NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Etelcalcetide for treating secondary hyperparathyroidism [ID908]

The following documents are made available to the consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Amgen
   - Renal Association and Royal College of Physicians
   - Kidney Research UK
   - Department of Health (provided a *no comment* response)

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SingleTechnology Appraisal

Etelcalcetide for treating secondary hyperparathyroidism

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comments received from consultees

Consultee	Comment [sic]	Response
Amgen	**1. Executive summary** We welcome the positive preliminary recommendation for etelcalcetide and the acknowledgement in the Appraisal Consultation Document (ACD), based on clinical and patient expert views, that an intravenous calcimimetic could improve adherence and would be a valuable option for patients with secondary hyperparathyroidism (SHPT). We also welcome the Committee's acceptance of these advantages of etelcalcetide, and the importance of having different treatment options available for treating SHPT. We have carefully reviewed the Appraisal Committee's consideration of the evidence presented for etelcalcetide, and the preliminary recommendation outlined in the ACD, and have some concerns that the ACD does not reflect the superior comparative efficacy of etelcalcetide vs. cinacalcet, and may overstate the uncertainties in its estimated cost-effectiveness. In the sections that follow, we reiterate the superior, clinically meaningful efficacy of etelcalcetide over cinacalcet, demonstrated based on robust assessment of clinically meaningful endpoints that are known to impact long-term outcomes. Although we do acknowledge there could be uncertainty in the economic evaluation, we believe that the ICER (including the confidential PAS discount) for etelcalcetide vs. cinacalcet is well within the upper bound of the usual threshold range for cost-effectiveness, is stable to a range of sensitivity analyses, and remains cost-effective when considering the ERGs preferred base case analysis.	The committee was aware of the multiple uncertainties in relation to the extrapolation of the hazard ratios from EVOLVE. It agreed that because there is uncertainty in establishing the long-term benefits of etelcalcetide compared with cinacalcet (for outcomes such as mortality, fracture and cardiovascular events) and higher associated costs, etelcalcetide should be recommended as an option for people with secondary hyperparathyroidism for whom a calcimimetic is indicated, only if cinacalcet is not considered suitable. See section 4.11 of the FAD.

Consultee	Comment [sic]	Response
	We therefore propose that the ACD be amended and that the following considerations are appropriately reflected in the final appraisal determination: • Etelcalcetide is statistically and clinically superior to cinacalcet; • Etelcalcetide at the PAS discount price is highly likely to be cost-effective compared with cinacalcet. Whilst welcoming the positive preliminary recommendation for etelcalcetide, we feel the final recommendation should reflect this clinical and economic evidence. Taken alongside the accepted adherence advantages of etelcalcetide to patients and clinicians, we believe this evidence supports the use of etelcalcetide as a treatment option in all chronic kidney disease (CKD) patients with SHPT on haemodialysis when calcimimetic treatment is indicated, rather than only those in whom cinacalcet is not suitable.	
	2. Etelcalcetide has clinically meaningful superior efficacy vs. cinacalcet • **Robust and compelling evidence supports the clinical and statistical superiority of etelcalcetide over cinacalcet, based on endpoints that are accepted by the Committee as clinically important and meaningful outcomes, and which are known to impact long-term clinical outcomes in patients with SHPT.** • **We are therefore concerned that the ACD omits any reference to the clinical and statistical superiority of etelcalcetide over cinacalcet. Moreover, we feel the Committee's conclusion that "*…etelcalcetide has similar efficacy to cinacalcet…*", used to justify the preliminary recommendation, is factually incorrect based on the available evidence.**	The FAD has been updated to reflect the committee's acknowledgement that in the active comparator-controlled trials etelcalcetide was non-inferior to cinacalcet for the primary outcome measure. It also noted that etelcalcetide was superior to cinacalcet for the secondary endpoints in this trial (more than 30% and more than 50% reduction in mean parathyroid hormone levels. See sections 4.4 and 4.5 of the FAD.

Consultee	Comment [sic]	Response
	• **We propose that the ACD should be amended to reflect clearly the clinical and statistical superiority of etelcalcetide over cinacalcet.** 2.1 Etelcalcetide trial data demonstrate superior efficacy vs. cinacalcet Our submission to NICE presented full details of the clinical trial programme for etelcalcetide, including the robust, active-controlled, double-blind, double-dummy, phase 3, randomised trial of etelcalcetide vs. cinacalcet (study 20120360). [1] This trial was of good quality (i.e. low risk of bias) as acknowledged by the Appraisal Committee (ACD Table: Summary of appraisal committee's key conclusions, p16), and has high external validity based on the PICO considerations below: Patients – The Committee concluded patients enrolled in the trial were generally representative of those with SHPT in the UK (ACD section 4.3, p7), as was noted by the clinical expert consulted by the evidence review group (ERG), who also stated that the median baseline parathyroid hormone (PTH) level of patients in this trial (median PTH around 900pg/mL) was reflective of the population who would currently receive cinacalcet (ERG report, section 3.1.3, p38). Intervention and Comparator – Etelcalcetide and cinacalcet were both dosed in the trials in line with the recommendations in their respective Summaries of Product Characteristics. Outcomes – The primary efficacy measure in the trial was the proportion of patients achieving a >30% reduction from baseline in PTH, which was deemed to be clinically meaningful in SHPT patients by the European Medicines Agency (EMA) when granting the positive marketing authorisation for etelcalcetide. [2] The ACD also reports (ACD section 4.5, p8): "…The Committee concluded that the primary outcome of more than 30% reduction in parathyroid hormone levels is a clinically important and meaningful outcome…". As detailed in our submission, the trial was designed first to test the non-inferiority of etelcalcetide vs. cinacalcet for this endpoint, and also pre-specified tests of superiority for the	

Consultee	Comment [sic]	Response
	secondary endpoints of proportion of patients achieving >50% and >30% reduction from baseline in PTH if non-inferiority was achieved. Etelcalcetide achieved non-inferiority for the primary endpoint, and superiority for this and the more stringent endpoint of a >50% reduction from baseline in PTH compared with cinacalcet. This is reflected in our submission, and in the current Summary of Product Characteristics (SmPC) for etelcalcetide, which states: "Parsabiv was non-inferior to cinacalcet for the primary endpoint, and was superior to cinacalcet for the secondary endpoints of proportion of patients achieving > 30% reduction from baseline in mean PTH during the EAP (68.2% Parsabiv versus 57.7% cinacalcet; p = 0.004); and proportion of patients achieving > 50% reduction from baseline in mean PTH during the EAP (52.4% Parsabiv versus 40.2% cinacalcet; p = 0.001)". [3] Of note, the numbers needed to treat (NNTs) for etelcalcetide vs. cinacalcet (i.e. vs. an active treatment) for these clinically important and meaningful endpoints are less than 10, which is generally considered to be indicative of an effective treatment. [4] Furthermore, the relative proportion of patients achieving a reduction in PTH concentrations of >30% or >50% did not differ significantly across any of the pre-specified subgroups compared with the whole trial population (see Figure 12 of our original submission and Figure 3 in the published manuscript). In addition to this, during the EAP etelcalcetide demonstrated a statistically significant reduction in serum calcium levels from baseline vs. cinacalcet, and significantly reduced phosphate levels from baseline. [1, 5] **In summary:**	

Consultee	Comment [sic]	Response
	• **Robust phase 3 RCT data, obtained in SHPT patients reflective of those in clinical practice, demonstrate that etelcalcetide is statistically significantly superior to cinacalcet based on its effects on PTH-related endpoints.** • **The EMA and NICE Appraisal Committee agreed these endpoints are clinically important and meaningful in patients with SHPT.** • **The low NNTs for these endpoints, obtained with etelcalcetide against an active treatment, confirm these statistically significant results in favour of etelcalcetide reflect clinically significant improvements over cinacalcet.** • **Results consistently favoured etelcalcetide across all subgroups.**	
	2.2 Association between biomarkers used in etelcalcetide trials and clinical outcomes is well established The primary and secondary endpoints of the etelcalcetide trials reflected reductions in PTH, serum calcium and phosphate levels. As reported in our submission, although the trials did not directly assess clinical outcomes, large retrospective observational studies consistently indicate that uncontrolled PTH, calcium and phosphate levels are associated with a range of adverse clinical events, including fractures, CV events and death, in haemodialysis patients with SHPT. [6-8] A cohort study by Danese et al observed that simultaneous control of PTH, calcium, and phosphate was associated with increased survival compared with control of one or two of these parameters and, furthermore, long-term consistent control of these biomarkers was associated with better survival than episodic control. [6] The specific risk associated with uncontrolled PTH levels has been demonstrated in a Dialysis Outcomes and Practice Patterns Study (DOPPS), which followed 35,655 dialysis patients over 15 years (1996-2011) and observed increasing risks of mortality with increasing PTH levels. [8] Further compelling evidence of the central role of PTH in the development of adverse clinical events is evident from the change in the clinical course of SHPT when PTH is more effectively controlled. The large EVOLVE (Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events)	The committee agreed that etelcalcetide is effective in terms of reducing parathyroid hormone levels by the target percentages in the trial. However it was uncertain of the generalisability of this specific surrogate outcome to long-term outcomes such as cardiovascular events and death. The committee agreed that the primary outcome of more than 30% reduction in parathyroid hormone is a good indicator of the effectiveness of a treatment on the blood biochemistry and therefore a clinically relevant outcome; however, it concluded that it is highly uncertain whether a 30% reduction in parathyroid hormone (from a variable baseline level) would translate into directly proportional improvements in long-term outcomes such as survival, incidence of

Consultee	Comment [sic]	Response
	RCT, when adjusted for important confounding factors (see Section **Error! Reference source not found.**), observed cinacalcet, a potent inhibitor of PTH secretion, reduced the risks of all-cause mortality and major CV events when added to background phosphate binder and vitamin D sterols. [9, 10] **In summary:** • **It is well established that uncontrolled PTH, as well as calcium and phosphate disturbances, is associated with a range of adverse clinical consequences for patients with SHPT** • **It is accepted that achievement of greater control of PTH, alongside calcium and phosphate levels, is associated with a reduction in the risk of these adverse clinical consequences for patients with SHPT.** • **For this reason, clinical practice guidelines, such as the internationally-respected KDIGO clinical practice guidelines [11], indicate the aim of treatment in SHPT is to correct the levels of PTH, serum calcium and phosphate. This view is confirmed by clinical expert opinion reported in the ACD (section 4.2, p6).** • **The primary and secondary endpoints of the etelcalcetide trials therefore reflect reductions in biomarkers that are used in clinical practice to guide treatment and have a well-established association with clinical outcomes in patients with SHPT. The conclusion that etelcalcetide is clinically superior to cinacalcet, based on a robust trial using these endpoints, is therefore compelling.** • **As there is evidence that long-term consistent control of these biomarkers is associated with better survival than episodic control [6], the importance of adherence to treatment should not be underestimated.**	fractures, incidence of cardiovascular events and need for parathyroidectomy, which were not measured in the trials. See sections 4.4 and 4.5 of the FAD.

