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Evidence Review Group Report commissioned by the NIHR HTA Programme on behalf of NICE

Etelcalcetide for treating secondary hyperparathyroidism

ERRATUM

Produced by Southampton Health Technology Assessments Centre (SHTAC)

Authors Karen Pickett, Research Fellow, SHTAC
Jo Lord, Professorial Fellow in Health Economics, SHTAC
Micah Rose, Research Fellow, SHTAC
Jonathan Shepherd, Principal Research Fellow, SHTAC
Petra Harris, Research Fellow, SHTAC

Correspondence to Jonathan Shepherd
Southampton Health Technology Assessments Centre (SHTAC)
University of Southampton
First Floor, Epsilon House
Enterprise Road, Southampton Science Park
Southampton SO16 7NS
www.southampton.ac.uk/shtac

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors

K Pickett (Research Fellow) critically appraised the clinical effectiveness systematic review, drafted the report and project managed the review. J Lord (Professorial Fellow in Health Economics) critically appraised the health economic systematic review, critically appraised the economic evaluation and drafted the report. M Rose (Research Fellow) critically appraised the health economic systematic review, critically appraised the economic evaluation and drafted the report. J Shepherd (Principal Research Fellow) critically appraised the clinical effectiveness systematic review, drafted the report and is the project guarantor. P Harris (Research Fellow) critically appraised the clinical effectiveness systematic review and drafted the report.

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LIST OF ABBREVIATIONS

AE	Adverse event
AIC	Academic-in-confidence
BSAP	Bone specific alkaline phosphatase
BNF	British National Formulary
cCa	Corrected calcium
cCa x P	Corrected calcium-phosphate product
CI	Confidence interval
CIC	Commercial in confidence
CG	Clinical Guideline
CHMP	Committee for Medicinal Products for Human Use
CKD	Chronic kidney disease
CRD	Centre for Reviews and Dissemination
CS	Company submission
CSR	Clinical Study Report
CTX	Collagen type 1 cross-linked C-telopeptide
CV	Cardiovascular
EAP	Efficacy assessment phase
ERG	Evidence Review Group
EUCTR	European Union Clinical Trials Register
FDA	Food and Drug Administration
FGF-23	Fibroblast growth factor-23
HR	Hazard Ratio
HRQoL	Health Related Quality of Life
ICTRP	International Clinical Trials Registry Platform
IPCW	Inverse probability of censoring weights
IPE	Iterative Parameter Estimation
ITC	Indirect treatment comparison
ITT	Intention to treat
KDIGO	Kidney Disease: Improving Global Outcomes
KDQOL-36	Kidney Disease Quality of Life
LILACS	Literature in the Health Sciences in Latin America and the Caribbean
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NHS	National Health Service
NHSEED	National Health Service Economic Evaluation Database
NMA	Network meta-analysis
P	Phosphate
PB	Phosphate binders
Pg	Picogram
PTH / iPTH	Parathyroid hormone / intact parathyroid hormone
PTx	Parathyroidectomy
RCT	Randomised controlled trial
RPSFTM	Rank Preserving Structural Failure Time Model
SAE	Serious adverse event
SHPT	Secondary hyperparathyroidism

SLR	Systematic literature review
SmPC	Summary of product characteristics
TA	Technology Appraisal
UKCTG	UK Clinical Trials Gateway
VD	Vitamin D
WHO	World Health Organisation

SUMMARY

Scope of the company submission

The company's submission (CS) generally reflects the scope of this appraisal issued by the National Institute for Health and Care Excellence (NICE). This was to appraise the clinical and cost-effectiveness of etelcalcetide (an intravenous calcimimetic drug) within its marketing authorisation for the treatment of secondary hyperparathyroidism (SHPT) in people with chronic kidney disease (CKD), receiving haemodialysis (i.e. those with end-stage kidney disease). The comparators specified in the scope and the company's decision problem were: established clinical practice without calcimimetics (dietary modification to restrict phosphate, phosphate binders (PB) and analogues of vitamin D (VD)), for use in a broad population of people with CKD who have SHPT, and the calcimimetic cinacalcet, for use specifically in a population of patients with refractory SHPT (that is, refractory to established clinical practice without calcimimetics). The Evidence Review Group (ERG) considers that the submission may not provide evidence about the relative efficacy of etelcalcetide and cinacalcet in the population with refractory SHPT (this is discussed further below), and in this respect, the CS does not fully meet the scope of this appraisal.

Summary of submitted clinical effectiveness evidence

The CS included a systematic literature review, which identified three relevant randomised controlled trials (RCTs) of etelcalcetide versus the comparators specified in the scope. The CS also included brief findings from three non-RCTs as supporting data. The company did not conduct a network meta-analysis or formal indirect comparison, and the ERG agrees with this decision, as head-to-head trial evidence is available.

The systematic review identified and included the following evidence:

- Two phase III, double-blind, multicentre RCTs of etelcalcetide (plus PB/VD) versus placebo (plus PB/VD) administered for 26 weeks in a broad population of people with CKD with SHPT, receiving haemodialysis (trials 20120229 and 20120230). The trials were of a similar design and the company presented pooled analyses of results from the two trials in addition to separate results. The trials included a total of 1023 participants (10 were from the UK).
- One phase III, double-blind, multicentre RCT of etelcalcetide (plus PB/VD) versus cinacalcet (plus PB/VD) administered for 26 weeks in a broad population of people with CKD with SHPT, receiving haemodialysis (trial 20120360) (N = 683).
- Two phase III, single arm extension studies to trials of etelcalcetide including trials 20120229, 20120230 and 20120360 (studies 20120231 (N = 891) and 20130213 (N = 902)).

- One phase III single arm study of the efficacy and safety of patients switching from cinacalcet to etelcalcetide (study 20120359, N = 158). The reasons for switching were not provided.

The phase III RCTs measured scope-specified outcomes, including various measures of parathyroid hormone (PTH), serum levels of calcium and phosphate, health-related quality of life (HRQoL) (in the cinacalcet-controlled trial only) and adverse events (AEs). The CS uses the pg/mL unit to describe PTH levels, but we note that in the UK, PTH is measured in pmol/L units. Therefore, where we discuss PTH in this report, we lead with the pg/mL units, but supply the equivalent pmol/L units in brackets. We note the trials did not measure the target PTH used in practice for patients receiving dialysis as an outcome. The target used in practice is a PTH of 2-9 times the upper limit of normal of the reference limit of the laboratory test used, which we note translates to a PTH range of around 130-600 pg/mL (13.8 – 63.6 pmol/L). The trials also did not use the target ranges for phosphate and calcium used in clinical practice as outcomes. The trials did not measure the longer-term outcomes specified in the scope: survival, incidence of fractures, incidence of cardiovascular events and need for parathyroidectomy. Instead, these were extrapolated from the primary PTH outcome measured in the trials ('proportion of patients achieving a >30% reduction in mean PTH from baseline during the efficacy assessment phase (EAP)') for use in the economic model.

- The results of the trials showed participants treated with etelcalcetide (plus PB/VD) were statistically significantly more likely to achieve a > 30% reduction in mean PTH from baseline during EAP than those treated with placebo (plus PB/VD) (pooled analysis: 8.9% versus 74.7%, respectively, stratified odds ratio (95% confidence intervals (CIs): 31.60 (21.59, 46.25), p < 0.001; data pooled from intention-to-treat (ITT) analyses). Etelcalcetide (plus PB/VD) was found to be both non-inferior and superior to treatment with cinacalcet (plus PB/VD) on this outcome (superiority analysis: cinacalcet 57.7% versus etelcalcetide 68.2%, odds ratio (95% CIs): 1.59 (1.16, 2.17), p = 0.004; ITT analysis).
- Proportionally more participants treated with etelcalcetide (plus PB/VD) achieved a mean PTH of ≤ 300 pg/mL (31.8 pmol/L) during the EAP than those treated with placebo (plus PB/VD) in both placebo-controlled trials (pooled analysis: 51.5% versus 4.9%, respectively, stratified odds ratio (95% CIs): 27.02 (16.62, 43.93, p < 0.001); data pooled from ITT analyses).
- Proportionally more participants treated with etelcalcetide (plus PB/VD) [redacted] than those treated with cinacalcet (plus PB/VD) [redacted] also achieved this target in the cinacalcet-controlled trial (odds ratio, 95% CIs and p-value not reported in the CS; [redacted]).

Participants treated with etelcalcetide (plus PB/VD) had greater reductions in phosphate levels than those treated with placebo (plus PB/VD) (not ITT analyses) in the placebo-controlled trials. There was no difference between etelcalcetide and cinacalcet, though, in the proportion of participants reaching the phosphate target used in the cinacalcet-controlled trial (an ITT analysis; not a target used in practice). Participants treated with etelcalcetide (plus PB/VD) experienced greater reductions in calcium than those treated with placebo (i.e. PB/VD alone) (who experienced a slight increase) or cinacalcet. HRQoL in the cinacalcet-controlled trial did not appear to change substantially over time in either the etelcalcetide or cinacalcet arms, though scores were slightly lower in the etelcalcetide arm by week 26 (lower scores indicating reduced HRQoL). Neither of the calcium or HRQoL outcomes were analysed in the ITT population. The most common AE experienced by participants treated with etelcalcetide in all three trials was an asymptomatic decrease in blood calcium. This AE was experienced by a higher proportion of patients treated with etelcalcetide (plus PB/VD) (68.9%) compared with cinacalcet (plus PB/VD) (59.8%) in the cinacalcet-controlled trial, and by a higher proportion of patients treated etelcalcetide than those treated with placebo (i.e. PB/VD alone) in the placebo-controlled trials (etelcalcetide 63.8%, placebo 10.1%). Rates of symptomatic hypocalcaemia events and cardiac failure were also higher with etelcalcetide than placebo or cinacalcet.

Summary of submitted cost effectiveness evidence

The company's submission to NICE included a systematic review of published economic evaluations (cost-effectiveness, cost-utility and cost-benefit studies), and a de novo economic model.

Inclusion criteria in the company's systematic review were in line with the NICE scope: treatments for SHPT in adult patients receiving haemodialysis for CKD. The search identified 16 economic evaluations, none of which evaluated etelcalcetide. Of the 16 studies identified, three studies in particular were used to inform the economic model:

- A PenTAG Health Technology Assessment (HTA) by Garside and colleagues provided assumptions and data sources.
- An economic evaluation by Belozeroff and colleagues, based on the EVOLVE RCT of cinacalcet (and PB/VD) compared with placebo (and PB/VD), informed the model structure

and input parameters. The EVOLVE trial was a large (n=3883 patients) international trial, with long follow-up (up to five years).

- An economic evaluation by Eandi and colleagues, provided a biomarker based risk-prediction equation that was used to predict long-term outcomes of calcimimetic therapy in a scenario analysis.

The company submitted a de novo Markov-type state transition model to estimate the cost effectiveness of etelcalcetide compared with cinacalcet, or compared with standard therapy alone (PB/VD) for treatment of SHPT in adult patients receiving haemodialysis for CKD. The model consists of health states representing the three principal adverse events related to SHPT: all-cause mortality; non-fatal clinical fractures (Fx); and non-fatal cardiovascular (CV) events (including myocardial infarction, hospitalisation for unstable angina, heart failure and peripheral arterial disease). Patients begin the model in the event-free state, and over time may experience one or more non-fatal CV events and/or bone fractures. After one non-fatal event, patients are at higher risk of recurrence of the same type of event. Parathyroidectomy (PTx) was included in the model as an incident event, rather than as a health state or treatment. This means that the model cannot reflect long-term costs or health effects of parathryroidectomy.

Treatment effectiveness is modelled using hazard ratios for each of the principal events and PTx. Background event rates were calculated from the placebo arm of the EVOLVE trial. Hazard ratios for cinacalcet compared to PB/VD were derived from a covariate-adjusted lag-censored analysis of the EVOLVE trial. The lag-censored approach attempts to account for high rates of treatment discontinuation and switching in the EVOLVE trial. The lag time for censoring, of six months after discontinuation, was pre-specified and informed by expert opinion. Hazard ratios for etelcalcetide were extrapolated from those estimated for cinacalcet from EVOLVE, by assuming a linear relationship between the proportion of patients achieving a >30% reduction in PTH and log-hazard ratios. The company estimated proportions of patients achieving a > 30% reduction in PTH from baseline for all interventions from a ‘naïve’ (unadjusted) pooling of the pivotal phase III etelcalcetide trials (20120229, 20120230, and 20120360). Discontinuation of cinacalcet treatment was modelled using a Weibull curve fitted to EVOLVE trial data, etelcalcetide discontinuation was assumed to be equivalent to cinacalcet discontinuation. Adverse events were not modelled, as the company argued that calcimimetics are well-tolerated with an event profile consistent with pre-existing comorbid conditions associated with SHPT.

Health related quality of life (HRQoL) was informed by a systematic review that identified five HRQoL studies, one of which was an analysis of EQ-5D data from the EVOLVE trial by Briggs and colleagues. This was used as the source of utilities in the model, including a utility value for patients on dialysis but 'event free', and disutilities for the first three months after an event and subsequently.

The company also conducted a systematic review of resource use and costs, but only used one of the seven cost-of-illness studies identified in the model: a study by Pockett and colleagues (2014) that estimated the cost of parathyroidectomy. Other resource use was obtained from the pivotal etelcalcetide trials (20120229, 20120230, and 20120360). Costs included drug costs, monitoring costs, and acute event costs. Dialysis costs were not included in the base case, but were evaluated in a scenario analysis. Unit costs were derived from NHS sources (NHS Drug Tariff, British National Formulary, NHS Reference Costs).

Base case cost-effectiveness results are presented in Table 1. The company only presented pairwise comparisons: etelcalcetide vs. PB/VD in the broad licensed population, and etelcalcetide compared to cinacalcet in refractory SHPT. We note that in both analyses, the etelcalcetide outcomes were identical, based on the broad SHPT population in the EVOLVE trial. Therefore this analysis does not reflect risks for the refractory group, for whom cinacalcet is an appropriate comparator. We discuss this further below.

Table 1 Company base case cost effectiveness results

	Total Costs	**Incremental Costs**	**Total QALYs**	**Incremental QALYs**	**ICER (£/QALY)**
Base case cost effectiveness results: broad licensed population (etelcalcetide vs. PB/VD)					
PB/VD	[redacted]	-	3.788	-	-
Etelcalcetide*	[redacted]	[redacted]	4.109	0.321	[redacted]
Base case cost effectiveness results: refractory SHPT (etelcalcetide vs. cinacalcet)					
Cinacalcet*	[redacted]	-	4.040	-	-
Etelcalcetide*	[redacted]	[redacted]	4.109	0.069	[redacted]

QALYs, quality-adjusted life-years; ICER, incremental cost-effectiveness ratio; PB, phosphate binders; VD, vitamin D; *In addition to PB/VD

The company presented deterministic sensitivity analyses and scenario analyses, as well as a probabilistic sensitivity analysis. The ICER for etelcalcetide in all deterministic analyses against any

comparator was consistently greater than £30,000/QALY. Probabilistic analyses showed that the probability of etelcalcetide being cost effective was very low at a threshold of £30,000/QALY.

Commentary on the robustness of submitted evidence

Strengths

- The company literature searches included a wide range of electronic databases and other sources. The company appears to have included all relevant RCTs in clinical effectiveness review; the ERG evaluated the search strategies as fit-for-purpose and the ERG's update searches did not identify any additional relevant RCTs. The clinical effectiveness review followed standard systematic review procedures and, on the whole, data were appropriately synthesised. We consider there is a low chance of systematic error in the review, based on the methods reported in the CS.
- The review identified relevant international phase III RCTs that included a large number of participants and which were of an overall good quality. Clinical expert advice to the ERG indicates that the included patients were generally representative of those seen in practice in the UK.
- The model structure reflected the nature of SHPT and its impacts on patient outcomes. The model was also well implemented, and we did not identify any important coding errors. The choice of sources for the main input parameters - effectiveness, utility and resource use/costs – were informed by systematic literature reviews. The model and results were clearly described in the CS and response to clarification questions, and justification was given for most important modelling decisions. The company also used a range of approaches to explore the impact of major structural uncertainties over the extrapolation of six-month intermediate outcomes to estimate long-term risks and health outcomes. A number of key modelling assumptions and data sources were conservative, and did not unreasonably exaggerate the effects or cost-effectiveness of etelcalcetide.

Weaknesses and areas of uncertainty

- The single identified cinacalcet-controlled trial included a broad population of patients with SHPT, rather than specifically those with refractory SHPT in whom cinacalcet is the comparator of relevance to the scope. It is uncertain if, as the company argues, the subgroups of patient who had previously been treated with cinacalcet is representative of people refractory to treatment with PB/VD alone. The strength of this argument depends on

how cinacalcet is used in the countries in which the trials took place – that is, whether it tends to be used as an initial treatment in a broad population of patients or as a second-line treatment for patients specifically with refractory SHPT. In this respect, the CS does not fully meet the company's decision problem or the final NICE scope. We attempt to adjust the etelcalcetide trial results to reflect the different risks of patients who are 'refractory' to standard treatment in the economic model (see additional ERG analysis below).

- The trials included in the review did not measure the most clinically relevant outcomes – that is, survival, incidence of cardiovascular events and bone fractures, and achievement of the PTH target currently used in UK clinical practice for patients receiving haemodialysis (2-9 times the upper limit of the normal reference range; around 130 – 600 pg/mL; 13.8 – 63.6 pmol/L). This means it is uncertain how etelcalcetide impacts on longer-term outcomes compared with cinacalcet and standard of care without calcimimetics. The company presented different methods to estimate this relationship for the economic model. However, direct evidence is lacking.
- It is also uncertain what proportion of patients would meet the PTH target used in practice when treated with etelcalcetide compared with treatment with cinacalcet or with standard of care without calcimimetics. Relatedly, drug doses in all three trials were titrated to a PTH target of ≤300pg/mL (31.8 pmol/L), but we suggest, based on clinical advice we received, that this is not necessarily reflective of clinical practice. The clinical expert consulted by the ERG noted 300pg/mL is in the middle of the 2-9 times the upper limit of normal reference range, but that in practice, clinicians would not specifically target this. That is, they would aim for a PTH range of 150 – 300 pg/ml (15.9 – 31.8 pmol/litre), but they would accept a PTH in the range of 2-9 times the upper limit of the normal reference range in selected patients (around 130 – 600 pg/mL; 13.8 – 63.6 pmol/L) depending on levels of other parameters such as calcium and phosphate. Therefore, the treatment protocols (i.e. PTH target and drug doses administered to reach this target) used in the trials may not be fully reflective of current practice in the UK. Outcomes may be different to those found in the trials when using the less stringent treatment target (i.e. in patients who are left with a higher PTH). This also means that longer-term outcomes in the economic model were not extrapolated from the most clinically relevant PTH endpoint (i.e. the less stringent target used for some patients in practice), which could impact on the rates of longer-term outcomes estimated and, hence, cost-effectiveness.
- The CS states the safety profile of etelcalcetide is similar to cinacalcet, but we consider this is not entirely justified: there were higher rates of asymptomatic decreased blood calcium

symptomatic hypocalcaemia and cardiac failure with etelcalcetide than cinacalcet. Clinical expert advice to the ERG indicated that symptomatic hypocalcaemia or very low calcium would likely result in increased health care resource utilisation to manage these AEs. Information about the effect of etelcalcetide treatment and related adverse effects on patient utility is also lacking. These factors are not included in the economic model.

- The extrapolation from the short-term biochemical outcomes measured in the etelcalcetide trials to patient-relevant outcomes introduces considerable uncertainty over the economic results. The model relies particularly on the EVOLVE trial for this extrapolation, and for other parameters, including estimates of long-term risks, discontinuation rates, utilities and resource use. As stated, this was a large long-term trial, however, results are confounded by some imbalance in patient characteristics at baseline, and by high rates of discontinuation: 71% of patients randomised to placebo and 67% patients randomised to cinacalcet. Treatment switching was also a problem: with many patients in both arms starting commercially-available cinacalcet, or undergoing parathyroidectomy or kidney transplant. The company has presented several analyses that attempt to correct for baseline co-variates and non-adherence, but it is not clear whether these successfully minimise bias.
- The log-linear method used to extrapolate from the etelcalcetide primary outcome (≥30% reduction in PTH) is reasonable, but entails a strong assumption. For this analysis, the company used a 'naïve' method of pooling data from the phase III etelcalcetide trials, which we consider inappropriate. To examine the impact of this, we applied a simple method of indirect treatment comparison (ITC) in the model, which gave quite different results (see below).
- The company presented another method of extrapolation that did not rely on EVOLVE: using a published algorithm to predict the risk of clinical events based on biomarker measurements for patients in the etelcalcetide trials. However, evidence for the validity of this prediction algorithm was not presented. On balance, we consider that the EVOLVE-based methods are preferable.
- The economic model had a number of other drawbacks. It included acute care costs and disutility for patients undergoing parathyroidectomy, but excluded any longer-term savings or health effects that might be associated with this procedure. This tends to favour etelcalcetide, because it was estimated (through the extrapolation method outlined above) to cause a large reduction in the use of this procedure. It is not possible, without major restructuring of the model, to explore the impact of this omission. Costs for CV events and fractures were limited to initial acute treatment. Re-admissions and ongoing outpatient,

community and primary care costs were not included. Thus, cost savings associated with better management of SHPT are likely underestimated. It is also uncertain whether some model parameters (mortality, CV, fracture and PTx rates, drug doses) are representative for a UK population, as they come from US or international (EVOLVE) data.

Summary of additional work undertaken by the ERG

We conducted a number of scenario analyses to further test the robustness of the company's base case economic analyses:

- We used a simple chained method of indirect comparison to estimate the proportion of patients achieving >30% reduction in PTH for use in the extrapolation of EVOLVE risks. Our preferred approach only used the phase III etelcalcetide trials. Results differed from the company's approach: 8.9% with PB/VD alone, 66.1% with cinacalcet and PB/VD, and 75.6% with etelcalcetide and PB/VD (compared with 8.9%, 57.1% and 72.1% respectively in the company's analysis). This led to a small increase in the ICER for etelcalcetide vs. PB/VD [redacted]), but a much larger increase in the ICER for etelcalcetide vs. cinacalcet [redacted]). For comparison, we also conducted analyses using results from an ERG meta-analysis of cinacalcet (plus PB/VD) versus placebo (plus PB/VD) RCTs. This highlighted the heterogeneity of these data, and the sensitivity of the etelcalcetide versus cinacalcet comparison to the method of pooling used. This point was further emphasised in a scenario analysis provided by the company in response to a clarification question. This used the secondary outcome of the proportion of patients reaching a PTH of ≤ 300 pg/mL, rather than the PTH reduction target, and led to more favourable ICERs, although they did not fall below £30,000 per QALY gained.
- ICERs are also sensitive to the method used to adjust EVOLVE results for non-adherence. The company presented four methods in the CS. In response to a clarification question, they provided estimates of effects using two complex methods of adjustment: the Rank Preserving Structural Failure Time Model (RPSFTM) and Iterative Parameter Estimation (IPE) approaches, which we consider more appropriate than the lag-censored approach used in the base case. These methods yielded lower ICERs: for example the IPE method gave an ICER of [redacted] for etelcalcetide vs. PB/VD alone and [redacted] for etelcalcetide vs. cinacalcet.
- The company's base case assumed equal rates of discontinuation from etelcalcetide and cinacalcet. In the active-controlled trial (20120360), the rate of discontinuation in the etelcalcetide arm was higher than that in the cinacalcet arm, although this difference was not

statistically significant (HR [redacted]. Introducing this HR into the model, we found that the ICER for etelcalcetide vs. cinacalcet increased ([redacted]).

- The analysis of EQ-5D data from EVOLVE by Briggs and colleagues, estimated a significant independent utility gain of 0.02 (95% CI 0.01 to 0.03) for patients on cinacalcet, after adjusting for clinical events. This suggests that there may be a symptomatic improvement with cinacalcet. In their base case, the company excluded this effect, but they conducted scenario analysis in which they assumed that it applied equally to both calcimimetics, and led to a very small decrease in the ICERs for etelcalcetide. We also tested the impact of a differential utility effect for the two drugs. For the etelcalcetide versus cinacalcet comparison, the ICER rose to [redacted] when we applied the utility gain to cinacalcet only.
- The company reported a post-hoc subgroup analysis for patients who had discontinued cinacalcet due to lack of efficacy, adverse events or intolerability. The effectiveness of etelcalcetide was not significantly lower in this population – although we note that the power for this analysis would have been low. Nevertheless, it does suggest that a sequenced approach to use of calcimimetic drugs might be appropriate. We therefore adapted the model to conduct an incremental analysis including two sequenced calcimimetic strategies. To avoid out of scope comparisons, we did not consider treatment starting with cinacalcet for patients not refractory to PB/VD alone, or PB/VD alone for refractory patients. In both groups, treatment with etelcalcetide (with PB/VD) followed by PB/VD alone was dominated by a sequenced strategy.
- A drawback with this analysis, as with the company's base case, is that it assumes equivalent outcomes on calcimimetic treatment for patients who are 'refractory' and 'non-refractory' to treatment with PB/VD alone. We consider this unlikely, and so conducted subgroup analysis in which we varied the proportion of patients assumed to achieve >30% reduction in PTH on PB/VD alone – indicating how 'refractory' they might be to this treatment. The ICER for etelcalcetide vs. PB/VD alone was higher for patients with a higher probability of responding to PB/VD alone. The ICER for etelcalcetide compared with cinacalcet rose more steeply for this easier to treat group.

The ERG preferred base case differs from the company base case in two key respects: the method of pooling results of the etelcalcetide trials ('simple ITC' rather than naïve pooling); and the method for estimating hazard ratios for clinical events from EVOLVE (IPE rather than the lag-censored approach). Assuming a population in which 8.9% of patients would achieve >30% reduction in PTH on standard treatment (the mean for placebo arms of 20120229 and 20120230), the ICERs for etelcalcetide are: [redacted] compared with PB/VD alone or [redacted] compared with cinacalcet. However, if we assume that patients who meet NICE criteria for treatment with cinacalcet (i.e. with refractory SHPT) are less likely to respond to PB/VD alone (e.g. if 4.9% achieve >30% reduction in PTH, as in the placebo arm of company's subgroup analysis for patients who have discontinued cinacalcet), the etelcalcetide versus cinacalcet ICER is lower [redacted]. Conversely, patients being considered for treatment with PB/VD alone (i.e. non-refractory), are more likely to respond (e.g. 17.1% achieve >30% reduction in PTH, as in the placebo arm of the ERG meta-analysis of cinacalcet trials). In this group, the ERG base case ICER for etelcalcetide vs PB/VD is [redacted]

Finally, the table below shows an incremental analysis including appropriate sequenced strategies for refractory and non-refractory patients (4.9% vs 17.1% responding to PB/VD respectively), following ERG base case assumptions. None of the strategies has an ICER below £30,000 per QALY – a finding that was robust to a range of scenario analyses.

Table 2 ERG base case: incremental analysis with sequenced strategies

Treatment strategy	*Total Costs*	*Total QALYs*	*Incremental Costs*	*Incremental QALYs*	**ICER** *£/QALY*
Non-refractory to PB/VD alone (17.1% target PTH)					
PB/VD alone	[redacted]	3.788	-	-	-
Etelcalcetide *	[redacted]	4.097	[redacted]		
Etelcalcetide – cinacalcet *	[redacted]	4.285	[redacted]	0.497	[redacted]
Refractory to PB/VD alone (4.9% target PTH)					
Cinacalcet *	[redacted]	4.070	-	-	-
Etelcalcetide *	[redacted]	4.135	[redacted]		
Cinacalcet – etelcalcetide *	[redacted]	4.301	[redacted]	0.231	[redacted]
Etelcalcetide – cinacalcet *	[redacted]	4.326	[redacted]	0.025	[redacted]

QALYs, quality-adjusted life-years; ICER, incremental cost-effectiveness ratio; PB, phosphate binders; VD, vitamin D;
* In addition to PB/VD, and followed by PB/VD alone on discontinuation of final calcimimetic drug

1 Introduction to ERG Report

This report is a critique of the company's submission (CS) to NICE from Amgen on the clinical effectiveness and cost effectiveness of etelcalcetide for secondary hyperparathyroidism (SHPT) in people with chronic kidney disease (CKD), receiving haemodialysis. It identifies the strengths and weaknesses of the CS. A clinical expert was consulted to advise the ERG and to help inform this review.

Clarification on some aspects of the CS was requested from the company by NICE and the ERG on 18th November 2016. A response from the company via NICE was received by the ERG on 6th December 2016 and this can be seen in the NICE committee papers for this appraisal.

2 BACKGROUND

2.1 Critique of company's description of underlying health problem

The ERG considers the CS provides a generally clear and accurate overview of the nature and clinical consequences of SHPT. As stated in the CS, SHPT is a complication of CKD that develops due to a progressive worsening of kidney function over time. It is characterised by increases in serum PTH, and calcium and phosphate level abnormalities. The CS states on p. 25 and p. 12 that calcium and phosphate levels are elevated in secondary hyperparathyroidism. The ERG notes, however, that while phosphate levels are elevated, calcium levels are initially low in SHPT.[1, 2] As is also stated in the CS, if SHPT is uncontrolled, there is an increased risk patients will develop vascular calcification and bone disease, which in turn may contribute to the risk of cardiovascular events, fractures and death.[1-3]

The CS uses the pg/mL unit to describe PTH levels, but we note that in the UK, PTH is measured in pmol/L units. Therefore, where we discuss PTH in this report, we lead with the pg/mL units, but supply the equivalent pg/mL units in brackets to aid the reader's interpretation.

2.2 Critique of company's overview of current service provision

The CS provides a generally clear and accurate overview of how SHPT is managed in patients with CKD, receiving haemodialysis, in clinical practice. The CS refers to relevant guidelines, including

NICE clinical guidelines (CGs) 182,[4] 157[5] and technology appraisal (TA) 117[6] about the general management of CKD in adults, the management of hyperphosphatemia and the use of the drug cinacalcet for treating SHPT in patients with end-stage renal disease on maintenance dialysis, respectively. As is noted in the CS, NICE CG 182[4] does not provide direct information about how SHPT should be managed and CG 157[5] relates only to managing hyperphosphatemia. Hyperphosphatemia can increase PTH levels and potentially result in SHPT developing. The CS also refers to the 2009 international Kidney Disease: Improving Global Outcomes (KDIGO) guideline (for the diagnosis, evaluation, prevention and treatment of mineral and bone disorders in CKD),[3] which provides more specific guidance on how SHPT should be managed, and the CS correctly notes that the UK Renal Association has taken up the KDIGO guideline recommendations about treatment targets.[7] The ERG's clinical advisor stated that management of bone and mineral disorders in CKD in practice is based on the KDIGO guideline.

Treatment initiation and PTH target

The company outlines that the 2009 KDIGO guideline suggests a target PTH level of around 2-9 times the upper limit of normal of the reference limit for the laboratory test used. As acknowledged in the CS, if PTH is above or below this range, the KDIGO guideline recommends treatment should be initiated or changed (although treatment decisions are based on trends in biochemical parameters rather than measures taken at a single time point).[3] We note this translates to a PTH range of around 130-600 pg/mL (13.8 – 63.6 pmol/L).[3, 8] Clinical expert advice to the ERG is that this target reference range represents a normal PTH level in CKD patients receiving haemodialysis and that it is employed in practice. In the treatment pathway presented in CS Figure 2 (p. 36), the company, however, uses a PTH level of > 300 pg/ml (31.8 pmol/L) to define the 'uncontrolled' PTH level at which treatment would be initiated. The company also presents prevalence estimates of SHPT among people with CKD receiving dialysis based on a definition of a PTH level of > 300 pg/ml, which the ERG notes is based on the older National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NFK KDOQI) clinical practice guideline.[9] This guideline suggests a PTH target range of 150-300 pg/mL (15.9-31.8 pmol/L) when testing and treating patients[8] (we also note this treatment target is specified in NICE TA 117 for when using cinacalcet[6]). There is therefore a lack of clarity in the CS about which criteria are used in practice to initiate treatment. The clinical expert consulted by the ERG stated that a PTH level of 613 pg/mL (65 pmol/L) is used as a criterion to initiate treatment locally in her practice, which the ERG notes is in line with the KDIGO guideline, but she also acknowledged that some other centres use 800 pg/mL (85 pmol/L) as a starting criterion

(based on NICE TA 117 guidance for the use of cinacalcet). Therefore, the cut-off used in practice is higher than proposed in the CS.

In terms of treating SHPT, the clinical expert consulted by the ERG stated clinicians aim for a PTH range of 150 – 300 pg/ml (15.9 – 31.8 pmol/L), but they accept a PTH in the range of 2-9 times the upper limit of the normal reference range in selected patients, depending on levels of other parameters such as calcium and phosphate.

Current clinical practice

The aim of treatment of SHPT among patients with CKD, receiving haemodialysis, is to manage phosphate, calcium and PTH levels so that they are within the normal ranges for dialysis patients. PB/VD are used to try to normalise calcium and phosphate levels. Dietary modification can include reduction in phosphate intake. The clinical expert consulted by the ERG stated that in her clinic, patients are always referred to a dietician and dietary modification is always combined with treatment with PB/VD.

The CS accurately outlines that the calcimimetic drug cinacalcet is only recommended by NICE TA 117[6] for a specific group of patients with end-stage renal disease who have refractory SHPT (that is, who are refractory to established clinical management): those who have a PTH level > 800 pg/ml (84.8 pmol/L), a normal or high adjusted serum calcium level and in whom surgical parathyroidectomy (a treatment option that involves removing the parathyroid glands) is contraindicated. The SmPC indication for cinacalcet is, more widely, people with end-stage renal disease with SHPT who are on maintenance dialysis treatment. The CS makes the case that cinacalcet is not generally used within the restrictions outlined in TA 117[6] in practice; it tends to be used to treat any patients who are refractory to treatment with PB/VD. Clinical expert advice to the ERG supports this. The ERG's expert stated that if PTH levels continued to rise despite treatment with PB/VD and dietary modification, cinacalcet is used. This use of cinacalcet in practice is also reflected in NICE's final scope for this appraisal, which states that cinacalcet is a comparator of interest when it is used to treat people with refractory SHPT. The expert who advised the ERG stated cinacalcet is used in practice in combination with PB/VD as appropriate.

Clinical expert advice to the ERG is that cinacalcet tends to be used in practice in preference to parathyroidectomy. Historically, surgery was an option for progressive SHPT (i.e. when PTH cannot be controlled), but now patients would tend to be prescribed cinacalcet. This advice to the ERG

supports the company's positioning of surgery as a treatment option after cinacalcet in the current clinical pathway (CS Figure 2, p. 36).

The CS argues that there is poor adherence to treatment with cinacalcet among patients in practice. The evidence cited in the CS to support the claim about adherence problems to cinacalcet was from [redacted] and real-world drug discontinuation rates in Italy and France (defined as a prescription gap of 30 days). The ERG questions if the real-world evidence cited is representative of adherence rates in England and suggests it is uncertain if there is generally poor adherence to cinacalcet in England. The clinical expert consulted by the ERG stated that in her experience, patients did not tend to have a problem adhering to cinacalcet, as it is a tablet that is taken once a day and does not have any specific unpleasant side effects that may affect adherence. The expert acknowledged that the pill burden is generally high in dialysis patients, but that patients have more difficulty adhering to PB than cinacalcet.

