Author's response to reviews

Title: Effect of cinacalcet availability and formulary listing on parathyroidectomy rate trends

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Author's response to reviews: see over
First we would like to thank editors and reviewers for thoughtful comments that were very helpful. We are pleased to be given the opportunity of submitting a revised manuscript and we hope you find our substantial revision and changes to the manuscript satisfactory. Point by point answers to comments can be found below.

**Response to reviewers**

**Reviewer 1**

1. *There really is not a strong case made for undertaking this analysis. The authors cite prior research reporting changes in PTX rates over time in the US and suggest these change may be related to other treatment options and guidelines, but are vague on how these differences are important here.*

We restructured the introduction to make our case more convincing. In summary, we are extending the period of analysis of prior study from 2007 to 2010. This doubles the observation period of PTX rates after cinacalcet introduction, allowing evaluation of long-term effects such as delayed PTX.

2. *Why is it important to analyze PTX trends in a “real world” setting? Is there an inherent “value” placed on PTX? Should we be trying to increase or decrease rates? The more relevant policy question is which alternative is most cost-effective way to manage SHPT, not whether PTX rates are increasing or decreasing.*

Cinacalcet has been shown to reduce PTX in short-term RCT. However, RCT often include compliant patients that tolerate the drug well. When given in a “real world” setting, tolerability of the drug may affect its efficacy. Also, short-term RCT would not capture delayed PTX by one or two years. These points are mentioned on page 4.

PTX is considered the last option for treatment of secondary hyperparathyroidism. Therefore, it is considered when medical treatment (such as phosphate control and vitamin D) has failed. Because PTX is a relatively cheap intervention at only one point in time, an expensive drug taken for many years cannot be cheaper. However, to evaluate the cost-effectiveness of cinacalcet in the overall management of SHPT is a more complex issue and is beyond the scope of this study.

3. *The authors need to explain how the formulary process works in Canada for readers who are from other countries.*

We explained briefly the process on page 6, first paragraph of Intervention period.

4. *Figure 1 shows a cohort catchment period of 1/1/99-12/31/10 whereas the methods report the cohort catchment period as spanning 1/1/01-12/31/10. Please clarify this discrepancy.*

The time span was different because we use data from 2 years prior in order to evaluate comorbidities and incident/prevalent status. Start of the study is really 2001. In figure 1,
patients that ended follow-up before 2001 were excluded (n=2950). However, we agree that this is confusing and simplified the chart by removing those patients.

5. How was a prior history of PTX or kidney transplant ascertained?

Prior PTX was ascertained using the same method as for the outcome. Codes for kidney transplant are given on page 5, last paragraph.

6. What were the criteria that Amgen used to “carefully select” patients who received cinacalcet between Sept 2004-June 2006?

Unfortunately, no specific criteria are available. Physicians were aware that only a few patients could receive the drug through this plan. Therefore, the list of potential patients was already relatively short before being presented to Amgen.

7. What do the investigators mean by “rigorously analyzed” with respect to requests for cinacalcet use? This sounds like a prior authorization program (that’s what it would be called in the US).

Before being reimbursed for a selected patient a prior authorization needs to be obtained from RAMQ by filling a form. We clarified this point on page 7, first paragraph.

8. Please explain why age, sex and dialysis modality would change over time. What evidence is there that these are related to PTX? (p. 7)

It is well described (in USA and Canada at least) that the dialysis population is getting older. This may be explained by various factors including improved survival and initiation of dialysis among older patients than before. Description of those changes may be in found in the USRDS annual report (for USA) or CORR (for Canada). We added those references to the text. These patients’ characteristics may also influence PTX rates, as shown in Slinin et al. (reference now provided in the text).

What is meant by mean age (p. 8), as in, when was age calculated?

On pages 9, mean age was calculated at index date (2001 for prevalent patient and dialysis initiation for incident patients). We changed the sentence to make it clearer.

We have data presented in different sets of time periods: bimonthly PTX rates, patient characteristics every two years, medication exposure every year. These should be reconciled to a more consistent time presentation, particularly given the high mortality rates in chronic dialysis patients. 9. Why was medication use calculated on an annual basis when the PTX rates were bimonthly?

Patients’ characteristics are now presented annually in Table 1. Bimonthly rates were chosen for PTX since this led to the most efficient numbers of points in the ARIMA models. (see page 7, Statistical analysis section) However bimonthly rates are
more variable than annual rates. Therefore trends are easier to capture visually when presented annually, explaining while we preferred to present subgroup PTX rates annually instead of bimonthly.

In addition, there is no justification for the study of medications at all, especially the dosing. The decision to calculate average daily dose over a 12 month period in chronic dialysis patients who may switch off/on and back & forth between these medications is problematic and undermines any potential conclusions. This whole section is distracting to the purpose of the study.