Consultee	Comment [sic]	Response
	2.3 Implications for the ACD etelcalcetide over cinacalcet, based on robust phase 3 RCT data, and demonstrated consistent results across all pre-specified subgroups (re-iterated in brief in Section 2.1 of this document). Our submission also detailed how the biomarkers used in the etelcalcetide trials are used in clinical practice to guide treatment and have a well-established association with clinical outcomes in patients with SHPT (re-iterated in brief in Section 2.2 of this document). We are therefore disappointed that, despite this compelling evidence, no reference to the clinical and statistical superiority of etelcalcetide over cinacalcet is made in the ACD. Moreover, despite this compelling evidence of the clinical and statistical superiority of etelcalcetide over cinacalcet, the ACD states twice (section 4.12, p13, and in the Summary of appraisal committee's key conclusions, p14): "Given that etelcalcetide has similar efficacy to cinacalcet but higher associated costs, the committee considered that it should be recommended as an option for people with secondary hyperparathyroidism whom a calcimimetic is indicated, only if cinacalcet is not considered suitable". We feel this conclusion on the comparative efficacy of etelcalcetide does not reflect the robust clinical evidence base for etelcalcetide, and note this is also inconsistent with the EMA's interpretation of the clinical data for etelcalcetide based on the agreed wording of the SmPC, which states: "Parsabiv was non-inferior to cinacalcet for the primary endpoint, and was superior to cinacalcet for the secondary endpoints of proportion of patients achieving > 30% reduction from baseline in mean PTH during the EAP … and proportion of patients achieving > 50% reduction from baseline in mean PTH during the EAP…". [3] **We therefore conclude:**	In section 4.4 of the FAD the committee acknowledged that in the active comparator-controlled trials etelcalcetide was non-inferior to cinacalcet for the primary outcome measure. It also noted that etelcalcetide was superior to cinacalcet for the secondary endpoints in this trial (more than 30% and more than 50% reduction in mean parathyroid hormone levels. However the committee concluded that it is highly uncertain whether a 30% reduction in parathyroid hormone (from a variable baseline level) would translate into directly proportional improvements in long-term outcomes such as survival, incidence of fractures, incidence of cardiovascular events and need for parathyroidectomy, which were not measured in the trials See sections 4.4 and 4.5 of the FAD.

Consultee	Comment [sic]	Response
	• **The ACD does not accurately reflect the clinical evidence base for etelcalcetide, as it omits any reference to the clinical and statistical superiority of etelcalcetide over cinacalcet.** • **The suggestions in the ACD that etelcalcetide has similar efficacy to cinacalcet is inconsistent with the available evidence, and is inconsistent with the interpretation of this evidence by the EMA reflected in the agreed wording of the SmPC.** • **We propose the ACD should be amended to clearly reflect the compelling evidence that demonstrates the clinical and statistical superiority of etelcalcetide over cinacalcet.**	In section 4.4 of the FAD the committee acknowledged that in the active comparator-controlled trials etelcalcetide was non-inferior to cinacalcet for the primary outcome measure. It also noted that etelcalcetide was superior to cinacalcet for the secondary endpoints in this trial (more than 30% and more than 50% reduction in mean parathyroid hormone levels. The FAD has been amended 4.11 (formerly 4.12) from "Given that etelcalcetide has similar efficacy to cinacalcet but higher associated costs, the committee considered that it should be recommended as an option for people with secondary hyperparathyroidism whom a calcimimetic is indicated, only if cinacalcet is not considered suitable" To "It agreed that because there is uncertainty in establishing the long term benefits of etelcalcetide compared with cinacalcet (for outcomes such mortality, fracture and cardiovascular events) and higher associated costs, etelcalcetide should be recommended as an option for people with secondary hyperparathyroidism whom a calcimimetic is indicated, only if cinacalcet is not considered suitable"

Amgen	3 Etelcalcetide is a cost effective alternative to cinacalcet • **Whilst we acknowledge there could be uncertainty around ICER estimates in our analysis, we believe that the incremental cost per QALY gained for etelcalcetide (including the [redacted] PAS discount) is highly likely to be considered cost-effective vs. cinacalcet** ○ **As stated in our submission, and acknowledged by the Committee, the EVOLVE trial provides the most robust outcomes data for calcimimetics with which to model etelcalcetide.** ○ **Our approach to account for the chance imbalance in baseline characteristics is aligned with the pre-specified multivariate analysis in EVOLVE and results are consistent with univariate analyses adjusting for age.** ○ **The ERG concluded that our approach to modelling long-term outcomes is reasonable, and ICER estimates vs. cinacalcet are consistently below the upper threshold that would typically be considered cost-effective across a range of sensitivity analyses.**	Comments noted. The committee was aware of the multiple uncertainties in relation to the extrapolation of the hazard ratios from EVOLVE (see section 4.8). The committee noted that several estimates were above £20,000 per QALY gained, and these still assumed a directly proportional effect of a 30% reduction in parathyroid hormone on long-term outcomes. The committee was aware that the parameter uncertainty associated with the hazard ratio for mortality alone increased the deterministic ICER by more than £10,000 per QALY gained. In addition, this does not include the uncertainty in the extrapolation from the EVOLVE trial and therefore this uncertainty is not reflected in the ICER estimates nor in the probabilistic sensitivity analyses. See section 4.11 of the FAD.
	• **We strongly disagree that the non-linear pricing of vials leads to uncertainty as is currently reported in the ACD.** • **We propose that the ACD should be amended to reflect that etelcalcetide is highly likely to be cost-effective vs. cinacalcet, and importantly to**	Comment noted. The FAD has been amended accordingly. The committee noted the company's comments that etelcalcetide was 'highly likely' to be cost effective but it considered that cost effectiveness was

Consultee	Comment [sic]	Response
	remove statements suggesting that non-linear pricing leads to uncertainty in the evaluation	highly uncertain because of uncertainties in extrapolating short-term surrogate outcomes from the etelcalcetide trials to long-term outcomes such as mortality.
	3.1 Appropriateness of covariate adjustments to account for chance imbalance in baseline characteristics in EVOLVE As stated in our submission, and acknowledged by the Committee, the EVOLVE trial provides the most robust outcomes data for calcimimetics with which to model etelcalcetide. Although the primary unadjusted ITT analysis from EVOLVE demonstrated that patients randomised to cinacalcet experienced numerically fewer composite events, the risk reduction was not statistically significant (relative hazard 0.93, 95% confidence interval (95% CI) 0.85 to 1.02; p=0.11). [9] However, as discussed in our submission and reported elsewhere, there was a chance imbalance in age between the cinacalcet and placebo arms of the trial, leading to a bias in the ITT analysis. [9, 12] The pre-specified multivariate analysis in EVOLVE (multivariate best fit model) adjusting for baseline characteristics showed a nominally significant hazard ratio (HR) for the primary composite end point of 0.88 (95% CI, 0.79 to 0.97; p = 0.008), which has been accepted by the EMA and included in the updated SmPC for cinacalcet in Europe. [9, 13]. An analysis adjusting for all baseline covariates showed similar results (0.88 [0.80, 0.98]). [9] The methods to derive HRs used to inform our base case lag-censored analysis follow the pre-specified multivariate analysis in principle, by including all baseline covariates and using a step-wise procedure to determine the best fit model. A multivariate analysis was used in our base case as it accounts for all potential measured confounding factors which could be unduly affecting the results.The HRs for the lag-censored multivariate best-fit model used to inform our base case analysis are reported in Table 1 below.	Comments noted. The committee agreed with the ERG that EVOLVE was the best available source of evidence for the long-term effects of calcimimetics, but it had concerns about the robustness of the estimates. It concluded that the company's estimates of the long-term benefits of etelcalcetide were highly uncertain because of the reliance on a trial of another treatment (cinacalcet), the results of which had been extensively adjusted, and the assumption that a higher rate of reduction in parathyroid hormone levels for etelcalcetide than cinacalcet would translate into a directly proportional reduction in mortality, fractures, cardiovascular events and parathyroidectomy. See section 4.8 of the FAD.

