THE EFFECTIVENESS AND COST-EFFECTIVENESS OF CINACALCET FOR SECONDARY HYPERPARATHYROIDISM IN END STAGE RENAL DISEASE PATIENTS ON DIALYSIS:

A SYSTEMATIC REVIEW AND ECONOMIC EVALUATION

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ABOUT THE PENINSULA TECHNOLOGY ASSESSMENT GROUP (PENTAG)

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- *Systematic Review Of Endoscopic Sinus Surgery For Nasal Polyps (2003)*
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- *The Effectiveness And Cost-Effectiveness Of Carmustine Wafers And Temozolomide For Newly Diagnosed High Grade Glioma (2005, In Press)*

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CONFLICTS OF INTEREST

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1.1 Background

Secondary hyperparathyroidism (SHPT) is common in end-stage renal disease (ESRD). It may develop early in chronic kidney disease (CKD) and progresses as renal function deteriorates. Normally, homeostatic control of serum calcium and phosphate levels is regulated within narrow bounds through parathyroid hormone (PTH). As kidney function deteriorates, the combined effects of reduced serum calcium, increased serum phosphate and decreased vitamin D activity lead to overactivity of the parathyroid glands as they try to maintain appropriate levels. Eventually, the parathyroids may develop reduced calcium-receptor and vitamin D receptor expression and so are less responsive.

There is an increased risk of vascular disease due to calcification in SHPT. SHPT is the main cause of renal bone disease which increases the risk of fracture. The relative impacts of calcium, phosphate and PTH, being complex, are unclear. Advanced SHPT can cause bone pain, muscle weakness and itching.

Current standard treatment for HPT is based reducing phosphate in the diet, use of phosphate binders (which contain calcium), vitamin D supplements and parathyroidectomy. Currently, the Renal Registry reports that 72% of people meet targets for PTH, 60% for phosphate and 63% meet target calcium levels.

Cinacalcet (Mimpara®, Amgen Inc) is the first of a new class of calcimimetic drugs, which acts on parathyroid calcium receptors to increase their sensitivity to serum calcium. This suppresses the production of PTH. This, in turn, reduces serum calcium and phosphate levels.

1.2 Objectives

To establish the effectiveness and cost-effectiveness of cinacalcet for the treatment of SHPT for people on dialysis due to ESRD.

1.3 Methods

1.3.1 Systematic Review

Electronic databases were searched for relevant published literature on the clinical effectiveness of cinacalcet for SHPT in ESRD. Updated searches were undertaken in February 2006. Included RCTs were critically appraised for internal and external validity. Relevant data were extracted and, as the largest trials were already pooled using patient level data, a narrative synthesis was carried out.

1.3.2 Cost-effectiveness

Electronic databases were searched for relevant published literature on the cost-effectiveness of cinacalcet for SHPT in ESRD. No studies were identified. An economic evaluation was submitted by Amgen, the manufacturers of cinacalcet, to the National Institute for Health and Clinical Excellence (NICE) as part of its appraisal of cinacalcet. This was critically appraised and compared to the authors' economic evaluation.

A Markov (state transition) model was developed by the authors in Excel. The model compared cinacalcet to current standard treatment with phosphate binders and vitamin D. A simulated cohort of 1000 people aged 55 with SHPT was modelled until the whole cohort was dead. Incremental costs and quality adjusted life years (QALYs) were calculated. Extensive one-way sensitivity analysis was undertaken as well as probabilistic sensitivity analysis.

1.4 Results

1.4.1 Number and quality of studies

We identified seven published reports of RCTs comparing cinacalcet plus standard treatment to standard treatment plus placebo. However, most of these papers related to four Amgen trials which were more fully reported, including pooled patient-level data, in the Medical Review of cinacalcet by the USA's FDA. We therefore based our review on four Amgen trials plus the three published papers that report different trials. Therefore a total of

seven trials were included in the systematic review including a total of 846 people randomised to received cinacalcet.

The trials were largely well-designed. The primary outcome for all the trials was a measure of serum PTH reduction. Only one paper provides information about patient based clinical outcomes. This used retrospective analysis of adverse effect data from the four main RCTs to assess the impact of cinacalcet on fracture, CV events, parathyroidectomy and mortality. However, most of the data is based on six-month follow up and it is unclear how the results should be extrapolated to the longer term. Some data comes from people who agreed to take part in an extension study after the original 6-month deadline and it is not know whether their characteristics are the same as the originally randomised population. Methods used for censoring in the analysis are unclear. In addition, death rates in the trials are half that reported for a similar age group by the UK Renal Registry. It is therefore unclear whether the results are applicable to the routine clinical population.

1.4.2 Summary of risks and benefits

Cinacalcet in addition to standard treatment is more effective at meeting target PTH levels than standard treatment plus placebo (40% vs 5% in pooled analysis, p<0.001). Of those patients meeting PTH targets, 90% also experienced a reduction in calcium-phosphate product levels compared to just 1% of those treated with placebo. Cinacalcet is more effective among those with moderately elevated PTH levels than those with very high levels of PTH, but in all cases is more effective than standard treatment alone at reaching target PTH levels (baseline PTH levels >32 to <53pmol/L 60% vs 11%; >53 to <85pmol/L 41% vs 2%; >85pmol/L 12% vs 0).

One paper reported patient based clinical outcomes using adverse effect data from four pooled RCTs. Significantly fewer people treated with cinacalcet were hospitalised for CV events (15.0 vs 19.7 CV events per 100 patient years, RR 0.61, p=0.005) although no difference was seen in all-cause hospitalisation or mortality. Significantly fewer fractures (3.2 vs 6.9 event per 100 patient years, RR 0.46, p=0.04) and parathyroidectomies (0.3 vs 4.1 event per 100 patient years, RR=0.07, p=0.00) were also seen with cinacalcet although this finding is based on small numbers. Given the short follow up it is not clear to what extent these results can be extrapolated to the longer term.

Withdrawal due to adverse effects was more common for those treated with cinacalcet than those treated with placebo (15% vs 8%). Pooled incidence of serious adverse effects was not different between the study arms. However, there was significantly more nausea (31% vs 19%, p<0.001) and vomiting (27% vs 15%, p<0.001) among those treated with cinacalcet. Vomiting was dose related.

1.4.3 Summary of costs

The PenTAG cost-utility model estimates the lifetime cost of standard treatment for SHPT at £6,533 for a person aged 55. The additional cost of cinacalcet is estimated at £21,167 (about £3800 annually). If the costs of dialysis are included in this assessment, standard care costs £81,523 and cinacalcet adds £25,423.

1.4.4 Summary of cost-effectiveness

Amgen submitted an estimate of cost-utility [redacted] This estimates the discounted incremental cost-effectiveness ratio (ICER) for cinacalcet in addition to standard care compared to standard care alone for people with SHPT is £35,600/QALY.

The PenTAG model estimates that, compared to standard treatment alone, cinacalcet in additional to standard care for SHPT costs an additional £21,167 and confers 0.34 quality adjusted life-years (QALYs, or 18 quality adjusted weeks) per person. The ICER is £61,890/QALY.

1.4.5 Analyses of uncertainty

One-way sensitivity analysis suggested that the model was particularly sensitive to a number of transition, utility and cost parameters. These were further investigated through threshold analyses. In most cases, even extreme adjustments to individual parameters did not result in an ICER below a willingness to pay (WTP) threshold of £30,000/QALY. An ICER of £30,000/QALY was estimated if the cost of cinacalcet were reduced from 14.5 pence/mg to 8 pence/mg. The ICER also fell below £30,000 in one-way threshold analysis if the relative risk of death associated with having “very uncontrolled” PTH levels (>85pmol/L) compared to meeting target levels of 32pmol/L was raised to 2.2 (compared to 1.1814 in the base case).

In probabilistic analysis only 0.5% of simulations showed cinacalcet to be cost effective at WTP of £30,000/QALY. The cost-effectiveness acceptability curve (CEAC) shows cinacalcet is only likely to be the most cost-effective treatment option above a WTP threshold of £62,000/QALY.

We evaluated the cost-effectiveness of only treating those with moderately uncontrolled PTH (>32 <85pmol/L). This reduced the ICER only slightly to £57,422/QALY. Only treating those with very uncontrolled PTH levels(>85pmol/L) increases the ICER to £81,479/QALY.

We also assess the impact of altering the assumptions in the model through using different data sources for the inputs. The range of ICERs for these analyse was £39,000 to £92,000/QALY.

1.5 Discussion

The systematic review shows that cinacalcet is effective at reducing levels of PTH in people with SHPT. However, the identified studies have short follow up and it remains unclear whether this impact will be maintained in the long term or what impact on parathyroidectomy, fracture, CV event and mortality will be seen over time.

Although there is considerable uncertainty in may of the parameters, extensive sensitivity analysis carried out as part of the cost-utility analysis shows that cinacalcet is unlikely to be considered cost-effective at usually acceptable levels of wiliness to pay.

This assessment comprises a comprehensive assessment of the effectiveness and cost-effectiveness of cinacalcet for SHPT by an independent team through systematic review and economic modelling.

Better information about the relative impact of different biomarkers on clinical outcomes would allow a more precise estimation of the impact of cinacalcet. In addition, the assessment has been hampered by the lack of long term follow up data for people treated with cinacalcet compared to standard care. Conclusions

Cinacalcet in addition to standard care is more effective than standard care plus placebo at reducing PTH levels without compromising calcium levels. However, there is limited information about the impact of this reduction on patient based clinical outcomes. Given the short follow up, it is unclear how this data should be extrapolated to the long term. Together

with the high drug cost, this leads to cinacalcet being unlikely to be considered cost-effective.

1.5.1 Suggested research priorities

1. Accurate estimates of the multivariate relationship between biochemical disruption in SHPT and long term clinical outcomes is of paramount importance if efforts to model the effectiveness of cinacalcet, or other similar agents, in the future.

2. Long term studies of the maintenance of PTH control in SHPT and of the clinical impact with cinacalcet are needed.

3. A better understanding of the epidemiology of fractures in SHPT is needed, including the pattern of fractures experienced in SHPT, their consequences in terms of health service use, quality of life and mortality.

4. The impact of fracture, CV events and very uncontrolled PTH levels on the quality of life of people with SHPT should be investigated.

1.6 LIST OF ABBREVIATIONS

AE	Adverse events
BDI	Beck depression inventory
BMD	Bone mineral density
BNF	British National Formulary
Ca	Calcium ion
CaxP	Calcium phosphate product
CaR	Calcium receptor (on the parathyroid gland)
CAPD	Continuous ambulatory peritoneal dialysis
CHF	Coronary heart failure
CKD	Chronic kidney disease
CRF	Chronic renal failure
CI	Confidence interval
CKD	Chronic kidney disease
CV	Cardiovascular
DOPPS	Dialysis Outcomes and Practice Patterns Study
EBT	Electron beam tomography
EPO	Erythropoetin
ESRD	End stage renal disease

GFR	Glomerular filtration rate
FCE	Finished consultant episode
FDA	Food and drug administration
HD	Haemodialysis
HES	Hospital episode statistics
HRG	Healthcare Resource Group
ICER	Incremental cost-effectiveness ratio
ITT	Intention to treat
KDBCS	Kidney disease burden score (on the KDQoL)
KDOQI	Kidney Disease Outcomes Quality Initiative
KDQ	Kidney disease questionnaire
KDQoL	Kidney disease – quality of life
MCS	Mental component score (of the SF-36)
NR	Not reported
NSRC	National Schedule of Reference Costs
OR	Odds ratio
P	Phosphate
PCS	Physical component score (of the SF-36)
PD	Peritoneal dialysis
PTH	Parathyroid hormone
QALY	Quality adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
RR	Relative risk
RRT	Renal replacement therapy
SD	Standard deviation
SF-36	Short-form 36 (QoL instrument)
SHPT	Secondary hyperparathyroidism
SIP	Sickness impact profile
TTO	Time trade off
VDR	Vitamin D receptor (on the parathyroid gland)

1.7 DEFINITION OF TERMS

Calcitriol	Active vitamin D_3.
Calciphylaxis	Deposition of calcium and phosphate in parts of the body other than the bones (for example in the blood vessels). Occurs faster when calcium and phosphate levels are high.
Dialysis vintage	The length of time that someone has been receiving dialysis treatment.
Glomerular filtration rate	The glomerular are renal capillary blood vessels actively involved in filtration. The GFR is a measure of the kidneys ability to filter and remove waste products.
Hypercalcaemia	High levels of serum calcium.
Hyperphosphataemia	High levels of serum phosphate
Hypocalcaemia	Low levels of serum calcium.
Hypophosphataemia	Low levels of serum phosphate
Myocardium	Heart muscle.
Osteoblast	Cells associated with bone formation
Osteoclast	Cells responsible for bone breakdown.
Osteodystrophy	Bone formation.
Osteitis fibrosa	A complication of SHPT in which the bone becomes softened and deformed, and may develop cysts. May lead to bone pain and fractures.
Renal Replacement Therapy	Dialysis or transplantation once renal function has deteriorated to such an otherwise fatal extent.
Tetany	Hyper-excitation of the nerves that may lead to muscle spasm and twitching, including of the vocal cords and epiglottis.
Uraemia	Urea and other nitrogen containing waste products found in the blood. Used to describe the constellation of symptoms of kidney failure including lethargy, depression, loss of appetite and oedema. Later symptoms include diarrhoea, anaemia, convulsions, coma.

2 Aim

The aim of this health technology assessment was to establish the effectiveness and cost-effectiveness of cinacalcet for the treatment of secondary hyperparathyroidism in people on dialysis due to end stage renal failure. The assessment was carried out to inform the appraisal of cinacalcet by the National Institute for Health and Clinical Excellence

3 Background

3.1 Description of underlying health problem

Chronic kidney disease (CKD) involves progressively decreasing kidney function. Recognised stages of CKD and commonly associated complications are shown in Table 1. Secondary hyperparathyroidism (SHPT) is a common complication of CKD.[1] It may develop in the early stages of CKD as a response to reduced serum calcium, typically as glomerular filtration rate (GFR) falls to around 80 to 40mL/min/1.73m^2 (normal GFR for an adult is around 100 mL/min/1.73m^2).[2] GFR is a measure of the kidneys' ability to filter and remove waste products, commonly indicated by clearance of creatinine (a muscle breakdown product).

SHPT is an adaptive response to the disrupted biochemistry in CKD and the loss of normal physiological controls results in reduced vitamin D levels, excessive levels of phosphate and low levels of calcium.[3] Metabolic disturbances of vitamin D, calcium, phosphate and PTH level are thus common in CKD. SHPT progresses as renal function deteriorates and most people with end stage renal disease (ESRD, C stage 5) will have SHPT to varying degrees. At this stage, the kidneys are no longer able to excrete waste products effectively or to help regulate water and salts or the body's acidity. The kidneys also influence haemoglobin production, blood pressure regulation and bone turnover.[4]

Table 1 Stages of chronic kidney disease (adapted from UK Renal Association[5]and USA KDOQI)

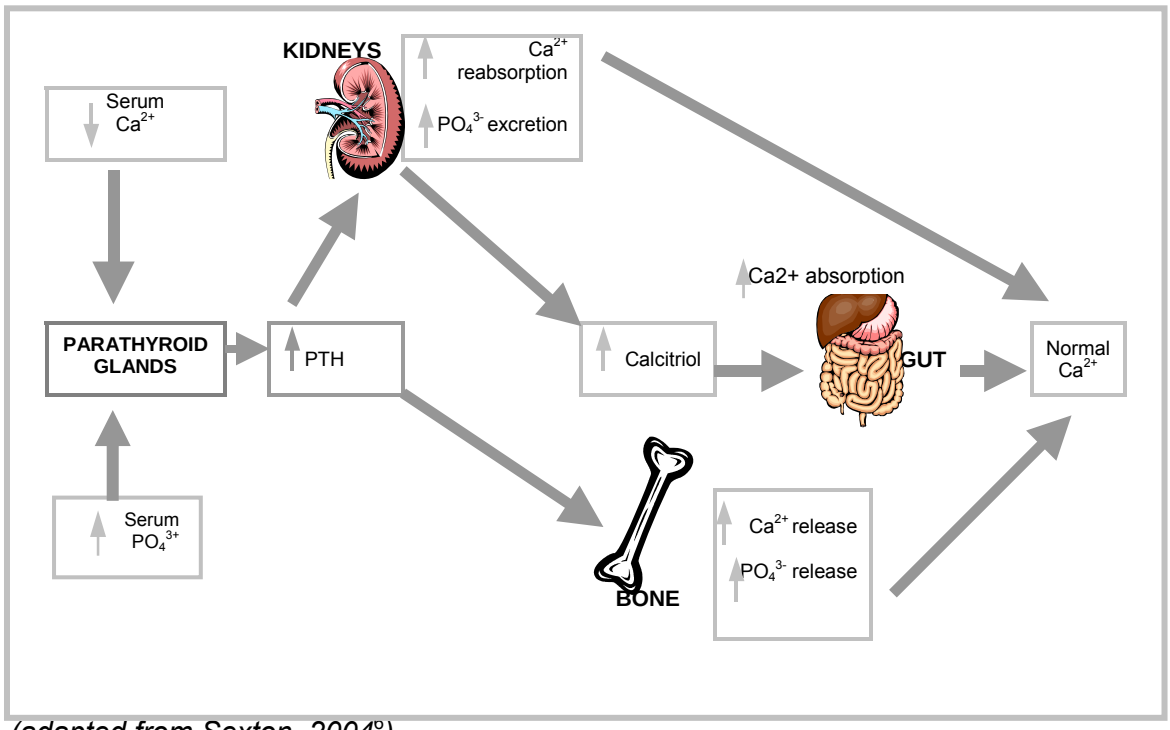
Stage	Description	GFR mL/min/1.73m^2	Common complications
1	Kidney damage with normal or increased GFR	≥ 90	Some hypertension
2	Kidney damage with mild reduction in GFR	60-89	Hypertension frequent Mild PTH elevation
3	Moderate reduction in GFR	30-59	Hypertension common Decreased Ca absorption Reduced Ph excretion More marked elevation of PTH Altered lipoprotein metabolism Reduced spontaneous protein intake Renal anaemia Left ventricular hypertrophy
4	Severe reduction in GFR	15-29	As above, more pronounce plus – Metabolic acidosis Hyperkalaemia Decreased libido
5	Kidney failure (ESRD)	<15 or dialysis	All the above, more severe plus – Salt and water retention (heart failure) Anorexia Vomiting Pruritis

GFR = Glomerular filtration rate, PTH = parathyroid hormone, Ca = Calcium, Ph = Phosphate, ESRD = End Stage Renal Disease

3.2 Normal homeostatic control

With normally functioning parathyroid glands, calcium and phosphate serum levels are regulated within narrow bounds through the responses of the kidneys, gut and bone (see Figure 1). A drop in serum calcium levels causes increased levels of parathyroid hormone (PTH) to be released. This acts on the bones (which release calcium and phosphate) and the kidneys (which reabsorb calcium but excrete phosphate). PTH also increases vitamin D activation in the kidney, stimulating increased calcium absorption from the gut.

Figure 1 *Normal physiological response to a fall in serum calcium levels (hypocalcaemia)*



(adapted from Sexton, 2004º)

Inactive vitamin D (cholecalciferol, vitamin D_3) is made when the skin is exposed to adequate sunlight and is also acquired through diet. These inactive forms are converted by the renal epithelial cells to the active form (calcitriol, $1,25(OH)_2D_3$). In people with CKD, renal hydroxylation is impaired so that levels of serum calcitriol remain low and the specific nuclear binding proteins, vitamin D receptors (VDRs), on the parathyroid glands are not sufficiently activated.[3;7] The amount of calcium that the gut absorbs also falls, resulting in less circulating serum calcium (hypocalcaemia). This is detected by the parathyroid glands which respond with increased PTH production. As levels of calcitriol are reduced, these low levels of calcium fail to be properly compensated. PTH levels rise still further, resulting in SHPT.[6]

Phosphate is acquired from dietary sources such as dairy products, meat and nuts. As kidney function decreases, phosphate excretion is reduced, resulting in hyperphosphataemia. Hypocalcaemia may be caused when increased phosphate complexes with serum calcium. High concentrations of phosphate directly stimulate the parathyroid glands.[6]

Extracellular calcium (as Ca^{2+} ion) is the main regulator of PTH.[8] Low levels of serum calcium cause a reduction in the activity of calcium-sensing receptors (CaRs) on the parathyroid cell membrane, leading to greater PTH secretion. High serum calcium levels have the opposite effect, suppressing PTH secretion. In patients with CKD, increasingly high levels of PTH are needed to maintain appropriate calcium levels.[6]

In combination, the physiological demand for calcium, with excessive serum phosphate and low calcitriol cause over-activity of the parathyroid glands and lead to SHPT. In advanced cases, parathyroid hyperplasia may give way to monoclonal proliferation with rapid cell proliferation leading to vigorous nodular growth with reduced CaR and VDR expression, sometimes called tertiary HPT. At this stage the parathyroid glands become less responsive to serum levels of vitamin D and calcium and PTH becomes more difficult to control.[3]

3.3 Impact of the loss of homeostasis

An overview of the main morbidity and mortality risks with SHPT is given here, and described in more detail at 3.6. Increases in the risks of cardiovascular events and renal bone disease are the major effects of SHPT. Additional clinical consequences include soft tissue calcification, hormonal disturbances, compromised immune system, neuro-behavioural changes and altered red blood cell production.

There is little evidence to establish the relative impact of SHPT as a risk factor for vascular disease in ESRD.[9] Some evidence is available that links SHPT with valvular calcification, vascular calcification and calciphylaxis.[9] As high phosphate levels cause both SHPT and calcification, the relative impact of SHPT is unclear. Calcification of the coronary arteries, which may be measured using electron beam tomography (EBT), has been shown to be more pronounced in those who are older, male, white, diabetic, have been on dialysis for longer or who have higher calcium and phosphate levels.[10;11]

There is evidence that levels of PTH at least four times higher than normal increase the risk of significant bone disease.[9]

Hyperphosphataemia and/or hypercalcaemia are risk factors for vascular calcification, calcification of aortic and mitral valve rings and peri-arterial calcification.[9] However, it may be difficult to interpret the results of phosphate levels taken pre-dialysis, as they may mirror protein intake. Low phosphate may thus indicate malnutrition.[9] Studies from the US have

suggested that survival is best among those with moderately elevated phosphate levels, patients who are thought to be fitter, well dialysed, more active and with good nutrition.[12]

While some studies have shown high levels of calcium (>3.0mmol/L) to be associated with increased mortality, other studies have not shown such a link.[9] Some studies also show low calcium levels to be associated with mortality, ischaemic heart disease and cardiac failure.[9]

3.3.1.1 Hyperparathyroid bone disease

Bone disease in patients with ESRD is complex. It is affected not only by hypocalcaemia and lowered synthesis of vitamin D associated with hyperparathyroidism, but also by conditions that underlie ESRD, such as diabetes, as well as treatment modalities such as calcium supplements, phosphate binders and dialysate.[13] Renal osteodystrophy affects at least three quarters of those with a GFR of <60mL/min/1.73m^2.[3] Two main types of renal bone disease are experienced with ESRD:

- High-turnover bone disease – caused by high PTH levels.
- Low-turnover bone disease – caused by low PTH levels.

Mixed osteodystrophy can also occur.

High turnover bone disease

PTH increases osteoclast activity and bone resorption leading to high turnover bone disease which may include the typical features of osteitis fibrosa.[7] Up to three-quarters of patients with ESRD on dialysis have high turnover bone disease.[3] Osteitis fibrosa can cause bone thinning, bowing and sometimes cysts, leading to bone pain (especially on exertion), painful joints, diminished vertebral height and fractures.[3;7]

Low turnover bone disease

Low-turnover bone disease has two main forms: osteomalacia and adynamic bone disease. In osteomalacia, often related to aluminium levels, reduced osteoblast activity is accompanied by changes to the mineralisation process which increase osteoid (uncalcified bone matrix) formation.

Adynamic bone disease is increasing in prevalence and has been recorded in 23%-50% of dialysis patients.[3] This condition involves diminished bone formation and reabsorption. It is thought to be the result of treatment choices for SHPT such as dialysis fluids high in calcium,

calcium-based phosphate binders and vitamin D replacement[3] and may be related to aluminium deposition. The resultant reduced uptake of calcium and phosphate leads to increased levels in the serum.[3] Such disorders can lead to bone deformities and spontaneous fractures although the degree of impact on morbidity and mortality is unknown.

Measuring fracture risk

Bone mineral density (BMD) can be measured using dual energy x-rays or CT scans to establish the amount of calcium compared to established norms. Results may be expressed as a Z-score, which compares BMD to an age- and sex-matched normal referent population. The WHO has established reference ranges for the general population. However, this only identifies the risk with osteoporosis and the relation of BMD to fracture risk for those with renal osteodystrophy is less clear cut. The impact of disordered biochemistry on fracture risk is discussed further in Section 3.6.3.

3.3.1.2 Soft tissue calcification

It has long been known that calcification of soft tissues is widespread among people with CKD.[11] This may be the result of hypercalcaemia or a high calcium phosphate (Ca x P) product. Calcification of the cardiac valves, aorta and coronary artery are associated with increased cardiovascular morbidity and mortality. Calcification may also be seen in lungs, eyes, joints and kidneys.[6]

High levels of serum phosphate may cause tissue calcification both directly and indirectly.[11]

3.4 Epidemiology of CKD and ESRD

SHPT starts early in the course of CKD and is fairly ubiquitous in ESRD. Incidence of CKD may be estimated in population-based studies using serum creatinine concentration, which is a widely used , though insensitive, investigative test.[9] Such studies may underestimate actual CKD incidence.[9]

Two population studies in the UK have used serum creatinine concentration as a marker for CKD.[9] The first, based in Grampian, estimates a CKD incidence of 450 per million population (using serum concentration of >300µmol/L to indicate CKD).[14] The second, based in South West Hampshire HA found an annual CKD incidence of 1700 per million population

(using serum creatinine concentrations of >150µmol/L, 95% CI 1562, 1849) (source Drey, 2000 quoted by the Renal Association[9]).

Two UK studies have estimated the annual incidence of ESRD based on creatinine concentrations of more than 500µmol/L at 148 and 132 per million population (based on Feest 1990, in Devon and the North-West, quoted by the Renal Association,[9] and Khan 1994, based in Grampian, respectively.[14]) Figures based on the Renal Registry in England suggest that 104 people per million population start renal replacement therapy (RRT) each year (about 6000 people) of which 3% will receive a kidney transplant within 90 days while the remainder receive dialysis.[15] The prevalent population receiving RRT in 2003 was 632 per million population (about 33,500 people). About half these will have had a kidney transplant while the remainder are receiving dialysis.[4]

Acceptance rates for RRT may also be used to estimate ESRD incidence, although these may also underestimate rates as they are influenced by detection, referral and acceptance levels.[15] The UK Renal Registry is estimated to cover 73% of the population of England and 100% of Wales. In 2003, 3556 patients were recorded as accepting RRT, giving a crude annual acceptance rate of 104 per million population.[15]

CKD is a disease of the elderly, with most of those affected in their 70s and 80s.[16] In a US study, two-thirds of the sampled population with grade three to five CKD were over 70 and three-quarters had a history of hypertension.[17] Median age at acceptance of RRT is 65 in the UK, although this is lower among ethnic minority populations, at 59.[15] This may relate to higher levels of diabetes among Indo-Asian populations and of hypertension in those of African and Afro-Caribbean origin,[9] although the age-profile of these populations are generally younger than the white population. Sixty-two percent of RRT patients are male; [12;15] an imbalance that is more pronounced in older populations.

CKD may be due to a number of different causes. Diabetes is the most common single underlying cause, present in 19% of patients according to the Renal Registry,[15] however, in many patients no underlying cause is identified.

3.5 Signs and Symptoms associated with SHPT

Symptoms from rapid falls in calcium levels include tetany (hyperexcitation of the nerves that may lead to muscle spasm and twitching, including of the vocal cords and epiglottis), convulsions and cardiac arrhythmia.[6] However, these are rare in ESRD where reductions to

a low calcium level (hypocalcaemia) are usually more gradual. High levels of calcium (hypercalcaemia) are more common, and may cause symptoms of muscle weakness, nausea, thirst, confusion and constipation.[6] These may be iatrogenic from treatment with calcium-based phosphate-binders and vitamin D (as calcitriol).

High levels of phosphate can cause itching, nausea and resistance to erythropoietin (a hormone that regulates the production of red blood cells in the marrow).

SHPT can cause renal bone disease, leading to bone pain and a higher risk of fracture. A reduced response to epoetin (an amino-acid that regulates red blood cell production) may result in anaemia. Cardiovascular calcification may involve the myocardium itself, the heart valves and arteries and can cause increased mortality.[3] Calcification may also been seen elsewhere, in the lungs, kidneys, eyes and joints. Other symptoms may include muscle pain or stiffness, irritability, fatigue and poor sleep.

3.6 Prognosis

Untreated ESRD is inevitably fatal without treatment. The death rate among those treated with dialysis therapy is remains high, at about 20% per year.[18] Abnormalities of mineral metabolism may cause significant bone disease and contribute to cardiovascular disease. Cardiovascular mortality is 10 to 100 times greater in patients undergoing dialysis than in the general population (for patients aged 75-85 and 25-34 respectively).[2;3] Half of all deaths among dialysis patients are attributed to cardiovascular disease.[19]

3.6.1 Factors influencing mortality risk

Age and the presence of co-morbidities influence survival in ESRD. The Renal Registry estimates only 39% of people starting RRT have no co-morbidity present. The five most frequent co-morbidities recorded are diabetes (26%), cardiovascular disease (25%), angina (19%), smoking (18.4%) and peripheral vascular disease (14%).[15] Multivariate analysis on data held by the UK Renal Registry shows that the five co-morbidities with the strongest association with mortality are liver disease (HR 1.69, 95% CI 1.19, 3.34); ischaemic/ neuropathic ulcers (HR 1.75, 95% CI 1.23, 2.49); malignancy (HR 1.69, 95% CI 1.32 to 2.15); diabetes (HR 1.65, 95% CI 1.35, 2.02) and cerebrovascular disease (HR 1.39, 95% CI 1.09, 1.78).[15]

The Renal Registry has classified risk groups for mortality based on age and presence of diabetes (Table 2).[9]

Table 2 *Median survival of risk groups in the Renal Registry*

Risk classification	Population	Median survival (yrs)
Low risk	Non diabetics aged <55	14.2
Medium risk	Non diabetics aged 55-64 Diabetics aged 15-54	7.4
High risk	Non diabetics aged 65+ Diabetics aged 55+	3.5

A UK study based on a hospital cohort of 292 people on dialysis (mean age 61 years) found that the severity of co-morbidity and functional status was a stronger predictor of mortality than age.[20] In addition, mortality is greater among those with low serum albumin and low cholesterol levels, associated with poor nutition.[21]

Mortality risk is associated with levels of serum phosphate, possibly because of its effect on vascular calcification.[5] A US study of 40,538 patients on thrice weekly dialysis assessed the impact of serum mineral levels on mortality over 18 months. Serum phosphate levels higher than 1.61mmol/L (5.0ml/dl) were associated with increased risk of death when adjustment was made for age, race or ethnicity, diabetes, time since initiation of dialysis as well as laboratory variables including parameters of mineral metabolism, nutritional status and haematological status.[18] Relative risk (RR) of death, compared with a reference population with phosphate serum concentrations of 1.29-1.61mmol/L (4.0-5.0mg/dl), is shown in Table 3.

Table 3 *Relative risk of mortality with elevated phosphate levels*[18]

Serum phosphate level mmol/L	Serum phosphate level mg/dl	Relative risk of mortality
1.61-1.94	5.0-6.0	1.07
1.94-2.26	6.0-7.0	1.25
2.26-2.58	7.0-8.0	1.43
2.58-2.91	8.0-9.0	1.67
≥ 2.91	9.0	2.02

Referent group Ph levels = 1.29-1.61mmol/L (4.0-5.0mg/dl)

The Renal Registry has also assessed relative mortality hazard for different levels of phosphate, calcium and calcium phosphate product by mode of dialysis HD and PD.[12] The results are shown in Appendix 8.1 page 191. Numbers have been extracted from a graph and rounded to 2 decimal places and so may be subject to inaccuracies. Data is not provided for higher serum levels where risks may be highest.

Several small observational studies have found no association between serum calcium levels concentration and risk of mortality.[10;22;23] However, the study by Block and colleagues (2004),[18] showed that raised calcium levels (adjusted for case mix as before) were also associated with increased mortality compared with those within the reference range of 2.25-2.38 mmol/L (9.0-9.5mg/dl). This was the case even when assessed within a narrow range of serum phosphate levels.

Finally, Block and colleagues (2004)[18] found that while high PTH concentrations greater than 63.6pmol/L (600pg/ml) were associated with increased risk of death in adjusted analysis, smaller increases of PTH 31.8-63.6pmol/L (300-600pg/mL) were not. Levels of PTH were higher among younger patients, women, black people and those without diabetes.

3.6.2 Factors influencing risk of cardiovascular events

A recent review of studies examining the link between serum calcium, phosphorous, calcium-phosphate product and PTH in ESRD with coronary artery calcification found mixed results.[24] The importance of such biomarkers remains unclear.

Block and colleagues' (2004) found that the risk of being hospitalised due to cardiovascular events was associated with serum phosphate levels.[18] Increase in risk by serum phosphate levels compared to a reference group with phosphate levels of 1.29 to 1.61 mmol/L (4.0-5.0mg/dl) are shown in Table 4. The same study found no association between cardiovascular hospitalisation and serum calcium levels. Levels of PTH greater than 63.6pmol/L (600pg/ml) were associated with greater risk (RR 1.17; 95% CI 1./06, 1.29) compared to those with reference levels of 15.9-31.8pmol/L (150-300pg/ml). The authors suggest that this is largely due to high risk among those with very high levels of PTH, greater than 95.4pmol/L (900pg/mL), among whom the RR of cardiovascular hospitalisation was 1.26 (95% CI 1.12, 1.42).[18]

Table 4 *Risk of cardiovascular hospitalisation by serum phosphate levels*[18]

Serum phosphate level mmol/L	Serum phosphate level mg/dl	Increased risk of cardiovascular hospitalisation (%)
1.61-1.94	5.0-6.0	10
1.94-2.26	6.0-7.0	15
2.26-2.58	7.0-8.0	29
2.58-2.91	8.0-9.0	28
≥ 2.91	9.0	38

Referent group Ph levels = 1.29-1.61mmol/L(4.0-5.0mg/dl)

Increased cardiovascular hospitalisation was also seen among patients who were male, white, had lower body weight or had diabetes.[18] In addition, it is suggested that some other traditional markers may be stronger indicators of CV risk than biomarkers even in the dialysis population, for example blood pressure, cholesterol, albumin and homocysteine levels.[12;25]

3.6.3 Factors influencing risk of fracture

A study of 101,039 patients with ESRD awaiting transplantation in the USA estimated the annual risk of hip fracture as 2.9/1000 patients.[26] PTH appears to be the most sensitive marker for disordered bone and mineral metabolism in CKD.[5;26] Elevated plasma PTH is negatively associated with measures of bone mineral density (BMD).[5;27]

Elevated PTH predicts the development of more severe hyperparathyroidism, which in turn is associated with increased skeletal and cardiovascular problems. However, detailed interpretation of the relationship of biomarkers with risk remains problematic. Block and colleagues (2004) found that phosphate concentration was significantly related to hospitalization for fracture. RR, per mg/dL increase in serum phosphate levels, was 1.12 (95% CI 1.03, 1.22).[18] Patient characteristics associated with increased risk of fracture included age, being female, lower weight and longer time on dialysis. PTH levels were weakly associated with hospitalisation for fracture. No relationship was seen with calcium levels.

3.7 Current service provision

Haemodialysis (HD) is the usual therapy for people with ESRD. Four-hour dialysis sessions three-times a week are typical.[4] Peritoneal dialysis (PD) is used by about 30% of UK patients as the initial treatment.[9] PD involves dialysis fluid changes four or five time daily, or overnight.[4] However, most patients in the UK undergo HD and some patients on PD may return to haemodialysis, especially in the last few months of life.[9] Studies comparing survival with different dialysis modalities are difficult to assess as patient groups are not usually comparable. However, a recent study of 1041 patients on dialysis followed for seven years in the USA found no difference in survival for those on PD compared to HD during the first year, but that an increased risk was seen from the second year onward (HR 2.34, 95% CI 1.19, 4.59).[28]

Dialysis may also address calcium balance. In the past high dialysate calcium concentration was used to allow calcium transport across the dialyser membrane. However, with increased use of calcium-containing phosphate binders and active vitamin D supplements which can lead to hypercalcaemia, lower concentrations are now recommended.[8]

While dialysis is lifesaving, at best it only replaces about 10% of normal renal function.[29] In addition to problems of SHPT, dialysis patients have other health problems such as water and salt retention, hypertension, anaemia, hyperlipidemia and heart disease.[29] A change of diet and fluid intake is required for patients undergoing dialysis. Treatment (iron and epoetin) may also be needed to treat anaemia.

