airflow-1 three year outcomes. American Journal of Respiratory and Critical Care Medicine 201(1):A119	46 patients followed for 3 years	Conference abstract reporting on the included Valipour 2019 paper. 3 year follow up was available for 65% of patients. Lung function remained stable in comparison to pre-treatment baseline and HRQOL did not worsen. Post-procedural GI side effects had resolved. No new safety concerns reported.	Conference abstract reporting on an included study (Valipour 2019)
Poggi C, Mantovani S, Pecoraro Y et al. (2018) Bronchoscopic treatment of emphysema: an update. Journal of Thoracic Disease 10(11):6274-6284.	Review article	Provides an overview of bronchoscopic treatment options for emphysema.	Review article
Polke M, Rötting M, Sarmand N et al. (2019) Interventional therapy in patients with severe emphysema: evaluation of contraindications and their incidence	231 patients	Retrospective analysis exploring reasons for excluding people from endoscopic lung volume reduction options. Only 5 patients received TLD in the context of clinical trials, with no further discussion of this.	Retrospective analysis, no patient outcomes reported.

Slebos DJ, Degano B, Valipour A et al. (2020) Design for 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 (AIRFLOW-3). BMC Pulmonary Medicine 20(1):41.	Study protocol	Study protocol for continuation of the work of the research group who conducted the 4 included studies. The primary endpoint will be comparison of time to first event of moderate/severe COPD exacerbations.	Study protocol
Slebos D-J, Klooster K, Koegelenberg C et al. (2014) Efficacy of targeted lung denervation in patients with moderate to severe COPD. European Respiratory Journal 44(58):1774.	22 patients followed for 1 year	Conference abstract reporting on outcomes from Slebos 2015 paper. 1 year outcomes reported. No new safety concerns are reported.	Conference abstract reporting on outcomes from the Slebos 2015 paper.
Slebos D-J, Klooster K, Koegelenberg C et al. (2014) Safety and feasibility of targeted lung denervation with moderate to severe COPD. European Respiratory Journal 44(58):P3720.	22 patients followed for 1 year	Conference abstract reporting on the Slebos 2015 paper. 1 year outcomes are provided (as in paper). No new safety concerns are reported.	Conference abstract reporting on the Slebos 2015 paper.

Slebos D-J, Klooster K, Koegelenberg C et al. (2015) Two-year safety of targeted lung denervation in patients with moderate to severe COPD. European Respiratory Journal 46(59):PA798.	22 patients followed for 2 years	Conference abstract reporting on the Slebos 2015 paper. 2 year outcomes are provided (paper reported to 1 year). 82% of patients completed 2 year follow up. No new safety concerns are reported.	Conference abstract reporting on the Slebos 2015 paper.
Slebos D-J, Shah P, Herth F et al. (2018) A double-blind, randomized, sham-controlled study of targeted lung denervation in patients with moderate to severe COPD. European Respiratory Journal 58(62):OA4929.	82 patients followed for 6 months	Conference abstract reporting on Slebos 2019 paper. 6 month outcomes are provided. No new safety concerns reported.	Conference abstract reporting on Slebos 2019 paper. 6 month outcomes provided (paper reports to 1 year).
Slebos D-J, Valipour A, Shah P et al. (2017) Targeted lung denervation improves COPD symptoms and health related quality of life at 6 months. European Respiratory Journal 50(61):PA818.	16 patients followed for 6 months	Conference abstract reporting on the open label confirmation study included within the Valipour 2019 paper. 6 month outcomes are provided. No new safety concerns reported.	Conference abstract reporting on the open label confirmation study included within the Valipour 2019 paper. 6 month outcomes are provided.
Suman P, Mohammed M. (2020) Flexible bronchoscopy. Investigations 48(4):257-262.	Review article	Provides an overview of advances in the field of bronchoscopy.	Review article

Thakkar M, von Groote-Bidlingmaier F, Bolliger C. (2012) Recent advances in therapeutic bronchoscopy. Swiss Medical Weekly 142:w13591.	Review article	Provides an overview of new techniques in therapeutic bronchoscopy.	Review article
Valipour A, Pison C, Kessler R et al. (2014) Bilateral targeted lung denervation in patients with COPD in a single procedure. European Respiratory Journal 44(58):1775.	15 patients followed for 90 days	Conference abstract reporting on outcomes from Valipour 2018 paper. 90-day outcomes reported. No new safety concerns are reported.	Conference abstract reporting on Valipour 2018 paper.
Valipour A, Pison C, Kessler R et al. (2015) Long-term safety of biliteral targeted lung denervation in patients with COPD in single procedure. European Respiratory Journal 46(59):PA799.	15 patients followed for 18 months	Conference abstract reporting on the Valipour 2018 paper. 18 month outcomes provided. No new safety concerns are reported.	Conference abstract reporting on the Valipour 2018 paper.
Valipour A, Shah P, Herth F. (2019) A double-blind, randomized, sham-controlled study of Targeted Lung Denervation in patients with moderate to severe COPD: AIRFLOW-2 one year outcomes. European Respiratory Journal 54(63):OA1615.	82 patients followed for 1 year	Conference abstract reporting on Slebos 2019 paper. 1 year outcomes provided, as in the paper. No new safety concerns reported.	Conference abstract reporting on Slebos 2019 paper. 1 year outcomes provided, as in the paper.

Valipour A, Shah P, Herth F et al. (2020) A double-blind, randomized, sham-controlled study of targeted lung denervation in patients with moderate to severe COPD: Airflow-2 two year outcomes. American Journal of Respiratory and Critical Care Medicine 201(1):A2489	82 patients followed for 2 years	Conference abstract reporting on the included Slebos 2019 paper and describing 2 year outcomes. Loss to follow up at 2 years is not provided. The authors report that the risk of severe COPD exacerbation was significantly lower in the treatment arm at 2 years (HR=0.38, p=0.04). No new safety concerns reported.	Conference abstract reporting on an include study (Slebos 2019)
Van Geffen W, Kerstjens H, Slebos D-J. (2017) Emerging bronchoscopic treatments for chronic obstructive pulmonary disease. Pharmacology & Therapeutics 179:96-101.	Review article	Provides a summary of emerging bronchoscopic treatments and their effect compared with lung rehabilitation and pharmacological therapies.	Review article