Crossover Patient Outcomes for Targeted Lung Denervation in Moderate to Severe Chronic Obstructive Pulmonary Disease

AIRFLOW-2 Trial Study Group; Conway, Francesca; Tonkin, James; Valipour, Arschang; Pison, Christophe; Schumann, Christian; Bonta, Peter I.; Kessler, Romain; Gesierich, Wolfgang; Darwiche, Kaid

Published in:
Respiration

DOI:
10.1159/000527455

Respiration

Research Article

Respiration 2022;101:1069–1074
DOI: 10.1159/000527455

Received: May 12, 2022
Accepted: September 6, 2022
Published online: October 27, 2022

Crossover Patient Outcomes for Targeted Lung Denervation in Moderate to Severe Chronic Obstructive Pulmonary Disease: AIRFLOW-2

Francesca Conway[a] James Tonkin[a] Arschang Valipour[b] Christophe Pison[c] Christian Schumann[d] Peter I. Bonta[e] Romain Kessler[f] Wolfgang Gesierich[g] Kaid Darwiche[h] Bernd Lamprecht[i] Dirk Skowasch[j] Philip J. Johnson[k] Dirk-Jan Slebos[l] Pallav L. Shah[a] on behalf of the AIRFLOW-2 Trial Study Group

[a]Royal Brompton Hospital, Chelsea and Westminster Hospital, National Heart and Lung Institute, Imperial College, London, UK; [b]Department of Respiratory and Critical Care Medicine, Karl-Landsteiner-Institute for Lung Research and Pulmonary Oncology, Klinik Floridsdorf, Vienna, Austria; [c]CHU Grenoble Alpes, Service Hospitalier Universitaire Pneumologie Physiologie, Inserm1055, Université Grenoble Alpes, Grenoble, France; [d]Clinic of Pneumology, Thoracic Oncology, Sleep and Respiratory Critical Care, Kempten and Immenstadt, Allgäu, Germany; [e]Department of Respiratory Medicine, Amsterdam University Medical Center, University of Amsterdam, Amsterdam, The Netherlands; [f]Service de Pneumologie, Nouvel Hôpital Civil, Université de Strasbourg, Strasbourg, France; [g]Asklepios-Fachkliniken, Munich-Gauting, Comprehensive Pneumology Center Munich, Gauting, Germany; [h]Department of Pulmonary Medicine, Section of Interventional Pneumology, Ruhrlandklinik – University Hospital Essen, University of Duisburg-Essen, Essen, Germany; [i]Department of Pulmonary Medicine, Kepler Universitatsklinikum GmbH, Linz, Austria; [j]Department of Internal Medicine II, Cardiology, Pneumology, University of Bonn, Bonn, Germany; [k]Nuvaira, Inc., Minneapolis, MN, USA; [l]Department of Pulmonary Diseases, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

Keywords
Chronic obstructive pulmonary disease · Emphysema · Bronchoscopy · Interventional pulmonology · Pulmonary medicine

Abstract
Background: Targeted Lung Denervation (TLD) is a potential new therapy for COPD. Radiofrequency energy is bronchoscopically delivered to the airways to disrupt pulmonary parasympathetic nerves, to reduce bronchoconstriction, mucus hypersecretion, and bronchial hyperreactivity. ***Objectives:*** This work assesses the effect of TLD on COPD exacerbations (AECOPD) in crossover subjects in the AIRFLOW-2 trial. ***Method:*** The AIRFLOW-2 trial is a multicentre, randomized, double-blind, sham-controlled crossover trial of TLD in COPD. Patients with symptomatic COPD on optimal medical therapy with an FEV1 of 30–60% predicted received either TLD or sham bronchoscopy in a 1:1 randomization. Those in the sham arm had the opportunity to cross into the treatment arm after 12 months. The primary end point was rate of respiratory adverse events. Secondary end points included adverse events, changes in lung function and health-related quality of life and symptom scores. ***Results:*** Twenty patients were treated with TLD in the crossover phase and were

Francesca Conway and James Tonkin contributed equally to this work.

