Responses to comments THELANCET-D-17-04610:

1. Please indicate after each of the reviewers' points the text changes which have been made (if any) and the line number on the revised manuscript at which your change can be found. [Line numbers can be added to your word document using the 'page layout' tab. Please select continuous numbers.]
Response:
We have added line numbers to the document.

2. When interpreting editorial points made by reviewers, please remember we will further edit the final manuscript if accepted
Response:
We agree with this.

3. Please indicate any authors who are full professors
Response:
This was already indicated in the first submission. Full professors are Bryan Williams, Abraham Kroon, Hannes Reuter, Gregg W. Stone and Mark Bates.

4. For randomised trials please follow the CONSORT reporting guidelines http://www.consort-statement.org and include a CONSORT checklist.
Response:
Not applicable.

5. Please follow CONSORT for abstracts (eg method of randomisation)
Response:
Not applicable.

6. At the end of the methods section please state the role of the funder in: data collection, analysis, interpretation, writing of the manuscript and the decision to submit. Please also state which author(s) had access to all the data, and which author(s) were responsible for the decision to submit the manuscript etc.
Response:

7. Please give 95% confidence intervals for hazard ratios/ odds ratios
Response:

8. Please limit the summary to pre-defined primary endpoints and safety endpoints.
Response:

9. Please report all outcomes specified in the protocol
Response:

10. Please explain any deviations from the protocol
Response:
Not applicable.

11. If any exploratory outcomes are reported that were not pre-specified, please make it clear that these analyses are post-hoc
Response:

12. p-values should be exact to 4 decimal places (eg $p<0.0001$). Two decimals are acceptable in tables for non-significant p-values.
Response:

13. Please provide absolute numbers to accompany all percentages
Response:

14. Please provide numbers at risk for Kaplan-Meier plots
Response:
Not applicable.

15. Please provide the text, tables and figures in an editable format.
Response:

16. For figures please consult
http://download.thelancet.com/flatcontentassets/authors/artwork-guidelines.pdf
Response:

17. If accepted, only 5-6 non-text items (figures or tables) can be accommodated in the print edition; additional material can be provided for a web appendix.
Response:

18. Please provide a research in context panel with 3 parts: Systematic review (which includes a description of how you searched for evidence and how you assessed the quality of that evidence); the added value of the study; and Interpretation of the totality of evidence when added to previous work.
Response:

19. If you have not yet done so, please return all signed authorship statements and conflict of interest forms. A paragraph summarizing authors' disclosures must be made in the manuscript, please.
Response:

20. For any personal communication, please provide a letter showing that the person agrees to their name being used. We also require signed statements from any named person in the acknowledgements saying that they agree to be acknowledged
Response:
Not applicable.

21. Please ensure there is a statement of contributions explaining what each author contributed at the end of the text
Response:

22. Please ensure that there is a section in the Methods section confirming ethics approval and consent from all patients has been obtained.
Response:

23. As corresponding author, please confirm that all authors have seen and approved of the final text
Response:
This confirmation has been added to the submission letter.

24. Our production system is not compatible with Endnotes. Please convert to normal text.
Response:

25. Please note our guideline length for research articles is 3000 words. Allowing for additional material requested by reviewers and editors we can allow a little leeway but we hope for final manuscript below 3500 words (4500 words for RCTs).
Response:

26. Please provide a revised manuscript, a tracked changes version showing the changes made, and a point-by-point response to ALL EDITORS' and reviewers' comments - typed immediately following each specific point.

Response:

27. PLEASE do not use boxes for replies. This slows checking and can result in a delayed decision.
Response:
We have not used boxes.

Reviewer #1: The authors performed a prospective, one-arm, open-label, proof of principle clinical trial to assess the safety of a endovascular baroreceptor amplification device in patients with resistant hypertension. The study participants were recruited at six European centres between December 2013 and February 2016. The primary outcome measure was the incidence of serious adverse events. Among the 30 participants, the authors found that the intervention to be effective in reducing blood pressure and that the safety profile was acceptable. The manuscript is very clearly written. The authors may wish to address the following comments:

1) Although this is a proof of principle trial and a small sample size is understandable, the statistical analysis section should describe the rationale of recruiting 30 patients.