Proposed place of etelcalcetide in the clinical pathway

The CS outlines that etelcalcetide will be used in a broad population of patients with CKD, receiving haemodialysis, who have SHPT. The company proposes etelcalcetide combined with PB/VD as an alternative initial treatment to PB/VD alone, and as an alternative to cinacalcet (combined with PB/VD) in patients who are refractory to initial treatment. The clinical expert consulted by the ERG perceived etelcalcetide as a potential alternative to cinacalcet (i.e. to be used to treat refractory patients), but as her patients tend to do well on cinacalcet, she would be unlikely to use etelcalcetide instead. Instead, the expert saw etelcalcetide as an option that could be used if cinacalcet does not work, if patients do not tolerate it or if patients have difficulty accessing cinacalcet (the expert explained that some general practitioners are reluctant to prescribe it, making access difficult). The expert considered it unlikely that etelcalcetide combined with PB/VD will be used as an initial treatment in practice instead of PB/VD alone. We therefore suggest that the company's positioning of etelcalcetide in the current clinical pathway is reasonable, but that it may not necessarily be used as an alternative to PB/VD alone in practice. There may be an additional position for etelcalcetide, which is in the treatment of patients refractory to PB/VD who have been treated with cinacalcet but who did not respond to it or could not tolerate it. Based on the expert's advice, we also suggest that etelcalcetide may be more likely to be used in practice with patients who are refractory to PB/VD, and who have had difficulty accessing cinacalcet or who have had

adherence difficulties. In line with the information in the CS, clinical expert advice to the ERG is that etelcalcetide is not expected to displace parathyroidectomy.

Potential impact of etelcalcetide on current service provision

The CS argues that etelcalcetide will have minimal impact on current service provision and the ERG agrees this is reasonable. The CS states etelcalcetide is administered intravenously during dialysis and can be administered either during or after rinse back (CS Table 2, p. 15). It is unclear from the CS if administration of etelcalcetide would incur additional costs to the NHS in terms of more staff time and increased duration of the dialysis session. In response to a clarification question about this (clarification response B8), the company stated that administration of etelcalcetide would not impact on a typical dialysis session and would be unlikely to be associated with additional costs. Expert advice to the ERG is that administration would not add to the length of the dialysis session.

As noted in the CS, the monitoring of biochemical parameters required when using etelcalcetide is the same as for when using cinacalcet. We note that the frequency of monitoring needed is similar to general patient monitoring already employed in practice (our conclusion here is informed by clinical expert advice to the ERG about current monitoring frequency).

Summary

In summary, the CS presents a generally accurate overview of current service provision, but does not clearly outline the PTH level used as a treatment initiation criterion. The ERG suggests that the CS may have overstated the adherence problem to cinacalcet and that it is uncertain to what extent patients adhere to it in practice. The CS presents a reasonable overview of the current treatment pathway, but expert advice to the ERG indicates that cinacalcet may sometimes be used as a first-line treatment in practice (in patients with high PTH levels) and this use of cinacalcet is not mentioned in the CS (although we acknowledge that this is outside the final scope). The company's proposed positioning of etelcalcetide in the treatment pathway is reasonable (i.e. as an initial treatment and as a treatment for those refractory to PB/VD alone), but we suggest that in practice it may be more likely to be used with patients refractory to PB/VD alone or with those who have not responded to or tolerated cinacalcet than as a first-line treatment.

2.3 Critique of company's definition of decision problem

Population

The population specified in the company's decision problem is people with CKD with SHPT, receiving haemodialysis (clinical expert advice to the ERG indicates that this is a population of patients with end-stage kidney disease). The patient population matches that specified in the final scope issued by NICE and that specified in the SmPC indication for etelcalcetide. The population is appropriate for the NHS. The ERG notes, however, as stated above, that etelcalcetide may be more likely to be used in practice to treat patients refractory to either PB/VD alone or cinacalcet combined with PB/VD rather than as a first-line treatment in the broader population, at least initially.

Intervention

In accordance with the final scope, the intervention described in the company's decision problem is etelcalcetide (brand name: Parsabiv). Etelcalcetide is a calcimimetic and is thought to work by reducing the production and secretion of the parathyroid hormone. In September 2016, the Committee for Medicinal Products for Human Use (CHMP) recommended the granting of a marketing authorisation for etelcalcetide. The company supplied the draft summary of product characteristics (SmPC) with its submission to NICE (this was subsequently published in November 2016). As outlined in the CS, the SmPC states etelcalcetide is administered intravenously during dialysis, either during or after rinse back. The starting dose is 2.5 mg three times per week, and the dose may be titrated every four weeks, as needed, to an individualised dose of between 2.5 mg and 15 mg three times per week to achieve a desired target PTH level (the SmPC does not specify an exact target). Unlike the final scope, the decision problem further states that etelcalcetide is expected to be used in combination with PB/VD in practice. This is in line with the SmPC, which states that etelcalcetide may be used alongside PB and/or VD sterols, as needed. Clinical expert advice to the ERG is that etelcalcetide would be combined with PB/VD in practice, supporting the company's statement in the decision problem. The CS states it is anticipated that treatment with etelcalcetide will be ongoing. The intervention described in the decision problem (i.e. etelcalcetide combined with PB/VD) is appropriate for the National Health Service (NHS) and reflects its licensed indication.

Comparators

The two comparators of interest listed in the company's decision problem are both those specified in the final scope:

- Established clinical practice without calcimimetic therapy (dietary modification, PB and VD analogues)
- Cinacalcet, specifically for people with refractory SHPT

These comparators are appropriate for the NHS and reflect how cinacalcet is used in clinical practice. The ERG considers, though, that none of the clinical effectiveness evidence presented in the CS directly provides information about the relative efficacy of etelcalcetide versus cinacalcet among people with refractory SHPT (see sections 3.1.2 3.1.3 and 3.4 for further discussion about this).

Outcomes

The company has listed all the outcomes specified in the final scope in their decision problem:

- Survival
- Incidence of fractures
- Incidence of cardiovascular events
- Need for parathyroidectomy
- Symptoms such as bone pain and itching or mobility
- Hospitalisation
- Serum levels of parathyroid hormone
- Serum levels of calcium and phosphate
- Health-related quality of life (HRQoL)
- Adverse effects of treatment

Clinical expert advice to the ERG is that biochemical parameters are clinically important, but what is most important is bringing these within particular ranges. In practice, treatment effectiveness and success is defined by normalisation of phosphate and calcium levels, and PTH falling within the normal target range for patients receiving dialysis (2-9 times the upper limit of the normal reference range). The expert stated, however, that what matters most to patients is that treatment is as effective as parathyroidectomy. The expert advised mortality and prevention of cardiovascular events (which can lead to mortality) are also the most clinically relevant outcomes to patients.

However, as discussed in section 3.1.5 of this report, the trials included in the submission only measured biochemical parameters (PTH, calcium and phosphate), HRQoL (in one trial – trial 20120360) and adverse effects of treatment. Survival, incidence of fractures, incidence of cardiovascular events and need for parathyroidectomy outcomes were estimated based on extrapolations of a PTH outcome measured in the trials to the incidence (hazard ratios) of these events, which in turn were used as inputs in the economic model. The trials also did not employ the

target PTH range used in practice in England as an outcome. This is discussed further in section 3.1.5.

Overall, the ERG considers the outcomes listed in the company's decision problem are appropriate and clinically meaningful, but (as is discussed further below), in practice in the CS, the trials presented did not measure the most clinically relevant outcomes – that is, survival, incidence of cardiovascular events and achievement of the PTH target currently used in UK clinical practice.

Economic analysis

The economic analysis specified in the decision problem matches the final scope and is appropriate for the NHS. The company has conducted a cost-utility analysis with a lifetime horizon. This is an appropriate time horizon when considering differences in costs and outcomes between treatments for patients with CKD with SHPT, receiving haemodialysis. Costs are considered from the NHS and Personal Social Services (PSS) perspective.

The company has used the "anticipated list price" (CS p. 18) cost of etelcalcetide in their model. It is unclear from the CS if and when the list price may change. On CS p. 18 (and at other points throughout the CS), the company states a patient access scheme (PAS) application for a confidential, simple discount on the list price of etelcalcetide has been submitted to the Department of Health (DH). The company states an addendum to the CS with the discounted price applied to the cost-effectiveness analyses will be forthcoming, but did not indicate a timescale for the expected decision by the DH or when the addendum will be submitted to NICE. We note the comparator drug cinacalcet does not have a PAS.

Other relevant factors

Subgroups

The final scope did not specify any patient subgroups of interest in this appraisal and the company has not specified any in their decision problem in the CS. On CS p. 49, the company lists a number of pre-planned subgroup analyses that were conducted in the trials, and reports the results of these in the CS. Of these subgroups, the ERG considers the following important: participants who had previously used cinacalcet (argued by the company to represent patients who are refractory to PB/VD alone) and participants of a black ethnicity. We consider the latter important as clinical expert advice to the ERG is that patients of an African Caribbean ethnicity with SHPT tend to have a poorer prognosis than other patients. The ERG also considers a post-hoc analysis of participants who were

treated with etelcalcetide following [redacted] that was presented in the CS a useful subgroup analysis. This is because, as stated earlier, the clinical expert consulted by the ERG suggested etelcalcetide may be used as a treatment option for patients who have not responded to or tolerated cinacalcet (although we acknowledge that the efficacy of etelcalcetide in this patient population is outside the final scope). The company's approach to these analyses and the ERG's evaluation of them is discussed in more detail in section 3.1.6.

Equality issues

The final scope does not identify any equity or equality issues related to the implementation of etelcalcetide in the NHS and the company has not specified any in its decision problem. The ERG has also not identified any equity or equality issues. The ERG's clinical advisor, though, noted that patients can have difficulties obtaining cinacalcet, as GPs can be reluctant to prescribe it due to its costs and concerns about monitoring. In many regions, there are shared care arrangements in place, whereby patients initially receive cinacalcet in secondary care and then patients are transferred to GPs when stable. The expert suggested that where cinacalcet is difficult to obtain in primary care a parenteral agent may be helpful.

3 CLINICAL EFFECTIVENESS

3.1 Critique of company's approach to systematic review

3.1.1 Description of company's search strategy

The CS reports two systematic literature searches [redacted]:

- Clinical trial data (search strategies provided in CS Appendix 3)
- Cost effectiveness, health related quality of life and cost and resource studies (search strategies provided in CS Appendix 5)

The ERG considers the searches to be fit-for-purpose. They are well designed and documented with the return of hits per line reported thus enabling transparency.

Core research databases were searched for both the clinical effectiveness and cost-effectiveness reviews. [redacted]. The search was also designed to find studies of a variety of trial designs rather than just RCTs. The original search filters that were consulted are referenced and have been adapted by the company for their purpose. [redacted]. The searches were constructed with a balance of descriptive index terms and free text terms with sets correctly combined, including the use of search filters.

One single search was carried out to identify cost effectiveness, HRQoL and cost and resource data rather than separate searches being conducted, however they contained appropriate filters for each facet.

[redacted] The results were checked by one researcher.

These searches identified a phase II study of etelcalcetide among 37 adults with SHPT on haemodialysis,[10] which was not identified by the company's clinical trial data searches (it was not listed among the included studies nor the excluded studies in the CS Appendix) despite the study being published online in December 2015. However, the study was included as a non-randomised study, in the CS (see study 20120331 in CS Table 20). This study is discussed further in section 3.1.3 of this report.

The ERG searched the following clinical trial databases on the 15th November 2016 for ongoing studies: UK Clinical Trials Gateway (UKCTG), clinicaltrials.gov, World Health Organisation (WHO) International Clinical Trials Registry Platform (ICTRP), ISRCTN Registry, EUCTR and PROSPERO. The results were screened by a researcher and no further relevant studies were identified.

In summary, it is considered that the searches conducted by the company to support the systematic reviews in the submission are generally comprehensive and are reported transparently.

3.1.2 Statement of the inclusion/exclusion criteria used in the study selection.

The company provides a description of the inclusion criteria for the systematic literature review (SLR) (CS Table 9, p. 41). [redacted]

The inclusion criteria in the CS are marked as academic-in-confidence (AIC). The ERG notes that this type of information is generally not regarded as confidential and is commonly available from published systematic review protocols.

The intervention specified in the inclusion criteria is etelcalcetide [redacted] The comparator criterion for cinacalcet in the submission is not limited to patients with refractory SHPT (as specified in the decision problem and NICE's final scope). The ERG does not consider this unreasonable but, as will be discussed in section 3.1.3, the only relevant trial identified in the SLR of etelcalcetide versus cinacalcet was conducted in a broad patient population rather than in patients with refractory SHPT. This does mean that the evidence included in the CS for etelcalcetide versus cinacalcet is not specifically relevant to the population of interest in the scope.

[redacted] (CS Table 9, p.41).

To be included, trials had to assess at least one of the following outcomes: [redacted]

The CS provides a flow diagram illustrating the number of records identified and included/excluded records at each stage of the SLR (CS Figure 4 p. 42). Reasons for the exclusion of studies at the full paper stage are provided and references listed in Appendix 3 (CS Appendix Table 2-8, p. 13 - 49). Twenty references are listed as excluded due to 'no data' in the flowchart and closer inspection of the references indicates that these all refer to conference abstracts or abstracts of ongoing trials (Appendix 3, Table 8 p. 48 - 49). The CS also provides a diagram detailing the etelcalcetide studies in the clinical development programme, which supported the marketing authorisation (CS figure 3, p. 38). These include studies conducted in Japan by an Amgen business partner and studies conducted by KAI Pharmaceuticals before its acquisition by Amgen.

The ERG concludes that the CS systematic review inclusion criteria broadly reflect the decision problem, the NICE final scope and the proposed population and licensed indication of etelcalcetide.

3.1.3 Identified studies

The SLR includes three phase III RCTs (published just after this ERG report was completed) relevant to the decision problem:

- Two studies compared etelcalcetide (plus PB/VD) with placebo (plus PB/VD) and are near identical in design (20120229 and 20120230).
- One study compared etelcalcetide (plus PB/VD) with cinacalcet (plus PB/VD)(20120360 – we refer to this as the cinacalcet-controlled trial in this report).

These trials were included as registration studies in the marketing authorisation application to the European Medicines Agency.[11] Clinical evidence is presented from the clinical study reports (CSRs),[12,13,14] summary regulatory documentation and conference presentations.

A small, four-week, phase II, placebo-controlled, ascending-dose trial (study 20120330) is described as less relevant to the decision problem compared with the three included phase III trials and not further discussed (CS p. 43). It is presumed by the ERG that the trial was excluded based on the inclusion criteria relating to treatment duration (minimum of 12 weeks), which is appropriate as calcimimetic treatment would generally be given long-term.

The CS states that the clinical development programme included five non-randomised controlled studies (non-RCTs), of which three were relevant to this submission (CS section 4.11). Given that the inclusion criteria for the company's SLR was restricted only to RCTs the process for identifying and including non-RCTs was not clear in the CS. A clarification request about the processes used to identify non-RCTs was submitted to the company. In response to this clarification request (clarification response A1), the company reiterated that non-RCTs were identified from company records as stated in section 4.1.1 of the submission and that the five non-RCTs referred to in the submission reflect the available non-randomised clinical data in the etelcalcetide clinical development programme (CS Figure 3). Further details about the studies are considered under 'Non-randomised trials' below and also in section 3.3 of this report.

The three included RCTs are phase III, multinational, double-blind trials. The CS includes CONSORT flowcharts for all three trials (CS Figures 6-8, p. 56 - 57), detailing the number of patients that discontinued/dropped out, with reasons.

The CS provides summary tables of the RCTs' characteristics. The first table details the trials' designs and methodologies (CS Table 11, p. 47 - 49). While the design of the three trials is broadly similar, the cinacalcet-controlled trial (20120360) differs to the placebo-controlled trials, as it tests for non-inferiority before testing for superiority (Table 3).

The main differences in eligibility criteria between the three trials are the required screening pre-dialysis PTH levels (cinacalcet-controlled trial PTH > 500 pg/mL (53.0 pmol/l); placebo-controlled trials PTH > 400 pg/mL (42.4 pmol)) and levels of stable dialysate calcium concentration (cinacalcet-controlled trial ≥ 2.5 mEq; placebo-controlled trials ≥ 2.25 mEq/L) (Table 3). Clinical expert advice to the ERG indicates that treatment would not currently be initiated in patients with a PTH < 600 pg/mL (63.6 pmol/l) in practice. We suggest therefore that the PTH level inclusion criterion may have resulted in the inclusion of some patients in the trials with PTH levels that are not reflective of the population treated in England. The only difference between the three trials in exclusion criteria was the time period of prior cinacalcet use (placebo-controlled trials within four weeks of screening; cinacalcet-controlled trial in the three months prior screening).

Only one of the included RCTs involved UK patients although this amounted to less than 20 people (Table 3). Patients in the placebo-controlled RCTs were stratified according to screening PTH (33% PTH < 600 pg/mL (63.6 pmol/l), 46% PTH 600 to 1000 pg/mL (63.6 to 106 pmol/l), 21% PTH > 1000 pg/mL (106 pmol)), region (54% North America, 46% non-North America) and recent cinacalcet use within eight weeks before randomisation (13% yes, 87% no) (CS p. 57). In the cinacalcet-controlled study (20120360), patients were stratified according to screening PTH (50% PTH < 900 pg/mL (95.4 pmol/l), 50% PTH ≥ 900 pg/mL (95.4 pmol/l)) and region (30% North America, 70% non-North America).

The placebo-controlled trials were conducted in the broad population of patients with SHPT in CKD of interest in the final scope and the company's decision problem for the PB/VD comparator. The cinacalcet-controlled trial is also conducted in a broad population, and not those specifically with refractory SHPT (the population specified in the company's decision problem and the final scope).

The treatment protocols (including doses and drug titration) reflect the licensed indication for etelcalcetide and licensed indication for cinacalcet. We note, however, that doses were titrated to target PTH levels to ≤300 pg/mL (31.8 pmol/l) in all three trials; this target does not reflect that used

in clinical practice (i.e. 2-9 times the upper limit of normal for the assay used, around 130 – 600 pg/mL; 13.8 – 63.6 pmol/L).

Table 3 Trial characteristics

Design, patient population and length of follow-up	Intervention	Comparator
Trial name: 20120229 *Design:* Phase III, double-blind, placebo-controlled, multicentre RCT (111 renal centres in six countries; UK: n=10 CSR[12]) N=508 (254 etelcalcetide + 254 placebo) *Inclusion:* Adults ≥ 18 years of age receiving haemodialysis (TIW) for ≥ 3 months; and had stable dialysate calcium concentration (≥ 2.25 mEq/L) and screening pre-dialysis PTH of > 400 pg/mL (42.4 pmol/l) and cCa ≥ 8.3 mg/dL. Participants who were receiving vitamin D sterols, phosphate binders, or calcium supplements must have been on stable doses. *Exclusion:* Received cinacalcet within 4 weeks of screening; had a parathyroidectomy within 3 months of dosing; were anticipated to undergo a parathyroidectomy or kidney transplant during the treatment period; history of certain cardiovascular diseases or cardiac abnormalities; history of seizure or receiving treatment for seizure disorder; pregnancy. *Length of follow-up: 26 week treatment period, followed by 30 day follow-up*	Etelcalcetide (IV administered 3 times weekly at end of each haemodialysis session) for 26 weeks. Starting dose of 5 mg - could increase at 4-week intervals by 2.5 mg or 5 mg on the basis of the pre-dialysis PTH and cCa concentrations obtained in the prior week. Dose range 2.5 mg to 15 mg.	Placebo identical to etelcalcetide (IV administered 3 times weekly at the end of each haemodialysis session) for 26 weeks.
	Background therapy: all received therapy which could have included calcium supplements, vitamin D sterols, nutritional vitamin D, and phosphate binders (as prescribed by the individual investigator).	
Trial name: 20120230 *Design:* as above (97 renal centres in six countries; UK: n=0 CSR [13]) *Patient population:* as above N=515 (255 etelcalcetide + 260 placebo) *Inclusion/exclusion*: as above *Length of follow-up:* as above	As above	As above
Trial name: 20120360 *Design:* Phase III, double-blind, double-dummy, multicentre RCT (164 renal centres in five countries; [redacted][14]) N=683 (340 etelcalcetide +oral placebo + 343 cinacalcet +IV placebo)	Etelcalcetide + oral placebo identical to cinacalcet (IV administered at end of each haemodialysis session) for 26 weeks. Starting dose 5 mg – could increase at 4-week intervals by 2.5	Oral cinacalcet + IV placebo identical to etelcalcetide (IV administered at end of each haemodialysis session) for 26 weeks.

Inclusion: Adults ≥ 18 years of age receiving haemodialysis (TIW) for ≥ 3 months; stable dialysate calcium concentration (≥ 2.5 mEq/L) and screening pre-dialysis PTH of > 500 pg/mL (53 pmol/l) and cCa >8.3mg/dL (within 2 weeks of randomisation and obtained by one central laboratory screening). Participants who were receiving vitamin D sterols, the vitamin D dose must have had no more than a maximum dose change of 50% within the 4 weeks before screening. Participants receiving calcium supplements or phosphate binders must have had no more than a maximum dose change of 50% within 2 weeks before screening. Phosphate binder doses must have been expected to remain stable for the duration of the study and calcium doses stable through randomisation, except as noted in the protocol. *Exclusion:* Participants who have received cinacalcet in the 3 months before screening; had a parathyroidectomy within 3 months of dosing; were anticipated to undergo a parathyroidectomy or kidney transplant during the treatment period; history of certain cardiovascular diseases or cardiac abnormalities; history of seizure or receiving treatment for seizure disorder; pregnancy. *Length of follow-up:* as above	mg or 5 mg on the basis of the pre-dialysis PTH and cCa concentrations obtained in the prior week. Dose range 2.5 mg to 15 mg.	Starting dose 30mg daily titrated every 4 weeks up to 180mg maximum.
	Background therapy: all received therapy with calcium supplements, phosphate binders, and nutritional vitamin D supplements as prescribed by the individual investigator. Prior ongoing treatment with calcitriol or vitamin D analogues had to remain constant for the duration of study; however, treatment with vitamin D was initiated, interrupted, or adjusted for reasons of safety.	

Table based on CS Table 11, p. 47 - 49.
cCa, corrected serum calcium; EAP, Efficacy assessment phase; P, phosphorous; PTH, parathyroid hormone.

Outcomes may be different to those found in the trials, therefore, when using the broader treatment target range.

The CS lists the primary and secondary outcomes measured in the RCTs (identical for the placebo-controlled trials), with additional tertiary outcomes and outcomes described as 'others'. Some of the outcomes in the latter two categories comprise exploratory outcomes (Table 4).

Table 4 Summary of trial outcomes and statistical aspects

Parameters	20120229 and 20120230	20120360
Outcomes	*Primary outcome:* Proportion of participants with > 30% decrease from baseline in mean PTH during the EAP (defined as weeks 20 to 27, inclusive). *Secondary outcomes:* • Proportion of subjects with pre-dialysis PTH ≤ 300 pg/mL (31.8 pmol/l) during the EAP (defined as weeks 20 to 27, inclusive)	*Primary outcome:* Test of non-inferiority for proportion of participants with > 30% reduction from baseline in mean pre-dialysis serum PTH level during the EAP. *Secondary outcomes:* Sequential test of superiority for: 1. Proportion of participants with > 50% reduction from baseline in mean pre-dialysis serum PTH during the EAP

	• % change from baseline in pre-dialysis PTH, cCa, cCa x P and P during the EAP (defined as weeks 20 to 27, inclusive) Tertiary and other outcomes include adverse events, changes in ECG and laboratory parameters, pharmacokinetic and biomarker amongst others	2. Proportion of participants with > 30% reduction from baseline in mean pre-dialysis serum PTH during the EAP 3. Mean number of days of vomiting or nausea per week in the first 8 weeks. • % change from baseline in mean pre-dialysis serum cCa during the EAP • % achieving mean pre-dialysis serum phosphorus ≤ 4.5 mg/dL during the EAP • Mean severity of nausea in the first 8 weeks • Mean number of episodes of vomiting per week in the first 8 weeks Tertiary and other outcomes include % of patients achieving mean predialysis serum PTH ≤ 300 pg/mL (31.8 pmol/l) during the EAP, adverse events, incidence of cCa, symptomatic hypocalcaemia and serum P, and health-related quality of life amongst others.
Statistical approach	*Sample size calculations*: details reported. *Statistical information:* A Cochran-Mantel-Haenszel test stratified by randomization stratification factors was used in the analysis of the primary endpoint. Secondary efficacy endpoints were only tested for significance if the primary endpoint was significant (P<0.05). The CS states a number of analysis sets were used to analyse outcomes – please see section 3.1.6 of this report for more information about these.	*Sample size calculations*: reported for non-inferiority and superiority testing. *Statistical information:* The primary endpoint analysis was based on a Mantel-Haenszel method, with missing data imputed using the non-inferiority null method. The pre-specified imputation method for the secondary endpoints of > 30% and > 50% reduction in PTH was non-responder imputation. The CS states a number of analysis sets were used to analyse outcomes – please see section 3.1.6 of this report for more information about these.
Pre-planned subgroups:	Please see section 3.3.5 of this report for details.	Please see section 3.3.5 of this report for details.

The second summary table provides details of statistical aspects of the etelcalcetide phase III RCTs (CS Table 12, p. 51 - 54), (see section 3.1.6) for our description and critique of the trials' statistical analysis). The company supplied all the references cited in the submission, including the CSRs for the three etelcalcetide trials. All three etelcalcetide RCTs were sponsored by Amgen Limited.

Baseline characteristics

The CS presents baseline characteristics are marked as AIC for the placebo-controlled trials, with some information of the cinacalcet-controlled trial also AIC. The CS states that baseline

characteristics of enrolled patients were well balanced between treatment groups (Table 14, p. 58) and that these characteristics were similar between the placebo-controlled trials (20120229 and 20120230), as they employed the same inclusion/exclusion criteria. The ERG agrees, with minor exceptions. Across the studies, the mean age of patients was largely similar (57 to 59 years) and included more male than female patients (female patients 36% to 45%) (Table 5).

The cinacalcet-controlled trial included a higher proportion of white (79% vs 67%) and European patients than the placebo-controlled trials (68% vs 42%, respectively). An annotation under the baseline characteristic table states that 'Europe' included Turkey, Israel and the Russian Federation. In the active trial, 86% of patients had a dialysis vintage of ≥ 1 year compared with 88% in the placebo-controlled trials.

The major differences in patient baseline characteristics between the cinacalcet-controlled trial and the placebo-controlled trials, mainly due to differences in inclusion criteria, were:

- Baseline dialysate calcium levels: Cinacalcet-controlled trial – around 45% of patients had levels ≥ 3.0 mEq/L; placebo-controlled trials – the majority of patients (around 90%) had ≥ 2.5 mEq/L)
- Median baseline PTH levels: Cinacalcet-controlled trial - around 900 pg/mL (95.4 pmol/l); placebo-controlled trials - around 700 pg/mL (74.2 pmol/l).
- Prior cinacalcet use: Cinacalcet-controlled trial – around 25% of patients; placebo-controlled trials – around 46% of patients

Of note, despite stable dialysate calcium concentration ≥2.25 mEq/L being an inclusion criterion in the placebo-controlled trials, at baseline 5% to 11% of patients in the arms of these trials had levels below this threshold.

Clinical expert advice to the ERG is that the baseline characteristics of participants in the trials are generally representative of patients seen in practice. The expert regarded the participants in the cinacalcet-controlled trial to have a higher median PTH (900 and 930 pg/mL in the etelcalcetide and cinacalcet trial arms respectively) than the median seen in clinical practice, but suggested this median PTH was reflective of the population who would currently be receiving cinacalcet.

Table 5 Baseline characteristics of patients in the etelcalcetide RCTs

	Study 20120229		Study 20120230		Study 20120360	
	Placebo (N = 254)	Etelcalcetide (N = 254)	Placebo (N = 260)	Etelcalcetide (N = 255)	Cinacalcet (N = 343)	Etelcalcetide (N = 340)
Mean (SD) age, years	57.1 (14.5)	58.4 (14.6)	59.0 (13.9)	58.4 (14.6)	55.3 (14.4)	54.0 (13.8)
Women, n (%)	114 (45)	103 (41)	95 (37)	93 (36)	151 (44)	148 (44)
Race, n (%)						
Black	69 (27)	72 (28)	80 (31)	64 (25)	52 (15)	54 (16)
White	175 (69)	173 (68)	169 (65)	163 (64)	277 (81)	261 (77)
Other or missing	10 (4)	9 (4)	11 (4)	28 (11)	14 (4)	25 (7)
Region, n (%)						
North America	129 (51)	132 (52)	150 (58)	146 (57)	105 (31)	103 (30)
Europe[a]	117 (46)	115 (45)	102 (39)	100 (39)	230 (67)	230 (68)
Australia / New Zealand	8 (3)	7 (3)	8 (3)	9 (4)	8 (2)	7 (2)
Primary cause of ESRD, n (%)						
Diabetes mellitus	78 (31)	67 (26)	84 (32)	79 (31)	66 (19)	77 (23)
Hypertension	65 (26)	63 (25)	58 (22)	64 (25)	80 (23)	70 (21)
Glomerulonephritis	30 (12)	39 (15)	45 (17)	30 (12)	61 (18)	78 (23)
PKD	20 (8)	19 (7)	22 (8)	16 (6)	36 (10)	27 (8)
Urologic	8 (3)	9 (4)	6 (2)	10 (4)	16 (5)	19 (6)
Unknown	9 (4)	11 (4)	13 (5)	17 (7)	32 (9)	23 (7)
Other	44 (17)	46 (18)	32 (12)	39 (15)	52 (15)	46 (14)
Dialysis vintage, n (%)						
0 to ≤ 1 year	35 (14)	29 (11)	32 (12)	31 (12)	48 (14)	46 (14)
> 1 to ≤ 5 years	124 (49)	120 (47)	121 (47)	127 (50)	146 (43)	149 (44)
> 5 years	95 (37)	105 (41)	107 (41)	97 (38)	149 (43)	145 (43)
Dialysate calcium[b], n (%)						
< 2.5 mEq/L	18 (7)	13 (5)	28 (11)	24 (9)		
≥ 2.5 mEq/L	236 (93)	239 (94)	231 (89)	229 (90)		
Missing	0 (0)	2 (1)	1 (<1)	2 (1)		
< 3.0 mEq/L					189 (55)	191 (56)
≥ 3.0 mEq/L					154 (45)	149 (44)
Mean (SD) [Median] PTH, pg/mL	820 (386) [706]	849 (520) [706]	852 (552) [726]	845 (464) [740]	1139 (707) [930]	1092 (623) [900]
Mean (SD) cCa, mg/dL	9.61 (0.60)	9.65 (0.66)	9.70 (0.69)	9.63 (0.65)	9.58 (0.67)	9.67 (0.71)
Mean (SD) P, mg/dL	5.78 (1.60)	5.95 (1.59)	5.83 (1.45)	5.76 (1.60)	5.82 (1.58)	5.81 (1.69)
Mean (SD) cCa x P, mg^2/dL^2	55.54 (15.81)	57.37 (15.51)	56.37 (14.50)	55.30 (15.27)	55.65 (15.37)	56.36 (17.15)
Medication use, n (%)						
Vitamin D sterols	185 (73)	191 (75)	160 (62)	160 (63)	206 (60)	200 (59)
Phosphate binders	213 (84)	216 (85)	220 (85)	202 (79)	165 (48)	172 (51)
History of prior cinacalcet use, n (%)	109 (43)	103 (41)	126 (48)	137 (54)	92 (27)	80 (24)

Table is a copy of CS Table 14, p. 58

cCa, corrected calcium; cCa x P, corrected calcium-phosphorus product; ESRD, end-stage renal disease; P, phosphorus; PKD, polycystic kidney disease; PTH, parathyroid hormone; SD, standard deviation.

[a] includes Austria, Belgium, Czech Republic, Denmark, Estonia, France, Germany, Greece, Hungary, Israel, Italy, Latvia, Lithuania, Netherlands, Poland, Portugal, Russian Federation, Spain, Sweden, Switzerland, Turkey, United Kingdom
[b] Categorization differs for 20120229/20120230 vs 20120360 due to difference in study eligibility criteria for dialysate calcium (≥ 2.25 vs ≥ 2.5 mEq/L, respectively)

It could be inferred that the higher median PTH of patients in this trial (itself being a possible artefact of the higher trial baseline eligibility criterion of >500 pg/mL (53.0 pmol/l)) means patients may more likely to be refractory to treatment with PB/VD. This would potentially increase the relevance of this study to the scope of the appraisal, though this is only our assumption.

We consider it likely that all relevant RCTs have been included in the CS.

Non-randomised trials

The CS presents three non-RCTs in support of the long-term efficacy of etelcalcetide, as stated above.

A single arm, multicentre, open-label, switch study (n=158) assessed the safety and efficacy of etelcalcetide after cinacalcet therapy is discontinued in patients with CKD receiving haemodialysis (20120359). However, patients only underwent a seven-day washout period before switching to etelcalcetide. The remaining two non-RCTs are long-term open-label extension studies of the included phase III trials (trial 20120231 'OLE1'[15,16] n=891 patients and trial 20130213[17] 'OLE2' n=902 patients). We present results of these studies in section 3.3.7 of this report.

In addition to the three non-RCTs, the CS also substantially uses data from the EVOLVE RCT (Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events)[18] in the CS cost-effectiveness section and economic model. This is a large (n=3883 participants) cardiovascular outcomes RCT comparing cinacalcet and placebo conducted in patients with CKD on dialysis. This RCT is used to support the company's estimate of clinical effectiveness (i.e. longer-term outcomes) in their economic model, and is discussed in more detail in section 4.3.5.1 of this report. We provide a critical appraisal of this trial in section 3.5.

Summary

In summary, whilst the placebo-controlled trials present evidence relevant to the scope, the ERG considers that the clinical effectiveness from the cinacalcet-controlled trial may not necessarily provide evidence about the relative efficacy of etelcalcetide versus cinacalcet among people with refractory SHPT (later in this report, in section 3.1.5, we consider it is uncertain if the subgroup

analyses by previous cinacalcet use presented in the CS are representative of patients with refractory SHPT, as suggested by the company). In this respect, the CS does not fully address the decision problem and NICE's final scope. We also note that the trials did not employ the now less stringent PTH target used in practice for dose titration, and so the trials do not fully reflect clinical practice. Outcomes may be different when using the broader target range.

3.1.4 Description and critique of the approach to validity assessment

A quality assessment using the criteria suggested by NICE[19] is provided in the CS for the three etelcalcetide RCTs (CS Table 15, p. 60). Table 6 shows the company's and the ERG's quality assessments of the three trials included in the SLR using these criteria.

