

Amgen Response to the Mimpara Assessment Report **(May 5th 2006)**

Summary

Amgen has read the Assessment Report with great interest and although there are aspects of its content that do not fully represent the clinical and economic evidence, we believe it to be a fair document representing a good quality piece of work. We have commented in detail on aspects of the Report and set out what we have taken as the main implications. We have also suggested how some further analysis could enhance the focus of the deliberations of the Appraisal Committee on groups of patients who will benefit from treatment with cinacalcet at a level of cost effectiveness which the Committee would find acceptable. This further health economic analysis could be carried out either by Amgen in discussion with PenTAG and the NICE Technical Lead, or by PenTAG in discussion with Amgen and the NICE Technical Lead.

In summary, the main conclusions appear to be:

- 1) Acceptance that the drug is efficacious;
- 2) Some concern over quality of studies, which we address below;
- 3) That use of the drug does not reach levels of cost effectiveness conventionally accepted by NICE. This we believe to be a key conclusion which would be modified if the PenTAG model were extended to allow more appropriate differentiation between subgroups of patients. The current modelling reflects appropriately neither the differential benefits achieved, depending on starting and finishing PTH levels of patients, nor the different dose levels required to produce these changes. It is our view that both of these need to be taken into account to come to an informed decision. This comment does not imply criticism of the PenTAG work. They were not provided with data in appropriate form to undertake such an analysis as Amgen had also not appreciated the significance of these aspects. These issues are discussed further in our commentary on the economic modelling, below.

Amgen Response to Issues Raised in the Assessment Report Relating to the Mimpara Clinical Data

Section 1.4.2

We welcome the in-depth summary of the cinacalcet clinical data and the Assessment Group's confirmation that cinacalcet is effective at meeting target PTH levels compared to the current standard of care. The report clearly accepts that the evidence of effectiveness is strong. However, the statement that cinacalcet is more effective among those with moderately elevated levels of PTH than among those with very high levels of PTH needs to be read with some care. It is certainly true that cinacalcet is more efficacious at reducing to target levels of PTH those patients who start close to those targets, rather than those who start further away. That should be no surprise and is fundamentally what the Assessment Report is saying. However, it does not follow that either the absolute reduction in PTH or the health benefit gained per dose of treatment is less in these higher PTH groups. Indeed the opposite is probably the case

Sections 3.6.2 and 3.6.3

The authors of the report share the view of the nephrology community that PTH is one of the important biomarkers of abnormal mineral metabolism in patients with end-stage renal disease. We do agree with the authors on the difficulty of linking biomarkers to final outcomes related to cardiovascular calcification or abnormal bone remodelling. Other biomarkers, such as cholesterol and albumin may have more established relationships with final outcomes, but the epidemiological literature on the role of PTH, while only emerging, supports the independent, yet significant, contribution of high PTH levels to mortality and cardiovascular complications. Better clinical evidence is needed to elucidate these relationships, not only for cinacalcet but also the treatments that currently make up the standard of care. In the meantime nephrologists worldwide have found consensus on target levels that balance the risk of cardiovascular complications with the risk of a dynamic bone disease and have commonly agreed on moderately elevated PTH levels as obtainable treatment targets. This consensus is reflected in the K/DOQI guidelines. Furthermore, K/DOQI guidelines stress the reduction of all markers of mineral metabolism, which is consistently achieved, to varying degrees, by cinacalcet. This joint reduction of all markers of mineral metabolism is not matched by the treatments that make up the current standard of care.

Section 4.6.1.4

This section discusses withdrawal from the Quarles study. This was a phase 2 study, with 71 patients. While it is true to say that withdrawal rates were higher in the placebo group than the cinacalcet group, the numbers for withdrawal were 4 and 2 respectively in the titration phase, and 7 and 4 respectively in the follow-up phase – due to the small overall numbers, it is likely that this is just an artefact of this one

study and is in contrast to the findings of all the other studies. Please see table below taken from the clinical study report for reasons for study withdrawal.