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Table 1: Hazard ratios extracted from the EVOLVE trial for cinacalcet vs. placebo (multivariate best fit model) – Source Belozeroff et al 2015 [14]

<table>
<tr><th></th><th>Lag-censored HRs[b] [95% CI]</th></tr>
<tr><td colspan="2">Cinacalcet vs placebo</td></tr>
<tr><td>All-cause mortality</td><td>0.80 [0.69, 0.91]</td></tr>
<tr><td>CV events[a] (non-fatal)</td><td>0.78 [0.67, 0.91]</td></tr>
<tr><td>Fractures (non-fatal)</td><td>0.73 [0.59, 0.92]</td></tr>
<tr><td>PTx (non-fatal)</td><td>0.25 [0.19, 0.33]</td></tr>
<tr><td colspan="2">CI, confidence interval; CV, cardiovascular; HR, hazard ratio; ITT, intention-to-treat; PTx, Parathyroidectomy
[a] Myocardial infarction, unstable angina, heart failure and peripheral vascular event
[b] Adjusted for baseline covariates: age, sex, race, region, body-mass index, time on dialysis history of CV disease, blood pressure, diabetes, retinopathy, tobacco use, type of vascular access, high density lipoproteins (HDL), Ca x P, and albumin. IXRS stratification factors (country and diabetes) were included in the model.</td></tr>
</table>

Nevertheless, it is stated in the ACD (section 4.8, pg 10) that the Committee were "…concerned that there were many adjustments for baseline characteristics made to the EVOLVE data to derive treatment effects, and it was unclear why so many adjustments were made and how valid they were."

Of all the baseline characteristics evaluated in EVOLVE, age was deemed to be the most clinically important covariate affecting the primary composite endpoint and a nominally significant interaction factor between treatment effect and the age subgroup (p=0.007) was identified. [9] In the EVOLVE analyses, it was demonstrated that a 1-year increase in age was associated with a 3% increase in the risk of experiencing the primary composite endpoint. [9] Despite enrolling 3,883 patients in EVOLVE there was a 0.8 years difference in mean age at baseline and a 1 year difference in median age (55 versus 54 years), an

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occurrence that therefore confounded estimates of treatment effectiveness. [9, 12] This chance imbalance in a major prognostic factor necessitates covariate adjustment. [15]

Results from the pre-specified univariate analysis adjusting for age in EVOLVE were similar to the multivariate analysis described above, showing a reduction in risk of the primary composite endpoint event (HR 0.88; 95% CI 0.81, 0.97; nominal p = 0.007).[9] Age-adjusted HRs for the modelled outcomes are presented in Table 2.

Table 2: Hazard ratios extracted from the EVOLVE trial for cinacalcet vs. placebo (age-adjusted) - source Amgen, Data on File 2017 [16]
<table>
<tr><th></th><th>Lag-censored HRs[b] [95% CI]</th></tr>
<tr><td colspan="2">Cinacalcet vs placebo</td></tr>
<tr><td>All-cause mortality</td><td></td></tr>
<tr><td>CV events[a] (non-fatal)</td><td></td></tr>
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<tr><td>PTx (non-fatal)</td><td></td></tr>
<tr><td colspan="2">CI, confidence interval; CV, cardiovascular; HR, hazard ratio; ITT, intention-to-treat; PTx, parathyroidectomy
[a] Myocardial infarction, unstable angina, heart failure and peripheral vascular event
[b] Hazard ratio and 95% CI were obtained from the Cox model. IXRS stratification. factors (country and diabetes) were included in the model.</td></tr>
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The HRs are consistent with the multivariate estimate used in our base case analysis and the point estimates fall well within the parameter ranges explored during the sensitivity and scenario analyses conducted. Of note, all sensitivity and scenario analyses resulted in ICERs for etelcalcetide vs. cinacalcet that remained within the usual threshold for cost-effectiveness. As such, we strongly believe that the covariate-adjustments used in the base case analysis provide a valid estimate of the treatment effect, and that any uncertainty associated with this is approach has been appropriately accounted for and does not influence the conclusions on cost-effectiveness.

In summary:
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Consultee	Comment [sic]	Response
	• **EVOLVE is acknowledged to be the best data source from which to model clinical outcomes; however, the chance imbalance in baseline characteristics necessitates covariate adjustment.** • **Our base case approach is aligned with the pre-specified multivariate analysis in EVOLVE which has been accepted by the EMA and included in the updated SmPC for cinacalcet in Europe.** • **Age was identified as the most clinically important covariate affecting estimates of the treatment effect in EVOLVE. Hazard ratios for cinacalcet vs. placebo are consistent across both multivariate and age-adjusted analyses.** • **This consistency confirms that the multivariate adjustment used in our base case analysis provides an appropriate estimate of the treatment effect, and our extensive assessments of uncertainty via sensitivity and scenario analyses allow us to conclude with confidence that etelcalcetide is a cost-effective treatment option vs. cinacalcet**	
	3.2 Uncertainty in extrapolating surrogate biomarkers to clinical outcomes in EVOLVE It is acknowledged in our submission that there is some uncertainty associated with the base case approach to extrapolate clinical outcomes from EVOLVE to the primary efficacy endpoint (ie. >30% PTH reduction) in the etelcalcetide trials. However, we feel this uncertainty has been overstated in the ACD and so we would dispute that it contributes to an "unsound" (section 4.8, pg 10) evaluation of the cost-effectiveness of etelcalcetide. In support of our concerns we refer to the ERG's own interpretation of our approach, as is stated in their report (section 4.3.4.5, pg 99): "The log-linear method used to extrapolate HRs for etelcalcetide from the EVOLVE results and etelcalcetide primary outcome, ≥30% reduction in PTH is reasonable").	Comments noted. The committee considered the company's comments that the appraisal consultation document overstated the uncertainty associated with estimates of the cost-effectiveness of etelcalcetide compared with cinacalcet. The committee was aware that the parameter uncertainty associated with the hazard ratio for mortality alone increased the deterministic ICER by more than £10,000 per QALY gained. In addition, this does not include the uncertainty in the extrapolation from the EVOLVE trial and therefore this uncertainty is not reflected in the ICER

Consultee	Comment [sic]	Response
	The primary assumption underpinning the present model is that a higher rate of reduction in PTH levels for etelcalcetide than cinacalcet would translate into a proportional reduction in mortality, fractures, cardiovascular events and parathyroidectomy. As discussed in Section 2.2, the link between PTH and other biochemical parameters to clinical outcomes is well established, and it is of note that NICE has previously acknowledged this relationship having accepted the ERG's approach to modelling clinical outcomes based on PTH levels in the 2007 Technology Appraisal of cinacalcet. [17] In our submission, we present extensive sensitivity and scenario analyses to address the uncertainty in our modelling approach and conclude that the ICERs for etelcalcetide vs. cinacalcet remain well within the typical threshold for cost-effectiveness. In particular, we would draw the Committee's attention to two specific analyses that we feel adequately mitigate uncertainty in our extrapolated approach: • Analysis of the achievement of PTH ≤ 300 pg/ml as a surrogate endpoint to extrapolate to clinical outcomes • An alternative methodology for modelling clinical outcomes from biochemical parameters observed in the etelcalcetide trials, utilising a published biomarker based risk-prediction equation Both analyses are discussed in more detail below. **3.2.1 Analysis of the achievement of PTH ≤ 300 pg/ml as a surrogate endpoint** The rationale for using the PTH reduction of at least 30% from baseline as the surrogate endpoint for extrapolation was that this is the pre-specified primary outcome of the etelcalcetide trials and is regarded by clinicians (and accepted by the Committee) to be a clinically important and meaningful outcome (see Section 2.1). However, in response to questions raised by the ERG, we acknowledged that achievement of PTH ≤300 pg/mL in observational studies has been associated with a reduced risk of all-cause mortality (compared with PTH values >300 pg/mL),	estimates nor in the probabilistic sensitivity analyses. See section 4.11 of the FAD. The committee concluded that it is highly uncertain whether a 30%

Consultee	Comment [sic]	Response
	decreased bone turnover and improved bone histology, which would support the use of this target as an appropriate surrogate endpoint to extrapolate to the clinical endpoints measured in EVOLVE. This analysis was conducted by the ERG and is detailed in their report; the resulting ICER vs. cinacalcet of £11,490 per QALY may suggest that our base case conservatively underestimates the long-term health benefit of etelcalcetide. Although this approach is also reliant on a linear extrapolation to the HRs derived from EVOLVE, the existing evidence base and clinical guidelines in this disease area are supportive of the relationship between the achievement of a PTH target ≤300 pg/ml and reduced clinical outcomes. We believe that this analysis confirms our conclusion that etelcalcetide is highly likely to be cost-effective vs. cinacalcet and reduces the uncertainty associated with linking biomarker data to clinical outcomes. **3.2.2 Alternative methodology using risk-based prediction equations** To further explore the validity of the base case extrapolation approach we also modelled clinical outcomes based on biomarker data (PTH, calcium and phosphate serum levels) measured within the etelcalcetide trials. This analysis does not rely on the linear extrapolation assumption used to link to EVOLVE and as noted in the ERG report (section 4.3.4.5, pg 98) provides "…*a useful check on the plausibility of the results, as they rely on different external sources of data"*. This analysis requires a risk prediction equation that translates biomarker measurements into event risks. Our systematic literature review of cost-effectiveness analyses identified such a risk-prediction equation from a study by Eandi et al. 2010 which was informed by large, observational datasets in the disease area. [18] Further details of the analysis are reported in Appendix 10 of our original submission. The cost-effectiveness results derived from the biomarker risked-based prediction equations were presented in our submission and are reiterated in **Error! Reference**	reduction in parathyroid hormone (from a variable baseline level) would translate into directly proportional improvements in long-term outcomes such as survival, incidence of fractures, incidence of cardiovascular events and need for parathyroidectomy, which were not measured in the trials. See section 4.4 and 4.5 of the FAD. The committee noted that the company presented an alternative method for modelling outcomes, using risk-based equations and although this alternative method was welcomed by committee, the committee understood that this approach had not been validated and therefore uncertainty remained. See section 4.11 of the FAD.