Table 6 Company and ERG assessment of trial quality

Element of bias assessment		Etelcalcetide vs Placebo 20120229	Etelcalcetide vs Placebo 20120230	Etelcalcetide vs cinacalcet 20120360
Was randomisation carried out appropriately?	CS	Yes	Yes	Yes
	ERG	Yes	Yes	Yes
Comment:				
Was the concealment of treatment allocation adequate?	CS	Yes	Yes	Yes
	ERG	Yes	Yes	Yes
Comment:				
Were the groups similar at the outset of the study in terms of prognostic factors?	CS	Yes	Yes	Yes
	ERG	Yes	Yes	Yes
Comment:				
Were the care providers, participants and outcome assessors blind to treatment allocation?	CS	Yes (Judged unclear on 'detection' bias in assessment using Cochrane criteria)	Yes (Judged unclear on 'detection' bias in assessment using Cochrane criteria)	Yes (Judged unclear on 'detection' bias in assessment using Cochrane criteria)
	ERG	Unclear	Unclear	Unclear
Comment: Although all three trials were double-blinded, individual investigators adjusted background therapy. The background therapy was the same in all trial arms, however, it is not clear whether the effects of etelcalcetide may have influenced the need for background therapy adjustment, and if so whether this would have compromised blinding. It was furthermore unclear how blinding was maintained because the CS did not provide information about whether patients in the comparator arms in all three studies underwent similar procedures to measure PTH and cCa concentrations to those in the etelcalcetide arms, which informed dose titration. It was also unclear who made decisions to titrate the dose and if they were blind to treatment allocation. The company's response to a clarification question about this suggests adequate procedures for performing dose titration were in place to blind investigators and patients to treatment allocation in the placebo-controlled trials (dose titration was performed by an interactive voice/web response system). CS Appendix states that centre personnel had access to the individual treatment assignment if it was essential to management of the patient. It was unclear if the central laboratory which carried out the biochemical assessments was blinded to the treatment assignment.				
Were there any unexpected imbalances in drop-outs between groups?	CS	No – a greater proportion of placebo recipients dropped out as met pre-specified criteria for study discontinuation after week 12 due to rising PTH (as would be expected). Otherwise, patient disposition was similar between groups.	No	No - patient disposition was similar between groups.
	ERG	No	No	No

Comment: Discontinuations were higher in the placebo groups, but this was not unexpected primarily due to pre-specified criteria for study discontinuation after week 12 due to rising PTH, In the cinacalcet trial, discontinuation rates from the study were similar between treatment arms.				
Is there any evidence to suggest that the authors measured more outcomes than they reported?	CS	No	No	No
	ERG	No	No	No
Comment:				
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	CS	Yes Appropriate imputation methods used to account for missing data	Yes Appropriate imputation methods used to account for missing data	Yes Appropriate imputation methods used to account for missing data
	ERG	Yes and Yes (for some outcomes only)	Yes and Yes (for some outcomes only)	Yes and Yes (for some outcomes only)
Comment: The company states that all outcomes were analysed using ITT, however from examination of the numbers of patients in CS Tables 17 and 18 some secondary efficacy endpoints do not appear to have been conducted using ITT analysis (vomiting and nausea, cCa, cCa x P, phosphate).				

The ERG's assessments of the three RCTs included in the SLR mostly agree with that of the company's. The company's summary for the three etelcalcetide trials, however, does not point out issues around blinding, which are mentioned in the quality assessments in the CS appendix. If it was essential to the management of the patient, centre personnel were un-blinded to the patient's individual treatment assignment (Table 6). As acknowledged in the CS appendix, it was also unclear if the central laboratory which carried out the biochemical assessments was blinded to the treatment assignment.

3.1.5 Description and critique of company's outcome selection

The outcomes in the CS match those listed in the NICE scope and the decision problem. Some of the outcomes are measured by the clinical trials and are reported in the clinical effectiveness section of the CS. These are:

- serum levels of parathyroid hormone (PTH)
- serum levels of calcium and phosphate
- HRQoL (only measured in one of the included clinical trials – the cinacalcet-controlled study 20120360, and only reported in the CSR of this study, not the CS itself). The HRQoL measure used in study 20120360 is the KDQOL-36 (Kidney Disease Quality of Life) instrument. No description of this instrument is given in the CS, or any results. Results are given in the CSR but without any discussion of their interpretation. Following a request for clarification by the ERG the

company provided a description of the KDQOL-36, stating that it has been validated. Tabulated results for the subscales are provided (clarification response question A.11)

- adverse effects of treatment

There does not appear to be any data reported in the CS for the following outcome from the scope: 'symptoms such as bone pain and itching or mobility hospitalisation'.

Other outcomes from the scope are reported in the economic evaluation section of the CS, based on extrapolation of clinical events from the EVOLVE trial, and these are used as input parameters to the economic model:

- survival
- incidence of fractures
- incidence of cardiovascular events
- need for parathyroidectomy

The company proposes that the endpoints assessed in the trials (PTH, calcium, phosphate) are clinically relevant (CS p. 78, p. 79 and p. 81). PTH is reported in a number of ways: as the proportion of patients achieving a >30% reduction in mean PTH from baseline (and also a >50% reduction in the cinacalcet-controlled trial 20120360); time to first occurrence of PTH > 30% reduction from baseline; the proportion of patients achieving a mean PTH of ≤ 300 pg/mL (31.8 pmol/l); and the percentage change from baseline in mean PTH (placebo-controlled studies 20120229 and 20120230). The trials reported in the CS did not employ target ranges of calcium, phosphate nor the target PTH range used in practice in England (2-9 times the upper limit of the normal reference range, around 130 – 600 pg/mL; 13.8 – 63.6 pmol/L). However, the two placebo-controlled trials did use the more stringent PTH target of 'achievement of mean PTH ≤ 300 pg/mL during EAP'. The company conducted the extrapolation to longer-term clinical outcomes in their economic model using the endpoint of 'achievement of a >30% reduction in mean PTH from baseline during EAP [efficacy assessment phase]' from the trials. The ERG notes that this outcome has previously been used in some trials of cinacalcet[21] and the CHMP assessment report of etelcalcetide (provided by the company with the submission to NICE) states it is a clinically meaningful endpoint.[11] Clinical expert advice to the ERG is that, in theory, this percentage reduction could bring PTH levels within the normal range for people receiving dialysis, but that if PTH was high to start with, this may not be enough. It is more clinically important for PTH to fall within a target range. The ERG therefore suggests using the target range currently used in practice may have been

a more ideal outcome to use for extrapolation to longer-term clinical outcomes (see section 4.3.5.1 of this report). However, as this was not measured in the studies, we recognise that the > 30% reduction from baseline outcome may be the best approximation to this.

Expert clinical advice to the ERG indicated it is unclear at present if extrapolation from biochemical endpoints to clinical events is appropriate. There is uncertainty within the field of nephrology about the most appropriate target ranges for biochemical parameters. It is suggested that survival cannot be predicted based on these. When PTH is uncontrolled, patients often have other medical issues which can also impact on longer-term outcomes. The ERG therefore has reservations about the usefulness of the extrapolation from biochemical parameters of the more clinically meaningful, longer-term outcomes in the CS. This is important as these estimated outcomes are among the key drivers of the company's economic model results (CS p. 82). We acknowledge, however, that extrapolation was a necessary approach to be able to estimate longer-term outcomes in the model, given that these outcomes were not measured in the etelcalcetide trials.

The following outcomes are presented in the CS although they are not listed in the NICE scope or the decision problem:

- Vomiting or nausea (only for the active-controlled study 20120360), reported in terms of mean number of days of vomiting or nausea per week in the first eight weeks; mean severity of nausea in the first 8 weeks; mean number of episodes of vomiting per week in the first eight weeks – presented in addition to patient incidence of nausea and vomiting as an adverse event).
- Reductions from baseline in fibroblast growth factor (FGF-23) (described as exploratory outcomes).
- Biochemical markers of high turnover bone disease, bone specific alkaline phosphatase (BSAP) and serum collagen type 1 cross-linked C-telopeptide (CTX) (described as exploratory outcomes).

As these outcomes are not listed in the scope and are not used to inform the economic model they are not described any further in this ERG report.

3.1.6 Description and critique of the company's approach to trial statistics

The CS reports the results for all the relevant measured outcomes listed in CS Table 16 (p. 61) in CS Section 4.7.2 (p. 61 - 69) for trials 20120229, 20120230 and 20120360. We note CS Table 11 (p. 49) states HRQoL was measured in the cinacalcet-controlled trial (using the KDQOL-36), but

results were not presented in the CS. Instead, these were available in the CSR and also provided in the company's response to clarification questions. Selected results from the non-RCTs are briefly narratively reported in CS Section 4.11.1 and 4.11.2 (p. 70 - 73). The CS clearly states interim data are presented for one of these studies (20130213, OLE2), as it is ongoing.

The CS reports the statistical methods used to analyse data and details about power calculations (CS p. 50 - 54). We note the trials were adequately powered. The CS states that in trial 20120360, the primary endpoint (percentage of participants with a > 30% reduction in PTH) was a non-inferiority analysis. The non-inferiority margin was set at 12% for the upper bound of the 95% two-sided confidence interval based on data collected in the EVOLVE trial.[18] Efficacy results are presented in the CS with measures of variance, p-values and, on the whole, the number of participants included in the analyses is clearly identified. The CS states the odds ratios presented for the primary endpoint in all three trials (percentage of participants with a > 30% reduction in PTH) was stratified. We note from the CSRs that these analyses were stratified by screening PTH category (< 600, ≥ 600 to ≤ 1000, and > 1000 pg/mL; i.e. < 63.6, ≥ 63.6 to ≤ 106, and > 106 pmol/l, respectively) and region (North America and non-North America), and, additionally, by cinacalcet use within eight weeks prior to randomization (yes and no) in the placebo controlled trials. It is unclear if there was any cross-over (treatment switching) in the trials, and, if so, whether results were adjusted for this. In response to a clarification question about this (clarification response A8), the company stated that crossover was not an option in the trials and crossover was therefore not assessed.

Regarding the HRQoL measure used in trial 20120360, [redacted] In response to a clarification question about this (clarification response A11), the company provided results from this measure from trial 20120360 for each of the five subscales of the measure. The company explained that scores can range from 0 to 100, with a higher score indicating better HRQoL. [redacted] It is unclear whether the analyses were stratified to control for the pre-specified baseline differences. P-values and CIs are not provided to test for statistically significant between- or within-group changes over time, so it is challenging to interpret the data. [redacted].

ITT analysis and other analysis sets

The CS mentions a number of different analysis sets were used in trials 20120229, 20120230 and 20120360, but the CS also does not mention all the different analysis sets used in the analysis of the 'achievement of a >30% reduction in mean PTH from baseline during EAP' that are presented in the trial CSRs. This is important, as this outcome was used to extrapolate longer-term outcome results for use in the economic modelling, and so this information is needed to understand whether or not the company has selected the more conservative analyses and results for presentation in the CS and to use for extrapolation. As is discussed in section 4.3.4, the extrapolated estimates of longer-term outcomes are among the main drivers of the model. We note from the CS and CSRs, the analysis sets mainly differ by the data imputation method used (e.g. last value carried forward, non-responder imputation, multiple imputation, no data imputation).

Although it is not explicitly stated in the CS, we note through cross-checking the methods and trial results in the CS with those in the CSR that results for the outcomes 'achievement of a > 30% reduction in mean PTH from baseline during EAP' and 'achievement of mean PTH ≤ 300 pg/mL during EAP' are provided in the CS for the ITT population for the placebo-controlled trials 20120229 and 20120230, with missing data appropriately imputed using non-responder imputation (the CS refers to this as a full analysis set (FAS) analysis). Of the other data analysis sets presented for the 'achievement of a > 30% reduction in mean PTH from baseline during EAP' outcome in the CSRs, we consider this the most appropriate and conservative analysis.

For the cinacalcet-controlled trial 20120360, the CS presents the results for two different analyses of the outcome 'achievement of a > 30% reduction in mean PTH from baseline during EAP'. The CSR states the non-inferiority null method was used for data imputation in the primary non-inferiority analysis, but it is unclear what this method involves. In response to a clarification question about this (clarification response A5), the company stated this was a multiple imputation under the non-inferiority null method that used an assumed 60% response rate (based on the EVOLVE trial) for cinacalcet patients and a 48% response rate for etelcalcetide patients (based on the 12% non-inferiority margin) to impute response status. The CS also presents results for achievement of a > 30% reduction in mean PTH from baseline during EAP as secondary endpoint (superiority) employing non-responder data imputation for missing data. The results for the 'achievement of a > 50% reduction in mean PTH from baseline during EAP' and 'achievement of a mean pre-dialysis P ≤ 4.5 mg/dL during the EAP' outcomes are presented for the ITT population.

In the economic model, the company has used a pooled response rate for the outcome 'achievement of a > 30% reduction in mean PTH from baseline during EAP' for etelcalcetide (which is used to extrapolate longer-term outcomes), created through pooling the numbers of participants who responded in the etelcalcetide arms in all three trials (this analysis is presented in Stollenwerk and colleagues, 2016[22]). The company has also used pooled results for the 'achievement of a > 30% reduction in mean PTH from baseline during EAP' from the two placebo arms of the placebo-controlled trials and selected one result for this outcome from the cinacalcet arm of the active-controlled trial to use for extrapolation in the model (see section 3.3.1 of this report).[22] We note through cross-checking the response rates used in the model with the data presented in the CS and CSRs, that the results from the most conservative analysis sets (the ITT analyses using non-responder imputation) have been selected to represent these response rates to placebo (i.e. PB/VD), etelcalcetide and cinacalcet in the model. We note, however, that the approach taken by the company to selecting these data breaks randomisation, as the point estimates are not from direct comparisons within trials and neither an adjusted indirect comparison nor NMA was used (which would have preserved randomisation). The approach taken by the company results in a larger cinacalcet and etelcalcetide difference, favouring etelcalcetide, than found in the cinacalcet-controlled trial of these drugs when using the non-responder data imputation analysis set (see Table 8 in section 3.3.1 of this report).

Safety outcomes were analysed using the safety analysis set in all three trials. This was defined as all randomised participants who received at least one dose of the study drug. If participants received the incorrect drug, they were analysed in the trial arm of the drug they actually received. We note this approach breaks randomisation.

Subgroups

The CS presents results for all the trial pre-specified subgroups as intended for all but one subgroup. CS Table 11 (p. 47) states pre-planned subgroup analyses were specified in trials 20120229 and 20120230 by region using the categories of North America or non-North America, but CS Figure 11 (67) presents the results for the treatment difference in the proportion of patients with > 30% reduction from baseline in PTH during EAP by the categories North America, Europe and Other instead.

The CS reports pre-specified subgroup analyses of patients who had and who had not previously used cinacalcet. In the placebo-controlled trials between 41% and 54% of patients had used cinacalcet within eight weeks prior to randomisation. In the cinacalcet-controlled trial 24% to 27% had previously used cinacalcet (NB. patients who had used cinacalcet within three months prior to screening were excluded from the trial). The company suggests later in the CS that patients who had previously been treated with cinacalcet are "representative of patients refractory to PB/VD alone" (CS p. 77). We acknowledge it is possible that these patients may have received treatment with cinacalcet because they were refractory to PB/VD alone, but the strength of this argument depends on how cinacalcet tends to be used in other countries, where the trials were conducted (few patients were recruited from the UK; please see section 3.1.3 for more detail). The cinacalcet SmPC does not restrict its use to refractory patients only (as it tends to be used in clinical practice in England); it is indicated for a broad patient population with CKD and SHPT who are receiving haemodialysis. The international KDIGO guideline recommends treatment with calcitriol or vitamin D analogues or calcimimetics or a combination of these for treating elevated PTH levels among patients receiving dialysis.[3] It is therefore possible that in the other countries involved in the trials, cinacalcet is not just used in patients refractory to treatment with PB/VD alone. The company's argument that these subgroups are representative of refractory patients may therefore not hold. This is important, as the one trial comparing cinacalcet (plus PB/VD) to etelcalcetide (plus PB/VD) identified in the CS (trial 20120360) included a broad patient population, and does not provide results specifically for the patient population with refractory SHPT that was stated to be of interest for the comparator cinacalcet in NICE's final scope. The CS therefore does not provide efficacy data directly for this population and it is uncertain if the subgroups of patients who had previously been treated with cinacalcet are representative of patients with refractory disease.

The company also reported a post-hoc subgroup analysis of the efficacy of etelcalcetide in a subgroup of patients who had previously discontinued cinacalcet [redacted] (CS p. 68) in the placebo-controlled trials 20120229 and 20120230 (NB. This is described as the 'cinacalcet failure subgroup' in the CS and is smaller than the subgroup described in the above paragraph, presumably because that subgroup includes patients who did not discontinue cinacalcet because of failure). The company appropriately highlights that the results of this analysis should be interpreted with caution due to it being post-hoc and based on small numbers of participants. Given the clinical expert consulted by the ERG suggested etelcalcetide may be used as a treatment option for patients who have not responded to or tolerated cinacalcet, we consider this is a useful subgroup analysis, but that it needs to be interpreted within the

limitations acknowledged by the company. In response to a clarification question (clarification response A7), the company also provided a similar post-hoc analysis using data from the cinacalcet-controlled trial 20120360.

3.1.7 Description and critique of the company's approach to the evidence synthesis

A narrative systematic review is provided, with data from the clinical trials provided in tables and figures, as well as in the text. The trial data in the CS is summarised from data provided in the CSRs.

No meta-analysis is reported, however, the CS does provide results of a pooled analysis of the two placebo-controlled RCTs (20120229, 20120230), termed the 'integrated analysis' (CS section 4.9). The pooled results are presented alongside the results from the respective individual trials. The justification for pooling these two studies is that they have a near-identical design and consistent results. The ERG agrees that the designs are very similar and that it is appropriate to pool the two studies. No detail is given on the methods used to pool the results (e.g. whether fixed or random-effects model, statistical heterogeneity etc). However, the ERG has replicated some of the analyses and found similar results, with no statistically significant heterogeneity identified. Pooled results are presented as odds ratios for dichotomous outcomes and mean differences for continuous outcomes.

The ERG also agrees with the decision not to meta-analyse the two-placebo-controlled trials with the cinacalcet-controlled trial (20120360), due to differences in the comparator which would not allow a meaningful interpretation of the results.

[redacted]Following a request for clarification by the ERG (clarification question A10) the company stated that the systematic review was performed to meet the needs of HTA bodies worldwide and was broader than the final scope issued by NICE. Given that head-to-head trial evidence for etelcalcetide with the comparators was available a formal indirect comparison feasibility assessment was not required for this CS. Given NICE's preference for direct evidence over indirect evidence[23] the ERG agrees that an indirect comparison was not essential.

However, the clinical effectiveness estimates used in the economic model in the CS for cinacalcet are derived only from the cinacalcet-controlled RCT included in the SLR (study 20120360). The ERG notes that other published trials of cinacalcet are available but these have not been included in the CS. The ERG asked the company to clarify how many studies comparing cinacalcet versus placebo and/or standard care that measured achievement of a >30% reduction in mean PTH from baseline as an outcome (as this is the main clinical effectiveness measure used in the economic model) that were identified and screened in their SLR, and to provide a reference list (clarification question A10). The company provided a list of four trials. The ERG notes that a Cochrane systematic review of calcimimetics for secondary hyperparathyroidism in CKD[21] includes a larger number of trials reporting this outcome (n=8), and it is not clear why all of these were not listed by the company in their clarification response. These trials may have potentially informed the extrapolation of treatment effects on clinical outcomes used in the economic model (see CS section 5.2.6). The ERG therefore conducted an exploratory meta-analysis of the eight RCTs comparing cinacalcet plus conventional therapy (PB/VD) with placebo (or no treatment) with conventional therapy for the outcome of >30% reduction in mean PTH from baseline (we report further details of this later in section 3.5.2). Statistically significant heterogeneity was present and this lends support to the justification not to conduct a NMA. However, given the fact that there is a wider set of evidence available for cinacalcet the ERG has conducted scenario analyses using these alternative effect estimates (see section 4.4 of this report).

3.2 Summary statement of company's approach

Table 7 provides the ERG's quality assessment appraisal of the company's systematic review of clinical effectiveness. As the table shows, the systematic review met all of the criteria indicating a good quality systematic review.

Inclusion screening on title and abstract, and on full paper, were conducted independently by two reviewers. It is not stated how many reviewers participated in data extraction and critical appraisal.

The submitted evidence generally reflects the decision problem defined in the CS, but, as is stated in sections 2.3, 3.1.3 and 3.1.6 of this report, the CS does not provide evidence for the relative efficacy of etelcalcetide and cinacalcet derived specifically among people with refractory SPHT, which was the population of interest in this appraisal for the cinacalcet comparator.

In summary, there is a low chance of systematic error in the systematic review based on the methods reported in the CS.

Table 7 Quality assessment (Centre for Reviews and Dissemination criteria) of CS review

CRD Quality Item: score Yes/ No/ Uncertain with comments	
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	[redacted]The patient population of interest for the cinacalcet comparator was not restricted in the CS systematic review inclusion criteria to only people with refractory SHPT (as specified in the decision problem and scope), but we consider this acceptable given the broad aims of the review. We also consider this acceptable as this would have resulted in the cinacalcet-controlled trial of etelcalcetide being excluded.
2. Is there evidence of a substantial effort to search for all relevant research? I.e. all studies identified	Yes (please see section 3.1.1 for our critique of the company's searches). [redacted]
3. Is the validity of included studies adequately assessed?	Yes, standard criteria have been used. CRD criteria are used for the three included RCTs (CS section 4.6, Table 15). In addition, the Cochrane Risk of Bias criteria are used to assess bias in the three RCTs and also the EVOLVE RCT (CS Appendix 4) which was used substantially in the CS to inform the economic model.
4. Is sufficient detail of the individual studies presented?	Yes. Key characteristics are tabulated and reported in the text, accompanied by illustrative figures. Limited data are given for the non-randomised studies in the CS (CS section 4.11). However further detail are provided in the CSRs for Study 20120359 (the switch study) and studies 20120231 and 20130213 (the phase 3 extension studies; CSRs were provided by the company in response to a request by the ERG, see clarification question C1).
5. Are the primary studies summarised appropriately?	5. Yes, see comments in relation to 'approach to the evidence synthesis' above.

3.3 Summary of submitted evidence

We present results below for the outcomes presented in the CS that meet NICE's final scope and the company's decision problem. We have prioritised the results for the 'Achievement of a > 30% reduction in mean PTH from baseline during EAP' in our presentation, as the results for this outcome are used in the company's economic model to extrapolate the longer-term outcomes of mortality, cardiovascular events, fractures and parathyroidectomy (see section 3.1.5 of this report for more detail about this). We have not summarised results for the biochemical markers of high turnover bone disease, BSAP and serum CTX, reductions from baseline in FGF-23 and mean

number of days or episodes of vomiting or nausea per week in the first eight weeks outcomes, as these outcomes are not listed in the scope and not used to inform the economic model (see section 3.1.4 of this report).

3.3.1 Summary of results for achievement of a > 30% reduction in mean PTH from baseline during EAP

Table 8 shows the results for the proportion of participants who achieved a > 30% reduction in mean PTH from baseline during EAP in the placebo-controlled studies (20120229 and 20120230) and in the cinacalcet-controlled study (20120360). We have presented results for the following analysis sets:

- the ITT analysis sets with missing data imputed as non-responders;
- the analysis that did not appear to use data imputation (see section 3.1.5 of this report for more information) from the cinacalcet-controlled study for this outcome (which was the analysis of the primary outcome in this trial; a non-inferiority analysis);
- the pooled analysis of the two placebo-controlled trials.

The point estimates used for this outcome in the economic model to extrapolate longer-term outcomes are also presented and highlighted in bold. We have presented these alongside the other results to aid comparison with the point estimates available from other analysis sets in the trials for this outcome, which offers insight into whether the company has selected the most appropriate data. Note that by selecting the particular data points used in the model, the company has essentially conducted an unadjusted indirect comparison (as the data for each intervention are not from the same trials) and that this approach breaks randomisation (please see section 4.3.5.1 for a further discussion of this).

The results show participants treated with etelcalcetide plus PB/VD were statistically significantly more likely to achieve a > 30% reduction in mean PTH from baseline during the EAP than those treated with placebo plus PB/VD. Etelcalcetide plus PB/VD was found to be both non-inferior and superior to treatment with cinacalcet plus PB/VD on this outcome.

We note the etelcalcetide plus PB/VD and cinacalcet plus PB/VD response rates the company has selected for use in the economic model to extrapolate longer-term outcomes result in a 14.4% difference between the two treatments in the proportion of participants who responded, favouring etelcalcetide. As stated, the company's approach to selecting these data breaks randomisation. We

note that the cinacalcet-controlled trial (20120360), comparing cinacalcet plus PB/VD and etelcalcetide plus PB/VD, resulted in a 10.5% difference in the proportion of participants who responded, favouring etelcalcetide, in the primary (noninferiority) endpoint. We suggest the company could have used the response rates from this analysis to conduct an economic scenario analysis to examine the impact of using these more conservative results on the incremental cost effectiveness ratios (ICERs). We have used the data from this analysis in our ERG scenario analyses (please see section 4.4). Additionally, in our base case, we have used an approach that does not break randomisation.

Table 8 Proportion of participants achieving a > 30% reduction in mean PTH from baseline during EAP – results presented in CS and those used for extrapolation

Trial / economic model	Source	Placebo plus PB/VD, % (n/N)	Cinacalcet plus PB/VD (C), % (n/N)	Etelcalcetide plus PB/VD (E), % (n/N)	C-E difference, %[a]	Treatment difference (95% CI), p-value	ERG Notes
Pooled analysis of placebo-controlled studies 20120229 and 20120230	CS Table 17 (p. 62)	**8.9** (46/514)	N/A	74.7 (380/509)	N/A	Stratified odds ratio: 31.60 (21.59, 46.25), p <0.001	Data pooled from ITT analyses using non-responder data imputation
Cinacalcet-controlled trial (20120360)	CS Table 18 (p. 65)	N/A	63.9 (198/310)	77.9 (232/298)	14	Stratified treatment difference[b]: -10.48 (-17.45, -3.51), no p-value reported	Data from study 20120360 primary non-inferiority endpoint (ITT analysis. Stratified treatment difference based on multiple imputation for missing data)
Cinacalcet-controlled trial (20120360)	CS Table 18 (p. 65)	N/A	**57.7** (198/343)	68.2 (232/340)	10.5	Odds ratio[c]: 1.59 (1.16, 2.17), p = 0.004	Data from study 20120360 secondary superiority endpoint (ITT analysis; missing data imputed as non-responders)
Point estimates used in the economic model	CS Figure 15 (p. 98)	**8.9** (46/514)	**57.7** (198/343)	**72.1**[d] (612/849)	14.4	N/A	Used in extrapolation; all point estimates from ITT analyses using non-responder data imputation

Bold text shows data point was used to extrapolate longer-term outcomes in the model. C, cinacalcet; CS, company's submission; E, etelcalcetide; ERG, evidence review group, ITT, intention-to-treat; N/A, not applicable.

[a] Calculated by the ERG.

[b] Mantel-Haenszel estimator of the difference in proportions (cinacalcet - etelcalcetide).

[c] [redacted]

[d] The sum of all patients achieving >30% PTH response in studies 20120229, 20120230 and 20120360 – see Stollenwerk et al., 2016[22]

3.3.2 Summary of results for other measures of serum levels of PTH

Table 9 shows the results for other PTH outcomes measured in the three trials included in the company's SLR. None of these outcomes were used to inform the economic model. Proportionally more participants treated with etelcalcetide plus PB/VD achieved a mean PTH of ≤ 300 pg/mL (31.8 pmol/L) during the EAP than those treated with PB/VD alone in both the placebo-controlled trials (study 20120229: 5.1% placebo versus 49.6% etelcalcetide; study 20120230: 4.6% placebo versus 53.3%) and in the pooled analysis of the placebo-controlled trials (4.9% placebo versus 51.5% etelcalcetide). Those treated with etelcalcetide plus PB/VD were statistically significantly more likely to achieve a PTH of ≤ 300 pg/mL (31.8 pmol/L) in both trials (20120229: OR 22.08 (95% CI 11.47, 42.48), p < 0.001; 20120230: OR 33.92 (95% CI 16.35, 70.37), p < 0.001) and the pooled analysis (OR 27.02 (95% CI 16.62, 43.93), p < 0.001) than those treated with placebo plus PB/VD. We note these results are from an ITT analysis, using non-responder imputation for missing data, which is a conservative approach. [redacted]

There were also consistent statistically significant favourable results for the etelcalcetide plus PB/VD arms versus the PB/VD (placebo) alone arms on the outcome '% change from baseline in mean PTH during the EAP' (placebo-controlled trials 20120229 and 20120230) (Table 9). These results were not from an ITT analysis. Participants treated with etelcalcetide plus PB/VD were statistically significantly more likely to achieve a > 50% reduction in mean PTH from baseline during the efficacy assessment phase than those treated with cinacalcet plus PB/VD (trial 20120360) (see Table 9). These results were from an ITT analysis.

The CS also reports Kaplan-Meier estimates of time to first occurrence of PTH > 30% reduction from baseline based on the pooled placebo-controlled trials (trials 20120229 and 20120230) and from the cinacalcet-controlled trial (20120360) (CS p. 63, p. 64 and p. 66). The CS states the results show approximately 35% of patients receiving etelcalcetide in both these analyses had a > 30% reduction in PTH from baseline at week 4.

Table 9 Results for other serum PTH outcomes

Outcomes	Study 20120229		Study 20120230		Pooled[a]		Study 20120360	
	Placebo (N = 254)	Etelcalcetide (N = 254)	Placebo (N = 260)	Etelcalcetide (N = 255)	Placebo (N = 514)	Etelcalcetide (N = 509)	Cinacalcet (N=343)	Etelcalcetide (N=340)
Achievement of mean PTH ≤ 300 pg/mL during EAP, n (%)	13 (5.1)	126 (49.6)	12 (4.6)	136 (53.3)	25 (4.9)	262 (51.5)	[redacted]	[redacted]
Stratified odds ratio (95% CI)	22.08 (11.47, 42.48)		33.92 (16.35, 70.37)		27.02 (16.62, 43.93)		Not reported in CS	
P value	p < 0.001		p < 0.001		p < 0.001		Not reported in CS	
% change from baseline in mean PTH during EAP							Not measured	
n	219	229	237	227	456	456		
Mean (SE)	13.00 (2.81)	-55.11 (1.94)	13.72 (2.50)	-57.39 (1.91)	13.37 (1.87)	-56.25 (1.36)		
Treatment difference, % Estimate (SE)	-71.11 (3.39)		-71.34 (3.15)		-71.30 (2.31)			
95% CI	-77.77, -64.46		-77.53, -65.14)		-75.84, -66.76			
P value	p < 0.001		p < 0.001		p <0.001			
Achievement of a > 50% reduction in mean PTH from baseline during EAP[b], n (%)	Not measured				N/A		138 (40.2)	178 (52.4)
Odds ratio (95% CI) (etelcalcetide:cinacalcet), P value							1.65 (1.21, 2.23), p = 0.001	

This table is a modified and merged version of CS Tables 17 (p. 62) and 18 (p. 65). CI, confidence interval; EAP, efficacy assessment phase; N/A, not applicable; SE, standard error; PTH, parathyroid hormone.

[a] Pooled results from studies 20120229 and 20120230.

[b] Missing data imputed using non-responder imputation.

3.3.3 Summary of results for other measures of measures of serum calcium and phosphate levels

Table 10 shows the results for the measures of serum calcium and phosphate taken in the three trials. None of these were used in the economic model. Participants receiving etelcalcetide plus PB/VD experienced a statistically significantly greater decrease in mean corrected calcium during the EAP than those treated with placebo plus PB/VD (trials 20120229 and 20120230) or cinacalcet plus PB/VD (trial 20120360) – participants in the placebo plus PB/VD arms experienced a slight increase in these levels. Those treated with etelcalcetide plus PB/VD also experienced a statistically significantly greater reduction in corrected calcium-phosphate product (cCa x P) and phosphate levels than participants treated with placebo plus PB/VD in the two placebo-controlled trials (trials 20120229 and 20120230). These outcomes were not measured in the cinacalcet-controlled trial. There was no statistically significant difference in the proportion of patients treated with etelcalcetide plus PB/VD and those treated with cinacalcet plus PB/VD who achieved a mean pre-dialysis phosphate level of ≤ 4.5 mg/dL during the EAP (ITT analysis). This outcome was not measured in the placebo-controlled trials.

3.3.4 Summary of Health related quality of life

HRQOL was reported for one of the trials, the cinacalcet-controlled trial 20120360. Results are not presented in the CS, but are available in the CSR and a summary is provided in the company's response to clarification questions from the ERG (question A11). HRQOL was measured using the KDQOL-36 which has five sub-scales reflecting general mental and physical functioning, symptoms (e.g. chest pain, itchy and dry skin etc) and effects of kidney disease (e.g. diet restrictions, personal worries, etc). Scores for each sub-scale are transformed on to a scale of 0 to 100, with higher scores representing higher quality of life.

Table 10 Results for serum calcium and phosphate outcomes

	Study 20120229		Study 20120230		Pooled[a]		Study 20120360	
	Placebo (N = 254)	Etelcalcetide (N = 254)	Placebo (N = 260)	Etelcalcetide (N = 255)	Placebo (N = 514)	Etelcalcetide (N = 509)	Cinacalcet (N=343)	Etelcalcetide (N=340)
% change from baseline in mean cCa during EAP								
n	219	229	237	227	456	456	310	298
Mean (SE)	1.18 (0.29)	-7.29 (0.53)	0.58 (0.29)	-6.69 (0.55)	0.87 (0.20)	-7.00 (0.39)	-6.28 (0.44)	-9.83 (0.49)
Treatment difference, % Estimate (SE)	-8.38 (0.58)		-7.20 (0.60)		-7.77 (0.42)		-3.48[b] (0.65)	
95% CI	-9.52, -7.23		-8.38, -6.03		-8.60, -6.94		-4.76, -2.21	
P value	<0.001		< 0.001		< 0.001		<0.001[c]	
% change from baseline in mean cCa x P during EAP							Not measured	
n	213	227	234	223	447	450		
Mean (SE)	-0.19 (1.44)	-14.34 (2.06)	-1.06 (1.42)	-15.84 (1.57)	-0.64 (1.01)	-15.09 (1.30)		
Treatment difference, % Estimate (SE)	-14.99 (2.41)		-14.58 (2.07)		-14.68 (1.59)			
95% CI	-19.73, -10.25		-18.65, -10.51		-17.81, -11.56			
P value	< 0.001		< 0.001		< 0.001			
% change from baseline in mean P during EAP							Not measured	
n	214	227	234	223	448	450		
Mean (SE)	-1.31 (1.42)	-7.71 (2.16)	-1.60 (1.42)	-9.63 (1.61)	-1.46 (1.00)	-8.66 (1.35)		
Treatment difference, % Estimate (SE)	-7.45 (2.47)		-8.04 (2.09)		-7.59 (1.62)			
95% CI	-12.31, -2.59		-12.15, -3.92		-10.77, -4.40			
P value	0.003		< 0.001		< 0.001			
Achievement of a mean pre-dialysis P ≤ 4.5 mg/dL during the EAP[d], n (%)	Not measured		Not measured		N/A		100 (29.2)	109 (32.1)
Odds ratio (95% CI)							1.15 (0.83, 1.59)	
P value (descriptive)							0.41	

This table is a modified and merged version of CS Tables 17 (p. 62) and 18 (p. 65). cCa, corrected serum calcium; CI, confidence interval; EAP, efficacy assessment phase; N/A, not applicable; P, phosphate; SE, standard error;.

[a] Pooled results from studies 20120229 and 20120230.

[b] Etelcalcetide:cinacalcet.