Table 8-8. Subjects Discontinued (ITT Subjects)

| Reasons | Placebo N = 35 n (%) | AMG 073 N = 36 n (%) | Total N = 71 n (%) |
|---|----------------------------|----------------------------|--------------------------|
| Total Discontinued | 11 (31) | 6 (17) | 17 (24) |
| Titration Phase | 4 (11) | 2 (6) | 6 (9) |
| Ineligibility determined | 1 (3) | 0 (0) | 1 (1) |
| Noncompliance | 1 (3) | 0 (0) | 1 (1) |
| Withdrawal requested | 1 (3) | 1 (3) | 2 (3) |
| Other | 1 (3) | 1 (3) | 2 (3) |
| Maintenance Phase | 0 (0) | 0 (0) | 0 (0) |
| Follow-Up Phase | 7 (20) | 4 (11) | 11 (16) |
| Administrative/Investigational decision | 1 (3) | 1 (3) | 2 (3) |
| Adverse event | 1 (3) | 0 (0) | 1 (1) |
| Death on study | 0 (0) | 1 (3) | 1 (1) |
| Withdrawal requested | 2 (6) | 2 (6) | 4 (6) |
| Other | 3 (9) | 0 (0) | 3 (4) |

Program: /stat/calci/c990740/analysis/final_all/statfiles/tables/programs/tab_prem_withdrwl.sas
 Output: /tables/outputs/rf/tab_03_prem_withdrwl (Date Generated: 28MAY2001)
 Data: /statdata/safssd/sasmap.ssd01

There is also a question raised as to how the missing data points were handled in the ITT analysis. Below are copies of the relevant sections of the study protocol with an explanation of the ITT analysis.

10.5.1.2 General Approach

The statistical methods will apply to the data collected up to the end of the maintenance phase. Data collected during the follow-up phase will be summarized only.

The primary analysis will be based on the ITT subjects. Any randomized subject who withdraws from the study during the titration phase will be considered a non-responder

in the analysis of endpoints expressed as proportions. The evaluable subset will be included in a secondary analysis.

Summary statistics (including n, mean, standard deviation [S.D.], median, minimum, and maximum) for continuous variables and number and percent for categorical variables will be presented. Ninety-five percent (95%) two-sided confidence intervals will be provided for the difference between means and between proportions for the two groups.

The ITT analysis will also be performed separately by age, sex, ethnic group, smoking status, and bone biopsy status as a stratified analyses.

Safety analyses will be based on all randomized subjects who receive at least one dose of study drug.

Every effort will be made to ensure the integrity of the trial is maintained by keeping treatment group assignment blinded during the study. Any unblinding of treatment code at any level (i.e., subject, investigator, and sponsor) will be documented. In the case of serious adverse events when breaking the blind is in the best interest of the subject, the Amgen SOP for unblinding clinical trials (AMG/020/01) will be followed. Data from subjects whose treatment codes are unblinded will be listed. The timing and reasons of unblinding will be included in the listing.

Proportion of subjects having a change in vitamin D analog dose during double-blind treatment

Summary statistics for the proportion of subjects having a change in vitamin D analog dose from baseline during double-blind treatment will be presented.

Missing Values

Subjects who withdraw from the study during the titration phase will be included in the ITT analyses as non-responders. All data from all subjects will be listed and tabulated. Subjects who withdraw from the study after the end of the titration phase will be incorporated into the analyses as follows:

For endpoints expressed as a proportion, the subject will be assumed a non-responder in the analysis. For endpoints expressed as a change from baseline, the last observation carried forward will be used in the analysis of the intention to treat population. In addition, sensitivity analyses to test the robustness of handling missing data will be performed using imputation techniques.

Efficacy Data Collected During The Follow-up Phase

Summary statistics will be presented for data collected during the follow-up phase. Only the primary and secondary efficacy endpoints will be summarized.

