Sir,

Secondary hyperparathyroidism (sHPT) is not a complication of chronic kidney disease (CKD), but part of a cybernetic process to protect the organism from potential adverse effects of phosphate accumulation. According to our present knowledge, far away from complete understanding of this process, in CKD both intact parathyroid hormone (iPTH) and fibroblast growth factor 23 (FGF23) are the regulating factors for decreasing phosphate by increasing phosphaturia and iPTH is the main factor for increasing calcium by increasing calcium reabsorption in the kidney and mobilizing calcium from the bone. 1,25(OH)₂ vitamin D is the connection between these two regulating mechanisms. FGF23 down regulates the 1-α-hydroxylase activity [1, 2] and is responsible for the reduced synthesis of 1,25 (OH)₂ vitamin D, the main factor of phosphate- and calcium-resorption control in the gut and therefore, of the total body phosphate and calcium load. Phosphate itself increases both the iPTH and FGF23 production. This consequently means that increases of iPTH and FGF 23 are both directed against phosphate accumulation (Figure 1).

FGF23 itself decreases iPTH synthesis and secretion in a negative feedback loop [3] and reduces phosphate mobilization from the bone via the decreased iPTH action. A decrease of 1,25 (OH)₂ vitamin D as a consequence of FGF23 increase allows further increase of iPTH. Both iPTH and 1,25 (OH)₂ vitamin D have short-term proresorptive and calcitropic effects on the activated osteoclast cells [4, 5]; however, long-term action of 1,25 (OH)₂ vitamin D results in a decreasing number of osteoblasts and osteoclasts, suggesting a state of low turnover, which is entirely contrary to the long-term action of iPTH. The mass transfers of calcium and phosphate to and from the bone at a certain time are the results of these opposite effects.

These are the major considerations in thinking about the results obtained in sHPT clinical trials such as IMPACT [6, 7]. As sHPT in CKD patients is a continuously ongoing cybernetic process and as this study had only a remarkably short observation time (28 weeks) within this process, it is crucial to know the pre-study washout iPTH of the patients and how iPTH changed during this washout period. Did all patients included in the study come up to the expectations of increasing iPTH during wash out? Almost two-thirds of the screened patients (62%) failed to meet the stipulated iPTH study entry criterion, namely the range 300 pg/mL < iPTH < 800 pg/mL after wash out.

What was the sHPT treatment in the pre-washout period? Active vitamin D or active vitamin D analogs? What was the proportion of patients on cinacalcet? Was there any change of medication? For example, from active vitamin D to cinacalcet or was there only an interruption of an ongoing active vitamin D treatment for the washout period? Considering that almost two-thirds of the patients failed prescreening, three stipulations have to be made: (i) the profile of the screening failure patients versus the ones which qualified for the study have to be laid open in detail—which is not the case, (ii) the conclusion is near that the screening has been very selective, but in this case more limiting on the cinacalcet arm (iii) there is limited information why particular patients failed the screening. The latter especially carries importance for trial results as this impacted the result predictive value serum calcium.

Treating sHPT does not necessarily mean lowering iPTH at a minimum in the shortest time frame, but avoiding continuous increasing of iPTH with the potential risk of parathyroidal autonomy, as the continuous phosphate accumulation in CKD drives the cybernetic system one way with continuously increasing FGF23.

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**Fig. 1** Cybernetic compartment model of CKD–MBD, modified from [11]. Dashed lines indicate negative feedback of an increasing concentration or factor; full lines indicate positive feedback of an increasing concentration or factor. P (Phosphate) and Ca (Calcium) indicate serum concentrations in the intravascular compartment. Parts of the system below the dark dashed line become less important as renal function decreases; however, extrasosseous calcification becomes more important to correct P/Ca metabolism. Parathyroid hormone (PTH), fibroblast growth factor 23 (FGF23).
Lowering iPTH is a dose-dependent effect of those drugs that decrease iPTH production or secretion. In the results of the IMPACT study paper however, there is only one information about dosing in the evaluation period, for example in the oral stratum the paricalcitol dose was 3.5 ± 3.5 μg (mean ± SD). As usually, 70% of the observations lie within one standard deviation of their mean, based on a theoretical normal distribution, ~15% of the patients had no paricalcitol medication at the end of the study assessment period. This might highly be likely the reason for the reincrease of iPTH during weeks 21–28. However, it may be presumed that these patients must have had higher doses of paricalcitol during weeks 1–21. To avoid leaving considerable uncertainty to the readers, it would have been necessary to show also the mean ± SD of serum calcium, serum phosphate and of the drug doses over time.