For the same reason as for subgroup PTX rates and because medication use was not the main focus, medication use is reported annually for simplicity and efficient use of space. While not being the main focus, we believe that presenting medication use is important for this study, since changes in medication use is a plausible alternative explanation for changes in rates as mentioned by the second reviewer. Because our design does not allow any robust inference between cinacalcet availability and PTX rates, we prefer to present trends of all factors that may have influenced the rates. Finally, we believe that dosing of phosphate binders is important to report. As we can see on Figure 4, calcium-based phosphate binders use does not appear to change over time. However, mean annual dosing shows that calcium-based phosphate binders dose did decrease with time, which may in part explain a reduction in PTX rates as suggested by the second reviewer. For these reasons, we would prefer to keep these analyzes.

10. The underlying study cohorts appear to have an increasing proportion of prevalent patients over time: wouldn’t this in turn increase SHPT rates over time and potentially increase PTX rates also?

We agree to this comment and mentioned this fact on page 13.

11. The current study looks at PTX rates in Quebec and they are quite different from PTX rates reported in the US during overlapping time periods. What are the implications of these differences? How generalizable are the present findings outside the Quebec system? The authors suggest that wider availability of cinacalcet in Quebec may have had a stronger effect on lowering PTX rates as compared to the US, but cinacalcet was on prior authorization (approval) per the authors after it was approved. This would mean that use was more restricted in Canada.

Prior authorization is easy to obtain for a patient satisfying the criteria described in the text (p.6). Since a patient not fulfilling these criteria would also clearly not have an indication for PTX, this prior authorization should not impact access. Reimbursement is the key factor since this drug is very expensive. For this reason, cinacalcet access for patients truly at risk for PTX is less limited in Quebec than in the US.
12. The broad calculation of doses of other medications does little to explain how individual patients were being managed clinically. In addition, as noted before, this aspect of the study is not well justified.

This study evaluates trends and not individual patients. Please refer to point 9 for our justification.

Table 1: not sure why this is reported on two-year increments

We now report annual data.

Table 2: data does not need to be in a table and should just be incorporated into the text

Done.

Table 3: analysis does not fit into the purpose of the study

We justified this table on point 8.

Figure 1: cohort catchment period does not match text in Subjects & Methods

The figure was changed as detailed on point 4.

Figure 3: no justification for breaking out PTX rates by these variables: when was age calculated?

Age, sex, and prevalent/incident status are important factors for SHPT. For this analysis, age is calculated at the beginning of every year (added to Figure 3 legend).

Figure 4: This analysis does not fit into the purpose of the study as noted above.

We justified this analysis in preceding points.

Reviewer 2

1.) There was a lack of complete or at least adequate ascertainment of cinacalcet use by all dialysis patients followed in this province during the period of observation, making it very difficult to determine to what extent, if at all, cinacalcet availability contributed to the observed declines in PTX rates.

We completely agree with the statement that ascertainment of cinacalcet use was not complete during the study period. However, time points when cinacalcet became available and reimbursed are well known. Because we were not trying to evaluate association between cinacalcet use and PTX at the patient-level, incomplete ascertainment of exposure does not influence the ARIMA model. This fact is now recognized on page 14 (last paragraph of discussion).
2.) Given the very low proportion of patients using cinacalcet in 2006, and the virtual absence of prescription claims prior to this time, it is hard to argue that this alone could account for the drop of PTH rates that started even prior to 2006 per Figure 2. The authors offer anecdotal data from Amgen about the number of patients that might have been treated with cinacalcet prior to 2006, but this is unconvincing and certainly not empirical evidence to draw inferences from.

The total number of PTX performed annually in years 2001 to 2004 ranged from 29 to 57. According to Amgen data, 60 patients (40 through their program and 20 from private insurance) received cinacalcet in 2005 and 90 (58 through their program and 32 through private insurance) in 2006. If 25 to 33% of patients receiving cinacalcet would have needed a PTX if not taking the drug, this would be enough to decrease rates by 50% as seen on Figure 2. While it remains speculative, this is highly plausible because those first patients were usually the patients with the most severe SHPT. We added the annual count of PTX in order to better interpret the impact of few patients receiving the drug. However, we clearly acknowledge on page 13 (first paragraph) that our study cannot establish a causal link between cinacalcet and PTX rates.

3.) It is unclear why the PTX rates remained stable with the increase in cinacalcet usage. One would surmise the opposite if cinacalcet where indeed the major mitigating factor. The authors argument about how only a few PTX would be needed to change the rates substantially is uncompelling.

As mentioned in the preceding points, PTX is a rare intervention reserved for very severe SHPT. Annual counts in the whole province is below 57 PTX. Because severe SHPT may not be completely controlled in all patients using cinacalcet, and because not all patients would tolerate or prefer cinacalcet over a PTX, it is expected that rates of PTX would not fall indefinitely. This point is detailed on page 11.

4.) An equally plausible, if note more plausible, explanation for the findings is the decreased use of calcium-based phosphorus binders which coincided with the fall in PTX, perhaps by decreasing the stimulus for hypercalcemia and thus, the clinical impetus for PTX.

We agree that other factors than cinacalcet may contribute or even completely explain the change in PTX rates. Among our list our alternative explanations, we included the decrease use of calcium-based phosphate binders on page 13.