Reviewer’s report

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)

Version: 0 Date: 16 Dec 2019

Reviewer: Chin Kook Rhee

Reviewer's report:

In this manuscript, the authors describe the protocol of AIRFLOW-3 study. AIRFLOW-3 is very important and promising study. This manuscript is basically valuable, however, I have some comments.

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.

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.

3. Page 8, 17th line. The authors mentioned that changes in spirometry and plethysmographic lung volume measures is secondary outcome. However, plethysmographic lung volume measures are missing in table 1. Also, 6MWT is missing.

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.

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?
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.

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.

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.

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.

3. In table 1, adverse event rates. I recommend to change from exacerbations & hospitalization to AEs, SAEs, and UADEs.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

Yes

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Yes

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

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