<table>
<tr><th>Consultee</th><th>Comment [sic]</th><th>Response</th></tr>
<tr><td></td><td>
source not found. below, alongside our base case results for comparison. Estimates for both the censored and ITT disaggregated analysis of the etelcalcetide trials are presented.

Table 3: Etelcalcetide (plus PB/VD) versus cinacalcet (plus PB/VD) – results of efficacy-based scenario analyses
<table>
<tr><th>Scenario</th><th>Incremental costs</th><th>Incremental QALYs</th><th>ICER (£/QALY)</th></tr>
<tr><td>Base case</td><td>£1,020</td><td>0.069</td><td>14,778</td></tr>
<tr><td>Eandi; censored*</td><td>£1,107</td><td>0.057</td><td>19,334</td></tr>
<tr><td>Eandi; ITT disaggregated</td><td>£1,180</td><td>0.074</td><td>15,975</td></tr>
</table>
* In the censored analysis, biomarker measurements were censored post-discontinuation of the investigational product.

As we concluded in our submission, the resulting ICERs are similar to the base case analysis and the incremental costs and incremental QALYs are consistent. We believe that this consistency with the base case results provides reassurance that the base case assumptions are plausible and that the uncertainty associated with the extrapolation approach is minimal. Etelcalcetide is therefore highly likely to be cost-effective vs. cinacalcet.

In summary:
</td><td></td></tr>
</table>

Consultee	Comment [sic]	Response
	• **Whilst we do acknowledge there could be uncertainty around estimates of the cost-effectiveness, we believe the impact of this is overstated in the ACD, and so suggestions that the analysis is 'unsound' are not warranted.** • **The ERG assessment report concludes that our extrapolation approach is reasonable and we have also demonstrated consistency across results using alternative approaches. ICERs vs. cinacalcet remain well within the typical threshold for cost-effectiveness when accounting for uncertainty.** • **We believe our treatment effect estimates based on the base case extrapolation approach are conservative, plausible, associated with minimal uncertainty, and demonstrate that etelcalcetide is highly likely to be cost-effective vs. cinacalcet.**	
	3.3 As correctly noted in the ACD, etelcalcetide is available in three vial sizes (2.5 mg, 5 mg and 10 mg) and the smaller 2.5 mg vial has a higher cost per mg than the larger 5 mg and 10 mg vials. However, we strongly disagree with the statement in the ACD that this introduces uncertainty in the appraisal. An extract from section 4.10, pg 11 has been reported below: *"The committee was concerned that this [non-linear pricing] introduced uncertainty in acquisition costs because if the larger dose vials were unavailable for any reason the incremental cost-effectiveness ratio (ICER) would increase, if a larger proportion of the more expensive 2.5-mg vials were used."* Amgen are fully committed to avoiding shortages of our products and strive to deliver our medicines to 'every patient, every time'. This is reflected in our very strong track record of timely medicines delivery across the UK and worldwide. We believe it is	Comment noted. The FAD has been updated accordingly.

Consultee	Comment [sic]	Response
	unreasonable to suggest that clinicians would routinely administer higher doses of etelcalcetide using multiple 2.5 mg vials, as opposed to utilising the larger, less costly vials. We therefore feel that these claims in the ACD are unfounded and refer to a hypothetical scenario that is highly unlikely to transpire in clinical practice. As such, we recommend that statements relating to the uncertainty in acquisition costs be removed in the final appraisal determination. The ACD also concludes that (section 4.10, pg 11) "*the company's approach of using the distribution of vial usage in the trials was not unreasonable, but the company's estimation of vial usage was associated with uncertainty because of the potential variability in costs depending on which vial sizes are used*." As stated in our 'PAS Addendum', a weighted average is used to calculate the average per mg price in the economic model. This approach ensures that the price of etelcalcetide is fully aligned with drug use, assuming that the minimum number of vials are used and vial sharing does not occur. As stated previously, we believe that it is unreasonable to suggest that clinicians would administer higher doses of etelcalcetide using multiple 2.5 mg vials, and therefore uncertainty associated with the vial distribution is minimal. Furthermore, although vial-sharing is highly unlikely to occur in UK clinical practice, any occurrence of this would ultimately result in a reduced cost of etelcalcetide and would not detract from conclusions that etelcalcetide is a cost-effective treatment option vs. cinacalcet. As such, we recommend that statements relating to the uncertainty associated with vial distribution be removed in the final appraisal determination. **In summary:** • **We strongly disagree that the non-linear pricing of vials leads to uncertainty in the appraisal as is currently reported in the ACD** • **Given Amgen's strong track record of timely medicines delivery, the hypothetical scenario whereby larger vials are unavailable is unlikely to transpire in clinical practice, and it is unreasonable to suggest clinicians would use multiple small vials when administering larger doses.**	

Consultee	Comment [sic]	Response
	• **We propose that statements around the uncertainty associated with the non-linear pricing of vials be removed in the final appraisal determination.**	

Consultee	Comment [sic]	Response
	3.4 Our submission presents robust, plausible estimates of the cost-effectiveness of etelcalcetide vs. cinacalcet. It has been acknowledged by the Committee that EVOLVE provides the best outcomes data for calcimimetics and we believe that the adjustments made for baseline covariates are both necessary to account for the chance imbalances between treatment arms and are appropriate to assess the true treatment effect (Section 3.1). The extrapolation methodology was supported by a clinically relevant and meaningful endpoint and was considered to be '*reasonable*' by the ERG; furthermore, ICERs were consistently below the typical cost-effectiveness threshold when alternative approaches to estimate the long-term benefits of etelcalcetide were investigated (Section 3.2). In addition to this, we believe statements around the uncertainty introduced by the non-linear pricing of vials are unsubstantiated and should be removed in the final appraisal determination (Section 3.3). Whilst we do acknowledge there could be uncertainty around ICER estimates, we believe that the incremental cost per QALY gained for etelcalcetide vs. cinacalcet (including the [redacted] PAS discount) is well within the upper bound of the usual threshold range for cost-effectiveness. This is true when considering the extensive sensitivity and scenario presented as a part of our original submission, and when taking the ERGs preferred base case analysis into account. **We therefore conclude:** • **The ACD overstates the uncertainty associated with estimates of the cost-effectiveness of etelcalcetide vs. cinacalcet. Extensive sensitivity and scenario analyses all confirm the ICER remains consistently below the upper threshold range.** • **We propose that the ACD should be amended to reflect that etelcalcetide is highly likely to be cost-effective vs. cinacalcet, and to remove statements suggesting that non-linear pricing leads to uncertainty in the evaluation.**	Comments noted. The committee considered the company's comments that the appraisal consultation document overstated the uncertainty associated with estimates of the cost-effectiveness of etelcalcetide compared with cinacalcet. The committee was aware that the parameter uncertainty associated with the hazard ratio for mortality alone increased the deterministic ICER by more than £10,000 per QALY gained. In addition, this does not include the uncertainty in the extrapolation from the EVOLVE trial and therefore this uncertainty is not reflected in the ICER estimates nor in the probabilistic sensitivity analyses. See section 4.11 of the FAD.

Consultee	Comment [sic]	Response
	4 Etelcalcetide is a clinically valuable treatment option for patients and clinicians Etelcalcetide is the first new treatment for SHPT in a decade. It is an intravenous calcimimetic that places control of administration in the hands of clinicians during haemodialysis sessions. The ACD makes several references to patient and clinician expert comments, which support the added value of etelcalcetide as a treatment option: "*People with secondary hyperparathyroidism would welcome a treatment that could be given at the same time as dialysis with no additional tablets to take*" "*Clinical experts stated that they spend a lot of time talking to people who have difficulty adhering to treatment*" "*…clinical and patient experts commented that an intravenous calcimimetic could improve adherence because it would be given at the end of haemodialysis sessions*" "*Taking into account the chronic nature of the condition, the availability of an additional treatment with a different mode of administration would be a valued option for people with secondary hyperparathyroidism*" Therefore, etelcalcetide has potential adherence advantages over cinacalcet, which were accepted by the Committee (ACD section 4.12, p13 and elsewhere) and are acknowledged to be of clinical value to patients and clinicians. As noted in section **Error! Reference source not found.**, as there is evidence that long-term consistent control of PTH and other biomarkers is associated with better survival than episodic control [6], improved adherence can bring enormous benefit to patients and clinicians. Taken alongside the established evidence that etelcalcetide is clinically superior to cinacalcet in all patient subgroups (see Section **Error! Reference source not found.**)	Comments noted. The committee accepted the advantages of having an intravenous calcimimetic option available for patients. It agreed that because there is uncertainty in establishing the long-term benefits of etelcalcetide compared with cinacalcet (for outcomes such as mortality, fracture and cardiovascular events) and higher associated costs, etelcalcetide should be recommended as an option for people with secondary hyperparathyroidism for whom a calcimimetic is indicated, only if cinacalcet is not considered suitable. See section 4.11 of the FAD.