[C] Stated in CS to be "descriptive" (CS Table 18, p. 65).

[d] Missing data imputed using non-responder imputation

[redacted]

[redacted]

Table from company's clarification response.

HRQoL measured by the KDQOL-36 is not used in the company's economic model. The ERG notes that the economic model base case analysis does not include a HRQoL benefit from calcimimetic treatment, though a HRQoL utility increment, based on EQ-5D data from the EVOLVE trial, is included in a scenario analysis (see section 4.3.5.4). The ERG has conducted a scenario analysis in which a utility increment is applied for both calcimimetics, and applied for cinacalcet only (see section 4.4.1.5).

3.3.5 Sub-group analyses results

The CS reports pre-specified sub-group analyses for the three RCTs based on baseline variables including patient demographic characteristics, severity of SHPT and prior use of

cinacalcet (CS section 4.8). (NB. To reiterate, the NICE scope for this appraisal does not specify any sub-groups to be analysed.)

For the two placebo-controlled trials results are presented as odds ratios for: the proportion of patients with > 30% reduction in PTH from baseline for sub-groups based on sex; age; race; screening iPTH level; prior cinacalcet use within eight weeks of randomisation; region; mode of dialysis; dialysis vintage; baseline dialysate calcium; baseline vitamin D sterol use; baseline calcium containing phosphate binder or calcium supplement use. There was a statistically significant difference between etelcalcetide and placebo for all sub-groups for this outcome, favouring etelcalcetide [redacted]).

[redacted]

Caution is urged in the interpretation of these analyses as although they were pre-defined they were not statistically powered to detect treatment differences, and confidence intervals for some sub-groups were very wide.

[redacted]

[redacted]

3.3.6 Summary of adverse events

The CS reports safety data from the three RCTs identified in the systematic review (the cinacalcet-controlled trial 20120360 and pooled results from the placebo-controlled trials 20120229 and 20120230) and from two of the non-RCTs included in the CS (20120231 and

20130213) which were single-arm extension studies to parents studies 20120229, 20120230, 20120359, and 20120360, 20120231 and 20120334 respectively. Data on the safety of etelcalcetide when switching from cinacalcet are also provided from a non-RCT (20120359). Safety analyses in the RCTs were based on the safety analysis set (see section 3.1.5 for a definition of this set). The CS provides data on the incidence of events in terms of the number and percentage of participants who experienced each event. AEs were not included in the economic model.

Table 11 shows the incidence of all treatment emergent AEs, SAEs, AEs leading to drug withdrawal and fatal AEs. AE rates were similar between etelcalcetide plus PB/VD and placebo plus PB/VD or cinacalcet plus PB/VD, with two exceptions: 1) proportionally more participants treated with etelcalcetide (91.7%) experienced treatment emergent AEs than those treated with placebo (79.9%), and 2) Proportionally more participants treated with etelcalcetide (2.7%) had fatal AEs than those treated with cinacalcet (1.8%). The CS states that none of the fatal AEs were considered to be related to the study drug.

Table 11 Overview of incidence of adverse events in etelcalcetide RCTs

	Total placebo-controlled studies		Study 20120360	
	Placebo (n=513)	Etelcalcetide (n=503)	Cinacalcet (n=341)	Etelcalcetide (n=338)
All treatment emergent AEs –n (%)	410 (79.9)	461 (91.7)	307 (90.0)	314 (92.9)
SAEs –n (%)	149 (29.0)	130 (25.8)	93 (27.3)	85 (25.1)
AEs leading to drug withdrawal –n (%)	13 (2.5)	9 (1.8)	16 (4.7)	19 (5.6)
Fatal AEs –n (%)	15 (2.9)	11 (2.2)	6 (1.8)	9 (2.7)
AEs=adverse events; SAE=serious adverse events Source: summary of clinical safety [24]; 20120360 CSR [25]				

This table is a direct reproduction of CS Table 24, CS p. 73 - 74.
AEs, adverse events; SAEs, serious adverse events.

Clinical expert advice to the ERG is that the main AE associated with etelcalcetide is decreased blood calcium and associated symptoms. The CS notes that during the trials asymptomatic decreases in blood calcium were classified as 'blood calcium decreased', and symptomatic events were classified as 'hypocalcaemia'. The most common AE experienced by participants treated with etelcalcetide in all three trials was an asymptomatic decrease in blood calcium (Table 12). This was experienced by around two-thirds of participants treated with etelcalcetide in the trials. Proportionally more patients treated with etelcalcetide plus PB/VD (63.8%) than those treated with placebo (i.e. PB/VD alone) experienced this AE (10.1%). A higher proportion of participants treated with etelcalcetide plus PB/VD (68.9%) than those treated with cinacalcet plus PB/VD (59.8%) also experienced this AE. Additionally, rates of symptomatic hypocalcaemia events were higher in the etelcalcetide

than the placebo or cinacalcet arms (Table 12). The CS reports that decreased blood calcium and symptomatic hypocalcaemia events rarely led to drug discontinuation, but did lead to some temporary discontinuations. There were no serious AEs of hypocalcaemia reported during the trials. Rates of events potentially associated with increased neuromuscular irritability secondary to low calcium, however, were higher in participants treated with etelcalcetide than placebo (CS p. 74). The clinical expert consulted by the ERG indicated that the higher rates of asymptomatic decrease in blood calcium and symptomatic hypocalcaemia observed with etelcalcetide would likely result in increased use of health care resource to manage these AEs. The expert stated that if calcium is very low or symptomatic due to treatment, patients are admitted to hospital for intravenous calcium. Low calcium would also require further blood tests even if admission was not required and likely more frequent clinical review.

Other common AEs (defined in the CS as ≥10% in the etelcalcetide group) were muscle spasms, nausea and diarrhoea, which occurred in a slightly greater proportion of participants treated with etelcalcetide than placebo. Vomiting was also a common AE among participants treated with etelcalcetide, but, along with nausea, occurred in a slightly higher proportion of participants treated with cinacalcet than etelcalcetide (CS p. 74; data not shown in Table 12). Proportionally more participants treated with etelcalcetide experienced hypotension than those treated with cinacalcet (Table 12).

In terms of AEs of special interest (Table 12), other than the increased incidence of hypocalcemia with treatment with etelcalcetide versus placebo or cinacalcet already noted, participants treated with etelcalcetide had higher rates of cardiac failure than those treated with placebo or cinacalcet. Those treated with etelcalcetide also had higher rates of adjudicated congestive heart failure requiring hospitalisation than those treated with placebo. The clinical expert consulted by the ERG considered these differences clinically significant, particularly the difference in rates between the etelcalcetide arm and cinacalcet arm in the cinacalcet-controlled trial.

The CS mentions that the cardiovascular events myocardial infarction and stroke were adjudicated by an independent committee during the placebo-controlled trials, but results for these events were not supplied in the CS. We note they were available in the CSRs and we present them in Table 12. As shown in Table 12, rates of stroke were similar between etelcalcetide and placebo, but rates of myocardial infarction were higher with etelcalcetide than placebo. Proportionally more patients receiving etelcalcetide also experienced an infusion reaction compared with those treated with placebo or cinacalcet.

Table 12 Incidence of common, notable and AEs of special interest in the three phase 3 trials

	Total placebo-controlled studies		Study 20120360	
Event of interest category, n (%)	**Placebo (N = 513)**	**Etelcalcetide (N = 503)**	**Cinacalcet (N = 341)**	**Etelcalcetide (N = 338)**
Selected common or notable AEs (from CS p. 74 - 75)				
Blood calcium decreased (asymptomatic)[a]	10.1%	63.8%	59.8%	68.9%
Hypocalcaemia (symptomatic)[b]	0.2%	7.0%	2.3%	5.0%
Hypotension	5.1%	6.0%	2.9%	6.8%
AEs of special interest (CS Table 25, p. 75)				
Adynamic bone	0 (0)	0 (0)	0 (0)	0 (0)
Cardiac failure	13 (2.5)	16 (3.2)	2 (0.6)	10 (3.0)
Adjudicated congestive heart failure requiring hospitalisation[c]	1.2%[d] Trial 20120229:[e] 2 (0.8) Trial 20120230:[e] 4 (1.5)	2.2%[d] Trial 20120229:[e] 7 (2.8) Trial 20120230:[e] 4 (1.6)	[redacted]	[redacted]
Convulsions	5 (1.0)	4 (0.8)	2 (0.6)	3 (0.9)
Hypersensitivity	19 (3.7)	22 (4.4)	17 (5.0)	19 (5.6)
Hypocalcemia[f]	53 (10.3)	330 (65.6)	207 (60.7)	240 (71.0)
Hypophosphatemia	2 (0.4)	7 (1.4)	3 (0.9)	5 (1.5)
Infusion reaction	91 (17.7)	99 (19.7)	53 (15.5)	68 (20.1)
Torsade de pointes-QT prolongation	3 (0.6)	6 (1.2)	0 (0)	1 (0.3)
Ventricular tachyarrhythmias	4 (0.8)	2 (0.4)	0 (0)	0 (0)
Adjudicated confirmed myocardial infarction	Trial 20120229: 2 (0.8)[e] Trial 20120230: 3 (1.2)[e]	Trial 20120229: 3 (1.2)[e] Trial 20120230: 5 (2.0)[e]	[redacted]	
Adjudicated confirmed stroke	Trial 20120229: 1 (0.4)[e] Trial 20120230: 2 (0.8)[e]	Trial 20120229: 1 (0.4)[e] Trial 20120230: 1 (0.4)[e]		

This table is a modified reproduction of CS Table 25, CS p. 75. AE, adverse event.
[a] Asymptomatic reduction in serum corrected calcium below 7.5 mg/dL or asymptomatic reduction in serum corrected calcium between 7.5 and < 8.3 mg/dL requiring medical management or deemed clinically significant by the investigator
[b] Symptomatic reduction in serum corrected calcium < 8.3 mg/dL
[c] Ns not reported in CS; %s provided only.
[d] Data reported in the CS.
[e] Data reported in trial CSRs
[f] Includes the following preferred terms: blood calcium decreased, hypocalcaemia, adjusted calcium decreased and Chvostek's sign

In the non-RCT extension studies, the most common AE was a blood decrease in calcium and the most frequently reported SAEs were hyperkalaemia (3.3%) and cardiac failure congestive (2.0%). [redacted] The CS states AE data from the non-RCT of participants switching from cinacalcet to etelcalcetide shows that it is safe to do so at a starting dose of 5 mg after cinacalcet has been discontinued for seven days.

3.3.7 Summary of non-randomised studies

The CS reports details of five non-controlled studies (CS section 4.11). Two of these are small (<40 patients) single-arm phase II studies assessing safety and efficacy of etelcalcetide (studies 20120331 and 20120334), and three are phase III studies. The CS considers the three phase III studies as providing evidence relevant to the decision problem. One of the phase III studies is an open-label single-arm study of patients who switched from oral cinacalcet to etelcalcetide (study 20120359). The other two phase III studies are extension studies of the RCTs included in the CS systematic review designed to assess the longer-term safety and efficacy of etelcalcetide (studies 20120231 and 20130213). The ERG agrees that the phase III studies are of greater relevance to the decision problem. Below is a description of the design of these studies, and their key efficacy and safety results that are currently available.

The switch study (20120359)

In this study patients on a stable dose of cinacalcet switched to etelcalcetide after a seven day wash out period. Etelcalcetide was administered at a dose of 5mg three times per week for four weeks. A total of 147 patients were included in the analysis (from an initial 158 enrolled patients). Brief efficacy results are provided in the CS, in terms of mean (standard error) percent change in PTH from baseline (a secondary endpoint): -3.9% (2.6%) at week 2, -7.8% (3.1%) at week 3, and -10.9% (2.9%) at week four. The CS concludes that etelcalcetide is efficacious in patients who switch from stable cinacalcet. The proportion of patients achieving > 30% decrease in PTH from baseline does not appear to have been measured in this study.

The long-term extension studies (20120231 and 20130213)

The study 20120231 (known as OLE1) was an open-label single arm extension study to the two placebo-controlled RCTs (20120229 and 20120230) and to the single-arm 'switch' study described above (20120359). The purpose of this study was to assess long-term (52 week) safety and efficacy of etelcalcetide. The efficacy assessments included changes from baseline in serum PTH, cCa, Phosphate (P) and cCa x P at 6 months (EAP6, weeks 20-26 inclusive), at 12 months (EAP12, weeks 46-53 inclusive) and during the last six weeks of treatment for those who completed at least eight weeks of treatment (EAP).

A total of 768 patients were enrolled from the two placebo-controlled trials (384 etelcalcetide-treated patients and 384 placebo-treated patients, as clarified by the company – clarification question A9) and 123 patients were enrolled from the switch study (combined total of 891

patients). A total of 682 patients (76.5%) completed the 52 week treatment period, and a further 201 patients completed both the 52 weeks treatment and the 30 day safety follow-up period. The CS reports that of the 687 patients who discontinued the study before the 30 day safety follow-up period, 476 discontinued due to protocol-specified criteria and entered a second long-term follow-up study (20130213, OLE2 – described below).

Table 13 reports the percentage of patients with a reduction of >30% in PTH, and the percentage with PTH ≤ 300 pg/ml (31.8 pmol/L) at the assessment time-points. Around two-thirds of patients achieved a >30% reduction in PTH from baseline over the treatment period, and just over half of the patients met the PTH target of ≤300pg/mL (31.8 pmol/L). The CS also reports that reductions were observed in mean PTH, cCa, cCa x P and P from baseline at each assessment timepoint (see CS Table 22).

Table 13 PTH outcomes with etelcalcetide in the 52-week open-label extension study (20120231)

	>30% reduction from baseline PTH % (95% CI)	**PTH ≤300pg/mL % (95% CI)**
EAP6	68.1% (64.6% to 71.4%)	55.5% (52.0% to 59.1%)
EAP12	67.5% (63.8%, to 71.0%)	56.4% (52.6% to 60.0%)
EAP	67.7% (64.2% to 70.9%)	57.3% (53.8% to 60.7%)

EAP6: the efficacy assessment phase at 6 months (week 20 to 26 inclusive). EAP12: the efficacy assessment phase at 12 months (week 46 to 53 (inclusive)). EAP: the efficacy assessment phase in the last 6 weeks before ending treatment, only for patients who completed a minimum of 8 weeks of treatment with etelcalcetide. This table is a reproduction of CS Table 21 (p. 72).

As mentioned above, there is a second open-label extension study (20130213, OLE2) which is on-going (final results are expected in May 2017; as stated in clarification response A9). This study is a follow-on to 20120231 (OLE1), from which a total of 476 patients rolled over into this current study. This study also includes 409 patients from the cinacalcet-controlled RCT (20120360) (211 patients from the cinacalcet arm and 198 from the etelcalcetide arm, as clarified by the company – clarification question A9). In addition, an unspecified number of patients from the single arm phase 2 study 20120334 were enrolled (the ERG deduces this to be 17 patients, as the total number of patients in the study is reported to be 902). An interim analysis is reported in the CS (data cut March 18th 2016), reflecting mean time on study drug of 391 days. The primary outcome was incidence of AEs, with efficacy outcomes (PTH, P target, cCa) as additional endpoints. The CS reports the proportion of patients with a PTH target within 2-9 times the upper limit of normal (as recommended by the KDIGO guideline) at three timepoints: 6 months (515/767 (67%)); 12 months (424/592 (72%); and 18 months (93/133 (70%)). We note this translates to a PTH range of around 130-600 pg/mL (13.8-63.6 pmol/L). The achievement of PTH target range appears to be sustained up to 18

months, though at this point in time only around 15% of the enrolled patients remained. Further efficacy results are presented in CS Table 23 (p. 73), indicating durable achievement of biochemical targets, though with reduced numbers of patients remaining in the study. [redacted]

3.4 Summary of clinical effectiveness

The systematic review in the CS identified two RCTs comparing etelcalcetide (plus PB/VD) to placebo (plus PB/VD) (trials 20120229 and 20120230) and one RCT comparing etelcalcetide to cinacalcet (trial 20120360) for the treatment of patients with CKD with SHPT, receiving haemodialysis. The CS also included results from three non-RCTs, as supporting data. Clinical expert advice to the ERG is that the baseline characteristics of participants in the trials are generally representative of patients seen in practice. The three trials were of a good quality, but the ERG judged they were at potential risk of performance, detection and attrition bias.

The results of the trials showed participants treated with etelcalcetide plus PB/VD were statistically significantly more likely to achieve a > 30% reduction in mean PTH from baseline during the efficacy assessment phase than those treated with placebo plus PB/VD. Etelcalcetide plus PB/VD was found to be both non-inferior and superior to treatment with cinacalcet plus PB/VD on this outcome. Proportionally more participants treated with etelcalcetide plus PB/VD achieved a mean PTH of ≤ 300 pg/mL (31.8 pmol/L) during the efficacy assessment phase than those treated with PB/VD alone in both the placebo-controlled trials and than those treated with cinacalcet (plus PB/VD) in the cinacalcet-controlled trial). Participants treated with etelcalcetide (plus PB/VD) had greater reductions in phosphate levels than those treated with placebo (plus PB/VD). There was no difference between etelcalcetide and cinacalcet, though, in the proportion of participants reaching the phosphate target used in the cinacalcet-controlled trial. Participants treated with etelcalcetide experienced greater reductions in calcium than those treated with placebo or cinacalcet. [redacted] HRQoL was measured in the cinacalcet-controlled trial only. HRQoL did not change substantially over time though scores were slightly lower in the etelcalcetide arm at week 26 (lower scores indicating reduced HRQoL). The most common AE experienced by participants treated with etelcalcetide in all three trials was an asymptomatic decrease in blood calcium. This AE was experienced by a higher proportion of patients treated with etelcalcetide (plus PB/VD) compared with cinacalcet (plus

PB/VD), and than patients treated with placebo (i.e. PB/VD alone). Rates of symptomatic hypocalcaemia events and cardiac failure were also higher with etelcalcetide than placebo or cinacalcet.

The company's interpretation of the evidence is, on the whole, appropriate and justified. The trial results suggest etelcalcetide is more effective than established clinical practice without calcimimetics (i.e. treatment with PB/VD alone) in the broad patient population specified to be of interest in the final scope and the company's decision problem for this comparator. The ERG has, however, otherwise identified the following concerns and uncertainties:

- The patient population in the head-to-head trial of etelcalcetide versus cinacalcet consisted of a broad SHPT population, rather than the specific population of people with refractory SHPT (i.e. refractory to PB/VD alone) that was specified to be of interest in the final scope.
- It is uncertain if the subgroups of participants in the trials who had previously been treated with cinacalcet are representative of people refractory to treatment with PB/VD alone, as the company suggests.
- The trials included in the review did not measure the most clinically relevant outcomes – that is, survival, incidence of cardiovascular events (which can lead to mortality) and achievement of the PTH target currently used in UK clinical practice for patients receiving haemodialysis (2-9 times the upper limit of the normal reference range).
- Relatedly, drug doses in all three trials were titrated to a PTH target of ≤300pg/mL (31.8 pmol/L) (CS p. 45), whereas in practice, they would be titrated to the 2-9 times the upper limit of the normal reference range (which translates to a PTH range of around 130-600 pg/mL; 13.8-63.6 pmol/L), and so the treatment protocols in the trials were not reflective of current practice in the UK. Outcomes in practice may be different when using the less stringent treatment target.
- It is uncertain how etelcalcetide may impact HRQoL compared with treatment with PB/VD alone, as HRQoL was not measured in the placebo-controlled trials.
- The statement in the CS (p. 77) that the safety profile of etelcalcetide is similar to cinacalcet is not entirely justified: there were higher rates of asymptomatic decreased blood calcium (acknowledged in the company's interpretation of the evidence on CS p. 78), symptomatic hypocalcaemia and cardiac failure with etelcalcetide than cinacalcet. Clinical expert advice to the ERG indicated that symptomatic hypocalcaemia or very low calcium would likely result in increased health care resource utilisation to manage these AEs.

- It is uncertain to what extent patients in England adhere to cinacalcet from the information in the CS (only expert opinion about this from a survey is provided). It is therefore uncertain if the company's argument that the relative efficacy of etelcalcetide versus cinacalcet may have been underestimated in the cinacalcet-controlled trial due to better adherence to cinacalcet in the trials than would be found in practice (CS p. 79) is justified.

3.5 Additional cinacalcet evidence

In this section we present additional evidence and analyses of the clinical effectiveness of cinacalcet by the ERG. This is provided because additional cinacalcet trial evidence not within the scope of the appraisal is used by the company to inform their economic evaluation. We therefore provide a critical appraisal of a large cinacalcet trial, the EVOLVE trial, as it is used substantially in the company's economic model (see section 4.3.4 of this report), and also an exploratory meta-analysis of cinacalcet studies.

3.5.1 Quality assessment of the EVOLVE trial

The company provides an assessment of the EVOLVE trial[18] in CS Appendix 4, using the Cochrane Collaboration 2011 risk of bias tool.[26] Table 14 shows the company's and the ERG's quality assessment of the trial. The ERG's quality assessment mostly agrees with that of the company. However, it is unclear if there was any bias in relation to blinding in patients and caregivers, as nearly a quarter of patients (23%) in the placebo group were provided off-protocol commercial cinacalcet and it is unclear if patients and caregivers were unblinded to treatment assignment in these instances.[27] The ERG therefore disagrees with the company's judgement of there being a low risk bias in the blinding of patients and caregivers. The CS's table contains a numerical summary of bias at the end, which contains a 1 against the number of 'unclear' risk of bias judgements, but this does not appear to refer to anything in the table or the appraisal in the CS appendix. Overall the ERG is of the opinion that the EVOLVE trial is a well conducted study and is informative for the economic evaluation in the CS.

Table 14 Company and ERG assessment of the EVOLVE trial

Bias	Domain	CS comments:	CS	ERG	ERG comments:
Selection bias	**Random sequence generation**	Randomisation was by interactive voice response system. Randomisation was stratified according to country and	Low risk	Low risk	
	Allocation concealment		Low risk	Low risk	

Bias	Domain	CS comments:	CS	ERG	ERG comments:
		diabetes status with the use of fixed blocks. The sponsor, investigators, and patients were unaware of the treatment assignments.			
Performance bias	**Blinding of participants**	Double-blind	Low risk	Unclear risk	Nearly a quarter (23%) of patients in the placebo group were provided off-protocol commercial cinacalcet [27],and it is unclear if this unblinded them to treatment assignment
	Blinding of caregivers	Double-blind	Low risk	Unclear risk	Nearly a quarter (23%) of patients in the placebo group were provided off-protocol commercial cinacalcet, [27] and it is therefore unclear if the caregivers were unblinded to treatment assignment
Detection bias	**Blinding of outcome assessment**	All primary and secondary end points were adjudicated by a blinded independent clinical-events classification group	Low risk	Low risk	
Attrition bias	**Incomplete outcome data**	All patients appeared to be accounted for appropriately in the analysis. 93% completed study follow up. Loss to follow-up was low at 3%	Low risk	Low risk	
Reporting bias	**Selective reporting**	Data were reported for all outcomes listed as assessed in the methods	Low risk	Low risk	
Other bias		Imbalance in age of patients randomised to each arm. High levels of drop out in both arms. Slower accrual of events than anticipated, trial extension required.	High risk of bias in primary unadjusted ITT based analysis	High risk for primary unadjusted ITT analysis	The CS states the risk of bias was due to a chance imbalance in age between the arms, a higher than expected incidence of treatment discontinuation in both arms and a high proportion of placebo recipients receiving commercially available

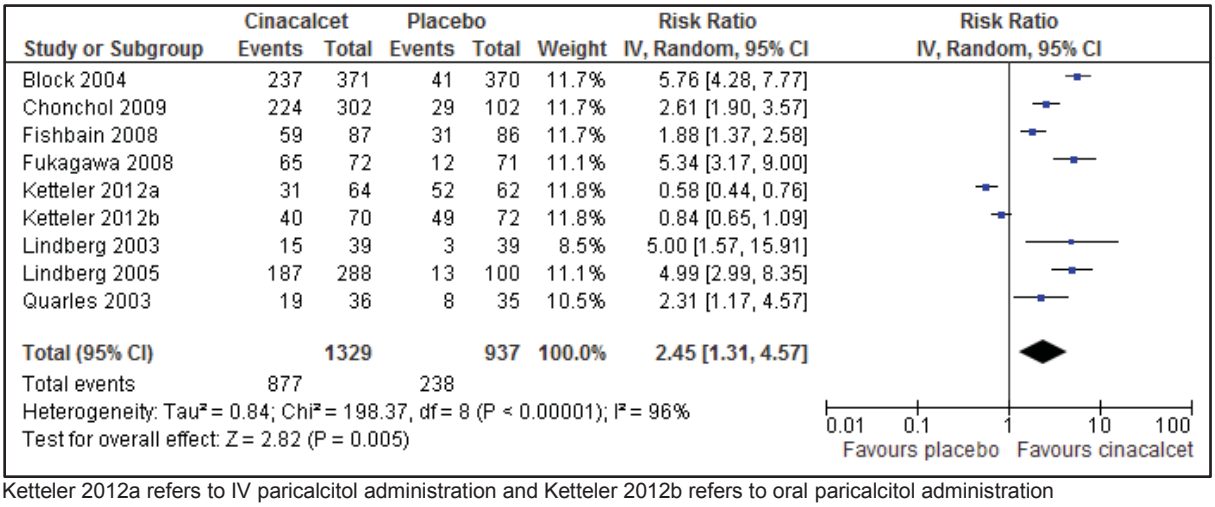
Bias	Domain	CS comments:	CS	ERG	ERG comments:
		High levels of use of commercial cinacalcet in placebo arm.			cinacalcet before the occurrence of a primary event (CS p. 33). The CS implies these factors may have biased findings unfavourably for cinacalcet (CS p. 33 and CS Appendix 4, pp. 54 to 55).
Summary of risk of bias		**Number of criteria "high risk of bias"**	**1**	**1**	
		Number of criteria "low risk of bias"	**7**	**5**	
		Number of criteria "unclear risk of bias"	**0**	**2**	

3.5.2 ERG meta-analysis of cinacalcet trials

As will be discussed in section 4.3.4 of this report, the company uses clinical effectiveness estimates of placebo, cinacalcet and etelcalcetide in their model taken from the three pivotal RCTs included in their SLR. We stated earlier (section 3.1.7) that there are alternative clinical trial-based estimates of cinacalcet and placebo available that could also be incorporated in the model. A Cochrane systematic review of calcimimetics for secondary hyperparathyroidism in CKD[21] includes 18 RCTs comparing cinacalcet plus conventional therapy (e.g. PB/VD) to conventional therapy. However, that review did not meta-analyse studies using the outcome of >30% reduction in mean PTH from baseline, the main outcome used in the economic analysis. The ERG therefore conducted an exploratory meta-analysis of this outcome, based on RCTs comparing cinacalcet plus conventional therapy (e.g. PB/VD) to conventional therapy, using data available from studies in the Cochrane systematic review to compare the response rates for cinacalcet and conventional therapy used in the model against the wider evidence base.

The ERG was able to access relevant outcome data from of eight[28-35] of the 18 studies included in the Cochrane review. The meta-analysis was performed using Cochrane Review Manager (RevMan) software, using a random effects model. In most of the studies cinacalcet was used with PB/VD, and the comparator group received placebo with PB/VD. The pooled relative risk was 2.45 (95% CI 1.31 to 4.57) favouring cinacalcet (Figure 1). There was statistically significant heterogeneity (I^2 = 96%). Whilst there was consistency in the direction of effects a notable exception is the study by Ketteler and colleagues.[32] This study randomised patients to receive either cinacalcet and low dose vitamin D (+PB) or the

vitamin D compound paricalcitol (+PB), then stratified them to receive treatments either intravenously or orally (NB. we have analysed these separately in the meta-analysis. In Figure 1 Ketteler 2012a refers to IV paricalcitol administration and Ketteler 2012b refers to oral paricalcitol administration). The results of this study show an effect in favour of paricalcitol (+PB), counter to all of the other studies in the meta-analysis. The Cochrane review does not discuss why this might be the case. However, removal of this study from the meta-analysis does not significantly change the overall estimate of effect, or substantially reduce the statistical heterogeneity observed (RR 3.56, 95% CI 2.37 to 5.36; I^2 = 83%).



Ketteler 2012a refers to IV paricalcitol administration and Ketteler 2012b refers to oral paricalcitol administration

Figure 1 – Meta-analysis of cinacalcet studies

Caution is advised in the interpretation of this exploratory meta-analysis as the ERG has not formally assessed the risk of bias of the included studies (though the Cochrane review judged that most of the evidence was of moderate to high quality, based on GRADE criteria). There are also likely to be differences between the trials in patient characteristics and treatment regimens (e.g. duration, dose etc). Furthermore, the Cochrane review which the studies were drawn from was last updated in 2014 (search current to February 2013) and newer studies may have been published since then. It is also noteworthy that the EVOLVE trial is not included in the analysis as it did not report the outcome of >30% reduction in mean PTH from baseline. Given that this is the largest published RCT of cinacalcet its inclusion would have resulted in a more complete set of studies. The results of this meta-analysis are used to inform the ERG cost-effectiveness analyses (see section 4.4).

4 COST EFFECTIVENESS

4.1 Overview of economic evidence

The company's submission to NICE includes:

i) A systematic review of published economic evaluations (cost-effectiveness, cost-utility and cost-benefit studies) of treatments for SHPT in adult patients receiving haemodialysis for CKD: see CS section 5.1 (page 83) and 4.2 below.

ii) A report of an economic evaluation undertaken for the NICE STA process. The company developed an economic model to estimate the cost effectiveness of etelcalcetide in addition to standard therapy (PB/VD) compared with cinacalcet in addition to PB/VD, or compared with PB/VD alone for treatment of SHPT in adult patients receiving haemodialysis for CKD: see CS section 5.2 (page 89) and ERG report section 4.3 below (page 77).

4.2 Company's review of published economic evaluations

The search for relevant economic evaluations was integrated in a wider search that also included studies reporting: health related quality of life (HRQoL) or utility data, CS section 5.3.1 (page 107) and ERG report 4.3.5.4 (page 106); and cost and resource use studies, CS section 5.4.1 (page 113) and ERG report section 4.3.5.5 (page 109).

The search strategy was appropriately constructed: see section 3.1.1 above for our full critique. Inclusion criteria for the company's systematic review are presented in Table 15. The population and interventions were in line with the NICE scope and the inclusion criteria were broad enough to give good confidence that all relevant studies would be captured. The reported screening and data extraction processes were appropriate.

None of the 16 CEAs identified evaluated etelcalcetide: they assessed a range of other treatments for SHPT including cinacalcet, vitamin D analogues (alfacalcidol, calcitriol and paricalcitol), standard care (PB/VD) and parathyroidectomy (PTx). The studies were published between 2006 and 2015, with only one UK study.[2] Most used Markov-type models, with health states defined by different combinations of SHPT control (e.g. levels of PTH), adverse events (cardiovascular events, fractures or surgical complications) or treatments (parathyroidectomy, transplantation) and mortality.

Table 15 Inclusion criteria for systematic review of economic evaluations

Criteria	Inclusion criteria
Population	Adult (≥ 18 years) CKD patients with SHPT undergoing haemodialysis.
Intervention & Comparators	• Etelcalcetide administered in line with its anticipated licensed dose • Cinacalcet • PB/VD (which may include one or more of the following - calcitriol, other vitamin D analogues, and/or phosphate binders) • Placebo as a comparator
Outcomes	**Economic Evaluations**, at least one of the following: • Cost and incremental cost • Quality adjusted life years (QALYs) and incremental QALYs • Incremental cost-effectiveness ratio (ICER) • Probability of being cost-effective at a given threshold (as reported). **Health-related quality of life and utility** • Health related quality of life (HRQoL) (including SF-36 or any instrument for which there is evidence that it can be mapped to health state utilities) • Health state utilities (including EQ-5D, SF-6D and • any directly elicited utilities using either time trade-off (TTO) or standard gamble (SG)) **Cost and resource** • Direct costs (including health care and social care) • Indirect costs (including time off work due to sickness and disability) • Patient cost (including any out of pocket expenses)
Study design	**Economic Evaluations**, eligible studies included: • Cost-effectiveness analyses (CEAs) • Cost-benefit analysis (CBA) • Cost-utility analysis (CUA) **Health-related quality of life and utility** • HRQoL or preference elicitation studies **Cost and resource** • Cost of illness studies

Reproduced from CS Table 27, page 84.

The company concluded that although none of the identified studies investigated the cost-effectiveness of etelcalcetide, they were useful for informing the development of the *de novo* model. Three studies in particular were used as key resources to inform the model design:

- The **PenTAG HTA** provided the most relevant analyses to address the decision problem, as it had been developed to inform the 2007 NICE technology appraisal of cinacalcet (TA117). (Garside and colleagues, 2007).[2] Some assumptions and data sources from this analysis were used in the company's model.
- **Belozeroff and colleagues** based their analysis on the EVOLVE trial, which the company considered to be the best available source of long-term outcome data on calcimimetics.[36] EVOLVE was a randomised placebo-controlled trial of cinacalcet, funded by Amgen.[18] The Belozeroff economic analysis was also funded by Amgen, and the submitted company model closely follows its model structure and many parameter sources.
- Additionally, the economic evaluation by **Eandi and colleagues**. was used to inform a scenario analyses to explore the long-term impact of calcimimetic treatment, as the publication presented a risk-prediction equation that was used to model clinical outcomes based on reductions in biomarker levels.[37]

In summary, the ERG considers that the company's systematic review of economic evaluations was well conducted and clearly reported. The review did not identify any studies that are directly relevant to the current decision problem, as no published studies have evaluated etelcalcetide for treatment of SHPT. The company made selective use of published economic evaluations of cinacalcet to inform the design and parameterisation of its economic model. The appropriateness of these data and assumptions are discussed below.

4.3 Company's submitted economic model

4.3.1 The reference case

The ERG assessment of the company's submitted model in relation to the NICE reference case is summarised in Table 16.

Table 16 NICE reference case requirements

NICE reference case requirements:	Included in submission	Comment
Decision problem: As per the scope developed by NICE	No	The population with refractory SHPT for whom cinacalcet is a comparator was not modelled (see 4.3.2 and 4.3.2.3).
Comparator: As listed in the scope developed by NICE	Yes	
Perspective on costs: NHS and PSS	No	Only acute NHS costs were included; non-acute and PSS costs are omitted (see 4.3.5.5).
Evidence on resource use and costs: Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes	Resource use and unit costs were appropriate for the NHS, but non-acute and PSS costs were omitted.
Perspective on outcomes: All direct health effects, whether for patients or, when relevant, carers	Yes	
Type of economic evaluation: Cost utility analysis with fully incremental analysis	No	The company conducted a CUA, but did not present a full incremental analysis (see 4.3.2.3).
Synthesis of evidence on outcomes: Based on a systematic review	No	Effect on PTH from naïve pooling of 3 etelcalcetide trials. Other studies of cinacalcet vs PB/VD were not included (see 4.3.5.1).
Time horizon: Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes	
Measuring and valuing health effects: Health effect should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life.	Yes	
Source of data for measurement of health-related quality of life: Reported directly by patients and/or carers.	Yes	EQ-5D data from EVOLVE study, assumed equivalent for cinacalcet and etelcalcetide (see 4.3.5.4).
Source of preference data: Representative sample of the UK population	Yes	
Equity considerations: An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit.	Yes	
Discount rate: 3.5% pa for costs and health effects	Yes	Scenario analyses for 0% and 6% discount rates.
Notes: ? = uncertain; N/A=not applicable		

4.3.2 The decision problem

4.3.2.1 Base case population

The population in the de novo economic model matches that of the scope and that specified in the SmPC indication for etelcalcetide: adults (≥18 years) with SHPT and CKD, receiving haemodialysis (see section 2.3, page 25 above). Effectiveness evidence used in the economic model was also consistent with this broad target population. The model relies on four key trials: 210120229 and 210120230 (placebo-controlled trials of etelcalcetide); 210120360 (head-to-head comparison of cinacalcet and etelcalcetide); and the EVOLVE trial[18] (cinacalcet vs. placebo), which was the main source of evidence for long-term effects and utilities. Baseline characteristics of the study participants are summarised in Table 17.