There is a remarkable imbalance in diabetes mellitus and cardiovascular disease both in the i.v. and in the oral stratum, and the death rate was higher in the paricalcitol group. However, that was not the purpose of this study and the study was not designed to answer that.

In my opinion, the well known and most important differences of the therapeutic effects of cinacalcet and paricalcitol are summarized in Table 2, in detail, the decrease of serum calcium and phosphate in the cinacalcet group versus the increase of calcium and phosphate in the paricalcitol group. The levels of AP and BAP decreased in the paricalcitol groups; however, conflicting with previous results [8, 9], the levels increased in both strata in the cinacalcet groups.

Both the stimulation of the vitamin D receptor and the modulation of the calcium-sensing receptor decrease iPTH; however, on the cybernetic regulation of calcium and phosphate they have substantially different effects. The authors have stressed the importance of alkaline phosphatase and FGF 23 in the study design paper [6]. However, in the results’ paper, there is no information about FGF 23 at all.

The readers want the authors to publish the complete impacting circumstances very carefully. Are there some results they would rather not tell or is it not to give importance to? Hemodialysis patients treated with cinacalcet results they would rather not tell or is it not to give importance to [8, 9], the levels increased in both strata in the cinacalcet group. However, in the paricalcitol groups; however, conflicting with previous results [8, 9], the levels increased in both strata in the cinacalcet groups.

In the IMPACT SHPT study, a number of subjects (62%) failed to meet the inclusion criteria of iPTH >300 pg/mL or iPTH <800 pg/mL following the washout period, with 41% of subjects failing to demonstrate an iPTH level of >300 pg/mL as described in the manuscript [7]. This suggests that only those patients who developed rising iPTH levels during washout were randomized and fall within the KDIGO recommendations that suggest

Conflict of interest statement. J.B. has received honoraria from Amgen, Genzyme, Shire and has been a consultant for Genzyme and Amgen.

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Reply

Sir,

We acknowledge the very cogent review of secondary hyperparathyroidism (SHPT) and the inter-relationships between iPTH, FGF23 and 1,25(OH)2 vitamin D in the setting of chronic kidney disease (CKD) by Dr Braun and would like to provide responses to the questions raised in the letter. Regarding the term of the study duration (28 weeks), the IMPACT SHPT study [1] was based on the design of the ACHIEVE study [2] comparing cinacalcet plus low-dose vitamin D with flexible doses of vitamin D without cinacalcet. We agree that longer term studies with extended observation periods are needed to determine the differential effects of calcimimetic and vitamin D therapies on long-term clinical outcomes in patients with SHPT in the setting of CKD. It is important to note, however, that several observational studies have described the beneficial effect of activated vitamin D on survival in CKD subjects prior to dialysis [3] and in haemodialysis subjects [4–6].

In the IMPACT SHPT study, a number of subjects (62%) failed to meet the inclusion criteria of iPTH >300 pg/mL or iPTH <800 pg/mL following the washout period, with 41% of subjects failing to demonstrate an iPTH level of >300 pg/mL as described in the manuscript [7]. This suggests that only those patients who developed rising iPTH levels during washout were randomized and fall within the KDIGO recommendations that suggest
patients with marked changes in iPTH initiate or change treatment [8]. This also implies that patients who were perhaps ‘overtreated’ at screening were unlikely to have been included. Furthermore, subjects with rising iPTH levels during the washout period would have been randomly assigned to either treatment group.

Only sparse medication data were collected on subjects not randomized; therefore, information on the prior SHPT treatments for subjects not randomized is not provided. Of the 272 randomized subjects, 47.4% were receiving vitamin D or a selective vitamin D receptor activator (alfacalcidol 12.9%; calcitriol 11.0%; doxercalciferol 6.3% or paricalcitol 17.3%), 2.6% were receiving cinacalcet and 14% were receiving a combination of vitamin D and cinacalcet prior to the washout period.

The parathyroid hormone (PTH) responses are indeed dependent upon the doses of the treatments employed to block expression or secretion. While the longitudinal information on the median doses were not provided in the primary results manuscript, additional information on doses and PTH responses were recently described in a poster presentation at the ERA/EDTA. In both strata, an increasing proportion of subjects achieved KDOQI iPTH levels at weeks 8, 16 and 28, despite lowering in paricalcitol dose. With cinacalcet treatment, however, there was minimal or no increase in the proportion of subjects achieving KDOQI iPTH levels. Additionally, the longitudinal effects of paricalcitol and cinacalcet treatment in both strata on calcium phosphorus and PTH were shown biweekly till week 28. We agree that changes in calcium, phosphorus, FGF23, AP and BAP are important biochemical markers to be considered in paradigms of SHPT treatment. These data are planned for publication in a subsequent manuscript.

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