Author's response to reviews

Title: A randomized, double-blind, placebo-controlled trial of calcium acetate on serum phosphorus concentrations in patients with advanced non-dialysis-dependent chronic kidney disease

Authors:

WAJEH QUNIBI (QUNIBI@UTHSCSA.EDU)
WOLFGANG C WINKELMAYER (winkelmayer@stanford.edu)
RICHARD SOLOMAN (Richard.Solomon@vtmednet.org)
MOUSTAFA MOUSTAFA (mamoustafa@hotmail.com)
PAUL KESSLER (pkessler@nabi.com)
CHIANG-HONG HO (ChiangHong.Ho@fmc-na.com)
JONATHAN GREENBERG (jonathan.greenberg@fmc-na.com)
JOSE A DIAZ-BUXO (Jose.Diaz-Buxo@fmc-na.com)

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Author's response to reviews: see over
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Authors:

WAJEH QUNIBI (Qunibi@uthscsa.edu)
WOLFGANG C WINKELMAYER (wcw1@stanford.edu)
RICHARD SOLOMAN (richard.solomon@uvm.edu)
MOUSTAFA MOUSTAFA (mamoustafa@hotmail.com)
PAUL KESSLER (pkeessler@nabi.com)
CHIANG-HONG HO (ChiangHong.Ho@fmc-na.com)
JONATHAN GREENBERG (Jonathan.Greenberg@fmc-na.com)
JOSE A DIAZ-BUXO (Jose.Diaz-Buxo@fmc-na.com)

Reviewer's report
Title: A randomized, double-blind, placebo-controlled trial of calcium acetate on serum phosphorus concentrations in patients with advanced non-dialysis-dependent chronic kidney disease
Version: 2 Date: 29 November 2010
Reviewer: Maurizio Gallieni
Reviewer's report:
This is a straightforward randomized placebo-controlled study assessing the effects of calcium acetate as P binder in CKD patients. It is the first study addressing the question with a correct methodology, although numerous previous non controlled studies arrived to similar conclusions as this article. Calcium acetate allowed good P and PTH control, but it also induced an increase in calcium levels. In the results section, the Authors report: “At 12 weeks, the percentage of subjects who had hypocalcemia was 5.4% and 19.5% for the calcium acetate and the placebo groups respectively.” A similar sentence should also be introduced for hypercalcemia, reporting its prevalence at 12 weeks (13.5%, according to figure 3B). The latter information should also be included in the abstract. The number of episodes of hypercalcemia during the 12 weeks of study should also be reported in the two groups.

Our Response: We have added the suggested sentence in the abstract and the results section as suggested by the reviewer. There were 18 episodes of hypercalcemia in the calcium acetate group and 5 in the placebo group. This statement was added to the manuscript on page 9.

The calcium x phosphate product is an artificial index, which has been much criticized (W C O'Neill. The fallacy of the calcium-phosphorus product. Kidney International 2007; 72: 792-796). This reviewer suggests that information on the CaxP product do not add much to what is already clear by looking at Calcium and phosphate singularly. It can therefore be removed form the text. Figures 2c and 3c should also be removed.
Response: We agree with the reviewer’s comment. We have removed CaxP product from the text and tables 1 & 2 and also removed figures 2c and 3c as suggested by the reviewer.

In the discussion, it should be stated that although Ca and P levels might be normal, it is possible to observe a positive calcium balance when high doses of calcium based binders are used.

Response: A statement was added in the discussion section “However, although serum calcium levels might be normal, it is possible to develop a positive calcium balance when high doses of calcium based binders are used”.

Level of interest: An article of limited interest
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests: Genzyme : Reimbursements for educational activities (lectures). Genzyme is the producer of Renagel, a P binder. It is a competitor of Calcium Acetate

Reviewer's report
Title: A randomized, double-blind, placebo-controlled trial of calcium acetate on serum phosphorus concentrations in patients with advanced non-dialysis-dependent chronic kidney disease
Version: 2 Date: 17 November 2010
Reviewer: David Wheeler

Reviewer's report:
The authors present the results of a randomised double-blind placebo-controlled trial of calcium acetate in CKD stage 4-5 patients not receiving dialysis at the time of recruitment. They may wish to consider the following comments in relation to their study.
1. More details of the interventional product are required. What is the dose? Is this product manufactured by one of the companies with which the authors are affiliated?