Section 4.6.1.5

The pooled analysis of cinacalcet safety data, as published by Cunningham and colleagues, was a first attempt to raise awareness among the medical community about the potential of cinacalcet to have a significant impact on final outcomes related to abnormal mineral metabolism. Amgen fully realises that these analyses were done post-hoc and in studies that were not set up to answer a question about final outcomes. However, we believe that the pooled analyses provide strong evidence for several reasons:

- 1) The safety experience was based on a comparison of almost 1200 patients enrolled at baseline. Regulatory authorities requested the studies to be conducted for a further 6 months with a subset of at least 500 patients to gain a better understanding of the long-term effects of cinacalcet. This request did not permit a differential selection of patients for the extension phase.
- 2) The survival curves only start to diverge after the titration phase, at the conclusion of which 1000 patients are still in the study. The ensuing 8 months were sufficient to establish relative risk reductions with relatively tight confidence intervals, in particular for cardiovascular complications and this despite the sharp decline in the patient population after month 6. It is generally recommended to stop survival curves if the number of patients at risk drops below 10, however more than 100 patients

contributed to the survival experience at month 12. We believe that the evidence can be interpreted as a strong signal in favour of cinacalcet, particularly in light of the biological plausibility. To address a specific point raised in the Assessment Report, depending on the outcome considered, different numbers of patients are considered failures, e.g. more patients experience cardiovascular hospitalisations than fractures, which explains the different numbers of patients still considered at risk in the survival analyses.

3) The 19% reduction in mortality is unlikely to be a chance event, given:
a) the biological plausibility, b) the epidemiological evidence published in the literature and cited by the authors of this report, and c) the fact that cinacalcet not only reduces PTH but also other, more established markers of abnormal mineral metabolism, such as phosphate, calcium and their product.

Section 4.6.1.5

The authors of the report write that only Quarles and colleagues (2003) report that placebo and active tablets were identical. We would like to clarify that all cinacalcet studies were double blind randomised placebo controlled trials, with identical tables and appropriate concealment of allocation. Below is an excerpt from the clinical study report from study 20000183 with an explanation of the blinding process – this is the same process for all the Amgen sponsored cinacalcet double-blind studies.

7.6.2 Blinding

Subject treatment assignment was blinded for this study. Bottles of study drug were labeled with a multi-language booklet label. The label contained the following information translated into the languages appropriate for the countries participating in the study: study number, blinded product identity, unique bottle identification number, directions for use and storage, lot number, and the name of the study sponsor. As each bottle was assigned to a subject, the subject identification number, initials, and date dispensed were written in the spaces provided on the label by the investigator or their designee.

To minimize the risk of subject treatment assignments becoming unblinded, the clinical manager and all Biostatistics, Data Management, and Safety Department personnel involved with the study were blinded to central laboratory-generated iPTH values (other than screening iPTH values) for the duration of the study. Clinical research associates (CRAs) and site personnel were not blinded to the iPTH values as this would have restricted their ability to monitor and conduct the study. iPTH values were not transferred into the Amgen clinical database until the day before unblinding the database (after all subjects had completed the study, all data had been collected from the study centers, and all clinical data queries had been resolved).

Access to the blinded treatment assignment was provided through the IVRS. The blind was not to be broken, except when knowledge of the treatment administered was absolutely necessary for the further management of the subject. In other circumstances, unblinding was to be considered a major protocol deviation. Whenever possible, the investigator was to contact the Amgen Clinical Manager (or delegate) before breaking the blind. The reason for unblinding was to be entered in the subject's case report form.

If the blind was broken in response to the occurrence of a serious adverse event, Amgen was to be notified within 1 working day, and a Serious Adverse Event form completed. In the case of accidental unblinding, the above procedure was to be followed, although a Serious Adverse Event form was not to be completed.

The reviewers also raise the potential for lack of concealment of allocation. This could be a potential issue due to the strong effect of cinacalcet on biochemical markers. We believe that potential breaches in concealment of allocation, or efficacy-related unblinding, are unlikely to introduce considerable biases, as the biomarkers can be considered hard measurable outcomes.

The report states that in Lien, there is inconsistency in reporting of lumbar spine measures as the BMD decreased in both groups with an improvement in T-score which was not deemed to be logical. However, as the paper reports there were no statistical differences in either BMD or T-scores in this group, so it is disingenuous to draw conclusions from this. The relationship between T-scores for a group of patients is not linear with BMD – T-scores are relative and dependent on age, race and gender, so it would be possible for a group of patients to have differing results for T-score compared with BMD. However, just to reiterate, there were no significant changes seen in lumbar spine measures of either BMD or T-score. Conversely, the cinacalcet treated group showed an increase in both T-score and BMD of the proximal femur compared with the placebo plus standard care group, consistent with a protective effect on cortical bone.