Transplant is a treatment option for those with ESRD although the number treated is not large. In newly diagnosed ESRD, about 3% will receive a kidney transplant within the first 90 days.[15] In England for 2004 to 2005, UK Transplant recorded a total of 1,783 kidney transplants. Hospital Episode Statistics show 63% of these were carried out in men at a mean age of 42 (HES code M01). There has been a steady increase in transplants since 1998/99 (n=1,327) although most recent figures are down 4% from 2003/2004.

For patients on dialysis, a number of additional treatments may be used to try and maintain homeostasis. The Renal Association has set standards for the levels of serum minerals and hormones for patients with ESRD. These are shown below in Table 5. The US National Kidney Foundation has also produced clinical guidelines, the K/DOQI for CKD and these are shown in Table 6. Conversion values from US units to UK units are shown in Table 7.

Some concerns about these targets have been noted, in particular the need for better clinical evidence to support any benefit of achieving these endpoints.[18;30]

Table 5 *UK Renal Association Standards for ESRD*

	Recommended serum values	Reference intervals[31]
Parathyroid hormone	< 4x the upper limit of normal	0.9-5.4 pmol/L
Serum phosphate	<1.8 mmol/L	0.8-1.45 mmol/L
Serum Calcium*	2.2 – 2.6 mmol/L	2.12-2.65 mmol/L

Table 6 *US National Kidney Foundation standards for CKD*

	Recommended serum values				
CKD stage	**GFR range mL/min/1.732**	**Phosphate mg/dl**	**Calcium* mg/dl**	**Ca x P mg^2/ml^2**	**Intact PTH pg/ml**
3	30-59	2.7-4.6	8.2-10.2	-	35-70
4	15-29	2.7-4.6	8.4-10.2	-	70-110
5	<15 or dialysis	3.5-5.5	8.4-9.5	<55	150-300
5 Converted to mmol/L		1.13-1.78	2.10-2.38	<4.4 $mmol^2/ml^2$	15.90-31.80

Table 7 *Conversion values for grams to moles.*

Serum Biomarker	From	To	Conversion factor (x)
Parathyroid hormone	pg/ml	pmol/L	0.106
Calcium	mg/dl	mmol/L	0.25
Phosphate	mg/dl	mmol/L	0.3229
Ca x Ph product	mg^2/dl^2	$mmol^2/L^2$	0.0807

Accurate detection of PTH levels may be challenging. In kidney disease, fragments of PTH, which are biologically inactive, may build up in the body. Many commercial, so called "intact", PTH assays detect these fragments and may thus overestimate the degree of SHPT.[5] Some assays which detect only whole PTH ("bio-intact" hormone) are available, but there is wide variation in the use of different assays in the UK.[12] This is why there are no

* Adjusted for albumin concentration in a pre-dialysis sample.

absolute levels given for circulating PTH. The renal Association target (within four times the upper range of normal) allows for variation resulting from the use of different assays.

The Renal Registry records that 61% of dialysis patients in England and Wales in 2002 had phosphate levels controlled at the recommended level shown in Table 7. Phosphate control was found to be slightly better for patients on HD, although success at achieving targets varied between centres.[15]

The use of different methods to correct measured serum calcium for albumin concentration leads to difficulties in measuring the success of UK centres in meeting Renal Association calcium level targets. Furthermore, different methods may also be used to measure serum albumin. However, 63% of people are believed to have calcium levels within the target range based on local corrected results. Median reported corrected calcium levels for all centres is about 2.4mmol/L.[15]

Comparison of PTH levels across the centres that inform the Renal Registry is also difficult due to the use of different assays. The median level for all dialysis patients is within the target, at about 19 pmol/L.[15] The Registry has tried to standardise the interpretation of data by using the median upper laboratory value from all assays used, and converting all measurements from grams to moles (giving a target of <32 pmol/L). Using this approach, about 66% of patients achieve the target although there is wide variation between units.[15] Achievement of the target is similar on HD and PD.

There is currently no Renal Association target for the calcium phosphate product (CaxP). However, 67% of people meet KDOQI CaxP targets of less than 4.4mmol^2/L^2 (54.5mg^2/ml^2). Again, there is a wide range across centres. Control of CaxP levels is better with PD than HD.[15]

3.8 Current treatment for secondary hyperparathyroidism

The Department of Health published National Services Frameworks for renal services in 2004 and 2005.[4;17] Treatment of SHPT currently includes:

- Reducing phosphate in the diet
- Phosphate binders
- Vitamin D supplements (in active forms such as calcitriol)

- Parathyroidectomy

3.8.1 Phosphate control

Reducing dietary phosphate may be difficult to achieve as some foodstuffs (e.g. fish, nuts and eggs) while high in phosphate, are also valuable protein sources. The Renal Registry suggests that dietician support in collaboration with the prescribing team produces good results in ensuring that phosphate target levels are achieved.[15]

Phosphate binders reduce phosphate absorption in the gut through binding to phosphate in food. Tablets are taken during phosphate rich meals. Three main types have been used:

1. Calcium-containing phosphate binders. These are cheap and may address hypocalcaemia but carry increased risk of hypercalcaemia due to intestinal absorption of unbound calcium.[8;22] This risk is increased if activated vitamin D is also given.

2. Aluminium-containing phosphate binders. Used extensively in the past but sparingly now despite the risk of aluminium toxicity being reduced since aluminium was removed from the water supply.

3. Polymer binders (such as sevelamer). As an expensive phosphate binder, this is often reserved for second line treatment in the UK.

3.8.2 Vitamin D supplements

Vitamin D, in active form, may be given to patients with CKD and, if given early in the illness, may prevent progression to HPT.[17] Vitamin D therapy aims to reduce PTH secretion by increasing absorption of calcium through the gut and by direct effect on PTH gene transcription. Treatment may lead to hypercalcaemia. Vitamin D analogues, especially if given in high doses intravenously, have been associated with increased calcium-phosphate product (CaxP) which may increase vascular calcification.[30]

3.8.3 Parathyroidectomy

Advanced SHPT may be resistant to medical treatment. In these cases, the parathyroid glands may be surgically removed (parathyroidectomy). Renal Association guidelines recommend surgery if medical management cannot maintain PTH levels below four times

the upper limit of normal, due to increased risk of significant bone disease at these levels.[9] In the US, KDOQI guidelines reserve parathyroidectomy for patients with severe hyperparathyroidism (persistent serum levels of intact PTH >88.0 pmol/L) that is associated with hypercalcaemia and/or hyperphosphataemia that is refractory to medical therapy.

Incomplete excision of the parathyroid glands may mean that levels of calcium and PTH remain high. However, there is also a danger that low serum calcium levels resulting from a sudden removal of PTH may lead to an increased risk of bone disease.[32] There may therefore be a need for large calcium and vitamin D intake, at least in the short term. Alternatively, sub-total parathyroidectomy or total parathyroidectomy with autograft of a small part of the gland in the arm, where it is accessible should further surgery be required, may be an option. Both latter methods are recommended by the KDOQI guidelines.

Parathyroidectomy may offer rapid improvement in quality of life for patients where very high PTH levels have led to symptoms such as bone pain, muscle weakness and itching.[33;34] Improvements in bone mineral density have also been reported following parathyroidectomy.[35] However, persistent and recurrent SHPT is not uncommon, with 22% recurrence requiring medical or further surgical intervention reported over five years.[36]

A large cross sectional study of over 17,000 dialysis patients in the USA, Europe and Japan showed a differences between countries in parathyroidectomy rates of between 0.5 and 1.8 per 100 patient years.[37] This study found a parathyroidectomy prevalence of 9.2% in the UK (1.5 per 100 patient years.)

In England for 2004 to 2005 there were 2,504 parathyroidectomies, 28% in men, among patients with a mean age of 59 (HES code B14). This figure also includes treatment for primary hyperparathyroidism and tumours. There has been a steady increase in parathyroidectomies since 1998/99 (n=1,407).

One serious but uncommon complication of parathyroidectomy, with a rate of around 1/100, is vocal cord paralysis. Nerves serving the vocal cords run close to the parathyroid glands and can be damaged during surgery.

3.8.4 Limitations of current treatment

Currently, Renal Association targets for phosphate levels are met by 61% of the dialysis population, and targets for calcium and PTH are met by 63% and 67% respectively.[15] Evidence from the USA shows only 5% of patients meeting all four KDOQI targets.[38]

Given the number of health problems that those on dialysis may have, such patients may take six to ten medicines daily.[29] Compliance is an issue. As many as 86% of dialysis patients are non-compliant with at least one aspect of their treatment.[29] Phosphate binders may have a poor taste, and may need to be taken in large quantities with each meal.[29] Non-compliance with dialysis has been shown to be associated with higher mortality.

3.9 Quality of life

Patients with ESRD on dialysis have significantly lower health-related quality of life (QoL) compared with the normal population. More severe grades of CKD have lower QoL with higher prevalence of QoL impairments.[39]

3.9.1 Quality of life measures

Impairments in QoL in ESRD patients are wide-ranging and relate to specific symptoms, reduced physical, psychological and social functioning and change in employment status. Measures of QOL should therefore take each of these domains into account. Cagney and colleagues (2000) undertook a literature review of QoL instruments used in people with ESRD.[40] They identified 47 papers, published between 1975 and 1999, containing evidence of reliability and validity testing. Within this set, 53 QoL instruments were used, most generic (82%) and some disease-specific (18%).

3.9.1.1 Generic measures of quality of life

The Sickness Impact Profile (SIP, Table 8) was the most frequently used generic measure identified by Cagney and colleagues (2000).[40] Both this and the SF-36 have been rigorously tested in the ESRD population and have reported striking differences in QoL compared with the general population. The SIP consists of 136 items, measuring 12 QoL dimensions. These are weighted by severity of dysfunction. Higher scores indicate greater dysfunction.

Table 8 *The dimensions of the generic Sickness Impact Profile (SIP)*

Physical	Psychosocial
Ambulation	Social interaction
Mobility	Communication
Body care	Alertness behaviour
Movement	Emotional behaviour
	Sleep and rest
	Eating
	Home management
	Recreation and pastimes
	Employment

A cross-sectional, multi-centre Spanish study assessed 1013 randomly selected people who had been receiving dialysis for at least 3 months (age 53 ±15 years, 88% on HD).[41] Severe impairment of quality of life was seen in 26% of people assessed using the SIP where a score $\geq$ 20 indicates the need for substantial daily care. In the general population, average scores are about five.

The SF-36 is scored from 0 to 100 with a higher score indicating a better perceived health status. Eight health domains are assessed: physical functioning, role–physical, bodily pain, general health, vitality, social functioning, role–emotional and mental health. Another Spanish group have published a number of studies using standardised SF-36 scores to investigate the impact of ESRD (n=170) compared with an age- and sex-matched general population sample (n=9151).[42] Better QoL than the general population is indicated by a score over zero, and a worse QoL relative to the general population is indicated by a score less than zero (Table 9).

The scores of those aged over 65 were closer to zero than those less than 65, showing that older people with ESRD experience less QoL loss than their younger counterparts compared to their peers. The standardised scores for patients under 65 were compared with those over 65. Significant differences were found in three domains (Table 9). Compared to similarly aged general population, the impact of ESRD is greater in terms of general health in older patients, whilst younger patients are more greatly affected in terms of physical role and physical functioning.

Table 9 *Standardised SF-36 scores comparing age <65 vs age >65 in patients on chronic haemodialysis*

	Age <65 years (n=71)	Age >65 years (n = 99)
Physical functioning **	-0.99 ± 1.07	-0.46 ± 0.87
Role - physical *	-0.53 ± 1.27	-0.09 ± 1.06
Bodily pain	-0.38 ± 1.01	-0.09 ± 0.98
General health **	-1.49 ± 0.93	-0.73 ± 0.85
Vitality	-0.53 ± 0.96	-0.25 ± 0.99
Social Functioning	-0.35 ± 1.49	-0.11 ± 0.99
Role - emotional	-0.56 ± 1.47	-0.27 ± 1.3
Mental health	-0.18 ± 1.13	-0.11 ± 1.14

**p<0.01; *p<0.05 for people aged <65 vs >65 on dialysis

The time-trade off (TTO) technique is a preference based method of evaluating QoL that has also been validated in the ESRD population. People are offered choices between living for a specified time in perfect health or living for a longer time with impaired health. A score of zero is equivalent to death and one represents full health. Negative scores, indicating a health state worse than death, are also possible.

We identified six papers that used TTO methods to obtain utility values among people with ESRD. These are summarised in Table 10. Utility estimates ranged from 0.39 to 0.93 (median = 0.69).

Table 10 *TTO values in ESRD*

Study and date	Sample	Age	Dialysis type	Utility Value (SD)
Churchill et al, 1984[43]	42	50	HD	0.58
	17	42	CAPD	0.66
Churchill et al, 1987[44]	60		Hospital HD	0.43 (0.26)
	57		Home HD	0.49 (0.23)
	52		CAPD	0.56 (0.29)
Churchill et al, 1991[45]	47		HD	0.44 (0.28)
de Wit et al, 1998[46]	46	NR	HD	0.87 (0.2)
	23		LCHD	0.93 (0.22)
	59		CAPD	0.86 (0.23)
	37		CCPD	0.93 (0.14)
de Wit et al, 2002[47]	69		HD	0.89 (0.15)
	66		PD	0.87 (0.21)
Hornberger et al, 1992[48]	58		NR	0.72 (NR)
Molzahn et al, 1996[49]	215		NR	0.39 (0.32)

HD = haemodialysis, CAPD = continuous ambulatory peritoneal dialysis, LCHD = limited care haemodialysis, CCPD = continuous cycling peritoneal dialysis, NR = not reported.

3.9.2 Disease specific measures of quality of life

Disease-specific questionnaires provide additional information related specifically to the condition and may be more responsive to clinical changes and treatment effects. The Kidney Disease Questionnaire (KDQ) and KDQoL (Table 11) have been adequately tested in the ESRD population.

The KDQOL-SF, one of the most widely used disease specific measures, uses 43 disease-specific items, 36 generic items and an overall health-ranking item. Development of the KDQOL incorporated field test data highlighting the thought processes of patients, what troubled them and the vocabulary they used to describe factors that affected their quality of life. Validity testing has involved correlating the KDQOL-SF with generic measures, such as EuroQOL, SF-36 and SIP, in patients with kidney disease.[50]

Table 11 *The dimensions of the disease-specific Kidney Disease Quality of Life Short Form (KDQOL-SF) questionnaire*

Generic	Disease-specific
Physical functioning	Symptom/problem list (sore muscles, headaches, cramp, itchy skin, shortness of breath, dizziness, nausea)
General health	Effects of kidney disease (restrictions on fluid/dietary intake, impact on work, travel and lifting objects)
Pain	Burden of kidney disease
	(extent to which kidney disease causes frustration and interference with life)
Role-physical	Work status
Emotional wellbeing	Cognitive function
Role-emotional	Quality of social interaction (extent of irritability with other people/isolation from others)
Social function	Sexual function
Energy and fatigue	Sleep
	Social support
	Dialysis staff encouragement (extent to which person feels supported and encouraged by dialysis staff)
	Patient satisfaction (with overall care received)
	Overall health rating

3.9.3 Factors associated with reduced quality of life in ESRD

Quality of life relating to ESRD directly is difficult to measure as reduction in QoL is only partly related to kidney failure itself; treatment, complications of kidney disease, comorbidity such as diabetes, cardiovascular disease etc., and sociodemographic factors, all have an impact on the perception of QoL. Poor QoL is associated with higher mortality.[51;52]

3.9.3.1 Impact of treatment on QOL

Amongst people on dialysis, the majority of studies looking at differences in QoL between haemodialysis (HD) and peritoneal dialysis (PD) report no significant difference in QoL.[53] Apparent differences in QoL between HD and PD may be attributable to differences in effective renal replacement, reduced clinical complications, lifestyles afforded by these treatment modalities or case-mix differences in patient populations.[53]

Dialysis is an intrusive and time-consuming treatment requires changes in people's lifestyle which may affect QoL. QoL outcomes may also have an impact on the dialysis regimen itself; almost 50% of withdrawals from dialysis are reported to be due to poor quality of life.[54]

Daily dialysis appears to improve QoL.[55-57] Nocturnal short-term daily dialysis performed six to seven times weekly may have beneficial effects on QoL.[55;58] Improvements in metabolic control, cardiovascular morbidity, and dialysis related symptoms, as well as physical and social function may be seen when dialysis is more frequent.

3.9.3.2 Other factors impacting on QOL

QoL may also be negatively affected by complications of chronic kidney disease and comorbid conditions, such as diabetes and cardiovascular disease.[53] Nutrition is an important factor influencing the morbidity and mortality of patients with ESRD[59] and anaemia has also been associated with poor QoL.[41] QoL and depression are closely linked and are also associated with increased comorbidity, worse nutritional status, anaemia, low renal function and a high rate of peritonitis.[60] The prevalence of depression in people with ESRD varies depending on the measure used to detect it, but studies suggest that up to 70% of people on dialysis have some degree of depression.[60] People on dialysis are less active than the normal population and increased physical activity in this group is recommended.[61] The effects of physical activity on self-reported physical functioning may be of clinical importance because these scores have been shown to be highly predictive of outcomes such as hospitalisation and mortality in haemodialysis patients.[61] Table 12 summarises elements associated with better and worse QoL in people on dialysis.

Table 12 *Factors related to health-related QoL in dialysis patients (adapted from Valderrabano et al 2001[53])*

Better QoL	Poorer QoL
Haematocrit/haemoglobin	Associated diseases (comorbidity)
Socioeconomic level	Diabetes
Educational level	Intermittent claudication
Dialysis schedule (daily dialysis, home haemodialysis, peritoneal dialysis)	Previous failed transplant
Black race	Female Sex
Physical exercise	Depression
	Poor nutritional status

3.10 Description of the new intervention - Cinacalcet

Licensing

Cinacalcet hydrochloride (trade name Mimpara® Amgen Inc.) was licensed by the European Medicines Agency (EMEA) in July 2004 for secondary hyperparathyroidism in people with end stage renal disease on maintenance dialysis and for the reduction of hypercalcaemia in people with parathyroid carcinoma. We are assessing the first of these indications.

Dosage

Patients are initially given a 30mg/day dose which is stepped up to a maximum of 180mg/day if lower doses fail to control PTH levels. Blood levels need to be monitored every two to four weeks over the initial treatment phase in order to optimise dose.

Costs

All costs are taken from the BNF number 50 (September 2005).

30 mg, 28-tab pack = £126.28 (£0.15/mg)

60 mg, 28-tab pack = £232.96 (£0.14/mg)

90 mg, 28-tab pack = £349.4 (£0.14/mg)

Pharmacology

Cinacalcet is a calcimimetic agent: it acts on the calcium-sensing receptors on the parathyroid glands to increase their sensitivity to extracellular calcium.[29] This quickly suppresses the production of PTH, and in turn may reduce serum calcium and phosphate levels.[62]

Precautions

As cinacalcet may lower the amount of calcium in the blood and low calcium levels may increase the chance of seizures, blood calcium levels need to be monitored.

On-label precautions include:

- Patients should report the symptoms of low blood calcium right away. Symptoms of low blood calcium include abnormal tingling sensations, muscle pain, cramping, spasms, and seizures.
- Cinacalcet may cause adynamic bone disease if parathyroid hormone levels drop too low.
- Patients with liver problems may need a lower dose of cinacalcet. Patients with liver problems should be monitored carefully during treatment.

Common adverse effects are:

- Nausea and vomiting
- Diarrhoea
- Muscle pain
- Dizziness
- High blood pressure
- Weakness and tiredness
- Loss of appetite

4 Systematic review of effectiveness

4.1 Research question

What is the effectiveness of cinacalcet compared to standard treatment for people on dialysis with hyperparathyroidism secondary to end stage renal disease?

4.2 Review team and Advisory Group

This review was carried out at PenTAG by Ruth Garside, Martin Pitt, Rob Anderson, Richard D'Souza, Stuart Mealing, Chris Roome, Ailsa Snaith, Karen Welch and Ken Stein.

An expert advisory group was formed for the project. This group was consulted during the assessment and provided comments on an early draft of the report. Members were Ms. Caroline Ashley, Dr. Henry Brown, Prof. Terry Feest, Dr. Jonathan Kwan, Prof. Alison MacLeod, Dr. Paul Roderick, and Dr. Robin Winney.

4.3 General methods

The review adopted the methodological approach published by the NHS Centre for Reviews and Dissemination (York) Report No. 4.[63]

4.4 Methods for systematic review of effectiveness

4.4.1 Inclusion and exclusion criteria

4.4.1.1 Inclusion

Intervention:

Cinacalcet HCl in licensed doses

Comparators:

Placebo or

"Standard care", which may include:

- Phosphate binders
- Vitamin D
- Parathyroidectomy

Population:

People with hyperparathyroidism secondary to ESRD on peritoneal or haemodialysis.

Study design:

Randomised controlled trials (RCTs) with at least 12 weeks follow up.

Outcomes:

- Mortality
- Incidence of cardiovascular events
- Incidence of fractures
- Health related quality of life
- Symptoms related to hyperparathyroidism
- Serum PTH, calcium, phosphate and calcium x phosphate product levels
- Parathyroidectomy
- Hospitalisation
- Adverse effects

4.4.1.2 Exclusion Criteria

Population:

People with renal disease not on dialysis.

Primary hyperparathyroidism

Study design:

RCTs with less than 12 weeks follow up.

Study designs other than RCTs

4.4.2 Search Strategy

Electronic databases were searched for published systematic reviews, RCTs, economic evaluations and ongoing research in March 2005 and updated in February 2006. Appendix 8.4 shows the databases searched and the strategy in full. Bibliographies of articles were also searched for further relevant studies, and the FDA website was searched for relevant material.

4.4.3 Identification of studies

Relevant studies were identified in two stages. Abstracts returned by the search strategy were examined independently by two researchers (RG and KS) and screened for inclusion or exclusion. Disagreements were resolved by discussion. Full texts of the identified studies were obtained. Two researchers (RG and KS) examined these independently for inclusion or exclusion and disagreements were resolved by discussion. The process is illustrated in Appendix 8.5.

4.4.4 Data Extraction strategy

Data were independently extracted by two researchers (AS and CR). Disagreements were resolved by discussion. Actual numbers were extracted where possible. In some cases data had to be extracted from graphs and may be subject to inaccuracies. Such data is identified in the data extraction sheets. Data extraction forms for each included study are shown in Appendix 7 (page 219).

4.4.5 Quality assessment strategy

Assessments of RCT quality were performed using the indicators shown below. Results were tabulated and these aspects described.

4.4.5.1 Internal validity

- **Sample size**
  - Power calculation at design
- **Selection bias**
  - Explicit eligibility criteria

- Proper randomisation and allocation concealment
- Similarity of groups at baseline

- **Performance bias**
- Similarity of treatment other than the intervention across groups

- **Attrition bias and intention to treat analysis**
- All patients are accounted for.
- Number of withdrawals specified and reasons described.
- Analysis undertaken on an intention to treat (ITT) basis.

- **Detection bias**
- Blinding
- Objective outcome measures
- Appropriate data analysis

Any potential conflict of interest was noted (for example, financial support provided to studies and/or authors by manufacturers of the interventions).

4.4.5.2 External validity

External validity was judged according to the ability of a reader to consider the applicability of findings to a patient group in practice. Study findings can only be effectively generalisable if they (a) describe a cohort that is representative of the affected population at large or (b) present sufficient detail in their outcome data to allow the reader to extrapolate findings to a patient group with different characteristics.

Generalisability of included studies was assessed by examining the age, sex and race profile of the included patients, as well as their baseline mineral and PTH serum levels. Studies that were representative of the UK population with regard to these factors were judged to have high external validity.

4.4.6 Methods of analysis

Details of the methodology and results of included trials are tabulated and described in the text. Results from RCTs are presented in the same tables; where study design renders cells inapplicable, they have been greyed out. Dashes in the tables indicate the information was

not reported. Where calculated by the authors, χ^2 statistics were derived using the CHIDIST function of Microsoft Excel.

We did not combine the results using meta-analysis because the major trials have already been reported in combination using patient level data.

Most of the papers report outcome measure in metric units. We have adjusted these in order to present them in standard units using the conversion factors shown below.

Table 13 *Conversion values for grams to moles*

Serum Biomarker	From	To	Conversion factor
Parathyroid hormone	pg/ml	pmol/L	0.106
Calcium	mg/dl	mmol/L	0.25
Phosphate	mg/dl	mmol/L	0.3229
Ca x Ph product	mg^2/dl^2	$mmol^2/L^2$	0.0807

4.5 Results of the systematic review - Quantity of research available

4.5.1.1 Number and type of trials identified

We identified three phase II RCTs with less than 12 week follow up.[64-67] These were excluded from the main review.

Seven published reports of RCTs investigating cinacalcet for patients with ESRD on dialysis were identified.[64;68-74] In addition, the FDA website contains its Medical, Statistical and Pharmacological Reviews of reports on four RCTs submitted by Amgen: trial numbers 20000172, 20000183, 20000188 and 20010141.[75] For simplicity, the remainder of the report refers to these trials by their last three digits only. These trials are summarised in Table 15.

Table 14 *Published RCTs of cinacalcet and their Amgen study numbers*

Publication	Amgen trial numbers	No. pts
Block 2004[68]	172 & 183	741
Cunningham 2005[69]	Post-hoc analysis of patients in 172, 183, 188 & 141	1184
Lien 2005[73]	Unclear - subgroup from 188 & 239	14
Lindberg 2003[70]	990101 (No further details)	78
Lindberg 2005[64]	20000188	395
Moe 2005[74]	Combined data from 172, 183 & 188	1136
Quarles 2003[72]	Study no. 730 (no further details)	71

Data from Amgen 172, 183, 188 and 141 appear to have be used for most of the identified publications. The paper by Block and colleagues (2004),[68] is based on Amgen 172 and 183, while Lindberg and colleagues (2005) is based on Amgen 188.[64] In addition, the paper by Moe and colleagues (2005) reports combined data from Amgen 172, 183 and 188. Separate data from these publications are only reported where it is presented in a form not available in the FDA data (for example, the achievement of K-DOQI guidelines). Similarly, the paper by Cunningham and colleagues (2005)[69] is a *post hoc* analysis of patients from all four Amgen trials (172, 183, 188 and 141) which looks at unique outcomes (such as fracture risk and mortality) and this data is reported here. This leaves three smaller RCTs, reported in publications by Lien and colleagues (2005, n=14),[73] Lindberg and colleagues (2003, n=78)[70]

and Quarles and colleagues (2003, n=71).[72] Lien and colleagues (2005) report on a subgroup of patients from Amgen 188 and from another study. They provide information about bone mineral density which is not reported in the main trial reports of Amgen 188. The other published reports are on based trials other than Amgen 172, 183, 188 and 141.

We have chosen to use the Amgen trial reports submitted to the FDA and reported on their Medical Review as the primary source for the review. This is for several reasons. There is more detail, in terms both of methodology and outcomes, in the FDA Medical Review. For example, information about seizures is not reported in the published papers. Also, many outcomes pooled across all three main trials are reported in the FDA Medical Review. As there are some small differences in the reported numbers between the Amgen trial data presented in the FDA Medical Review and the published reports, it was decided that only one source should be used.

4.5.1.2 Amgen trials reported by the FDA Medical Review

Amgen 172 (n=410), Amgen 183 (n=331), Amgen 188 (n=395)

Most of the evidence in the review comes from three, 6-month, randomised, double-blind, placebo-controlled phase III trials of patients with SHPT on dialysis. Amgen 172 and 183 used a 12-week dose-titration period followed by a 14-week period of efficacy-assessment and Amgen 188 had a 16-week dose titration and a 10-week efficacy assessment period. A total of 471 patients were randomised to placebo and 665 patients to cinacalcet across these three trials. Pooled data for these three trials were provided to the FDA.[75]

Amgen 141 (n=48)

This 52-week, multicentre, randomised, placebo-controlled, double-blind study was designed to evaluate the effects of cinacalcet on renal osteodystrophy (metabolic bone disease) in haemodialysis patients with secondary hyperparathyroidism. The study consisted of a 24-week dose-titration phase and a 28-week maintenance phase. A total of 48 patients were randomised in a 2:1 ratio to receive cinacalcet or placebo.

In all the above trials, patients were treated with 30mg once daily of cinacalcet or placebo. This dose could be increased to 50mg, 70mg, 90mg, 120 mg and 180mg over the titration phase if lower doses failed to control PTH levels.

4.5.1.3 Dosing information

The FDA submission from Amgen reported that at the completion of the three phase III trials 40% of patients were receiving 180mg once-daily of cinacalcet, while the remaining 60% of patients were equally divided among the 30mg, 60mg, 90mg and 120mg doses.[75]

Amgen 141 reported that at the end of the study (week 52) 19% of cinacalcet-treated patients were on 30mg dose, 6% were on 50mg dose, 9% were on 70mg dose, 22% were on 90mg dose, 13% were on 120mg dose and 31% were on 180mg dose.

Quarles and colleagues (2003) reported that 50% of the patients who completed the titration phase reached and sustained the 100 mg (maximum daily dose in this study) dose.[72] Daily doses of 75mg and 50mg were reached in 41% of patients, whereas 9% of patients did not escalate above 25mg (initial dose in this study).

Table 15 *Study Characteristics*

Study	Study design	Sample Size	Intervention	Comparator	Concurrent treatment	Setting	Length of treatment
Amgen 172	Phase III RCT	410	Cinacalcet 30mg with dose titration to 60, 90, 120 and 180mg (n = 205)	Placebo (n = 205)	Vitamin D sterols Phosphate binders	Multiple centres (63) United States and Canada	26 weeks (12-week dose-titration and 14- week efficacy assessment)
Amgen 183	Phase III RCT	331	Cinacalcet 30mg with dose titration to 60, 90, 120 and 180mg (n = 166)	Placebo (n = 165)	Vitamin D sterols Phosphate binders	Multiple centres (62) Europe and Australia	26 weeks (12-week dose titration and 14-week efficacy assessment)
Amgen 188	Phase III RCT	395	Cinacalcet 30mg with dose titration to 60, 90, 120 and 180mg (n = 294)	Placebo (n = 101)	Vitamin D sterols Phosphate binders	Multiple centres (60) United States, Canada and Australia	26 weeks (16-week dose titration and 10-week efficacy assessment)
Amgen 141	Phase II RCT	48	Cinacalcet 30 mg with dose titration to50, 50, 90, 120 and 180mg (n =32)	Placebo (n = 16)	Vitamin D sterols Phosphate binders Calcium supplements	Multiple centres (17) United States and Europe	52 weeks (24-week dose titration and 28-week efficacy assessment)
Block 2004	Combined analysis of two phase III RCTs (172 and 183)	741	Cinacalcet 30 mg with dose titration to 60, 90, 120 and 180mg (n = 371)	Placebo (n = 370)	Vitamin D sterols Phosphate binders	Multiple centres (125) North America, Europe and Australia	26 weeks (12-week dose titration and 14-week efficacy assessment)

Cunningham 2003	Combined analysis of four RCTs (172, 183, 188 and 141)	1184	Cinacalcet 20 or 30mg with dose titration through to 180mg (n=679)	Placebo (n = 487)	Vitamin D sterols Phosphate binders	Multiple centres (202) United States, North America, Europe and Australia	2 trials - 26 weeks (12-week dose titration and 14-week efficacy assessment) 1 trial – 26 weeks (16 week titration and 10 week efficacy assessment(1 trial – 52 weeks (24-week dose titration and 28 week efficacy assessment)

Table 15 (cont.)

Study	Study design	Sample Size	Intervention	Comparator	Concurrent treatment	Setting	Length of treatment
Lien 2005	Subgroup from RCT	14	Cinacalcet 30mg with dose titration to 60, 90, 120 and 180mg (n = 8)	Placebo (n = 6)	Vitamin D sterols Phosphate binders	Single centre (United States)	26 weeks (12-week dose titration and 14-week efficacy assessment) for haemodialysis subjects 18 weeks for pre-dialysis subjects
Lindberg 2003	RCT	78	Cinacalcet 20mg with dose titration through 30, 40 and 50mg (n = 39)	Placebo (n = 39)	Vitamin D sterols Phosphate binders	Multiple centres (25) United States and Canada	18 weeks (12-week dose titration and 6-week efficacy assessment)
Lindberg 2005	RCT	395	Cinacalcet 30mg with dose titration to 60, 90, 120 and 180mg (n = 294)	Placebo (n = 101)		Multiple centres (60) United States, Canada and Australia	26 weeks (16-week dose titration and 10-week efficacy assessment)
Moe 2005	Combined analysis of three phase III RCTSs (172, 183 and 188)	1136	Cinacalcet 30mg with dose titration to 60, 90, 120 and 180mg (n = 665)	Placebo (n = 471)	Vitamin D sterols Phosphate binder	Multiple centres (182) United States, Canada, Europe and Australia	26 weeks 2 trials (12-week dose titration and 14-week efficacy assessment) 1 trial (16 week dose titration and 10-week efficacy assessment)
Quarles 2003		71	Cinacalcet 25mg with dose titration to 50, 75 and 100mg (n = 36)	Placebo (n = 35)	Vitamin D sterols Phosphate binders		18 weeks (12-week dose titration and 6 week efficacy assessment)

iPTH = intact parathyroid hormone; Ca^{2+} = serum calcium; P = serum phosphate; Ca x P = serum calcium x phosphate product

4.6 Results of the systematic review - Quality of included trials

4.6.1 Internal validity

4.6.1.1 Sample size

Amgen 172, 183, 188 and 141 were appropriately powered for the primary outcomes under consideration. With the exception of the study by Quarles and colleagues (2003),[72] details of study power are lacking from the published trials.

4.6.1.2 Selection bias

Randomisation

Randomisation methods are generally not detailed in either the FDA Medical Review of the Amgen trials or the published trials. The exception is Quarles and colleagues (2003),[72] which describes randomisation using an interactive voice response system. Amgen 172,183 and 188 state that dose titration bottle numbers were provided by 'the IVRS' without further explanation. It therefore seems likely that an interactive voice response system was used for all these trials. Such a method of central allocation is sound.

Lien and colleagues (2005) analysed BMD data for RCT 'completers' at one study centre. It is not clear if all completers were included in this analysis, thus a potential source of selection bias cannot be ruled out.[73]

Similarity of groups at baseline

Individually, the studied groups in Amgen 172, 183, 188 and 141 appear well matched at baseline. However, in the pooled analysis by Cunningham and colleagues (2005)[69] there are significant differences in terms of age, ethnicity and dialysis modality at baseline. Presumably this is due to small differences in these individual trials being compounded when they are combined. A significantly higher proportion of people in the cinacalcet group were aged <65 years and younger mean age at randomisation was also reported. In addition, there were more black patients in the cinacalcet group. While lower age may bias in favour of cinacalcet, different racial mix may bias against cinacalcet. Prevalence of diabetes, a

potential confounder for the impact of race, were similar. There were more patients on peritoneal dialysis among those receiving cinacalcet.

