PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Can Patiromer allow for intensified Renin Angiotensin Aldosterone System Blockade with Losartan and Spironolactone leading to decreased albuminuria in patients with Chronic Kidney Disease, albuminuria and hyperkalaemia? An open-label randomised controlled trial - MorphCKD
AUTHORS	Mårup, Frederik; Peters, Christian; Christensen, Jeppe; Birn, Henrik

VERSION 1 – REVIEW

REVIEWER	Mjøen, Geir Oslo universitetssykehus Ulleval, Department of Nephrology
REVIEW RETURNED	24-Nov-2021

GENERAL COMMENTS	The study protocol is thorough and of good quality. The study seems worthwhile. I would only recommend modifcation, and that is to shorten the introduction. It is twice as long as it should be

REVIEWER	Barzilay, Joshua Kaiser Permanente, Endocrinology
REVIEW RETURNED	25-Nov-2021

GENERAL COMMENTS	Well done, clear protocol. Just a few clarifications/typos. I number them using the author page numbers: 1. Page 4, line 18 - An analysis... 2. Page 5, line 29 - why is the level is albuminuria different between those with and without DM? Please clarify. 3. Page 6, line 5. If a patient receives lisinopril 10 or losartan 25 or 50 prior to study enrollment, the protocol implies that the dose of RAAS will not be increased. If that is so - then you are not maximizing RAAS blockade. Are only those not on RAAS prior to study to have maximum RAAS blockade? Please clarify this point. 4. Page 6, line 21 - why the difference in ALB between DM and no DM, and why are you now using different cut points than before and specifically why these cut points? ..... Line 33 - why are you now using ALB >1000 mg? what is the rationale for this cut point? ..... Line 36 - "concealment"? This is an open study. The participant knows whether he is receiving the powder. What is concealed?

	5. Page 7 - line 26 - Albumin 6. Page 8 - line 5 - do you have data on which you rely to arrive at a 30% "failure" rate? 7. Page 10, line 8 - it sounds like you will have one morning urine at the start and end of the study. Yet you say there will be an average of 2 urines used to estimate ALB. Please clarify. ..... Line 11- PWV and PWA ARE measured.... 8. Page 11, line 23 - In case

VERSION 1 – AUTHOR RESPONSE

Reviewer: 2
Prof. Joshua Barzilay, Kaiser Permanente
Comments to the Author:
Well done, clear protocol.

Just a few clarifications/typos. I number them using the author page numbers:

1. Page 4, line 18 - An analysis...
Corrected.

2. Page 5, line 29 - why is the level is albuminuria different between those with and without DM? Please clarify.
Thank you for pointing to this, which is now clarified in the manuscript. The lower threshold for patients with diabetes is considered relevant as international guidelines suggest a more aggressive approach to treating albuminuria in this group of patients, where the renoprotective effects of treating lower levels of albuminuria is well documented.

3. Page 6, line 5. If a patient receives lisinopril 10 or losartan 25 or 50 prior to study enrollment, the protocol implies that the dose of RAAS will not be increased. If that is so - then you are not maximizing RAAS blockade. Are only those not on RAAS prior to study to have maximum RAAS blockade? Please clarify this point.
We fully agree to this point, which is now clarified in the discussion section. To avoid greater complexity, patients already receiving ACE-I/ARB were allowed to remain on their current dose and commence on Spironolactone. Alternatively, we would either have to include a large number of different ACE-Is and ARBs as potential study drugs or switch all patients to e.g. losartan. We agree that in clinical practice, an increase of ACE-I/ARB may be attempted prior to spironolactone, and we have now included this as one of the limitations of the study: “Fourth, patients on an ACE-I/ARB at inclusion may be on a sub-maximal dose of these medications when Spironolactone is added as per protocol to their current treatment. This was considered necessary to avoid the complexity of either having to manage a large number of different ACE-Is or ARBs as potential study drugs or requiring an initial switch to e.g. Losartan, which may increase the duration of the run-in phase significantly and thus, the risk of early participant drop out.”

4. Page 6, line 21 - why the difference in ALB between DM and no DM, and why are you now using different cut points than before and specifically why these cut points?
We have addressed the issue of different criteria of U-albumin excretion in DM and non-DM patients in our response to reviewer’s comment 2. A lower U-albumin excretion is accepted at randomization

to allow for some reduction of albuminuria resulting from the increase in RAAS-blockade during the run-in phase. These cut points (150/300 mg/g) were selected to allow for a further, clinically significant reduction in albuminuria during the study period. We have modified the text to clarify this.
..... Line 33 - why are you now using ALB >1000 mg? what is the rationale for this cut point?
This cut point refers to stratification at randomization only. The rationale is to minimize imbalances in patients with severe albuminuria as such may have a different pathophysiology and thereby response to treatment compared to patients with more moderate albuminuria. We have included this in the text
..... Line 36 - "concealment"? This is an open study. The participant knows whether he is receiving the powder. What is concealed?
This has now been clarified as “allocation concealment” implying that the physician does not which group the patient will be assigned to prior to randomization.

5. Page 7 - line 26 - Albumin
Corrected

6. Page 8 - line 5 - do you have data on which you rely to arrive at a 30% "failure" rate?
We are aware that this estimate is associated with uncertainty; however, unfortunately to our knowledge there are no data available to support a different estimate.

7. Page 10, line 8 - it sounds like you will have one morning urine at the start and end of the study. Yet you say there will be an average of 2 urines used to estimate ALB. Please clarify. ..... Line 11- PWV and PWA ARE measured....

Thank you for pointing to this potential misreading. We will perform one morning urine at baseline, two morning urines at randomisation and end of study respectively as per Table 1. This is now also emphasized in the “Data collection” section.

8. Page 11, line 23 - In case
Corrected
Reviewer: 1
Competing interests of Reviewer: none

Reviewer: 2
Competing interests of Reviewer: none