Response:
The primary endpoint of this study was the incidence of serious adverse events at 6 months and secondary endpoints included changes in office and 24-hour ambulatory BP. No formal hypothesis testing was planned. We decided to conduct an prespecified analysis of safety after 30 patients had completed the study. The safety and efficacy data of the first 30 patients should warrant future, randomized controlled studies with formal hypothesis testing. We have rewritten this in the Statistical analysis (line 213) as follows:
Line 214-215: **An prespecified analysis was planned of the incidence and nature of SAEs and UADEs after 30 patients had completed the study. Hypothesis testing was not pre-specified.**

2) In the Results section, it is reported that none of the variables tested in the univariate analyses appeared to be associated with change of 24-hr mean ambulatory SBP at six months. It is not clear why these variables in particular with selected as potential risk factors. Also, the results of these analyses should be reported (possible in an appendix). With a sample size of 30 patients, it is possible that some of these risk factors were not significantly associated with the outcome because of lack of adequate statistical power rather than lack of association. Therefore, reporting the results would allow the readers to judge whether there is no evidence for an association or the magnitude of change could potentially be clinically relevant but lack statistical significance.

Response:
The reviewer makes a very useful suggestion to include the data on potential factors influencing the BP response, with the caveat that as a first-in-man study focused primarily on the evaluation of safety, the study size may not have adequate statistical power to exclude an impact of these variables on the BP response. We now have carefully selected eight variables that potentially are predictors of the BP response due to the intervention that modifies sympathetic outflow: age, gender, baseline BMI, baseline 24-hour mean ambulatory SBP, baseline office heart rate, baseline eGFR, earlier renal denervation therapy, and site (right or left ICA) of device implant. These variables may be proxies for sympathetic activity or are procedure-related. We did a multivariate linear regression analysis and report the individual betas of these eight variables in supplemental table 1. We have rewritten this in the Statistical analysis as follows:
Line 222-224: **A multivariate linear regression model was applied to explore which baseline and procedural characteristics were related to the change in 24-hour mean ambulatory SBP at 6 months.**
And in the Results section:
Line 303-307: **In a multivariate linear regression analysis no association was found between change of 24-hour mean ambulatory SBP at 6 months and any of the following: age, gender, baseline BMI, baseline 24-hour mean ambulatory SBP, baseline office heart rate, baseline eGFR, earlier renal denervation therapy, and site (right or left ICA) of device implant (all p>0•05, supplemental table 1).**

3) The change in number of antihypertensive medications and DDD from baseline to six months follow-up was tested using paired t-test. Is this the right test considering the possibility that these

variables may be skewed? Was the distribution of these two variables checked?

Response:
The reviewer makes an important point. We have now tested the distribution of the change in number of antihypertensive medications and DDD and had to conclude that there was indeed no normality. The paired *t* test was therefore not correctly used. We re-analyzed the data with the appropriate nonparametric Wilcoxon Signed Rank test. We have rewritten this in the Statistical analysis as follows:
Line 224-225: **A Wilcoxon Signed Rank test was used to compare the change in number of antihypertensive medications and DDD from baseline to 6-month follow-up.**
Because of this non-normal distribution we now also present the data with median and interquartile range in the Results section:
Line 313-316: **Median number of antihypertensive medications was reduced by 0•50 (interquartile range 1•25 to 0•00; p=0•0020) and median DDD were reduced by 0•42 (interquartile range 2•13 to +0•09; p=0•010) units at 6 months.**

Reviewer #2: The authors present new clinical data on a device for endovascular baroreflex amplification in patients with severe hypertension. The hypothesis of the clinical trial is clearly stated and appropriate clinical background describing the clinical need for such a study is well done. THe protocol is described appropriately and the data is analyzed in an appropriate fashion, leading to conclusions that are not overstated and, in fact, are very carefully described as being positive in that they should stimulate additional study.