Populations were similar across the four trials, although there were some differences by age, region and ethnicity, and at study entry patients in the cinacalcet-controlled trial had higher mean PTH and fewer were taking phosphate binders than in the other studies. The company argued that, as the results in the three etelcalcetide trials were robust to subgroup analyses, "the efficacy of etelcalcetide is therefore consistent, regardless of the baseline demographics, SHPT severity, and prior use of cinacalcet" (CS page 67). They therefore chose to align the specific modelled population with that in the EVOLVE study, to provide consistency with the long-term clinical outcomes (CS section 5.2.1, page 89). In particular, they modelled a cohort aged 55 years with CKD, treated with maintenance haemodialysis 3 times a week for 3 or more months, with initial PTH levels of 300 pg/mL (31.8 pmol/L) or more (median approximately 700 pg/mL; 74.2 pmol/L).

We agree with the decision to align the modelled population with EVOLVE, as this is the primary source of data for estimation of long-term outcomes in the model. The initial starting age of 55 is also consistent with the Garside and colleagues HTA conducted for the NICE technology appraisal of cinacalcet.[2] However, there are two important limitations with the company's modelled population for this current appraisal.

Table 17. Baseline characteristics of participants in main clinical trials

	Study 20120229[12]		Study 20120230[13]		Study 20120360[14]		EVOLVE[18]	
Mean (SD) or n (%)	Placebo (N = 254)	Etelcalcetide (N = 254)	Placebo (N = 260)	Etelcalcetide (N = 255)	Cinacalcet (N = 343)	Etelcalcetide (N = 340)	Cinacalcet (N = 1948)	Placebo (N = 1935)
Age, mean (SD) years	57 (14.5)	58 (14.6)	59 (13.9)	58 (14.6)	55 (14.4)	54 (13.8)	55 (14.5)	54 (14.2)
Women	114 (45)	103 (41)	95 (37)	93 (36)	151 (44)	148 (44)	809 (42)	769 (40)
Ethnicity								
Black	69 (27)	72 (28)	80 (31)	64 (25)	52 (15)	54 (16)	409 (21)	428 (22)
White	175 (69)	173 (68)	169 (65)	163 (64)	277 (81)	261 (77)	1124 (58)	1116 (58)
Other or missing	10 (4)	9 (4)	11 (4)	28 (11)	14 (4)	25 (7)	415 (21)	391 (20)
Region								
North America	129 (51)	132 (52)	150 (58)	146 (57)	105 (31)	103 (30)	788 (40)	788 (41)
Europe [a]	117 (46)	115 (45)	102 (39)	100 (39)	230 (67)	230 (68)	741 (38)	730 (38)
Australia/ New Zealand	8 (3)	7 (3)	8 (3)	9 (4)	8 (2)	7 (2)	74 (4)	75 (4)
Latin America							345 (18)	342 (18)
Dialysis vintage								
0 to ≤ 1 year	35 (14)	29 (11)	32 (12)	31 (12)	48 (14)	46 (14)	45.4 months (median)	45.1 months (median)
> 1 to ≤ 5 years	124 (49)	120 (47)	121 (47)	127 (50)	146 (43)	149 (44)		
> 5 years	95 (37)	105 (41)	107 (41)	97 (38)	149 (43)	145 (43)		
PTH, pg/mL	820 (386) [706]	849 (520) [706]	852 (552) [726]	845 (464) [740]	1139 (707) [930]	1092 (623) [900]	[redacted] [695]	[redacted] [690]
cCa, mg/dL	9.61 (0.60)	9.65 (0.66)	9.70 (0.69)	9.63 (0.65)	9.58 (0.67)	9.67 (0.71)	[redacted]	[redacted]
P, mg/dL	5.78 (1.60)	5.95 (1.59)	5.83 (1.45)	5.76 (1.60)	5.82 (1.58)	5.81 (1.69)	[redacted]	[redacted]
Medication use								
Vitamin D sterols	185 (73)	191 (75)	160 (62)	160 (63)	206 (60)	200 (59)	1136 (58)	1124 (58)
Phosphate binders	213 (84)	216 (85)	220 (85)	202 (79)	165 (48)	172 (51)	1711 (88)	1722 (89)
Prior cinacalcet use	109 (43)	103 (41)	126 (48)	137 (54)	92 (27)	80 (24)		
Medical history								
CAD PVD MI CHF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bone fracture	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parathyroidectomy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

cCa, corrected calcium; P, phosphorus; PTH, parathyroid hormone; SD, standard deviation; CAD coronary artery disease; PVD peripheral vascular disease; MI myocardial infarction.
[a] includes Austria, Belgium, Czech Republic, Denmark, Estonia, France, Germany, Greece, Hungary, Israel, Italy, Latvia, Lithuania, Netherlands, Poland, Portugal, Russian Federation, Spain, Sweden, Switzerland, Turkey, United Kingdom

Source: Adapted from Table 14 CS page 58.

Firstly, although the modelled population is consistent with the scope and SmPC indication for etelcalcetide, cinacalcet is recommended by NICE for a narrower usage: for patients with SHPT who are refractory to standard therapy (PB/VD) and contraindicated to surgical

parathyroidectomy, with 'very uncontrolled' PTH levels >800pg/mL (84.8 pmol/L) and normal or high adjusted serum calcium level.[6] As the company noted, the scope for this current appraisal merely states that cinacalcet is a comparator for people with 'refractory SHPT'. The company thus presented results for two pairwise comparisons: etelcalcetide vs. cinacalcet for patients with refractory SHPT and etelcalcetide vs. PB/VD for the 'broad licensed population'. However, in the model both comparisons were based on the same evidence base and did not differentiate between patients who were or were not refractory to standard therapy (see discussion in sections 2.3, 3.1.2, 3.1.3 and 3.4 above).

A second limitation of the CS modelled population is that all of the patients are assumed to enter the model in the 'event-free' state, without a previous CVD event or bone fracture (see section 4.3.3 below). However, the evidence base is not restricted to this group. [redacted] The transition probabilities were calculated from EVOLVE and thus implicitly account for patients with prior events. However, the QALY loss associated with a first non-fatal CV event or fracture in the model is greater than that for subsequent events: the first event incurs a three-month utility loss for the acute period followed by an ongoing utility loss over the patient's lifetime, while a second event only incurs the acute period utility loss (see 4.4.2.2, page 134).

4.3.2.2 Subgroup analysis

The scope did not specify any subgroups for the appraisal, and the CS did not present cost-effectiveness for any subgroups, although the company did vary the initial age of the cohort in scenario analysis (from 45 to 65 years). This analysis reflected the rising mortality risk with age, but absolute risks of bone fracture and non-fatal CV events and the effects of treatment were assumed to be constant with age. The company justified the assumption of constant treatment effects by citing the results of the subgroup analyses of the three pivotal etelcalcetide trials (see section 3.3.5 page 60 above, and CS section 4.8 page 67-69).

However, we note the company's base case analysis depends on extrapolation of long-term event rates using data from EVOLVE. Although most subgroup analyses of the EVOLVE data did not show any difference in the relative effects of treatment, there was a significant interaction by age: patients aged 65 or older had a larger risk reduction with cinacalcet than

younger patients.[18] Thus, the company's scenario analysis may not adequately reflect true variation in cost-effectiveness by age.

Furthermore, as noted above (section 3.3.5, page 60), we urge caution in interpreting the subgroup analyses of the trial results, because they are likely to have low power. We also note that even when relative treatment effects are constant across patient subgroups, one would expect greater absolute benefits from calcimimetic treatment for patients with a lower propensity to achieve SHPT control with standard treatment: e.g. as for patients who have previously not responded to PB/VD alone. Similarly, with constant relative effects, absolute benefits from calcimimetic treatment would be greater for patients who are at higher background risk of CV or fracture events: e.g. as for patients who have already had a cardiovascular event or bone fracture. We consider the potential for additional subgroup analysis to explore the impact of such differences in section 4.4.2 page 132.

4.3.2.3 Intervention and comparators

The company states that the comparators used in the model were established clinical practice without calcimimetics and, for patients with refractory SHPT, cinacalcet (CS 5.2.3 page 93). This corresponds to the decision problem outlined in the NICE scope.

As previously noted, cinacalcet is currently only recommended by NICE for use in patients refractory to standard therapy, and with additional restrictions including 'very uncontrolled' PTH (exceeding 800 pg/mL; 84.8 pmol/L) and contraindication to surgical parathyroidectomy.[6] However, whilst cinacalcet is not currently recommended by NICE for as wide an indication as etelcalcetide's license, it may be used in a similar fashion in practice (see section 2.2 page 21 above). It is important to note that cinacalcet's license and its use in other countries, from where much of the data for its efficacy is derived, does cover this broader usage. We have also noted that evidence on etelcalcetide use in the 'PB/VD naïve' and 'PB/VD refractory' populations is lacking, and that in practice, the company model relies on the same evidence base for these two groups.

The similarity of the populations across the clinical trials, and the gaps between the evidence base and the NICE scope for etelcalcetide and the recommended usage for cinacalcet has implications for how the comparators are applied in the model. The company takes the position that only pairwise comparisons should be made:

- Etelcalcetide vs PB/VD for patients for the 'broad licensed indication'.
- Etelcalcetide vs cinacalcet for patients with refractory SHPT.

This approach is only legitimate if the two populations are mutually exclusive. However, the company model assumed the same characteristics and the same background risks for both populations. This can be seen, as modelled outcomes (life years and QALYs) were identical for etelcalcetide in the 'broad licensed indication' and 'refractory SHPT' populations (e.g. see CS Tables 58 to 61, p126). If the patients in the two comparisons are the same, or if there is an overlap of these populations, then a full incremental analyses comparing all three treatments would be feasible and appropriate. We consider the potential for differentiating between the refractory and non-refractory sub-populations, and conducting appropriate incremental analyses in section 4.4.2.1.

It might also be appropriate to consider sequences of treatment. There is a paucity of evidence for the 'PB/VD refractory' subgroup, as discussed above. However, we note that the model evaluates converse sequence, assuming that patients continue with PB/VD alone after discontinuation of either cinacalcet or etelcalcetide. It is also possible to model a sequence of calcimimetic treatment, with an initial trial of cinacalcet followed by etelcalcetide on discontinuation. [redacted]. It is even less clear whether the converse is true, as data on the efficacy of cinacalcet following etelcalcetide failure are not available. We explore modelling of calcimimetic sequencing in additional ERG analysis section 4.4.3.3.

4.3.3 Model structure and assumptions

The company presents a Markov-type health state transition model. The basic structure (illustrated in Figure 2) has four health states, reflecting the three principal adverse health events related to SHPT: all-cause mortality; non-fatal clinical fractures (Fx); and non-fatal cardiovascular (CV) events (including myocardial infarction, hospitalisation for unstable angina, heart failure and peripheral arterial disease). Note that stroke was not included in the definition of CV event, as it was not included in the primary composite outcome for EVOLVE, or as a secondary outcome in the etelcalcetide trials. However, the published economic evaluation based on the EVOLVE trial did include stroke in a scenario analysis.[36]

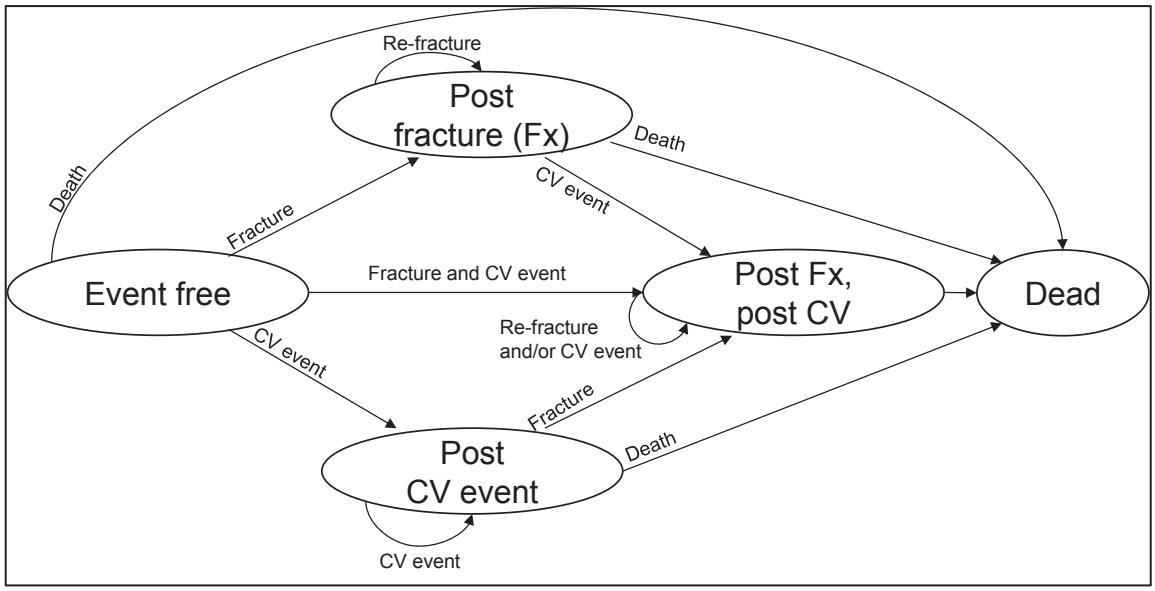


Figure 2. Basic Markov model structure
Reproduced from CS 5.2.2 Page 91

The model estimates health outcomes (Fx and CV events, life years and QALYs) and associated costs for a cohort of patients with SHPT receiving haemodialysis for CKD, from a starting age of 55 years up to a maximum age of 105. Patients are assumed to start in the 'event-free' health state, not having experienced a fracture or CV event. In each three-month cycle, patients may experience one or both of the non-fatal events (CV and/or Fx), they may die, or they may remain in the event-free state. After experiencing a first non-fatal Fx or CV event, patients move to the respective post-event states; post-Fx or post-CV. Patients can have both an Fx and CV event during the same three-month period, in which case they transfer to the post-Fx/post-CV state. After one non-fatal event, patients are at higher risk of recurrence of the same type of event. CV and fracture risks are held constant with age, but mortality risks do rise as patients age within the model.

The basic model structure is repeated for the three modelled treatment options: etelcalcetide, cinacalcet and PB/VD (Figure 3). Thus the full model contains 13 health states: the four non-fatal states for each of the three treatments, and the dead state. After discontinuation of a calcimimetic, it is assumed that patients switch to treatment with PB/VD only. In the CS, the strategies are compared in a pairwise fashion: etelcalcetide versus PB/VD alone; and etelcalcetide versus cinacalcet. In the ERG analysis, we also included a sequenced calcimimetic strategy (cinacalcet followed by etelcalcetide, and made full incremental, as well as pairwise comparisons (4.4.3 page 136).

Parathyroidectomy (PTx) was included in the model as an incident event, rather than as a health state or treatment. This limits the ability of the model to capture any long-term health benefits or harms or any costs or savings related to PTx. For each three-month period, a certain proportion of patients in the event-free, post-CV, post-Fx and post-Fx/post-CV states are assumed to undergo PTx. Members of the cohort can have more than one PTx, which reflects experience in the clinical trials, as a small number of patients had a second PTx after having a portion of parathyroid removed.[36] But the model only applies costs and disutility associated with the surgical procedure in the first three-month period, so that PTx is assumed to always increase costs and decrease QALYs. This favours etelcalcetide and to a lesser extent cinacalcet, because they are estimated to reduce PTx incidence compared with PB/VD. The company justified this approach by arguing that reliable data on long-term effects are not available (CS p91).[39] However, omitting any long-term benefits or cost savings is an extreme assumption that is likely to bias the results. The company conducted a scenario analysis excluding PTx, but did not test the effect of assuming a beneficial effect or cost savings from PTx. For comparison, the published economic evaluation based on the EVOLVE data by Belozeroff et al[36] included a scenario analysis in which PTx was assumed to have a beneficial effect, although the method of analysis was not clearly explained. Assuming a 20% reduction in events following PTx increased the estimated ICER for cinacalcet compared with PB/VD alone from $79,562 to $88,564 per QALY gained.

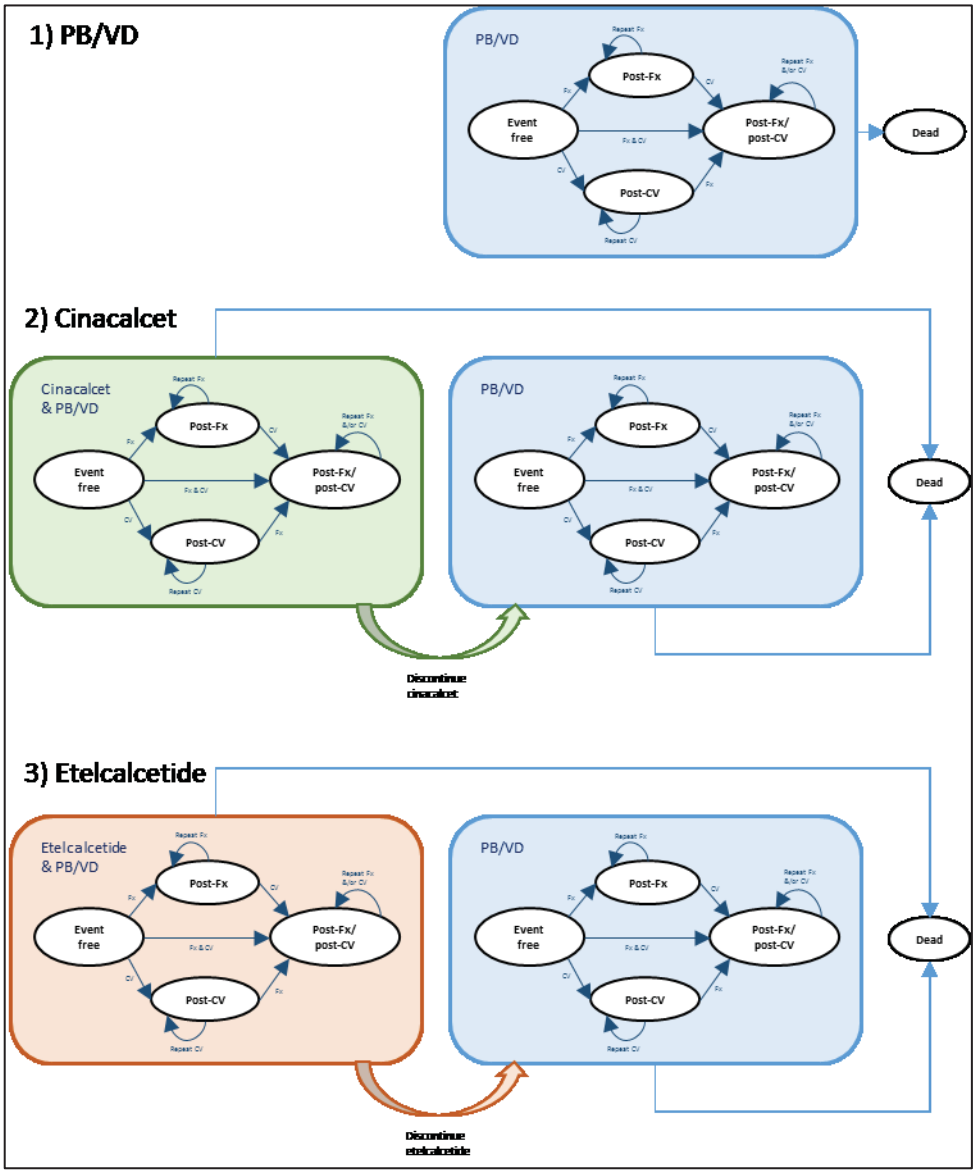


Figure 3. Treatment strategies modelled in CS

Transition probabilities under PB/VD were estimated from the placebo arm of the EVOLVE trial or from observational sources (see section 4.3.5.1 below). These background event rates were adjusted for etelcalcetide and cinacalcet treatment strategies using relative hazards estimated from the clinical evidence base (section 4.3.5.2). There were two main challenges in estimating the treatment effects: firstly, the etelcalcetide trials (20120229, 20120230 and 20120360) only measured intermediate outcomes (% of patients achieving >30% reduction in PTH) rather than the event rates needed for the model (mortality, Fx, CV and PTx incidence);[12-14] and secondly, the explicit modelling of calcimimetic discontinuation, as illustrated in Figure 3, requires estimates of discontinuation rates and adjustment of treatment effects. Discontinuation is modelled using a parametric survival curve fitted to EVOLVE data, and assumed to be the same for etelcalcetide and cinacalcet. Methods used for extrapolation and adjustment for non-adherence are described and critiqued below (section 4.3.5.3).

QALYs are calculated by weighting time spent in the non-fatal states according to estimated utilities for those states. The utility for the event-free state is an estimate for patients on haemodialysis, and does not vary by age or by the length of time spent on dialysis. Utility decrements were applied for the first three-months after an incident fracture or CV event, and then a lower decrement is applied for further time spent in the post-event state. The model does not include any explicit modelling of treatment-related adverse effects, which the company argues is justified due to "the mild nature and minor differences between the treatment groups" (CS 5.2.11, page 103). Utility parameters are discussed in more detail in section 4.3.5.4.

The model includes costs for time spent on drug treatment, including etelcalcetide, cinacalcet, phosphate binders and vitamin D, and costs for routine SHPT monitoring (with a fixed number of PTH, Ca and P tests per quarter). Each incident event (Fx, CV and PTx) event is assumed to incur a one-off cost, reflecting the cost of acute hospitalisation during the first three-month period (see 4.3.5.5 below). The model does not include ongoing healthcare costs for patients in the post-event states, unless they experience a repeat event, in which case the acute cost is applied again. Thus hospital outpatient follow up and treatment, primary and community health care, and social care associated with acute events are not included. This will underestimate the savings from avoiding cardiovascular events and bone fractures through better SHPT control, although cost-effectiveness results were not sensitive to event costs (CS section 5.7.2 p133-135).

CKD progression, changes in dialysis treatment and transplants are not modelled, and the base case model does not include dialysis costs. This is justified in the CS by the argument that the high cost of dialysis has the perverse effect of making treatments that prolong life for patients on dialysis (such as better treatment for SHPT) less cost-effective than less effective treatments of similar cost. A scenario analysis including dialysis costs is included in the CS. Whether or not to include costs not directly related to the interventions and comparators under evaluation is a controversial topic. The NICE Guide to the methods of technology appraisal recommends that costs related to the condition of interest and incurred in additional years of life gained as a result of treatment should be included in the reference-case analysis.[23] However, we suggest that in this case the 'condition of interest' is SHPT rather than CKD, so that it is reasonable to exclude dialysis costs in the base case analysis.

The CS includes a table setting out the justification for a number of analytical assumptions (CS Table 30, page 92). The model uses a lifetime time horizon, which is appropriate given the impact of SHPT on life expectancy and events with lasting effects on utility. A three-month time cycle is used, which offers a reasonable compromise between model practicality and capturing recurrent CV events and fractures: the model allows up to four of each type of event to occur within a year. A half-cycle correction is applied correctly.

4.3.4 Methods to estimate effects

4.3.4.1 Overview

In total, the company presented six methods for estimating treatment effects in their economic model, as summarised in Table 18 (CS section 5.2.5 and company response to clarification question B2). Here we present an overview of these methods. Further details and critique are provided in the following subsections.

Table 18. Methods to estimate treatment effects

EXTRAPOLATION FROM EVOLVE		
A) Lag-censored (base case)	Cinacalcet HRs estimated from EVOLVE (adjusted for non-adherence)	Etelcalcetide HRs estimated assuming log-linear relationship with primary outcome of etelcalcetide trials
B) ITT disaggregated		
C) RPSFTM adjusted		
D) IPE adjusted		
EANDI RISK PREDICTION SCHEME		
E) Censored	Biomarker data from etelcalcetide trials	Extrapolated to estimate HRs using relative risks from observational data
F) ITT disaggregated		

Treatment effectiveness is measured in the model by reduced incidence of SHPT-related adverse events: mortality, CV, Fx and PTx. Incidence rates for these events under standard treatment (PB/VD alone) were estimated from various data sources (section 4.3.5.1). These background event rates were then adjusted to estimate effects under calcimimetic treatment.

In the company's base case, event rates for cinacalcet were generated by adjusting the background rates by hazard ratios from the EVOLVE trial.[18] EVOLVE was a large (N = 3,883), international trial of cinacalcet compared with PB/VD alone in patients with SHPT on dialysis with follow up to 64 months.[18] As discussed above (section 4.3.2.1), the EVOLVE population is consistent with the proposed indication for etelcalcetide and similar to the populations in the key etelcalcetide trials, although with some differences. The EVOLVE trial was generally well-conducted (see Table 14 page 70 above), but had two important potential sources of bias: an age imbalance between the arms; and high rates of treatment discontinuation and uptake of commercially available cinacalcet.[40] Despite these drawbacks, we consider that the EVOLVE trial is the best-available source of evidence on long-term calcimimetic outcomes in an SHPT population, and an appropriate foundation for the economic model.

The primary outcome in the etelcalcetide trials (20120229, 20120230, 220120360)[12-14] was the percentage of patients achieving >30% reduction in mean PTH. These trials were not powered to detect incidence of the modelled events, so it is necessary to use some form of

extrapolation to estimate the effect of etelcalcetide for use in the model. In their base case, the company used results from EVOLVE, assuming a linear relationship between the proportion of patients achieving >30% reduction in mean PTH and the log of the HRs for the events of interest. They also conducted scenario analysis using a risk-prediction algorithm reported by Eandi and colleagues[37] to estimate event risks from biomarker data (PTH, calcium and phosphate) for participants in the etelcalcetide trials. The ERG view is that the EVOLVE-based method of extrapolation is preferable to the Eandi approach, due to a lack of evidence over the validity of the latter. However, we do have criticisms of the way in which the company extrapolated the EVOLVE data, which are discussed further below.

A complication for both methods of extrapolation relates to non-adherence and treatment switching. EVOLVE in particular suffered from high rates of discontinuation of the study drug and uptake of other treatments over the long follow up. The CS presented two methods to adjust for non-adherence: A) lag-censoring, in which patients (in both arms) were censored from the analysis six months after discontinuing the study drug (the company's preferred base case); and B) a 'disaggregation' method in which ITT estimates were adjusted to account for time spent on and off treatment. In response to a clarification question, the company presented two additional sets of results using formal methods to adjust EVOLVE data for non-adherence: C) the Rank Preserving Structural Failure Time Model (RPSFTM); and D) the Iterative Parameter Estimation (IPE) method.[41] They did also attempt to use another method: Inverse Probability of Censoring Weights (IPCW). However, they could not obtain estimates for all of the parameters required for the model, and so we do not discuss this further. Non-adherence was also an issue in the etelcalcetide trials (CS Table 13, page 53), and the company presented two methods of adjusting for this: E) simple censoring of patients on discontinuation of the allocated study treatment; and F) the same ITT disaggregation method used for EVOLVE.

The following sections give a description and critique of these methods; starting with the EVOLVE trial and the various methods used to correct for baseline covariates and non-adherence (section 4.3.4.2); followed by methods used to extrapolate the EVOLVE results to etelcalcetide (section 4.3.4.3); and then the Eandi method to estimate event rates using biomarker data from the etelcalcetide trials (section 4.3.4.4). We finish with a summary of the ERG position on the best methods for use in the economic model (section 4.3.4.5).

4.3.4.2 EVOLVE estimates of cinacalcet hazard ratios

The primary composite endpoint in the EVOLVE trial was time to death or first non-fatal cardiovascular event (including MI, hospitalisation for unstable angina, heart failure or peripheral vascular event). In the unadjusted ITT analysis, there was no statistically significant improvement in the primary composite endpoint (0.93 HR, 95% CI 0.85 to 1.02).[18] When the analysis was adjusted for baseline covariates, as specified in the study protocol,[38] the HR for the primary composite endpoint fell to 0.88 (95% CI 0.79 to 0.97). The best-fit multivariate model adjusted for a large number of baseline covariates [redacted]. The results of the adjusted ITT analysis for the events included in the economic model are shown in Table 19.

Non-adherence was a serious problem in EVOLVE.[40, 42] A large proportion of patients discontinued the study drug: 1,365 of 1,935 (71%) patients randomised to placebo and 1,300 of 1,948 (67%) patients randomised to cinacalcet. The duration of follow up was longer in the cinacalcet group than in the placebo group (median 21.2 months versus 17.5 months). Treatment switching was also a problem: with many patients in both cinacalcet and placebo arms starting commercially-available cinacalcet (11% and 23% respectively) or undergoing parathyroidectomy (7% and 14% respectively). Reasons for discontinuation differed between the groups.[40, 42] In the cinacalcet arm, the most frequent reasons for drop out were administrative decisions (22.1%), adverse events (15.7%) and parathyroidectomy or kidney transplant (15.7%). In the placebo arm, 19.8% of discontinuations were due to initiation of commercial cinacalcet, and 19.5% due to parathyroidectomy or kidney transplant.

The economic model portrays the discontinuation process explicitly, so it requires an estimate of the treatment effect while patients are on treatment and including any lingering effects after they stop treatment; but that is not diluted by loss of effect after patients have stopped treatment or confounded by the benefits or harms of other non-trial treatments. The company presented results that are compatible with the economic model for four methods of adjusting EVOLVE data for non-adherence (Table 19).[42] They also present some results for a fifth method, the Inverse Probability of Censoring Weights (IPCW) method. However, the sample size was too small to estimate results for the parathyroidectomy outcome, and so results were not available for all parameters needed for the model.

Table 19 EVOLVE hazard ratios with adjustments for non-adherence

	HR cinacalcet vs. placebo [95% CI]				
	ITT [2]	**Method A)** Lag-censored (*base case*) [2]	**Method B)** Disaggregated ITT [3]	**Method C)** RPSFTM [4]	**Method D)** IPE [4]
All-cause mortality	0.87 [0.78, 0.97]	0.80 [0.69, 0.91]	0.78 [0.63, 0.95]	[redacted]	[redacted]
CV event[1] (non-fatal)	0.85 [0.74, 0.97]	0.78 [0.67, 0.91]	0.76 [0.59, 0.95]	[redacted]	[redacted]
Fracture (non-fatal)	0.86 [0.72, 1.04]	0.73 [0.59, 0.92]	0.77 [0.55, 1.06]	[redacted]	[redacted]
PTx (non-fatal)	0.42 [0.34, 0.51]	0.25 [0.19, 0.33]	0.06 [0.00, 0.20]	[redacted]	[redacted]

HR, hazard ratio; CI, confidence interval; CV, cardiovascular; ITT, intention-to-treat; PTx, parathyroidectomy; RPSFTM rank-preserving structural failure time model; IPE iterative parameter estimation.

1. Myocardial infarction, unstable angina, heart failure and peripheral vascular event

2. CS Table 33. Results 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

3. CS Appendix 9 Table 95. ITT based HRs assumed to be a weighted average of HRs of persistent and non-persistent patients.

4. Company clarification response Table 5. Covariate adjustment consisting of the randomisation stratification factors (diabetes status and region), and age (> 65 vs. < 65 yrs)

Method A) Lag-censored analysis

The company pre-specified a six-month lag-censored sensitivity analysis as an attempt to balance the risks of these various potential biases. In this analysis, patients in both arms who stopped their randomised treatment were censored six months after discontinuation. The lag time of 6-months was specified in advance, based on medical expertise and previous clinical trials in the disease area show a persistent benefit from preventing vascular calcification.[42] It is these lag-censored values (adjusted for baseline covariates as explained above) that are used in the base-case economic analysis. The company stated that they favoured the lag-censored approach because of its simplicity; as it does not make such 'strong assumptions' as the other available approaches (CS section 5.2.6.2 p96-97). We agree that the lag-censoring does not require the distributional assumptions of RPSFTM and IPE (see below for discussion). However, it does require assumptions and the results may be biased if these are incorrect.

Lag censoring shares some limitations with per-protocol analysis or naïve censoring.[43] Firstly, the duration of lag is important for correctly attributing benefits and harms of treatments. In general, if the lag time is too short, premature censoring will miss some events that are related to the study treatment. Conversely, too long a lag may attribute events caused by other treatments to the study treatment. Another potential problem is that lag-censoring can unbalance the person-time of exposure between the arms: for example, if patients in one arm are more likely to stop the trial treatment or more likely to start another treatment, and if discontinuation or switching is related to the outcome of interest ('informative censoring'). Without more information on why patients switch, it is difficult to understand what the effects of lag-censoring will be.

In EVOLVE, non-trial treatments may have confounded results. Commencement of commercially-available cinacalcet in the placebo arm ('drop in') is likely to have diluted the estimated effectiveness of cinacalcet. Secondly, some patients in both arms had parathyroidectomy or kidney transplants ('co-interventions') during follow-up. These treatments might be expected to improve outcomes, again diluting the estimated benefit of cinacalcet (although we note that the effects of parathyroidectomy are uncertain). More patients received parathyroidectomy in the placebo arm than in the cinacalcet arm, and parathyroidectomy was more common in younger patients[18] Thus the use of lag censoring for patients who discontinued the study drug to receive parathyroidectomy, may have excluded more younger patients in the placebo arm.[43] However, the company did adjust the lag-censored results for age at baseline, which should have corrected for any such imbalance.

Beyond potentially making the placebo arm appear overly favourable due to switching to active treatment, lag-censoring both arms may have overestimated the effect of treatment in the cinacalcet arm.[43] When a patient in the cinacalcet arm discontinues due to an adverse event or to take commercially available cinacalcet or parathyroidectomy, this may represent a failure of cinacalcet. If we censor these patients prematurely, we will overestimate the real-world effectiveness of cinacalcet by removing the patients for whom cinacalcet did not work. The most appropriate approach for portraying the effect of treatment switching might be to only model switching in the placebo arm.[43] In this way, contamination of the placebo arm by cinacalcet or parathyroidectomy would be prevented, whilst still attributing non-compliance effects on cinacalcet to the cinacalcet arm.

Sensitivity analysis of the lag duration for the EVOLVE data had quite unpredictable results. Increasing the duration of lag from 0 to 18 months increased the HR for the primary

composite outcome from 0.79 (0.69 to 0.91) to 0.91 (0.82 to 1.00).[18] Thus there were more late events following discontinuation in the cinacalcet group than in the placebo group, reducing the apparent treatment effect as the lag time was extended. In response to a clarification question, the company replicated this analysis for the separate endpoints in the economic model. [redacted]

However, the company warned that these sensitivity analyses were not adjusted for baseline confounders. Therefore, it is difficult to draw conclusions from these analyses.