Karger@karger.com
www.karger.com/res

Correspondence to:
Pallav L. Shah, pallav.shah@imperial.ac.uk

subsequently followed up for 12 months (50% female, mean age 64.1 ± 6.9 years). After TLD, there was a trend towards a reduction in time to first AECOPD (hazard ratio 0.65, $p = 0.28$, not statistically significant) in comparison to sham follow-up period. There was also a reduction in time to first severe AECOPD in the crossover period (hazard ratio 0.38, $p = 0.227$, not statistically significant). Symptom scores and lung function showed stability. ***Conclusions:*** AIRFLOW-2 crossover data support that of the randomization phase, showing trends towards reduction in COPD exacerbations with TLD.

Introduction

Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) is a chronic respiratory disease characterized by fixed airway obstruction with respiratory symptoms usually caused by exposure to noxious particles or gases, commonly cigarette smoking [1]. It is a significant cause of morbidity and mortality. It is estimated to affect around 300 million people worldwide [2], with over 3 million people dying from the condition annually [3]. It comprises a variety of symptoms which can include breathlessness, cough, sputum production, and fatigue. The disease course of COPD varies between individuals. It is a chronic, progressive condition, with intermittent exacerbations.

COPD Exacerbations

COPD exacerbations are described as "acute worsening of respiratory symptoms, associated with a variable degree of physiological deterioration" [4]. They are usually characterized by shortness of breath, worsening cough, and there may be changes to the colour, consistency, or volume of sputum. They often have an infective precipitant (bacterial or viral), which leads to airways and systemic inflammation, and hyperinflation [5]. Patients who experience frequent exacerbations have a lower quality of life [6], higher hospitalization rate [7], and higher mortality [8] than those with a similar disease severity who do not suffer from frequent exacerbations. Exacerbations are also thought to contribute to decline in lung function [9]. Therefore, exacerbations contribute significantly to healthcare costs, decline in lung function, and mortality. COPD treatment remains an unmet need and new treatments are required. Non-pharmacological therapy in COPD, including smoking cessation and pulmonary rehabilitation, is vital in preserving lung function and reducing exacerbation frequency. Inhaled therapy is the mainstay of maintenance treatment and includes bronchodilators and inhaled corticosteroids. However, there are problems with current therapies, including the pharmacodynamics, and adherence, with under 40% of new users of tiotropium continuing treatment for 12 months [10]. Adverse effects including susceptibility to pneumonia from inhaled steroids further hamper their use. Current therapy is not disease modifying, and has only a modest role in reducing exacerbations, and despite pharmacological therapy, many patients remain symptomatic [11].

Targeted Lung Denervation

Targeted Lung Denervation (TLD) is a novel bronchoscopic therapy designed to reduce the clinical consequences of neural hyperactivity in obstructive lung diseases such as COPD through disruption of nerve signalling to and from the lung [12, 13]. In COPD, vagal activity is dysregulated, thus causing excessive bronchoconstriction, bronchial hyperreactivity, and mucus hypersecretion. These features commonly manifest in symptoms of breathlessness, sputum and cough, and exacerbations. The aim of TLD is to disrupt this neural aberrancy by delivering radiofrequency energy bronchoscopically to the airways using the denervation system (Nuvaira, Inc.).

The AIRFLOW-1 and AIRFLOW-2 study (NCT02058459) have seen patients undergo bilateral TLD [14]. Eighty-two patients were enrolled into the AIRFLOW-2 trial (patient inclusion criteria are discussed below), with moderate to severe symptomatic COPD. Data from the randomization phase of the trial showed that those treated with TLD had fewer respiratory-related adverse events and exacerbations requiring hospitalization during the randomized, sham-controlled AIRFLOW-2 clinical trial, compared to the sham arm [15]. Time-to-first severe COPD exacerbation was significantly lengthened in the TLD arm ($p = 0.04$, HR = 0.38) at 2 years post-TLD therapy and trended towards similar attenuation for moderate and severe COPD exacerbations ($p = 0.18$, HR = 0.71) [15]. TLD also appears to slow decline in lung function in patients with COPD [16]. The aim of this work was to evaluate the patients undergoing TLD as part of the crossover cohort, to establish whether the effects from the randomization phase showing reduced respiratory events post-TLD in COPD are supported.