Consultee	Comment [sic]	Response
	and is highly likely to be cost-effective vs. cinacalcet (see Section **Error! Reference source not found.**), we believe that this supports the use of etelcalcetide as a treatment option in all CKD patients with SHPT on haemodialysis when calcimimetic treatment is indicated, rather than only those in whom cinacalcet is not suitable. **References** 1. Block, G., et al., *Effect of Etelcalcetide versus Cinacalcet on Serum Parathyroid Hormone in Patients Receiving Hemodialysis with Secondary Hyperparathyroidism: a Randomized Clinical Trial.* JAMA, 2017. **317**(2): p. 156-164. 2. European Medicines Agency, *European Public Assessment Report: Parsabiv* 2016. 3. Amgen, *Parsabiv - EU Summary of Product Characteristics.* 2016. 4. Siwek, J. and D. Newman, *Introducing Medicine by the Numbers: A Collaboration of The NNT Group and AFP [Editorial].* Americal Family Physician, 2015(1 April). 5. Amgen, *20120360 Clinical Study Report.* 2015. 6. Danese, M.D., et al., *Consistent control of mineral and bone disorder in incident hemodialysis patients.* Clin J Am Soc Nephrol, 2008. **3**(5): p. 1423-9. 7. Jadoul, M., et al., *Incidence and risk factors for hip or other bone fractures among hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study.* Kidney Int, 2006. **70**(7): p. 1358-66. 8. Tentori, F., et al., *Recent changes in therapeutic approaches and association with outcomes among patients with secondary hyperparathyroidism on chronic hemodialysis: the DOPPS study.* Clin J Am Soc Nephrol, 2015. **10**(1): p. 98-109. 9. Chertow, G.M., et al., *Effect of cinacalcet on cardiovascular disease in patients undergoing dialysis.* N Engl J Med, 2012. **367**(26): p. 2482-94. 10. Parfrey, P., et al., *The clinical course of treated hyperparathyroidism among patients receiving hemodialysis and the effect of cinacalcet: The EVOLVE Trial.* J Clin Endocrinol Metab, 2013. **98**(4834-44). 11. KDIGO, *KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD).* Kidney Int Suppl, 2009(113): p. S1-130. 12. Parfrey, P.S., et al., *Lessons learned from EVOLVE for planning of future randomized trials in patients on dialysis.* Clinical Journal of the American Society of Nephrology, 2015: p. CJN. 06370615. 13. Amgen. *Mimpara (cinacalcet) Summary of Product Characteristics, EMA.* http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-	

Consultee	Comment [sic]	Response
	_Product_Information/human/000570/WC500028900.pdf *(access date 6 July 2015).* 2015 6 July 2015]; Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000570/WC500028900.pdf. 14. Belozeroff, V., et al., *Economic evaluation of cinacalcet in the United States: the EVOLVE trial.* Value in Health (accepted), 2015. 15. Chu, R., et al., *Assessment and implication of prognostic imbalance in randomized controlled trials with a binary outcome–a simulation study.* PLoS One, 2012. **7**(5): p. e36677. 16. Amgen, *Data on File. EVOLVE - Cox regression model adjusted for age.* 2017. 17. NICE, *Cinacalcet for the treatment of secondary hyperparathyroidism in patients with end-stage renal disease on maintenance dialysis therapy.* NICE technology appraisal guidance 117, 2007. 18. Eandi, M., et al., *Economic Evaluation of Cinacalcet in the Treatment of Secondary Hyperparathyroidism in Italy.* Pharmacoeconomics, 2010. **28**(11): p. 1041-1054.	

Comments received from clinical experts and patient experts

Nominating organisation	Comment [sic]	Response
Renal Association and Royal College of Physicians	2.1 Has all of the relevant evidence been taken into account? The evidence is detailed in the committee papers and the committee discussion as detailed in the ACD. I feel that all appropriate evidence has been taken into account.	Comments noted.
Renal Association and Royal College of Physicians	2.2 Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? The clinical effectiveness documentation is accurate and reflects the discussions which took place. The cost effectiveness discussions have also been accurately documented.	Comments noted.

Nominating organisation	Comment [sic]	Response
Renal Association and Royal College of Physicians	.3 Are the recommendations sound and a suitable basis for guidance to the NHS? The recommendations allow the use of calcimimetics in patients with secondary hyperparathyroidism when indicated as determined by the nephrologist. I agree that calcimimetic use should not be determined by exact PTH or calcium levels as each patient is individual and the indication depends on the ability to manage the hyperparathyroidism with first line agents. The recommendations are suitable for guidance within the NHS	Comments noted.
Renal Association and Royal College of Physicians	2.4 Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? I am not aware of, nor can I identify, any aspects of these recommendations which would lead to unlawful discrimination.	Comments noted.

Nominating organisation	Comment [sic]	Response
	Thank you for sending through the consultation document. We are broadly happy with the evidence but have two comments Summary page 15 Point 4.1, 4.2 People with secondary hyperparathyroidism would welcome a treatment that could be given at the same time as dialysis with no additional tablets to take, which may improve adherence to treatment. The patient experts highlighted a patient survey, which revealed that most people would prefer to avoid surgery if possible. The committee accepted the advantages of having an intravenous calcimimetic option available. This cites patient experts. We would prefer this wording to say that Kidney Research UK specifically undertook a survey amongst 185 patients, which revealed a preference to avoid surgery if possible. This could also be referenced. And the recommendations in 1.1 make no mention of patient choice. It states where calcimimetic is indicated, but does not note that patient choice in treatment was a key finding of the survey above. Surely therefore patient choice should be mentioned as a factor when prescribing?	Comments noted. The committee considererd that cost-effectiveness estimates are highly uncertain because of uncertainties in extrapolating short-term surrogate outcomes from the etelcalcetide trials to long-term outcomes such as mortality. However, the committee accepted the advantages of having an intravenous calcimimetic option available. Given that there is uncertainty in establishing the long-term benefits of etelcalcetide compared with cinacalcet (for outcomes such as mortality, fracture and cardiovascular events) and higher associated costs, the committee considered that it should be recommended as an option for people with secondary hyperparathyroidism for whom a calcimimetic is indicated, only if cinacalcet is not considered suitable.

Comments received from commentators

None

Comments received from members of the public

None

Summary of comments received from members of the public

None

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Etelcalcetide for the treatment of secondary hyperparathyroidism [ID908]

Response to appraisal consultation document

Prepared by:

24th March 2017

File name	Version	Contains confidential information	Date
Etelcalcetide_ID908_Amgen Response to ACD_24th March 2017 [ACIC]		Yes AIC: Highlighted in yellow and underlined CIC: Highlighted in blue and underlined	24 March 2017

Contents

1 Executive Summary

We welcome the positive preliminary recommendation for etelcalcetide and the acknowledgement in the Appraisal Consultation Document (ACD), based on clinical and patient expert views, that an intravenous calcimimetic could improve adherence and would be a valuable option for patients with secondary hyperparathyroidism (SHPT). We also welcome the Committee's acceptance of these advantages of etelcalcetide, and the importance of having different treatment options available for treating SHPT.

We have carefully reviewed the Appraisal Committee's consideration of the evidence presented for etelcalcetide, and the preliminary recommendation outlined in the ACD, and have some concerns that the ACD does not reflect the superior comparative efficacy of etelcalcetide vs. cinacalcet, and may overstate the uncertainties in its estimated cost-effectiveness.

In the sections that follow, we reiterate the superior, clinically meaningful efficacy of etelcalcetide over cinacalcet, demonstrated based on robust assessment of clinically meaningful endpoints that are known to impact long-term outcomes. Although we do acknowledge there could be uncertainty in the economic evaluation, we believe that the ICER (including the confidential PAS discount) for etelcalcetide vs. cinacalcet is well within the upper bound of the usual threshold range for cost-effectiveness, is stable to a range of sensitivity analyses, and remains cost-effective when considering the ERGs preferred base case analysis.

We therefore propose that the ACD be amended and that the following considerations are appropriately reflected in the final appraisal determination:

- Etelcalcetide is statistically and clinically superior to cinacalcet;
- Etelcalcetide at the PAS discount price is highly likely to be cost-effective compared with cinacalcet.

Whilst welcoming the positive preliminary recommendation for etelcalcetide, we feel the final recommendation should reflect this clinical and economic evidence. Taken alongside the accepted adherence advantages of etelcalcetide to patients and clinicians, we believe this evidence supports the use of etelcalcetide as a treatment option in all chronic kidney disease (CKD) patients with SHPT on haemodialysis when calcimimetic treatment is indicated, rather than only those in whom cinacalcet is not suitable.

2 Etelcalcetide has clinically meaningful superior efficacy vs. cinacalcet

- **Robust and compelling evidence supports the clinical and statistical superiority of etelcalcetide over cinacalcet, based on endpoints that are accepted by the Committee as clinically important and meaningful outcomes, and which are known to impact long-term clinical outcomes in patients with SHPT.**
- **We are therefore concerned that the ACD omits any reference to the clinical and statistical superiority of etelcalcetide over cinacalcet. Moreover, we feel the Committee's conclusion that "*…etelcalcetide has similar efficacy to cinacalcet…*", used to justify the preliminary recommendation, is factually incorrect based on the available evidence.**
- **We propose that the ACD should be amended to reflect clearly the clinical and statistical superiority of etelcalcetide over cinacalcet.**

2.1 Etelcalcetide trial data demonstrate superior efficacy vs. cinacalcet

Our submission to NICE presented full details of the clinical trial programme for etelcalcetide, including the robust, active-controlled, double-blind, double-dummy, phase 3, randomised trial of etelcalcetide vs. cinacalcet (study 20120360). [1] This trial was of good quality (i.e. low risk of bias) as acknowledged by the Appraisal Committee (ACD Table: Summary of appraisal committee's key conclusions, p16), and has high external validity based on the PICO considerations below:

Patients – The Committee concluded patients enrolled in the trial were generally representative of those with SHPT in the UK (ACD section 4.3, p7), as was noted by the clinical expert consulted by the evidence review group (ERG), who also stated that the median baseline parathyroid hormone (PTH) level of patients in this trial (median PTH around 900pg/mL) was reflective of the population who would currently receive cinacalcet (ERG report, section 3.1.3, p38).

Intervention and Comparator – Etelcalcetide and cinacalcet were both dosed in the trials in line with the recommendations in their respective Summaries of Product Characteristics.