Section 4.6.2

The pooled mortality rate in the clinical trials was 7 per 100 patient-years, while the expected mortality rate for a similarly aged population in the UK renal registry is ~ 17 per 100 patient-years. However, the cardiovascular hospitalisation rate in the UK dialysis population appeared to be only 10 per 100 patient-years, while a rate of 23 per 100 patient-years was found in the pooled trial data. Whatever the reasons for

these discrepancies, these findings do not give strong support to the hypothesis that the trial population was healthier than a typical UK dialysis population.

Section 4.6.3.1

Evidence on the appropriate control of PTH is evolving as new research studies emerge that increase our knowledge about the pathogenesis of cardiovascular complications as a function of abnormal mineral metabolism. PTH targets of < 200pg/ml were agreed with the regulatory authorities prior to initiation of all cinacalcet clinical trials. These decisions were based on the best knowledge at the time, but it is now apparent that more moderate targets are clinically reasonable. Clinical over suppression of PTH, while always a risk, is much less likely with the more moderate treatment targets and appropriate use of titration algorithms. Moreover, EU observational data (Young NDT 2003) currently demonstrate that 50% of patients with ESRD remain below 150pg of PTH per ml.

Section 4.6.3.4

This section states that Lindberg and colleagues (2003) report that mean serum calcium levels increased by 4.7% in the cinacalcet arm compared to no change in the placebo arm. This is actually incorrect – Lindberg and colleagues reported that mean serum calcium levels *decreased* by 4.7% in the cinacalcet arm compared to no change in the placebo plus standard care arm (p<0.001).

Section 5.6.2.1

One of the parameters used in the sensitivity analysis of the cost-effectiveness model is cost of dialysis. This seems inappropriate. If costs of dialysis are taken into account, then any treatment giving an improvement in mortality outcome, even if it cost nothing, could potentially be deemed not to be cost effective, as prolonging life of ESRD patients will prolong dialysis time and therefore incur the associated costs of dialysis. The assessment turns from being one of cinacalcet to, in part, one of dialysis. As the cost effectiveness of dialysis is widely believed to exceed NICE conventional thresholds we potentially have the paradox that the more effective is a drug at keeping ESRD patients alive the less cost-effective it appears.

Amgen Response to Issues Raised in the Assessment Report Relating to the Mimpara Health Economic Data

We note that the economic model we submitted has been rejected. The grounds for this relate not to the model structure but to its base in the meta-analysis undertaken by Cunningham et al (2005). There seems to be a concern about the clarity of some of the Cunningham reporting and we have addressed this in our clinical section above. More fundamentally, there is a concern that the size of the patient numbers included in Cunningham et al is insufficient to support the long term extrapolation of outcome for which it has been used. While believing that our approach is a defensible one, we accept it has weaknesses, particularly relating to the small patient numbers on which key extrapolations have been based. Our judgement was that direct trial evidence taken from trials would be preferred by NICE even though patient numbers were low. PenTAG have preferred the indirect evidence taken from the Fresenius database reported by Block et al (2004) with its much larger patient numbers. We accept that this may be a superior approach and we are happy to work within the broad approach of PenTAG which we accept is defensible and reasonable.

Whilst we accept the broad approach taken by PenTAG, there is some very important analysis which has not been done which we would like to request should be undertaken as soon as it is feasible. The fact that this has not been addressed by PenTAG to date is not an intended criticism of the work of that group. PenTAG have probably taken things as far as possible given the data available to them. Additionally, Amgen failed to undertake the kind of subgroup analysis that the structure and approach taken by PenTAG demonstrates to be necessary. However, we do have the patient level data to make such an analysis possible and can provide PenTAG with the necessary analyses from that dataset.

There is a further issue with the PenTAG work that the percentage of patients estimated to be controlled in their model after treatment is less than our own patient level data would lead us to expect. We are not sure of the reason for this and would like to discuss it with the PenTAG team.