Methods and Methods

The AIRFLOW-2 trial (NCT02058459) was a multicentre, double-blind, randomized, sham-controlled, crossover study. The study design and recruitment is previously described [15]. Study

Table 1. Patient demographics

	Average	Standard deviation
Age, years	64.05	6.9
Male sex	10	50.0%
BMI	26.25	3.7
Smoking, pack-years	41.10	28.1
Emphysema score,* %	22.40	11.3
FEV_1 (L)	1.13	0.3
FVC (L)	3.13	1.3
FEV_1% predicted	41.41	7.3
FVC% predicted	89.41	22.4
SGRQ-C	49.43	16.2
CAT	17.45	6.6
mMRC	2.05	0.6

FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; L, litres; SGRQ-C, Saint George's Respiratory Questionnaire for COPD; CAT, COPD assessment test; mMRC, modified Medical Research Council dyspnea score. * Emphysema score presented as % of voxels with attenuation below –950 Hounsfield Units.

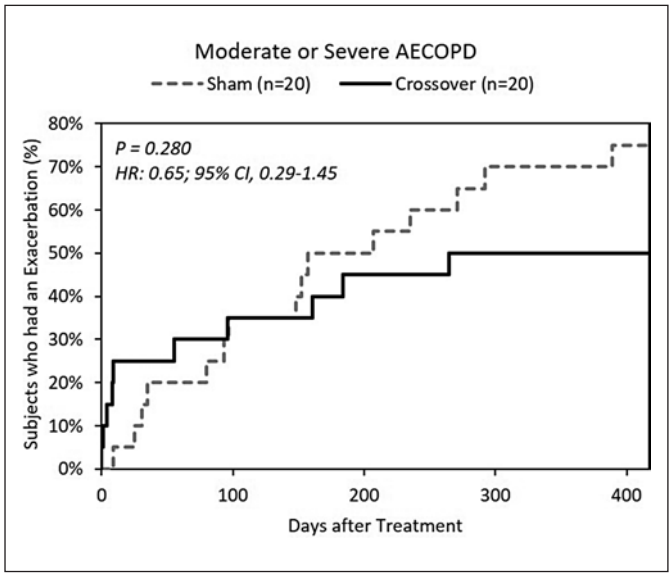

Fig. 1. Moderate or severe exacerbations in sham arm and TLD crossover arm.

recruitment was conducted between July 2016 and May 2017. Subjects provided written informed consent to study participation and the study protocol was approved by the relevant Ethics Committees. Please see online supplementary Material for Ethics Committees and approval numbers for each participating site (for all online suppl. material, see www.karger.com/doi/10.1159/000527455). One hundred ninety-four subjects were screened and 82 subjects were randomized. Subjects aged between 40 and 75 with spirometry-confirmed COPD with a post-bronchodilator ratio of forced expiratory volume in 1 second (FEV_1)/forced vital capacity <0.70 and FEV_1 of 30–60% predicted were enrolled. Patients had to be symptomatic, assessed as either a COPD Assessment Test (CAT) score ≥10 or modified Medical Research Council dyspnea scale (mMRC) score ≥2. There was no baseline exacerbation requirement for patients. Patients with significant respiratory or cardiac co-morbidities were excluded.

Blinded patients were randomized in a ratio of 1:1 receiving either sham bronchoscopy or bronchoscopic treatment with TLD (Nuvaira, Inc., USA) [15]. Following the 12.5-month follow-up visit, eligible patients in the sham group were offered TLD treatment forming the crossover group. The impact of TLD on exacerbations of COPD was analysed in these crossover patients 1 year following TLD treatment. A standard log-rank statistic was used to compare time-to-event data between groups.

Results

Of 39 sham subjects unblinded at 1- year follow-up, only 6 subjects continued follow-up without crossing over to TLD treatment. Three sham subjects exited the study prior to the crossover opportunity and three sham subjects exited the study early to seek another interventional treatment. Seven sham subjects failed to meet crossover eligibility criteria, leaving 20 crossover subjects who received TLD treatment and were followed for an additional year (50.0% male, age 64.1 ± 6.9 years). The mean FEV_1% predicted of this cohort was 41.4% ± 7.3%. The demographics of the population are displayed in Table 1. The occurrence of COPD exacerbations for these subjects was compared between year 1 follow-up as sham patients during AIRFLOW-2 (sham) and year 2 follow-up as patients treated with TLD (crossover).