Method B) ITT persistence disaggregated

The second method reported in the CS for adjusting the EVOLVE results for non-adherence entailed disaggregation of ITT-based estimates for time when patients were 'persistent' (on-treatment) and 'non-persistent' (off-treatment) (CS Appendix 9). Persistence with cinacalcet was measured as the proportion of time when patients were under observation when they were taking cinacalcet: mean in the range 60% to 63% for the events of interest. Given the assumption that the HR equals 1 for times when patients were non-persistent, HRs could be calculated for times when patients were persistent. Effectively, this approach entails attributing all events observed during follow up to the period when patients were adherent to the allocated treatment. This approach does not take any account of confounding due to treatment switching (drop-in or drop-out of cinacalcet) or co-intervention (parathyroidectomy or transplant).

Method C) Rank Preserving Structural Failure Time Model (RPSFTM)

RPSFTM is a 'complex method' for correcting estimates of treatment effect for non-random treatment cessation or switching.[44] It is based on an accelerated failure time (AFT) model, in which it is assumed that exposure to treatment has a multiplicative effect on survival time. The method works by estimating 'counterfactual' survival times that would have been observed if patients had received no treatment, and identifying a value for the treatment effect which yields the same counterfactual time for patients in both groups.
The company appropriately applied the 'full-recensoring' to both arms to avoid informative censoring, and adjusted for randomisation stratification factors (diabetes and region) as well as age (clarification response B2).

The company argues that the RPSFTM method makes strong assumptions on survival and that its assumptions may not be plausible. The simple 'one-parameter' version of RPSFTM entails two key assumptions: i) that there is only random variation between groups at

baseline, apart from the treatment allocated; and ii) that the treatment effect per unit of time is equal for all patients, no matter when the treatment is received (the 'common treatment effect' assumption).[44] The former assumption is not true for EVOLVE, but by adjusting for covariates at baseline (notably age) the company will have mitigated the effect of imbalance between the groups at baseline. The 'common treatment effect' assumption is more problematic. As noted by Latimer et al, it is unlikely that this will ever be 'exactly true', although the real concern is whether it is likely to be 'approximately true': whether "the treatment effect received by switchers can at least be expected to be similar to the effect received by patients initially randomised to the experimental group".[44] This is difficult to assess, but if we look at the data from EVOLVE, it appears that there might be an effect of cinacalcet on efficacy in the placebo group (see Chertow and colleagues Figure S4 and S6 in the Supplementary Material).[18] In the ITT analysis, the between-group difference in PTH and calcium appear to wane over time. But with lag-censoring, there appears to be a consistent gap between the two treatments. Lag-censoring was conducted irrespective of when the switch occurred, so this would seem support the assumption of a common treatment effect

Method D) Iterative Parameter Estimation (IPE)

IPE is an extension of the RPSFTM method. It also relies on an accelerated failure time model, but differs in that an iterative procedure is used to obtain the estimate of effect. A parametric failure time model is fitted to the observed data to obtain an initial estimate of effect (in the analysis of the EVOLVE data reported by Kubo et al, a Weibull model was used.[42] This is used to estimate failure times for patients who switch treatment, and the treatment effect is estimated by comparing the estimated failure times between the groups. This process is then repeated until the new estimate is sufficiently close to the previous one. As with RPSFTM, the company applied IPE which used a full-recensoring method (to avoid informative censoring), and adjusted for diabetes, region and age. However, in this case they state that they only applied the method to the cinacalcet arm: so that uptake of cinacalcet in the placebo arm (treatment drop-in) is not accounted for. This should yield a more conservative estimate of the relative treatment effect. Like the RPSFTM method, IPE is also susceptible to bias if the 'common treatment assumption' does not hold. It also requires assumptions to fit the parametric survival function.

4.3.4.3 Extrapolation of EVOLVE efficacy to etelcalcetide

As stated, the etelcalcetide trials recorded achievement of ≥30% reduction in mean PTH over approximately six months as primary the outcome. In order to model long-term events, the company used HR estimates from EVOLVE linked to intermediate outcomes from the etelcalcetide trials. The etelcalcetide trial results used for this extrapolation are reported in Table 20. These data are from a simple pooled unadjusted analysis of the three etelcalcetide trials conducted by Stollenwerk and colleagues, which 'broke randomisation'.[22] A more appropriate method would have been to use an indirect adjusted meta-analysis method based on between-arm estimates of treatment effects from the three trials (see section 4.4.3 of this report).

Table 20 Proportion achieving ≥30% reduction of PTH in the etelcalcetide trials

	Number achieved (n)	Total number (N)	Proportion of patients (%)	Source
Etelcalcetide	612	849	72.1%	Stollenwerk et al. 2016[22]
Cinacalcet	198	343	57.7%	
Placebo	46	514	8.9%	

(CS Table 32, p. 97)

The company assumed that there was a linear relationship between the log of the HRs (as the log transformation ensures HRs between 0 and infinity) and the proportion of patients achieving a ≥30% reduction in PTH. This relationship is illustrated in Figure 4, and the resulting estimates of HRs are reported in Table 21.

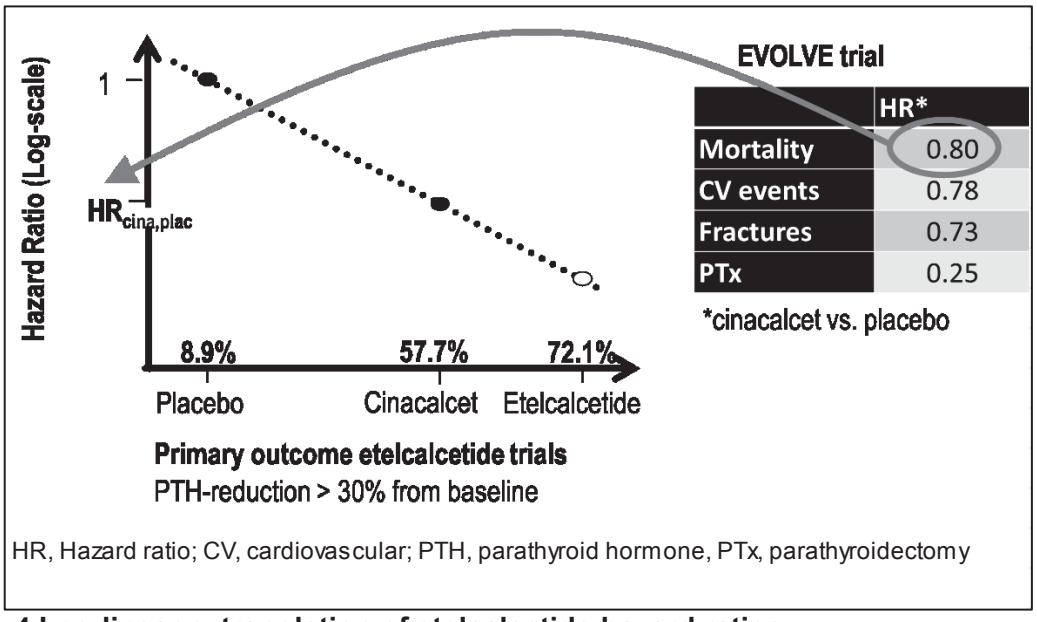


Figure 4 Log-linear extrapolation of etelcalcetide hazard ratios
(CS Figure 15, p. 98)

Table 21 Etelcalcetide HRs from log-linear extrapolation: <30% reduction in mean PTH

	Method A) Lag-censored HRs[3] [95% CI]	**Method B)** ITT based HRs[3] [95% CI]
Etelcalcetide vs. cinacalcet[2]		
All-cause mortality	0.94 [0.88, 0.98]	0.96 [0.91, 0.99]
CV events[1] (non-fatal)	0.93 [0.87, 0.98]	0.96 [0.90, 0.99]
Fractures (non-fatal)	0.91 [0.83, 0.98]	0.95 [0.89, 1.01]
parathyroidectomy (non-fatal)	0.66 [0.51, 0.81]	0.77 [0.65, 0.88]
Etelcalcetide vs. placebo[2]		
All-cause mortality	0.75 [0.62, 0.89]	0.84 [0.72, 0.96]
CV events[1] (non-fatal)	0.72 [0.59, 0.88]	0.81 [0.68, 0.96]
Fractures (non-fatal)	0.67 [0.50, 0.89]	0.82 [0.64, 1.04]
parathyroidectomy (non-fatal)	0.17 [0.11, 0.25]	0.33 [0.24, 0.43]

Source: Stollenwerk et al.2016 [22]

1. Myocardial infarction, unstable angina, heart failure and peripheral vascular event
2. Linear extrapolation on the log-hazard ratio scale linked to the primary endpoint of the etelcalcetide trials
3. 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

The assumption of a log-linear relationship between an intermediate outcome and long-term HRs is not unusual, although this is not supported with any empirical data. The method used to pool data results from the etelcalcetide trials is unconventional, and it is not clear whether the results might be sensitive to different methods of estimation, or to the use of a different intermediate outcome measure to link the etelcalcetide trial results to the EVOLVE estimates of event HRs. In response to a clarification question (B4), the company supplied an alternative extrapolation based on the achievement of a mean PTH of <=300 pg/mL (31.8 pmol/L), which yielded very different results, see Table 22. This illustrates the potential sensitivity of results to the choice of intermediate outcome, however, we note that the threshold of 300 pg/mL does not reflect current clinical target for treatment of patients with SHPT (2-9 times normal, corresponding to 130-600 pg/ml; 13.8-63.6 pmol/L).[3]

Table 22 Etelcalcetide HRs from log-linear extrapolation: <300 pg/mL mean PTH

	Method A) Lag-censored HRs[3] [95% CI]	**Method B)** ITT based HRs[3] [95% CI]
Etelcalcetide vs. cinacalcet[2]		
All-cause mortality	[redacted]	[redacted]
CV events[1] (non-fatal)	[redacted]	[redacted]
Fractures (non-fatal)	[redacted]	[redacted]
parathyroidectomy (non-fatal)	[redacted]	[redacted]
Etelcalcetide vs. placebo[2]		
All-cause mortality	[redacted]	[redacted]
CV events[1] (non-fatal)	[redacted]	[redacted]
Fractures (non-fatal)	[redacted]	[redacted]
parathyroidectomy (non-fatal)	[redacted]	[redacted]

Source: Company response to clarification question B4, Table 7, page 26

1. Myocardial infarction, unstable angina, heart failure and peripheral vascular event
2. Linear extrapolation on the log-hazard ratio scale linked to the primary endpoint of the etelcalcetide trials
3. 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

4.3.4.4 Eandi et al. risk prediction scheme

Eandi and colleagues modelled long-term efficacy of cinacalcet using a biomarker-based risk prediction scheme. They used PTH, calcium and phosphorus measurements in several observational data datasets to formulate their risk-prediction scheme.[37] In the CS model, the risk prediction equation is applied at the individual patient level to biomarker measurements from the etelcalcetide trials. In these trials, biomarker measurements were taken every two to four weeks. Any missing data were linearly interpolated. The results were calculated using two simple methods for adjusting for non-adherence: censored HRs; and ITT estimates of HRs for persistent patients, using the disaggregation method (CS Appendix 9).

Table 23 Etelcalcetide HRs based on the Eandi et al. risk prediction scheme

	Method E) Censored HRs[1] [95% CI]	**Method F)** ITT based HRs[1] [95% CI]
Etelcalcetide vs. cinacalcet		
All-cause mortality	0.94 [0.88, 1.01]	[redacted]
CV events (non-fatal)	0.99 [0.95, 1.03]	[redacted]
Fractures (non-fatal)	0.98 [0.76, 1.26]	[redacted]
Parathyroidectomy (non-fatal)	0.81 [0.63, 1.04]	[redacted]
Etelcalcetide vs. placebo		
All-cause mortality	0.78 [0.65, 0.93]	[redacted]
CV events (non-fatal)	0.94 [0.77, 1.15]	[redacted]
Fractures (non-fatal)	0.86 [0.34, 2.16]	[redacted]
Parathyroidectomy (non-fatal)	0.37 [0.15, 0.95]	[redacted]

CV, cardiovascular; HR, hazard ratio

[1] Subjects were censored at discontinuation of the investigational product

(CS Table 36 and 37, pp. 101-102)

4.3.4.5 ERG conclusions on methods for modelling treatment effects

The EVOLVE trial represents the best-available source of estimates for the long-term impact of calcimimetic treatment. The trial was large, with long follow up, but was prone to bias due to selective discontinuation of treatment, and switching of patients in the placebo arm to active treatments. Nevertheless, we consider that it represents a more satisfactory method of extrapolation than the alternative Eandi and colleagues risk prediction scheme. The latter was based on a range of observational data sources, and not supported by evidence of validation. We note, however, that the Eandi-based analyses do provide a useful check on the plausibility of the results, as they rely on different external sources of data.

A major drawback of EVOLVE was contamination from treatment switching. Thus some method of adjusting for treatment switching is needed. It is reassuring that the results were reasonably consistent across the different estimation methods presented in Table 19. As might be expected, ITT gave the least favourable results for cinacalcet – presumably because it did not adjust for dilution of effect due treatment switching in the placebo arm (to cinacalcet or parathyroidectomy). The lag-censored approach yielded relatively conservative estimates compared with the other methods of adjusting for adherence. However, the choice of time lag is essentially arbitrary. Although the decision to use a six-month lag was based on discussions with clinicians, the 'correct' lag depends on various factors that are difficult to assess: including the persistence of benefits of reduced calcification after cessation of treatment, and the timing of when patients in the placebo arm switched to cinacalcet or had parathyroidectomy. The results were relatively robust to the

duration of lag, but this in itself suggests that the lag-adjusted results are similar to simple censored, per protocol results (lag time of 0) which is generally thought to introduce a high level of bias.[44]

On theoretical grounds, we suggest that one of the more formal methods of adjustment for treatment switching should be preferred. The IPCW method did not converge for the parathyroidectomy outcome, so does not provide all parameters needed for the economic model. The remaining methods both require the assumption that there is a 'common treatment effect', regardless of when patients are treated. This might be true, but it is also possible that earlier control of PTH has greater benefits as it avoids calcification that might have long-lasting effects. The fact that IPE and RPSFTM methods estimate a 'full treatment effect' – i.e. all patients in the active arm and no patients in the control arm receive cinacalcet - is not a major drawback given the model structure. However, this does rely on the assumption that the degree of treatment adherence and cessation rates in the EVOLVE trial are reflective of clinical practice. On balance, we have chosen to use the EVOLVE IPE method in our base case analysis, but repeat our analyses with other available estimation methods: including EVOLVE ITT, and the Eandi risk prediction method.

The log-linear method used to extrapolate HRs for etelcalcetide from the EVOLVE results and etelcalcetide primary outcome, ≥30% reduction in PTH is reasonable. However, the simple pooling of data from the etelcalcetide trials is not appropriate, as it breaks randomisation. Instead, we use a simple chained indirect comparison in our base case analysis (see section 4.4.3).

4.3.5 Input parameters

The main data sources used to estimate model parameters are summarised in Table 24. Methods and parameter values are described and critiqued in the following sections.

Table 24 Summary of sources used to inform model parameters

Aspect	Data	Source
Background clinical event rates	All-cause mortality by age	Base case: Boer et al.[45] Sensitivity analysis: EVOLVE[18]
	Event rates: CV (initial and repeat); Fx (initial and repeat); & PTx	EVOLVE[18]
Treatment effects	Proportion of patients achieving >30% PTH reduction	Etelcalcetide trials[12-14]
	Hazard ratios of clinical events (CV, Fx and PTx)	Base case: EVOLVE [18] Sensitivity analysis: Eandi et al.[37]
Discontinuation	Persistence of calcimimetics (Weibull survival function)	Base case: EVOLVE[18] Sensitivity analysis: Reams et al.[46] and Urena et al.[47]
Utility	Utility for patients on dialysis and event disutilities (Fx, CV and PTx).	Briggs analysis of EVOLVE data[48]
Adverse events	Treatment related adverse events not modelled	
Resource use and costs	Drug use and unit costs	Etelcalcetide trials [12-14] BNF and Drug Tariff [49, 50]
	Monitoring frequency and costs	Cinacalcet HTA[2] Reference Costs[51]
	Costs of fractures and cardiovascular events	Reference Costs[51]
	Cost of parathyroidectomy	Pockett et al.[52]: Proton renal database, BNF and Reference costs
	Dialysis frequency and costs	Etelcalcetide trials [12-14] NICE cinacalcet HTA[2]

4.3.5.1 Background event rates

All-cause mortality

The company used background mortality rates for dialysis patients with SHPT reported in a published economic evaluation of cinacalcet.[45] Boer and colleagues estimated mortality rates from four year follow-up (2000 to 2004) of 60,000 dialysis patients with PTH of 300 pg/mL (31.8 pmol/L) or more from a large United States administrative database. The company also used mortality rates from EVOLVE for sensitivity analysis. For this, they analysed the placebo arm only, excluding patients who had received commercial cinacalcet, to reflect the 'PB/VD alone' population. At a starting age of 55 years, as per the base case model, there is limited impact of using either source, although EVOLVE gives a steeper escalation of mortality rates with age (see Table 25). The company viewed the Boer and colleagues estimates as the most appropriate source, because the observations were from before cinacalcet introduction and the population was large enough to provide mortality by specific age groups. They argued that the smaller sample size in EVOLVE meant that the estimates were less stable at the extremes of age ranges (CS Section 5.2.10).

Table 25 Background mortality rates used in the economic model

Age-group	Background mortality rate	
Source	Boer et al.[45]	EVOLVE placebo arm; Table 14-4.118.3[53]
18-34 years	0.045	[redacted]
35-44 years	0.074	[redacted]
45-54 years	0.094	[redacted]
55-64 years	0.126	[redacted]
65-74 years	0.165	[redacted]
75-84 years	0.219	[redacted]
85+ years	0.261	[redacted]

Source: CS Table 38, p. 102

On balance, we agree that the Boer and colleagues data provides the best available estimates of mortality rates for the model. Although the EVOLVE estimates might be more compatible with other parameter estimates used in the model and include patients from some European countries (though few from the UK), the Boer and colleagues estimates do appear to be more stable, and give a reasonable fit for available UK data: see Figure 5, reproduced from the 2015 UK Renal Registry report.[54] These estimates are not directly applicable to the model, as they include patients without SHPT, and some patients on cinacalcet. Nevertheless, it is reassuring that these results are broadly consistent. In particular, we note that the registry data for patients in England are similar to the Boer and

colleagues data, rising to around 300 deaths per 1,000 person years for patients aged 85 and over.

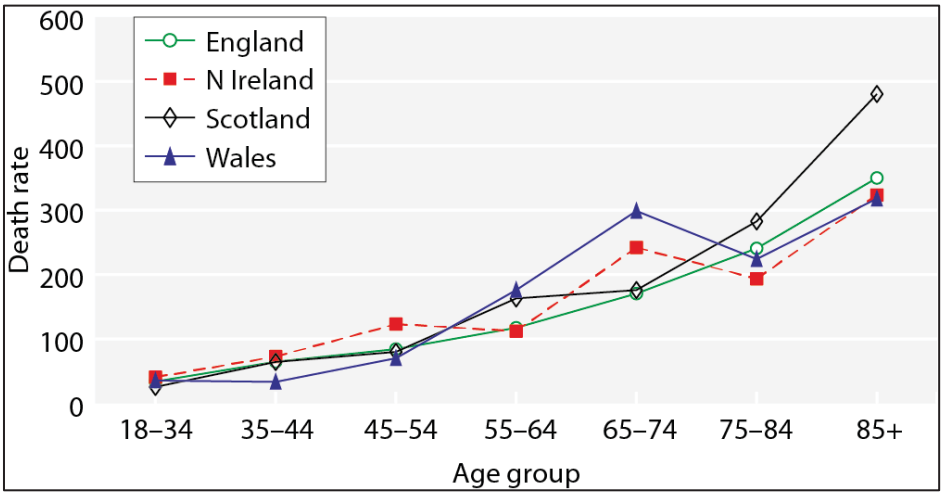


Figure 5. One year death rate per 1,000 patient years by UK country and age group for prevalent dialysis patients, 2013 cohort

Reproduced from UK Renal Registry Report, 2015.[54]

Other event rates

The background incidence rates for non-fatal CV events, fracture and parathyroidectomy under standard treatment are displayed in Table 26. These were derived from the placebo arm of the EVOLVE trial. The company stated that they chose this source due to its alignment with the assumptions and population of the decision-analytic model. We agree that EVOLVE is the best available source of estimates for background event rates in the model. The results might not reflect current UK practice, but we have not identified a better or more representative source of data. For comparison, the Garside and colleagues HTA, conducted to inform the NICE appraisal of cinacalcet[2], used a slightly higher rate of 0.1023 initial CV hospitalisations per year for patients with 'controlled SHPT', based on a published analysis of a US administrative data source.[55] This rate was then increased using a relative risk for patients with uncontrolled SHPT and for subsequent CV events. Rates of bone fractures in the Garside and colleagues analysis were also based on US administrative data, yielding an estimate of 0.0280 initial fractures per year for patients with controlled SHPT - lower than the EVOLVE estimated used in this current appraisal. Garside and colleagues based their estimate of PTx rates (0.1 per year) on clinical judgement.

To align the event rates with the EVOLVE-based efficacy estimates in their base case model, the company used lag-censored estimates of CV, fracture and PTx rates (see section 4.3.5.1 above). This does, however, create inconsistency when alternative methods are used to adjust for non-adherence in the EVOLVE data (as in our base case model). For

consistency with the primary composite endpoint in EVOLVE, the company excluded stroke from cardiovascular event incidence in the model. No increase in mortality after the occurrences of CV events and fractures was taken into account, which is appropriate to avoid double-counting against all-cause mortality which is already captured within the model.

Table 26 Background event rates (events per person year) with PB/VD alone

Parameter	Estimate	Standard Error	Source
Non-fatal CV[1]			EVOLVE trial, placebo arm; Lag-censored event rates.[38]
- first event	[redacted]	[redacted]	
- subsequent event	[redacted]	[redacted]	
Non-fatal bone fracture			
- first event	[redacted]	[redacted]	
- subsequent event	[redacted]	[redacted]	
Parathyroidectomy			
- All events	[redacted]	[redacted]	

CV, cardiovascular

[1] Myocardial infarction, unstable angina, heart failure and peripheral vascular event

From CS Table 39, page 103

The incidence of CV events, bone fracture and parathyroidectomy were assumed to be constant with age. Of course in the general population, incidence of cardiovascular disease increases with age. This is also true for patients on renal dialysis, although the gradient is less steep.[56] Therefore, it is not unreasonable to use a single event rate for non-fatal CV. However, the incidence of bone fracture in patients with CKD has a steep age gradient, particularly in women. The company's scenario analysis for older patients (age 65) is therefore likely to underestimate the background incidence of bone fracture, and to some extent CV events, and hence to underestimate the benefit and cost-effectiveness of achieving better SHPT control.

4.3.5.2 Treatment effects

The hazard ratios for etelcalcetide compared with placebo (PB/VD) and cinacalcet used in the submitted company model are given in Table 27. Methods A, B, E and F were provided in the CS section 5.2.5. The results for Methods C and D are given for comparison. These were estimated by the ERG using HRs for cinacalcet versus placebo presented in company clarification response Table 5 (p22) and using the extrapolation method described in CS Section 5.2.6.3 (p97-99).

Table 27. Estimated hazard ratios used in company model

	HR [95% confidence interval]					
	EVOLVE based extrapolation				**Eandi et al. risk prediction**	
	Method A) Lag-censored	Method B) Disaggregated	Method C) RPSFTM *	Method D) IPE *	Method E) Censored	Method F) Disaggregated
Etelcalcetide vs. PB/VD only						
Mortality	0.75 [0.62, 0.89]	[redacted]	[redacted]	[redacted]	0.78 [0.65, 0.93]	[redacted]
Non-fatal CV	0.72 [0.59, 0.88]	[redacted]	[redacted]	[redacted]	0.94 [0.77, 1.15]	[redacted]
Fractures	0.67 [0.50, 0.89]	[redacted]	[redacted]	[redacted]	0.86 [0.34, 2.16]	[redacted]
Parathyroidectomy	0.17 [0.11, 0.25]	[redacted]	[redacted]	[redacted]	0.37 [0.15, 0.95]	[redacted]
Etelcalcetide vs. cinacalcet						
Mortality	0.94 [0.88, 0.98]	[redacted]	[redacted]	[redacted]	0.94 [0.88, 1.01]	[redacted]
Non-fatal CV	0.93 [0.87, 0.98]	[redacted]	[redacted]	[redacted]	0.99 [0.95, 1.03]	[redacted]
Fractures	0.91 [0.83, 0.98]	[redacted]	[redacted]	[redacted]	0.98 [0.76, 1.26]	[redacted]
Parathyroidectomy	0.66 [0.51, 0.81]	[redacted]	[redacted]	[redacted]	0.81 [0.63, 1.04]	[redacted]

HR, hazard ratio; CI, confidence interval; RPSFTM rank-preserving structural failure time model; IPE iterative parameter estimation. CV myocardial infarction, unstable angina, heart failure and peripheral vascular event.

Sources: CS Table 34 p98, Table 35 p100, Table 36 p100-101, Table 37 p101

* Estimated by ERG from company clarification response Table 5 p22, and CS Table 32 p96: confidence interval not available

4.3.5.3 Treatment discontinuation

Cinacalcet discontinuation

Discontinuation for cinacalcet was captured as explicit model inputs with patients in the Markov model transitioning from on-treatment to PB/VD alone upon discontinuation. Several sources of discontinuation data were considered for cinacalcet: the EVOLVE trial, US Medicare data [46] and a European observational study.[47] Table 28 reports cinacalcet discontinuation data from these three sources. Persistence was modelled using a Weibull distribution.[36] The company justify this choice based on the model fit, measured using the AIC statistic.

Table 28 One-year calcimimetic persistence data

Population	N	1-year persistence	Source
EVOLVE trial population, cinacalcet trial arm	1,938	71% (KM); 72% (parametric)	Amgen data on file; own analyses
US Medicare dialysis patients with prescription drug coverage (Part D); cinacalcet	17,763	27% (as reported); 28% (parametric)	Reams et al. 2015;[46] own analyses
Europe: observational study; cinacalcet	1,865	76%	Urena et al. 2009[47]

KM, Kaplan-Meier
(CS Table 40, p. 104)

Etelcalcetide discontinuation

No long term discontinuation data was available for etelcalcetide, so data from the etelcalcetide-cinacalcet head-to-head trial were used. Table 29 shows the discontinuation data from the head-to-head trial. Whilst the table shows that mean discontinuation on etelcalcetide is 20% higher than cinacalcet, the company assumed equivalent discontinuation due to lack of statistical significance. We present ERG scenario analyses around this assumption in section 4.4.

Table 29 Discontinuation of etelcalcetide and cinacalcet in 20120360

Study 20120360	Cinacalcet	Etelcalcetide
Number of subjects	341 (100%)	338 (100%)
Discontinuation within follow-up	59 (17.3%)	67 (19.8%)
Censored[1]	282 (82.7%)	271 (80.2%)
Discontinuation by time [95% CI]		
Week 4	[redacted]	[redacted]
Week 8	[redacted]	[redacted]
Week 12	[redacted]	[redacted]
Week 16	[redacted]	[redacted]
Week 20	[redacted]	[redacted]
Week 24	[redacted]	[redacted]
Week 26	[redacted]	[redacted]
Rate ratio of discontinuation based on Cox regression:		
	HR	**95% CI**
Cinacalcet	[redacted]	[redacted]
Etelcalcetide	[redacted]	[redacted]

[1]No discontinuation up to week 26
(CS Table 43, p. 106)

4.3.5.4 Health related quality of life

The company conducted a systematic review to identify HRQoL studies (CS 5.3.3 page 107). The review identified five studies reported in six papers. Three of these measured quality of life in terms of SF-36 scores: a Greek study by Malindretos 2012, a Chinese study by Lun 2014 and a French study by Filipozzi 2015 with completion of self-administered questionnaires for 50, 30 and 124 SHPT patients respectively.[57-59] A study from Canada estimated utilities via the Time Trade-Off (TTO) method based on evaluations by 199 members of the general population.[60] The most recent study by Briggs 2016 estimated utilities based on the EQ-5D instrument administered to 3,547 SHPT patients in the EVOLVE trial.[48]

Of the two studies that estimated utilities, the Briggs and colleagues study was considered to be the most appropriate choice by the company.[48, 60] Briggs and colleagues used EQ-5D, with domain values supplied by patients and utility scores derived from the UK EQ-5D algorithm. It was the only study identified that was directly in line with NICE methodological guidance and was conducted alongside the pivotal cinacalcet study, EVOLVE.[48]

The company did not model the impact of adverse events on utility. The justification provided for this is that etelcalcetide is well tolerated, with an adverse event profile similar to that of

cinacalcet. They note that, although etelcalcetide was associated with increased incidence of hypocalcaemia compared with cinacalcet or placebo, but that these events were "typically mild or moderate in severity and rarely led to permanent discontinuation of etelcalcetide" (CS p. 103).

There was no direct evidence of utility effects with etelcalcetide – as the trials did not include EQ-5D. However, the KDQOL-36 (Kidney Disease Quality of Life questionnaire) was measured in study 20120360; scores were nearly equal with a tendency towards slightly better QoL for cinacalcet compared to etelcalcetide.[14] It is difficult to draw conclusions given the baseline differences between the arms and other possible confounding factors.

The utility values used in the model are presented in Table 30.

Table 30 Utility estimates used in the decision-analytic model

Utility values	Value	Standard error	Source
Utility dialysis	0.71	0.013	Briggs 2016 (Table 3)
Absolute utility decrements			
CV event months 1-3	0.19	0.014	Briggs 2016 (Table 1; Table 3, error propagation)
CV event after month 3	0.14	0.014	Briggs 2016 (Table 1; Table 3, error propagation)
Fracture months 1-3	0.31	0.023	Briggs 2016 (Table 3)
Fracture after month 3	0.12	0.020	Briggs 2016 (Table 3)
PTx months 1-3	0.06	0.020	Briggs 2016 (Table 3)
PTx after month 3	-	-	Assumption, based on non-significance (p=0.653)
Calcimimetic treatment	-	-	Conservative assumption, as published point estimate implied a slight utility increase

(CS Table 45, p. 111)

The data used in the model differed from the Briggs and colleagues estimates in two respects: Briggs and colleagues found that parathyroidectomy improved quality of life, with a non-significant 0.01 long-term utility benefit; and that calcimimetic treatment (specifically cinacalcet) improved quality of life, with a statistically significant 0.02 ($p < 0.001$) utility improvement. In the company base case model, both of these values are zero, although they conducted a scenario analysis in which the utility gain from treatment was applied to both cinacalcet and etelcalcetide. We repeat this scenario analysis, but also conduct an

exploratory scenario analysis in which we apply the utility gain for cinacalcet, but not etelcalcetide. This is intended to reflect the lack of utility evidence for etelcalcetide.

The HRQoL data presented by the company was derived from appropriate systematic searches that identified an appropriate study conducted in a relevant population with methods fully in compliance with the NICE Reference Case.[23]

Adverse events

Adverse events were not modelled, as the company argued that treatment was generally well tolerated, the adverse event profile was consistent with underlying comorbidities of people with SHPT, and that the safety profile of etelcalcetide is similar to cinacalcet (CS section 5.2.11 page 103). They did note that incidence of decreased blood calcium and symptomatic hypocalcaemia was higher among patients who received etelcalcetide compared with placebo or cinacalcet; but argued that these events were typically mild or moderate in severity and rarely led to permanent discontinuation of etelcalcetide.

This was in line with the PenTAG model used to inform NICE's appraisal of cinacalcet in TA117.[2]

4.3.5.5 Resource use and costs

The company conducted a systematic literature to identify cost and resource use data for the economic model. This review was conducted as part of a larger systematic review, as described in section 4.2 above (CS 5.4.1 page 111). The full search strategy was reported in CS Appendix 5. The systematic literature review identified seven studies (reported in seven papers) that contained information on the cost of SHPT. Data on the studies identified is presented in Table 31.

Table 31 Summary of cost of illness studies

First author, year	Analysis Countries	Cost year	Defining population	Time horizon (months)	Currency	Patients (N)	Mean age (years)	SD (yrs)	% male
Duenas 2010[61]	UK	NR	Undergoing PTx	12	GBP (£)	100	49.0	14.0	NR
Schumock 2011[62]	USA	NR	After PTx	12	USD ($)	19	NR	NR	NR
			Before PTx	12	USD ($)	2704	52.4	NR	45.2
Lee 2011[63]	USA	2010	High adherent patient (MPR>=80%)	12	USD ($)	1372	63.7	12.8	55.5
			Low adherent patient (MPR<=80%)	12	USD ($)	1304	59.9	12.9	52.5
			Non-adherent cinacalcet patients	12	USD ($)	2247	61.8	13.8	52.5
Chiroli 2012[64]	Hungary; Italy; Portugal; Spain; Turkey	2006	Patients with mild SHPT (PTH level of 300-600 pg/ml)	1	EUR (€)	1343	62.0	14.8	57.0
			Patients with severe SHPT (PTH level >800 pg/ml)	1	EUR (€)	472	57.5	15.6	49.0
			SHPT patients	1	EUR (€)	6369	63.0	14.7	57.0
Pockett 2012[52]	UK	2011	Undergoing PTx	12	GBP (£)	124	51.1	13.8	NR
Lee 2013[65]	USA	2011	On dialysis type not reported	1	USD ($)	41927	64.4	14.4	57.7
				12	USD ($)	41927	64.4	14.4	57.7
				Event Only	USD ($)	41927	64.4	14.4	57.7
Pockett 2014[66]	UK	2010-2011	Undergoing PTx _Costs from database	4	GBP (£)	124	51.1	13.8	46.8
				36	GBP (£)	124	51.1	13.8	46.8
			Undergoing PTx _Costs From questionnaire	4	GBP (£)	79	53.0	6.0	NR
				36	GBP (£)	79	53.0	6.0	NR

MPR Medication Possession Ratio; PTH parathyroid hormone; PTx parathyroidectomy; SHPT secondary hyperparathyroidism
GBP Great Britain Pounds Sterling; USD United States Dollars; EUR Euros

(CS Table 46, p. 112)

Of the costs identified through the systematic review, only the costs of parathyroidectomy from Pockett and colleagues were used in the model.[66] Costs used within the model reflect the UK NHS perspective and consist of following components: drug acquisition costs, treatment monitoring costs, event costs and dialysis costs.

Drug acquisition costs

The use of calcimimetics was derived from the pivotal etelcalcetide trials.[12-14] Drug use was derived from all patients who received at least one non-missing dose of the investigational product. Patients who received commercial cinacalcet were excluded. The doses were measured during the EAP. The doses of cinacalcet used in the cinacalcet-controlled trial (20120360) were similar to the dose found in EVOLVE ([redacted] vs. 66.8 mg/day).[14, 18] Table 32 reports the calcimimetic use in the model.

