Author's response to reviews

**Title:** Differential effects of phosphate binders on pre-dialysis serum bicarbonate in end-stage kidney disease patients on maintenance haemodialysis

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**Author's response to reviews:** see over
Reviewer 1:

1. The stated aim of the study was "to investigate the effects of phosphate binders on pre-dialysis serum bicarbonate in ESKD patients on maintenance haemodialysis". However, there is no control group to inform the reader whether 'other' binders have a positive, negative or neutral effect on serum bicarbonate - we cannot tell. All one can say is that renagel is different from the rest.

Response: The reviewer highlights a good point, and we thank the reviewer for an opportunity to re-word the study intention. To clarify the intention of the study, we have changed the aim of the study to reflect this and to now say “to investigate the differential effects of phosphate binders on pre-dialysis serum bicarbonate in ESKD patients on maintenance haemodialysis when comparing patients taking different binders”. (Please see page 1,2,3)

2. In my own unit it is standard practice to prescribe oral sodium bicarbonate to all patients whose venous bicarbonate is below target - were none of the study patients taking sodium bicarbonate? If not, I am surprised that they were able to achieve the bicarbonate levels reported.

Response: We appreciate the reviewer’s concerns and need to add to the text that it was standard practice to supplement bicarbonate at monthly blood audit in both units when serum bicarbonate fell below 18. Given the results, the use of these supplements either bicarbonate bath 40mmol/L or oral supplements would only bias toward a negative effect in the study for subjects taking sevelamer hydrochloride. (Please see page 8)

3. The authors mention a concern about long-term effects of lanthanum but reference a paper which studied it for 6 years without any adverse effects – this comment seems inappropriate.

Response: We have now re-worded that “despite concerns about long term effects of lanthanum long-term follow up for 6 years has not supported these concerns” by referencing a paper. (Please see page 4 and reference number 18)

4. There are a few typographical errors in the references which need correcting - for example references 1, 5, 8, 9, 10, 13 etc. Some of these may be special character errors by the computer.

Response: We have now corrected these typographical errors.
Reviewer 2:

The authors have identified 292 patients that I presume remained on HD during the 18 month study period (Dec 2008 – June 2010). These patients switched phosphate binder usage during the 18 month study period. Were these patients removed from the subsequent analysis? If a patient that switched phosphate binder, moved from 1 group to another, this means their data does not really represent the effect of “long term” usage. Please provide the number of patients that remain at each of the 6 month study points. Please provide information of the baseline phosphate binder usage in Table 3.

Response: We have now added the numbers of patients that remained at each of the 6 month study period in Table 3. The numbers of patients were 292 at June 2009, 260 at December 2009 and 237 at June 2010. Distributions of patients eat each category of phosphate binders were as follow: Group A (Calcium and/or Aluminum binders) approximately 34%-37%, Group B (Sevelamer hydrochloride alone) 27%-29%, Group C (Lanthanum carbonate alone) 8%-9%, Group D (Sevelamer hydrochloride and Calcium and/or Aluminum binders) 21%-23% and Group E (Lanthanum carbonate and Calcium and/ Aluminum binders) 7%-8. There was only 5-10% of patients who switched phosphate binders categories. To take account into this effect, multilevel mixed-effects linear regression was used allowing both random and fixed effects of medication along the different study period.

The authors should also provide the demographic information in Table 2 for the different groups.

Response: For the above information that reviewer requested, we have now added demographic information for each group of phosphate binders usage at baseline in Table 2.

The study design means that the “pre” phosphate binder bicarbonate values are not available. Hence, it is possible that differences are due to bias by indication.

Response: Given the previous reports on acidosis with sevelamer hydrochloride use, the patient were less likely to be placed on sevelamer hydrochloride if they are already acidotic. This may possibly bias to a negative effect, by indication.