After TLD treatment, the proportion of patients experiencing a moderate or severe AECOPD (exacerbation requiring treatment with antibiotics or systemic steroids, with or without hospitalization) decreased from 75% (sham, year 1) to 50% (crossover, year 2). The proportion of patients experiencing a severe AECOPD (exacerbation requiring hospitalization) decreased from 25% (sham, year 1) to 10% (crossover, Year 2). Time-to-first-event analyses were performed to compare the risk of AECOPD before and after TLD. Risk for moderate or severe AECOPD (Fig. 1) after TLD was not significantly reduced but was lower in the treatment group (HR: 0.65, 95% CI: 0.29–1.45, $p = 0.28$). Risk of severe AECOPD also did not show significant reduction after TLD but was lower in the treatment group (HR: 0.38, 95% CI: 0.08–1.97, $p = 0.23$) (Fig. 2).

Table 2. Lung function and health-related quality of life scores, baseline and 12 months

Post-bronchodilator	Baseline pre-randomization	12 months post-randomization	Baseline pre-crossover	12-month post-crossover
FEV_1 (L)	1.13±0.27	1.04±0.28	1.08±0.25	1.00±0.30
FEV_1%	41.4±7.3%	38.5±7.7%	40.6 ±8.6%	39.6±9.4%
FVC (L)	3.13±1.27	2.93±1.13	2.99±1.17	2.59±0.94
CAT	17.5±6.6	16.6±6.4	20.0±6.9	17.7±6.8
SGRQ-C	49.4±16.2	52.9±14.7	NC	53.5±15.5

Lung function and health-related quality of life scores for 20 crossover subjects across blinded sham and unblinded TLD follow-up periods. Per protocol, SGRQ-C was not collected (NC) during crossover eligibility review.

Table 3. Serious adverse events occurring within 12 months of the sham procedure and the crossover TLD procedure

	Sham, *n* (%)	Crossover, *n* (%)
All cause	6 (30)	4 (20)
Respiratory	5 (25)	3 (15)
Gastrointestinal	0 (0)	0 (0)
Cardiac	0 (0)	0 (0)
Other	4 (20)	2 (10)

Values are number of patients (% of patients) experiencing serious adverse events after either sham or crossover TLD procedure, demonstrating favourable safety profile of TLD.

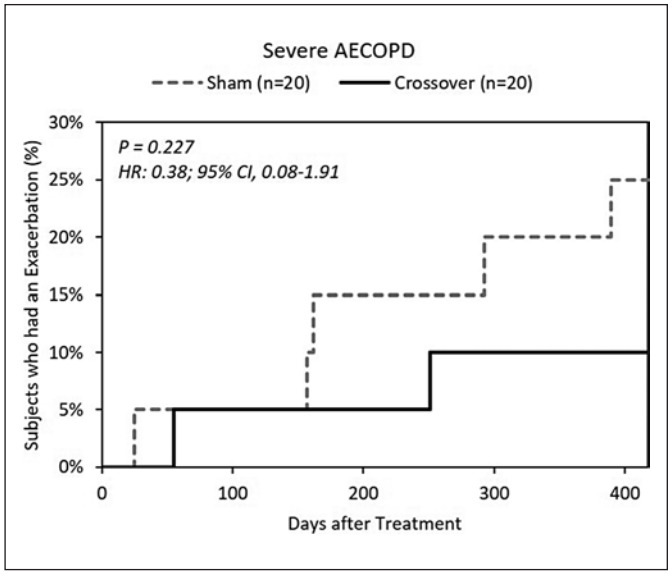

Fig. 2. Severe exacerbations in sham arm and TLD crossover arm.

Health-related quality of life measures including St George's Respiratory Questionnaire for COPD (SGRQ-C) and COPD Assessment Test (CAT), along with lung function (FEV_1), were not statistically different over the two follow-up periods, shown in Table 2. Adverse events were also noted and provide additional support to the AIRFLOW-2 trial regarding the safety of TLD in patients with moderate to severe COPD. Gastrointestinal safety was supported with no serious adverse events during either follow-up period. The number and percentage of patients experiencing serious adverse events by category is demonstrated in Table 3, confirming a favourable safety profile of TLD.

Discussion

COPD exacerbations are associated with poor disease prognosis, increased mortality risk, and increased healthcare costs [17]. Here, we present a crossover cohort with fewer subjects experiencing a COPD exacerbation following TLD, which is consistent with previously published data. The hazard ratios comparing AECOPD risk before versus after TLD for the crossover cohort were similar to the hazard ratios comparing sham versus TLD in the randomized cohort [15]. While underpowered to show statistical significance, the similar numerical effect might indicate reproducibility of treatment effect in terms of impact on exacerbations.