Table 32 Calcimimetic drug consumption from the etelcalcetide trials

Drug	Dose (mg/day)[1]	SE	Total exposure (person years)	Source
Etelcalcetide: placebo trials	[redacted]	[redacted]	[redacted]	Table 11-6.1.2[67]
Etelcalcetide: head-to-head trial	[redacted]	[redacted]	[redacted]	
Weighted average	[redacted]	[redacted]		
Cinacalcet	[redacted]	[redacted]	[redacted]	

[1]Based on the on-treatment population in the etelcalcetide trials
(CS Table 47, p. 113)

Vitamin D and phosphate use was assumed to be the same across all model arms. This is consistent with the assumptions of the PenTAG model of cinacalcet and PB/VD.[2] However, this is not consistent with measured usage in the EVOLVE trial, which identified lower use and dose of vitamin D among cinacalcet patients, and greater use of calcium containing phosphate binders among cinacalcet patients (Chertow and colleagues, Supplementary Appendix Figure S7).[18]

Point estimates for PB/VD use were derived by pooling data from all three etelcalcetide trials. For some types of vitamin D, drug prices were not available through the BNF or the NHS Drug Tariff. To compensate for this, doses were shifted to drugs where prices were available using a published algorithm that calculates 'paricalcitol equivalent dose.' The doses used in the model are reported in Table 33. Full details of the algorithm were provided in CS Appendix 16.

Table 33 Pooled Vitamin D and phosphate binder use from etelcalcetide trials

Drug	Dose		Drug	Dose	
Vitamin D dose	**mcg/day**	**SE**	**Phosphate binder dose**	**g/day**	**SE**
Alfacalcidol (oral)	0.070	0.005	Aluminium containing	0.040	0.007
Alfacalcidol (IV)	0.009	0.002	Calcium containing	0.570	0.031
Calcitriol (oral)	0.050	0.003	Lanthanum carbonate	0.210	0.016
Calcitriol (IV)	0.006	0.001	Magnesium containing	0.030	0.005
Doxercalciferol (oral)	0.001	0.000	Magnesium & calcium containing	0.005	0.002
Doxercalciferol (IV)	0.270	0.018	Sevelamer	1.730	0.058
Paricalcitol (oral)	0.020	0.005			
Paricalcitol (IV)	0.350	0.024			
Total equivalent dose (Paricalcitol)	*1.293*	*0.047*			

(CS Table 48, p. 114) Source Table 11-6.10.2 and Table 11-6.3.13.)[68]

The ERG found the use of the algorithm to have limitations. The algorithm calculates dose equivalents, which is not the same as calculating cost equivalents. The algorithm also does not shift resource use by the market shares provided in the model, and in the process gives more share to more expensive drugs. We did not find this to be a realistic adjustment. A market share based shifting would be more representative of actual resource use, and less computationally intensive. However, given that the costs for PB/VD are identical across all three model arms, and that the cost of PB/VD is small, any changes to PB/VD resource use will have no effect on the model.

Drug costs

Drug costs were derived from the BNF and the NHS Drug Tariff (April 2016). The estimated list price for etelcalcetide was [redacted] /mg. Where more than one pack size was available, market share data from the NHS prescription cost analysis was used to determine average cost per unit.[69] Full cost details were provided in CS Appendix 16. Table 34 reports average drug costs used in the model.

We checked the list prices and found minor inconsistencies in pricing for PB/VD. As these treatments are assumed to be identical across all treatment arms in the model, these minor discrepancies will have little effect on cost-effectiveness.

Table 34 Average drug cost per unit used in the model

Calcimimetics	**Cost (£/mg)**	**Source**
Cinacalcet	0.145	BNF 62, Prescription Cost Analysis, England, 2015 [49, 69]
Etelcalcetide	[redacted]	Estimated company list price
Vitamin D	**Cost (£/mcg)**	**Source**
Alfacalcidol (oral)	0.223	BNF 62, NHS Drug Tariff (April 2016) Prescription Cost Analysis, England, 2015[49, 50, 69]
Alfacalcidol (IV)	2.080	
Calcitriol (oral)	0.683	
Calcitriol (IV)	Not available	
Doxercalciferol (oral)	Not available	
Doxercalciferol (IV)	Not available	
Paricalcitol (oral)	2.480	
Paricalcitol (IV)	2.480	
Phosphate binders	**Cost (£/g)**	**Source**
Aluminium containing	0.127	BNF 62, NHS Drug Tariff (April 2016), Prescription Cost Analysis, England, 2015 [49, 50, 69]
Calcium containing	0.103	
Lanthanum carbonate	2.590	
Magnesium containing	0.193	
Magnesium & calcium containing	0.307	
Sevelamer	1.041	

(CS Table 49, p. 114-115)

Event costs

Four cardiovascular events; myocardial infarction, unstable angina, heart failure, and peripheral vascular disorders; were included in modelled costs for cardiovascular events. For each individual type of cardiovascular event, a weighted average cost consisting of elective (long-stay), non-elective (long stay) and day-case hospitalisations was calculated using NHS Reference Costs.[51] In the model, these four events are weighted using their relative frequency among cardiovascular events. Costs for fractures were similarly derived from NHS Reference Costs using a weighted average of non-elective and elective long stay costs and day-case costs. Parathyroidectomy costs were derived from Pockett and colleagues[66] and inflated to 2015 values using the Hospital and Community Health Services (HCHS)[70] index reports event costs used in the model.

Table 35 Event costs

Parameter	Value	Weight	Source
Myocardial infarction (MI)	£ 2,196	21.6%	NHS Reference Costs (EB10A-E; NEL, EL, DC schedules)
Unstable angina (UA)	£ 1,187	6.6%	NHS Reference Costs (EB12A-C and EB13A-D; NEL, EL, DC schedules)
Heart failure (HF)	£ 2,750	31.2%	NHS Reference Costs (EB03A-E; NEL, EL, DC schedules)
Peripheral Vascular Disorders (PVD)	£ 2,342	40.6%	NHS Reference Costs (YQ50A-F; NEL, EL, DC schedules)
Weighted average cost CV-related hospitalization	£ 2,362		Weighted as above
Weighted average cost fracture-related hospitalisation	£ 2,669		NHS Reference Costs (HD39D-G; NEL, EL, DC schedules)
Parathyroidectomy	£ 5,108		Pockett and colleagues[66] HCHS[70]

HCHS, Hospital and community health services
(adapted from CS Table 50, p. 115)

The model only accounts for acute event costs. It is likely that long-term components of care have been missed by the model, leading to an underestimation of costs for modelled events. All of the events modelled may require further care after the acute event, with some events requiring substantial additional care.

Monitoring costs

Monitoring costs were included in the model broadly in line with the PenTAG model.[2] Monitoring costs were applied to all live SHPT subjects across all model arms. The CS model differs from the PenTAG model slightly in that it does not increase the frequency of PTH testing after parathyroidectomy. Costs were derived primarily from the PenTAG model and inflated to 2015 prices using the HCHS index.[2, 70] Table 36 reports the resource use and costs used for monitoring costs in the model.

Table 36 Monitoring costs (CS Table 51, p. 116)

Parameter	Value	Source
Frequency of PTH tests (per quarter)	1	Garside et al. 2007[2]
Frequency of Calcium tests (per quarter)	3	
Frequency of Phosphate tests (per quarter)	3	
Unit cost of PTH test	£ 24.99	Garside et al. 2007; HCHS[2, 70]
Unit cost of Calcium test	£ 1.19	National Schedule of Reference Costs 2014-15[51]

Dialysis costs

Consistent with the PenTAG model and common modelling practice in the chronic kidney disease area, the cost of dialysis was not included in the base case analysis.[2] A scenario analysis was conducted to evaluate the effect of adding dialysis costs to the analysis. Table 37 reports the parameters of this analysis.

Table 37 Dialysis costs (CS Table 52, p. 116)

Parameter	Value	Source
Cost of haemodialysis session	£162.24	Garside et al. 2007; HCHS[2, 70]
Number of sessions per month	12.8	Etelcalcetide trials, Table 11-6.4[71]
Cost of dialysis (per month)	£2,076	

4.3.6 Model validation

The company undertook assessment of face validity, performed a technical validation, and compared the model to previous models in the disease area. In addition to the validation conducted by the company, the ERG checked the model for internal and external consistency, face validity, and technical correctness.

4.3.6.1 Internal consistency

The company described several internal governance and review processes designed to ensure face validity, including:

- Having the model reviewed by individuals from multiple disciplines through company internal model governance processes.
- Using an external virtual model advisory board to contribute to the model. This consisted of modelling experts in calcimimetic treatment.
- A UK-specific advisory board that consisted of a team of two clinicians and two health economics experts reviewed the model.

The company undertook internal face validity checks in each of July 2014, July 2015 and January 2016, and involved experts in the areas of nephrology, health economics, decision-analytic modelling, and biostatistics. External advisors reviewed draft models and corresponding technical reports in December 2014 and in December 2015. The UK specific advisory board convened in February 2016, providing feedback on assumptions and parameter inputs.

The company explained that during model-development, internal technical validity checks were performed continuously. Technical validity checks included the confirmation of valid ranges and plausibility checks for probabilities and results. In addition to technical validity checks conducted by the company internal modelling team, members of the virtual advisory board reviewed the technical report and model for technical validity.

In addition to the previously described technical validity checks, quality-control checks were conducted by an external vendor. Quality control procedures followed a pre-specified protocol and covered (among others) the following components:

- Checking the equations for mathematical correctness
- Alignment of the technical report with programming
- Valid ranges for model parameters
- Plausibility of changes in results when varying single input parameters

- Checking visual basic coding

The company did not provide details of the quality assurance protocol and processes or any formal checklists used by any reviewers of the model.

The ERG conducted quality assurance checks to ensure consistency of reported and utilised parameters, to check the validity of parameter choices, and to verify and validate the technical elements of the model. In general, the model was technically correct, with some minor errors in the calculation of cost parameters that had minimal impact on model results.

4.3.6.2 External consistency

The company informed their de novo cost-effectiveness model with previous cinacalcet cost-effectiveness models conducted by Garside and colleagues, Belozeroff and colleagues and Eandi and colleagues. The CS model adds new data and evidence that has become available since the publication of those models. The company undertook a comparison of the key differences between their model and previously published models in CS Appendix 18. The company identified no other cost-effectiveness models of etelcalcetide in their systematic literature review, and therefore did not cross-check the results of their model against alternative models.

We considered the external validity checks conducted by the company to be thorough and sufficient.

4.3.7 Cost effectiveness results

Results from the economic model are presented (section 5.6, page 125 of the CS) as an incremental cost per QALY gained for etelcalcetide and PB/VD compared with PB/VD alone for patients in the 'broad licensed population' and for etelcalcetide and PB/VD compared with cinacalcet and PB/VD in patients with refractory SHPT (Table 38). These results are based on an anticipated list price for etelcalcetide. Note that both groups are estimated to have the same QALY and cost if treated with etelcalcetide, because they are assumed to have the same PTH response and background risks of morality, CVD events, bone fractures and incidence of parathyroidectomy in the company's base case analysis. If there is an overlap population of patients who might be considered for PB/VD, cinacalcet or etelcalcetide, an incremental analysis would be appropriate (see 4.4.1.6 below).

Table 38 Cost effectiveness results: base case at anticipated list price

	Total Costs	Incremental Costs	Total QALYs	Incremental QALYs	ICER (£/QALY)
Broad licensed population (etelcalcetide vs. PB/VD)					
PB/VD	[redacted]	-	3.788	-	-
Etelcalcetide*	[redacted]	[redacted]	4.109	0.321	[redacted]
Population with refractory SHPT (etelcalcetide vs. cinacalcet)					
Cinacalcet*	[redacted]	-	4.040	-	-
Etelcalcetide*	[redacted]	[redacted]	4.109	0.069	[redacted]

QALYs, quality-adjusted life-years; ICER, incremental cost-effectiveness ratio; PB, phosphate binders; VD, vitamin D;
* In addition to PB/VD

4.3.8 Assessment of uncertainty

Deterministic sensitivity analyses

Deterministic sensitivity analysis (DSA) was conducted individual parameters, or for groups of parameters that were individually unlikely to affect the results. The parameters included, lower and upper values and rationale for the range tested are shown in Table 39, reproduced from CS Table 56 page 124. The choice of parameters to include and ranges for variation are appropriate.

Table 39 Ranges used for deterministic sensitivity analyses

Variable	Base case	Lower	Upper	Rationale for range
HR mort. (vs. cina)	0.94	0.88	0.98	95% CI
HR CV (vs. cina)	0.93	0.87	0.98	95% CI
HR fracture (vs. cina)	0.91	0.83	0.98	95% CI
HR PTx (vs. cina)	0.66	0.51	0.81	95% CI
HR mort. (vs. PB/VD)	0.75	0.62	0.89	95% CI
HR CV (vs. PB/VD)	0.72	0.59	0.88	95% CI
HR fracture (vs. PB/VD)	0.67	0.50	0.89	95% CI
HR PTx (vs. PB/VD)	0.17	0.11	0.25	95% CI
Mortality rates (multiplier)	1	0.8	1.2	Joint assessment of all age ranges; mortality not varied probabilistically
CV rate (baseline)	[redacted]	[redacted]	[redacted]	95% CI
Fracture rate (baseline)	[redacted]	[redacted]	[redacted]	95% CI
PTx rate	[redacted]	[redacted]	[redacted]	95% CI
Recurrent CV events	[redacted]	[redacted]	[redacted]	95% CI
Recurrent fracture events	[redacted]	[redacted]	[redacted]	95% CI
Utility dialysis	0.71	0.69	0.74	95% CI
Utility decrements (multiplier)	1	0.8	1.2	Joint assessment
Dose: etelcalcetide	[redacted]	[redacted]	[redacted]	95% CI
Dose: cinacalcet	[redacted]	[redacted]	[redacted]	95% CI
PB/VD drug usage (multiplier)	1	0.8	1.2	Joint assessment
Monitoring costs (multiplier)	1	0.8	1.2	Joint assessment
Event costs (multiplier)	1	0.8	1.2	Joint assessment

Cina, cinacalcet; HR, hazard ratio; CV, cardiovascular; PTx, parathyroidectomy; PB, phosphate binder; VD, Vitamin D; SE, Standard error

[1]Exact confidence intervals according to Clopper and Pearson [72]

The DSA results are shown in the tornado diagrams in Figure 6 and Figure 7 for etelcalcetide compared with PB/VD and cinacalcet respectively. None of the values tested brought the ICER for etelcalcetide compared with PB/VD or with cinacalcet to below £30,000 per QALY. The results were most sensitive to the HR for mortality. ICERs were also moderately sensitive to: the HRs for cardiovascular events and fractures; the background (absolute) mortality rates and utility for the population under standard treatment; and the dose of etelcalcetide (and cinacalcet for the E vs C comparison).

Figure 6

Figure 7

Scenario analysis

The company performed selective scenario analyses to test the impact of some key assumptions (Table 40).

Table 40 Summary of company base case and scenario analyses

Parameter	Base case analysis	Alternative scenarios
Age at baseline	55 years	45; 65 years
Discount rate	3.5%	0%; 6%
Parathyroidectomy	As an outcome	Not included
Hazard Ratios for cinacalcet vs. PB/VD	EVOLVE: Lag-censored	EVOLVE: ITT, disaggregation Eandi: Censored Eandi: ITT disaggregation
Age-specific mortality rates	Boer et al.	EVOLVE
Persistence	EVOLVE	Reams et al. Urena et al.
Utility values	No impact calcimimetics	Including calcimimetic impact
Drug use etelcalcetide	Pooled trial data	Head-to-head study data
Dialysis costs	Excluded	Included

Results are shown in Table 41. None of the analyses brought the ICERs for etelcalcetide below £30,000 per QALY. ERG interpretation is summarised below:

- Alternative methods of estimating long-term effectiveness gave results that were broadly similar to the base case. ICERs obtained using the company's method of disaggregating ITT results were more favourable for etelcalcetide than the base case, which used lag-censored estimates from EVOLVE. Conversely, the Eandi-extrapolated estimates censored at treatment discontinuation were less cost-effective. See section 4.4.1.3 (page 127) below for ERG analysis and discussion of other methods of adjusting EVOLVE data for non-adherence (RPSFTM and IPE).
- ICERs were lower when the higher mortality rates from EVOLVE were used instead of the Boer registry data, and also with an older cohort (starting at age 65 years). Thus treatment is more cost-effective in a cohort with higher background risks.
- ICERs were a little more favourable for etelcalcetide when the utility gain with cinacalcet estimated from EVOLVE was applied to both calcimimetics.
- Use of higher rates of discontinuation from the Reams US Medicare data (rather than EVOLVE) improved cost-effectiveness. This might appear counter-intuitive, but reflects the fact that in the base case analysis, etelcalcetide is not cost-effective: so higher discontinuation reduces QALYs, but this is offset by a greater fall in costs.

Table 41 Scenario analysis: base case with anticipated list price

Scenario	Incremental costs	Incremental QALYs	ICER
Broad licensed population (etelcalcetide vs. PB/VD)			
Base case	[redacted]	**0.321**	[redacted]
Efficacy: EVOLVE ITT disaggregated	[redacted]	0.346	[redacted]
Efficacy: Eandi; censored	[redacted]	0.247	[redacted]
Efficacy: Eandi; ITT disaggregated	[redacted]	0.292	[redacted]
Age at baseline: 45 years	[redacted]	0.317	[redacted]
Age at baseline: 65 years	[redacted]	0.316	[redacted]
PTx: not included (rate=0)	[redacted]	0.320	[redacted]
Mortality: EVOLVE	[redacted]	0.310	[redacted]
Discontinuation: Reams et al	[redacted]	0.145	[redacted]
Discontinuation: Urena et al.	[redacted]	0.358	[redacted]
Utility: Impact calcimimetic treatment	[redacted]	0.366	[redacted]
Calcimimetic drug use: EAP; head to head	[redacted]	0.321	[redacted]
Dialysis costs: included	[redacted]	0.321	[redacted]
Discount rate: 0%	[redacted]	0.412	[redacted]
Discount rate: 6%	[redacted]	0.274	[redacted]
Population with refractory SHPT (etelcalcetide vs. cinacalcet)			
Base case	[redacted]	**0.069**	[redacted]
Efficacy: EVOLVE ITT disaggregated	[redacted]	0.074	[redacted]
Efficacy: Eandi; censored	[redacted]	0.057	[redacted]
Efficacy: Eandi; ITT disaggregated	[redacted]	0.074	[redacted]
Age at baseline: 45 years	[redacted]	0.067	[redacted]
Age at baseline: 65 years	[redacted]	0.069	[redacted]
PTx: not included (rate=0)	[redacted]	0.069	[redacted]
Mortality: EVOLVE	[redacted]	0.067	[redacted]
Discontinuation: Reams et al	[redacted]	0.031	[redacted]
Discontinuation: Urena et al.	[redacted]	0.078	[redacted]
Utility: Impact calcimimetic treatment	[redacted]	0.070	[redacted]
Calcimimetic drug use: EAP; head to head	[redacted]	0.069	[redacted]
Dialysis costs: included	[redacted]	0.069	[redacted]
Discount rate: 0%	[redacted]	0.089	[redacted]
Discount rate: 6%	[redacted]	0.059	[redacted]

- With higher doses of calcimimetics (and no change in effectiveness), treatment costs increase and results are less cost-effective.
- Exclusion of parathyroidectomy from the model causes small increases ICERs for etelcalcetide, because etelcalcetide is estimated to reduce the incidence of parathyroidectomy, and only short-term costs and disutility of parathyroidectomy are modelled. The impact including any ongoing health benefits, or cost savings from reduced use of medication, is unknown.

- Finally, we note that inclusion of the cost of dialysis makes calcimimetic treatment appear less cost-effective. As noted by the company, this reflects the high cost of dialysis, and that the model does not reflect any change in effectiveness associated with the inclusion or exclusion of dialysis costs.

Probabilistic sensitivity analysis

The CS reported a probabilistic sensitivity analysis (PSA), conducted on their base case analysis (CS section 5.7.1, p129). This was thorough and well-conducted, reflecting uncertainty around most input parameters, with input distributions based on empirical data where possible (Table 42).

Table 42 Summary of distributions for probabilistic analysis

Variable	Point estimate	Uncertainty measure (e.g. SE or 95% CI)	Distribution	Source
EVOLVE-based HRs vs. cina /PB/VD	By mortality, CV event, fractures and PTx		Log-normal	Etel trials + EVOLVE [12-14] [18]
Mortality rates	Age-specific	Not varied probabilistically, as based on large registry data; no uncertainty measures reported		Boer et al. 2012[45]
CV rate (initial)	[redacted]	SE = 0.005	Gamma	EVOLVE [18]
Fracture rate (initial)	[redacted]	SE = 0.003	Gamma	EVOLVE [18]
PTx rate	[redacted]	SE = 0.003	Gamma	EVOLVE [18]
CV rate (recurrent)	[redacted]	SE = 0.024	Gamma	EVOLVE [18]
Fracture rate (recurrent)	[redacted]	SE = 0.047	Gamma	EVOLVE [18]
Utility dialysis	0.71	[0.69, 0.74]	Beta	Briggs et al.[73]
Utility decrements (CV, fracture, PTx)	By type of event, short-term vs. long-term		Normal	Briggs et al.[73]
Calcimimetic persistence	Regression parameters and covariance matrix of parametric distribution		Multivariate normal	EVOLVE[18]
Drug usage (calcimimetics, PBs, VDs)	Point estimates and SEs by trial arm		Gamma	Etel trials [12-14]
Monitoring costs	Testing frequency by type of test (PTH, Ca and P)		Gamma	Garside et al. 2007[74]; NHS 2014/15 [51]
Event costs	By type of event		Gamma	NHS 2014/15 [51]

The point estimates from the PSA were close to those in the deterministic analysis (ICER of [redacted] for etelcalcetide compared with PB/VD and [redacted] compared with cinacalcet). Cost Effectiveness Acceptability Curves (CEACs) from these two comparisons are shown in [redacted] and **Error! Reference source not found.**. These show that the probability that etelcalcetide is cost-effective in either comparison at a threshold of £30,000 per QALY is very low.

4.4 Additional work undertaken by the ERG

We made a number of extensions to the company's base case model to explore further the robustness of the results.

4.4.1 Additional scenario analyses

4.4.1.1 Efficacy of SHPT control: 30% reduction in PTH

The company model used naïve pooling from the three pivotal phase III etelcalcetide RCTs to estimate the proportion of patients expected to achieve the target 30% reduction in PTH over the six month study period (see section 4.3.4.3 earlier). We consider that it would have been more appropriate to use an indirect form of meta-analysis based on between-arm estimates of treatment effects – ideally a Network Meta-Analysis (NMA) to integrate data from all relevant comparisons. In addition to the three etelcalcetide trials, the ERG identified eight RCTs comparing cinacalcet with placebo and/or standard care and conducted a meta-analysis (see section 3.5.2). Briefly, there was statistically significant heterogeneity, which lends support to the companies' decision not to conduct a NMA. One trial in particular, Ketteler and colleagues, was particularly heterogeneous in effects.[32]

We added a simple chained method of indirect comparison to the model to retain between-arm randomised evidence, and to explore the impact of the wider evidence base from the cinacalcet vs. placebo trials. There are three potential chains of evidence that could be used to generate indirect comparisons: only using evidence from the etelcalcetide trials, using all available evidence (etelcalcetide trials, plus ERG meta-analysis of cinacalcet), and using all available evidence excluding Ketteler and colleagues.[32] We consider the chain of evidence based on the three etelcalcetide trials (Scenario 2 in Table 43) to be the most robust source of evidence. The chain starts with the observed mean effect from the company's integrated analysis of the placebo arms of trials 20120229 and 20120230 (8.9% of patients achieve ≥30% PTH reduction), and uses the odds ratio (31.6) from these two trials to estimate the effect for etelcalcetide (75.6% achieve ≥30% PTH reduction). The odds ratio (1.59) from the cinacalcet-controlled trial 20120360 is then used to estimate the effect of cinacalcet (66.6%). This chained approach suggests that both calcimimetics are more effective than placebo than does the company's naïve pooling approach. The company's approach overestimates the relative effectiveness of etelcalcetide compared with cinacalcet: mean odds ratio of 1.89 (72.1% vs 57.7% response), compared with 1.59 from the covariate-adjusted, lag-censored analysis of trial 20120360 (75.6% vs. 66.6% response). Table 43 provides efficacy estimates used under different indirect treatment comparisons.

Table 44 shows the implications of using different methods to estimate the relative effects of the etelcalcetide and comparators. Compared with the company's base case, our preferred analysis (scenario 2) yields a slightly higher ICER for the comparison of etelcalcetide vs. PB/VD [redacted]), but a much higher ICER for the etelcalcetide vs. cinacalcet comparison [redacted]).

Table 43 Methods of pooling efficacy estimates: % achieving 30% reduction in PTH

Scenario	Placebo: PB/VD alone	Cinacalcet & PB/VD	Etelcalcetide & PB/VD
1) CS base case - naïve pooling	**8.9%**	**57.7%**	**72.1%**
2) Simple ITC: E vs P; E vs C	8.9%	66.1%	75.6%
3) Simple ITC: C vs P (all trials) & E vs C	25.4%	62.2%	72.4%
4) Simple ITC: C vs P (all trials) & E vs P	25.4%	62.2%	91.5%
5) Simple ITC: C vs P (no Ketteler [1]) & E vs C	17.1%	60.7%	71.1%
6) Simple ITC: C vs P (no Ketteler [1]) & E vs P	17.1%	60.7%	86.7%

ITC indirect treatment comparison; E vs P etelcalcetide + PB/VD vs placebo (PB/VD alone); E vs C etelcalcetide + PB/VD vs cinacalcet + PB/VD; C vs P cinacalcet + PB/VD vs placebo (PB/VD alone)

Table 44 Scenario analysis by method of pooling efficacy: anticipated list price

Scenario	Incremental costs	Incremental QALYs	ICER
Etelcalcetide vs. PB/VD comparison			
1) CS base case - naïve pooling	[redacted]	**0.321**	[redacted]
2) Simple ITC: E vs P; E vs C	[redacted]	0.291	[redacted]
3) Simple ITC: C vs P (all trials); E vs C	[redacted]	0.316	[redacted]
4) Simple ITC: C vs P (all trials); E vs P	[redacted]	0.432	[redacted]
5) Simple ITC: C vs P (no Ketteler); E vs C	[redacted]	0.307	[redacted]
6) Simple ITC: C vs P (no Ketteler); E vs P	[redacted]	0.388	[redacted]
Etelcalcetide vs. cinacalcet comparison			
1) CS base case - naïve pooling	[redacted]	**0.069**	[redacted]
2) Simple ITC: E vs P; E vs C	[redacted]	0.039	[redacted]
3) Simple ITC: C vs P (all trials); E vs C	[redacted]	0.065	[redacted]
4) Simple ITC: C vs P (all trials); E vs P	[redacted]	0.181	[redacted]
5) Simple ITC: C vs P (no Ketteler); E vs C	[redacted]	0.056	[redacted]
6) Simple ITC: C vs P (no Ketteler); E vs P	[redacted]	0.137	[redacted]

ITC indirect treatment comparison; E vs P etelcalcetide + PB/VD vs placebo (PB/VD alone); E vs C etelcalcetide + PB/VD vs cinacalcet + PB/VD; C vs P cinacalcet + PB/VD vs placebo (PB/VD alone)

As Table 43 shows, all of the ITC methods yield similar effectiveness estimates for cinacalcet. However, the proportion of patients achieving the 30% target for reduction in PTH with standard treatment is much higher in the cinacalcet vs. placebo trials: 25.4% if all trials are included, or 17.1% if the Ketteler and colleagues trial is omitted.[32] Consequently, the

estimated effects for etelcalcetide differ substantially, depending on whether they are calculated using the odds ratio from the placebo-controlled trials or the cinacalcet-controlled trial.

We draw the following conclusions from this analysis.

- The company's base case overestimates the cost-effectiveness of etelcalcetide due to the naïve pooling of data from the etelcalcetide trials.
- The outcome data from the placebo-controlled cinacalcet trials and the placebo-controlled etelcalcetide trials is heterogeneous. The proportion of patients achieving the target 30% reduction of PTH in the placebo arms of the cinacalcet trials was two or three times the proportion in etelcalcetide trials. This lends support to the company's decision not to attempt a network meta-analysis, and highlights the difference between the population in the cinacalcet trials that in the etelcalcetide trials.
- Cost-effectiveness is sensitive to the proportion of patients meeting the ≥30% PTH reduction target when treated with PB/VD alone – this point is evaluated further in section 4.4.2.1.

4.4.1.2 Efficacy of SHPT control: PTH ≤ 300 pg/mL

The company base case used the primary outcome from the etelcalcetide trials (% with ≥30% PTH reduction) to extrapolate long-term risks from EVOLVE. A patient may achieve a ≥30% PTH reduction and still have PTH levels above the 2-9 times normal PTH range that is considered safe. Therefore, achievement of PTH levels within the target range might be a better predictor of long-term clinical outcomes. In response to a clarification question (B4), the company provided an additional scenario analysis that used the percentage of patients achieving a mean PTH ≤ 300 pg/mL (31.8 pmol/L) (see Table 9) to extrapolate EVOLVE risks. They noted that patients in the placebo-controlled trials were more likely to achieve this target than those in the cinacalcet-controlled trial, due to different inclusion criteria (baseline PTH ≥ 400 pg/mL vs. PTH ≥ 500 pg/mL respectively). To adjust for this difference, in addition to the base case naïve pooling approach described above, the company estimated the proportion of patients achieving the PTH target on cinacalcet by applying the relative risk from the cinacalcet-controlled trial to the proportion from the placebo-controlled trials. We extended this analysis using the simple ITC approach in Scenario 2 above.

Results of these analyses are shown in Table 45. They are more favourable to etelcalcetide than the equivalent analysis based on the primary outcomes in Table 43 above. However, these analyses do not take account of potential harm from hypocalcaemia, a potential risk for patients on dialysis with PTH ≤ 300 pg/mL. Additionally, achievement of PTH ≤ 300 pg/mL does not directly correspond to the range of PTH values that clinical expert opinion to the ERG was considered clinically meaningful, 2-9 times the upper limit of normal PTH (130-600 pg/mL; 13.8-63.6 pmol/L). The validity of this analysis is therefore unclear.

Table 45 Scenario analysis by method of pooling efficacy: anticipated list price

Scenario	Incremental costs	Incremental QALYs	ICER
Etelcalcetide vs. PB/VD comparison			
1) CS base case: >30% PTH reduction	[redacted]	**0.321**	[redacted]
7) ≤ 300 pg/mL- naïve pooling	[redacted]	0.463	[redacted]
8) ≤ 300 pg/ML - Simple ITC E vs C	[redacted]	0.377	[redacted]
9) ≤ 300 pg/ML - Simple ITC E vs C & E vs P	[redacted]	0.348	[redacted]
Etelcalcetide vs. cinacalcet comparison			
1) CS base case: >30% PTH reduction	[redacted]	**0.069**	[redacted]
7) ≤ 300 pg/mL - naïve pooling	[redacted]	0.212	[redacted]
8) ≤ 300 pg/ML - Simple ITC E vs C	[redacted]	0.126	[redacted]
9) ≤ 300 pg/ML - Simple ITC E vs C & E vs P	[redacted]	0.096	[redacted]

PTH parathyroid hormone; E vs P etelcalcetide + PB/VD vs placebo (PB/VD alone); E vs C etelcalcetide + PB/VD vs cinacalcet + PB/VD

4.4.1.3 Method of extrapolation

As alternatives to the lag-censoring and disaggregation approaches to adjusting for non-adherence in the EVOLVE trial presented in the CS, we extended the model to include two additional methods: RPSFTM and IPE. Hazard ratios for these methods were provided by the company in response to a clarification question B2. For ease of comparison, we present the results of these analyses alongside the Eandi and colleagues risk prediction algorithm extrapolation from the CS (Table 46).

We conclude:

- ICERs are sensitive to the method of extrapolation to long-term outcomes and adjustment for non-adherence, although none of the methods tested in scenario analysis brought the ICERs for etelcalcetide below £30,000 per QALY.

- We consider the EVOLVE-based comparisons to be preferable, due to the lack of validation of the Eandi and colleagues risk prediction algorithm (see 4.3.4.5 page 98). However, we note that the company could have attempted independent validation of the risk prediction algorithm in the EVOLVE dataset.
- We also note that non-adherence in EVOLVE does compromise its robustness, and that the log-linear method of extrapolation to etelcalcetide is not validated. This introduces considerable structural uncertainty in the model results.
- The complex methods of adjusting for non-adherence in EVOLVE (RPSFTM and IPE), yield results that are more favourable for etelcalcetide than the company's preferred lag-censored analysis. On balance, the ERG considers that the IPE or RPSFTM approaches are preferable to the other approaches on theoretical grounds that these methods have produced low levels of bias in simulation studies.[75]

Table 46 Scenario analysis by method of extrapolation: anticipated list price

Scenario	Incremental costs	Incremental QALYs	ICER
Etelcalcetide vs. PB/VD comparison			
A) CS base case – EVOLVE lag-censored	[redacted]	**0.321**	[redacted]
B) EVOLVE ITT disaggregated	[redacted]	0.346	[redacted]
C) EVOLVE RPSFTM	[redacted]	0.381	[redacted]
D) EVOLVE IPE	[redacted]	0.358	[redacted]
E) Eandi; censored	[redacted]	0.247	[redacted]
F) Eandi; ITT disaggregated	[redacted]	0.292	[redacted]
Etelcalcetide vs. cinacalcet comparison			
A) CS base case – EVOLVE lag-censored	[redacted]	**0.069**	[redacted]
B) EVOLVE ITT disaggregated	[redacted]	0.074	[redacted]
C) EVOLVE RPSFTM	[redacted]	0.081	[redacted]
D) EVOLVE IPE	[redacted]	0.076	[redacted]
E) Eandi; censored	[redacted]	0.057	[redacted]
F) Eandi; ITT disaggregated	[redacted]	0.074	[redacted]

ITT intention to treat; RPSFTM Rank preserving structural failure time model; IPE iterative parameter estimation

4.4.1.4 Discontinuation of etelcalcetide and cinacalcet

In the base case, the company assumed that etelcalcetide and cinacalcet discontinuation rates were equal because no statistically significant difference was observed in the head-to-head trial (etelcalcetide vs. cinacalcet HR [redacted]. Further, they argue that it is plausible that IV administration of etelcalcetide will lead to improved adherence in clinical practice.

However, we noted in section 3.3.6 that some adverse events were more common with etelcalcetide than with cinacalcet or PB/VD alone: particularly asymptomatic reductions in blood calcium and symptomatic hypocalcaemia (Table 12). The CS reported that decreased blood calcium and symptomatic hypocalcaemia rarely led to drug discontinuation, but did lead to some temporary discontinuations. It is therefore possible that the higher rate of etelcalcetide discontinuation observed in the cinacalcet-controlled trial, although not statistically significant, is reflective of a genuine trend. Furthermore, it is conventional in cost-effectiveness modelling to include mean parameter values irrespective of statistical significance, but to model sampling uncertainty through probabilistic sensitivity analysis.

We therefore adapted the model to allow us to explore the impact of including the hazard ratio for discontinuation from the cinacalcet-controlled trial 210120360 in scenario analysis. The results are presented in Table 47.

