Author's response to reviews

**Title:** Conversion to lanthanum carbonate monotherapy effectively controls serum phosphorus with a reduced tablet burden: a multicenter open-label study

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**Author's response to reviews:** see over
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Rachel Gallears
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Dear Ms. Gallears,

On behalf of my coauthors, I am pleased to resubmit the manuscript titled, “Conversion to lanthanum carbonate monotherapy effectively controls serum phosphorus with a reduced tablet burden: a multicenter open-label study” (MS 1568284527443805) for publication in BMC Nephrology.

We have revised the manuscript to address the concerns of the reviewers. Please find enclosed a detailed response to the reviewers’ comments (changes indicated in red text) and a copy of the revised manuscript (clean and tracked change versions).

Please continue to direct all correspondences to me at the contact information listed below. Please do not hesitate to contact me should you have any questions. Thank you in advance for considering the manuscript for publication.

Sincerely,

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Response to Reviewer Comments

Reviewer 1 (Rajnish Mehrotra)
In this study, the investigators present the results of a large phase IV study done with lanthanum carbonate in which HD patients treated with other phosphate binders were switched to a 16-week period of treatment with lanthanum carbonate. The study enrolled 2763 subjects at 223 sites. The authors report that switching patients to lanthanum carbonate maintained the serum P in the same range as with the previous medications but was associated with a lower tablet burden, lower total daily dose, and greater patient and physician satisfaction and preference.

These general findings have been reported before for the drug lanthanum carbonate - the difference is that this is the largest assessment of the issue to date.

1. There is some form of disconnect in the argument presented - I agree with the authors that a lower tablet burden is a desirable thing with regard to patient adherence. But if adherence improves, so should serum P level. However, it did not. This demonstrates that while lowering tablet burden is good, it is not sufficient to affect the outcome of interest. This should be discussed more in the Discussion.
   We agree with the reviewers comment. If adherence improves over time we might expect the dose to decrease without the impact on phosphate levels. Unfortunately, this study is too short and does not capture the adherence data necessary to make this conclusion. The following sentence has been added to the second paragraph on page 13, “This observation plus findings from Chiu et al [14] suggest that although tablet burden may improve treatment compliance and quality of life, lowering or raising the number of pills does not necessarily influence phosphate levels.”

2. The authors present the results of daily dose in Figure 6. I would rather prefer for them to present the change in tablet burden. Patients don't really care how many mg of a drug there is in a tablet or a capsule but the number of tablets they need to take.
   Results of daily dose were presented in a figure because the study was based on the 500 mg tablet, which is generally not used when a 3 g dose is needed. However, we agree that patients are generally more concerned with the number of tablets rather than the dose they have to take. Thus, results of daily dose shown in Figure 6 have been replaced with the change in tablet burden. The figure legend for Figure 6 (p. 23) has been revised to read (changes noted in red text), “Figure 6. Tablet Burden Comparison
   Comparison of tablet burden of previous treatment with phosphate binders and treatment with lanthanum carbonate (intent to treat population). LC=lanthanum carbonate; SEM=standard error of the mean. *P<0.0001 for week 12 and 16 values from paired t test on change from baseline values. †The “Others” category consists mainly of combination therapies.” The figure depicting these data is provided as a separate file.

The first paragraph under “Daily Dose and Tablet Burden” has also been updated to reflect the change in the figure and now reads (p. 10; changes noted in red text), “There were significant reductions for all previous treatment groups in tablet burden (P<0.001; Figure 6) and daily dose (P<0.0001) at weeks 12 and 16 of treatment with lanthanum carbonate. The mean daily dose was significantly reduced from 7.2 g at baseline to 2.8 and 2.7 g at weeks 12 and 16, respectively (P<0.0001). Reductions in
daily tablet burden at week 12 ranged from 2.2±0.15 pills for patients previously
receiving calcium-based therapy (week 12) to 8.4±0.40 pills for patients previously
receiving 'other' treatments. Similar reductions were seen at week 16.”

“(Figure 6)” has been deleted from the first sentence of the secondary paragraph in
this same section (p. 10).

3. In the abstract, I would urge the authors to include the % of patients with controlled
serum P with the drug at the end of the 16 weeks. Furthermore, I think for the
authors to report the mean dose of the drug only among those with controlled level
is not a correct representation of the prescribing pattern to be experienced in
clinical practice. I would suggest that the authors report the mean drug dose in ALL
patients in the study or remove it.

As noted on page 8 of the manuscript, the percentage of patients with controlled
serum phosphate levels at the end of 16 weeks was 41.6%. This information has also
been added to the abstract (p. 2).

The statement in the abstract that read “Most patients with controlled serum
phosphorus were effectively managed with ≤3.0 g/d of lanthanum carbonate” has
been deleted.

The following sentence has been added to the first paragraph under “Daily Dose and
Tablet Burden,” (p. 10) “The mean daily dose was significantly reduced from 7.2 g at
baseline to 2.8 and 2.7 g at weeks 12 and 16, respectively (P<0.0001).”