Response:
We thank the reviewer for their supportive comments.

Reviewer #3: Title Endovascular baroreflex amplification for resistant hypertension: a safety and proof-of-principle cohort study.

Wilko Spiering and colleagues reported the results of a prospective, first in human, open-label study using a novel endovascular baroreceptor amplification device (MobiusHD) to treat resistant hypertension.
The first objective of the present study was to test the safety of the device. The authors reported 20% (N=5) of serious adverse events, particularly 2 strokes were observed.
The second objective was to observed changes in office BP and 24-hour ambulatory BP at 6 months of follow-up.

My comments are the following

1) The scientific background of the device is very low. The authors mentioned some experiments in canine models. However, no report has been previously published to demonstrate the effect of the MobiusHD device on the baroreflex. In comparison, baroreceptor activation therapy demonstrated in animal models specific hemodynamic (heart rate, increase baroreflex sensitivity), hormonal (decrease of norepinephrine but no effect of RAAS) and kidney (sodium excretion) effects. Particularly in the present report, there was no change of heart rate during the follow-up period, which is not expected if the device inhibit the sympathetic nervous system.

Response:
[Mark's work to be added]

2) The rationale of the MobiusHD device is not detailed enough. Is there a sufficient radial stress on

the carotid artery to reshape the sinus? It would be very important if the authors can demonstrate a change in carotid artery diameters before and after the implantation using Doppler ultrasound or echo-tracking.

Response:
[Mark's work to be added]

3) MobiusHD device have been implanted both on the left and the right side of patients. The authors did not report the changes of BP in each subgroups. This point is of particular interest because for baroreceptor activation therapy drop of BP were greater on the right side.

Response:
The reviewer raises an important observation from the baroreflex activation therapy studies where a greater BP reduction is reported with electrical stimulation of the right ICA compared with the left ICA. As was discussed above we did a multivariate linear regression analysis to explore which baseline and procedural characteristics were related to the change in 24-hour mean ambulatory SBP at 6 months, including site of device implantation (left versus right). As is shown in supplemental table 1 the regression coefficient of right-sided implantation was 13.23 (95% CI -4.24 to 30.70) in this model. The reduction in 24-hour mean ambulatory SBP at 6 months was 18 (SD 20) mmHg for the 19 patients who received the device in the right ICA versus 26 (SD 18) mmHg for the 11 patients who received the device in the left ICA. We therefore must conclude from this small sample that there is no indication that patients have a greater reduction in BP with a right (or left) device implantation.

4) There were no data reported changes of the carotid artery on the area of the device implantation using Doppler ultrasound or CT angiogram to control for neoatherosclerosis proliferation (which can appears during the first six months) or hypertrophy of the carotid wall. It is an important concern regarding safety data.

Response:
[Data from Suji to be added]

5) It is difficult to draw conclusion regarding the BP changes in this study because of its design as mentioned by the authors in the discussion. The main limit is the absence of data regarding true treatment adherence with plasma/urine detection because self-reported diary compliance is not superimposable.

Response:
We agree that this first-in-human, open-label safety study is insufficient to draw any firm conclusions on BP changes. However, we know from multiple studies that patients with resistant hypertension are characterized by poor adherence to antihypertensive medication. If the MobiusHD does not lower BP, we only can conclude that the 'BP-lowering effects' we have noticed must be explained by use of *more* antihypertensive medication. We think this is not very realistic in this cohort of patients with resistant hypertension, but of course cannot be 100% sure of this by design of this study. As stated in the paper, only sham-controlled, double blind, randomized controlled trials will give insight in the true BP-lowering effects of this device. These trials (CALM-START and CALM-II) are now under way. In both these trials use of antihypertensive medication will be carefully measured.

6) Regarding the safety of the procedure, it is quite embarrassing that the two patients having stroke were not explored using cerebral MRI. What was the reason to not perform this exploration?