Small differences in baseline characteristics were also noted in other trials but their impact on biochemical results is unknown. In Amgen 141, the proportion of diabetic patients was almost twice as great in the placebo group compared to the cinacalcet group, although this difference (44% vs 25%) was not statistically significant. The study by Quarles and colleagues (2003) had more men in the control than the treatment arm.[72]

Table 16 *Summary of quality criteria for included RCTs*

Study	Power calc.	Randomisation method	Allocation concealment	Assessors blinded?	Groups similar at baseline	ITT	Protocol violations specified	Missing value treatment	Attrition	All patients accounted for
Amgen 172 (n=410)	Yes	1:1 stratified by baseline PTH and Ca x P. Method not stated (but IVRS is quoted in titration methods)	Numbered bottles but no further details given	"Double blind" - no details given	Yes	Yes	Specified, numerous but if anything would underestimate the efficacy of cinacalcet	Adequate - 3 analyses undertaken yielding similar results- 1) count as non responders. 2) exclude. 3)LOCF	Similar proportions (77% placebo vs 71% cinacalcet) completed the trial	Yes
Amgen 183 (n=331)	Yes	1:1 stratified by baseline PTH and Ca x P Method not stated (but IVRS is quoted in titration methods)	Numbered bottles but no further details given	"Double blind" - no details given.	Yes	Yes	Specified, numerous evenly distributed between treatments	Adequate - 3 analyses undertaken yielding similar results- 1) count as non responders. 2) exclude. 3)LOCF	Significantly more pts receiving placebo completed the trial (80% vs 64% p=0.002○) Main reason is AEs 23% vs 5%	Yes Withdrawal reasons specified

Amgen 188 **(n=395)**	Yes	3:1 stratified by baseline PTH and dialysis modality Method not stated (but IVRS is quoted in titration methods)	Numbered bottles but no further details given	"Double blind" - no details given	Yes	Yes	Specified and distributed evenly between treatments	Adequate - 3 analyses undertaken yielding similar results- 1) count as non responders. 2) exclude. 3)LOCF	About ¾ of each group completed the study	Yes Withdrawal reasons specified
Amgen 141 **(n=48)**	yes	2:1 methods not stated	Unclear	"Double blind" - no details given	Generally yes but incidence of diabetes higher in the placebo group (44% vs 25%)	Yes	Specified and distributed evenly between treatments	Not stated	Withdrawals twice as frequent in cinacalcet group (38% vs 19%. NS○)	Yes Withdrawal reasons specified
Study	**Power calc.**	**Randomisation method**	**Allocation concealment**	**Assessors blinded?**	**Groups similar at baseline**	**ITT**	**Protocol violations specified**	**Missing value treatment**	**Attrition**	**All patients accounted for**

Cunningham 2005 **(n=1184)**	Not stated	Study pools patients from numbered trials 141, 172, 183, 188.	Numbered bottles but no further details given	"Double blind" but no details given	Yes But significant differences in proportion of patients aged < 65 yrs (77% vs 71%), age at randomisation (53 yrs vs 54.7yrs), ethnicity, and dialysis modality	Yes	Not stated	Not clear in survival analyses. For subjective measures 238 pts provided no efficacy data and were excluded, 22 provided no baseline data and were excluded.	Not clear	Not detailed
Lien 2005 **(n=14)**	No	Included 14 patients who completed numbered trials 188† (n=10) and 239* (n=4) at one centre	No details	"Double blind" but no details given	More males in the placebo group	No	Yes	No. Analysis on completers only	Not relevant as analyses is on completers only	Yes

Lindberg 2003 (n=78)	Not stated	1:1 method not stated	No details given	"Double blind" but no details given	Yes	Yes	None specified	Not clear but for the primary outcome variable missing values would be classed as non-responders	Similar proportions of patients completed the study (87% & 82%)	Yes but reasons for withdrawal not stated

Study	Power calc.	Randomisation method	Protocol violations specified	Groups similar at baseline	Assessors blinded?	Allocation concealment	ITT	Missing value treatment	Attrition	All patients accounted for
Moe 2005 (n=1136)	Not stated	Pooled re-analysis of results from numbered trials 172,183 and 188	None specified	Yes	"Double blind" but no details given	No details given	No	Not described	Not detailed but 74% overall completed the trials	No
Quarles 2003 (n=71)	Yes	1:1 Interactive voice response system	None stated	More women in placebo group 51% vs 25%. p= 0.04○)	"Double blind" but no details given	Identical tablets . No further details given	Yes	Not detailed	5.5% withdrew from cinacalcet group vs 11.4% from placebo group (NS○). No reasons given	No - data at week 18 suggests 1 cin group and 3 placebo group patients are unaccounted for.

* FDA study number 20010239 was conducted in patients not receiving dialysis and is excluded from this review

† There is a discrepancy between the designs of the FDA study number 20000188 and that described in the methods section of Lien

○ Calculated by PenTAG

4.6.1.3 Performance bias

Similar proportions of both arms were initially receiving vitamin D sterols and phosphate binders in Amgen trials 141, 172, 183 and 188 as well as Lindberg and colleagues (2003)[70] and Quarles and colleagues (2003).[72]

Lindberg and colleagues (2003)[70] reported similar levels of vitamin D sterol and phosphate binder use in both in cinacalcet and placebo arms during the study.

Subgroup analyses by the numbered Amgen trials and Quarles and colleagues (2003)[72] reported that greater percent reductions from baseline in PTH were observed in the cinacalcet group regardless of whether they had an increase, decrease or no change in vitamin D sterol dose from baseline.

Protocol violations were well described for Amgen trials 172, 183 and 188, and although numerous, were not considered likely to bias the results.

The published trials provided little or no information on protocol violations.

4.6.1.4 Attrition bias and intention to treat analysis

Different rates of attrition between active and control groups were observed in the trials, particularly study 183 where 80% of the placebo group completed the study compared to 64% of the cinacalcet study (p=0.002, calculated by PenTAG).

In contrast with the other trials, the withdrawal rates from the trial by Quarles and colleagues (2003)[72] were higher in the placebo group. This paper does not report reasons for withdrawal. Although stated as an ITT analysis this data set is not defined and there is no detail on how missing data points were handled.

4.6.1.5 Detection bias

Allocation concealment

Most trials report that numbered bottles were used and that the trials were “double blind” but further details are not provided. Only Quarles and colleagues (2003)[72] report that placebo and active tablets were identical. In addition, given that biochemical measures generally

deviated between cinacalcet and placebo groups early in therapy, it is questionable if concealment of allocation was maintained throughout the study.

Analysis

The study by Cunningham and colleagues (2005)[69] is a retrospective, post-hoc analysis of Amgen 172, 183, 188, 141. Data for mortality, fracture, parathyroidectomy and cardiovascular (CV) events based on safety monitoring in the original trials were synthesised. Most of this data is based on trials with six-month follow up, with only between 268 and 305 patients remaining at risk in the study at week 38 (from the original 1184 included). Most of these are people participating in a study extension, and it is not reported how these patients were selected, or whether they are representative of the originally randomised population. Baseline characteristics already differed – with significantly more people under 65, fewer white people and more people on PD in the cinacalcet arm. No adjustment is made in the analysis for these potential confounders. By the end of the analysis, around 21% of the originally randomised population were still providing data. The titration phase of the trials appear to contribute more than half of the total patient-weeks of exposure.

There is a lack of transparency about censoring the survival analysis carried out by Cunningham and colleagues (2005).[69] Depending on the outcome reported, different numbers of patients are reported at risk at the same time point and there is no explanation for this.

To enable comparison of event rates between cinacalcet and placebo groups, the number of events was expressed as the event rate per 100 subject years. Using this way of presenting data, a patient exposed to a drug for 1 year contributes as much data as, for example, 4 patients exposed for 13 weeks each. The following formula was used to calculate the event rate per 100 patient years:

$$\text{Event rate per 100 years} = \frac{\text{Events}}{\text{Duration of exposure in the group}} \times 100$$

Total exposure is expressed as patient years, and is a crude rate, unmodified for any potential covariates. The duration of exposure in the cinacalcet group was 1.27 times the duration of exposure in the placebo group. However, 1.44 times more patients were originally randomised to cinacalcet due to asymmetric randomisation in the trials. The relatively reduced exposure for those receiving cinacalcet is due to more withdrawals. This

reduces the numbers of people at risk of adverse events proportionally more for those receiving cinacalcet compared with those receiving standard treatment. Only around 28% of those receiving standard treatment and 18% of those receiving cinacalcet provided at 52 weeks. The results at one year are thus based on a very small proportion of the original study population.

The difference in the number of parathyroidectomies needed in each group and the associated very small p-value (p=0. 009) would appear convincing. The reduction in risk indicates that one parathyroidectomy would be prevented for every 26 patients treated with cinacalcet rather than placebo (= 1/0.041-0.003). However, data is sparse with only one parathyroidectomy recorded in the cinacalcet group and 12 in the control group. A reduction in parathyroidectomy rate is biologically plausible, as one of the key determinants driving the decision to proceed to parathyroidectomy would be biochemical measures. However, it is unclear, given the short follow up and small numbers, whether it is possible to extrapolate these results to the longer term.

There were significantly fewer fractures among those treated with cinacalcet. The curves for placebo and cinacalcet diverge early in treatment (by week 12 of the titration phase).

Although significantly fewer cardiovascular-related hospitalisations were reported with cinacalcet, no difference was seen in hospitalisation for all causes. In the cinacalcet arm, the survival curves show no events between weeks 28 and 40. This is not in keeping with the trend observed through earlier and later time points where events appear to be recorded at regular intervals. The plateau period coincides with the time of greatest attrition: 61% in the placebo arm and 68% in the cinacalcet arm. This difference in attrition may affect the results of the comparison if these patients are excluded from analysis. The rate of events after this plateau period appears faster than before, an effect of many patients being censored during weeks 28-40.

Despite apparent difference in fracture and CV event, no significant difference was observed in all-cause hospitalisation or all-cause mortality in this study. Again, this may indicate that short term follow up is insufficient to identify clinically important differences.

4.6.2 External validity

Biochemical markers were used as the primary outcome in Amgen 172, 183 and 188, and by Lindberg and colleagues (2003)[70] and Moe and colleagues (2005)[71] (reanalysis of pooled

data from Amgen 172, 183 and 188). While the maintenance of these markers within defined ranges is a treatment goal, the impact of this on important clinical outcomes, such as CV events and mortality, and fractures is still uncertain.

The main outcome measures for the trials relate to achieving PTH levels below targets (e.g. ≤ 26.5pmol/L) or minimum reductions of a certain level (at least 30%). However, over-suppression of PTH may also be problematic, potentially leading to adynamic bone disease at levels below 10.6pmol/L. Limited information about this is presented in the FDA Medical Review, but none is reported in the published trials.

Whilst, in general, study groups were well matched in the trials, some contained a higher number of black participants than may be expected in a UK population being considered for treatment. Data from the UK Renal Registry suggest that 3.2% of the UK dialysis population are black whilst in Amgen trials 172, 188 and 141 the proportions of black participants were 58%, 65% and 37% respectively. It is known that black patients tend to have a higher parathyroid gland mass predisposing them towards more severe SHPT which may be treatment resitant.[76] However, stratified analysis showed no indication that the response to treatment varies by ethnicity.[68]

The assay used to measure PTH values in the trials was the Nichols IRMA intact assay. Other assays may report PTH values higher or lower than this. For example the Nichols Advantage intact PTH assay reports values 30-50% higher than those recorded by the IMRA assay meaning that undetected over-suppression of PTH is a possibility.[75]

Lien reports BMD measurements in a small group of patients participating in other trials. There appears to be an inconsistency in the reporting of lumbar spine measures. The BMD was observed to decrease in both groups yet an improvement in T-score is reported, which is not logical. The relevance of the findings of this small study are therefore not clear.

Amgen 172 and 183 restricted the proportion of recruited people who had very high levels of PTH (>800pg/ml, 85pmol/L) to 20%. In Amgen 188 there was no such restriction and 40% of those recruited to the trial had levels of PTH >85pmol/L. However, as trial data is reported by subgroup, extrapolation of the results to the appropriate patient group remains possible.

The analysis of clinical outcomes by Cunningham and colleagues (2005)[69] reports mortality rates of 5.2 per 100 patient years for those treated with cinacalcet and 7.4 per 100 patient years for those receiving standard treatment. This is much lower than the rates reported in by the UK Renal Registry, where overall mortality rates are 15.0 per 100 patient years for the

prevalent dialysis population (16.0 per 100 patient years in those aged 55-64).[15] This suggest that the population recruited into Amgen 172, 183, 188 and 141 are much fitter than the general clinical population in the UK.

All trials were supported by Amgen and employees of the company are co-authors on all the trials apart from published report by Lien.

4.6.2.1 Summary of study quality

BOX 1 *Summary of quality of included trials*

- *There are seven published reports of RCTs of cinacalcet compared with placebo. However, five of these were based on the results of three phase III RCTs (Amgen 172, 183 and 188) and one phase II RCT (Amgen 141). As these numbered trials were reported more fully in the US FDA Medical Review of the Amgen submission for approval, we used this source for our review. Data from published journal articles was reported where it provided new information.*
- *The RCTs appear to be well designed with appropriate sample sizes. A total of 846 patients were randomised to receive cinacalcet.*
- *Patient characteristics among individual trials were similar across the cinacalcet and placebo arms. However, pooled analysis showed significant differences in age, ethnicity and dialysis modality.*
- *Patients appear to have been randomised centrally in the main RCTs. Although it is not clear if allocation concealment could have been maintained given the very different responses between cinacalcet and placebo arms, the objective nature of outcome measures should minimise any threat to validity.*
- *For all trials, the primary outcome was decrease in the levels of serum PTH. One report provides a retrospective analysis of pooled trial data to identify the relevant clinical outcomes of parathyroidectomy, CV event, fracture and mortality. However, as most trials provide only 6-month follow up, it is unclear whether differences in these outcomes can be extrapolated to long term use, particularly where absolute numbers of events are small.*
- *When pooled for analysis of clinical outcomes, there are baseline differences in age, race and mode of dialysis between the placebo and cinacalcet arms. No adjustment is made for this in the analysis. Further, data for 12 months is based on data from a small planned RCT and those from the 6-month RCTs who agreed to an extension. Details of this population are not supplied.*
- *Details of censoring in survival analysis are not given, and reported numbers of patients at risk are different depending on the outcome analysed.*
- *The trials contain a greater percentage of black patients than would be found in a UK population. Some studies suggest that there is a predisposition to more severe SHPT among black people. Treatment response in the trials showed no relation to ethnicity.*
- *All trials were supported by the manufacturers of cinacalcet.*

4.6.3 Results of included trials

The following outcomes reported in the RCTs are summarised in this section:

1. Percentage of patients achieving a mean PTH level of ≤ 26.5 pmol/L.

- Subgroup analysis of patients achieving a mean PTH level of ≤ 26.5 pmol/L according to:
  - Baseline PTH level
  - Baseline Ca level
  - Baseline P level
  - Baseline CaxP level
  - Duration of dialysis (dialysis vintage)

2. Reduction in mean PTH levels by at least 30% in all patients.

- Subgroup analyses of the reduction in mean PTH levels by at least 30% according to:
  - Baseline PTH level
  - Baseline Ca level
  - Baseline P level
  - Baseline CaxP level
  - Duration of dialysis (dialysis vintage).

3. Percentage change in mean PTH from baseline.
4. Percentage change in mean serum Ca from baseline.
5. Percentage change in mean serum P from baseline.
6. Percentage change in mean CaxP from baseline.
7. Percentage of patients with mean PTH level of ≤ 26.5 pmol/L and a reduction from baseline in CaxP.

- Subgroup analyses of the percentage of patients with mean PTH level of ≤ 26.5 pmol/L and a reduction from baseline in CaxP by:
  - Baseline iPTH level
  - Baseline Ca level.

8. Percentage of patients achieving the KDOQI targets for serum PTH, Ca, P and CaxP.
9. Bone mineral density in the femur and lumbar spine.
10. Clinical outcomes. Number of:
    - Parathyroidectomies
    - Hospitalisations for CV events
    - Hospitalisations for all-causes
    - Fractures
    - Mortality.
11. Quality of life.
12. Adverse effects.

4.6.3.1 Percentage of all patients achieving a mean intact parathyroid hormone (PTH) level of ≤ 26.5 pmol/L

Three phase III trials (Amgen 172, 183, 188) measured the proportion of people achieving the target of a mean PTH value ≤ 26.5 pmol/L during efficacy-assessment phase as the primary outcome of interest.

All three trials demonstrated that significantly more people treated with cinacalcet achieved target mean PTH levels during the efficacy-assessment phase (pooled analysis 40% vs. 5%; p<0.001; odds ratio 12.33 [95% CI 7.96, 19.09]).

The smaller Amgen 141 reported that 53% of people treated with cinacalcet, compared with 6% of those treated with placebo, achieved target mean PTH levels.

Of the published trials, only Quarles and colleagues (2003)[72] reported this outcome, finding that overall, significantly more people treated with cinacalcet achieved the target than those treated with placebo (p=0.029).

The FDA Medical Review reports over-suppression of PTH (below 10.6pmol/L) in Amgen 141, 172, 183 and 188.[75] Of those reported as reaching the target levels, about half in each trial had PTH levels of <10.6pmol/L (ranging from 6% to 17% of the total population). It is noted that at several weeks during the trial 25% of people had such levels of PTH. Other

PTH assays used in clinical practice may report values 30-50% higher than the assay used in these clinical trials.

Subgroup analysis of percentage of patients achieving a mean PTH level of ≤ 26.5 pmol/L by baseline PTH

Pooled analysis of three trials (Amgen 172, 183, 188) showed that more people treated with cinacalcet with lowest baseline PTH achieved target mean PTH levels compared with patients in the higher baseline PTH strata. However, absolute risk difference between cinacalcet and placebo reduces with higher baseline PTH levels. Confidence intervals associated with the odds ratios for these subgroups are very wide and overlap *(*Table 17*).*

Table 17 *Achievement of PTH levels ≤ 26.5 pmol/L by baseline PTH levels and dialysis mode*

	All (%)		Baseline PTH >31.8 and <53 pmol/L (%)		Baseline PTH >53.0 and <84.8 pmol/L (%)		Baseline PTH >84.8 pmol/L (%)		Pts on peritoneal dialysis (%)	
	Cinacalcet	Placebo	Cinacalcet	Placebo	Cinacalcet	Placebo	Cinacalcet	Placebo	Cinacalcet	Placebo
Amgen172 (N= 410)	41[a]	4	52	5	41	4	15	0	N/A	N/A
Amgen183 (N = 331)	46[a]	7	65	14	44	2	9	0	N/A	N/A
Amgen188 (N = 395)	35[a]	6	65	24	39	0	10	0	38	0
Pooled data 172, 183, 188 (N = 1136)	40[a]	5	60	11	41	2	12	0	NR	NR
Pooled data OR (95% CI)	12.33 (7.96, 19.09)		10.85 (6.36, 18.49)		23.83 (8.28, 68.58)		10.85 (2.01, 58.50)		NR	NR
Amgen141 (N=48)	53	6	NR	NR	NR	NR	NR	NR	NR	NR
Quarles 2003 (N = 71)	44[b]	20	NR	NR	NR	NR	NR	NR	NR	NR

NA = not applicable; NR = not reported

[a] p <0.001 *versus* placebo; [b] p=0.029 *versus* placebo

Subgroup analysis of achievement of a mean PTH level of ≤ 26.5 pmol/L by baseline Ca x P, Ca^{2+} and P levels ands dialysis vintage

Table 18 to Table 21 show no significant effects in subgroup analyses according to baseline calcium, phosphate, CaxP or dialysis vintage.

Table 18 *Percentage of people achieving a mean PTH ≤ 26.5 pmol/L according to baseline serum calcium- phosphate (CaxP) product value*

	Achievement of PTH level ≤26.5pmol/L					
	All subjects (%)		Baseline Ca x P <5.65 $mmol^2/L^2$(%)		Baseline Ca x P > 5.65 $mmol^2/L^2$(%)	
	Cinacalcet	Placebo	Cinacalcet	Placebo	Cinacalcet	Placebo
Amgen 172 (N = 410)	41[a]	4	43	5	37	2
Amgen 183 (N = 331)	46[a]	7	49	9	37	0
Pooled data for Amgen 172, 183, 188 (N=1136)	40[a]	5	43	7	30	1
OR (95% CI)	12.33 (7.96, 19.09)		10.41 (6.57, 16.49)		29.84 (7.09, 126)	

[a] p <0.001 versus. placebo

Table 19 *Achievement of mean PTH < 26.5 pmol/L according to baseline serum calcium value*

	Achievement of PTH level ≤26.5pmol/L					
	All subjects		Baseline serum calcium < 2.75 mmol/L		Baseline serum calcium > 2.75 mmol/L	
	Cinacalcet	Placebo	Cinacalcet	Placebo	Cinacalcet	Placebo
Pooled data for Amgen 172, 183, 188 (N = 1136)	40[a]	5	41	6	23	0
OR (95% CI)	12.33 (7.96, 19.09)		11.86 (7.63, 18.44)		10.33 (1.81, 59.06)	

iPTH = intact parathyroid hormone N = number of subjects enrolled in study

[a] p <0.001 *versus*. placebo

Table 20 *Achievement of mean PTH ≤ 26.5 pmol/L according to baseline serum phosphate value*

	Achievement of PTH level ≤26.5pmol/L					
	All subjects		Baseline serum phosphate <2.10 mmol/L		Baseline serum phosphate ≥ 2.10 mmol/L	
	Cinacalcet	Placebo	Cinacalcet	Placebo	Cinacalcet	Placebo
Pooled data for Amgen 172, 183, 188 (N = 1136)	40[a]	5	44	8	33	2
OR (95% CI)	12.33 (7.96, 19.09)		8.93 (5.50, 14.52)		30.95 (10.32, 92.87)	

[a] p <0.001 versus. placebo

Table 21 *Achievement of mean PTH ≤ 26.5 pmol/L during efficacy assessment according to duration of dialysis*

	Achievement of PTH level ≤26.5pmol/L							
	All subjects		Duration of dialysis >0-1 year		Duration of dialysis > 1-5 years		Duration of dialysis >5 years	
	Cinacalcet	Placebo	Cinacalcet	Placebo	Cinacalcet	Placebo	Cinacalcet	Placebo
Pooled data 172, 183, 188 (N = 1136)	40[a]	5	51	10	44	4	31	5
OR (95% CI)	12.33 (7.96, 19.09)		11.70 (3.94, 34.73)		19.98 (10.12, 39.47)		7.47 (3.71, 15.06)	

[a] p <0.001 versus. placebo

4.6.3.2 Achievement of a reduction in mean PTH levels from baseline of at least 30%

Pooled analysis of Amgen 172, 183 and 188, Amgen 141, Lindberg and colleagues (2003)[70] and Quarles and colleagues (2003)[72] found significantly more people treated with cinacalcet achieved a reduction of at least 30% in mean PTH compared with of placebo-treated patients.[75] (Table 22)

Subgroup analysis of the achievement of a reduction in mean PTH levels of at least 30% by baseline iPTH, CaxP, calcium and phosphate levels

The response rate for people treated with cinacalcet who achieved ≥ 30% reduction in PTH was similar among all subgroups of baseline severity in the pooled analysis of three Amgen trials (172, 183, 188) in the FDA Medical Review. The published papers did not report such subgroup analysis. Odds ratios for higher baseline CaxP product (>5.65mmol^2/L^2) suggest that such levels may be associated with greater mean PTH reduction in people treated with cinacalcet. However, given the number of sub-group analyses carried out on the dataset, this finding may be a types I error and should be viewed with caution. For baseline calcium and phosphate levels, 95% confidence intervals are very wide and overlap between the groups.(Table 23, Table 24 and Table 25)

Impact of dialysis vintage was also explored (Table 26). In this case too, the confidence intervals are very wide and overlap between the three categories of dialysis duration.

It should be noted that the reported reductions in patients with high baseline levels of PTH may still leave these patients with high PTH levels.

Table 22 *Percentage of people achieving a reduction in mean PTH of at least 30% from baseline according to baseline PTH value*

	Achievement of a reduction in PTH level of at least 30%									
	All subjects		Baseline PTH ≥ 31.8 and <53 pmol/L		Baseline PTH >53.0 and <84.8 pmol/L		Baseline PTH >84.8 pmol/L		Subjects on peritoneal dialysis	
	Cinacalcet	Placebo	Cinacalcet	Placebo	Cinacalcet	Placebo	Cinacalcet	Placebo	Cinacalcet	Placebo
172 (N = 410)	61[a]	11	58	8	64	18	65	8	NA	
183 (N=331)	68[a]	12	67	NR	73	NR	61	NR	NA	
88 (N = 395)	59[a]	10	65	24	63	7	51	6	62	0
Pooled data 172, 183, 188 (N=1136)	62[b]	11	62	12	68	13	56	6	NR	
Pooled data OR (95% CI)	NR		10.79 (6.46, 18.04)		14.75 (8.37, 25.98)		21.44 (9.25, 49.68)		NR	
Lindberg et al 2003 (N=78)	38[d]	8	NR	NR	NR	NR	NR	NR	NR	NR
Quarles et al 2003 (N=71)	53[e]	23	NR	NR	NR	NR	NR	NR	NR	NR

NA Not applicable. NR not reported

[a] p<0.001 versus. placebo

[b] p=0.029 versus. placebo

[c] nominal p<0.001 versus. placebo

[d] p = 0.001 versus. placebo

[e] p = 0.009 versus placebo

Table 23 *Achievement of a reduction in mean PTH of at least 30% from baseline according to baseline Ca x P value*

	Achievement of a reduction in PTH level of at least 30%					
	All subjects		Baseline Ca x P ≤ 5.65 $mmol^2/L^2$		Baseline Ca x P > 5.65 $mmol^2/L^2$	
	Cinacalcet	Placebo	Cinacalcet	Placebo	Cinacalcet	Placebo
172 (N = 410)	61[a]	11	60	14	65	5
183 (N = 331)	68[a]	12	66	NR	76	NR
188 (N = 395)	59[a]	10	NR	NR	NR	NR
Pooled data for 172, 183, 188 (N = 1136)	62[a]	11	62	14	63	4
Pooled data OR (95% CI)	NR		10.38 (7.19, 14.97)		46.59 (18.23, 119)	

[a] p <0.001 *versus* placebo

Table 24 *Achievement of a reduction in mean PTH >30% according to baseline calcium value*

	Achievement of a reduction in PTH level of at least 30%					
	All subjects		Baseline calcium < 2.75 mmol/L		Baseline calcium ≥ 2.75 mmol/L	
	Cinacalcet	Placebo	Cinacalcet	Placebo	Cinacalcet	Placebo
Pooled data 172, 183, 188 (N = 1136)	62[a]	11	62	12	62	4
Pooled data OR (95% CI)	Not reported		13.14 (9.29, 18.59)		25.15 (6.37, 99.28)	

[a] p <0.001 *versus* placebo

Table 25 *Achievement of a reduction in mean PTH of at least 30% according to baseline serum phosphate value*

	Achievement of a reduction in PTH level of at least 30%					
	All subjects		Baseline phosphate <2.10 mmol/L		Baseline phosphate ≥ 2.10 mmol/L	
	Cinacalcet	Placebo	Cinacalcet	Placebo	Cinacalcet	Placebo
Pooled data for 172, 183, 188 (N = 1136)	62[a]	11	63	13	62	8
Pooled data OR (95% CI)	NR		11.31 (7.47, 17.12)		20.08 (11.17, 36.08)	

NR= not reported

[a] p <0.001 versus placebo

Table 26 *Achievement of a reduction in mean PTH of at least 30% according to duration of dialysis*

	Achievement of a reduction in PTH level of at least 30%							
	All subjects		Dialysis duration 0-1yr		Dialysis duration >1-5 yrs		Dialysis duration >5 yrs	
	Cinacalcet	Placebo	Cinacalcet	Placebo	Cinacalcet	Placebo	Cinacalcet	Placebo
Pooled data 172, 183, 188 (N = 1136)	62[a]	11	66	20	61	10	60	10
Pooled data OR (95% CI)	NR		8.38 (3.41, 20.59)		16.70 (10.09, 27.64)		13.08 (7.57, 22.59)	

[a] p <0.001 *versus* placebo

4.6.3.3 Percentage change in mean PTH from baseline

Pooled analysis of the three main Amgen trials (172, 183, 188) shows that treatment with cinacalcet resulted in a significantly greater decrease from baseline in mean PTH (p<0.001) compared to placebo *(*Table 27*)*.[75] The same was true for the trials reported by Lindberg and colleagues (2003) and Quarles and colleagues (2003) (p<0.001 for both).[70;72]

Trial 141 reported that, at the end of the study, mean plasma PTH concentrations were reduced by 54% in the cinacalcet group compared with an increase of 36% in the placebo group.[75]

Both Lindberg and colleagues (2003)[70] and Quarles and colleagues (2003)[72] reported significantly greater decreases in mean PTH levels with cinacalcet compared with placebo (p<0.001).

4.6.3.4 Percentage change in serum Ca^{2+} from baseline

Pooled analysis of the three Amgen trials (172, 183, 188) shows mean serum calcium concentration was reduced by 6.7% in the cinacalcet group, compared with an increase of 0.5% in the placebo group (p<0.001).[75] Trial 141 reports that mean serum calcium concentration was reduced by 5% in the cinacalcet group compared with an increase of 2% in the placebo group.[75] The FDA review of these trials notes that changes in calcium levels were not correlated with changes in PTH.[75]

Lindberg and colleagues (2003) report that mean serum calcium levels increased by 4.7% in the cinacalcet arm compared to no change in the placebo arm. This was a significant

different (p<0.001).[70] Similarly, a significant difference was found by Quarles and colleagues (2003) (Table 27).[72]

4.6.3.5 Percentage change in serum phosphate from baseline

Pooled analysis of Amgen 172, 183, 188 showed mean serum phosphate concentration was reduced by 7.8% in the cinacalcet group, compared with a 0.3% reduction in the placebo group (p<0.001).[75]

Trial 141 reported mean serum phosphate concentration was reduced by 10% in the cinacalcet group compared with a decrease of 14% in the placebo group.[75]

The FDA Medical Review of the Amgen trials notes that changes in serum phosphate levels were not correlated with changes in PTH.

Significant differences were also shown by Lindberg and colleagues (2003) and by Quarles and colleagues (2003) with reductions in the cinacalcet arm and increases in the placebo arms (Table 27).[70;72]

4.6.3.6 Percentage change from baseline in serum Ca x P

In the pooled analysis of Amgen 172, 183 and 188, mean serum Ca x P concentration was reduced by 13.8% in the cinacalcet group, compared with an increase of 0.1% in the placebo group (p<0.001).[75]

Similarly, significant differences were found by both Lindberg and colleagues (2003) and Quarles and colleagues (2003).[70;72] (See Table 27).

Table 27 *Percentage change in mean serum levels of iPTH, Ca, P, and CaxP*

	% change mean PTH		% change mean Ca^{2+}		% change mean P		% change mean CaxP	
	Cinacalcet	Placebo	Cinacalcet	Placebo	Cinacalcet	Placebo	Cinacalcet	Placebo
172 (N = 410)	- 38.4[a]	+ 9.5	- 6.3[a]	+ 0.5	- 7.1[a]	+ 1.1	-13.0[a]	+1.5
183 (N1 = 330)	- 47.5[a]	+ 8.8	- 7.6[a]	+ 0.4	- 9.9[a]	- 0.9	- 16.7[a]	- 0.7
188 (N = 395)	- 40.3[a]	+ 4.1	- 6.5[a]	+ 0.9	- 7.2[a]	- 2.2	- 12.9[a]	- 1.4
Pooled data 172,183, 188 (N = 1136)	- 41.5[c]	+ 8.1	- 6.7[c]	+ 0.5	- 7.8	- 0.3	- 13.8[a]	+ 0.1
141 (N=48)	-54	+36	-5	+2	-10	-14	NR	NR
Lindberg et al 2003 (N = 78)	- 26[a]	+ 22	- 4.7[a]	0	- 7.5[f]	+ 10.9	- 11.9[a]	+ 10.9
Quarles et al 2003 (N = 71)	- 32.5[a]	+ 3.0	- 4.6[a]	+ 2.6	-2.6[h]	+ 7.0	- 7.9[i]	+ 11.0

[a] p<0.001 *versus*. placebo
[b] p=0.029 *versus*. placebo
[c] nominal p<0.001 *versus*. placebo
[d] p = 0.001 *versus*. placebo
[e] p = 0.009 *versus* placebo
[f] p = 0.003 *versus* placebo
[g] p = 0.039 *versus* placebo
[h] p = 0.217 *versus* placebo
[I] p = 0.013 *versus* placebo

4.6.3.7 Achievement of mean PTH ≤26.5 pmol/L and a reduction from baseline in Ca x P

Amgen 172 and 183 reported the percentage of people who showed both a mean PTH ≤ 26.5 pmol/L and a reduction from baseline in CaxP. Amgen 173 found that 36% of the cinacalcet-treated patients compared with 1% of patients in the placebo group achieved both these targets (p<0.001). Since 41% of cinacalcet-treated patients had a mean PTH ≤ 26.5 pmol/L, approximately 90% of patients who achieved an PTH of 26.5 pmol/L also had reductions in Ca x P.[75]

In trial 183 42% of the cinacalcet group compared with 5% in the placebo group had both a mean PTH ≤ 26.5 pmol/L and a reduction from baseline in Ca x P during the efficacy assessment phase, (p<0.001). As 46% of patients had a mean PTH ≤ 26.5 pmol/L, approximately 91% of patients who achieved an PTH ≤ 26.5 pmol/L also had reductions in Ca x P.[75]

Table 28 *Achievement of mean PTH ≤ 26.5 pmol/L and a reduction from baseline in Ca x P*

	PTH ≤26.5 pmol/L and a reduction from baseline in serum Ca x P (% subjects)	
	Cinacalcet	Placebo
172 (N = 410)	36[a]	1
183 (N = 331)	42[a]	5

[a] p<0.001 *versus*. placebo

Subgroup analysis by baseline PTH

In trial 172, results from those achieving both a mean PTH ≤ 26.5pmol/L and a reduction from baseline in CaxP were analysed by baseline PTH. Forty-five percent of cinacalcet-treated patients with PTH levels of >32 <53pmol/L achieved this endpoint compared with 37% of those with PTH levels of >53 <85pmol/L, and 15% of those with PTH levels of >85 pmol/L.[75]

Subgroup analysis by baseline CaxP

Details of people achieving both a mean PTH ≤ 26.5 pmol/L and a reduction from baseline in CaxP were also analysed according to baseline CaxP level in the 172 trial. Similar proportions of people treated with cinacalcet in each baseline Ca x P stratum achieved a mean PTH ≤26.5 pmol/L and a reduction from baseline in Ca x P (35% of those with CaxP <5.65 [mmol/L/]^2 and 39% of those >5.65 [mmo/L]^2). For patients who received placebo, the proportions who achieved the endpoint in each baseline stratum ranged from 0% to 5%.[75]

4.6.4 Achievement of KDOQI targets for serum levels

The study by Moe and colleagues (2005) combines data from Amgen 172, 188 and 183 to identify the proportion of patients achieving the KDOQI guidelines for mineral and PTH serum levels (as shown in Table 6 on page 35, Renal Association targets are shown in Table 5 on page 35).[71] Significantly more patients treated with cinacalcet achieved these targets than those receiving placebo (p<0.001 see Table 29*).*

Table 29 *Achievement of KDOQI standards (Moe and colleagues, 2005).*[71]

	% pts achieving K/DOQI targets (pooled data)		
	Placebo (n=409)	Cinacalcet (n=547)	p-value
Mean PTH < 31.8 pmol/L			
Baseline	<1	<1	
Maintenance phase	10	56	<0.001
Mean Serum Calcium 2.10-2.37 mmol/L			
Baseline	33	32	
Maintenance phase	24	49	<0.001
Mean Serum Phosphate 1.13-1.78 mmol/L			
Baseline	31	33	
Maintenance Phase	33	46	<0.001
Mean CaxP <4.44 mmol^2 /L^2			
Baseline	34	37	
Maintenance Phase	36	65	<0.001
Mean PTH < 31.8 pmol/L and CaxP <4.44 mmol^2 /L^2			
Baseline	0	0	
Maintenance Phase	6	41	<0.001

4.6.5 Impact of cinacalcet on bone mineral density

The trial by Lien and colleagues (2005), reports on a small subgroup of 14 patients from Amgen 188 and Amgen trial 239.[73] Change in bone mineral density (BMD) between baseline and six-months are reported. On cinacalcet, a significant increase in femoral BMD was shown against a significant decrease with placebo. Changes in lumbar BMD were not significant (Table 30). Analysis of differences between groups was not reported.

Table 30 *Changes in bone mineral density (Lien and colleagues, 2005)*[73]

	Placebo (N=6)		Cinacalcet (N=8)	
	Baseline (mean ± SD)	End of study (mean ± SD)	Baseline (mean ± SD)	End of study (mean ± SD)
Femur BMD (g/cm^2)	0.921 ± 0.250	0.904 ± 0.244 [a]	0.945 ± 0.169	0.961 ± 0.174[a]
Femur T-score	-1.03 ± 1.56	-1.30 ± 1.70	-0.76 ± 1.10	-0.65 ± 1.16 [a]
Lumbar spine BMD (g/cm^2)	1.156 ± 0.276	1.149 ± 0.288	1.283 ± 0.219	1.269 ± 0.221
Lumbar Spine T-score	-0.72 ± 2.31	-0.63 ± 2.23	-0.52 ±1.69	-0.39 ± 1.69

[a] P<0.05 compared with baseline

4.6.6 Impact of cinacalcet on cardiovascular events, fracture, parathyroidectomy and death

The study by Cunningham and colleagues (2005) uses adverse event data from the Amgen 172, 183, 188 and 141 to assess the impact of cinacalcet on fracture, cardiovascular events, hospitalisation and mortality.[69] Results are shown in Table 31. No significant difference was seen in overall mortality or all-cause hospitalisation. However, significant differences were seen at 6-12 month follow up in cardiovascular hospitalisation, fracture and parathyroidectomy (Table 31).

Table 31 *Impact of cinacalcet on the risk of fracture, CV event, parathyroidectomy and mortality – pooled AE data*

	Event count		Events per 100 pt yrs			
	Placebo n=487	Cinacalcet n=697	Placebo	Cinacalcet	RR (95% CI)	P
Mortality	NR	NR	7.4	5.2	0.81 (0.45-1.45)	0.47
CV hospitalisation	77	72	19.7	15.0	0.61 (0.43-0.86)	0.005
All-cause hospitalisation	NR	NR	71.0	67.0	1.03 (0.87-1.22)	0.74
Fracture	20	12	6.9	3.2	0.46 (0.22-0.95)	0.04
Parathyroidectomy	12	1	4.1	0.3	0.07(0.01-0.55)	0.009

NR = Not reported

4.6.7 Quality of Life

Cunningham and colleagues also reports quality of life from combined data from Amgen 172, 183, and 188.[69] No significant differences in the change over time were found for most of the domains measured by the SF-36. There was a significant difference in the change in scores for people treated with cinacalcet compared with placebo in the physical component score (0.5 vs -0.8, p=0.01) and the bodily pain score (0.6 vs -1.0, p=0.02). There was no difference overall between the study arms in self-assessed decline in physical status. However, more people in the cinacalcet arm reported an increased of 5 points or more (26% vs 20%, p=0.03).