4. I don’t mean to sound self-serving but I would urge the authors to discuss their
findings in light of our recent publication on pill burden, quality of life, and
adherence (Chiu et al, CJASN 2009) - a study that has external validity given that it
was done at three different sites in the United States and is the only study to have
considered pill burden (as distinct from number of medications).

This reference has been cited to support the following new statements added to the
second paragraph on page 13, “In a study conducted at 3 dialysis units across the
United States, higher pill burden was associated with lower health-related quality of
life and was not found to improve control of serum phosphate levels [14].” and “This
observation plus findings from Chiu et al [14] suggest that although tablet burden may
improve treatment compliance and quality of life, lowering or raising the number of
pills does not necessarily influence phosphate levels.”

5. There are two issues that need clarification. At this time, the 250 mg tablet is not
available in the United States but was used in the study. The authors should present
the time period over which the subjects were recruited. Moreover, the authors
should clarify if the older formulation or the new "optimized" formulation was used
for the study. Second, it is unclear why the dose was capped at 3750 mg. Moreover,
did the patients at the higher dose continue to use either the 250-or 500 mg dose or
could be switched to the 750 mg or 1000 mg dose? That would be useful information
for the readers when considering pill burden.

The study was conducted between January and December 2005. This information has
been added the first sentence under “Study Design” (p. 4) and reads as follows
(change noted in red text): "This was an open-label, phase IV, multicenter study
conducted in the United States between January and December 2005.”
The original chewable formulation of lanthanum carbonate was used for the study. The first sentence under “Study Medication” (p. 5) has been revised to read (change noted in red), “The original formulation of lanthanum carbonate was supplied by patients’ local pharmacies using the TrialCard® prescription program (TrialCard Inc, Cary, NC, USA); each card was study-specific and individually coded.” Also on page 13, seventh sentence in the second paragraph indicates that patients were taking the original larger lanthanum carbonate formulation (no longer manufactured).

Dosing complied with the US Food and Drug Administration approved Prescribing Information for Fosrenol® (lanthanum carbonate). According to the prescribing information for Fosrenol®, doses beyond 3750 mg/d have not been studied; thus 3750 mg/d is considered the maximum recommended dose. All patients initiated lanthanum carbonate at a dose of 1500 mg/d, divided with meals. The dose was titrated upward or downward every 2 to 3 weeks in increments of 750 mg/d to achieve target PSPL or a maximum daily dose of 3750 mg was reached. No patients entering the study previously received lanthanum carbonate. The last sentence under “Study Medication” (p. 5) has been revised to read (changes noted in red text), “All patients, regardless of prior therapy, received an initial daily dose of 1500 mg (250-mg or 500-mg tablets) in divided doses with meals that was adjusted, if necessary, in 2 to 3 weekly increments of 750-mg per day, up to the recommended maximum dose of 3750 mg per day to achieve serum phosphorus levels within the KDOQI guidelines target range of 3.5 to 5.5 mg/dL [1.13–1.78 mmol/L]).

6. The authors have to be careful about over-interpreting the "preference" and "satisfaction" data, particularly for the physicians. These physicians were, after all, investigators in a study sponsored by the manufacturer - they probably had good opinions about the drug and hence, this finding has limited external validity.

The statement in the fifth paragraph of the Discussion section (p. 14) that addresses limitations with regard to physician bias has been strengthened to read as follows (changes noted in red text), “Physicians were compensated for their time and involvement in this study, and thus, physician bias with regard to product preference and satisfaction cannot be excluded.”

Reviewer 2 (Patrick C. D’Haese)

In their interesting paper Vemuri et al based on a study in a 2763 patients from 223 US dialysis centres present further evidence for conversion to lanthanum carbonate monotherapy to effectively control serum phosphate with a reduced tablet burden. This paper is of substantial importance for the nephrology community.

The paper is well written and the study set up is straightforward and methods are appropriate and well described. In view of the high number of participating centres the risk for bias of the results of this industry-sponsored study is limited although it can’t be excluded as correctly stated by the authors. The discussion is based on sound data and is written in a balanced way. The limitations of the study are clearly stated and reference has adequately been made to existing literature data.
Minor remarks

1. Page 5: It should be clearly mentioned who took off the interviews and completed questionnaires (nurse, nephrologists, specialized interviewers …). Who prepared the questionnaires?

The questionnaires were completed by the investigators (ie, physicians) and patients. For the product satisfaction questionnaire, the subject version consisted of 7 items and the investigator version consisted of 6 items. The questionnaire assessed the rater’s satisfaction with the current medication that the patient had been receiving for hyperphosphatemia at baseline and weeks 12 and 16; questions were rated on a scale ranging from “strongly agree” (1) to “strongly disagree” (4). For the product preference questionnaire, the subject version consisted of 6 items and the investigator version consisted of 7 items. This questionnaire was administered at weeks 12 and 16 to determine the patient and investigator’s preference of medication (ie, study medication vs previous medication for hyperphosphatemia).