Response:
We agree with the reviewer that cerebral MRI, more specific diffusion-weighted MRI, would have given more specific information whether cerebral ischemia was present in both cases. The protocol of the study prescribed to assess for intracranial thrombus of hemorrhage using CT scan or MRI if a new neurological deficit was determined during post-procedure monitoring. In both patients CTA was performed according to the local protocol. No MRI was performed afterwards since this would not have changed the conclusion that ischemia occurred and would not have influenced treatment. We would like to emphasize that diffusion-weighted cerebral MRI will be performed in all subsequent studies if there are any cerebral sequelae. This has been an important learning point from this first-in-human study.

7) One quarter of patients were previously treated with renal denervation, which may have also several interaction with sympathetic nervous system particularly renal baroreflex.

Response:
This is an important finding of the study, i.e. that the MobiusHD device appeared to reduce BP where renal denervation had previously been unsuccessful. One can only speculate as to the reasons for this. An obvious reason is that renal denervation did not succeed in these patients in achieving its objectives of adequately denervating the kidneys and/or reducing central sympathetic drive. A similar reason has been suggested for the failure of the Symplicity HTN-3 study to meet its primary objective of lowering BP. One could also hypothesize that the 8 patients that were treated with renal denervation before were 'pretreated' and that therefore their BP response would even be more pronounced. However, the multivariate regression analysis did not indicate that earlier treatment with renal denervation was a predictor for the BP response, but again this small sample size does not allow to draw any firm conclusions on this.

Reviewer #4: This is a proof-of-principle clinical trial, first in man with a novel endovascular baroreceptor amplification device in patients with resistant hypertension. Patients were treated with, a stent-like device implanted in the carotid artery designed to enhance baroreceptor sensitivity. The primary endpoint was the incidence of serious adverse events (SAE) at 6 months. Secondary endpoints included changes in office and 24-hour ambulatory BP. Mean age was 52 years and 50% were male. Mean baseline office BP was 184/109 mmHg, and mean baseline 24-hour ambulatory BP was 166/100 mmHg, despite use of a mean of 4·4 antihypertensive drugs. Device implant was successful in all 30 patients (100%). Six months after implantation 5 SAEs had occurred in 4 patients (13·3%). 24-hour ambulatory BP was reduced by 15/8 (95% CI, 7-23/3-13) at 3 months, and by 21/12 (95% CI, 14-29/7-16) mmHg at 6 months ($p<0·005$ both for SBP and DBP compared with baseline). The authors interpret the data as endovascular baroreceptor amplification using the MobiusHD device was effective in lowering BP, with an acceptable safety profile.

This is a very interesting study with a novel device. It is consistent with data from the previous RHEOs trial where surgical implantation to stimulate the baroreceptor also resulted in a sustained fall in BP. The paper is well written and is clearly a pilot study as the authors state. The problem lies with data presentation.

Response:
We thank the reviewer for their interest in our findings.

1) Figure 3 provides little meaningful information. It should be changed into figure 3a and 3b where the baseline means and subsequent systolic BP with SD are shown at baseline, 3 and 6 months. Same should be done with diastolic BP (3b). With statistics in the graph much like the SYMPLICITY-3 data

were shown in the Bakris, et.al. JACC, 2015. Same holds for figure 4. If want to reduce figure number then would only show the ABPM data and put office data in text since this was a safety trial.

Response:
We thank the reviewer for this helpful suggestion and we have amended the figure accordingly.

2) Table 2 is problematic, while it shows number of events it is unclear whether some of these occurred in same person. Thus, suggest a more traditional rank order of adverse events with percentage of patients with each problem and in legend describe how many people had more than one adverse event. The current table is just a listing and have no idea about number of events in individual participants.

Response:
We thank the reviewer for this helpful suggestion and we have amended the table accordingly.

3) Last table adds nothing and is generally not significant-would omit and can add a sentence in the text.

Response:
This table has been deleted.