4.6.8 Adverse effects

Full details of reported adverse effects are shown in the extraction tables (Appendix 6). Adverse effects were reported in different ways across the trials. Only three published trials

(Block 2003;[68] Lindberg 2005;[64] Moe 2005[71]) included adverse events, reporting only a selection of those in the FDA Medical Review.

4.6.8.1 Deaths

All deaths that occurred on-study and within 30 days of discontinuation, withdrawal, or completion of the study were recorded by Amgen 172, 183 and 188.[75] There was no significant difference between study arms. Fifteen (3%) of patients randomised to receive placebo and 14 (2%) randomised to cinacalcet died during these core 6-month trials. The causes of death in the cinacalcet-treated patients were not unusual for this population.

Trial 141 reported 3 deaths (9%) in the cinacalcet group and 2 (13%) in the placebo group. Two patients receiving cinacalcet died of cardiac arrest. One subject receiving cinacalcet died of sepsis. In the placebo group one subject died of intracranial haemorrhage and one of pulmonary embolism.[75]

4.6.8.2 Serious adverse events

The FDA Medical Review of cinacalcet considered a serious adverse event or reaction was any untoward medical occurrence that at any dose resulted in death, was life-threatening, required or prolonged hospitalisation, resulted in significant disability, or was a congenital anomaly/birth defect.[75]

The pooled incidence of serious adverse effects from Amgen 172, 183 and 188 was 31% in the placebo group and 29% in the cinacalcet group. No individual serious adverse event occurred in more than 2% of patients. The most common serious adverse events included (placebo, cinacalcet) vascular access thrombosis (2%, 2%), pneumonia (2%, 2%), sepsis (2%, 2%), and non-cardiac chest pain (<1%, 2%). Serious adverse events of cardiac arrest occurred in 1% of patients in each treatment group (6 placebo, 9 cinacalcet). Cardiac arrest was fatal in 10 patients (3[<1%] placebo and 8 [1%] cinacalcet).[75]

4.6.8.3 Withdrawal due to adverse events

Withdrawals due to adverse events in the pooled data for Amgen 172, 183 and 188 occurred in 8% of patients receiving placebo compared with 15% (p=0.005*) of patients receiving cinacalcet. The most common individual events leading to withdrawal, were (placebo, cinacalcet) nausea (1%, 5%, p=0.001),vomiting (<1%, 4%), diarrhoea (<1%, 2%), and abdominal pain (<1%, 2%).[75]

Trial 141 reported that four (13%) patients in the cinacalcet group and 0 (0%) patients in the placebo group withdrew because of adverse events. Adverse events that most commonly resulted in withdrawal involved the gastrointestinal system, with one subject each who withdrew due to dyspepsia, nausea and vomiting.

All adverse events

Pooled data for Amgen 172, 183 and 188 were not reported. Adverse event rates of 90%, 93% and 91% were reported in the cinacalcet-treated groups of the individual trials respectively, compared with similar values (95%, 93% and 93%) in the placebo groups.

Ninety-seven percent of patients in the cinacalcet arm of Amgen 141 and 100% of patients in the placebo group reported at least one adverse event during the study. The most common adverse events were (cinacalcet, placebo) nausea (44%, 44%), abdominal pain (44%, 19%,), and vomiting (41%, 31%). These differences were not significant.†

Specific adverse events

As cinacalcet may cause calcium levels to fall and low calcium is associated with seizures, pack data advises states that such serum levels should be closely monitored. In addition, recognised common adverse effects include, nausea and vomiting, diarrhoea, muscle pain, dizziness, high blood pressure, weakness and tiredness and loss of appetite.

Nausea and Vomiting

Nausea and vomiting were the two most commonly reported adverse events and the most frequent reasons for premature withdrawal from the trials.

* Calculated by PenTAG
† calculated by PenTAG

The incidence of nausea in the cinacalcet groups in the pooled data for Amgen 172, 183 and 188 was higher than in the placebo groups (31% vs 19%, p<0.001*). Similarly, the incidence of vomiting was significantly higher in the cinacalcet group (27% vs15%, p<0.001*). Vomiting was dose-related, while nausea was not.

In the smaller Amgen 141, the incidence of nausea in both the cinacalcet and placebo groups was 44%. Forty-one percent of patients in the cinacalcet-group experienced vomiting compared with 31% of the placebo-group (not significant*).

Hypocalcaemia

Approximately 25% of people receiving placebo and 65% of people receiving cinacalcet in the pooled trials developed at least one serum calcium level <2.1 mmol/L. A similar pattern of hypocalcaemia in drug vs placebo-treated patients was noted in analyses stratified by baseline PTH levels and CaxP products.

In Amgen 141, three adverse events of asymptomatic hypocalcaemia (two cinacalcet, one placebo) were reported.

Seizures

Five percent of patients in the cinacalcet and placebo groups reported having a history of seizures at baseline across the three pooled trials (172, 183 and 188). Eleven (2%) of the cinacalcet patients experienced at least one seizure, five of whom had a history of seizures. Two (0.4%) of those receiving placebo had at least one seizure during the trials both of whom had a history of seizures (p=0.054). It is not known whether this represents a true risk attributable to the drug through hypocalcaemia.

No seizures were reported in Amgen 141.

4.6.9 Summary of results of the systematic review

BOX 2 Summary of results from the systematic review

BIOCHEMICAL OUTCOMES

- *All included trials show that cinacalcet is significantly more effective at reducing PTH levels to below target levels of 26.5pmol/L or less than placebo (40% vs 5% in pooled analysis).*
- *Of people achieving target levels for PTH, 91% also had reductions in CaxP levels.*
- *More patients treated with cinacalcet achieved a reduction of at least 30% in mean PTH level compared to placebo (62% vs 11% in pooled analysis).*
- *Patients treated with cinacalcet showed significantly greater percentage changes from baseline in mean levels of calcium (-6.7% vs +0.5%), phosphate (-7.8% vs +0.3%) and CaxP product (-13.8% vs +0.1%) compared to those treated with placebo.*
- *A large number of subgroup analyses were undertaken on biochemical outcomes according to severity of biochemical derangement and dialysis duration. Most of these were not significant and the trends in results are difficult to interpret. There is some suggestion that cinacalcet may be more effective in less advanced disease. These findings should be treated with caution due to the risk of type I error.*

CLINICAL OUTCOMES

- *One trial provided results on important patient-based outcomes (parathyroidectomy, CV event, fracture and mortality) using pooled data from four RCTs. However, trial follow up was only for 6-12 months and it is not known whether extrapolation of these results to the long term is valid.*
- *Significantly fewer patients treated with cinacalcet were hospitalised for CV events (RR 0.61, p=0.005) although no significant difference was seen in all cause hospitalisation or mortality.*
- *There were significantly fewer fractures (RR 0.46, p=0.04) and parathyroidectomies (RR 0.07, p=0.009) in the cinacalcet arm compared to the placebo arm. However, this finding is based on small numbers.*

ADVERSE EVENTS

- *Withdrawal due to adverse effects was reported in more cinacalcet patients than those receiving placebo (15% vs 8%;) most commonly for GI disturbances.*
- *Significantly more people treated with cinacalcet experienced nausea (31% vs 19%) and vomiting (27% vs 15%).*
- *Eleven (2%) of cinacalcet patients experienced seizures compared to 2 (0.4%) of those treated with placebo (p=0.0054).*

5 Cost effectiveness

5.1 Aim of the economic evaluation

To establish, based on available data, the cost-utility of cinacalcet for treating hyperparathyroidism secondary to ESRD in dialysis patients compared with standard treatment.

5.2 Research Question

What is the cost-effectiveness of cinacalcet for treating hyperparathyroidism secondary to ESRD in people on dialysis compared with standard treatment?

5.3 Systematic review of cost effectiveness studies

5.3.1 Methods

5.3.1.1 Search Strategy and Critical Appraisal Methods

Electronic databases were searched using the strategy shown in Appendix 3.

5.3.1.2 Inclusion and exclusion criteria

Studies were included if they were cost-utility analyses of cinacalcet compared with standard treatment for people with ESRD on dialysis with secondary hyperparathyroidism.

5.3.1.3 Published cost-effectiveness studies

No cost-utility studies in the relevant populations were identified.

5.3.1.4 Cost-effectiveness study provided by industry

One cost-utility study was submitted to the NICE appraisal process by Amgen.

5.3.2 Economic evaluation of cinacalcet submitted by Amgen

5.3.2.1 Design

Cost-effectiveness was estimated using a decision model: [redacted] The main features of the model were as follows:

Starting cohort(s)

[redacted]

Interventions compared

1) Cinacalcet in addition to standard treatment - vitamin D and phosphate binders.

2) Standard treatment with vitamin D and phosphate binders.

Model structure

[redacted]

Figure 2 *Flow diagram of the Amgen Markov model*

Academic in confidence removed

Main outcomes simulated

[redacted]

Assumed benefit of cinacalcet

[redacted]

Data sources

[redacted] Costing was conducted from a UK NHS perspective.

Sub-group analyses

Separate analyses are reported for those with moderate or severe SHPT defined as those with PTH levels of 300 to ≤ 800 pg/mL (32-64pmol/L) and >800 pg/mL (>64pmol/L) respectively.

The key trade-offs in the Amgen model are therefore:

1. [redacted]

2. [redacted]

3. [redacted]

4. [redacted]

Conducted by

The industry submission on the cost-effectiveness of cinacalcet (Mimpara®) was conducted by Amgen Ltd. Appendix 7 of this submission was a commissioned systematic review of the literature on preference-based health state and utility values amongst people with ESRD.

Summary of Amgen cost-utility results

The main (deterministic) results of the Amgen comparison of cinacalcet with standard care for SHPT are shown in Table 32. [redacted]

[redacted]

Table 32 *Amgen base case cost-utility analysis by initial severity of SHPT (discounted results)*

	Cost (£)	Incremental cost (£)	QALYs	Incremental QALYs	ICER (£/QALY)
All patients					
Standard care	[redacted]		[redacted]		
Cinacalcet plus standard care	[redacted]	[redacted]	[redacted]	[redacted]	35,600
Patients with moderate[a] SHPT:					
Standard care	[redacted]		[redacted]		
Cinacalcet plus standard care	[redacted]	[redacted]	[redacted]	[redacted]	30,400
Patients with severe[b] SHPT:					
Standard care	[redacted]		[redacted]		
Cinacalcet plus standard care	[redacted]	[redacted]	[redacted]	[redacted]	48,300

Source: Amgen industry submission, Table 7 p.32. [a] PTH >31.6 and <84.2 pmol/L (> 300 and ≤800 pg/ml). [b] PTH >84.2 pmol/L (>800 pg/ml).

5.3.2.2 Overall appraisal

The economic evaluation of Mimpara® submitted by Amgen appears to be a well conducted analysis of the main relevant cost and health consequences of the decision problem specified in the NICE scope. The methods and results are described with commendable clarity, and an appropriate selection of sensitivity analyses are presented, including a probabilistic sensitivity analysis.

The "cost consequence analysis" – in which they examine the cost per person achieving control of PTH levels – is appropriately reported separately from the reference case. This cost-utility analysis relied upon additional assumptions about lower required doses of vitamin D and phosphate binders for those treated with cinacalcet, based on data from the OPTIMA trial (currently unpublished).

Our main concern with the Amgen analysis is with [redacted]. Furthermore, the validity of extrapolating these short-term effectiveness findings to the remaining life-time of people with end-stage renal disease is uncertain.

5.3.2.3 Major weaknesses of the industry analysis

[redacted]

1. [redacted]
2. [redacted]
3. [redacted]
4. [redacted]

Other limitations

- [redacted]
- [redacted]
- [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

Any other divergences from NICE reference case requirements?

None.

5.4 PenTAG cost-utility model

The systematic review of cinacalcet found that most existing trials of cinacalcet provide short-term data (6-12 months follow up) using biomarkers as outcomes, whereas the crucial data to establish both long term effectiveness and cost-effectiveness of cinacalcet are patient-based clinical outcomes such as cardiovascular (CV) events, fractures and mortality. One paper, by Cunningham and colleagues[69] does report these outcomes for short term follow up. However, as we were uncertain how to extrapolate this data, we have explored it in a scenario analysis. Our approach for the base case has been to use evidence from the RCTs of cinacalcet about impact on levels of PTH and then use data from large cohort studies about the consequent risk of important outcomes contingent on biochemical levels.

A major challenge to modelling the effect of cinacalcet in the long term is the need to account for the combined impact of changes in the different biochemical markers. We identified only one study, based on routine data in a Canadian population, that has examined the relationship between calcium, phosphate, PTH and dialysis duration in combination on mortality.[80] The study population was 515 British Columbian patients (69% on haemodialysis), followed from 2000 to 2002. The analysis demonstrates the complexity of the relationship, with significant interactions between biochemical measures and dialysis duration. We considered using the results of this study as the basis for modelling the cost effectiveness of cinacalcet, but rejected this approach for two main reasons. Firstly, the study was based on routine data which, while reflecting the quality of care in the British Columbian setting, may not be applicable to the UK. Secondly, only mortality was reported and our objectives included the estimation of the impact of cinacalcet on morbidity. In addition, only very limited data is available from the cinacalcet trials about the impact on combined biomarkers.

We have therefore modelled the impact of biochemical factors individually on outcomes. The base case looks at the impact of PTH control. Additional scenario analysis looks at PTH and CaxP product control with cinacalcet. These analyses are rendered somewhat speculative by their univariate nature and the paucity of available data. This is currently an unavoidable limitation on modelling in this condition, which cannot be addressed without appropriate multivariate analysis of large cohorts of people in ESRD. The likely impact on conclusions, in terms of direction and size of bias, is unclear.

5.4.1 Summary description of the PenTAG model

A Markov (state transition) model was developed in Microsoft Excel® (Microsoft Corporation, Redmond, WA, USA). The structure of the model was informed by current literature and expert opinion on the progression of secondary hyperparathyroidism (SHPT) in patients with end stage renal disease and its treatment.

The model estimates the incremental cost-utility of adding cinacalcet to the current standard treatment of SHPT in ESRD. Cost-utility provides an estimate of the costs (in pounds), and benefits, (in quality-adjusted life-years, QALYs), of treatments. The incremental analysis shows the difference in cost and benefits between the two treatments.

The population is those with ESRD on dialysis with SHPT. The treatments compared are cinacalcet as an addition to standard treatment and standard treatment alone. In the base case a hypothetical cohort of 1000 ESRD patients with SHPT are modelled until the whole cohort has died. The initial starting age for the cohort is 55 years old, based on the mean age of participants in Amgen RCTs 172 and 183 and reported by Block and colleagues.[68] Other trials do not supply mean age but report the percentage of their sample under or over 65. The model uses a cycle length of three months.

In the main, costs from 2004 are used as these are the most recent available data for many standard sources. The exception is drug costs, where currently available 2005 costs are used. We have not applied an inflation factor for two reason, firstly, inflated costs are based on assumptions and so may be subject to inaccuracies and secondly, current inflation rates are low, minimising the necessity of inflating subsequent year costs particular for only one year, as would be the case here.

5.4.2 Structure of the model

Figure 3 is a summary diagram of the model presented as a decision tree. Figure 4 presents a more detailed influence diagram of the model. The square junction represents a decision node – in this case, clinicians may decide to treat with standard care alone or with standard care plus cinacalcet. The circular junctions are chance nodes - the proportion of people experiencing different events at these chance nodes are based on probabilities drawn from the literature. Initial treatment for one cycle (three months) of either standard treatment alone or standard treatment plus cinacalcet is followed by patients being stratified into three

levels of PTH control reflecting findings after the titration period from pooled analysis of Amgen 172, 183 and 188.

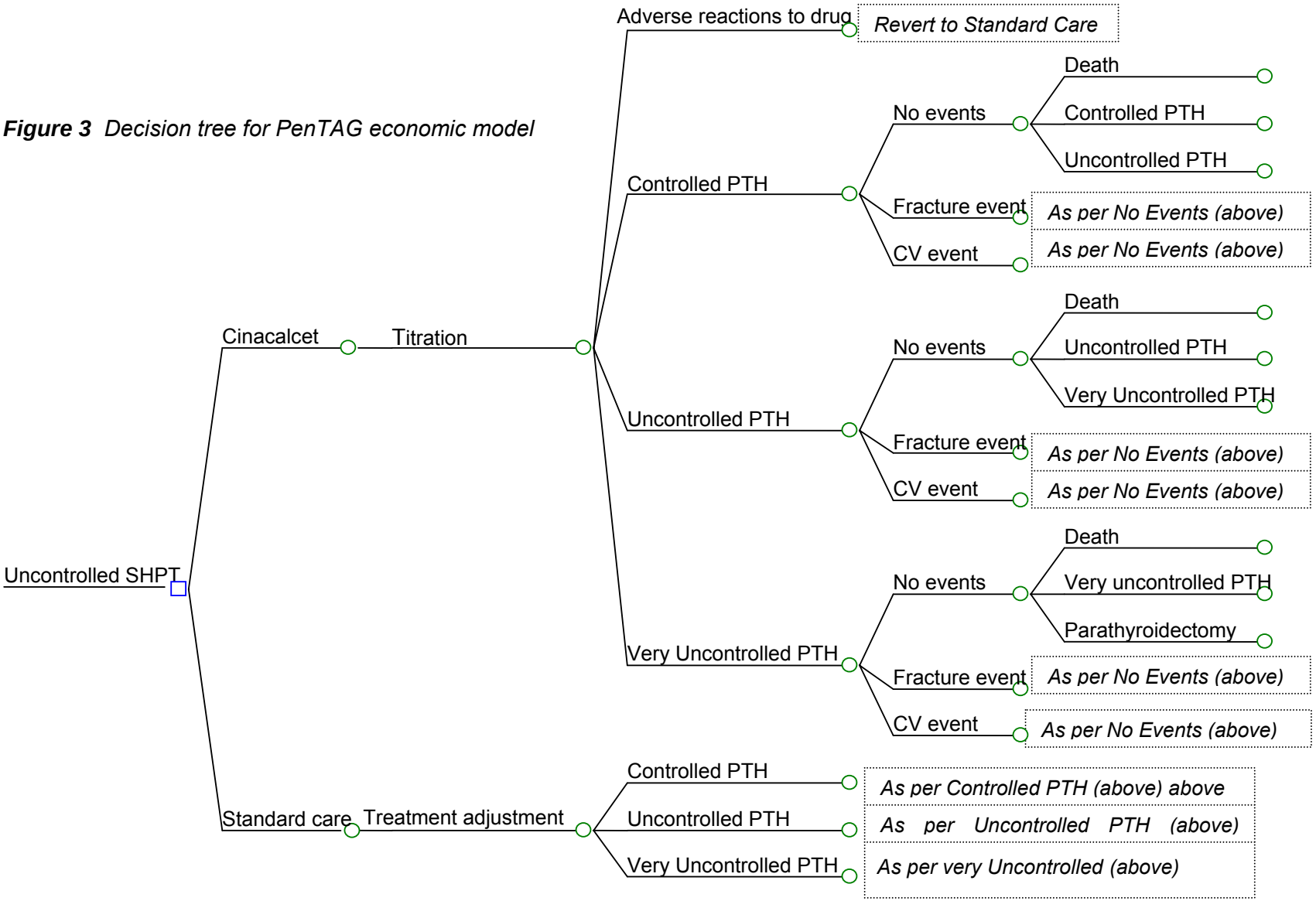
People are considered "controlled" if they have a PTH level of 32pmol/L or less, in accordance with Renal Association standards. They are defined as "uncontrolled" if they have a PTH of between 33 and 84pmol/L, and "very uncontrolled" if they have a PTH level of 85pmol/L or more based on definitions in the cinacalcet trials. Those with "very uncontrolled" PTH are further subdivided into patients who are eligible or ineligible for parathyroidectomy. Two "post-surgical" outcomes are modelled – for patients with or without adverse surgical effects. Parathyroidectomy only occurs in patients with "very uncontrolled" levels of PTH.

PTH levels that are not controlled result in a greater risk of cardiovascular (CV) events or fractures which are in turn associated with greater risk of mortality. In each cycle, stratified by degree of biochemical control, people can experience the following events:

- No fracture or CV event (event free)
- CV event
- Fracture
- Death from CV causes
- Death from other causes.

The chance of having a subsequent CV or fracture event is increased after an initial event of that type. Patients may die from any health state from either CV or other causes.

Figure 3 *Decision tree for PenTAG economic model*

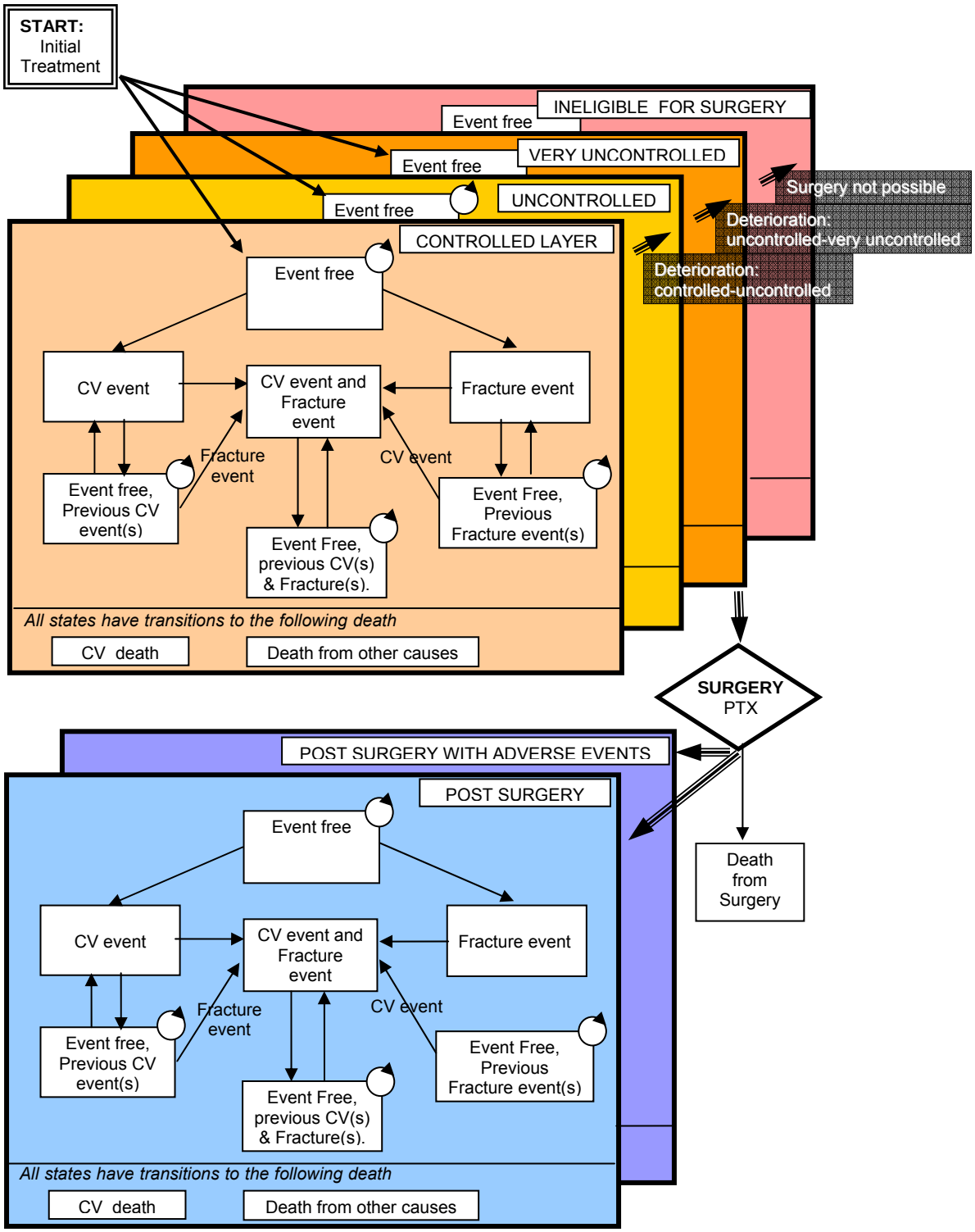


The influence diagram for the model is shown in Figure 4. Health states are shown as white boxes (e.g. "Event free" or "CV event with hospitalisation") and possible movements between these states are shown as arrows. The different degrees of control over PTH levels are shown as the different shaded strata in the diagram (e.g. "controlled" or "uncontrolled" PTH levels). Surgical status (pre- or post- parathyroidectomy) is also presented as different, shaded strata. Table 33 contains a list of health states used in the model.

Table 33 *Description of health states used in the economic model*

Disease state	Description
Event free	Patient has never had either a CV event or fracture serious enough to require hospitalisation
CV event	Patient has a CV event requiring hospitalisation. Patient has never had a major fracture.
Fracture event	Patient has a Fracture event. Patient has never had a CV event serious enough to require hospitalisation.
Event free - History of CV event	Patient has previously had at least one CV event requiring hospitalisation. Patient has never had a major fracture serious. Patient experiences no new adverse event in the current cycle
Event free - History of fracture	Patient has previously had at least one fracture. Patient has never had a CV event serious enough to require hospitalisation. Patient experiences no new adverse event in the current cycle
CV & Fracture event	Patient has either: A Fracture event and has previously had at least one CV event requiring hospitalisation. or A CV event requiring hospitalisation and has previously had at least one fracture event.
Event free – CV & fracture history	Patient has had at least one CV event and at least one fracture event. Patient experiences no new event in the current cycle
CV death	Patient dies form cardiac causes
Non-CV death	Patient dies from non-surgically related, non-cardiac causes
Surgical death	Patient dies from surgical related causes

Figure 4 *Influence diagram for cost-utility model*



People in both cinacalcet and standard treatment arms enter the "initial treatment" phase during which those on cinacalcet go through the titration phase to establish the appropriate controlling dose. Based on pooled trial data from the systematic review, 7% of people treated with cinacalcet withdraw from treatment due to adverse effects at this stage. These people are simulated in the same way as those in the cohort not treated with cinacalcet and they accumulate the risks, costs and benefits associated with standard treatment. These costs and benefits for patients withdrawing from cinacalcet treatment continue to be counted within the cinacalcet arm.

The cohort modelled in the standard treatment arm receives alterations to their treatment to attempt to bring PTH level under control during this initial treatment phase. After the initial treatment phase, PTH levels in both arms will be "controlled", "uncontrolled" or "very uncontrolled," based on the data from the systematic review and people enter the corresponding strata of the model.

The seven health states visible with "controlled" PTH levels in Figure 4 are replicated for all degrees of PTH control and the two post-parathyroidectomy strata. Thus each of the model strata (PTH "uncontrolled", "very uncontrolled" etc.) duplicates the health states and structure shown for "controlled" PTH levels in the model. The thin arrows between boxes represent possible transitions experienced by the cohort within each of the strata, with transitions permitted in the direction of the arrows and circular arrows representing staying in the same health state for another model cycle or cycles.

In addition, patients in the standard treatment arm can move to progressively more "uncontrolled" states representing loss of PTH control over time. This is shown by the thicker, double arrows representing movement between model strata in Figure 4. Surgery itself is modelled as a transition (rather than a health state) that is applied to eligible patients with "very uncontrolled" PTH levels.

Within a Markov state transition model, patients reside in one of a number of discrete health states. At regular time intervals (the model cycle) people make at most one transition between states. A three-month cycle was felt appropriate to accurately capture the clinical pathways for SHP. Before and after each cycle, all patients must be in one of the health states in the model. This means that, for example, a patient currently in the 'event free' state (EVF) can move to either the "fracture" state (FRE) or "CV event" state (CVE) or remain in the "event free" state. People remaining in a particular health state are represented on the influence diagram (Figure 4) by circular arrows. The possible transitions between states are

identical in all of the different model strata. The probabilities attached to each transition during each model cycle are based, where possible, on published data, and, where no data was available, on expert opinion (see section 5.5). The impact of changes in these probabilities on the final cost-utility value is explored using sensitivity analyses.

During each cycle people may either experience no serious event, a major fracture or a CV event. In addition, there may be deterioration in the control of PTH levels with people moving to a more severe degree of HPT, for example, becoming "uncontrolled" having had "controlled" PTH. Members of the cohort move to a state that reflects their previous event history, but at a more severe degree of HPT. It is possible to both move between strata and experience an event in the same cycle.

On reaching "very uncontrolled" levels of PTH, people become candidates for parathyroidectomy. Those that have successful parathyroidectomy enter one of the post-surgical states where they remain until they die. People that are deemed ineligible for surgery remain with the risks associated with "very uncontrolled" levels of PTH until they die. This is also the case for those for whom surgery is unsuccessful at controlling PTH.

Differences in costs and benefits between the arms of the model are based on the different proportions of people who have "controlled", "uncontrolled" or "very uncontrolled" levels of PTH after standard treatment alone or with cinacalcet. Relative risks (RRs) of having a fracture, CV event or of mortality depend on the PTH level and are taken from the literature. Patients with "controlled" PTH levels have been taken as the baseline throughout, with the risk of an event occurring with more uncontrolled PTH levels being relative to this baseline group. This may overestimate the risk for people with more uncontrolled PTH and so bias the model in favour of cinacalcet. However, Renal Registry data shows that 66% of the UK RRT population under current treatment regimens have controlled PTH levels.[12] The impact of different RRs is explored in sensitivity analysis.

Death may occur from any of the health states. The death rate is assumed to be dependent on age, and is therefore modelled as a time-dependant variable. Death from CV causes and death from other causes is possible in all of the model strata. In addition, there is a small risk of death as a complication of parathyroidectomy.

Unless otherwise specified, all references to people with "very uncontrolled" levels of PTH refers to both those eligible and those ineligible for surgery.

A half cycle correction was not added to the model, as the cycle length was felt to be sufficiently short for this not to be necessary. This is unlikely to have a significant impact on the results.

5.5 Sources of estimates used in the PenTAG cost-effectiveness models

5.5.1 Transitions between health states

5.5.1.1 Effectiveness of standard treatment alone and plus cinacalcet in reducing PTH levels

Table 34 shows the distribution across the model strata of each of the cohorts at the start of each model. The systematic review shows how many people had "controlled" PTH levels after the titration phase with standard treatment alone or with cinacalcet. We have assumed that the impact of standard treatment plus placebo reported in the trials will be the same as for standard treatment alone in clinical practice.

The proportions that where "uncontrolled" or "very uncontrolled" were not reported in the cinacalcet trials. Data supplied by the Renal Registry showed that, of those who did not have PTH levels below the target level, 70% had PTH levels between 32 and 85 pmol/L while 30% had PTH levels of more than 85pmol/L (Dr David Ansell, personal communication 24/2/06). We have used this data to distribute those without controlled PTH between these two degrees of control.

Table 34 *Effectiveness of cinacalcet and standard treatment in controlling PTH levels*

Variable	Value	Source	Comments
Differential percentage of withdrawals in each arm of the model.	0.07	Pooled RCT data	15% withdrawal from treatment arm and 8% placebo from main RCT data pooled, section 4.1.12.3.
Proportion of the standard treatment cohort having "Controlled" PTH levels on completion of the titration phase	0.05	Pooled RCT data	This systematic review Table 9 shows proportion of each cohort that have a PTH <=32pmol/L after titration
Proportion of the standard treatment cohort having "uncontrolled" PTH levels on completion of the titration phase	0.665	Assumption based on pooled RCT data and Renal registry	95% of those treated with cinacalcet do not achieve target PTH levels. Of those that are not controlled assume 70% are "uncontrolled"
Proportion of the standard treatment cohort having "Very uncontrolled" PTH levels on completion of the titration phase	0.285	Assumption based on pooled RCT data and Renal registry	95% of those treated with cinacalcet do not achieve target PTH levels. Of those that are not controlled assume 30% remain "very uncontrolled"
Proportion of the cinacalcet cohort entering the "Controlled" subpopulation on completion of the titration phase	0.4	Pooled RCT data	Table 9 shows proportion of each cohort that have a PTH <=26.5pmol/L after treatment
Proportion of the cinacalcet cohort having "uncontrolled" PTH levels on completion of the titration phase	0.42	Assumption based on pooled RCT data and Renal registry	60% of those treated with cinacalcet do not achieve target PTH levels. Of those that are not controlled assume 70% are "uncontrolled"
Proportion of the cinacalcet cohort having "Very uncontrolled" PTH levels on completion of the titration phase	0.18	Assumption based on pooled RCT data and Renal registry	60% of those treated with cinacalcet do not achieve target PTH levels. Of those that are not controlled assume 30% are "very uncontrolled" .

5.5.1.2 Progression of hyperparathyroidism over time

Control of serum PTH levels tends to worsen over time for people on dialysis. This may be due to a number of factors such as gradual worsening of disease or lack of compliance with treatment, which is known to be important. The model takes this into account by allowing "deterioration" of control so that people receiving standard treatment can move from having "controlled" PTH to being "uncontrolled", and from having "uncontrolled" PTH levels to having "very uncontrolled" levels. Advice from our clinical advisory group was sought to

establish the extent of such deterioration. However, as opinion varied and no published data was available, we have made an assumption based on the range of information supplied by the clinical experts (Table 35). We have explored the impact of this assumption in extensive sensitivity analysis.

It is unclear how we should extrapolate the effectiveness of cinacalcet beyond the length of the trials as it is not known whether consistent control is more or less likely with cinacalcet compared to standard treatment. Compliance could be an issue with cinacalcet in clinical practice as it adds to the burden of medication and may cause adverse effects such as nausea. However, in the absence of relevant data, we have assumed that there was no loss of control over time with cinacalcet. The impact of this assumption was explored in sensitivity analysis.

Table 35 *Loss of control of PTH over time (deterioration).*

Variable	Value	Source	Comments
Proportion of people with "controlled" PTH levels that become "uncontrolled" each cycle in the standard treatment arm (per year)	0.1	Assumption	No published data available. Information from EAG varied.
Proportion of people with "uncontrolled" PTH levels that become "very uncontrolled" each cycle in the standard treatment arm (per year)	0.2	Assumption	No published data available. Information from EAG varied.
Proportion of people with "controlled" PTH levels that become "uncontrolled" each cycle in the cinacalcet arm (per year)	0	Assumption	No published data available. Information from EAG varied.
Proportion of people with "uncontrolled" PTH levels that become "very uncontrolled" each cycle in the cinacalcet arm (per year)	0	Assumption	No published data available. Information from EAG varied.

5.5.1.3 Mortality

Background death rates are derived from the cumulative average survival probabilities after the initial 90-days on dialysis reported in the Renal Registry for ten-year age bands.[12] The probability of death at the start and end of these 10-year categories are likely to be different.

We therefore interpolated death rates for individual ages using the methods described in Appendix 8. Illustrative values are shown in Table 36.

Table 36 *Cumulative 1-year probability of death due to all causes*

Age group (yrs)	1-yr mortality	Source
45 – 54	0.083	Renal Registry
55 – 64	0.150	Renal Registry
65 – 74	0.213	Renal Registry
75 – 84	0.276	Renal Registry
85 +	0.354	Renal Registry

Relative mortality risk based on PTH levels

Having established the overall mortality rate by age, the impact of PTH levels is estimated using a large US cohort study by Block and colleagues (2004).[18] This assessed the impact of various biochemical markers on the risk of adverse events occurring. PTH levels were divided into six ranges (<150pg/ml, 150-300pg/ml, 300-600pg/ml, 600-900pg/ml, 900-1200pg/ml, ≥ 1200pg/ml). These are equivalent to values of <16pmol/L, 16-32pmol/L, 32-64pmol/L, 64-95pmol/L, 95-127pmol/L and ≥ 127pmol/L). The RR of mortality occurring in each of these PTH ranges was reported. We derived RR for the ranges used in our model for those with "controlled", "uncontrolled" and "very uncontrolled" PTH using the methods described in Appendix 9 (p.264). Table 37 summarises the RR values used in the model. These are applied to the age dependant probabilities of all-cause death to obtain the required cycle probability of death in each of the model strata.

Table 37 *Relative Risk modifiers for all cause mortality for different degrees of PTH control*

Degree of PTH control	Value	Source	Justification/comments
"Controlled "	1.0	Block et al, 2004[16]	USA data based on 40,538 dialysis people. Baseline range used in all calculations is 150–300pg/ml (16-32 pmol/L), therefore RR is 1
"Uncontrolled"	1.0613	Block et al, 2004[16]	USA data based on 40,538 dialysis people. Paper reports RR's for six different PTH ranges. Plot of RR's against PTH shows a linear relationship. Value imputed using a PTH level of 550pg/ml (58pmol/L)
"Very uncontrolled"	1.1824	Block et al, 2004[16]	USA data based on 40,538 dialysis people. Paper reports RR's for six different PTH ranges. Plot of RR's against PTH shows a linear relationship. Value imputed using a PTH level of 1200pg/ml (127pmol/L)

Surgical mortality is described below in the parathyroidectomy section on page 116.

5.5.1.4 Cardiovascular related transition probabilities

The rate at which initial, non-fatal cardiovascular events occur has been assumed to be constant. The risk of having a subsequent cardiovascular event is assumed to be higher once an event has previously occurred.

