Author’s response to reviews

Title: 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)

Authors:

Dirk Slebos (d.j.slebos@umcg.nl)
Bruno Degano (bdegano@chu-grenoble.fr)
Arschang Valipour (arschang.valipour@wienav.at)
Pallav Shah (pallav.shah@imperial.ac.uk)
Gaetan Deslée (gdeslee@chu-reims.fr)
Frank Sciurba (sciurbafc@upmc.edu)

Version: 1 Date: 20 Jan 2020

Author's response to reviews:

January 17, 2020

RE: PULM-D-19-00568

Dear Editor,

Thank you for the opportunity to respond to the thorough review provided for our manuscript “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)”. We are thrilled for the potential acceptance to BMC Pulmonary Medicine. Please find our responses to the reviewer’s comments and observations below. If additional clarification or details are required, please let us know.

Sincerely,
Prof. Dirk-Jan Slebos

Reviewer #1

Major comments

1. In abstract, the authors stated that the sham group will be allowed to cross over at 1 year. However, there is no description regarding cross over in the manuscript. Please provide detailed protocol regarding the cross over.

Language has been added into the section “Blinding and Group Allocations” (Page 11, Lines 18-20) to specify that all sham patients will be offered the opportunity to undergo TLD therapy and followed for up to 4 years.

2. Page 8, 3rd line. The authors stated that the primary endpoint is a comparison of time-to-first event for moderate or severe exacerbation. However, in table 1, time-to-first exacerbation is listed in secondary endpoints.

The authors thank the reviewer for identifying this discrepancy and have updated the manuscript to reconcile this error. The manuscript has been updated in the Primary Outcome Measures section (Page 8, Line 4) to accurately reflect the primary endpoint (time-to-first event moderate/severe COPD exacerbation), which was initially placed under the secondary endpoint heading. The initial wording under the primary endpoint heading referred to the primary objective. In addition, Table 1 (Page 21) has been updated for clarity that secondary endpoints do include severe COPD exacerbations, as well as other time-to-first event exacerbation categories. The Secondary Outcome Measures section has also been updated to reflect this language (Page 8, Lines 14-15 and Page 8, Lines 20-21), as well as the secondary outcomes section of the discussion (Page 17, Line 4).
3. Page 8, 17th line. The authors mentioned that changes in spirometry and plethysmographic lung volume measures is secondary outcome. However, plethysomographic lung volume measures are missing in table 1. Also, 6MWT is missing.

RV, measured using plethysmography, has been added into Table 1. The 6MWT is an ancillary analysis; therefore, text regarding the 6MWT has been removed from the Secondary Outcomes Measures section (Page 8, Lines 14-21). A thorough review of all primary and secondary endpoints was performed to ensure no further errors are present.

4. It is not clear regarding inclusion criterion of inhaler. Is use of LAMA and LABA mandatory to be enrolled? How about ICS+LABA? Patients with only LAMA or LABA are not eligible to this study? I think this needs to be clearly demonstrated in table 2.

Table 2, Point 10, indicates that LAMA and LABA are required; however, alternative medication regimens are allowable if the patient was a non-responder or has a medical contraindication to this optimal medical therapy. The term “at least” has been added (Page 22) to clarify that LAMA/LABA for \( \geq 12 \) months are the desired baseline. Triple therapy patients are eligible for study participation. Further, text has been added to the Screening Assessments section (Page 10, Line 8) to highlight flexibility in the inclusion criteria.

5. Will not the authors analyze rate of COPD exacerbation? Is there any plan to compare rate of moderate to severe exacerbation between two groups?

Rates of COPD exacerbation will be analyzed as additional analyses but are not included as specific primary or secondary endpoints. The manuscript has been drafted to focus on the primary and secondary endpoints only.

6. It will be great if the authors provide study visits and testing as table. It will be helpful for readers to better understand the study protocol.
A table regarding study visits and testing will be supplied as supplementary material (Supplemental Appendix 1) as the size of the table is too large for the manuscript. Language supporting the availability of the supplemental appendix has been added to the section “Screening Assessments” (Page 10, Lines 1-2).

7. It is not clear whether medication change during the study is allowed. Please describe specifically in method which medication is allowed to add during the study period.

It is critical for the interpretation of study results that respiratory medications be controlled similarly across all subjects at all sites. However, during the study, changes in COPD medications are permitted for a legitimate medical need to protect the subject and will not be documented as a protocol deviation. All medication changes will be closely monitored and recorded in the case report forms (CRFs). Additional language has been included in the Respiratory Medication section on Page 11, Lines 4-6.

Minor Comments:

1. Page 6, 20th line. GOLD 2/3 severity is not exactly equal to FEV1 30~60% predicted. I recommend to delete the expression of GOLD 2/3 severity.

The expression of GOLD 2/3 severity has been removed from the Overview section of Methods on Page 6, Line 22.

2. Page 6, 20th line. The authors stated that patient with a history of moderate-to-severe COPD exacerbation in the 12 months is inclusion criterion. However, this should be changed to history of more than 2 moderate or one severe exacerbation.