Due to COPD being a progressive condition, and lung function deteriorating with age, it is notable that these outcomes were observed despite subjects' disease states advancing at least 16 months (and as many as 30 months) between sham and crossover treatment dates. The group of sham patients who did not elect to crossover continued to exacerbate over the second year of follow-up, and the

original TLD group continued to show a lower rate of severe AECOPDs at 2 years follow-up despite many more patients at risk for their first exacerbation [18].

A reduction in exacerbation frequency may reduce decline in lung function, reduce mortality, and improve quality of life. As exacerbations incur a large financial burden, if TLD is found to be effective at reducing respiratory-related hospitalizations, this could have a significant beneficial effect on healthcare resource utilization and financial benefits.

The primary limitation of this study is the small number of subjects and the known heterogeneity in the timing of COPD exacerbation events within a given group of patients [19]. Although this analysis of crossover subjects was not powered for any outcome, the observed hazard ratios for time-to-first-event are consistent with previous studies of TLD in a similar patient population. For moderate or severe AECOPD, the current study's hazard ratio of 0.65 is similar to the 0.66 value observed during the randomized phase of AIRFLOW-2. The severe AECOPD hazard ratios are also similar with values 0.38 and 0.35, respectively [15]. A strength of this analysis is that subjects act as their own controls, comparing AECOPD during a 1-year blinded period (no active treatment) against a later 1-year open period (active treatment).

A further limitation is challenges in recording methods of exacerbations. As patients are frequently provided with a "rescue pack" of antibiotics, they often self-medicate for what they perceive to be an exacerbation without a medical consultation. This is a common limitation to many studies evaluating exacerbations. There is also recall bias as many patients do not remember how many times they have needed their rescue pack in the preceding year. Beyond patients acting as their own controls, the study attempted to further mitigate risk of recall bias, by providing patients with a memory aid where they were advised to document the details of any exacerbations or infections. Medication utilization was also recorded by the patient and researcher. Furthermore, the patients were regularly contacted by the study team who also kept a record of patient-reported exacerbations.

The findings of this study support previously reported COPD exacerbation risk reduction following TLD. Fewer crossover patients experienced an AECOPD in the year following treatment compared to their own prior year exacerbation history. Exacerbation risk has been consistently observed during the randomization phase of the AIRFLOW-2 trial and the 2nd year of follow-up in AIRFLOW-2 [15, 18]. We believe the paired outcomes from this small study, which confirm previously presented results of a randomized, double-blind study, provide added support for the impact of TLD on risk reduction for moderate or severe COPD exacerbations. A prospective randomized, double-blind, sham-controlled study [20] is currently underway and recruiting a larger numbers of patients (AIRFLOW-3) which will further explore the efficacy of TLD in reducing COPD exacerbations.

Acknowledgments

The authors thank Alexander Peterson for his contribution to this research; Dr. Martin Mayse, the inventor of TLD therapy; NAMSA for statistical analysis support; the AIRFLOW-2 research team; and the volunteer study participants.

Statement of Ethics

All participants have given their written informed consent to participate in the study. The study protocol was approved by all relevant ethics boards, see online supplementary Table.

Conflict of Interest Statement

All clinical trial expenses were reimbursed by the study sponsor (Nuvaira, Inc.). AV and DJS are the co-principal investigators for this study. All other authors declare that they have no conflicts of interest to disclose.

Funding Sources

All clinical trial expenses were reimbursed by the study sponsor (Nuvaira, Inc.).

Author Contributions

Francesca Conway, James Tonkin, Arschang Valipour, Christophe Pison, Christian Schumann, Peter I. Bonta, Romain Kessler, Wolfgang Gesierich, Kaid Darwiche, Bernd Lamprecht, Dirk Skowasch, Philip J. Johnson, Dirk-Jan Slebos, and Pallav L. Shah were involved in the work reported, whether that was in study design, patient recruitment, data acquisition, data analysis, or interpretation of findings. All authors took part in drafting, revising, or critically reviewing the article and approved the final manuscript.