Death from cardiovascular causes

Three different causes of mortality are modelled: CV death, death from other causes, and surgical deaths (which accounts for the small proportion of those patients who die due to parathyroidectomy). Death from other causes represents a relatively stable background level of mortality within the model that varies slightly depending on the level of PTH control, but which is consistent for all the health sates at a given degree of PTH control. CV death is the main source of differential death rates between the states at each degree of SHPT severity. To derive the CV death transition probabilities for each health state in the model, two types of data have been combined. Firstly, the overall proportion of the death rate for the population know to be attributable to CV causes, and secondly, the relative risk of CV death for each health state compared to the "event free" state. These two types of data have been obtained from a range of sources and combined to derive the values for CV death transition probabilities for each modelled health state as described in Appendix 10.

The transition probabilities relating to death from CV causes for each health state in the model are calculated from the standard treatment arm of the model. These probabilities are then applied equally to the cinacalcet arm of the model. Reduced CV mortality in the cinacalcet arm can arise in two ways, firstly through more of the population having "controlled" PTH levels and so having a lower overall death probability. Secondly, through a lower proportion of the population at all levels of PTH control occupying health states related to CV events and fractures which carry higher risk. For example, if CV events are reduced with cinacalcet then the associated state occupancy of this high risk state will be reduced and the number of CV deaths will be lower.

Variation of CV death risk between health states

The risk of CV death for people who have a CV event is likely to be higher than for those who have not had a CV event. In the model, this means a greater risk of CV death for people occupying health states "CV event" or "post-CV event" compared with those occupying the "event free" health state. In addition, the risk of CV death is greater for patients with "uncontrolled" or "very uncontrolled" levels of PTH compared with those with "controlled" levels. Finally, the risk of dying from a subsequent CV event increases if people have a history of either CV events or major fractures. This means that different transition probabilities for CV death are needed both for the different strata of the model and for the different health states within each strata.

Determining the CV death risk during CV hospitalisation

In a US based study of 34,189 patients on long term dialysis, Herzog and colleagues (1998) describe long term survival after an acute myocardial infarction (MI).[81] In-hospital mortality for patients suffering from MI was 26%. We therefore assumed that the probability of CV death for patients hospitalised for a CV event is on average 0.26 across the layers. This is the probability of death from CV causes from the model health state "CV event requiring hospitalisation."

Determining the CV death risk during and after fractures

Mittalhenkle and colleagues[82] explored the risk of mortality over five years associated with hip fracture in ESRD patients in the USA. The study included 7636 patients with a hip fracture and 22896 matched controls. In people with no history of CV disease, a hip fracture led to an 84% increase in the risk of CV mortality when compared to people with no history of fracture. In those with a history of CV disease, a hip fracture led to a 91% increased risk of CV related death compared to a similar person with no fracture. We have assumed that

the increased risk CV death following all major fractures is not significantly different to that for hip fracture. Therefore, the relative risk of CV death after having had a major fracture requiring hospitalisation is 1.84. This is applied to the health states "Fracture event requiring hospitalisation" and "Event free with a history of fracture". For patients who have had both a non-fatal CV event and a previous fracture (occupying the "Event free - previous CV and fracture events" health state), the relative risk of death in is 1.91 compared to those who have had neither of these events (the "event-free" health state in the model). Again, these values have been assumed to apply regardless of the level of control of PTH levels.

Determining the CV death risk for patients with CV and Fracture history

We have assumed that the risk of CV related death for those who have a history of both a fracture and a CV event is the same as for those who have only had a previous CV event. Since few people enter this health state in the model, the impact on the model results is unlikely to be significant. Table 38 summarises the relative risk modifiers for people who have had fractures or CV events compared to the risk of CV-related death for people who have no history of CV event or fracture.

Table 38 *Relative risk of CV death in different health states compared to the "event free" health state.*

Health state	Value	Source	Justification
Death from CV event (CVE)	13.20	Herzog (1998)[81]	Derived from reported mortality for dialysis patients hospitalised due to CV event (0.26).
Event free, previous CV event (CVH)	2.9	Renal Registry[15]	Mortality with CV disease for England and Wales
Fracture event with hospitalisation (FRE)	1.84	Mittalhenkle et al (2004)[82]	See text, section 5.5.1.4
Event free with previous fracture event (FRH)	1.84	Mittalhenkle et al (2004)[82]	See text, section 5.5.1.4
CV event and fracture event experience (CFE)	1.91	Mittalhenkle et al (2004)[82]	See text, section 5.5.1.4.
Event free with previous fracture and CV event (CFH)	1.91	Mittalhenkle et al (2004)[82]	See text, section 5.5.1.4

First cardiovascular hospitalisation

In a study of 40,538 people on dialysis, Block and colleagues (2004)[18] report 5876 cardiovascular hospitalisations over the 12–18 month follow up period, based on ICD-9

codes. This gives a rate of 0.1023 events per patient year. The corresponding baseline cycle probability of a CV event is therefore 0.02662.

Block and colleagues[18] also report the relative risk (RR) of cardiovascular hospitalisation for people with PTH levels ≥ 600pg/ml (64pmol/L) or ≥ 900pg/ml (95pmol/L) compared to those with PTH levels of 150-300pg/dl (16-32pmol/L). The RR are shown in Table 39. These values have been used to represent the RR for patients in the model with "uncontrolled" and "very uncontrolled" PTH levels. Derived values used in the model are shown in Table 40.

Table 39 *Relative risk of CV event according to levels of PTH control*

Degree of PTH control	Value	Source	Justification/comments
"Controlled "	1.0	Block et al, 2004[18]	USA data based on 40,538 dialysis people. Baseline range used in all calculations is 16-32pmol/L. Paper only reports statistically significant RR's for PTH >64, therefore RR is 1
"Uncontrolled"	1.17	Block et al, 2004[18]	USA data based on 40,538 dialysis people. We assume that the RR for PTH > 64pmol/L represents those with "uncontrolled" PTH in the model.
"Very uncontrolled"	1.26	Block et al, 2004[18]	USA data based on 40,538 dialysis people. We assume that the RR for PTH >95pmol/L represents those with "very uncontrolled" PTH in the model.
Post surgical	1.26	Modeller assumption	Assumption has been made that CV calcification is irreversible, and therefore after surgery the risk of a CV event is the same as for those with "very uncontrolled" PTH.
Post surgical with adverse events	1.26	Modeller assumption	Assumption has been made that CV calcification is irreversible, and therefore after surgery the risk of a CV event is the same as for those with "very uncontrolled" PTH.

Table 40 *Cycle probability of an initial CV event by extent of PTH control.*

PTH levels	Controlled	Uncontrolled	Very uncontrolled	Post surgery
Event probability	0.02662	0.03114	0.03354	0.03354

Subsequent cardiovascular events

A subsequent CV event is defined as hospitalisation due to CV problems in people with a history of hospitalisation for a CV event. It is assumed that the probability of having a subsequent CV event serious enough to require hospitalisation increases once one has already occurred. As assuming the modelled population was all CV event naive would

underestimate the risk of CV events, we have assumed that some of the starting cohort already have a history of CV event. Based on data from the Renal Registry, 15.7% of people in the model enter the "Previous CV event" health state in the first cycle after the initial treatment phase. The available data only provide estimates of the risk of a subsequent heart failure event after an initial admission for heart failure. It is unclear how representative this is of the subsequent risk of other CV events and this is a potential limitation of the model. We used this value because a large US cohort study of dialysis patients (n=40,538) showed that heart failure is the most common CV cause of hospitalisation, accounting for 3.3% of admission.[18] Other frequent causes were chest pain (3%), cardiac arrest (0.9%), acute myocardial infarction (0.8%) and angina pectoris (0.8%).

In a retrospective cohort study of 1,995 US dialysis patients, Trespalacios and colleagues examined the risk factors associated with both initial and subsequent hospitalisations for people with and without prior congestive heart failure (CHF).[83] Table 41 shows the numbers of people in this study hospitalised for heart failure who had a history of CHF.

Table 41 *Calculation of risk modifier for subsequent CV event given a previous event*[83]

	Hospitalised for HF	Not hospitalised for HF	Totals
No prior history of CHF	103	928	1031
Prior history of CHF	188	658	846
Totals	291	1586	1877

The risk ratio for hospitalisation in people with a history of CHF compared to people with no history of CHF is (103/1031)/(188/846) = 2.224 (95% CI 1.781, 2.778). The probability of a subsequent admission for CHF is the transition probability for an initial CV event multiplied by this value (Table 42).

Table 42 *Cycle probability of an subsequent CV event occurring by degree of PTH control*

PTH level	Controlled	Uncontrolled	Very uncontrolled	Post surgery
Probability of a subsequent CV event	0.05920	0.06927	0.07459	0.07459

5.5.1.5 Fracture related transition probabilities

We were unable to identify any published information about the epidemiology of fractures specifically in the ESRD population. We have used hip/femur fractures as the identifier for

major fractures due to renal osteodystrophy. Within the model, each hip fracture also incurs the cost and reduction in utility due to fractures at other sites based on the distribution of fractures in the general population.[84] Major fractures are modelled explicitly through patient movement to the relevant health state, with associated costs, a reduction in quality of life (utility) and increased risk of mortality. For the associated minor fracture, the impact on utility value and cost is modelled for one cycle.

We have assumed that the pattern of fractures in renal osteodystrophy is the same as in the general population. This is a limitation but no data about the pattern of fracture in ESRD was identified. Neither osteoporosis data, based mostly on older women, nor general population data is an ideal match for this population. Although osteoporotic fractures may be more similar to those due to renal osteodystrophy than the general population, there are differences in these groups. Moreover, there are no straightforward definitions of osteoporotic fractures. Previous technology assessments about osteoporosis have used general population studies, and assumed that those at specific sites are osteoporotic.[85]

The risk of having an initial fracture is based on constant risk and is not time dependent which may underestimate the number of fractures experienced. After having the first fracture, the risk of having subsequent fractures is higher. The rate at which first fractures occur depends on PTH levels.

Initial fractures

A US based study of over 100,000 people awaiting kidney transplantation reported a hip fracture rate of 2.9 events per 1000 patient years.[26] In the general population of England and Wales hip fractures represent 10.35% of all reported fractures (24,934 out of 240,857 fractures).[84]

As was the case with mortality, it is necessary to modify this baseline rate of hip fractures to reflect the risk of an event occurring at each level of PTH control. Only one relevant study, by Kim and colleagues, was identified.[86] This study is only available in abstract form and included 10,018 patients on dialysis in the USA. It reports the hazard ratio for fracture by different PTH levels. The risk of fractures for those with PTH levels of more than 85pmol/L was increased by 94% compared to those with PTH levels of 16-32pmol/L.

The study by Kim and colleagues (2004)[86] reports HR separately for people with PTH levels of 32-53pmol/L and 53-85pmol/L. Kim and colleagues (2004) reports that those with PTH levels of 32-53pmol/L have a reduced risk of fracture compared to the reference population

(16-32pmol/L), which seems counterintuitive. The HR for both PTH categories have 95% confidence intervals that include one. In order not to bias against cinacalcet in the base case, we have used the HR reported by Kim and colleagues for patients with PTH levels of 53-85pmol/L for those with "uncontrolled" PTH. The impact of this assumption has been explored through sensitivity analysis. Table 43 shows the hazard ratios used in the PenTAG model to estimate the probability of fracture depending on the degree of PTH control.

Table 43 *Modifiers for initial fractures at different levels of PTH control*

PTH levels	Value	Source	Justification/comments
"Controlled	1.0	Kim et al, 2004[86]	Base case for HR's published in the abstract. USA study of 10,018 dialysis patients
Uncontrolled	1.12	Kim et al, 2004[86]	HR of fracture for patients with PTH levels of 500-800pg/ml (53-85 pmol/L). USA study of 10,018 dialysis patients.
Very uncontrolled	1.94	Kim et al, 2004[86]	Weighted average of the HR's published in the abstract. USA study of 10,018 dialysis patients
Post surgical	1.0	Kim et al, 2004[86]	Post-surgical risk of fracture assumed the same as in the controlled group
Post surgical with adverse events	1.0	Kim et al, 2004[86]	Post-surgical risk of fracture assumed the same as in the controlled group

Applying these values to the baseline annual rate, and adjusting for cycle length leads to the transition probabilities shown in Table 44. These probabilities are only applied to transitions from health states where the patient has no history of a fracture.(e.g from EVF, CVE or CVH) to states where a fracture occurs (FRE and CFE).

Second and Subsequent fractures

Based on a meta-analysis of studies assessing the increased risk of subsequent fracture after initial fracture in osteoporosis, Stevenson and colleagues report that the relative risk of a subsequent hip fracture after initial hip fracture is 2.3.[87] This value was applied to all of the model strata. Multiplying the probabilities of initial fracture in each of the model strata by this value gives the probability of a subsequent fracture depending on the degree of PTH control (Table 44). These probabilities are applied to transitions from health states where a patient has a history of a fracture.

Table 44 *Cycle probability of an initial and subsequent fracture by level of PTH control*

PTH levels	Controlled	Uncontrolled	Very uncontrolled	Post surgery
Initial fracture probability	0.000726	0.00081	0.00141	0.000726
Subsequent fracture probability	0.00167	0.00187	0.00324	0.00167

5.5.1.6 Parathyroidectomy transition probabilities

The model only allows parathyroidectomy for patients whose levels of PTH are "very uncontrolled". Input from clinicians in the expert advisory group (EAG) suggested that use of parathyroidectomy is variable. A 10% annual rate of parathyroidectomy for those with "very uncontrolled" levels of PTH has been used. For the modelled cohort, a constant transition probability has been used. In addition, the EAG suggested that about 15% of people aged 55 would be unsuitable for surgery, rising to 25% for those aged 75. This has been assumed to increase at a linear rate.

The number of people in the cohort with "very uncontrolled" PTH levels at the start is based on the numbers from the pooled data of the RCTs included in the systematic review (see Table 34).

People having a successful parathyroidectomy are assumed to have the same risk of a fracture event as people with "controlled" PTH levels (i.e. RR=1). It has been assumed that cardiovascular calcification is irreversible, meaning that the risk of a CV event post surgery stays the same as it was pre-surgery for those with "very uncontrolled" PTH levels.

The model does not assume that surgery is always successful. Two studies of people undergoing parathyroidectomy, one in 60 people in the USA and one in 148 people in Spain, both report an 8% failure rate, resulting in continued hyperparathyroidism or re-operation.[88;89] We model 8% of people returning to having "very uncontrolled" PTH after surgery (Table 45). Those that do have a successful operation no longer suffer from SHPT and do not require a repeat operation. Potentially, this is a limitation of the model as it may overestimate effectiveness and underestimate the total number of parathyroidectomies.

In addition, 1% of those receiving parathyroidectomy experience a serious adverse event, such as vocal cord damage. and they enter the "Post-parathyroidectomy – adverse effects" stratum of the model. Here, they attract the same risks and benefits as those who continue to have "very uncontrolled" levels of PTH.

Given the assumptions made in the calculation of this value, the uncertainty in its derivation are explored in sensitivity analysis.

***Table 45** Proportion of parathyroidectomies which fail to control PTH*

Variable	Value	Source	Comments
Proportion of operations that are unsuccessful in controlling patients biomarkers	0.08	Jofre et al, 2003[88]	12/148 PTX required re-operation or retained PTH levels over 97.5pmol/L.
		Kim et al 1994[89]	5/60 persistent or recurrent HPT.

Surgical mortality

Surgical mortality data was taken from on a matched cohort study by Kestenbaum and colleagues (2004).[90] People with ESRD (n=4,558) who underwent an initial parathyroidectomy were matched with those not undergoing surgery based on age, race, gender, cause of ESRD, dialysis duration and dialysis modality. Post-parathyroidectomy, the risk of death is initially increased in the first 90 days post-surgery (RR =1.84) but subsequently mortality is reduced (RR=0.87). In the model, the RR of death after surgery applied relative to those with "very uncontrolled" PTH. Table 46 shows the relative risk data used in the first and subsequent model cycles post-surgery.

***Table 46** Relative risk of mortality related to parathyroidectomy*

Variable	Value	Source	Comments
Post surgical (first 90 days)	3.356	Kastenbaum et al, 2004[90]	Short term increase in the risk of death compared to patients who didn't have surgery. Value represents an 84% increase in risk compared to those with "Very uncontrolled" PTH.
Post surgical with adverse events (first 90 days)	3.356	Kastenbaum et al, 2004[90]	Short term increase in the risk of death compared to patients who didn't have surgery. Value represents an 84% increase in risk compared to those with "Very uncontrolled" PTH.
Post surgical (after 90 days)	1.029	Kastenbaum et al, 2004[90]	Long term reduction in the risk of death compared to patients who didn't have surgery. Value represents a 13% reduction in risk compared to those with "Very uncontrolled" PTH.
Post surgical with adverse events (after 90 days)	1.029	Kastenbaum et al, 2004[90]	Long term reduction in the risk of death compared to patients who didn't have surgery. Value represents a 13% reduction in risk compared to those with "Very uncontrolled" PTH.

5.5.2 Utilities

We searched for utility values assigned by general population samples, as a societal perspective is preferred by NICE. We also wanted to identify sources which had used a preference-based method for measuring utility. The time trade off (TTO) method has been established as being adequately tested in an ESRD population.[40]

5.5.2.1 Utility values for ESRD

A search for utility values in ESRD was undertaken using the strategy described in Appendix 3. Only one paper, by de Wit and colleagues (1998) identified societal values for people with ESRD on dialysis. In this case, Dutch people with ESRD completed the EQ-5D and these results were translated by de Wit and colleagues using the preference based scores obtained by Dolan for EQ-5D states from a representative sample of the UK population.[91] Utility values are shown in Table 47. In the UK, 73% of dialysis people receive haemodialysis (HD) and 27% peritoneal dialysis (PD) so the model used a weighted average for the utility value of 0.6735.[12]

Table 47 *Utility values for dialysis given by a general population sample*

Study and date	Dialysis type	Utility Value (SD)
de Wit et al[46]	Haemodialysis	0.66 (0.29)
	Limited care haemodialysis	0.81 (0.24)
	Continuous ambulatory peritoneal dialysis	0.71 (0.29)
	Continuous cycling peritoneal dialysis	0.81 (0.19)

5.5.2.2 Impact of PTH level on utility

We did not identify any papers that reported utility value by PTH level and only one paper that looked at any measure of quality of life in relation to this measure. Knight and colleagues[51] measured the physical and mental health components of the SF-36 in 14,815 people with ESRD in the USA. They did not find any significant association with PTH levels and either physical or mental health, although there was a trend of higher mean PTH levels in groups with worsening QoL scores. However, it should be noted that in levels of PTH are not particularly high in this study.[51] Also, bone pain and pruritus are common symptoms of hyperparathyroidism and studies have reported an increase in QoL after parathyroidectomy as a result of these resolving. Advice from clinical experts suggested that there was not likely to be an impact on QoL with “uncontrolled” PTH compared to “controlled”, but that

people with "very controlled" PTH levels would be adversely affected. The model therefore incorporates a scaled reduction of 15% in utility for those in the event-free health state who have "very uncontrolled" PTH.

5.5.2.3 Utility values for CV events

No studies were identified that provided utility values for people with ESRD after experiencing a cardiac event. We identified two relevant studies, by Nease and colleagues (1995)[92] and Martin and colleagues (1999).[91] However, in both cases, these papers report the impact of ongoing symptoms as having relatively high utility scores of 0.96 and 0.98 respectively. We have assumed that the reduction in utility will be ongoing after people have recovered from hospitalisation due to a CV event. This ongoing scaled health reduction is calculated by multiplying the value for ESRD by the value for angina.

We also sought values assessing the impact of acute CV events requiring hospitalisation, such as myocardial infarction (MI) and this was applied to a single cycle (three months). The Harvard Cost Effectiveness Analysis (CEA)[93] database of health state utility values gives a value of 0.71 for congestive heart failure based on a community rating using the TTO method (taken from the Beaver Dam Health). Congestive heart failure is the most common cardiovascular reason for hospitalisation among those with ESRD, accounting for 3.3% of hospitalisations whilst cardiac arrest and acute myocardial infarction account for 0.9% and 0.8% respectively.[18]

Table 48 *Scaled reduction in utility value for cardiovascular events*

Single Health state	Value	Source	Justification
Congestive heart failure	0.71	Harvard CEA database[93]	Congestive HF the most common reason for CV hospitalisation for pts with ESRD.[18] Value used in model is this multiplied by value for ESRD for one cycle.
Chronic cardiovascular disease	0.97	Nease et al (1995)[92] and Martin et al (1998) [91]	Weighted mean of values for angina or dyspnoea symptoms. Applied to people with ESRD after CV event cycle.
CEA = cost-effectiveness analysis, HF = heart failure, CV = cardiovascular, ESRD = End stage renal disease			

5.5.2.4 Utility values for fracture

No studies were found that assessed the quality of life impact of fractures in people with ESRD. Fracture studies tend to be either in the general population or in those with

osteoporosis. Extrapolating data from either of these populations to those with ESRD is not ideal. General population data is likely to contain more young, very active people while osteoporosis studies tend to be in elderly women. However, because osteoporosis fractures are more likely to follow a similar pattern to fractures due to bone disease in ESRD than the general population, this was felt to be a more relevant source of utility estimates.

Brazier and colleagues[94] recently conducted a systematic review of utility values for osteoporosis related conditions. They recommend a set of values as a "reference case" for economic models of osteoporosis which they suggest should be applied in the first year to population norms for the relevant populations. These are based on EQ-5D values. For subsequent years, Brazier and colleagues suggest that a value of half the initial impact should be used for major fractures, but no impact for minor fractures. We have used the hip fracture value as a proxy for all major fracture events, and humerus fracture values for minor fractures.

Table 49 *Scaled reduction in utility values for fractures*

Single Health state	Value	Source	Justification
Hip fracture (first cycle)	0.797	Brazier et al[94]	Reference case based on recent SR of osteoporosis literature.
Hip fracture (subsequent cycles)	0.8985	Brazier et al[94]	Reference case for subsequent impact of hip fracture in SR based on author experience.
Proximal humerus fracture (one cycle)	0.981	Brazier et al[94]	Reference case based on recent SR of osteoporosis literature.

SR = systematic review

5.5.2.5 Utility values and parathyroidectomy

People who have a successful parathyroidectomy are assumed to gain control of PTH levels and have the same values for all health states as for a person whose PTH is "controlled". People who have adverse effects due to parathyroidectomy are assumed not to benefit from this surgery in terms of quality of life gains, and so keep the same utility values as people with "very uncontrolled" PTH levels. As the impact of surgery itself was assumed to be short, no utility decrement was modelled.

Table 50 *Summary of utility values used in the economic model*

Disease state	Value	Source	Justification
Event free survival	0.6735	de Wit et al[46]	European study using societal values of utility found HD 0.66 and PD 0.71. Weighted value based on 73% HD 27% PD in the UK.[12]
CV event (with hospitalisation)	0.4782	Harvard CEA database[93]	Congestive HF the most common reason for CV hospitalisation for pts with ESRD (utility 0.71).[18] Value used in model is this multiplied by value for ESRD for one cycle.
Event free - previous CV event	0.6533	Nease et al[92] and Martin et al[91]	Weighted mean of values for angina or dyspnoea symptoms (utility 0.97). Applied as an ongoing scaled reduction to ESRD pts after CV event.
Fracture event (with hospitalisation)	0.5368	Brazier et al[94]	Reference case based on recent SR of osteoporosis literature for hip fracture (utility 0.797). Applied as reduction for one cycle.
Event free – previous fracture	0.6051	Brazier et al [94]	Reference case for subsequent impact of hip fracture in SR based on author experience (utility 0.8985). Applied as ongoing scaled reduction to ESRD pts after fracture event.
CV event and fracture experience	0.3811	See above	Assume that impact of these is compound.
Event free – previous CV and fracture events	0.5870	See above	Assume that the impact of these reductions is compound. Applied to subsequent states.
Impact of having "uncontrolled" PTH levels	x 1	Author assumption	Assume that there is no impact on QoL of PTH levels of 33-84pmol/L for patients whose PTH levels are "uncontrolled" compared to patients who have controlled PTH.
Impact of having "very uncontrolled" PTH levels	x 0.85	Author assumption	Assume that a scaled reduction of 15% is applied to all health states for patients whose PTH levels are "very uncontrolled" compared to patients who have "controlled" PTH.
Post-parathyroidectomy	As for people with "controlled" PTH levels	Author assumption	Assume that post-successful surgery, patients have controlled PTH levels.
Post-parathyroidectomy with adverse effects	As for people with "very uncontrolled" PTH levels	Author assumption	Assume that after surgery people with adverse effects have the same QoL as people with "very uncontrolled" PTH levels.

5.5.3 Identification and measurement of resource use

5.5.3.1 Perspective and costing principles

Costing was conducted using a variety of data sources to determine the amount and valuation (unit costs) of resources used. An NHS perspective was used.

The types of NHS resource use initially intended for inclusion in the analysis were:

1. Resources which are consumed at different rates during or after treatment with Cinacalcet, compared with during or after standard treatment.
2. Resources related to treatments, procedures, service contacts, adverse events or other potentially cost-inducing events that may differ between those treated with cinacalcet and standard treatment (either because of trial or other evidence suggesting that they actually differ, or because there may be differences in survival between intervention and comparator).
3. Resources for which there is a probable opportunity cost (i.e. those which would, in all likelihood, otherwise be used for some other purpose or patients within the NHS).

5.5.3.2 Resource use included in the analysis

Ultimately the following types of resource use were included in our base case analysis:

- Cinacalcet (during initial treatment phase and maintenance)
- Annual cost of standard care for SHPT (vitamin D and phosphate binders) for people with ESRD on dialysis
- Hospital resources to treat those CV-related adverse events that lead to hospitalisation
- Hospital resources to treat major fractures that lead to hospitalisation
- Hospital resources to treat minor fractures that lead to hospitalisation
- Hospital resources to conduct parathyroidectomies
- Regular blood tests for PTH, Calcium and Phosphate levels

Table 51 *Types of resource use consumed by comparator*

Type of resource use	Cinacalcet	Control	Justification for inclusion
Cinacalcet (drug) during maintenance phase	✓	x	Integral to taking Cinacalcet
Cinacalcet (drug) during titration phase	✓	x	Integral to taking Cinacalcet
Cost of vitamin D and phosphate binders	✓	✓	May differ between Cinacalcet and standard treatment arm
CV-related hospitalisations	✓	✓	Trial evidence that these occur at a different rate in those on Cinacalcet
Major fracture-related hospitalisations	✓	✓	Trial evidence that these occur at a different rate in those on Cinacalcet
Minor fracture-related hospitalisations	✓	✓	Trial evidence that these occur at a different rate in those on Cinacalcet
Parathyroidectomies	✓	✓	Trial evidence that these occur at a different rate in those on Cinacalcet
Tests for PTH, calcium and phosphate levels	✓	✓	Regular testing in those on and not on Cinacalcet, and increased frequency of some tests in period following parathyroidectomy

5.5.3.3 Costs not included in the analysis

The following costs, initially considered for possible inclusion, were not included in the analysis for the reasons described.

Dialysis costs

In the base case analysis, we have not included the background cost of dialysis for all patients in both arms of the model. This is likely to bias the analysis in favour of cinacalcet. If cinacalcet leads to survival gains, there will be significant cost implications for the NHS due to the need for dialysis during those added years of life. The handling of health care costs in added years of life due to an intervention is a methodological issue of considerable controversy.[78;79] Current conventions recommend that medical costs that are "related to the intervention" should be included in cost-effectiveness analysis. It could be debated to what extent dialysis is related to SHPT as opposed to being related to the more broad underlying condition of ESRD. In addition, dialysis is a very expensive treatment that has already been accepted as standard for this population although it may not be deemed cost-effective. We assess the impact of including dialysis costs in sensitivity analysis.

5.5.3.4 Amount of different resources used

The amount of different resources used is either dependent on the amount of time spent in a particular disease state, or the incidence of particular events (such as treatments or hospitalisations). Table 52 below lists the amount of resources used and the source.

It is unclear how much prescriptions of vitamin D and phosphate binders may change with the addition of cinacalcet. The dosage included in the cinacalcet trials was largely fixed by study protocol. The expert advisory group felt that cinacalcet might reduce the need for phosphate binders and, in particular, might result in less use of expensive drugs such as sevelamer which may be used more commonly when cheaper drugs appear not to be working.

There is no published evidence on this issue, so in the base case we assume equal levels of consumption of phosphate binders and vitamin D in both arms of the model. On the basis of expert clinical opinion we did, however, assume that the more expensive phosphate binder, sevelamer, would be reserved for patients with “very uncontrolled” PTH levels. Therefore, because cinacalcet influences how many patients’ PTH levels become “very uncontrolled”, this may lead to fewer patients on cinacalcet consuming sevelamer.

Table 52 *Mean quantities of resources used with uncertainty and data source*

Resource type	Amount	Unit	SD	Source
Cinacalcet dose during maintenance phase (for patients with initial PTH > 32pmol/L)	94.4	Mg/day	[redacted]	[redacted]
Cinacalcet dose during titration phase (for patients with initial PTH > 32pmol/L)	81.6	Mg/day	[redacted]	[redacted]
Phosphate binders	16% taking none 38%* or 86% taking calcium carbonate 11% taking calcium acetate 48%* or 0% taking sevelamer	Mean dose: 6 tabs/day 3 tabs/day 12 tabs/day	N/A N/A N/A N/A	Audit of 510 SHPT patients being treated in Belfast City Hospital Northern Ireland (Dr Henry Brown, personal communication 15/02/06) Mean doses not supplied, so assumed (expert advice). *sevelamer only taken when PTH is "very uncontrolled". With controlled and uncontrolled PTH it is assumed the sevelamer 48% would be on calcium carbonate instead.
Vitamin D	37.3% taking none 62.7 taking Vitamin D	Patient-specific data (median 250 ng/day, range 36 – 2,143ng/day	N/A	Audit of 510 SHPT patients being treated in Belfast City Hospital Northern Ireland (Dr Henry Brown, personal communication 15/02/06)
CV-related hospitalisations	CV event incidence rates according to level of PTH control. See section 5.3.1.3 on transition probabilities.			
Major fracture-related hospitalisations	Major fracture event incidence rates according to level of PTH control. See section 5.3.1.2 on transition probabilities.			
Minor fracture-related hospitalisations	Determined as a multiple (approx ×9) of the incidence of major fracture-related hospitalisations (which varies according to both level of PTH control and whether there has been a previous major fracture). Se section 5.3.1.2 on transition probabilities.			
Parathyroidectomies	See section on transition probabilities.			
Frequency of PTH tests (for people in both with cinacalcet and standard treatment arms)	1	Per quarter	0.5-2.0	Expert advisory group
Frequency of calcium and phosphate tests (for people in both with cinacalcet and standard treatment arms) except**	1	Per month	0.5-2.0	Expert advisory group
**Higher frequency of calcium test in 3 months following parathyroidectomy (for people in both with cinacalcet and standard	1	Per week	0.5 - 2	Expert advisory group

treatment arms)				

5.5.3.5 Unit costs used in the model

The main unit costs, their base case values and ranges for sensitivity analysis, and their justification for use are described in Table 53. A more detailed description of sources and justification can be found in the sections following Table 53.

Dialysis costs are not used in the base case, but are used for sensitivity analysis. Methods of calculating dialysis costs are shown in Appendix 11 on page 270.

Table 53 *Unit costs (2005 prices)*

Resource	Unit cost (£)	unit	Lower value (£)	Upper value (£)	Source (justification)
Cinacalcet	0.145	per mg	N/A	N/A	List price of Mimpara® from British National Formulary No. 50[69;95] mean price per mg of 30mg (15.03p) and 60mg (13.87p) 28-tab packs.
Calcium carbonate (phosphate binder)	0.0933	per 1250mg	N/A	N/A	List price of Calcichew® from British National Formulary No. 50[69;95].
Calcium acetate (phosphate binder)	0.1099	per 1000mg	N/A	N/A	List price of Phosex® from British National Formulary No. 50[69;95].
Sevelamer (phosphate binder)	0.682	per 800mg	N/A	N/A	List price of Renagel® from British National Formulary No. 50[69;95].
Aluminium hydroxide (phosphate binder)	0.0313	per 475mg	N/A	N/A	List price of Alu-Cap® from British National Formulary No. 50[69;95].
(Vitamin D)	0.1953 0.3203 0.4883	per 250ng per 500ng per1000ng	N/A	N/A	List price of Alfacalcidol® from British National Formulary No. 50[69;95].
CV-related hospitalisation	1,287	per FCE	881	2,021	Weighted average of average unit cost for HRGs E29, E37, E18, A22, E22, E11, D37, Q17 and E42; from NHS NSRC 2004[77] Table for Non-elective inpatient episodes, in NHS Trusts and PCTs. See Table 54 for calculation.
Major fracture-related hospitalisation	4,620	per FCE	3,184	5,824	Weighted average of average unit cost for HRGs H84, H82, H36 and H39; from NHS NSRC 2004[77] Table for Non-elective inpatient episodes, in NHS Trusts and PCTs. See Table 55 for calculation.
Minor fracture-related hospitalisation	[redacted]	per FCE	[redacted]	[redacted]	[redacted]of average unit cost for HRG H45; from NHS NSRC 2004[77] Table for Non-elective inpatient episodes, in NHS Trusts and PCTs

Parathyroidectomy	1,998	per FCE	1,470	2,428	Average unit cost for HRG K02; from NHS NSRC 2004[77] Table for Elective inpatient episodes, in NHS Trusts and PCTs.
PTH level tests	[redacted]	per test	[redacted]	[redacted]	Amgen Industry submission
Calcium level test	4	per test	2	6	Laboratory Manager, Dept of Clinical Chemistry, RD&E Hospital, Exeter
Phosphate level test	4	per test	2	6	Laboratory Manager, Dept of Clinical Chemistry, RD&E Hospital, Exeter

5.5.3.6 Cost of CV-related hospitalisations

Table 54 below shows how the case-mix of hospitalisations for different cardiovascular events was used to calculate a weighted average cost per CV hospitalisation (including lower and upper estimates). The case-mix was derived from the combined data on CV events in both trial arms of the four trials pooled by Cunningham and colleagues[69] but reported in full detail in the Amgen submission to NICE.

Table 54 *Weighted average cost per CV-related hospitalisation*

	As per NSRC 2004 (£)[a]					*Weighted average*		
	Mean	*Low*	*High*	*HRG*	*%*[b]	*Mean*	*Low*	*High*
Arrhythmias	987	810	1,766	E29	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac tamponade, others	1,155	684	1,696	E37	[redacted]	[redacted]	[redacted]	[redacted]
Heart failure	1,519	1113	2,394	E18	[redacted]	[redacted]	[redacted]	[redacted]
Stroke	2,330	1288	3,636	A22	[redacted]	[redacted]	[redacted]	[redacted]
Ischemic heart disease	9,37	720	1,642	E22	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial infarction	1,458	1090	2,199	E11	[redacted]	[redacted]	[redacted]	[redacted]
Pulmonary oedema	1,262	760	1,759	D37	[redacted]	[redacted]	[redacted]	[redacted]
Peripheral vascular disease	1,964	1095	2,827	Q17	[redacted]	[redacted]	[redacted]	[redacted]
Valve disorders	1,580	848	2,106	E42	[redacted]	[redacted]	[redacted]	[redacted]
Weighted average cost of a CV-related hospitalisation					[redacted]	[redacted]	[redacted]	[redacted]

[a] Source: NHS National Schedule of Reference Costs 2004[77] for non-elective inpatient finished consultant episodes (Table TNELIP, in Combined tables for NHS Trusts and PCTs)

[b] Source: Appendix 3 of Amgen submission to NICE for Mimpara®.

Abbreviations: NSRC = National Schedule of Reference Costs; HRG = Healthcare Resource Group

5.5.3.7 Cost of fractures

Fractures in the model were classed as "major" fractures (all of which are assumed to result in hospitalisation) and "minor" fractures. The mix of fracture locations and severity was taken from the four trials of the Cunningham paper[69] (and which were fully reported in Appendix 3 of the Amgen industry submission to NICE for Mimpara®). According to data from the four Amgen trials reported by Cunningham (but only reported in the Amgen industry submission for Mimpara®, Appendix 3), [redacted] of minor fractures attract the cost of hospital inpatient treatment.