Development of the PenTAG HE model

The PenTAG conclusion on cost effectiveness is based on the results from a model that is reasonably well conceived in its structure and uses the data available to the Assessment Team in a reasonable manner. As a consequence of the insights the PenTAG approach gives we have realised that both the PenTAG model and our own model suffer from a failure correctly to separate out what is the cost effectiveness of treating particular subgroups of patients defined by starting PTH level, finishing PTH level and dosage received.

The PenTAG model did not distinguish dosage according to the starting or finishing level of PTH. The assumption in their model was that the quantity of drug used is the same irrespective of starting or finishing PTH level. Mortality rates related to PTH levels were derived from the Block et al 2004 paper. Three different states - and accordingly PTH levels - were distinguished:

- "Controlled" state: 150-300 pg/ml – RR of dying 1.00 (reference)

- “Uncontrolled” state: mean 550 pg/ml – RR: 1.0613
- “Very uncontrolled” state: mean 1200 pg/ml – RR: 1.1824

CV related hospitalization rates were also derived from Block et al 2004:

- Uncontrolled: RR 1.07
- Very uncontrolled: RR 1.26

Fracture related probabilities are based on a congress report (initial fractures) and data on osteoporosis (second and subsequent fractures) by Stevenson et al. No published information about the epidemiology of fractures specifically in the ESRD population was found by the modellers. The Block et al paper showed that PTH was directly associated with the risk of fracture related hospitalization, albeit weakly ($p=0.035$); this evidence was not used in the model but perhaps should have been.

Subgroup analysis in the PenTAG model

The Assessment Group’s subgroup analysis refers to the systematic review in the Assessment Report which states that cinacalcet appears to have more impact on people who start with “uncontrolled” PTH (>32 to <85pmol/L) than those with “very uncontrolled” PTH (>85pmol/L). Based on this, the model provides a subgroup analysis for different sets of patients. The analysis for the “uncontrolled” subgroup shows an ICER of £57K (£61K base case). Whereas for the “very uncontrolled” patients the ICER is higher than the base case at £81K. However, the key point is that these subgroup ICERs relate to whole cohorts of patients irrespective of dose of drug received and of finishing PTH. The ICERs reflect the fact that they are taken from the reporting of trials that set out to try to titrate dose to a level at which preset PTH targets (lower than K/DOQI targets) are reached. The clinical studies were designed to investigate efficacy, not cost effectiveness. There will be in those trials, therefore, some patients who were titrated up to high doses at high cost to achieve a final, small reduction to a target when more modest doses may already have achieved large reductions in PTH. Furthermore, the initial reductions from a high level of PTH would have much greater health benefit than the final small reductions, even though the latter might have cost more to achieve. At the margin there will be patients on whom higher amounts are spent to achieve relatively little health gain. The overall calculations fail to separate out those patients whom it would be relatively more cost effective to treat because the subgroups currently mix those whom it would be cost effective to treat with those whom it would not be, at current NICE thresholds.

The modellers have tried to approach the subgroup question sensibly but have been handicapped by the fact that we have not provided to them data analysed in the appropriate way. Amgen did not do this because we only appreciated its significance once we had seen the PenTAG model

