Author's response to reviews

Title: Comparison of velcalcetide (AMG 416) and cinacalcet in rodent models of uremia

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Author's response to reviews:

Reviewer 1 comments and responses

Comment 1. Cinacalcet is usually given per os daily, while velcalcetide would be given i.v. three times per week in dialysis patients. Although the authors insisted that the dose they employed in this experiment was comparable, did they also consider such different mode of administration.

Response: In the text we demonstrate that the short-term pharmacologic effects of cinacalcet and velcalcetide in these models are similar at the doses selected (e.g., p9, lines 12-15; p10, line 12). We also show that the level of cinacalcet tested have been shown in preclinical studies (p12, lines 9-12 and cited references) to be efficacious, and to correlate (on an exposure basis) with doses used in the clinic.

For two different molecules administered by different routes it is quite difficult to demonstrate that the dosing is comparable, and we do not make this claim beyond the pharmacologic observations noted above. We also describe the significant differences in pharmacokinetic properties between the two molecules and the important effects that this may have on their pharmacologic performance (p11). The change in route of administration for velcalcetide vs cinacalcet is an important potential advantage for this new medication. Overall we feel that this presents a fair comparison of the properties of velcalcetide and cinacalcet.

Comment 2. How was the changes of serum phosphorus level and urinary calcium excretion?

Response: We agree that these would be important supporting aspects to
measure. As mentioned in the paper (p12, line 5) we were unable to measure serum phosphorus in this study. This was due to study design limitations and limitations on sampling due to the number of other parameters being measured. However, the effects of velcalcetide on phosphorus has been described in a separate study which is cited in the text (ref 5). It was also not possible to measure urinary excretion in these studies.

Comment 3. How was the degree and changes of parathyroid hyperplasia at sacrifice?
Response: As discussed in the paper, the 1K1C model is an acute model of uremia which does not result in parathyroid hyperplasia observed in longer-term, chronic models (p11, line 5).

In the 5/6 Nx study we were not able to collect glands at the end of the study due to study design limitations as the study was conducted with an external contract laboratory. However, the effects of velcalcetide on parathyroid hyperplasia have been reported elsewhere as cited in the text (ref 5; p12, line 18).

Reviewer 2 comments and responses
Comment 1. It is worth stressing that on this topic clinical studies are expected more than animal ones, given that most information supplied by the present study has been already established.
Response: We certainly agree that clinical studies will be of the greatest relevance for assessing treatment options in this field. However, data from such a head-to-head clinical study between these two agents will not be available for some time, if at all. While the underlying pharmacologic properties of these two agents have indeed been reported previously, we feel that the detailed comparison of the agents in these two preclinical models will add value to the field.

Comment 2. The kinetics of calcium has been grossly described: given the critical importance of this point, a more detailed description of the behaviour of calcium changes in the hours following the administration of the two drugs would be worth reporting.
Response: Thank you for the suggestion. We have added a new table (table 1) with acute data points following the first week of dosing and the last week in the 5/6 nephrectomy study.

Comment 3. A table showing the number of the PTH and Ca values at the different times might be more informative than some figures.
Response: We have incorporated this information in the table described in our response to comment 2.

Comment 4. In the figure 3B it seems there is a rebound phenomenon of PTH levels at the 16th hour in the cinacalcet group: this is an unusual phenomenon, not yet described (as far as I know). Could the authors comment on this?
Response: We believe that this phenomenon makes sense in terms of the physiology as in response to reduced serum calcium, a “rebound” in PTH can occur as the body perceives a state of hypocalcemia. We have added some text
to more clearly point out this observation and our hypothesis for the cause. This edit is shown in the revised manuscript, starting on p12, line 22.

Comment 5. In the background section, some comment on which could be the claimed benefits for the use of this new drug as compared with cinacalcet would also be welcome.

Response: We have modified the text in the background section to make the potential benefits more clear (p5, line 1-4).