Table 55 *Cost of fracture-related hospitalisations*

	As per NSRC 2004 (£)[a]					*Weighted average (£)*		
	Mean	*Low*	*High*	*HRG*	*%*[b]	*Mean*	*Low*	*High*
Hip fractures, intracapsular	4,839	3,546	6,029	H84	[redacted]	[redacted]	[redacted]	[redacted]
Hip fractures, extracapsular	5,265	3,733	6,405	H82	[redacted]	[redacted]	[redacted]	[redacted]
Lower extremity fractures	3,500	1,473	4,213	H36	[redacted]	[redacted]	[redacted]	[redacted]
Upper extremity fractures	2,083	1,179	2,690	H39	[redacted]	[redacted]	[redacted]	[redacted]
Weighted average cost of a CV-related hospitalisation					[redacted]	[redacted]	[redacted]	[redacted]
Minor fractures/dislocations	1,168	554	1241	H45	[redacted]	[redacted]	[redacted]	[redacted]

a. Source: NHS National Schedule of Reference Costs 2004[77] for non-elective inpatient finished consultant episodes (Table TNELIP, in Combined tables for NHS Trusts and PCTs).

b. Source: Appendix 3 of Amgen submission to NICE for Mimpara®.

c. Approximately half of all hip fractures are intracapsular (Singer et al. 1998[96])

NSRC = National Schedule of Reference Costs; HRG = Healthcare Resource Group

5.5.4 Health states costs per cycle and state transitions

The way in which costs described above are applied in the decision model are shown in Table 56. No costs are attached to death. Costs of parathyroidectomy are attached to all transitions from any of the "very uncontrolled" PTH (and eligible for surgery) health states to either of the "post-surgery" health states.

Table 56 *Application of costs by health states*

General description	Health states
Cost of cinacalcet (titration phase)	The titration state in the Cinacalcet arm of the model
Cost of cinacalcet (maintenance)	All maintenance health states in the Cinacalcet arm of the model except those following parathyroidectomy
Cost of vitamin D and phosphate binders	All health states in all arms of the model
Cost of regular PTH, Ca and Ph tests	All health states in both arms of the model
Cost of CV Event	All CV event (with hospitalisation) health states
Cost of (major) Fracture event	All fracture event (with hospitalisation) health states
Cost of occasional minor fractures	Effectively all health states in both arms of model (applied as a proportion of the major fracture rate for each level of PTH control)

5.5.4.1 Discounting

In accordance with Treasury advice, costs and benefits were discounted at 3.5%.[97]

5.5.5 Dealing with uncertainty

5.5.5.1 One way sensitivity analysis

Extensive one-way sensitivity analyses were undertaken to explore which of the input parameters, when varied independently of the other model inputs, have the greatest impact on the incremental cost-effectiveness of cinacalcet. These analyses examined the impact of:

- Transition probabilities (including percentage of patients with "controlled", "uncontrolled" and "very uncontrolled" PTH levels, the number of people ineligible for surgery and suffering adverse effects of surgery, the annual rate at which fractures occur, the annual rate at which CV events occur, the percentage of fractures classified at "major", the percentage of people with "controlled" PTH levels whose levels become "uncontrolled" each year and the percentage of people with "uncontrolled" PTH levels whose levels become "very uncontrolled" each year and the percentage of patients)
- Relative risks (including the risk of fracture, CV event and mortality for people with different degrees of lack of control of PTH levels).

- Utility values (including quality of life for people with ESRD, the scaled reductions associated with fracture, CV events and increasingly lack of control of PTH levels, and the quality of life for patients having adverse effects after parathyroidectomy).

- Costs (including the cost of cinacalcet and impact of dose changes, the cost of parathyroidectomy and the cost of treating fractures and CV events.)

5.5.6 Probabilistic Simulation

Probabilistic sensitivity analysis (PSA) was also undertaken. A Monte Carlo simulation was developed to explore the impact of underlying parameter uncertainty on cost-effectiveness. In this stochastic approach, the Markov model is run 1000 times for the hypothetical cohort using input values randomly drawn from probability density functions in each model run. In these simulations, ranges and distributions used were sampled from the transitions, utility values and costs shown in Table 57.

Table 57 *Ranges and distributions used in the probabilistic sensitivity analysis.*

Parameter	Available range data	Source	Type of data	Distribution
General modifiers				
Proportion of fractures classified as major	None	Author assumption that S.E. is 1/10th of the central estimate	Assumption	Beta.
Proportion of patients unsuitable for surgery	None	Author assumption that S.E. is 1/10th of the central estimate	Assumption	Beta.
Modifier for multiple fractures	[1.4, 3.3]	Stevenson et al[87]	Lowest and highest RR for multiple fractures by different sites	Normal..
Modifier for multiple CV events	[1.781, 2.776]	Derived from data in Trespalacios et al[83]	95% CI derived using standard formulae for a 2x2 matrix.	Normal.
Yearly probability of surgery	[5, 20]	Maximum and minimum values estimated by Expert Advisory Group	Clinical opinion and assumption	Beta.
RR of death either during surgery or shortly after	[1.52, 2.22]	Kestenbaum et al[90]	95% CI	Lognormal.
Proportion of deaths that are CV related	None	Author assumption that S.E. is 1/10th of the central estimate	Assumption	Beta.
Proportions of operations that are unsuccessful	[5, 20]	Author assumption that S.E. is 1/10th of the central estimate	Assumption	Beta.
Proportion receiving standard treatment having "controlled" PTH	[4, 20]	Systematic review, Table 17	Minimum and maximum levels from individual trials	Beta.
Proportion receiving standard treatment having "very uncontrolled" PTH	[13,52]	Renal Registry shows that 34% (range 13%-52%) of HD population does not meet target levels for PTH Figure 9.18, Chapter 9 p. 10[15]	Minimum and maximum values from individual trusts	Beta.
Proportion receiving cinacalcet having "controlled" PTH	[35 , 46]	Systematic review, Table 17	Minimum and maximum levels from individual trials	Beta.
Proportion receiving cinacalcet having "very uncontrolled" PTH	None	Author assumption that S.E. is 1/10th of the central estimate	Assumption	Beta.
Differential dropout rate between two arms of the model	None	Author assumption that S.E. is 1/10th of the central estimate	Assumption	Beta.
Proportion of people with "controlled" PTH that become "uncontrolled" each cycle (both arms)	[0.05, 0.5]	Input from expert advisory group	Clinical opinion and author assumption	Lognormal.

Parameter	Available range data	Source	Type of data	Distribution
Proportion of people with "uncontrolled" PTH that become "very uncontrolled" each cycle (both arms)	[0.05, 0.5]	Input from expert advisory group	Clinical opinion and author assumption	Lognormal.
Proportion adverse effects after surgery (both arms)	None	Author assumption that S.E. is 1/10th of the central estimate	Assumption	Beta.
Risk of death in CVE compared to EVF	none	Author assumption that S.E. is 1/10th of the central estimate	Assumption	Normal.
Risk of death in CFE state compared to EVF	[1.76, 2.07]	Mittalhenkle et al[82]	95% CI for used parameter	Normal.
Risk of death in FRE state compared to EVF	[1.70, 2.00]	Mittalhenkle et al[82]	95% CI for used parameter	Normal.
Risk of death in CVH state compared to EVF	none	Renal Registry – author assumption that S.E is 1/10th of the central estimate	Assumption	Normal.
Risk of death in CFH state compared to EVF	[1.76, 2.07]	Mittalhenkle et al 2004[82]	95% CI for used parameter	Normal.
Risk of death in FRH state compared to EVF	[1.7, 2.00]	Mittalhenkle et al 2004[82]	95% CI for used parameter	Normal.
Fractures				
Yearly rate of an initial major fracture event	[1.7, 6.1] hip fractures per 1000 pt yrs fractures	Ball et al[26]	Min and max for different subgroup analyses	Lognormal.
Risk of fracture for those with "uncontrolled" PTH levels compared to those with "controlled" PTH	[0.73, 1.72]	Kim et al[86]	95% CI	Lognormal.
Risk of fracture for those with "very uncontrolled" PTH levels compared to those with "controlled" PTH	[1.36, 2.76]	Kim et al[86]	95% CI	Lognormal.
Death event				
Age dependant probability of death	[-13.166,-11.309] [2.314, 2.762]	Derived using data in renal registry	95% CI's for log lambda and gamma parameters used in calculation of each probability.	Bivariate normal.
Relative risk of death both arms	[0.9087, 0.9715] [0.0002, 0.0003]	Derived from Block et al[18]	95% CI's for slope and intercept parameters used in calculation of category estimates	Bivariate Normal.
Reduction in death risk post	[0.80, 0.94]	Kestenbaum et al[90]	95% CI	Normal.

Parameter	Available range data	Source	Type of data	Distribution
surgery				
CV event				
Percentage of people starting the model assumed to have a history of CV event	None	Author assumption that S.E. is 1/10th of the central estimate	Assumption	Beta.
Yearly probability of having an initial CV event	None	Author assumption that S.E. is 1/10th of the central estimate	Assumption	Beta.
Risk of CV event with "uncontrolled" PTH	[1.06, 1.29]	Block et al[18]	95% CI for PTH >= 600	Lognormal.
Risk of CV event with "very uncontrolled" PTH	[1.12, 1.42]	Block et al[18]	95% CI for PTH >= 900	Lognormal.
Risk of CV event post surgery	[1.12, 1.42]	Block et al[18]	95% CI for PTH >= 900	Lognormal.
Cinacalcet dose information				
Dose during titration phase	[redacted]	Cunningham et al[69] as cited in Appendix 2 of the Amgen industry submission	Central value +/- 1S.D.	Normal.
Dose in all pre surgical strata	[redacted]	Cunningham et al[69] as cited in Appendix 2 of the Amgen industry submission	Central value +/- 1S.D.	Normal.
General costs in both arms of the model				
Cost of parathyroidectomy	[1470, 2428]	Average unit costs for HRG H45 from NHS NSRC 2004. [77]	Upper and lower quartiles	Lognormal.
Cost of PTH test	[redacted]	Amgen industry submission	Upper and lower quartiles	Lognormal.
Cost of CV related hospitalisation	[881, 2021]	Weighted average unit cost for relevant HRGs. [77]	Upper and lower quartiles	Lognormal.
Cost of Major fracture related hospitalisation	[3184, 5824]	Weighted average unit cost for relevant HRGs. [77]	Upper and lower quartiles	Lognormal.
Cost of minor fracture	[redacted]	[redacted] average unit cost for HFG H45	Upper and lower quartiles	Lognormal.
Background care cost for people on dialysis ESRD (where included)	[1956, 5864]	Costs of hospital based dialysis inflated to 2005/6 coats based on 2003 HTA monograph by Mowatt et al.[98]	Upper and lower quartiles	Lognormal.
Utility values				
Value associated with a patients on HD	[0.58, 0.74]	Table 47	SD = 0.29	Beta.
Value associated with a patients on PD	[0.64, 0.78]	Table 47	SD = 0.29	Beta.
CV event	None	Author assumption that S.E. is 1/10th of the central estimate	Assumption	Beta.
History of CV event	[0.67, 1.00]	Weighted mean value for angina and	interquartile range	Beta.

Parameter	Available range data	Source	Type of data	Distribution
		dyspnoea, Martin et al (1998)[99]		
Fracture state	[0.651,1.00]	Value for first year after fracture from Brazier et al (2002)[94]	95% CI	Beta.
History of fracture state	[0.8255, 1.00]	Long term impact of hip fracture assumed to have ½ the impact of first year by Brazier et al[94]		Beta.
Disutility associated with a minor fracture	[0.978, 0.986]	Brazier et al[94]	95% CI	Beta.
Scaled reduction applied to baseline utility for those with "uncontrolled" PTH levels	[0.8,1]	Assumption	Assumption	Uniform.
Scaled reduction applied to baseline utility for those with "very uncontrolled" PTH levels	[0.8, uncontrolled decrement]	Assumption	Assumption	Constrained Uniform.
Scaled reduction applied to baseline utility in post surgical with adverse effects	[0.8,0.99]	Assumption		Uniform.

5.6 Cost-effectiveness of cinacalcet

5.6.1 Base case results of cost effectiveness

Base case results for the economic model are shown in Table 58 on a per patient basis. For the modelled cohort, when dialysis costs are not included cinacalcet marginally improves quality adjusted life years (0.34 quality adjusted years, per patient), but costs an additional £21,167 per patient.

Table 58 *Discounted base case cost-effectiveness results per patient for cinacalcet (dialysis costs excluded)*

	Costs (£)	QALYS	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Standard care only	6,533	3.04	-	-	-
Cinacalcet plus standard care	27,700	3.39	21,167	0.34	61,890

We also assessed the impact of including dialysis costs. The ICER increases in this analysis as small survival improvements carry the additional cost of dialysis treatment. Results are shown in Table 59.

Table 59 *Discounted base case cost-effectiveness results per patient for cinacalcet (dialysis costs included)*

	Costs (£)	QALYS	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Standard care only	81,523	3.04	-	-	-
Cinacalcet plus standard care	106,946	3.39	25,423	0.34	74,334

5.6.1.1 Event counts

Few differences in patient relevant outcomes are predicted by the model (see Table 60). The exception is parathyroidectomy; a significant number of operations are avoided by the use of cinacalcet ($p<0.001$).

In both arms of the model, the number of multiple CV events is high. This is due to a relatively large number of people having at least one CV event and some people having multiple events. Based on Renal Registry data, we have assumed that 15.7% of those entering the model have existing cardiovascular disease and so enter the model in the

"history of CV" health state rather than the "event free" health state. They are subject to the increased risk of a further CV event and are counted as having had multiple CV events.

Approximately 2% of both arms experience a major fracture (hip/femur). This means that about 20% will have a minor fracture.

The cost of treating 1000 people in order to avoid one CV event, major fracture or parathyroidectomy are shown in Table 60.

Table 60 *Patient relevant outcomes in the economic model for 1000 people*

	Standard treatment alone. n (%)	Standard treatment plus cinacalcet. n (%)	Difference. n (%)	Discounted cost per event avoided. £
At least one major fracture	25 (2.5)	21 (2.1)	4 (0.4)	5,291,750
More than one major fracture	1 (0.1)	1 (0.1)	0	-
At least one CV event	438 (43.8)	434 (43.4)	4 (0.4)	All CV events
More than one CV event	726 (72.6)	687(68.7)	39 (3.9)	492,256
Parathyroidectomy	211 (21.1)	64 (6.8)	147 (14.7)	143,993
Surgical mortality	9 (4.3% of surgeries)	3 (4.7% of surgeries)	0.4%	-

The few differences between comparators are largely explained by the relatively high background death rate for this population. Any differences in mortality risk between the arms depend on differences in the number of people who have "uncontrolled" and "very uncontrolled" PTH levels compared to those who have "controlled" levels. The relative risk of adverse effects such as fracture, CV event and death are slight between these levels of PTH control (RR = 1.12 for fracture, 1.17 for CV event and 1.0505 for death). People with "very uncontrolled" PTH have higher RR of all major events than those with more controlled PTH levels. However, because a parathyroidectomy is likely for these people, the risk of a fracture quickly returns to the same level as those with "controlled" PTH levels post-surgery, and the risk of death is reduced to a level close to that experienced by the controlled group. In order to assess the impact of parathyroidectomy on cost-utility, we assessed the impact of removing it as an option in the model. If parathyroidectomy ceases to be a treatment option for anyone, the ICER drops by 12%, however it remains well above usual levels of willingness to pay at £54,119 per QALY.

It is possible to make a tentative comparison between the number of events predicted by the PenTAG model and those reported by Cunningham and colleagues.[69] This analysis

assumes that the risk of an event is constant over time, and an approximate risk ratio is calculated based on the number of events reported and the aggregated state-occupancy in each arm of the model. In all cases, confidence intervals in the two analyses of relative risk overlap (Table 61).

Table 61 *Comparison of event risk between PenTAG model outputs and Cunningham and colleagues*

	PENTAG MODEL			CUNNINGHAM ET AL DATA		
	Events per 100 pt yrs			Events per 100 pt yrs		
	Standard treatment	Cinacalcet	Risk Ratio (95% CI)	Standard treatment	Cinacalcet	Risk Ratio (95% CI)
CV event	20.7	17.9	0.87 (0.80, 0.94)	19.7	15.0	0.61 (0.43, 0.86)
Fractures (major and minor)	4.5	3.4	0.75 (0.63, 0.90)	6.9	3.2	0.46 (0.22, 0.95)
Parathyroidectomy	3.7	1.0	0.28 (0.21, 0.36)	4.1	0.3	0.07 (0.01, 0.55)

Although there are few differences in the number of CV outcomes between PenTAG model arms, the timing is affected by cinacalcet. Median survival for the cinacalcet cohort is five years, and median survival for the standard treatment cohort is four and a half years. People taking cinacalcet have a small survival advantage that increases slightly over time (see Table 62). Over 80% of the cohort is dead in both arms by 10 years of follow up.

Table 62 *Survival predicted by the model base case*

	Survival 25th centile (yrs)	Median survival (yrs)	Survival 75th centile (yrs)
Standard treatment plus Cinacalcet	2.25	5.00	8.75
Standard treatment alone	2.00	4.50	8.00

5.6.2 Sensitivity analysis

The two primary outputs from a cost-effectiveness model are discounted costs and QALYs for the two being compared. The differences between these are the incremental cost and incremental QALYs of cinacalcet in comparison with standard treatment. The incremental cost-effectiveness ratio (ICER) and net benefit are two common ways of combining these two outputs of incremental cost and incremental benefit into one metric.

The ICER is the ratio of the incremental cost of treatment and the incremental benefits of treatment (i.e. cost difference/benefit difference). While this is useful in many situations, the fact that the ICER is a ratio measure makes the metric unstable. As benefit differences approach zero the ICER is often difficult to interpret in one-way sensitivity analysis where effects are non-linear.

Net benefit is calculated by first assigning a cost value to a benefit unit. The incremental benefit of the treatment arm of the model can then be rescaled in terms of cost using this valuation. If a QALY is valued at £30,000, for example, then a marginal benefit of 100 QALYs between arms is valued at £3,000,000. The net benefit of the treatment can then be calculated by offsetting the incremental cost against the incremental benefits of treatment (i.e. the benefit difference between arms expressed in pounds minus the cost difference expressed in pounds).

The advantage of reporting net benefit is that it behaves in a more linear way than the ICER and incorporates a willingness to pay threshold which makes it easier to interpret. The disadvantage of using net benefit is that it relies on a specific level of valuation for each unit of benefit. In the case of our analysis we have used the commonly assumed maximum willingness to pay of £30,000 per QALY.

5.6.2.1 One way sensitivity analyses

One way sensitivity analyses for a range of transition probability, utility and cost values were used to examine the impact of the uncertainty associated with individual inputs. These have been expressed graphically showing the net-benefit of new values based on a QALY value of £30,000. Because of the number of parameters use in the model, the results are presented on separate graphs for transitions (Figure 4), costs (Figure 5) and utilities (Figure 6). Bars that appear to the right of the axis represent a higher net benefit with cinacalcet, while those to the left of the axis show lower net benefit. An improvement of 100% is necessary for cinacalcet to be considered cost-effective at £30,000/QALY. In this (deterministic) analysis, the model appears particularly sensitive to:

Transitions

- The difference between model arms in the proportion of people that have "very uncontrolled" levels of PTH (>85pmol/L).
- The differential rate of disease progression between the cinacalcet and standard care arms.
- The percentage of patients who withdraw from cinacalcet treatment.
- The relative risk of death for people with "uncontrolled" levels of PTH.
- The relative risk of death for people with "very uncontrolled" levels of PTH

Utilities

- The difference in quality of life for people with "very uncontrolled" PTH levels compared to people with "controlled" PTH levels.

Costs

- The price of cinacalcet.
- Differential cost of cinacalcet depending on the degree of PTH control.
- Whether or not the cost of dialysis is included in the analysis.

The relative risk of a CV event for people whose PTH levels are not controlled did not have a large effect in this analysis. We investigated this further by using a scaled increase in RR of CV event across all degrees of uncontrolled PTH levels in the cinacalcet arm. Through this method we found that cinacalcet would become cost effective only if the number of initial CV

events were reduced by 57% and the number of multiple CV events were reduced by 83% compared to the standard treatment arm.

Fracture risk also appeared to have little impact. Investigating this, we found that if there were no fractures in the cinacalcet arm, the ICER fell to £60,746 per QALY.

Figure 4 *One way sensitivity analysis for transition inputs in the economic model – percentage change in net benefit at willingness to pay of £30,000/QALY*

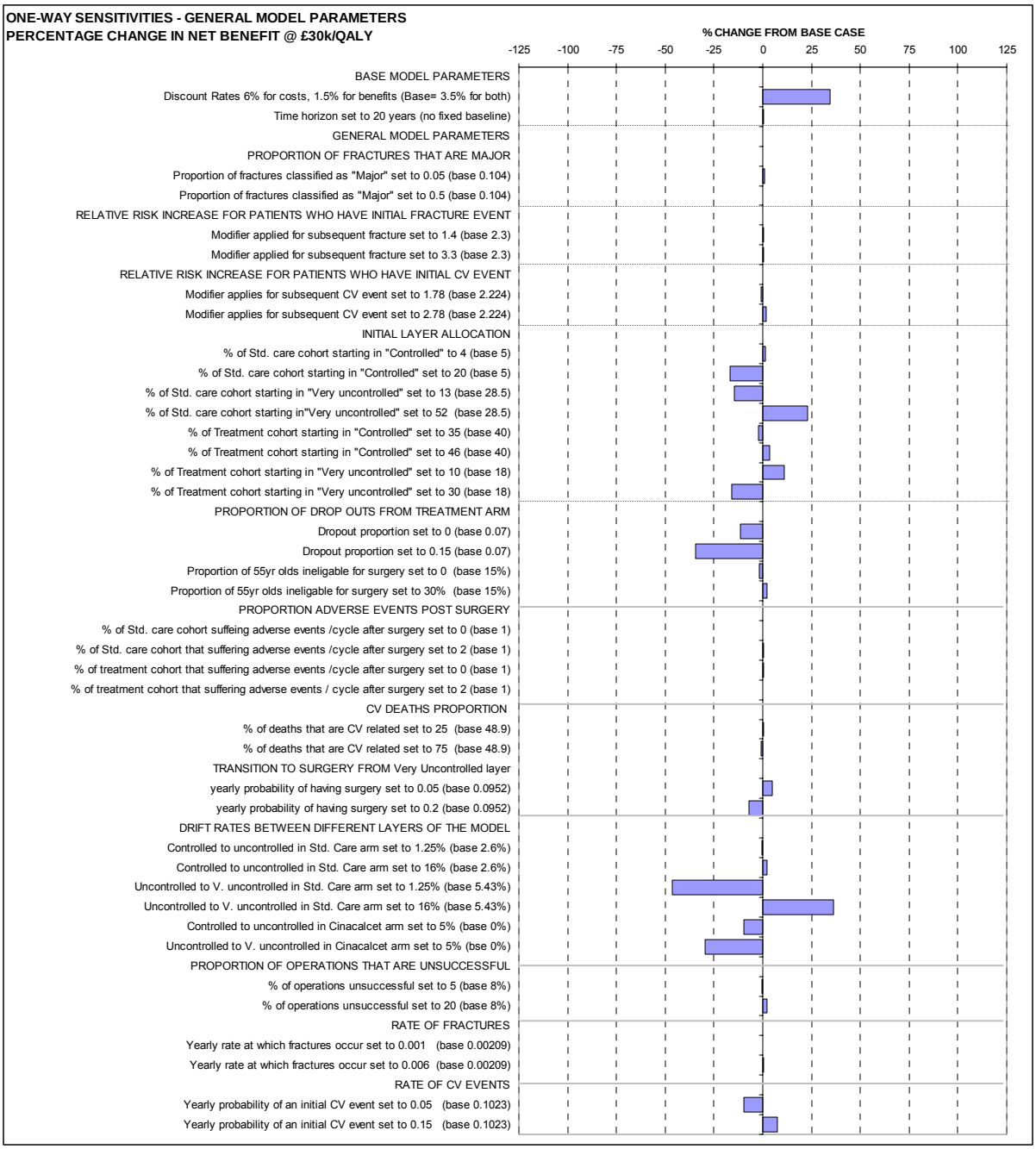


Figure 5 (continued)

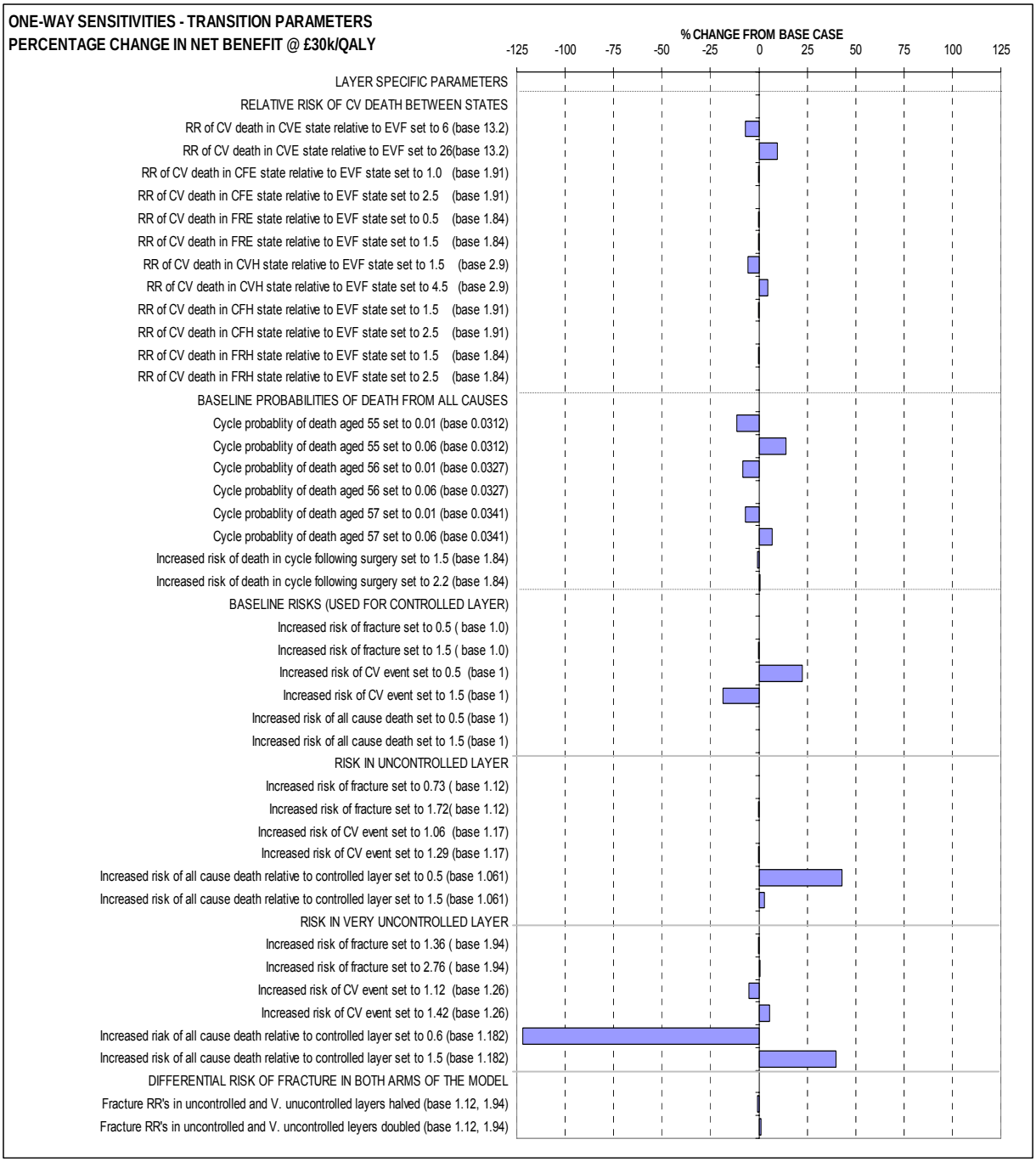


Figure 5 *One way sensitivity analysis for cost inputs in the economic model - percentage change in net benefit at willingness to pay of £30,000/QALY*

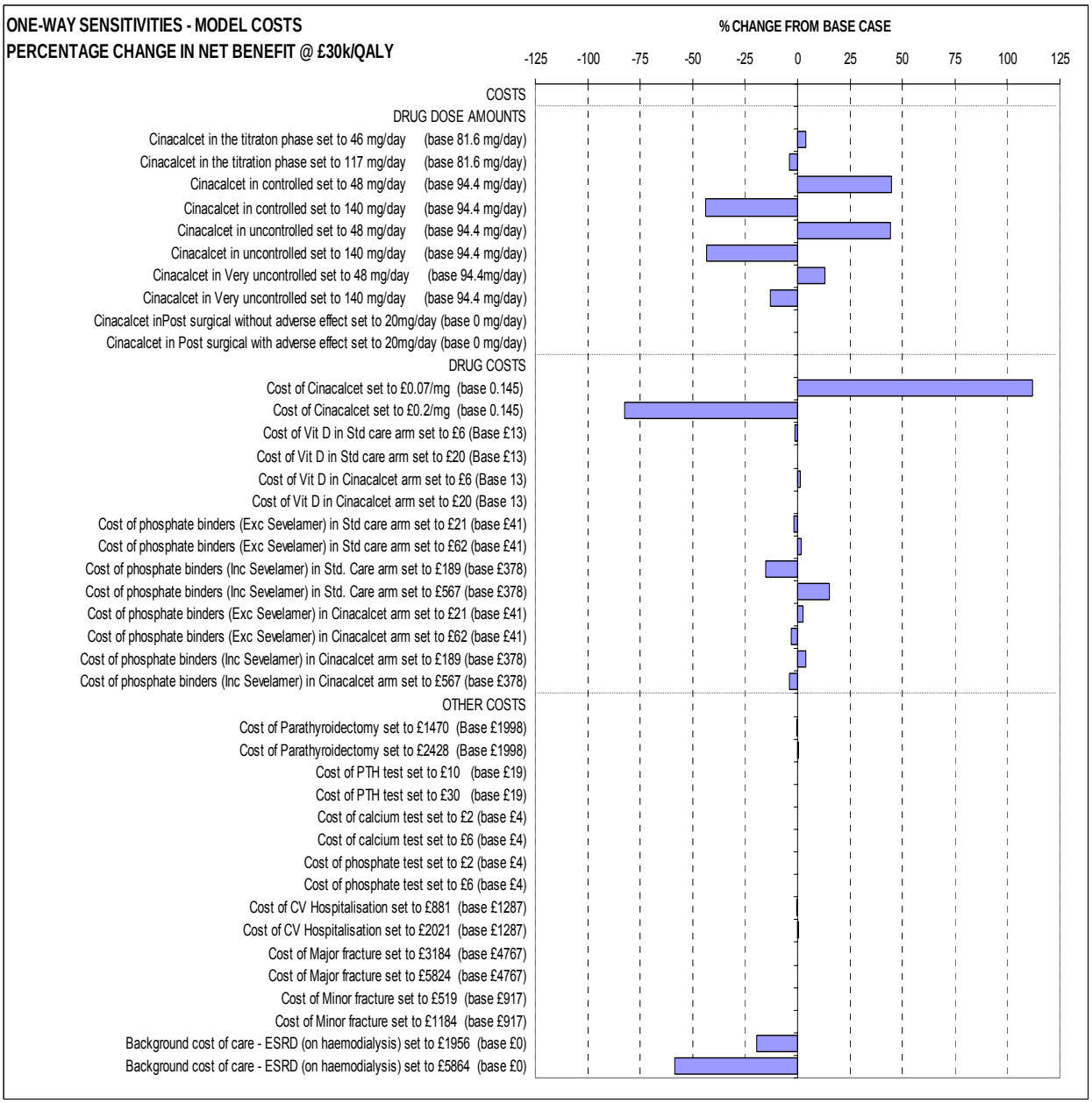
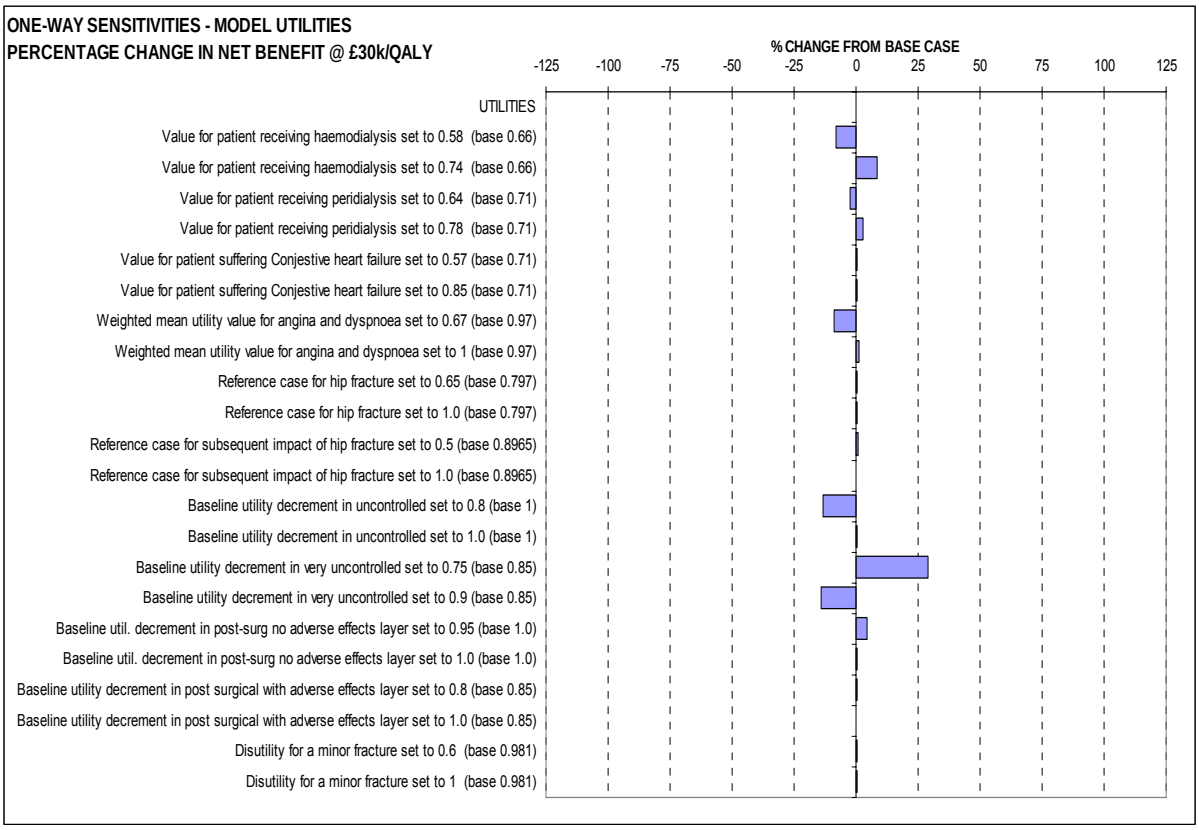


Figure 6 *One way sensitivity analysis for utility values in the economic model - percentage change in net benefit at willingness to pay of £30,000/QALY*



Threshold analyses

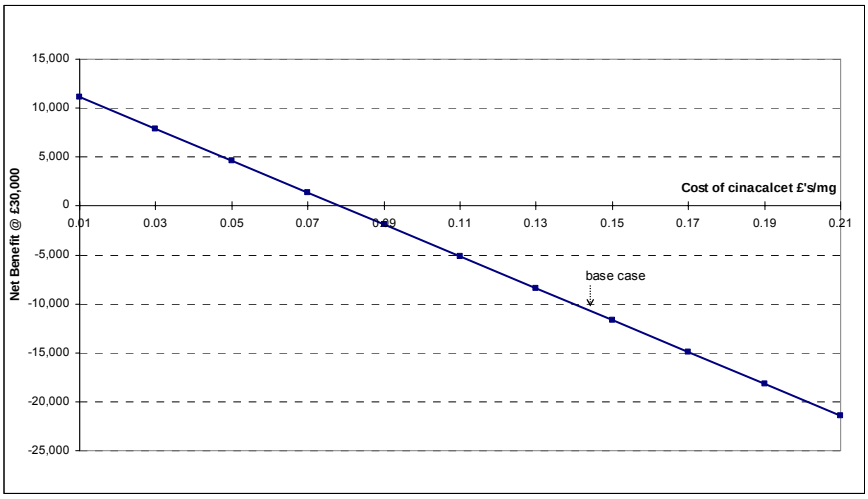
The one-way sensitivity analysis reveals those inputs to which the model is most sensitive. We explored whether independent alterations in these key inputs could affect the ICER to such an extent that cinacalcet might be considered cost-effective.

These graphs are also expressed as net benefit at an assumed willingness to pay threshold of £30,000 per QALY. Cost-effectiveness is shown as positive net benefit values.

Threshold analysis for the cost of cinacalcet

Threshold analysis for the cost of cinacalcet shows that it would be considered cost-effective (at a WTP threshold of £30,000/ QALY) if the cost were reduced to eight pence or less per mg from the current cost of 14.5p per mg (Figure 7).