Table 47 Scenario analysis by discontinuation assumptions: anticipated list price

Scenario	Incremental costs	Incremental QALYs	ICER
Etelcalcetide vs. PB/VD comparison			
CS base case: EVOLVE, HR = 1	[redacted]	**0.321**	[redacted]
EVOLVE, HR = [redacted]	[redacted]	0.284	[redacted]
Reams et al HR = 1	[redacted]	0.145	[redacted]
Reams et al HR = [redacted]	[redacted]	0.115	[redacted]
Etelcalcetide vs. cinacalcet comparison			
CS base case: EVOLVE, HR = 1	[redacted]	**0.069**	[redacted]
EVOLVE, HR = [redacted]	[redacted]	0.033	[redacted]
Reams et al HR = 1	[redacted]	0.031	[redacted]
Reams et al HR = [redacted]	[redacted]	0.001	[redacted]

HR hazard ratio

It can be seen that discontinuation assumptions have little impact on the estimated ICER for etelcalcetide compared with PB/VD alone. However, the ICER for etelcalcetide vs. cinacalcet is much more sensitive. Introducing a higher discontinuation rate for etelcalcetide than for cinacalcet, reduces incremental QALYs, and although incremental costs also fall, the net effect is that the ICER increases considerably. We conclude that real-world rates of discontinuation in the UK for cinacalcet and for etelcalcetide are likely to be important drivers for cost-effectiveness.

4.4.1.5 Utility benefits of calcimimetics

In the base case model, the company assumed that there was no utility benefit from taking either calcimimetic. However, the Briggs and colleagues analysis of EVOLVE EQ-5D data showed an independent utility gain of 0.02 (95% CI 0.01 to 0.03) with cinacalcet, after adjusting for incidence of clinical events and baseline EQ-5D (4.3.5.4 page 106).[48] This might be explained by a direct effect on SHPT symptoms.

The company conducted scenario analysis, including a utility gain for cinacalcet-controlled trial 20120360 trial showed that patients on cinacalcet appear to have slightly better quality of life than patients on etelcalcetide. Therefore it is reasonable to assume that benefits of cinacalcet identified in the EVOLVE trial (Briggs and colleagues)[48] may not apply to etelcalcetide. To reflect the lack of direct evidence on the utility effects of etelcalcetide using EQ-5D, we add two scenarios in which we apply the utility gain for cinacalcet but assume no or a lower effect (0.01) for etelcalcetide (see Table 48).

Table 48 Scenario analysis for calcimimetic utility gain: anticipated list price

Scenario	Incremental costs	Incremental QALYs	ICER
Etelcalcetide vs. PB/VD comparison			
CS base case: no utility gain	[redacted]	**0.321**	[redacted]
Utility gain of 0.02 for both calcimimetics	[redacted]	0.366	[redacted]
Utility gain 0.01 for E and 0.02 for C	[redacted]	0.344	[redacted]
Utility gain of 0.02 for cinacalcet only	[redacted]	0.321	[redacted]
Etelcalcetide vs. cinacalcet comparison			
CS base case: no utility gain	[redacted]	**0.069**	[redacted]
Utility gain of 0.02 for both calcimimetics	[redacted]	0.070	[redacted]
Utility gain 0.01 for E and 0.02 for C	[redacted]	0.047	[redacted]
Utility gain of 0.02 for cinacalcet only	[redacted]	0.024	[redacted]

E etelcalcetide; C cinacalcet

Assuming the same direct utility gain for cinacalcet and etelcalcetide slightly improves etelcalcetide cost-effectiveness compared to PB/VD and also improves cost-effectiveness of etelcalcetide compared with cinacalcet. Assuming no or a lower utility gain with etelcalcetide than with cinacalcet is much less favourable. In the absence of direct evidence for etelcalcetide, it is difficult to determine which of these scenarios is more plausible. As noted in section 3.3.6 some adverse events are higher in etelcalcetide patients, suggesting the assumption of equal utility gain might not be appropriate.

4.4.1.6 Sequencing of calcimimetics

The final ERG scenario analysis relates to the possibility of sequenced use of the calcimimetics. The company noted that some patients in the placebo-controlled trials of etelcalcetide had previously discontinued cinacalcet due to lack of efficacy, adverse reactions or intolerability (CS 4.8.1.2 page 68). They conducted a post-hoc subgroup analysis, and found that the effectiveness of etelcalcetide was lower but not significantly different in this 'cinacalcet failure' subgroup (see section 3.3.5 above). Although they correctly urge caution over the interpretation of this result, due to the small sample size and post hoc nature of the analysis, the company suggests that: "This supports the efficacy of etelcalcetide as a 2nd-line calcimimetic in those who have previously failed cinacalcet treatment" (CS page 68). Our clinical advisor also suggested that because of the better evidence base and longer experience with cinacalcet, clinicians might prefer an initial trial of cinacalcet for patients whose SHPT cannot be adequately controlled on PB/VD alone, before considering the use of etelcalcetide (section 2.2 above).

The company model assumes that after discontinuation of either calcimimetic drug, patients would continue on PB/VD alone (see Figure 3 on page 85 above). We adapted this approach to include two additional sequenced treatment strategies:

- The 'cinacalcet-etelcalcetide' strategy: cinacalcet and PB/VD → etelcalcetide and PB/VD → PB/VD alone, with each switch corresponding to discontinuation of the previous treatment. This strategy is only within scope for 'refractory' patients who have previously failed to achieve adequate SHPT control on PB/VD treatment alone.
- The 'etelcalcetide-cinacalcet' strategy: etelcalcetide and PB/VD → cinacalcet and PB/VD → PB/VD alone, with each switch corresponding to discontinuation of the previous treatment. This is within scope for the 'broad licensed population', who might not be refractory to PB/VD treatment alone.

Table 49 shows the results of these analyses. Some treatment strategies are out of scope for some patient groups; consequently, we do not include strategies that start with cinacalcet for the broad licensed patient population, or PB/VD alone for refractory patients.

Table 49 Incremental analysis with sequenced calcimimetics: base case with anticipated list price

Treatment strategy	*Total Costs*	*Total QALYs*	**Vs. PB/VD alone**		**ICER** *£/QALY*
			Incremental Costs	*Incremental QALYs*	
Non-refractory to PB/VD alone (broad licensed population)					
PB/VD alone	[redacted]	3.788	[redacted]	0.000	[redacted]
Etelcalcetide *	[redacted]	4.109	[redacted]	0.321	[redacted]
Etelcalcetide – cinacalcet *	[redacted]	4.278	[redacted]	0.489	[redacted]
Refractory to PB/VD alone					
Cinacalcet *	[redacted]	4.040	[redacted]	0.252	[redacted]
Etelcalcetide *	[redacted]	4.109	[redacted]	0.321	[redacted]
Cinacalcet – etelcalcetide *	[redacted]	4.251	[redacted]	0.463	[redacted]
Etelcalcetide – cinacalcet *	[redacted]	4.278	[redacted]	0.489	[redacted]

QALYs, quality-adjusted life-years; ICER, incremental cost-effectiveness ratio; PB, phosphate binders; VD, vitamin D;
* In addition to PB/VD, and followed by PB/VD alone on discontinuation of final calcimimetic drug

This analysis should be considered illustrative only, since it assumes that the effectiveness of each calcimimetic drug does not differ for patients who have or have not previously discontinued the other calcimimetic. As noted, there is some evidence to support this assumption for etelcalcetide, but not for cinacalcet. The analysis suggests that etelcalcetide followed by PB/VD on discontinuation would be extendedly-dominated for both populations:

- In the non-refractory population, etelcalcetide followed by cinacalcet on discontinuation (ICER [redacted]) is more cost-effective than etelcalcetide followed by PB/VD alone (ICER [redacted]).
- In the refractory population, etelcalcetide followed by PB/VD is dominated by both calcimimetic sequences. Cinacalcet-etelcalcetide has an ICER of [redacted] compared with cinacalcet, and etelcalcetide-cinacalcet as an ICER of [redacted].

However, as with the company's analyses, this scenario analysis assumes that both 'refractory' and 'non-refractory' populations have the same propensity to attain SHPT control with standard treatment (PB/VD), which is unlikely. We consider this issue further in the subgroup analysis presented below.

4.4.2 Additional subgroup analyses

4.4.2.1 Propensity for SHPT control on PB/VD alone

In the company base case, only 8.9% of patients treated with PB/VD alone are assumed to achieve the 30% PTH reduction target over 6 months: the observed rate in the pooled placebo arms of trials 20120229 and 20120230. This figure fell to 4.9% for placebo arm

patients who had previously discontinued cinacalcet due to lack of efficacy, adverse reactions or intolerability (CS Table 19 page 68). However, as noted above, the ERG meta-analysis of cinacalcet trials (see section 3.5.2) indicated that 25.4% of patients in the placebo arms achieved the same target, or 17.1% if the outlier Ketteler and colleagues trial is excluded.[32] Therefore, the proportion of patients in routine practice that would respond to PB/VD treatment alone is highly uncertain. One might reasonably expect this to differ at different points in the care pathway. In particular, we suggest that patients who have already not responded to an adequate trial of treatment with PB/VD alone, have a lower propensity to attain the 30% PTH reduction target. Therefore, we vary the proportion of patients attaining this target with PB/VD alone in scenario analyses below to illustrate how the cost-effectiveness may differ for 'refractory' patients.

To implement this approach, we used the simple indirect comparison method using odds ratios from the three etelcalcetide trials: scenario 2 in Table 43 (page 125). This allowed us to vary the proportion of patients achieving the PTH reduction target on PB/VD alone: from 4.9% and 25.4% (see Table 50).

Table 50 Scenario analysis by propensity to achieve target: anticipated list price

Scenario	Incremental costs	Incremental QALYs	ICER
Etelcalcetide vs. PB/VD comparison			
CS base case: 8.9% achieve PTH target	[redacted]	**0.321**	[redacted]
Simple ITC: 4.9% achieve PTH target	[redacted]	0.310	[redacted]
Simple ITC: 8.9% achieve PTH target	[redacted]	**0.291**	[redacted]
Simple ITC: 17.1% achieve PTH target	[redacted]	0.275	[redacted]
Simple ITC: 25.4% achieve PTH target	[redacted]	0.268	[redacted]
Etelcalcetide vs. cinacalcet comparison			
CS base case: 8.9% achieve PTH target	[redacted]	**0.069**	[redacted]
Simple ITC: 4.9% achieve PTH target	[redacted]	0.058	[redacted]
Simple ITC: 8.9% achieve PTH target	[redacted]	**0.039**	[redacted]
Simple ITC: 17.1% achieve PTH target	[redacted]	0.024	[redacted]
Simple ITC: 25.4% achieve PTH target	[redacted]	0.017	[redacted]

ITC indirect treatment comparison; PTH parathyroid hormone

As described previously (section 4.4.1.1), the estimated ICERs are higher using the ERG 'simple ITC' approach than in the company's base case. With the simple ITC approach, ICERs are sensitive to the percentage attainment of the PTH reduction target in the PB/VD alone group. The relevance and impact of this sensitivity differ between the 'refractory' and 'non-refractory' populations:

- A higher proportion of non-refractory patients, for whom the comparison with PB/VD alone is relevant, are likely to attain the 30% PTH reduction target. Thus, the company base case analysis that assumes only 9% will respond to standard treatment, is likely to over-estimate cost-effectiveness of etelcalcetide in this population.
- Refractory' patients, for whom the comparison with cinacalcet is more relevant, are less likely to attain the target PTH reduction on PB/VD alone. Thus the very high ICERs for patients with a greater propensity to achieve the PTH reduction target are less relevant. Nevertheless, even with an assumed 5% of patients reaching the target, the ICER is still estimated to be above £100,000 per QALY.

4.4.2.2 Patients with previous events

As noted in section 4.3.2.2, some patients in the etelcalcetide trials and EVOLVE had already experienced a cardiovascular event or fracture prior to randomisation. However, the model assumed that all patients entered in the 'event free' state. We adapted the model to enable subgroup analysis to test the impact of this assumption, by starting the cohort in one of the post-event states. See Table 51 for results for cohorts starting in the 'prior fracture' and 'prior CV event' health states.

Table 51 Scenario analysis by history of clinical events: anticipated list price

Scenario	Incremental costs	Incremental QALYs	ICER
Etelcalcetide vs. PB/VD comparison			
CS base case: patients start 'event free'	[redacted]	**0.321**	[redacted]
Previous fracture	[redacted]	0.263	[redacted]
Previous CV event	[redacted]	0.259	[redacted]
Etelcalcetide vs. cinacalcet comparison			
CS base case: patients start 'event free'	[redacted]	**0.069**	[redacted]
Previous fracture	[redacted]	0.057	[redacted]
Previous CV event	[redacted]	0.055	[redacted]

CV cardiovascular (MI, hospitalisation for unstable angina, peripheral vascular event or heart failure)

In general, one would expect the cost-effectiveness of a preventive intervention to improve for patients with a higher background risk. However, in this scenario analysis ICERs were higher for patients with prior fracture or CV event than for patients who started event free. This is explained by the way in which the utility and mortality impacts of events are modelled. Patients with a previous fracture or CV event are at higher risk of recurrent events. But this does not increase mortality, as all-cause mortality is modelled separately. The QALY loss

due to morbidity is also lower for a second event than for a first event: the first event incurs a three-month acute decrement in utility and ongoing utility loss over the patient's remaining lifetime, whereas subsequent events only incur the acute utility loss.

4.4.3 ERG preferred analysis

The main sources of data and methods used in the ERG base case analysis are summarised in Table 52.

4.4.3.1 ERG base case

Table 52. Summary of parameter sources and assumptions in ERG base case

Aspect	Parameters	Source
Population characteristics	**PTH control with PB/VD alone**: % achieving >30% mean reduction in PTH over 6 months	Pooled placebo arms of etelcalcetide trials 20120229 and 20120230 Placebo arms of ERG meta-analysis for non-refractory subgroup [12, 13]
	All-cause mortality by age	US dialysis registry, Boer et al[45]
	Clinical risks with PB/VD alone: CV (initial and repeat); fracture (initial and repeat); and parathyroidectomy	EVOLVE placebo arm[38]
Treatment effects	**Relative effects on PTH control**: relative risks estimated from odds ratios, with simple chained ITC	Etelcalcetide vs. PB/VD: pooled trials 20120229 & 20120230 Etelcalcetide vs. cinacalcet: head to head trial 20120360 [12-14]
	HRs for clinical events CV (initial and repeat); fracture (initial and repeat); and parathyroidectomy	EVOLVE adjusted for baseline co-variates and non-adherence (IPE) Extrapolated to etelcalcetide assuming linear relationship between PTH control and log HRs (company response to Clarification B2)
Discontinuation	**Persistence with cinacalcet**; fitted Weibull survival function	EVOLVE[38]
	HR for discontinuation; etelcalcetide vs. cinacalcet	Not included in base case[14]
Utility	**Utility for dialysis patients**: not varied by age	Briggs analysis of EVOLVE data [48]
	Utility decrement with events: first three months and subsequent for CV events, fractures and parathyroidectomy	Briggs analysis of EVOLVE data No ongoing effect of parathyroidectomy – model not structured appropriately[48]
	Utility effect of calcimimetics	Not included in base case
Adverse events	**Treatment related adverse events**	Not modelled
Resource use and costs	**Drug use and unit costs**	Pooled etelcalcetide trials, with minor corrections to BNF/tariff prices
	Monitoring frequency and costs	Garside HTA & Reference Costs [2, 51]

	Costs of Fx and CV events	Reference Costs[51]
	Cost of PTx	Proton renal database, BNF and Reference costs[49, 51, 52]
	Dialysis frequency and costs	Not included in base case

This differs from the company base case in two key respects:

- The method of pooling data on the proportion of patients achieving the primary PTH reduction target in the etelcalcetide trials: 'simple ITC' rather than naïve pooling (Table 43 page 125).
- The method estimating hazard ratios for clinical events from the EVOLVE trial: IPE rather than lag-censored method of adjusting for non-adherence (Table 19 page 91).

The results in Table 53 follow the company's approach and only compare etelcalcetide with PB/VD for 'non-refractory' patients and with cinacalcet for 'refractory' patients, and assume that the same proportion (8.9%) of 'refractory' and 'non-refractory' patients attain the PTH reduction target with PB/VD treatment alone. The ICER for etelcalcetide compared with PB/VD alone is very similar to the company's base case estimate. However, our analysis leads to a much larger ICER for etelcalcetide compared to cinacalcet. This is driven primarily by the change in the method of estimating the proportions of patients reaching the target reduction in PTH with PB/VD alone: from the naïve pooling approach in the company's base case, to our simple chained method of indirect comparison.

Table 53 ERG base case: anticipated list price

Treatment strategy	*Total Costs*	*Total QALYs*	*Incremental Costs*	*Incremental QALYs*	**ICER** *£/QALY*
Non-refractory to PB/VD alone (8.9% target PTH reduction)					
PB/VD alone	[redacted]	3.788			
Etelcalcetide *	[redacted]	4.114	[redacted]	0.325	[redacted]
Refractory to PB/VD alone (8.9% target PTH reduction)					
Cinacalcet *	[redacted]	4.070			
Etelcalcetide *	[redacted]	4.114	[redacted]	0.044	[redacted]

QALYs, quality-adjusted life-years; ICER, incremental cost-effectiveness ratio; PB, phosphate binders; VD, vitamin D;
* In addition to PB/VD, and followed by PB/VD alone on discontinuation of final calcimimetic drug

As with the company's base case, deterministic sensitivity analysis showed that the ERG base case was very sensitive to HRs for mortality, and moderately sensitive to HRs for CV events and fractures, absolute mortality rates under PB/VD, utility for the event-free state, and calcimimetic doses.

4.4.3.2 ERG subgroup analysis

We also present a subgroup analysis, assuming differing propensity for PTH reduction between the two subgroups: 17.1% for non-refractory, based on the ERG meta-analysis of cinacalcet vs placebo trials (section 3.5.2); and 4.9% for refractory, based on the company's subgroup analysis of etelcalcetide vs. placebo for patients who discontinued cinacalcet (section 3.3.5) – see Table 54. Compared with the above ERG base case analysis, this leads to a small increase in the ICER for etelcalcetide vs. PB/VD alone for patients who are not refractory to PB/VD alone; and a decrease in the ICER for etelcalcetide vs. cinacalcet for the refractory population.

Table 54 ERG subgroup analysis: anticipated list price

Treatment strategy	*Total Costs*	*Total QALYs*	*Incremental Costs*	*Incremental QALYs*	**ICER** *£/QALY*
Non-refractory to PB/VD alone (17.1%% target PTH reduction)					
PB/VD alone	[redacted]	3.788	-	-	-
Etelcalcetide *	[redacted]	4.097	[redacted]	0.308	[redacted]
Refractory to PB/VD alone (4.9% target PTH reduction)					
Cinacalcet *	[redacted]	4.070	-	-	-
Etelcalcetide *	[redacted]	4.135	[redacted]	0.065	[redacted]

QALYs, quality-adjusted life-years; ICER, incremental cost-effectiveness ratio; PB, phosphate binders; VD, vitamin D;
* In addition to PB/VD, and followed by PB/VD alone on discontinuation of calcimimetic drug

4.4.3.3 ERG analysis with sequenced calcimimetics

We suggest that the sequenced use of calcimimetics should also be considered, as described in section 4.4.1.6 (page 131 above). Table 55 shows the results of an incremental analysis, including sequenced strategies where appropriate. We assume that first-line use of cinacalcet for non-refractory patients, and that continued use of PB/VD alone for refractory patients would be outside the current scope. The analysis entails the assumption that the effectiveness (OR) of each calcimimetic drug does not differ for patients who have previously discontinued the other calcimimetic drug.

In both populations, the strategy of using etelcalcetide and PB/VD followed on by PB/VD alone on discontinuation of etelcalcetide is extendedly dominated, as sequenced strategies of calcimimetics (with PB/VD and followed by PB/VD alone) offer a more cost-effective alternative.

- In the non-refractory group, the etelcalcetide-cinacalcet sequence has an ICER of [redacted] compared with PB/VD alone.

- In the refractory group, the cinacalcet-etelcalcetide sequence has an ICER of [redacted] compared with cinacalcet. The converse sequence, etelcalcetide-cinacalcet has a higher ICER of [redacted] compared with cinacalcet-etelcalcetide.

Table 55 ERG subgroup analysis with sequenced calcimimetics: anticipated list price

Treatment strategy	*Total Costs*	*Total QALYs*	*Incremental Costs*	*Incremental QALYs*	**ICER** *£/QALY*
Non-refractory to PB/VD alone (17.1% target PTH)					
PB/VD alone	[redacted]	3.788	-	-	-
Etelcalcetide *	[redacted]	4.097	[redacted]		
Etelcalcetide – cinacalcet *	[redacted]	4.285	[redacted]	0.497	[redacted]
Refractory to PB/VD alone (4.9% target PTH)					
Cinacalcet *	[redacted]	4.070	-	-	-
Etelcalcetide *	[redacted]	4.135	[redacted]		
Cinacalcet – etelcalcetide *	[redacted]	4.301	[redacted]	0.231	[redacted]
Etelcalcetide – cinacalcet *	[redacted]	4.326	[redacted]	0.025	[redacted]

QALYs, quality-adjusted life-years; ICER, incremental cost-effectiveness ratio; PB, phosphate binders; VD, vitamin D;
* In addition to PB/VD, and followed by PB/VD alone on discontinuation of final calcimimetic drug

4.4.3.4 ERG assessment of uncertainty

The extent of uncertainty around the ERG analysis for the two populations, and including sequenced calcimimetic treatment strategies is illustrated in in the Cost Effectiveness Acceptability Curves (CEACs) in **Error! Reference source not found.**. These show that there is a very low probability, in either population, that a etelcalcetide-containing strategy would be cost-effective at a threshold of £30,000 per QALY gained. This conclusion was also robust to the main structural uncertainties investigated in the company's scenario analysis (Table 40) and our additional analysis (see Appendix).

4.5 Summary

The company submitted a systematic review of economic evaluations, quality of life and cost of illness studies; as well as a de novo economic model. The systematic review was well conducted and clearly reported. We considered the systematic review to be of high quality and appropriate scope.

The company model was based on a previous model on treatment for SHPT in dialysis patients with CKD, with a structure adapted from the economic evaluation of the EVOLVE RCT by Belozeroff and colleagues.[36] We consider the model structure to be generally appropriate, although the way in which parathryroidectomy was modelled did not enable inclusion of any long term effects or cost savings related to this procedure, which is likely to have favoured etelcalcetide. The intervention, comparators, and outcomes closely matched the NICE reference case. The EVOLVE trial of cinacalcet is used to extrapolate the long-term clinical outcomes of etelcalcetide. This trial was conducted in a population broadly consistent with the etelcalcetide license and the etelcalcetide clinical effectiveness evidence base.

The company chose to analyse only pairwise comparisons of etelcalcetide to PB/VD (in the 'broad licensed indication') and cinacalcet (in patients with 'refractory SHPT'), and did not report an incremental analysis. This is inconsistent with the fact that in the company's analysis, the outputs (life years and QALYs) with etelcalcetide were identical in both the broad licensed indication and in refractory patients, indicating that both groups would be suitable for all three modelled treatments.

The company used lag-censored data from the EVOLVE trial to model the comparative efficacy of PB/VD and cinacalcet. The company assumed that there was a linear relationship between proportion of patients achieving a ≥30% reduction in PTH and the log-hazard ratios for events. This assumption was not based on empirical evidence and no attempts to validate this assumption were made.

We found the company's approach to costing, and measurement of HRQoL to be appropriate and consistent with the NICE Reference Case. Long-term costs of acute events were not included in the model, which is likely to result in an underestimation of costs. Utility estimates were obtained from a well-conducted analysis of EQ-5D data from the EVOLVE trial, which compared cinacalcet with placebo. In their base case analysis, the company did

not include any direct utility effect associated with calcimimetic treatment (in addition to the utility benefits associated with prevention of CV events, fractures, and parathyroidectomy). They conducted a scenario analysis, assuming equal utility gains with etelcalcetide as had been observed with cinacalcet. However, it is uncertain whether this assumption is valid.

The ICER for etelcalcetide compared to PB/VD in the broadly licensed population was [redacted]. In the comparison against cinacalcet, described by the company as being in a refractory SHPT population, the ICER was [redacted]. The hazard ratio for all-cause mortality had the greatest effect on cost-effectiveness in the company's one-way sensitivity analyses. No scenario analyses brought the ICER for etelcalcetide compared to any treatment below £30,000/QALY. PSA found that compared to PB/VD in the broadly licensed population etelcalcetide had only a 0.6% chance of being cost-effective at £30,000/QALY, when compared to cinacalcet the probability of cost-effectiveness at £30,000/QALY falls to 0%.

We found that there were a number of limitations to the company's approach, including:

- It did not adequately incorporate variation in effects between patient groups for the efficacy of PB/VD in lowering PTH.
- It used inadequate synthesis methods to determine etelcalcetide hazard ratios compared to PB/VD and cinacalcet.
- It did not allow for the possible treatment sequences which may occur in practice, i.e. cinacalcet with PB/VD followed by etelcalcetide with PB/VD followed by PB/VD alone in refractory patients.

We conducted scenario and sub-group analyses that addressed these and further areas of uncertainty. The results are sensitive to variations in input parameters and assumptions, particularly for patients with refractory SHPT.

5 End of life

NICE end of life treatment criteria were not applicable and not included in the CS.

6 Innovation

The company suggests etelcalcetide is innovative because its mechanism of action is distinct from that of cinacalcet and because it is the only IV administered calcimimetic. The company argues this method of administration gives health care professionals complete

control over the administration process and may therefore enhance adherence, which the company suggests is a problem with cinacalcet, the only other calcimimetic approved to treat SHPT in patients with CKD, receiving haemodialysis. [redacted]

7 DISCUSSION

7.1 Summary of clinical effectiveness issues

The company identified three large phase III RCTs of etelcalcetide (plus PB/VD) versus cinacalcet (plus PB/VD) (trial 20120360) or placebo (plus PB/VD) (trials 20120229 and 20120230) in people with SHPT in CKD, receiving haemodialysis. These trials were judged by the ERG to be of a generally good quality, although we considered there to be some risk of performance, detection and attrition bias on some outcomes. The key issue the ERG has identified with the evidence presented in the CS is that there is uncertainty in the extent to which the evidence provided by the company reflects the relative efficacy of etelcalcetide and cinacalcet among people with refractory SHPT. The cinacalcet-controlled trial included a broad patient population and not those specifically with refractory SHPT. The company argues that subgroups of patients with a history of cinacalcet use in the three trials are likely to be representative of those with refractory SHPT. We suggest the strength of this argument depends on how cinacalcet is used in the countries where the trials were conducted (that is, whether it is used as an initial treatment in a broad range of patients or more specifically in those with refractory SHPT). In this respect, the CS does not fully meet the decision problem or the final scope.

Another key issue is that the trials did not measure the most clinically relevant outcomes of survival, incidence of cardiovascular and achievement of the PTH target currently used in UK clinical practice for patients receiving haemodialysis (2-9 times the upper limit of the normal reference range). Relatedly, drug doses in all three trials were titrated to a PTH target of ≤300pg/mL (31.8 pmol/L) (CS p. 45), whereas in practice, they would be titrated to the 2-9 times the upper limit of the normal reference range. Therefore, the treatment protocols used in the trials do not reflect current practice in the UK. Outcomes may be different to those found in the trials when using the broader treatment target range.

7.2 Summary of cost effectiveness issues

The company base case was presented as two pairwise comparisons in different populations. Patients within the broad licensed use of etelcalcetide could have etelcalcetide or PB/VD. The ICER for etelcalcetide in this group was [redacted]. For patients refractory to PB/VD the ICER for etelcalcetide compared with cinacalcet was [redacted].

The key assumption of the company model is that there is a linear relationship between achieving a ≥30% reduction in PTH and the log of the hazard ratio for events related to SHPT; including, death, CV, Fx, and PTx events. There is no published empirical data to support this log-linear assumption; however, assumption is required to predict long-term outcomes as there is a lack of mature event data for etelcalcetide. If this relationship is assumed, then the choice of baseline response for PB/VD is crucial. The cinacalcet trials reported better PTH responses for PB/VD-treated patients than in the pivotal etelcalcetide trials. This may indicate that the company base case overestimates the effectiveness of etelcalcetide. An alternative assumption for predicting long-term efficacy for etelcalcetide requires using the risk prediction equation formulated by Eandi and colleagues.[37] This risk prediction equation was limited by its use of heterogeneous observational studies to formulate the prediction equation.

The company did not report attempts to validate the Eandi and colleagues risk prediction equation using EVOLVE data, or to validate the assumption of a log-linear relationship between PTH reduction and risk of events related to SHPT using EVOLVE trial data. Without any such validation, the legitimacy of any set of assumptions tying short term efficacy to long-term results will remain in doubt.

We examined alternative assumptions with relation to treatment sequencing in an attempt to more sufficiently represent likely clinical practice. However, this analysis is limited by insufficient data and the need to make assumptions about effectiveness of treatments when taken at different points in the treatment sequence. Uncertainty around efficacy of drug sequences cannot be resolved without further evidence.

Overall, the company made a strong, clear submission; however, it remains a submission held together by unvalidated assumptions. We have attempted to present a reinforced analysis, but there remains significant uncertainty as to the comparability of the populations

in the trials and the long-term comparative effectiveness of etelcalcetide. The ERG base case estimate for the cost effectiveness of etelcalcetide requires some strong assumptions.

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9 APPENDICES

ERG Scenario analyses

Table 56 Scenario analysis: ERG base case with anticipated list price

Scenario	NON REFRACTORY *(17.1% >30% PTH reduction)*		
	Cost	*QALYs*	*ICER*
	Etelcalcetide vs. PB/VD alone		
ERG Base case	[redacted]	0.308	[redacted]
≤300 mg/dL: simple ITC	[redacted]	0.388	[redacted]
Method of extrapolation			
EVOLVE lag-censored	[redacted]	0.275	[redacted]
EVOLVE disaggregated	[redacted]	0.297	[redacted]
EVOLVE RPSFTM	[redacted]	0.328	[redacted]
Eandi; censored	[redacted]	0.247	[redacted]
Eandi; disaggregated	[redacted]	0.292	[redacted]
Discontinuation			
HR etel vs cina [redacted]	[redacted]	0.273	[redacted]
22% year 1 (Reams)	[redacted]	0.139	[redacted]
Utility calcimimetic			
0.02 for both	[redacted]	0.354	[redacted]
0.02 cina, 0.01 etel	[redacted]	0.331	[redacted]
0.02 cina only	[redacted]	0.308	[redacted]
Other			
PTx: excluded	[redacted]	0.307	[redacted]
Dialysis costs included	[redacted]	0.308	[redacted]

Table 57 Scenario analysis: ERG base case with anticipated list price

Scenario	NON REFRACTORY *(17.1% >30% PTH reduction)*		
	Cost	*QALYs*	*ICER*
	Etel-cina vs. PB/VD alone		
ERG Base case	[redacted]	0.497	[redacted]
≤300 mg/dL: simple ITC	[redacted]	0.581	[redacted]
Method of extrapolation			
EVOLVE lag-censored	[redacted]	0.442	[redacted]
EVOLVE disaggregated	[redacted]	0.479	[redacted]
EVOLVE RPSFTM	[redacted]	0.529	[redacted]
Eandi; censored	[redacted]	0.373	[redacted]
Eandi; disaggregated	[redacted]	0.439	[redacted]
Discontinuation			
HR etel vs cina [redacted]	[redacted]	0.473	[redacted]
22% year 1 (Reams)	[redacted]	0.331	[redacted]
Utility calcimimetic			
0.02 for both	[redacted]	0.577	[redacted]
0.02 cina, 0.01 etel	[redacted]	0.554	[redacted]
0.02 cina only	[redacted]	0.531	[redacted]
Other			
PTx: excluded	[redacted]	0.495	[redacted]
Dialysis costs included	[redacted]	0.497	[redacted]

Table 58 Scenario analysis: ERG base case with anticipated list price

Scenario	REFRACTORY *(4.9% >30% PTH reduction)*		
	Cost	*QALYs*	*ICER*
	Etelcalcetide vs. cinacalcet		
ERG Base case	[redacted]	0.347	[redacted]
≤300 mg/dL: simple ITC	[redacted]	0.388	[redacted]
Method of extrapolation			
EVOLVE lag-censored	[redacted]	0.310	[redacted]
EVOLVE disaggregated	[redacted]	0.335	[redacted]
EVOLVE RPSFTM	[redacted]	0.369	[redacted]
Eandi; censored	[redacted]	0.247	[redacted]
Eandi; disaggregated	[redacted]	0.292	[redacted]
Discontinuation			
HR etel vs cina [redacted]	[redacted]	0.307	[redacted]
22% year 1 (Reams)	[redacted]	0.156	[redacted]
Utility calcimimetic			
+ 0.02 for both	[redacted]	0.393	[redacted]
+ 0.02 cina, + 0.01 etel	[redacted]	0.370	[redacted]
+ 0.02 cina only	[redacted]	0.347	[redacted]
Other			
PTx: excluded	[redacted]	0.346	[redacted]
Dialysis costs included	[redacted]	0.347	[redacted]

Table 59 Scenario analysis: ERG base case with anticipated list price

Scenario	REFRACTORY *(4.9% >30% PTH reduction)*		
	Cost	*QALYs*	*ICER*
	Cina-etel vs. cinacalcet		
ERG Base case	[redacted]	0.231	[redacted]
≤300 mg/dL: simple ITC	[redacted]	0.258	[redacted]
Method of extrapolation			
EVOLVE lag-censored	[redacted]	0.204	[redacted]
EVOLVE disaggregated	[redacted]	0.222	[redacted]
EVOLVE RPSFTM	[redacted]	0.245	[redacted]
Eandi; censored	[redacted]	0.162	[redacted]
Eandi; disaggregated	[redacted]	0.193	[redacted]
Discontinuation			
HR etel vs cina [redacted]	[redacted]	0.205	[redacted]
22% year 1 (Reams)	[redacted]	0.236	[redacted]
Utility calcimimetic			
+ 0.02 for both	[redacted]	0.265	[redacted]
+ 0.02 cina, + 0.01 etel	[redacted]	0.248	[redacted]
+ 0.02 cina only	[redacted]	0.231	[redacted]
Other			
PTx: excluded	[redacted]	0.230	[redacted]
Dialysis costs included	[redacted]	0.231	[redacted]

Table 60 Scenario analysis: ERG base case with anticipated list price

Scenario	REFRACTORY *(4.9% >30% PTH reduction)*		
	Cost	*QALYs*	*ICER*
	Etel-cina vs. cina - etel		
ERG Base case	[redacted]	0.025	[redacted]
≤300 mg/dL: simple ITC	[redacted]	0.040	[redacted]
Method of extrapolation			
EVOLVE lag-censored	[redacted]	0.022	[redacted]
EVOLVE disaggregated	[redacted]	0.024	[redacted]
EVOLVE RPSFTM	[redacted]	0.026	[redacted]
Eandi; censored	[redacted]	0.021	[redacted]
Eandi; disaggregated	[redacted]	0.028	[redacted]
Discontinuation			
HR etel vs cina [redacted]	[redacted]	0.022	[redacted]
22% year 1 (Reams)	[redacted]	-0.014	[redacted] *
Utility calcimimetic			
+ 0.02 for both	[redacted]	0.025	[redacted]
+ 0.02 cina, + 0.01 etel	[redacted]	0.020	[redacted]
+ 0.02 cina only	[redacted]	0.014	[redacted]
Other			
PTx: excluded	[redacted]	0.025	[redacted]
Dialysis costs included	[redacted]	0.025	[redacted]

* ICER for cina-etel compared with etel-cina