Outcomes – The primary efficacy measure in the trial was the proportion of patients achieving a >30% reduction from baseline in PTH, which was deemed to be clinically meaningful in SHPT patients by the European Medicines Agency (EMA) when granting the positive marketing authorisation for etelcalcetide. [2] The ACD also reports (ACD section 4.5, p8): "*…The Committee concluded that the primary outcome of more than 30% reduction in parathyroid hormone levels is a clinically important and meaningful outcome…".*

As detailed in our submission, the trial was designed first to test the non-inferiority of etelcalcetide vs. cinacalcet for this endpoint, and also **pre-specified tests of superiority** for the secondary endpoints of proportion of patients achieving >50% and >30% reduction from baseline in PTH if non-inferiority was achieved.

Etelcalcetide achieved non-inferiority for the primary endpoint, **and superiority** for this and the more stringent endpoint of a >50% reduction from baseline in PTH compared with cinacalcet. This is reflected in our submission, and in the current Summary of Product Characteristics (SmPC) for etelcalcetide, which states: "*Parsabiv was non-inferior to cinacalcet for the primary endpoint, and was superior to cinacalcet for the secondary endpoints of proportion of patients achieving > 30% reduction from baseline in mean PTH during the EAP (68.2% Parsabiv versus 57.7% cinacalcet; p = 0.004); and proportion of patients achieving > 50% reduction from baseline in mean PTH during the EAP (52.4% Parsabiv versus 40.2% cinacalcet; p = 0.001)".* [3] Of note, the numbers needed to treat (NNTs) for etelcalcetide vs. cinacalcet (i.e. vs. an active treatment) for these clinically important and meaningful endpoints are less than 10, which is generally considered to be indicative of an effective treatment. [4]

Furthermore, the relative proportion of patients achieving a reduction in PTH concentrations of >30% or >50% did not differ significantly across any of the pre-specified subgroups compared with the whole trial population (see Figure 12 of our original submission and Figure 3 in the published manuscript).

In addition to this, during the EAP etelcalcetide demonstrated a statistically significant reduction in serum calcium levels from baseline vs. cinacalcet, and significantly reduced phosphate levels from baseline. [1, 5]

In summary:

- **Robust phase 3 RCT data, obtained in SHPT patients reflective of those in clinical practice, demonstrate that etelcalcetide is statistically significantly superior to cinacalcet based on its effects on PTH-related endpoints.**
- **The EMA and NICE Appraisal Committee agreed these endpoints are clinically important and meaningful in patients with SHPT.**
- **The low NNTs for these endpoints, obtained with etelcalcetide against an active treatment, confirm these *statistically significant* results in favour of etelcalcetide reflect *clinically significant* improvements over cinacalcet.**
- **Results consistently favoured etelcalcetide across all subgroups.**

2.2 Association between biomarkers used in etelcalcetide trials and clinical outcomes is well established

The primary and secondary endpoints of the etelcalcetide trials reflected reductions in PTH, serum calcium and phosphate levels. As reported in our submission,

although the trials did not directly assess clinical outcomes, large retrospective observational studies consistently indicate that uncontrolled PTH, calcium and phosphate levels are associated with a range of adverse clinical events, including fractures, CV events and death, in haemodialysis patients with SHPT. [6-8]

A cohort study by Danese et al observed that simultaneous control of PTH, calcium, and phosphate was associated with increased survival compared with control of one or two of these parameters and, furthermore, long-term consistent control of these biomarkers was associated with better survival than episodic control. [6]

The specific risk associated with uncontrolled PTH levels has been demonstrated in a Dialysis Outcomes and Practice Patterns Study (DOPPS), which followed 35,655 dialysis patients over 15 years (1996-2011) and observed increasing risks of mortality with increasing PTH levels. [8] Further compelling evidence of the central role of PTH in the development of adverse clinical events is evident from the change in the clinical course of SHPT when PTH is more effectively controlled. The large EVOLVE (Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events) RCT, when adjusted for important confounding factors (see Section 3.1), observed cinacalcet, a potent inhibitor of PTH secretion, reduced the risks of all-cause mortality and major CV events when added to background phosphate binder and vitamin D sterols. [9, 10]

In summary:

- **It is well established that uncontrolled PTH, as well as calcium and phosphate disturbances, is associated with a range of adverse clinical consequences for patients with SHPT**
- **It is accepted that achievement of greater control of PTH, alongside calcium and phosphate levels, is associated with a reduction in the risk of these adverse clinical consequences for patients with SHPT.**
- **For this reason, clinical practice guidelines, such as the internationally-respected KDIGO clinical practice guidelines [11], indicate the aim of treatment in SHPT is to correct the levels of PTH, serum calcium and phosphate. This view is confirmed by clinical expert opinion reported in the ACD (section 4.2, p6).**
- **The primary and secondary endpoints of the etelcalcetide trials therefore reflect reductions in biomarkers that are used in clinical practice to guide treatment and have a well-established association with clinical outcomes in patients with SHPT. The conclusion that etelcalcetide is clinically superior to cinacalcet, based on a robust trial using these endpoints, is therefore compelling.**
- **As there is evidence that long-term consistent control of these biomarkers is associated with better survival than episodic control [6], the importance of adherence to treatment should not be underestimated.**

2.3 Implications for the ACD

Our submission presented the robust clinical and statistical superiority of etelcalcetide over cinacalcet, based on robust phase 3 RCT data, and demonstrated consistent results across all pre-specified subgroups (re-iterated in brief in Section 2.1 of this document). Our submission also detailed how the biomarkers used in the etelcalcetide trials are used in clinical practice to guide treatment and have a well-established association with clinical outcomes in patients with SHPT (re-iterated in brief in Section 2.2 of this document).

We are therefore disappointed that, despite this compelling evidence, no reference to the clinical and statistical superiority of etelcalcetide over cinacalcet is made in the ACD.

Moreover, despite this compelling evidence of the clinical and statistical superiority of etelcalcetide over cinacalcet, the ACD states twice (section 4.12, p13, and in the Summary of appraisal committee's key conclusions, p14): "*Given that etelcalcetide has similar efficacy to cinacalcet but higher associated costs, the committee considered that it should be recommended as an option for people with secondary hyperparathyroidism whom a calcimimetic is indicated, only if cinacalcet is not considered suitable*". We feel this conclusion on the comparative efficacy of etelcalcetide does not reflect the robust clinical evidence base for etelcalcetide, and note this is also inconsistent with the EMA's interpretation of the clinical data for etelcalcetide based on the agreed wording of the SmPC, which states: *"Parsabiv was non-inferior to cinacalcet for the primary endpoint, and was superior to cinacalcet for the secondary endpoints of proportion of patients achieving > 30% reduction from baseline in mean PTH during the EAP … and proportion of patients achieving > 50% reduction from baseline in mean PTH during the EAP…".* [3]

We therefore conclude:

- **The ACD does not accurately reflect the clinical evidence base for etelcalcetide, as it omits any reference to the clinical and statistical superiority of etelcalcetide over cinacalcet.**
- **The suggestions in the ACD that etelcalcetide has similar efficacy to cinacalcet is inconsistent with the available evidence, and is inconsistent with the interpretation of this evidence by the EMA reflected in the agreed wording of the SmPC.**
- **We propose the ACD should be amended to clearly reflect the compelling evidence that demonstrates the clinical and statistical superiority of etelcalcetide over cinacalcet.**

3 Etelcalcetide is a cost-effective alternative to cinacalcet

- **Whilst we acknowledge there could be uncertainty around ICER estimates in our analysis, we believe that the incremental cost per QALY gained for etelcalcetide (including the [redacted] PAS discount) is highly likely to be considered cost-effective vs. cinacalcet**
    - **As stated in our submission, and acknowledged by the Committee, the EVOLVE trial provides the most robust outcomes data for calcimimetics with which to model etelcalcetide.**
    - **Our approach to account for the chance imbalance in baseline characteristics is aligned with the pre-specified multivariate analysis in EVOLVE and results are consistent with univariate analyses adjusting for age.**
    - **The ERG concluded that our approach to modelling long-term outcomes is reasonable, and ICER estimates vs. cinacalcet are consistently below the upper threshold that would typically be considered cost-effective across a range of sensitivity analyses.**
- **We strongly disagree that the non-linear pricing of vials leads to uncertainty as is currently reported in the ACD.**
- **We propose that the ACD should be amended to reflect that etelcalcetide is highly likely to be cost-effective vs. cinacalcet, and importantly to remove statements suggesting that non-linear pricing leads to uncertainty in the evaluation.**

3.1 Appropriateness of covariate adjustments to account for chance imbalance in baseline characteristics in EVOLVE

As stated in our submission, and acknowledged by the Committee, the EVOLVE trial provides the most robust outcomes data for calcimimetics with which to model etelcalcetide. Although the primary unadjusted ITT analysis from EVOLVE demonstrated that patients randomised to cinacalcet experienced numerically fewer composite events, the risk reduction was not statistically significant (relative hazard 0.93, 95% confidence interval (95% CI) 0.85 to 1.02; p=0.11). [9] However, as discussed in our submission and reported elsewhere, there was a chance imbalance in age between the cinacalcet and placebo arms of the trial, leading to a bias in the ITT analysis. [9, 12]

The pre-specified multivariate analysis in EVOLVE (multivariate best fit model) adjusting for baseline characteristics showed a nominally significant hazard ratio (HR) for the primary composite end point of 0.88 (95% CI, 0.79 to 0.97; p = 0.008), which has been accepted by the EMA and included in the updated SmPC for

cinacalcet in Europe. [9, 13]. An analysis adjusting for all baseline covariates showed similar results (0.88 [0.80, 0.98]). [9]

The methods to derive HRs used to inform our base case lag-censored analysis follow the pre-specified multivariate analysis in principle, by including all baseline covariates and using a step-wise procedure to determine the best fit model. A multivariate analysis was used in our base case as it accounts for all potential measured confounding factors which could be unduly affecting the results.The HRs for the lag-censored multivariate best-fit model used to inform our base case analysis are reported in Table 1 below.