Figure 7 *Threshold analysis for the cost of cinacalcet*



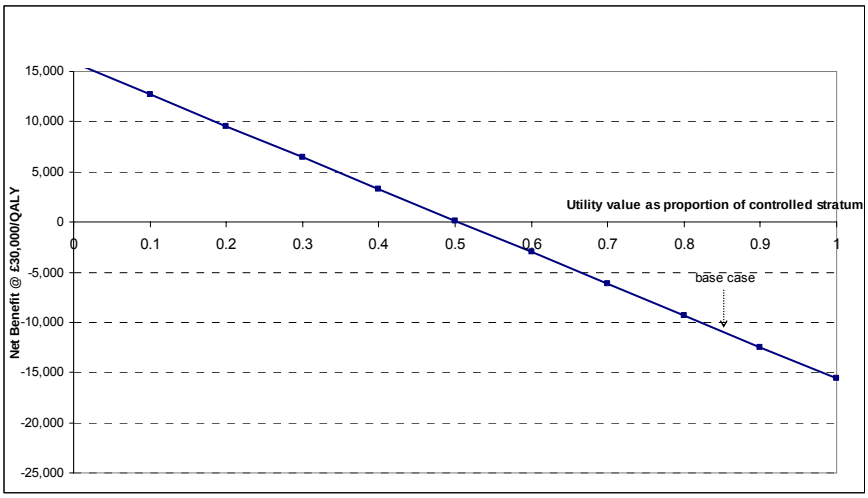
Threshold analysis for the quality of life for people with "very uncontrolled" PTH

In the base case, people with “very uncontrolled” levels of PTH are assumed to experience a 15% reduction in their quality of life compared to those with “controlled” levels of PTH. Given that the potential benefit of cinacalcet lies in its ability to control PTH levels for more people, a difference in quality of life between having “controlled” PTH and “very uncontrolled” PTH influences cost-effectiveness.

Figure 8 shows that if the utility value for people with “very uncontrolled” PTH was the half that for people with “controlled” PTH (base case 0.6735), then cinacalcet may be considered cost-effective. This assumes that the symptoms of “very uncontrolled” PTH levels reduce the utility value for those in the “event free” state to 0.3368 (from the base case value of

0.5725). As all other utilities values following CV events or fractures are applied as a scaled reduction to the "event free" health state in the model, all these utility values for people with "very uncontrolled" PTH levels will also be reduced.

Figure 8 *Threshold analysis showing utility value for people with "very uncontrolled" PTH as a proportion of that for people with "controlled" PTH levels*

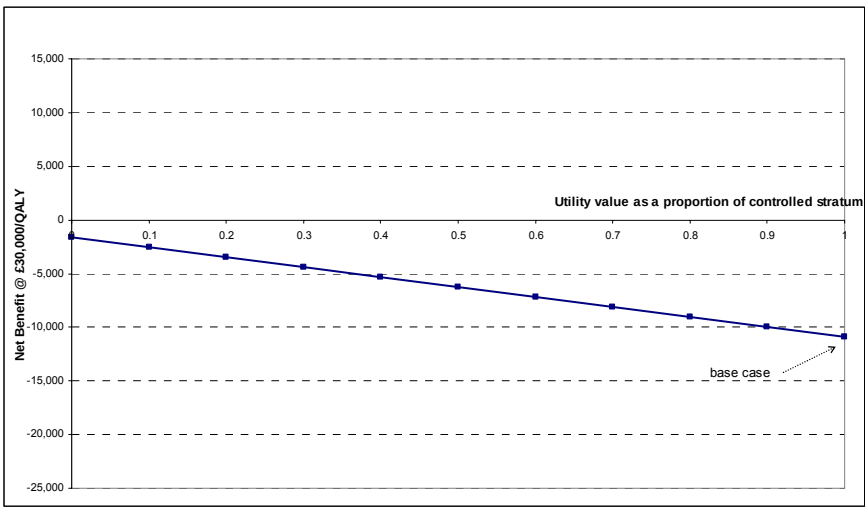


Threshold analysis for the quality of life for people after parathyroidectomy

In the base case, people who have had a successful parathyroidectomy are assumed to have the same quality of life as those with "controlled" levels of PTH. Given that a potential benefit of cinacalcet is reducing the need for parathyroidectomy, lower quality of life for people after parathyroidectomy compared to those who have "controlled" levels of PTH , will have a favourable effect on cost-effectiveness.

Figure 9 shows that as the utility value for people who have had a parathyroidectomy decreases, the benefit of cinacalcet treatment increases. However, even if the impact of parathyroidectomy were so bad that the utility value afterwards were zero (as bad as being dead), cinacalcet would still not be cost-effective at a willingness to pay threshold of £30,000 per QALY.

Figure 9 *Threshold analysis showing utility value post-parathyroidectomy as a proportion of that for people with controlled PTH levels*

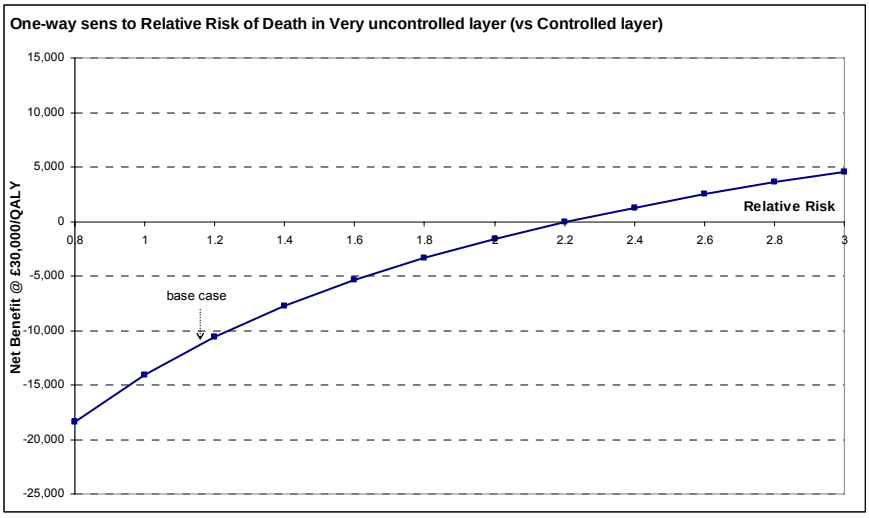


Threshold analysis for the relative risk of death for "uncontrolled" PTH levels

In the base case, people who have "very uncontrolled" levels of PTH are at slightly greater risk of death than those with "controlled" levels of PTH (RR=1.1824). As a potential benefit of cinacalcet is reducing the number of people who have uncontrolled levels of PTH, larger RR of adverse effects of "very uncontrolled" PTH levels will increase the benefit of cinacalcet.

Figure 10 shows that if the risk of death for people with "very uncontrolled" PTH levels were increased to more than double (RR=2.2) that of those in "controlled" levels of PTH, cinacalcet could be considered cost-effective at a willingness to pay threshold of £30,000 per QALY.

Figure 10 *Threshold analysis of the relative risk of death for people with "very uncontrolled" PTH levels compared with "controlled" PTH*



As RR of death is also increased for those with "uncontrolled" PTH levels, we further explored this parameter as a two-way sensitivity analysis. We found that the ICER could be reduced to below £30,000/QALY if the relative risk of mortality for those with "uncontrolled" and "very uncontrolled" PTH levels compared to those with "controlled" levels were both increased by a scale factor of 0.6994. Such an increase in RR increases the median survival for those treated with cinacalcet from 5.00 years to 6.00 years, avoiding 99 deaths in the first five years compared to those treated with standard treatment alone.

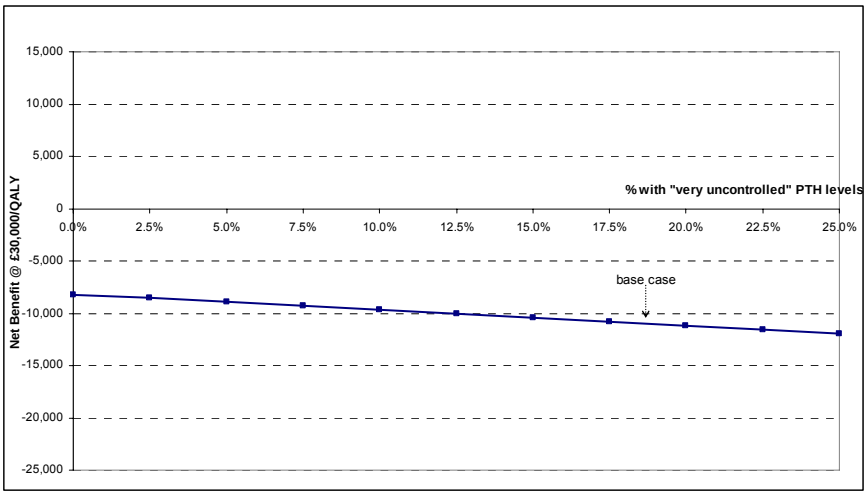
Threshold analysis for the percentage of people treated with cinacalcet who have "very uncontrolled" levels of PTH

In the base case, 18% of people with SHPT who receive cinacalcet still have "very uncontrolled" levels of PTH after the titration phase compared to 28.5% of those treated with

standard treatment. Data from the Renal Registry was used to assign the proportion of people who did not reach target levels of PTH to having "uncontrolled" or "very uncontrolled" levels of PTH. We assessed the impact of altering this percentage through threshold analysis.

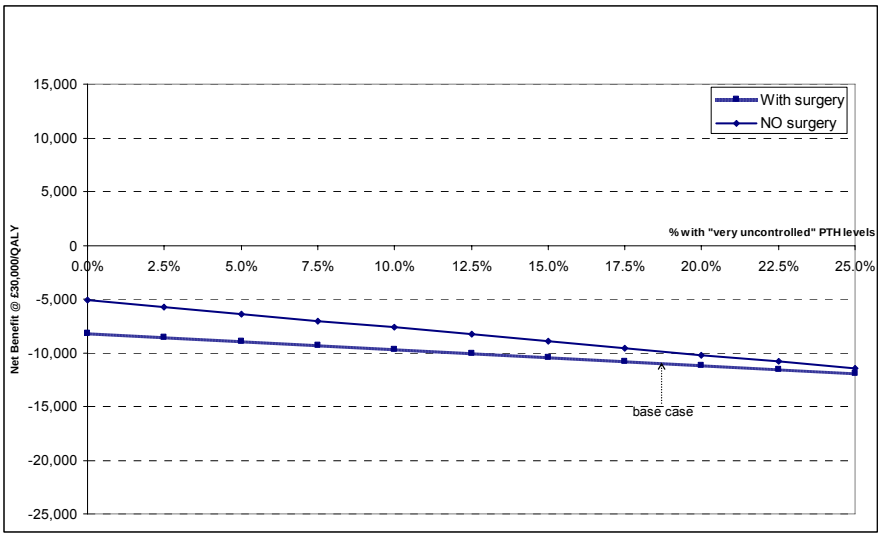
Figure 11 shows that even if treatment with cinacalcet resulted in no people retaining very uncontrolled levels of PTH, cinacalcet would not be considered cost-effective at a willingness to pay threshold of £30,000.

Figure 11 *Threshold analysis of the proportion of people who have "very uncontrolled" levels of PTH despite treatment with cinacalcet*



Parathyroidectomy is a relatively positive treatment in our model – with advantages after surgery in terms of risk and utility. It is only available to those with "very uncontrolled" levels of PTH. We therefore wanted to explore if this was confounding the impact of PTH control – with those having "very uncontrolled" levels of PTH actually benefiting because of the impact of surgery. We therefore explored the impact of different proportions of people having "very controlled" levels of PTH with cinacalcet, but removed surgery as a treatment option. The results are shown in Figure 12. This shows that, in the absence of parathyroidectomy, even if no patients have a "Very uncontrolled" level of PTH, cinacalcet is still not cost-effective at a willingness to pay threshold of £30,000 per QALY.

Figure 12 *Threshold analysis of the proportion of people who have "very uncontrolled" levels of PTH despite treatment with cinacalcet where parathyroidectomy is not a treatment option*



Two-way Sensitivity analysis for disease progression

There are currently no data about how well SHPT is controlled over time with cinacalcet. Our base case assumes that once PTH levels are "controlled", people treated with cinacalcet will remain controlled for the rest of their lifetime. By contrast, those receiving standard treatment progress from "controlled" PTH levels to "uncontrolled" at a rate of 10% a year and from "uncontrolled to "very uncontrolled" at 20% a year. We investigated the impact of introducing a rate of disease progression with cinacalcet. A two way analysis was undertaken, with progression from "controlled" PTH levels to "uncontrolled" levels and from "uncontrolled" PTH to "very uncontrolled" levels examined simultaneously. The results are shown in

Table 63. The ICER increases if disease progression occurs despite treatment with cinacalcet. If the rates are equal to, or greater than those with standard care, then cinacalcet is dominated, conferring fewer QALYs for greater cost.

Table 63 *Impact of disease progression with cinacalcet on the ICER*

Annual rate of progression from "uncontrolled" to "very uncontrolled" PTH levels	Annual rate of progression from "controlled" to "uncontrolled" PTH levels with cinacalcet					
	0%	10%	20%	30%	40%	50%
0%	61,890	74,175	77,281	78,648	79,413	79,901
10%	113,744	1,111,669.95	Dominated	Dominated	Dominated	Dominated
20%	137,573	Dominated	Dominated	Dominated	Dominated	Dominated
30%	150,774	Dominated	Dominated	Dominated	Dominated	Dominated
40%	159,115	Dominated	Dominated	Dominated	Dominated	Dominated
50%	164,856	Dominated	Dominated	Dominated	Dominated	Dominated

5.6.3 Probabilistic Simulation

Outputs for the Monte-Carlo simulation are shown graphically below. For the modelled cohort, these illustrate the ICER values for 1000 simulated trials. A cost-effectiveness acceptability curve (CEAC) has also been calculated showing, at different levels of willingness to pay for an additional QALY, the probability that cinacalcet is cost-effective.

The simulation output (**Figure 13**) shows that cinacalcet is cost-effective in just 0.5% of simulations undertaken – although slightly more QALYs are always accrued, the additional costs of treatment means that the ICER is almost always greater than £30,000 per QALY. The CEAC shows that cinacalcet is unlikely to be the most cost-effective option below a willingness to pay threshold of about £62,000

We also ran probabilistic analysis for the base case including the cost of dialysis, which show similar results (**Figure 14**).

Figure 13 *Simulation output (1000 trials) for the base case and CEAC showing the probability that cinacalcet is cost-effective at various levels of willingness to pay (dialysis cost excluded)*

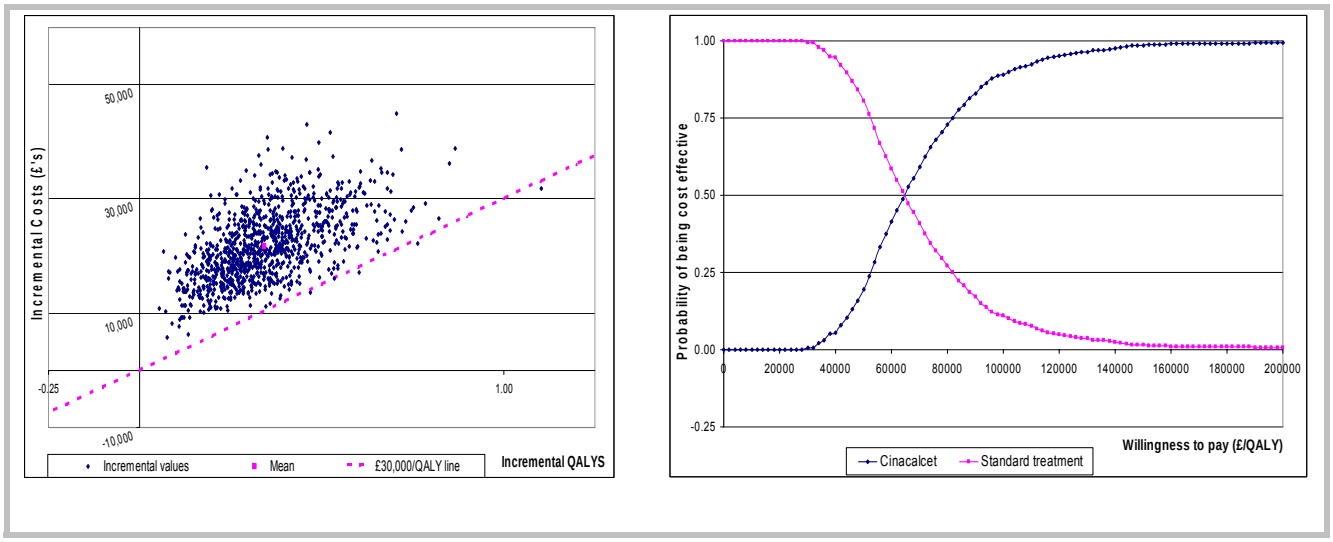
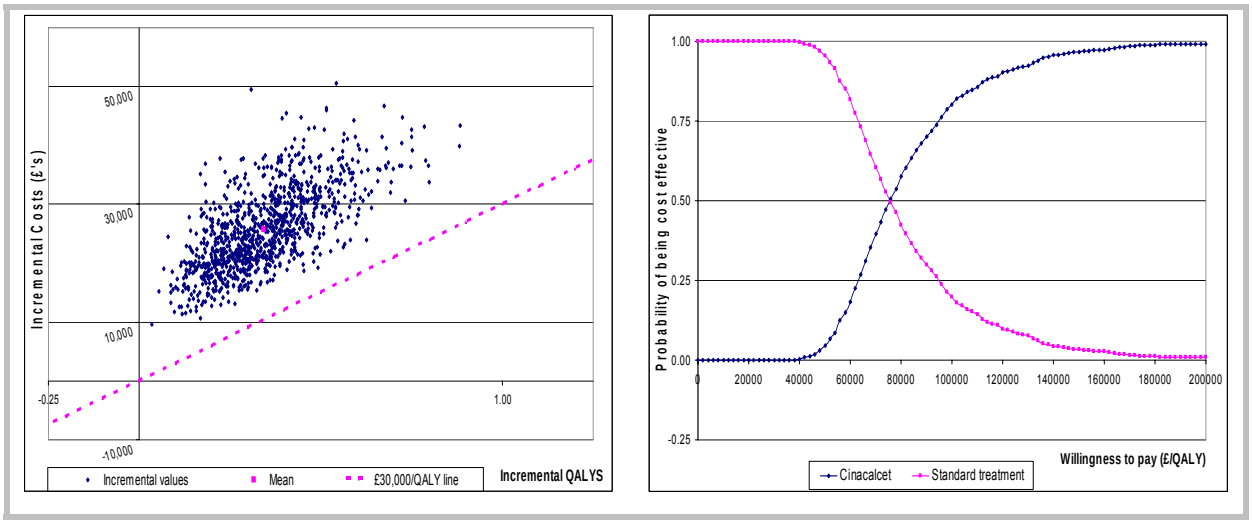


Figure 14 *Simulation output (1000 trials) for the base case and CEAC showing the probability that cinacalcet is cost-effective at various levels of willingness to pay (dialysis costs included)*



5.6.4 Cost-effectiveness for people with different degrees of SHPT

From the systematic review, cinacalcet appears to have more impact on people who have "uncontrolled" PTH (>32 to <85pmol/L) than those with "very uncontrolled" PTH (>85pmol/L) we investigated the cost-utility for these two groups separately. The results are shown in Table 64 and Table 65. Although the ICER is lower in people with "uncontrolled" PTH than in people with "very uncontrolled" PTH levels, in neither case is cinacalcet likely to be considered cost-effective.

Table 64 *Cost-effectiveness of cinacalcet in people with "uncontrolled" levels of PTH and colleagues (dialysis costs excluded)*

	Costs (£)	QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Standard treatment only	6,466	3.06	-	-	-
Standard treatment plus cinacalcet	27,905	3.43	21,438	0.37	57,442

Table 65 *Cost-effectiveness of cinacalcet in people with "very uncontrolled" levels of PTH and colleagues (dialysis costs included)*

	Costs (£)	QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Standard treatment only	6,667	3.02			
Standard treatment plus cinacalcet	27,155	3.27	20,488	0.25	81,479

5.6.5 Scenario analyses

5.6.5.1 Methods for Scenario Analysis 1 based on Cunningham and colleagues

Our base case model uses RR of fracture, CV events and mortality according to the level of PTH control achieved with cinacalcet compared to standard treatment. However, we also wanted to examine the impact of using the data reported by Cunningham and colleagues.[69] This would both provide validation, and allow more direct comparison of our model's results with those submitted to NICE by Amgen, [redacted]

The analysis by Cunningham and colleagues[69] does not rely on intermediate markers (serum levels of PTH, Ca and P) but directly relates treatment with cinacalcet to the risk of fracture and CV events and overall mortality in the short term. In order to emulate this we simplified our model structure so that all patients treated with cinacalcet have the same

average risk of adverse events and all those treated with standard treatment have the same average risk of adverse effects. That is, the strata representing different levels of PTH control in our base case model are effectively collapsed into one.

Differences between the arms of the model thus come from the reported within-trial difference in average risk of fracture, CV event and death based on treatment choice of cinacalcet or standard care. These are taken from the analysis by Cunningham and colleagues[69] which is based on retrospective data for six months of follow up of 1136 people, and 12 months follow up of 48 people with secondary hyperparathyroidism. Additional data also comes from a six month extension period in one of the 6-month studies (n=266).

Incorporating fracture data from Cunningham and colleagues[69]

We used fracture rates on standard treatment reported by Cunningham and colleagues.[69] This is reported as event rates per 100 patient years so we calculated the equivalent rate per year and applied this as a constant annual probability in the model.

No distinction was made in the report by Cunningham and colleagues (2005)[69] between major and minor fractures, but rather between "upper" and "lower" extremity fractures. In order to incorporate this data into the PenTAG model we used the rate for all fractures in the standard treatment arm of 0.069 events per year as reported by Cunningham and colleagues.[69] As in the PenTAG model base case, we assume that 10.36% of these are major fractures. Neither the report by Cunningham and colleagues[69] nor the model supplied by Amgen make allowance for increased risk of a subsequent fracture after the initial fracture, so we also assumed that the risk for subsequent fractures was the same as for initial fractures.

Rates of fracture for patients treated by cinacalcet are derived from the hazard ratio reported in Cunningham and colleagues (2005).[69]

Incorporating cardiovascular event data from Cunningham and colleagues[69]

In the PenTAG base case model, CV events are derived from a baseline probability of an event occurring for patients with "controlled" PTH levels, and applying a suitable RR value for people with more "uncontrolled" levels of PTH based on the literature. Cardiovascular events are reported in the same way as fracture data by Cunningham and colleagues (2005)[69] and are incorporated into the PenTAG model in the same way. In order to compare the values used in our base case model and in the version of the model using Cunningham data, we have taken a weighted average of the values for people with all severities of PTH

level and compared this to the value derived in the base case model. Annual risks shown in the two versions of the model are shown in Table 66.

Rates are lower in our base case than reported in the Cunningham data. Reasons for this are not clear. It could be that the small, selected sample with extrapolation from brief follow-up in the paper by Cunningham and colleagues[69] lead to overestimation both the incidence of CV events and the difference between standard treatment and cinacalcet in the longer term.

Table 66 *Comparison of the relative risk values used in the modelled scenarios*

Description of parameter	PenTAG model using Cunningham et al (2005)[69]	PenTAG base case model
Annual probability of CV event in people receiving standard treatment only	0.1788	0.12103
Annual probability of CV event in people receiving standard treatment plus cinacalcet	0.13929	0.10704

As was the case with fractures, no modification is made for increased risk of CV event after and initial CV event. The model submitted to NICE by Amgen incorporates the increased risk for subsequent events by modifying the base probability but the method used is not stated so we have not been able to replicate this analysis.

Incorporating parathyroidectomy data from Cunningham and colleagues[69]

Rates of parathyroidectomy reported by Cunningham and colleagues[69] were used in the PenTAG model in the same way as fracture and CV event data. The model assumes that only one parathyroidectomy is possible.

Mortality data

The mortality rate reported by Cunningham and colleagues[69] is artificially low when compared to known mortality rates in large cohort studies such as the Renal Registry. We therefore used the age-specific average ten year probabilities of death as reported in the Renal Registry for all-cause death (Table 67). [redacted]

Data used to populate the PenTAG model based on data from Cunningham and colleagues[69] is shown in Table 67.

Table 67 *Data used in Scenario Analysis 1 using data from Cunningham and colleagues*[69]

	Events per 100 pt years with standard treatment	HR applied for cinacalcet	Source
Parathyroidectomy	4.1	0.07	Cunningham et al[69]
Fracture	6.9	0.46	Cunningham et al[69]
CV hospitalisation	19.7	0.61	Cunningham et al[69]
Mortality	16.25	0.81	Age specific death rate from the Renal Registry assumed to represent death rate with standard treatment. HR for additional cinacalcet taken from Cunningham et al[69]

All of the utilities, drug doses and costs used to populate the original PenTAG model have been retained, as has the rate of withdrawal from cinacalcet treatment.

5.6.5.2 Sensitivity analysis for Scenario Analysis 1 based on data from Cunningham and colleagues.

We undertook probabilistic sensitivity analysis for this scenario. Most of the range data, for utilities, costs, and some general assumptions, were as for the base case. Where different parameters were used, these are shown in Table 68.

Table 68 *Parameter ranges used in Scenario Analysis 1 based on Cunningham, and colleagues data*

Parameter	Available range data	Source	Type	Distribution
Yearly rate of a fracture event	[redacted]	Industry Submission	[redacted]	Lognormal.
Yearly probability of CV events	[redacted]	Industry Submission	[redacted]	Beta
Yearly Probability of surgery	[redacted]	Industry Submission	[redacted]	Beta.
Age dependant yearly probability of death for category 55-64 years old	[redacted]	Industry Submission	[redacted]	Beta.
Age dependant yearly probability of death for category 65-74 years old	[redacted]	Industry Submission	[redacted]	Beta.
Age dependant yearly probability of death for category 75-84 years old	[redacted]	Industry Submission	[redacted]	Beta
Age dependant yearly probability of death for category 85+ years old	[redacted]	Industry Submission	[redacted]	Beta.

Parameter	Available range data	Source	Type	Distribution
Hazard ratio associated with reduction in CV events between arms of model	[redacted]	Industry Submission	[redacted]	Lognormal.
Hazard ratio associated with reduction in fracture events between arms of model	[redacted]	Industry Submission	[redacted]	Lognormal.
Hazard ratio associated with reduction in mortality events between arms of model	[redacted]	Industry Submission	[redacted]	Lognormal.
Hazard ratio associated with reduction in surgery events between arms of model	[redacted]	Industry Submission	[redacted]	Lognormal.

5.6.5.3 Results for the cost-effectiveness of cinacalcet in Scenario Analysis 1 based on data from Cunningham and colleagues[69]

The cost-effectiveness of cinacalcet using data from the Cunningham report in the PenTAG model is shown in Table 69. Compared to the base-case in the PenTAG base case, incremental costs and QALYs with cinacalcet are higher, and the ICER is lower. However, cinacalcet is still not likely to be considered cost-effective at usually acceptable levels of willingness to pay. Our results using the Cunningham data are only slightly higher than the figure of £35,600/QALY reported in the Amgen submission to NICE.

Table 69 *Cost-effectiveness of cinacalcet using data from Cunningham and colleagues (dialysis costs excluded)*

	Costs (£)	QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Standard treatment only	9,021	3.10	-	-	
Standard treatment plus cinacalcet	38,060	3.77	29,039	0.68	42,999

Using the Cunningham data, the model predicts greater incremental survival with cinacalcet than the PenTAG base case. This is illustrated below in Table 70. The PenTAG base case shows a slight long term survival advantage with cinacalcet. This is more pronounced using the Cunningham data as the proportion of the cohort surviving is both smaller in the standard care arm and larger in the cinacalcet arm of the model.

Table 70 *Survival analysis of standard treatment and cinacalcet arms of the model using data from Cunningham and colleagues*

	Survival 25th quartile	Median survival	Survival 75th quartile
Standard treatment alone	1.75	4.25	8.25
Standard treatment plus cinacalcet	2.25	5.50	10.50

5.6.5.4 Results of PSA for scenario analysis 1

Outputs for the PSA excluding costs of dialysis are shown graphically in Figure 15. In 5.8% of simulations, cinacalcet is cost-effective at a WTP threshold of £30,000 per QALY. It is dominated (costs more but confers fewer QALYs) in 0.5% of simulations. The cost-effectiveness acceptability curve (CEAC) predicts a very small possibility of cinacalcet being cost effective at £30,000/QALY, and only becoming cost-effective above a WTP threshold of about £44,000/QALY.

Outputs for the PSA including costs of dialysis are shown graphically in Figure 16. In this analysis no simulations show cinacalcet having an ICER of less that £30,000/QALY and it is dominated in 0.5% of simulations. The CEAC shows cinacalcet likely to be more cost effective than standard care above a willingness to pay threshold of about £66,000 per QALY.

Figure 15 *Simulation output (1000 trials) for Scenario Analysis 1 based on Cunningham and colleagues and cost-effectiveness acceptability curve showing the probability that cinacalcet is cost-effective at various levels of willingness to pay (dialysis costs excluded).*

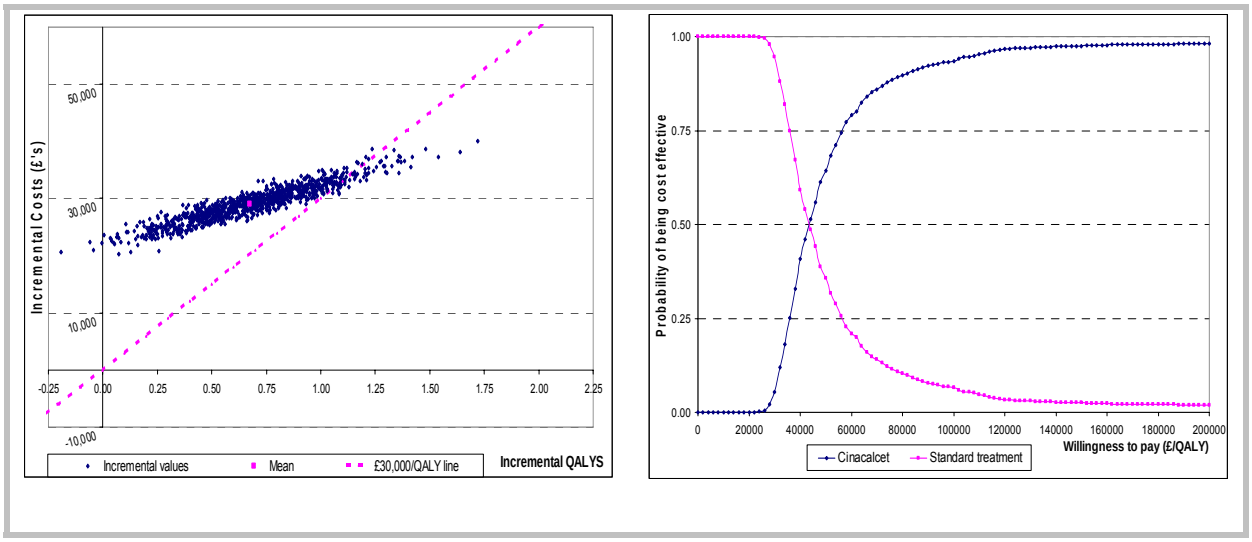
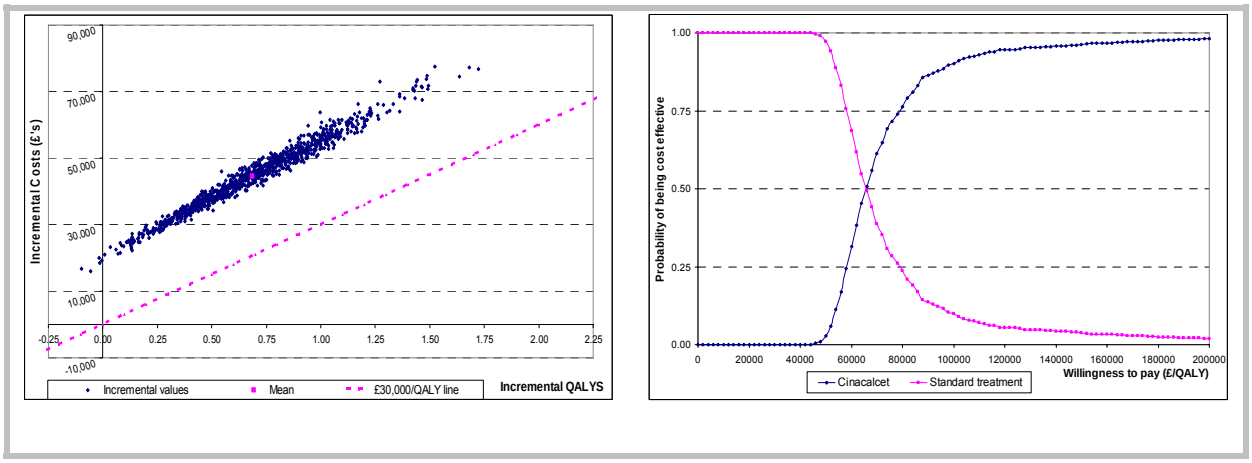


Figure 16 *Simulation output (1000 trials) for Scenario Analysis 1 based on Cunningham and colleagues and cost-effectiveness acceptability curve showing the probability that cinacalcet is cost-effective at various levels of willingness to pay (dialysis costs included)*



5.6.6 Scenario analysis 2: Exploration of the impact of cinacalcet through estimated impacts on calcium-phosphate product control

Due to data limitations, we have based our model on a single bio-marker for risk of adverse events. This is a limitation for two reasons: first, it is known that the levels of PTH, Ca and Ph are interconnected, and second, PTH levels may not be the strongest marker of risk for CV events or mortality. However, the systematic review shows that there is very limited information about the impact of cinacalcet on other biochemical markers especially in relation to its impact on PTH. The only available information is that 91% of those treated with cinacalcet who achieve a PTH level of ≤ 26.5pmol/L also have a reduction in CaxP levels from their baseline level.

We have explored the potential impact of this in our model although the analysis should be regarded as purely exploratory.

5.6.6.1 Methods for Scenario Analysis 2 on the impact of cinacalcet on calcium-phosphate product.

Percentage of people meeting both PTH and CaxP targets

We have assumed that all of those who are reported as having a "reduction" in CaxP product in the systematic review have a reduction to below the KDOQI guideline target of ≤ 4.4mmol^2/L^2 (there is currently no Renal Association target for this marker). All those not achieving a "reduction" are assumed to have elevated CaxP product levels, despite having "controlled" PTH levels. We have also assumed that none of those who have "uncontrolled" or "very uncontrolled" PTH have a CaxP that reaches KDOQI target levels. These assumptions are likely to bias in favour of cinacalcet. In effect, this is a "best case scenario" for cinacalcet because it assumes that nearly all of those with "controlled" PTH levels achieve target levels for CaxP while none of those with "uncontrolled" PTH do so.

Relative risk of CV and mortality

Relative risks (RR) of CV event and mortality are based on the risk at different levels of CaxP, again taken from the paper by Block and colleagues (n=40,538).[18] This paper reports RR for CaxP levels in 5mg^2/dl^2 bands from <30mg^2/dl^2 to >80mg^2/dl^2. As the confidence intervals for all those below 44mg^2/dl^2 contain one, we have also used this as our reference range. A plot of the RR of mortality against the midpoints of these value-ranges was then taken, and a linear trend fitted. We used the relative risk of mortality for the

midpoint of this fitted trend line, which equate to the risk at $72mg^2/dl^2$. Although this is somewhat arbitrary, it was not considered inappropriate in the context of an exploratory analysis. This gives a RR of mortality of 1.63 for people who do not have CaxP control compared to those with CaxP levels that meet the KDOQI targets.

A similar process was undertaken to establish the RR of CV event for people with CaxP based on findings of Block and colleagues.[18] This gives a RR of CV event of 1.38 for people who do not have CaxP control compared to those with levels that meet the KDOQI targets.

The RR of mortality and CV event for people with "controlled" PTH is a weighted average of the risk for those with elevated CaxP and those whose CaxP levels meet the target level (Table 71).

Relative risk of fracture

As PTH levels are thought to be the best marker of bone disease, we have continued to use the RR for fracture based on PTH levels as in the base case.

Data used to populate the model for both arms after the initial treatment (titration phase) are shown in Table 71. These are based on the average populations with controlled PTH and CaxP levels (Table 28).

Table 71 *Cohort proportion used in scenario analysis 2 based on CaxP impact*

			Percentage of cohort in each group after initial treatment			
			Standard treatment		Cinacalcet treatment	
	CaxP target met (%)	CaxP target NOT met (%)	CaxP target met (%)	CaxP target NOT met (%)	CaxP target met (%)	CaxP target NOT met (%)
"Controlled" PTH levels	91	9	4.55	0.45	36.4	3.6
"Uncontrolled" PTH levels	0	100	0	66.5	0	42.0
"Very Uncontrolled" PTH levels	0	100	0	28.5	0	18.0

5.6.6.2 Sensitivity analysis for Scenario Analysis 2 based on calcium-phosphate product levels

We undertook probabilistic sensitivity analysis (PSA) to explore the impact of underlying parameter uncertainty on cost-effectiveness. Most of the data used was the same as in the

base case economic model. Different ranges and sources used for the proportion of patients entering different levels of CaxP control, and are shown in Table 72.