The language has been updated per request in the Overview section of the Methods on page 6, Line 22 through page 7, line 1.
3. In Table 1, adverse event rates. I recommend to change from exacerbations & hospitalization to AEs, SAEs, and UADEs.

Table 1 has been retitled and reconfigured to more clearly define the primary and secondary endpoints, including the removal of the term “adverse event rates” on page 21.

Reviewer #2

Introduction: Last sentence: "The primary objective......:" Is the main objective to compare the number of acute exacerbations in one year or to compare the "time to first exacerbation"? The primary outcome mentions the latter. Both are different and need to be clarified.

The manuscript has been updated in the Primary Outcome Measures section (Pages 7, Line 15 & page 8, line 4) to clarify that the primary objective is to reduce moderate or severe COPD exacerbations which will be assessed by the primary endpoint of time-to-first moderate or severe COPD exacerbation.

Methods: “Randomization will be stratified ......:" How is it proposed to stratify based on prior PR? We understand that patients need to fulfil criteria for optimum medical treatment before getting the planned intervention, however, the protocol requirement assumes that all participating sites have a structured PR program running. The authors should justify why this is required. Similarly, the reason for stratification based on ICS use should be justified as to why multiple parameters are being used for randomization? Any impact of such a strategy on sample size and power of study should be clearly mentioned. If this has been already been considered then it should be mentioned.

We would like to first clarify that stratification is based on participation in pulmonary rehabilitation maintenance rather than pulmonary rehabilitation in general. Due to the limited access of pulmonary rehabilitation programs, experience with pulmonary rehabilitation or ongoing pulmonary maintenance were not required inclusion criterion. However, it is well established that participation in pulmonary rehabilitation impacts secondary endpoints of the protocol; therefore, to ensure the measured effects of TLD are not due to varied pulmonary rehabilitation maintenance programs, we developed a stratification process to ensure both the TLD and sham groups have participants with similar levels of pulmonary maintenance.
Pharmacological management with ICS is optional; however, the impact of ICS administration would likely affect the primary endpoint, as ICS administration has been linked to decreased COPD exacerbations. To ensure appropriate assessment of the treatment effect of TLD using moderate or severe COPD exacerbation as a primary endpoint, it is important to stratify the use of ICS between TLD and sham groups.

The use of multiple parameters to stratify randomization does not have an impact on the statistical power of the trial.

A sentence addressing these stratification measures has been included in the Overview section of the Methods on Page 7, Lines 9-10.

Patient recall and recruitment: "Phone visit follow-ups .....:" Authors should discuss whether this can be a source of recall bias. The frequency of phone calls should be mentioned. Memory aids should be described in more details; are these similar to symptom diary cards?

Page 9, section “Patient Recall and Recruitment” has been updated (Page 9, Lines 12-13) to specify that phone call follow-ups will occur monthly, excluding months where an in-person follow-up visit is completed. Further, details on the memory aid have been expanded to explain that the aid will record daily symptoms of exacerbation, any changes to medications, and unscheduled office or ER visits and hospitalizations.

Blinding and Group Allocations:

At each site, the first three participants......:" if the first three participants in each site are going to be analyzed separately, will this not deplete the total patient pool and compromise the calculated sample size? Or will they be also included in the ITT analysis? Please clarify.

The first three participants at each site are not included in the statistical power-calculation of the study and will not be included in the analysis for the endpoints of the trial. The completion of 3 procedures per site prior to randomization are included for training and operational purposes. A study total of 520 subjects (n= 120 roll-in + n=400 randomized) is estimated based on the number of sites (n=40). Clarifying language has been added to the Statistical Analysis section (Page 13, Lines 2-6) to highlight only randomized participants are included in the primary and secondary endpoint analyses.

Table 3: Exclusion criteria point No 19:
Authors need to explain the genesis of these contraindications, whether they were adapted from a previous study, or have been specifically kept to allow patients to be considered for Bronchoscopic lung volume reduction procedures?

The contraindications listed for Exclusion Criteria No. 19 are related to the technological specifications of the device and the mechanism of action for the procedure. These contraindications have been developed following numerous animal studies and clinical trials. Additional detail related to airway size and diseased lung tissue are provided below.

Screening chest CTs are required to ensure compliance with the current Instructions for Use (IFU), which specify the recommended airway size for each size of catheter (small, medium, and large). Chest CT scans prior to the procedure are required to ensure the airways are of appropriate size consistent with the IFU. Further, due to known adverse events, sufficiently long mainstem bronchi are required to perform the procedure to reduce risk to the patients. These adverse events have been previously reported.

The targeted lung denervation procedure delivers radiofrequency energy through the bronchial tissue to attenuate/ablate the branches of the vagus nerve and denervate the lung. Therefore, diseases or conditions such as severe bullous disease, lobar attenuation, and emphysema which result in abnormal or diseased lung parenchyma are not ideal candidates for TLD. In the case of emphysema, patients who have \( \geq 50\% \) emphysema are excluded due to the reduced benefit from the procedure.

Finally, discovery of a mass which requires treatment would result in additional therapy which may affect the results of the study.