Table 1: Hazard ratios extracted from the EVOLVE trial for cinacalcet vs. placebo (multivariate best fit model)

	Lag-censored HRs[b] [95% CI]	**Source**
Cinacalcet vs placebo		Belozeroff et al 2015 [14]
All-cause mortality	0.80 [0.69, 0.91]	
CV events[a] (non-fatal)	0.78 [0.67, 0.91]	
Fractures (non-fatal)	0.73 [0.59, 0.92]	
PTx (non-fatal)	0.25 [0.19, 0.33]	

CI, confidence interval; CV, cardiovascular; HR, hazard ratio; ITT, intention-to-treat; PTx, parathyroidectomy
[a] Myocardial infarction, unstable angina, heart failure and peripheral vascular event
[b] Adjusted for baseline covariates: age, sex, race, region, body-mass index, time on dialysis, history of CV disease, blood pressure, diabetes, retinopathy, tobacco use, type of vascular access, high density lipoproteins (HDL), Ca x P, and albumin. IXRS stratification factors (country and diabetes) were included in the model.

Nevertheless, it is stated in the ACD (section 4.8, pg 10) that the Committee were "*…concerned that there were many adjustments for baseline characteristics made to the EVOLVE data to derive treatment effects, and it was unclear why so many adjustments were made and how valid they were.*"

Of all the baseline characteristics evaluated in EVOLVE, age was deemed to be the most clinically important covariate affecting the primary composite endpoint and a nominally significant interaction factor between treatment effect and the age subgroup (p=0.007) was identified. [9] In the EVOLVE analyses, it was demonstrated that a 1-year increase in age was associated with a 3% increase in the risk of experiencing the primary composite endpoint. [9] Despite enrolling 3,883 patients in EVOLVE there was a 0.8 years difference in mean age at baseline and a 1 year difference in median age (55 versus 54 years), an occurrence that therefore confounded estimates of treatment effectiveness. [9, 12] This chance imbalance in a major prognostic factor necessitates covariate adjustment. [15]

Results from the pre-specified univariate analysis adjusting for age in EVOLVE were similar to the multivariate analysis described above, showing a reduction in risk of the primary composite endpoint event (HR 0.88; 95% CI 0.81, 0.97; nominal p = 0.007).[9] Age-adjusted HRs for the modelled outcomes are presented in Table 2.

Table 2: Hazard ratios extracted from the EVOLVE trial for cinacalcet vs. placebo (age-adjusted)

	Lag-censored HRs[b] [95% CI]	Source
Cinacalcet vs placebo		Amgen, Data on File 2017 [16]
All-cause mortality	[redacted]	
CV events[a] (non-fatal)	[redacted]	
Fractures (non-fatal)	[redacted]	
PTx (non-fatal)	[redacted]	

CI, confidence interval; CV, cardiovascular; HR, hazard ratio; ITT, intention-to-treat; PTx, parathyroidectomy
[a] Myocardial infarction, unstable angina, heart failure and peripheral vascular event
[b] Hazard ratio and 95% CI were obtained from the Cox model. IXRS stratification factors (country and diabetes) were included in the model.

The HRs are consistent with the multivariate estimate used in our base case analysis and the point estimates fall well within the parameter ranges explored during the sensitivity and scenario analyses conducted. Of note, all sensitivity and scenario analyses resulted in ICERs for etelcalcetide vs. cinacalcet that remained within the usual threshold for cost-effectiveness. As such, we strongly believe that the covariate-adjustments used in the base case analysis provide a valid estimate of the treatment effect, and that any uncertainty associated with this is approach has been appropriately accounted for and does not influence the conclusions on cost-effectiveness.

In summary:

- **EVOLVE is acknowledged to be the best data source from which to model clinical outcomes; however, the chance imbalance in baseline characteristics necessitates covariate adjustment.**
- **Our base case approach is aligned with the pre-specified multivariate analysis in EVOLVE which has been accepted by the EMA and included in the updated SmPC for cinacalcet in Europe.**
- **Age was identified as the most clinically important covariate affecting estimates of the treatment effect in EVOLVE. Hazard ratios for cinacalcet vs. placebo are consistent across both multivariate and age-adjusted analyses.**
- **This consistency confirms that the multivariate adjustment used in our base case analysis provides an appropriate estimate of the treatment effect, and our extensive assessments of uncertainty via sensitivity and scenario analyses allow us to conclude with confidence that etelcalcetide is a cost-effective treatment option vs. cinacalcet.**

3.2 Uncertainty in extrapolating surrogate biomarkers to clinical outcomes in EVOLVE

It is acknowledged in our submission that there is some uncertainty associated with the base case approach to extrapolate clinical outcomes from EVOLVE to the primary efficacy endpoint (ie. >30% PTH reduction) in the etelcalcetide trials. However, we feel this uncertainty has been overstated in the ACD and so we would

dispute that it contributes to an "*unsound"* (section 4.8, pg 10) evaluation of the cost-effectiveness of etelcalcetide. In support of our concerns we refer to the ERG's own interpretation of our approach, as is stated in their report (section 4.3.4.5, pg 99): "*The log-linear method used to extrapolate HRs for etelcalcetide from the EVOLVE results and etelcalcetide primary outcome, ≥30% reduction in PTH is reasonable").*

The primary assumption underpinning the present model is that a higher rate of reduction in PTH levels for etelcalcetide than cinacalcet would translate into a proportional reduction in mortality, fractures, cardiovascular events and parathyroidectomy. As discussed in Section 2.2, the link between PTH and other biochemical parameters to clinical outcomes is well established, and it is of note that NICE has previously acknowledged this relationship having accepted the ERG's approach to modelling clinical outcomes based on PTH levels in the 2007 Technology Appraisal of cinacalcet. [17]

In our submission, we present extensive sensitivity and scenario analyses to address the uncertainty in our modelling approach and conclude that the ICERs for etelcalcetide vs. cinacalcet remain well within the typical threshold for cost-effectiveness. In particular, we would draw the Committee's attention to two specific analyses that we feel adequately mitigate uncertainty in our extrapolated approach:

- Analysis of the achievement of PTH ≤ 300 pg/ml as a surrogate endpoint to extrapolate to clinical outcomes
- An alternative methodology for modelling clinical outcomes from biochemical parameters observed in the etelcalcetide trials, utilising a published biomarker based risk-prediction equation

Both analyses are discussed in more detail below.

3.2.1 **Analysis of the achievement of PTH ≤ 300 pg/ml as a surrogate endpoint**

The rationale for using the PTH reduction of at least 30% from baseline as the surrogate endpoint for extrapolation was that this is the pre-specified primary outcome of the etelcalcetide trials and is regarded by clinicians (and accepted by the Committee) to be a clinically important and meaningful outcome (see Section 2.1). However, in response to questions raised by the ERG, we acknowledged that achievement of PTH ≤300 pg/mL in observational studies has been associated with a reduced risk of all-cause mortality (compared with PTH values >300 pg/mL), decreased bone turnover and improved bone histology, which would support the use of this target as an appropriate surrogate endpoint to extrapolate to the clinical endpoints measured in EVOLVE.

This analysis was conducted by the ERG and is detailed in their report; the resulting ICER vs. cinacalcet of £11,490 per QALY may suggest that our base case conservatively underestimates the long-term health benefit of etelcalcetide. Although this approach is also reliant on a linear extrapolation to the HRs derived from EVOLVE, the existing evidence base and clinical guidelines in this disease area are supportive of the relationship between the achievement of a PTH target ≤300 pg/ml and reduced clinical outcomes.

We believe that this analysis confirms our conclusion that etelcalcetide is highly likely to be cost-effective vs. cinacalcet and reduces the uncertainty associated with linking biomarker data to clinical outcomes.

3.2.2 **Alternative methodology using risk-based prediction equations**

To further explore the validity of the base case extrapolation approach we also modelled clinical outcomes based on biomarker data (PTH, calcium and phosphate serum levels) measured within the etelcalcetide trials. This analysis does not rely on the linear extrapolation assumption used to link to EVOLVE and as noted in the ERG report (section 4.3.4.5, pg 98) provides "…*a useful check on the plausibility of the results, as they rely on different external sources of data"*.

This analysis requires a risk prediction equation that translates biomarker measurements into event risks. Our systematic literature review of cost-effectiveness analyses identified such a risk-prediction equation from a study by Eandi et al. 2010 which was informed by large, observational datasets in the disease area. [18] Further details of the analysis are reported in Appendix 10 of our original submission.

The cost-effectiveness results derived from the biomarker risked-based prediction equations were presented in our submission and are reiterated in Table 3 below, alongside our base case results for comparison. Estimates for both the censored and ITT disaggregated analysis of the etelcalcetide trials are presented.

Table 3: Etelcalcetide (plus PB/VD) versus cinacalcet (plus PB/VD) – results of efficacy-based scenario analyses

Scenario	Incremental costs	Incremental QALYs	ICER (£/QALY)
Base case	£1,020	0.069	14,778
Eandi; censored*	£1,107	0.057	19,334
Eandi; ITT disaggregated	£1,180	0.074	15,975

* In the censored analysis, biomarker measurements were censored post-discontinuation of the investigational product.

As we concluded in our submission, the resulting ICERs are similar to the base case analysis and the incremental costs and incremental QALYs are consistent. We believe that this consistency with the base case results provides reassurance that the base case assumptions are plausible and that the uncertainty associated with the extrapolation approach is minimal. Etelcalcetide is therefore highly likely to be cost-effective vs. cinacalcet.