Response: Under Study Design; top of page 6 it is stated that “The starting dose of study drug was guided by the serum phosphorus level at the end of the washout period. Patients with serum phosphorus levels between 4.5 and 5.0 mg/dL received an initial dose of 1 gelcap per meal; those with phosphorus levels between 5.1 and 6.0 mg/dL started with 2 gelcaps per meal and those with phosphorus levels > 6.0 mg/dL were administered a starting dose of 3 gelcaps per meal. Study participants returned for follow-up visits every 2 weeks. During these visits, the dose was titrated up to a maximum of 15 gelcaps per day. If, after 3 months of treatment, the serum phosphorus level remained > 5.5 mg/dL, or the iPTH was still > 110 pg/mL despite maximum daily dose of 15 gelcaps, the study protocol required that such subjects be withdrawn from the study for failure to control”.
Under results; second line it is stated that “calcium acetate (PhosLo® 667 mg capsules; Fresenius Medical Care North America, Waltham, MA, USA), the sponsor of the study.

2. As the authors concede, the study would have been made more interesting if urinary phosphate excretion had been reported. Likewise, measurement of serum fibroblast growth factor-23 levels would have made this manuscript more competitive.

Response: We agree with the reviewer’s comment. Unfortunately, these important measurements were not part of the protocol at the time the study was designed and conducted.

3. The high dropout rate was clearly a problem and needs to be explained in more detail. What happened to patients in whom phosphate remained “uncontrolled” (>5.5 mg/dl) despite taking 15 tablets per day. Were these patients compliant based on pill counts? It is assumed (but not stated) that no patients started dialysis during the study.

Response: As stated under discussion on page 14, a major limitation of our study is the drop-out rate and withdrawal rate for failure to control serum phosphorus or iPTH levels. In order to address the impact of the dropouts, an ITT analysis was used where all patients who received at least one dose of the study drug were included. This conservative analysis which was based on all randomized subjects may have lowered the percentage of those who achieved target serum phosphorus and iPTH levels in calcium acetate-treated patients. Moreover, as a consequence of the requirement that participants with uncontrolled hyperphosphatemia be removed from the study after 3 months, a large proportion of patients in the placebo group left the study at that time point. Thus, by such design, informative censoring was introduced into the study.

4. Was the PTH higher in the calcium acetate treated group because the serum calcium was higher or serum phosphate was lower? Might the potential cardiovascular benefits of a lower serum phosphate levels be offset by higher serum calcium levels? What is the evidence that hypocalcaemia (which occurred more commonly in the placebo group) is harmful? These issues should be discussed in more detail.

Response: It is difficult to dissect the effects of serum calcium and serum phosphorus on PTH secretion. As stated under results page 10, at 12 weeks, iPTH was significantly lower in the calcium acetate group compared with placebo. Under discussion, page 12, we stated that “calcium acetate can correct hypocalcemia which is a critical factor in stimulating PTH secretion and induction of parathyroid gland hyperplasia. During this study, hypocalcemia was observed in 5.4% and 19.5% for the calcium acetate and the placebo groups respectively. On the other hand, there was a small but significant increase in serum calcium in the calcium acetate group rendering it more effective than placebo in suppressing PTH secretion (Table 2 and Figure 2B)”. The reviewer then asked “Might the potential cardiovascular benefits of a lower serum phosphate levels be offset by higher serum calcium levels?” The potential role of serum calcium in cardiovascular disease is not well-studied and is controversial. Thus it is difficult to be precise in
answering the reviewer’s question. Finally, the reviewer asked “What is the evidence that hypocalcaemia (which occurred more commonly in the placebo group) is harmful?”. Severe hypocalcemia can lead to symptoms such as tetany but chronic hypocalcemia of milder degrees may be associated with increased risk of death in some but not all studies. We have not discussed these issues in details due to the space limitations.

5. The authors need to comment on dietary phosphate restriction (if any) and whether dietary phosphate intake was likely to have changed during the course of the study in either group.

Response: Patients were instructed to continue their diet as before the study. The following statement was added at the top of page 6 “Patients were instructed to continue their usual diet”.

6. Page 3. The syndrome of the CKD-Mineral Bone Disorder is not “newly described”, but perhaps newly redefined.

Response: The phrase “newly described” was deleted from page 3.

7. The authors discuss the KDOQI guidelines on management of the mineral bone disorder, but not mention the newer KDIGO guidelines that superseded.

Response: The reviewer is accurate but we only mentioned KDOQI because at the time the study was designed, KDOQI guidelines recommend that serum phosphorus be maintained within the target range of 2.7 to 4.6 mg/dL in stages 3 and 4 CKD but KDIGO guidelines were not released.

Level of interest: An article of importance in its field
Quality of written English: Needs some language corrections before being published
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests: In making a decision, the editorial board need to bear in mind that the reviewer is involved in two similar studies.