The first paragraph of the Assessments section (pp. 5–6) has been modified to read as follows (changes noted in red text): “The intent-to-treat (ITT) population included all patients who received at least 1 dose of study medication and underwent at least 1 primary efficacy evaluation. The primary objectives of the study were to evaluate efficacy and patient and physician satisfaction and preference. Predialysis serum phosphorus was measured at screening, at baseline visit, and at the end of the titration (week 12) and maintenance (week 16) periods of lanthanum carbonate treatment. A questionnaire that assessed satisfaction with phosphate-binder medication was completed by the patient and physician at baseline and at weeks 12 and 16 using a 7-item questionnaire for patients and a 6-item questionnaire for physicians; questions were rated on a 4-point Likert scale with answers ranging from “strongly agree” to “strongly disagree.” For patients taking medication for hyperphosphatemia before participating in the study, a product preference questionnaire was completed by patients and physicians to determine preference for lanthanum carbonate or previous medication at weeks 12 and 16 using a 6-item questionnaire for patients and a 7-item question for physicians that addressed various aspects of treatment and overall preference.”

2. Page 6, para 3: “… alkaline phosphatase …’ Did they measure total alkaline phosphatase or the liver isoenzyme?

Total alkaline phosphatase was measured. The word “total” has been added before “alkaline phosphatase” on page 6 of the manuscript.

3. Page 7: How did the investigators check compliance of therapy?

Treatment compliance was not directly assessed in this study other than via the physician satisfaction questions, “patient compliance,” and “easy to take medication.” The patient satisfaction questionnaire also included a compliance item, “rarely missed a dose.”

The following sentence has been added to the end of the second paragraph under “Statistical Analysis” (p. 7), “Treatment compliance was measured indirectly through questions provided on the physician and patient satisfaction questionnaires (“patient compliance,” “rarely missed a dose,” and “easy to take medication”).
4. Page 8: ‘… stomach sickness …’ Although not significant (?) was the incidence of this adverse event lower or higher in the lanthanum carbonate group? Overall, 19.7% of patients reported to “feel sick to stomach” at baseline and this decreased to 16.8% of patients at week 12 (P=0.1176). In all groups (binder naïve, previous sevelamer HCl, previous calcium-based, and other therapies) the percentage of patients who reported to “feel sick to stomach” improved from baseline, with findings for other therapies being the only group to achieve statistical significance (23.9% at baseline vs 15.1% at week 12; P=0.0348). As noted on page 11 of the manuscript, the most common adverse events reported by all patients (N=2643) during the study were gastrointestinal and included diarrhea (5.4%), nausea (7.9%), and vomiting (5.0%). Comparison of the incidence of adverse events at baseline and at study endpoint was not determined. No change has been made to the manuscript.

5. Page 9: The investigators noticed a significant reduction in tablet burden when using lanthanum carbonate. Perhaps they should comment in the discussion on what the impact of this might have on the cost-price for treatment. In general, lanthanum carbonate and sevelamer are both more expensive than calcium-based binders. No cost analysis was conducted in this study to determine the impact reduced tablet burden may have had on the cost of treatment. Without such data, we do not feel it would be appropriate to speculate. No change has been made to the manuscript.

6. Page 10: Did the authors measure ionized calcium. If so these data should be reported as this directly relates to the significant increase in PTH. Corrected calcium (ie, albumin-adjusted serum calcium) rather than ionized calcium was measured in this study. On page 6, second sentence of the first full paragraph has been revised to read (change noted in red), “Serum parathyroid hormone (PTH), corrected (ie, albumin-adjusted) serum calcium, and calcium × phosphorus (Ca × P) product were also measured at screening, baseline visit, and weeks 12 and 16 of treatment with lanthanum carbonate.” The word “corrected” has also been added before “Ca” in the first sentence under “Laboratory Assessments” (p. 11).

7. Page 11, para 1: Was the incidence of AE’s with lanthanum carbonate different from that observed with their previous medication? This study did not compare adverse events reported with lanthanum carbonate with adverse events that might have occurred with previous medications. The incidence of adverse events reported with lanthanum carbonate during the study was consistent with the known safety profile for this product.

On page 11, the first paragraph under “Safety and Tolerability of Converting to Lanthanum Carbonate” begins with the following “The incidence of adverse events reported during the study was consistent with the known safety profile for lanthanum carbonate.”
8. Page 11, para 2: Again it is not clear whether the authors measured the liver isoenzyme of alkaline phosphatase. If not the rise in total alkaline phosphatase seen at weeks 12 and 16 could have been due to an increase in the bone alkaline phosphatase fraction which is reasonable in view of the increase in PTH, in other words a normalization of the bone formation rate. Perhaps this could be mentioned in the discussion?

Total alkaline phosphatase was measured as indicated in question 2.

The last sentence in the last paragraph of the Discussion has been revised to read (p. 15, changes noted in red text), “There was a statistically significant increase in PTH after a change to treatment with lanthanum carbonate, thus it is reasonable to suggest that the increase in alkaline phosphatase observed at weeks 12 and 16 may have been due to normalization of bone formation rate (ie, increased bone alkaline phosphatase fraction).”