Reviewer's report

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

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Reviewer: Theresa I Shireman

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

The authors clarified several points as requested but there remain a few concerns.

Major Compulsory Revisions
1. The justification for this study remains weak. The “new” arguments call for a person level analysis to test whether cinacalcet delays the time to PTX and whether some patients cannot tolerate cinacalcet side effects (end of first paragraph). The paper does present work that can answer the question of whether the availability and formulary listing of cinacalcet modified the trend in PTX rates. This is a very basic question and is not particularly compelling: e.g., we find out that yes, PTX rates changed. The implications of this for patient care are unknown. At least the investigators do not overstate the importance of their findings. My concern is that Amgen will try to exploit these results to their benefit without a full understanding of the “health” implications, though I understand that is beyond the control of the investigators.

Authors’ response:
Unfortunately, a person-level analysis was not possible because parathormone levels were not available as mentioned in the discussion. To clarify the rationale to conduct this study, we added the following sentence in the introduction: “In a recent placebo-controlled trial, 18% of patients in the cinacalcet group discontinued the drug because of adverse events and 7% underwent a PTX.”

I remain unconvinced by their simple insertion of the statement as justifying this work.

As mentioned by the reviewer, we were careful not to overstate our results and detailed the limitations during 2 pages in the discussion (pages 13-14). What third parties, including Amgen, will try to say using our results is out of our control. However, we would think that Amgen will prefer to use the results of the
recent EVOLVE trial where cinacalcet did reduced the incidence of PTX.

The authors are correct that they cannot control how Amgen would use these results: I understand that.

Essential revisions
2. Age is computed differently for incident (during the observation period) and prevalent patients. It should be computed the same way for all subjects to avoid artificial findings.

The authors have corrected this appropriately.

Discretionary Revisions
3. The 4th response from the authors states that they included a cohort catchment period going back to 1999 to collect comorbidities, but I neither see anywhere in the methods the definition of comorbidities nor in the results the presentation of those analyses.

The authors have clarified this information in the manuscript.

4. The authors did not discuss the generalizability of their findings beyond Quebec as requested.

Authors’ response:
“Finally, this study is limited to a single Canadian province, and results may not be generalized to other populations with different healthcare practices.”

This really does not address how/why generalizability is an issue, just as the whole manuscript has not directly dealt with the overall picture here. The trade-offs between PTX and cinacalcet may well be driven by economic incentives. What is important is how Canadian health care policies might differ from other countries/provinces. This would provide a better context for the work.

5. Since persons with private insurance do not have observable prescription claims, it seems they should be excluded entirely.

Authors’ partial response:
Except that some patients were excluded (n=10678 instead of 12795) and that the PTX count was lower (172 instead of 267), results were similar. For the ARIMA, January 2006 remained statistically significant, but June 2005 was also significant.

Okay, so persons with private insurance coverage should indeed be excluded but weren’t.

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:

As I previously disclosed, I had a contract with Amgen 06/01/08 – 12/31/09 to study the cost-effectiveness of cinacalcet.