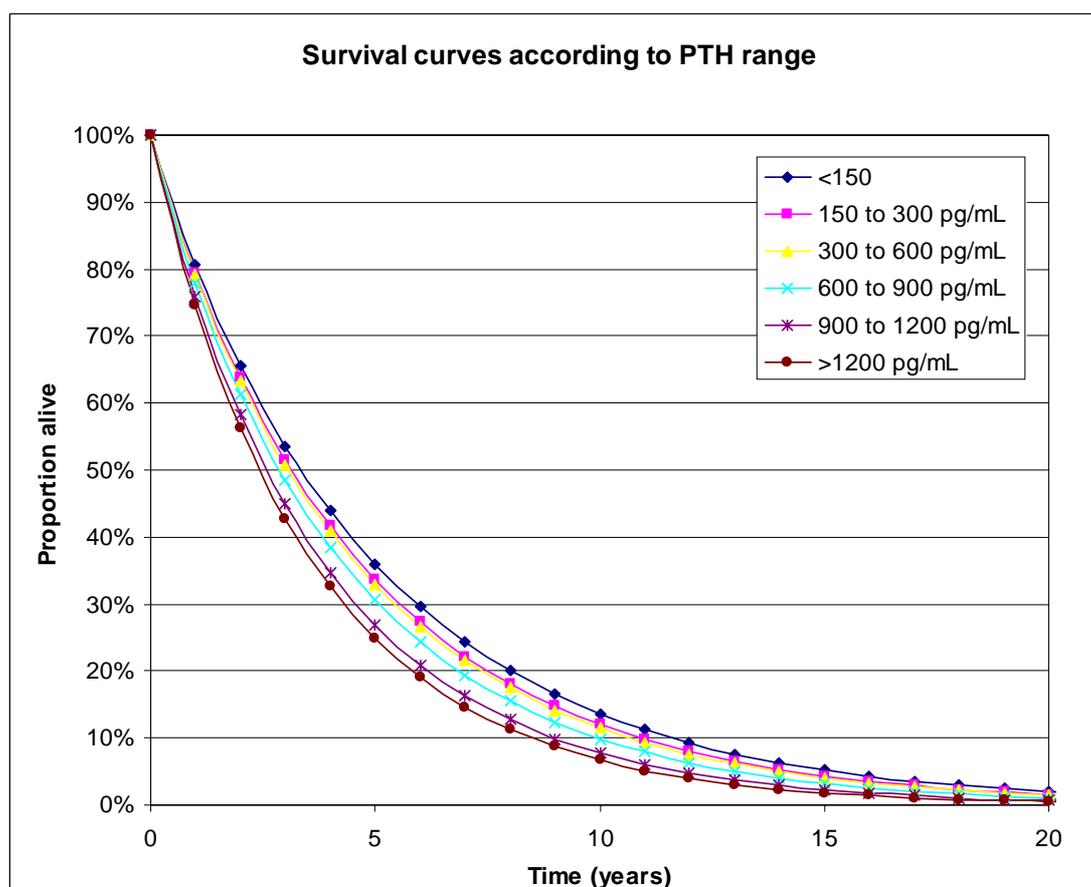
In the analysis, below, we show the difference these changes make in the context of a partial modelling exercise, undertaken for illustrative purposes only, which takes into account mortality effects alone (i.e. omitting cost savings from CV events, hospitalisations, fractures and operations avoided). We are confident the results will be similar in type in the more comprehensive PenTAG model, but inclusive of more patients in the cost effective groups.

We request that we supply to NICE the relevant analyses from the patient level data to allow this analysis by PenTAG or that Amgen undertake it and have it checked by PenTAG in their model. We further request that these results be put to the Appraisal Committee.

Analysis based on mortality effects alone with no cost offsets

This analysis aims to assess which subgroups of patients with end stage renal disease (ESRD) can be treated cost-effectively with cinacalcet if only mortality effects are considered. The only benefits included in the model are those that relate to the mortality risk associated with raised PTH. In order to assess the long-term survival impact of raised PTH a simple survival model was developed by applying the relative risk of mortality for various PTH ranges from Block et al(2004) to a survival curve for ESRD patients based on data from the USRDS database (Figure 1) in the same way as PenTAG did in their model. The reference range with no increased risk of mortality is given by Block et al as a PTH between 300 and 600pg/mL and these patients are assumed to have the same survival as those in the USRDS database.

Figure 1 Survival according to PTH range



Using the survival curves in Figure 1, the lifetime survival benefits of moving a patient from one PTH level to another were calculated, assuming, like PenTAG, that the final PTH achieved is maintained in the long-term. The QALYs gained by moving patients between PTH levels are given in Table 1. In this analysis (undertaken for

illustrative purposes only) a constant health related quality of life utility value of 0.59 for the experience of ESRD has been applied although Amgen would agree this value should be 0.6735 in the PenTAG model as stated in the Assessment Report. From this we have calculated the maximum amount that can be spent to achieve this QALY gain for a cost per QALY threshold of £30,000. This was then converted to a maximum annual drug cost by dividing the total cost by the number of expected life-years. This assumes that patients remain on the same dose for their whole lifetime in order to maintain a constant PTH level. The maximum drug cost per annum is given in Table 2. It should be noted that only mortality benefits are included in this model and that cost savings from hospitalisations avoided and QALY benefits from events avoided are not included. Their inclusion would considerably increase the drug costs that would allow the cost effectiveness thresholds to be met.