In summary:

- **Whilst we do acknowledge there could be uncertainty around estimates of the cost-effectiveness, we believe the impact of this is overstated in the ACD, and so suggestions that the analysis is 'unsound' are not warranted.**
- **The ERG assessment report concludes that our extrapolation approach is reasonable and we have also demonstrated consistency across results using alternative approaches. ICERs vs. cinacalcet remain well within the typical threshold for cost-effectiveness when accounting for uncertainty.**
- **We believe our treatment effect estimates based on the base case extrapolation approach are conservative, plausible, associated with minimal uncertainty, and demonstrate that etelcalcetide is highly likely to be cost-effective vs. cinacalcet.**

3.3 Uncertainty associated with the non-linear pricing of vials

As correctly noted in the ACD, etelcalcetide is available in three vial sizes (2.5 mg, 5 mg and 10 mg) and the smaller 2.5 mg vial has a higher cost per mg than the larger 5 mg and 10 mg vials. However, we strongly disagree with the statement in the ACD that this introduces uncertainty in the appraisal.

An extract from section 4.10, pg 11 has been reported below:

"The committee was concerned that this [non-linear pricing] introduced uncertainty in acquisition costs because if the larger dose vials were unavailable for any reason the incremental cost-effectiveness ratio (ICER) would increase, if a larger proportion of the more expensive 2.5-mg vials were used."

Amgen are fully committed to avoiding shortages of our products and strive to deliver our medicines to 'every patient, every time'. This is reflected in our very strong track record of timely medicines delivery across the UK and worldwide. We believe it is unreasonable to suggest that clinicians would routinely administer higher doses of etelcalcetide using multiple 2.5 mg vials, as opposed to utilising the larger, less costly vials. We therefore feel that these claims in the ACD are unfounded and refer to a hypothetical scenario that is highly unlikely to transpire in clinical practice. As such, we recommend that statements relating to the uncertainty in acquisition costs be removed in the final appraisal determination.

The ACD also concludes that (section 4.10, pg 11) "*the company's approach of using the distribution of vial usage in the trials was not unreasonable, but the company's estimation of vial usage was associated with uncertainty because of the potential variability in costs depending on which vial sizes are used*."

As stated in our 'PAS Addendum', a weighted average is used to calculate the average per mg price in the economic model. This approach ensures that the price of etelcalcetide is fully aligned with drug use, assuming that the minimum number of vials are used and vial sharing does not occur. As stated previously, we believe that it is unreasonable to suggest that clinicians would administer higher doses of etelcalcetide using multiple 2.5 mg vials, and therefore uncertainty associated with the vial distribution is minimal. Furthermore, although vial-sharing is highly unlikely to occur in UK clinical practice, any occurrence of this would ultimately result in a reduced cost of etelcalcetide and would not detract from conclusions that etelcalcetide is a cost-effective treatment option vs. cinacalcet. As such, we recommend that statements relating to the uncertainty associated with vial distribution be removed in the final appraisal determination.

In summary:

- **We strongly disagree that the non-linear pricing of vials leads to uncertainty in the appraisal as is currently reported in the ACD**
- **Given Amgen's strong track record of timely medicines delivery, the hypothetical scenario whereby larger vials are unavailable is unlikely to transpire in clinical practice, and it is unreasonable to suggest clinicians would use multiple small vials when administering larger doses.**

- **We propose that statements around the uncertainty associated with the non-linear pricing of vials be removed in the final appraisal determination.**

3.4 Implications for the ACD

Our submission presents robust, plausible estimates of the cost-effectiveness of etelcalcetide vs. cinacalcet. It has been acknowledged by the Committee that EVOLVE provides the best outcomes data for calcimimetics and we believe that the adjustments made for baseline covariates are both necessary to account for the chance imbalances between treatment arms and are appropriate to assess the true treatment effect (Section 3.1). The extrapolation methodology was supported by a clinically relevant and meaningful endpoint and was considered to be '*reasonable*' by the ERG; furthermore, ICERs were consistently below the typical cost-effectiveness threshold when alternative approaches to estimate the long-term benefits of etelcalcetide were investigated (Section 3.2). In addition to this, we believe statements around the uncertainty introduced by the non-linear pricing of vials are unsubstantiated and should be removed in the final appraisal determination (Section 3.3).

Whilst we do acknowledge there could be uncertainty around ICER estimates, we believe that the incremental cost per QALY gained for etelcalcetide vs. cinacalcet (including the [redacted] PAS discount) is well within the upper bound of the usual threshold range for cost-effectiveness. This is true when considering the extensive sensitivity and scenario presented as a part of our original submission, and when taking the ERGs preferred base case analysis into account.

We therefore conclude:

- **The ACD overstates the uncertainty associated with estimates of the cost-effectiveness of etelcalcetide vs. cinacalcet. Extensive sensitivity and scenario analyses all confirm the ICER remains consistently below the upper threshold range.**
- **We propose that the ACD should be amended to reflect that etelcalcetide is highly likely to be cost-effective vs. cinacalcet, and to remove statements suggesting that non-linear pricing leads to uncertainty in the evaluation.**

4 Etelcalcetide is a clinically valuable treatment option for patients and clinicians

Etelcalcetide is the first new treatment for SHPT in a decade. It is an intravenous calcimimetic that places control of administration in the hands of clinicians during haemodialysis sessions. The ACD makes several references to patient and clinician expert comments, which support the added value of etelcalcetide as a treatment option:

> "*People with secondary hyperparathyroidism would welcome a treatment that could be given at the same time as dialysis with no additional tablets to take*"
>
> "*Clinical experts stated that they spend a lot of time talking to people who have difficulty adhering to treatment*"
>
> "*…clinical and patient experts commented that an intravenous calcimimetic could improve adherence because it would be given at the end of haemodialysis sessions*"
>
> "*Taking into account the chronic nature of the condition, the availability of an additional treatment with a different mode of administration would be a valued option for people with secondary hyperparathyroidism*"

Therefore, etelcalcetide has potential adherence advantages over cinacalcet, which were accepted by the Committee (ACD section 4.12, p13 and elsewhere) and are acknowledged to be of clinical value to patients and clinicians. As noted in section 2.2, as there is evidence that long-term consistent control of PTH and other biomarkers is associated with better survival than episodic control [6], improved adherence can bring enormous benefit to patients and clinicians.

Taken alongside the established evidence that etelcalcetide is clinically superior to cinacalcet in all patient subgroups (see Section 2) and is highly likely to be cost-effective vs. cinacalcet (see Section 3), we believe that this supports the use of etelcalcetide as a treatment option in all CKD patients with SHPT on haemodialysis when calcimimetic treatment is indicated, rather than only those in whom cinacalcet is not suitable.

5 References

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Etelcalcetide for treating secondary Hyperparathyroidism

Appraisal consultation document response

[redacted]

On behalf of Renal Association and Royal College Physicians

1. Recommendations:

1.1 Etelcalcetide is recommended as an option for treating secondary hyperparathyroidism in adults with chronic kidney disease on haemodialysis, only if:

- treatment with a calcimimetic is indicated but cinacalcet is not suitable and
- the company provides etelcalcetide with the discount agreed in the patient access scheme.

1.2 This guidance is not intended to affect the position of patients whose treatment with etelcalcetide was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop.

2. Comments:

2.1 Has all of the relevant evidence been taken into account?

The evidence is detailed in the committee papers and the committee discussion as detailed in the ACD. I feel that all appropriate evidence has been taken into account.

2.2 Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The clinical effectiveness documentation is accurate and reflects the discussions which took place. The cost effectiveness discussions have also been accurately documented.

2.3 Are the recommendations sound and a suitable basis for guidance to the NHS?

The recommendations allow the use of calcimimetics in patients with secondary hyperparathyroidism when indicated as determined by the nephrologist. I agree that calcimimetic use should not be determined by exact PTH or calcium levels as each patient is individual and the indication depends on the ability to manage the hyperparathyroidism with first line agents.

The recommendations are suitable for guidance within the NHS.

2.4 Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

I am not aware of, nor can I identify, any aspects of these recommendations which would lead to unlawful discrimination.

Thank you for sending through the consultation document.

We are broadly happy with the evidence but have two comments

Summary page 15 Point 4.1, 4.2

People with secondary hyperparathyroidism would welcome a treatment that could be given at the same time as dialysis with no additional tablets to take, which may improve adherence to treatment.

The patient experts highlighted a patient survey, which revealed that most people would prefer to avoid surgery if possible.

The committee accepted the advantages of having an intravenous calcimimetic option available.

This cites patient experts. We would prefer this wording to say that Kidney Research UK specifically undertook a survey amongst 185 patients, which revealed a preference to avoid surgery if possible. This could also be referenced.

And the recommendations in 1.1 make no mention of patient choice. It states where calcimimetic is indicated, but does not note that patient choice in treatment was a key finding of the survey above. Surely therefore patient choice should be mentioned as a factor when prescribing?

Thanks

[redacted]

Kidney Research UK

Etelcalcetide for treating secondary Hyperparathyroidism

Appraisal consultation document response

Dr Helen Eddington
On behalf of Renal Association and Royal College Physicians

1. Recommendations:

1.1 Etelcalcetide is recommended as an option for treating secondary hyperparathyroidism in adults with chronic kidney disease on haemodialysis, only if:

- treatment with a calcimimetic is indicated but cinacalcet is not suitable and
- the company provides etelcalcetide with the discount agreed in the patient access scheme.

1.2 This guidance is not intended to affect the position of patients whose treatment with etelcalcetide was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop.

2. Comments:

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The evidence is detailed in the committee papers and the committee discussion as detailed in the ACD. I feel that all appropriate evidence has been taken into account.

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The recommendations are suitable for guidance within the NHS.

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I am not aware of, nor can I identify, any aspects of these recommendations which would lead to unlawful discrimination.