Data Availability Statement

Data are available on demand at Nuvaira, Inc., Minneapolis, MN, USA. Further enquiries can be directed to the corresponding author.

References

1 Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, Bourbeau J, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report. GOLD executive summary. Am J Respir Crit Care Med. 2017;195(3):557–82.

2 Adeloye D, Chua S, Lee C, Basquill C, Papana A, Theodoratou E, et al. Global and regional estimates of COPD prevalence: systematic review and meta-analysis. J Glob Health. 2015;5(2):020415.

3 Mortality GBD. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015;385(9963):117–71.

4 Seemungal TA, Donaldson GC, Bhowmik A, Jeffries DJ, Wedzicha JA. Time course and recovery of exacerbations in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2000;161(5):1608–13.

5 Hurst JR, Wilkinson TM, Perera WR, Donaldson GC, Wedzicha JA. Relationships among bacteria, upper airway, lower airway, and systemic inflammation in COPD. Chest. 2005;127(4):1219–26.

6 Seemungal TA, Donaldson GC, Paul EA, Bestall JC, Jeffries DJ, Wedzicha JA. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1998;157(5 Pt 1):1418–22.

7 Garcia-Aymerich J, Farrero E, Félez MA, Izquierdo J, Marrades RM, Antó JM, et al. Risk factors of readmission to hospital for a COPD exacerbation: a prospective study. Thorax. 2003;58(2):100–5.

8 Soler-Cataluña JJ, Martínez-García MA, Román Sánchez P, Salcedo E, Navarro M, Ochando R. Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. Thorax. 2005;60(11):925–31.

9 Donaldson GCST, Seemungal A, Bhowmik JA, Wedzicha JA. Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. Thorax. 2002;57(10):847–52.

10 Breekveldt-Postma NS, Koerselman J, Erkens JA, Lammers JW, Herings RM. Enhanced persistence with tiotropium compared with other respiratory drugs in COPD. Respir Med. 2007;101(7):1398–405.

11 Lipson DA, Barnhart F, Brealey N, Brooks J, Criner GJ, Day NC, et al. Once-daily single-inhaler triple versus dual therapy in patients with COPD. N Engl J Med. 2018;378(18):1671–80.

12 Zaccone EJ, Undem BJ. Airway vagal neuroplasticity associated with respiratory viral infections. Lung. 2016;194(1):25–9.

13 Audrit KJ, Delventhal L, Aydin O, Nassenstein C. The nervous system of airways and its remodeling in inflammatory lung diseases. Cell Tissue Res. 2017;367(3):571–90.

14 Valipour A, Asadi S, Pison C, Jondot M, Kessler R, Benneddif K, et al. Long-term safety of bilateral targeted lung denervation in patients with COPD. Int J Chron Obstruct Pulmon Dis. 2018;13:2163–72.

15 Slebos DJ, Shah PL, Herth FJ, Pison C, Schumann C, Hubner RH, et al. Safety and adverse events after targeted lung denervation for symptomatic moderate to severe COPD (AIRFLOW): a multicenter randomized controlled trial. Am J Respir Crit Care Med. 2019;200(12):1477–86.

16 Hartman JE, Conway F, Degano B, Augustijn SWS, Herth FJF, Mayr A, et al. Rate of lung function decline slows in the 3 years after targeted lung denervation in COPD. Respir Med. 2021;188:106604.

17 Halpin DM, Miravitlles M, Metzdorf N, Celli B. Impact and prevention of severe exacerbations of COPD: a review of the evidence. Int J Chron Obstruct Pulmon Dis. 2017;12:2891–908.

18 Valipour A, Shah PL, Herth FJ, Pison C, Schumann C, Hübner RH, et al. Two-year outcomes for the Double-Blind, Randomized, Sham-Controlled Study of targeted lung denervation in patients with moderate to severe COPD: AIRFLOW-2. Int J Chron Obstruct Pulmon Dis. 2020;15:2807–16.

19 Han MK, Quibrera PM, Carretta EE, Barr RG, Bleecker ER, Bowler RP, et al. Frequency of exacerbations in patients with chronic obstructive pulmonary disease: an analysis of the SPIROMICS cohort. Lancet Respir Med. 2017;5(8):619–26.

20 Slebos DJ, Degano B, Valipour A, Shah PL, Deslée G, Sciurba FC, et al. 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 Pulm Med. 2020;20(1):41.