Table 1 Lifetime QALY gain per person when moving permanently from one PTH level to another

| Initial PTH (pg/mL) | Final PTH (pg/ml) | | | |
|---------------------|-------------------|------------|------------|-------------|
| | 150 to 300 | 300 to 600 | 600 to 900 | 900 to 1200 |
| 300 to 600 | 0.052 | | | |
| 600 to 900 | 0.234 | 0.181 | | |
| 900 to 1200 | 0.481 | 0.429 | 0.247 | |
| >1200 | 0.610 | 0.557 | 0.376 | 0.129 |

Table 2 Maximum annual drug costs that can be spent cost-effectively in order to achieve various changes in PTH assuming a cost per QALY threshold of £30,000

| Initial PTH (pg/mL) | Final PTH (pg/ml) | | | |
|---------------------|-------------------|------------|------------|-------------|
| | 150 to 300 | 300 to 600 | 600 to 900 | 900 to 1200 |
| 300 to 600 | £ 335 | £ - | £ - | £ - |
| 600 to 900 | £ 1,499 | £ 1,186 | £ - | £ - |
| 900 to 1200 | £ 3,084 | £ 2,801 | £ 1,731 | £ - |
| >1200 | £ 3,910 | £ 3,644 | £ 2,634 | £ 1,001 |

By comparing the costs in Table 2 to the annual costs of various doses (30, 60, 90, 120 and 180 mg daily) of cinacalcet we have determined which doses can be given cost-effectively to achieve the various changes in PTH. For example, a daily dose of 60mg costs £3037 per annum (Prices taken from BNF 51 online, accessed 10th April) and it is possible to give this dose cost-effectively to those patients whose PTH is greater than 1200pg/mL before treatment, provided that it is under 600pg/mL after treatment, and to those patients whose PTH is between 900 and 1200pg/mL before treatment provided that it is under 300pg/mL after treatment. The doses which can be given cost-effectively are summarised in Table 3.

Table 3 Doses that can be given cost-effectively in order to achieve various changes in PTH assuming a cost per QALY threshold of £30,000

| Initial PTH (pg/mL) | Final PTH (pg/ml) | | | |
|---------------------|-------------------|------------|------------|-------------|
| | 150 to 300 | 300 to 600 | 600 to 900 | 900 to 1200 |
| 300 to 600 | - | - | - | - |
| 600 to 900 | - | - | - | - |

| | | | | |
|-------------|-------------|-----------|------|---|
| 900 to 1200 | 30mg / 60mg | 30mg | 30mg | - |
| >1200 | 30mg / 60mg | 30 / 60mg | 30mg | - |

In order to assess the number of patients who can be cost-effectively treated using the PenTAG approach and NICE threshold values, it would be necessary to determine the number of patients who would achieve the various PTH changes for the doses given in Table 4. Analysis of patient level data from three phase 3 studies (20000172, 20000183 and 20000188) and two phase 3b studies (20030187 (OPTIMA) and 20040143 (SENSOR)) would allow the assessment of the number of patients making the specified changes in PTH for each dose increase (0 to 30mg, 30mg to 60mg etc) in those trials, although because of the nature of those trials a separate calculation would have to be done to calculate the share of the general ESRD population that would be eligible. Our own preliminary analysis shows that there are significant numbers of patients within our trial populations whose cost/change combination would meet the NICE criteria for cost effectiveness.

Recasting the Assessment Group's analysis in this way would allow NICE to identify those patients who can benefit from treatment at a conventional NICE level of cost effectiveness and to set discontinuation rules for therapy to avoid continuing treatment into levels of cost ineffectiveness rather than returning patients to standard care. NICE has done this on previous occasions. Amgen would be happy to provide the necessary analyses from the patient level data to undertake this work and to collaborate directly with the Assessment Team to carry it out, if that would prove helpful.