Table 72 *Range and distribution data used in scenario analysis 2 based on CaxP levels*

Parameter	Available range data	Source	Type of data	Distribution
Proportion receiving standard treatment having "controlled" CaXP	[1,5]	Author assumption.	Values represent +/- 50% of central estimate	Beta.
Proportion receiving standard treatment having "Very uncontrolled" CaXP	[14.25, 42.75]	Author assumption.	Values represent +/- 50% of central estimate	Beta.
Proportion receiving cinacalcet having "controlled" PTH	[18.2, 54.6]	Author assumption.	Values represent +/- 50% of central estimate	Beta.
Proportion receiving cinacalcet having "uncontrolled" PTH	[9, 27]	Author assumption.	Values represent +/- 50% of central estimate	Beta.
Differential dropout rate between two arms of the model	None	Author assumption that S.E. is 1/10th of the central estimate	Assumption	Beta.
Proportion of those with "controlled" PTH that become "uncontrolled" each cycle (both arms)	[0.05, 0.5]	Input from expert advisory group	Clinical opinion and author assumption	Lognormal.
Proportion of those with "uncontrolled" PTH that become "very uncontrolled" each cycle (both arms)	[0.05, 0.5]	Input from expert advisory group	Clinical opinion and author assumption	Lognormal.
Proportions that suffer adverse effects after surgery (both arms)	None	Author assumption that S.E. is 1/10th of the central estimate	Assumption	Beta.
Fracture				
Yearly rate of an initial major fracture event	[1.7, 6.1] hip fractures per 1000 pt yrs	Ball et al[26]	Min and max for different subgroup analyses	Lognormal.
Risk of fracture for those with "uncontrolled" PTH levels compared to those with "controlled" levels	[0.73, 1.72]	Kim et al[86]	95% CI	Lognormal.
Risk of fracture for those with "very uncontrolled" PTH	[1.36, 2.76]	Kim et al[86]	95% CI	Lognormal.

Parameter	Available range data	Source	Type of data	Distribution
levels compared to those with "controlled" levels				
Death event				
Age dependant probability of death	[-13.166,-11.309] [2.314, 2.762]	Derived using data in renal registry	95% CI's for log lambda and gamma parameters used in calculation of each probability.	Bivariate normal.
Risk of death in any of the strata in either arm of the model.	[-1.9817, 0.12329] [0.0205, 0.02551]	Derived from Block et al[18]	95% CI's for slope and intercept parameters used in calculation of category estimates	Bivariate Normal.
Reduction in death risk post surgery	[0.80, 0.94]	Kestenbaum et al[90]	95% CI	Normal.
CV event				
Yearly probability of having an initial CV event	None	Author assumption that S.E. is 1/15th of the central estimate	Assumption	Beta.
Risk of CV event in any of the model strata	[0.2586, 0.8353] [0.0066, 0.0167]	Derived from Block et al[18]	95% CI's for slope and intercept parameters used in calculation of category estimates	Bivariate Normal.

5.6.6.3 Results for Scenario Analysis 2 using data on calcium-phosphate product levels

The results for this speculative analysis are shown below in Table 73. The ICER is considerably reduced from our model that bases the risk of adverse effect solely on PTH levels. However it is still higher than is usually accepted as representing a cost-effectiveness option.

Table 73 *Scenario Analysis 2 for the cost effectiveness of cinacalcet based on the impact on CaxP levels (dialysis costs excluded)*

	Costs (£)	Utilities (QALYs)	Incremental costs	Incremental QALYs	ICER (£/QALY)
Standard treatment only	5,089	2.38	-	-	-
Standard treatment plus cinacalcet	23,512	2.85	18,422	0.47	38,855

More conservative assessment of the impact of cinacalcet on CaxP levels.

This analysis is likely to be biased in favour of cinacalcet since it assumes that all those with reduced levels of CaxP also have a reduced levels of PTH. Any of the patients that have uncontrolled PTH levels are therefore considered to also have uncontrolled CaxP levels. For a more conservative assessment, we used data from the Renal Registry which shows that 67% of people on renal replacement therapy have controlled CaxP levels which meet the KDOQI guidelines.[15] We used this more conservative estimate to run second version of this exploratory model. Data used to populate this model are shown in Table 70 and the results are shown in Table 71. The ICER in this estimate is higher, due to more people with uncontrolled PTH now being assumed to have control of CaxP levels and so having a lower RR of mortality and CV events.

Table 74 *Cohort proportions used in the conservative exploratory model of CaxP impact*

			Percentage of cohort in each group after initial treatment			
			Standard treatment		Cinacalcet treatment	
	CaxP target met (%)	CaxP target NOT met (%)	CaxP target met (%)	CaxP target NOT met (%)	CaxP target met (%)	CaxP target NOT met (%)
"Controlled" PTH levels	0.91	0.09	4.55	0.45	36.4	3.6
"Uncontrolled" PTH levels	0.67	0.33	44.33	22.17	28.0	14.0
"Very Uncontrolled" PTH levels	0.67	0.33	19.0	9.5	12.0	6.0

Table 75 *Speculative analysis for the cost effectiveness of cinacalcet based on the impact on CaxP levels – conservative estimate(Dialysis costs excluded)*

	Costs (£)	Utilities (QALYs)	Incremental costs	Incremental QALYs	ICER (£/QALY)
Standard treatment only	4,742	3.2	-	-	-
Standard treatment plus cinacalcet	27,885	3.46	23,142	0.25	91,894

5.6.6.4 Results of PSA for Scenario Analysis 2 based on calcium-phosphate product levels

Outputs for the Monte-Carlo simulation are shown graphically in **Figure 17**. For the modelled cohort in the scenario analysis based on CaxP levels, this illustrates the ICER values of 1000 simulated trials. The CEAC shows the probability that cinacalcet is cost-effective, in scenario 2, at various levels of willingness to pay for an additional QALY.

Figure 17 shows the PSA results when dialysis costs are excluded. Cinacalcet is cost-effective at a willingness to pay (WTP) threshold of £30,000 per QALY in 5.8% of simulations. Cinacalcet only becomes likely to be cost-effective above a WTP threshold of around £40,000/QALY.

Figure 18 shows the PSA results when dialysis costs are included. None of the simulations show cinacalcet to be cost-effective at a WTP threshold of £30,000 per QALY. Cinacalcet only becomes likely to be cost-effective above a WTP threshold of £60,000/QALY.

Figure 17 *Simulation output (1000 trials) for Scenario Analysis 2 based on CaxP control and cost-effectiveness acceptability curve showing the probability that cinacalcet is cost-effective at various levels of willingness to pay (dialysis costs excluded).*

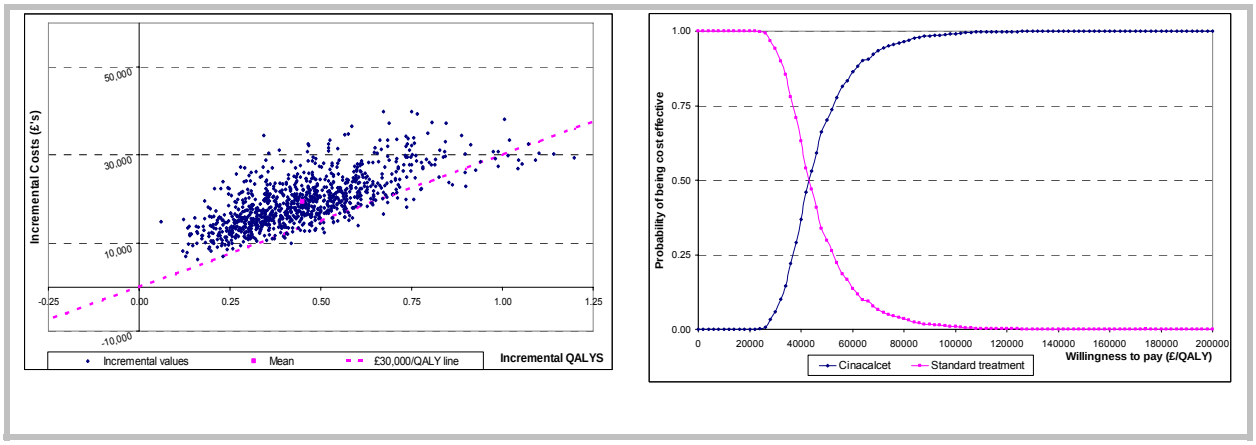
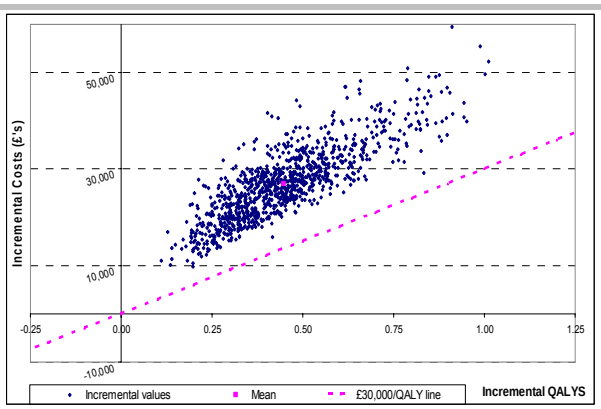


Figure 18 *Simulation output (1000 trials) for Scenario Analysis 2 based on CaxP control and cost-effectiveness acceptability curve showing the probability that cinacalcet is cost-effective at various levels of willingness to pay (dialysis costs excluded)*


Incremental Costs (£'s)
50,000
30,000
10,000
-10,000
-0.25
0.00
0.25
0.50
0.75
1.00
1.25
Incremental values
Mean
£30,000/QALY line
Incremental QALYS

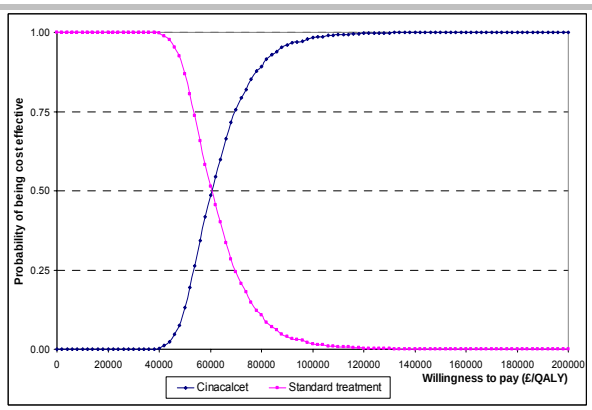

Probability of being cost effective
1.00
0.75
0.50
0.25
0.00
0
20000
40000
60000
80000
100000
120000
140000
160000
180000
200000
Cinacalcet
Standard treatment
Willingness to pay (£/QALY)

Table 76 *Summary of model uncertainty*

	Source of variable	Level of uncertainty in the data	Impact of uncertainty on the model	Overall rating of importance
Transitions				
RR of death for people with "very uncontrolled" PTH	Cohort study	High	Very high	Very important
RR of death for people with "uncontrolled" PTH	Cohort study	High	High	Important
Disease progression	Clinician opinion	Very high	High	Important
Percentage of people who withdraw from treatment with cinacalcet	Experience in RCTs	Moderate	Moderate	Moderately Important
Differential proportion of people with "very uncontrolled" levels of PTH	Systematic review	Low	Moderate	Not Important
Utilities				
Utility reduction with "very uncontrolled" PTH levels	Clinician opinion	Very high	High	Important
Utility reduction with "uncontrolled" PTH levels	Clinician opinion	Very high	Moderate	Moderately Important
Costs				
Inclusion of dialysis costs in the analysis	Author assumption based on input from NICE	High	High	Important
Dose of cinacalcet	Use in RCTs	Moderate	High	Moderately Important
Cost of cinacalcet	List price	Low	Very high	Not important

5.6.7 Potential Model Limitations

There is convincing evidence of the impact of cinacalcet on serum biomarkers such as PTH and calcium-phosphate product. However, the long-term clinical implications of this are unclear. Crucially, the evidence for an impact on clinical events such as mortality, CV event, fracture and parathyroidectomy is based on one, short-term, post-hoc analysis. We therefore used data from large cohort studies about the risk of clinical events in relation to levels of biomarkers, particularly PTH.

Serum levels of biomarkers such as PTH, Ca and Ph are interrelated and complex. Furthermore, the relationship between combinations of biomarkers and long term clinical outcomes is complex and has not been characterised. The covariance between markers is unknown. We have therefore modelled PTH independently, which may over- or under-estimate the risk of clinical events. However, the assumptions used here in modelling calcium-phosphate product with PTH levels probably provide an optimistic view for the impact of cinacalcet on the risk of long term consequences.

It is not known whether control of PTH with cinacalcet will be sustained. It is possible that underlying disease progression will still occur, or that effectiveness may not be sustained over the long term. Compliance is also a known problem, with up to 86% of dialysis non-compliant with at least one aspect of their treatment.[29] Cinacalcet is an additional medication for people who may already be taking large amounts of medication. Further, cinacalcet is associated with increased nausea and vomiting. Our base case assumes that there is no loss of control with cinacalcet, but that disease progression does affect those treated with standard care. This is likely to bias in favour of cinacalcet.

Parameters within the model are differentiated both between the degree of PTH control (the model strata) and between health states within each of these model strata. However, the model does not accommodate interactions between these two sources of variance. Any co-variance there might be between the degree of control of PTH and the relative risk of CV death between the health states within the strata is not modelled (for example, if a non-fatal CV event confers greater relative risk of mortality for those with “very uncontrolled” levels of PTH compared to those who have “controlled” levels of PTH). As there are insufficient data to model these possible interactions we have assumed equivalent relative risk at all degrees of PTH control. As it seems unlikely that there is a negative interaction between these two types of risk, this may bias against cinacalcet.

A number of assumptions have had to be made in relation to fracture in this population. The pattern of fractures experienced in people with ESRD due to SHPT is not clear so general population data has been used. The interaction between the risks of first fracture or CV events and subsequent events is also unclear. The risk of death from fractures in people with renal osteodystrophy from SHPT is not well understood and assumptions from a different condition have been included. The paucity of evidence in relation to many of these factors has led to the need to make a range of linked assumptions, about which much uncertainty must remain. The direction of any potential bias is not clear.

Over-suppression of PTH by cinacalcet is not included in the model. Assuming that downward dose adjustment would take place in such cases, the model will overestimate the treatment costs for cinacalcet.

The model is based on cinacalcet trial populations which have an average age of 55. The average age of accepting RRT in the UK, however, is 65. It is not known whether the effectiveness of cinacalcet if affected by age. Younger age is likely to bias the model in favour of cinacalcet as background death rates would be higher among older people.

Quality of life in SHPT is not well understood and so assumptions based on clinical opinion have been made in the model on the amount of reduction in utility according to level of biochemical control.

Quality of life following cardiovascular events or fractures in this population are not known and may be different from values obtained in the general population or other disease groups. Assumptions based on different populations have been included in the model and the impact of any bias this may introduce is not clear.

We have excluded the cost of dialysis in our base case analysis. However, it is usually accepted that costs relating to the treatment of the condition under examination should be included in cost-effectiveness analyses. It is certainly arguable that, as SHPT is so closely associated with ESRD, costs of ESRD, should be included. The exclusion of dialysis costs favours cinacalcet in the analysis.

The model assumes some changes to standard medical treatment of SHPT with the addition of cinacalcet based on clinical opinion. The model therefore assumes that people with refractory SHPT are more likely to receive expensive non-calcium based phosphate-binders. In reality, clinical practice is likely to vary between centres. Assuming more use of these expensive drugs in people with “very uncontrolled” PTH may bias in favour of cinacalcet.

5.7 Comparison of Amgen and PenTAG economic evaluations

5.7.1 Differences in structure and inputs

Table 77 shows the main differences between the PenTAG and Amgen economic analyses. In general, similar types of resource use are captured in both analyses and most of the unit costs are also similar.

There are major differences between the analyses with regard to the assumptions that drive effectiveness. [redacted]

Most importantly, the transition probabilities which govern the different rates of these events, and different mortality between cinacalcet and standard treatment, are based on different sources. [redacted] In contrast, for the PenTAG analysis, we separately modelled the level of PTH control as the main driver of the risk of these events. This is one of the major factors accounting for differences between results.

Table 77 *Comparison of Amgen and PenTAG base case analyses of cinacalcet highlighting main differences in study design*

	Amgen analysis	PenTAG analysis
Type of model	[redacted]	Markov model
Outputs	Costs	Costs
	QALYs	QALYs
Start age and time horizon	[redacted]	A 55-year-old mixed sex cohort
	[redacted]	Followed until all are dead
Model structure [redacted]	[redacted]	Includes parathyroidectomy and post-parathyroidectomy states
[redacted]	[redacted]	Models the risk of CV and fracture events as a function of level of PTH control
	[redacted]	
	[redacted]	
	[redacted]	
	[redacted]	
	[redacted]	
	[redacted]	
	[redacted]	
Cycle length	[redacted]	3 months
Allowable Transitions	[redacted]	Can experience both types of major event in same 3-month period
	[redacted]	
	[redacted]	
Population modelled	[redacted]	Patients with PTH > 31.6 pmol/L (>300pg/mL)
	[redacted]	
Background utility before experiencing major fracture or CV events	[redacted]	0.6735 for those with controlled PTH. 0.6398 for "uncontrolled" PTH levels 0.6062 for "very uncontrolled" PTH levels.
CV event assumptions	[redacted]	Initial 3-month utility of 0.478, then 0.6533 thereafter.
	[redacted]	Cost of event: £1,287
Major fracture event assumptions	[redacted]	Initial 3-month utility of 0.5368, then 0.6051 thereafter.
	[redacted]	Cost of event: £4,767
Utility after both CV and major fracture event	[redacted]	Initial 3-month utility of 0.384, then 0.5870 thereafter
Post-parathyroidectomy assumptions	[redacted]	Assumed same utility levels as having controlled PTH, and same utility impacts of adverse events as pre-parathyroidectomy.
	[redacted]	
	[redacted]	Higher mortality in immediate post-parathyroidectomy period, same as those with controlled PTH levels.
Costs included	Cinacalcet	Cinacalcet
		Background cost of dialysis
	[redacted]	Hospital treatment of CV events
	[redacted]	Hospital treatment of major fractures
	[redacted]	Treatment of minor fractures
	[redacted]	Parathyroidectomy
	[redacted]	Regular blood tests for PTH, calcium and phosphate levels

Mortality a function of	[redacted]	Age-related non-surgical (all-cause) mortality, Plus excess mortality associated with: having Uncontrolled and Very uncontrolled PTH levels; peri-operative mortality (following parathyroidectomy); and post-parathyroidectomy

5.7.2 Differences in outputs between the Amgen and PenTAG models

The base case ICERs of the two analyses differ by more than £26,000 (in the PenTAG analysis cinacalcet produces extra QALYs at a cost of £61,800 per QALY, compared with £35,600 in the Amgen analysis). Below, we try to explain the most probable reasons for this difference, but since there are so many different numerical assumptions (parameters) in each model, and also substantive differences in the structural assumptions in each model, an exhaustive analysis of why the base case ICERs are so different is not possible here. Table 78 summarises some key outputs from each analysis.

The difference in ICER arises from cinacalcet yielding both [redacted] lower estimated QALY gains, and generating [redacted] higher costs in the PenTAG analysis. However, in terms of their predictions of overall survival, the two models seem similar, for example resulting in a difference in mean incremental survival of less than a month (0.07 of a year). This suggests that differences in estimated QALY gains due to cinacalcet are explained by how much time people spend in health states of differing utility weight.

Table 78 *Key differences in outputs for the Amgen and PenTAG models*

	Amgen analysis	PenTAG analysis
% surviving 5 years, cinacalcet	[redacted]	50.1%
% surviving 5 years, standard care	[redacted]	47.4%
% surviving 10 years, cinacalcet	[redacted]	19.5%
% surviving 10 years, standard care	[redacted]	16.8%
Mean survival - cinacalcet	[redacted]	6.25
Mean survival - standard care	[redacted]	5.62
Incremental survival (years):	[redacted]	0.63
Mean QALYs - cinacalcet	[redacted]	3.39
Mean QALYs - standard care	[redacted]	3.04
Incremental QALYs:	[redacted]	0.34
Mean cost - cinacalcet	[redacted]	£27,670
Mean cost - standard care	[redacted]	£6,533
Incremental cost:	[redacted]	£21,167
Incremental cost/QALY (discounted)	£35,600	£61,890
Incremental cost/QALY (undiscounted)	[redacted]	£ 55,633

Figure 19 shows a comparison of the two models [redacted]

Figure 19 *Markov state occupancy in years for each model and comparator*

Academic in confidence removed

Although the pattern of state occupancies generated by each model is broadly similar, there are a few notable differences which may partly explain the differences in estimated QALYs and costs between the two analyses:

- [redacted]
- [redacted]
- [redacted]

[redacted]

How these state occupancies translate into QALY gains or losses in each model is shown in Figure 20 and Figure 21. Because of the different model structures, and the more complicated system of utility values used in the PenTAG model, it is not possible to produce directly equivalent graphs. Figure 20 shows that the QALY gains (undiscounted) of cinacalcet in the Amgen model [redacted]

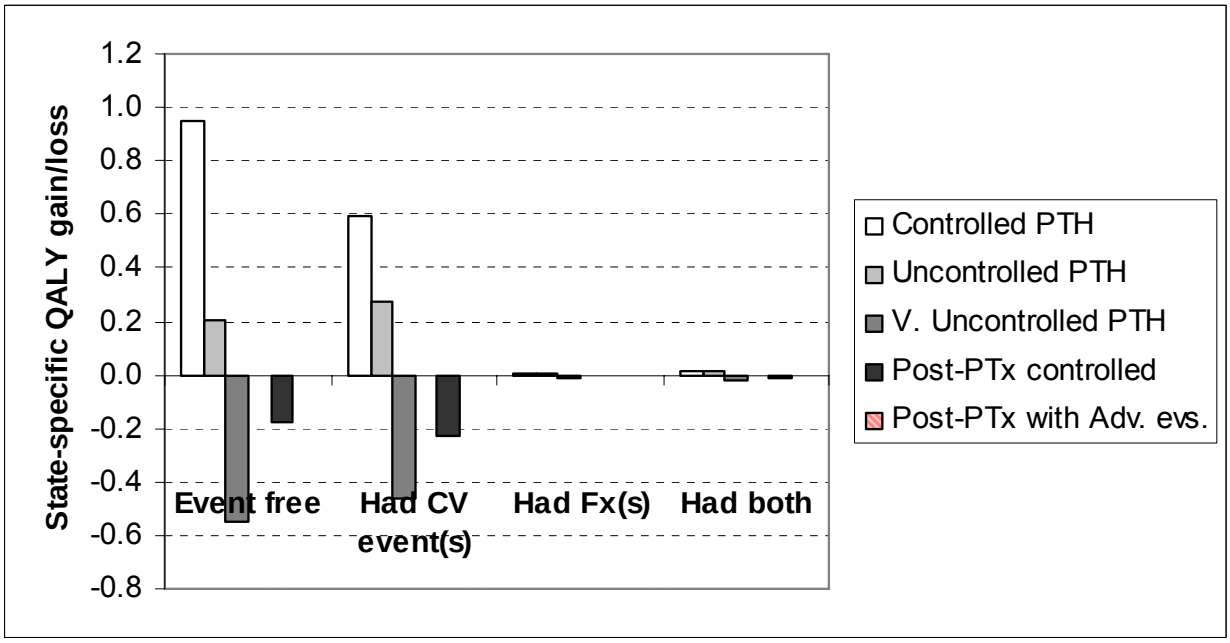
In contrast, in the PenTAG model, the QALY gains due to cinacalcet are not associated with changes in the proportion of people experiencing both types of adverse event (Figure 21). Instead, more than two thirds of the QALY gains in the PenTAG model arise from a combination of people spending more time in event free health states and avoiding "very uncontrolled" PTH. The remaining QALY gains are due almost entirely to fewer and delayed occurrence of CV events (again, combined with less of their survival time being with "very uncontrolled" PTH). Time spent in fracture-only-related Markov health states has almost no impact on the QALY gain due to cinacalcet in either analysis.

[redacted] in the PenTAG analysis deaths associated with CV events or a history of a past CV event are modelled separately, and account for almost half of all deaths (either with cinacalcet or standard care). [redacted]

Figure 20 *State-occupancy by utility weight in the Amgen model*

Academic in confidence removed

Figure 21 *Summary of the source of QALY gains and losses in the PenTAG model*



An explanation of the differences in incremental cost between the two analyses would require full reporting of the mean life-time occurrence of major and minor fractures, CV events and parathyroidectomies, for both cinacalcet and standard care. [redacted]

[redacted]

We have not therefore formally assessed how the cost differences between the two analyses have arisen.

However, the state occupancy comparisons - presented above to explain the difference in estimated QALY gain - suggest that a key explanation of incremental cost differences between the analyses would be:

1. [redacted]

2. [redacted]

3. [redacted]

5.8 Current service cost and impact of new treatments

Existing costs for people with ESRD are high: haemodialysis costs about £18,000 annually, and peritoneal dialysis £9,000. The cost of standard treatment for SHPT is modest; our model predicts it will cost £6,500 for the lifetime of a 55 year old (median survival five years).

Using costs obtained from our economic model it is possible to estimate the impact of adopting cinacalcet as additional treatment for those with uncontrolled SHPT. There are approximately 6,000 people on dialysis with elevated PTH levels in England and Wales (Table 79). Assuming that the lifetime cost (median survival = five years) in our model for a 55 year old is the average cost for this population, the cost to treat all those in England and Wales would be about £131,000,000.

Using data in Table 79 for an average Hospital Trust serving about 250,000 people, 29 people on dialysis would have SHPT. The additional cost of treating these people for a median of five years with cinacalcet would be £613,000.

Table 79 *Estimated number of people with ESRD and elevated PTH levels*

Parameter	Data	Source
Prevalence of RRT	636 pmp	Renal Registry
% of those on RRT on dialysis	54%	Renal Registry
Population England and Wales	53,045,600	Census 2001
Number of people on dialysis in England and Wa\les	18,218	Calculated
% of people with PTH levels above 32pmol/L	34%	Renal Registry
Number of people with elevated PTH levels	6194	Calculated

5.9 Summary of the results of the cost-effectiveness analysis

BOX 3 Summary of results of the cost-effectiveness analysis

- *No published cost-utility studies of cinacalcet were identified. Amgen submitted a Markov model to NICE which estimated an ICER of £35,600/QALY. Subgroup analyses of those with moderate and severe HPT produced estimates £30,400 and £48,300/QALY respectively.*
- *PenTAG designed a Markov model to assess the cost-utility of cinacalcet in addition to standard care compared to standard care alone for people with SHPT with ESRD.*
- *A cohort of 1000 55 year olds was modelled until all the cohort was dead.*
- *The base case showed that cinacalcet conferred a small number of additional QALYs (0.34) for an additional £21,167 per person, giving an ICER of £61,890/QALY. This is not likely to be considered cost-effective.*
- *One-way sensitivity analyses showed that the model was sensitive to the cost of cinacalcet, the utility value for people with "very uncontrolled" levels of PTH and to the relative risk of mortality for people with "very uncontrolled" levels of PTH compared to those with "controlled" PTH.*
- *Probabilistic sensitivity analysis showed that cinacalcet was only likely to be cost-effective at levels of willingness to pay over £62,000/QALY.*
- *Subgroup analysis in people with moderately "uncontrolled" levels of PTH only reduced the ICER but cinacalcet was still not likely to be considered cost-effective (£57,400/QALY).*

6 Discussion

6.1 Summary of Findings

Cinacalcet is more effective than standard treatment in bringing SHPT under control, as measured using PTH and other markers of biochemical disruption in SHPT in people with ESRD. However, there is very limited evidence about the impact of this on clinically important outcomes such as cardiovascular events and death. Evidence of the impact of cinacalcet on biochemical markers is also short term.

The economic evaluation suggests that, under almost all assumptions, the incremental cost effectiveness of introducing cinacalcet would be greater than £30,000 per QALY from the perspective of the UK NHS.

The economics of introducing cinacalcet are subject to much uncertainty, but based on the modelling carried out in this assessment, cinacalcet is unlikely to be considered a cost effective intervention by NHS commissioners. Only above a willingness to pay threshold of £62,000/QALY is there a good chance that cinacalcet is cost-effective.

6.2 Interpretation of Findings

Despite evidence that cinacalcet does bring biochemical markers of SHPT to target levels more effectively than standard treatment, a combination of factors leads to cinacalcet appearing to represent relatively poor value for money. The background death rate for people with ESRD is high, even among the relatively young cohort modelled. Conversely, the relative risk of mortality for people with slightly elevated PTH levels appears low so the potential impact of cinacalcet may therefore be limited. The impact of SHPT on cardiovascular event rates, and potential for control of this risk, is particularly important in the evaluation of cinacalcet. Cinacalcet is expensive and, even if we exclude dialysis costs and assume that there will be some cost-savings due to reduced phosphate binder treatment, cinacalcet is unlikely to be considered cost effective.

The place of parathyroidectomy appears to vary between UK centres, based on the availability of surgeons and clinician preferences. Surgery appears to be an effective therapy, despite relatively frequent recurrence. Recent Australian management advice for

SHPT suggests that parathyroidectomy should remain the preferred treatment option for those with PTH levels elevated above 85pmol/L.[36] Without trial evidence comparing cinacalcet and parathyroidectomy, the optimal treatment approach remains unknown.

The published evidence for the direct impact of cinacalcet on outcomes such as CV event, fracture and mortality is limited to one retrospective analysis of the four main RCTs of its biochemical effects. The short follow-up, lack of detail about the people who entered the trial extension and unclear censoring procedures, as well as the inclusion of a fitter population than is found in clinical practice, make interpretation of these results difficult.

6.2.1 Strengths and weaknesses

6.2.1.1 Strengths of the evaluation

The systematic review of the effectiveness and cost-effectiveness of cinacalcet in SHPT is comprehensive and has been carried out by an independent research team.

PenTAG's economic evaluation allows exploration of the potential for cinacalcet to be used at different levels of PTH control and for the impact of different risk markers to be explored.

6.2.1.2 Potential limitations of the evaluation

Evidence for the direct impact of cinacalcet on CV events, fractures and mortality is very limited. The relationship between biomarkers and long term outcomes is complex and not well characterised, and the covariance between different markers is unknown. We have therefore modelled the impact of single biomarkers, such as PTH levels, which may over- or under-estimate the risk of clinical events. However, the assumptions used here in modelling calcium-phosphate product provide an optimistic view of the potential risk of long term consequences with cinacalcet treatment.

The main source for relative risk data based on biochemical markers was the large, US cohort study by Block and colleagues. We used this because it was recent, was the largest identified study and provided data about fracture, CV hospitalisation, and mortality risk in the same cohort for the key biochemical markers. However, we have assumed that this data is accurate and applicable to the UK population.

It is not known for how long biochemical control will be maintained in people who achieve it with cinacalcet. The impact of disease progression and of compliance with medication regimes may be important but are not currently characterised. Our base case assumption that progression to more severe degrees of HPT continues fairly rapidly with standard treatment but is arrested with cinacalcet is likely to bias the results in favour of cinacalcet.

The possibility of over-suppression of PTH by cinacalcet is not reflected in the model. Assuming that downward dose adjustment would take place in such cases, the model may overestimate the treatment costs for cinacalcet.

A number of assumptions have been used to model fractures in ESRD as we were unable to identify specific data in the relevant population. The pattern of fractures experienced in people with ESRD due to SHPT is not well documented so we have used general population data on fracture distribution in the model. It is not known whether and how this is different from the pattern of fractures in people with ESRD. In addition, the interaction between the risks of first fracture and subsequent events is unclear in this population and we have assumed that this is similar to the risks for people with osteoporosis. Also, the risk of death associated with fractures in people with renal osteodystrophy associated with SHPT is not well understood. Again, we have based our assumptions on data from those with osteoporosis. It is not clear whether these assumptions will over- or under- estimate risk for renal osteodystrophy. The paucity of evidence in relation to many of these factors has led to the need to make a range of linked assumptions, about which much uncertainty must remain.

The risk of a subsequent CV event after an initial CV event is not known in this population. We identified data relating to the additional risk of subsequent heart failure after an initial event. It is not known if this is an under- or over- estimate of the risk of all CV events after any initial CV event.

The model assumes a reduction in the use of expensive phosphate binders might be expected in people who respond to cinacalcet. Data for the exact mix and dosage of drugs used with and without cinacalcet is scarce.

The impact of drug regimen changes on patients is also unknown. It is possible that the quantity and type of drugs taken may influence quality of life and compliance. If cinacalcet were to prove a more reliable method of controlling PTH in the long term, this may reduce anxiety this aspect of ESRD. In addition, cost-benefits in terms of less clinical time, and less specialist dietician input are possible but as yet undocumented.

Quality of life (QoL) in SHPT is not well understood and we have made assumptions based on clinical opinion as to the reduction in utility according to level of biochemical control. QoL (SF-36) data collected with the cinacalcet trials suggested that there was little difference in QoL for those treated with cinacalcet compared to those treated with standard care The model may thus have overestimated the impact of PTH levels on QoL and so the impact of cinacalcet. Conversely, there were differences in two items of the SF-36 - the physical component and bodily pain scores. If such elements were affected at lower degrees of SHPT than were modelled, the impact of cinacalcet may have been underestimated.

Quality of life changes following CV events or fractures in this population are not well characterised and may be different from values obtained in the general population or other disease groups. Assumptions based on non-ESRD populations have been included in the model and the size and direction of any bias introduced is not clear.

Diabetes is known to adversely affect survival for those with ESRD. Our model has not explicitly considered the impact of diabetes in people treated with cinacalcet for SHPT. The impact on clinical outcomes of controlling PTH in diabetic and non-diabetic populations is not known. Those with diabetes already have increased risk of CV events and the proportion of risk attributable to SHP may be relatively low, leading to a limited potential role for cinacalcet. The trial data used to populate the model included about 30% people with diabetes which is similar to 27% diabetes comorbidity recorded by the UK Renal Registry. However, mortality in the trials was low for the relevant age-group reported in the Renal registry. It is possible that those diabetics included in the trials were fitter or had better controlled diabetes than in usual clinical practice.

The model predicts median survival of five years with cinacalcet and 4.5 years with standard care. The Renal Registry estimates median survival for people at medium mortality risk at 7.4 years (for non-diabetics under 55 and diabetics aged 55-64) and for people at high risk at 3.5 years (for diabetics over 55 and non-diabetics aged over 65). It is not clear whether this is an over- or under- estimate of the risk for people with SHPT.

The scope for this report has been the effectiveness of cinacalcet in people with existing SHPT. It is not known if preventing the progression to HPT initially is possible with cinacalcet and whether this could be a more useful indication. Similarly, the impact of avoiding calcification in younger populations could reap greater benefits.

6.3 Interpretation in the Context of Other Studies in the Area

No published economic evaluations of cinacalcet in SHPT were identified. The PenTAG model is more comprehensive and flexible than the model submitted to NICE by the manufacturers of cinacalcet, although both models adopt a similar basic structure.

The PenTAG model replicates the findings of the Amgen model when appropriate adjustments to input parameters are made.

6.4 Need for Further Research

1. Accurate estimates of the multivariate relationship between biochemical disruption in SHPT and long term clinical outcomes is of paramount importance to improve future efforts to model the effectiveness of cinacalcet, or other similar agents.

2. Long term studies of the impact on clinical outcomes and of the maintenance of PTH control in SHPT with cinacalcet treatment are needed.

3. A better understanding of the epidemiology of fractures in SHPT is needed, including the pattern of fractures experienced in SHPT and their consequences in terms of health service use, quality of life and mortality.

4. The impact on quality of life of fracture, CV events and very uncontrolled PTH levels in people with SHPT in dialysis should be investigated.

7 Conclusions

Cinacalcet is more effective in bringing SHPT under control than standard care, as measured using PTH (40% vs 5%) and other markers of biochemical disruption in SHPT. However, there is very limited direct evidence about the impact of this on clinically important outcomes such as cardiovascular events and death.

The economic evaluation suggests that, under almost all assumptions, the incremental cost effectiveness of introducing cinacalcet would be considerably greater than £30,000 per QALY from the perspective of the UK NHS.

The economics of introducing cinacalcet are subject to much uncertainty, but based on the modelling carried out in this assessment, cinacalcet is unlikely to be considered a cost effective intervention by NHS commissioners.

8 Appendices

8.1 Appendix 1: Renal registry reports of mortality risk according to serum phosphate, calcium and calcium-phosphate product[15]

Relative hazard of mortality by dialysis modality by phosphate levels.

Serum phosphate level mmol/L	Relative hazard of mortality – HD	Relative hazard of mortality - PD
0.9	1.05	1.07
1	1.03	1.05
1.1	1.02	1.03
1.2	1.01	1.02
1.3	1.01	1.00
1.4	1.00	1.00
1.5	1.00	1.00
1.6	1.01	1.00
1.7	1.01	1.00
1.8	1.03	1.01
1.9	1.05	1.02
2.0	1.06	1.04
2.1	1.09	1.06
2.2	1.11	1.08
2.3	1.15	1.11
2.4	1.18	1.15
2.5	1.22	1.20
2.6	1.27	1.25

Relative hazard of mortality by dialysis modality by calcium levels.

Serum calcium level mmol/L	Relative hazard of mortality – HD	Relative hazard of mortality - PD
2.0	1.08	1.08
2.5	1.04	1.04
3.0	1.00	1.00
3.5	1.00	1.00
4.0	1.00	1.00
4.5	1.03	1.00
5.0	1.05	1.03
5.5	1.09	1.07
6.0	1.14	1.12
6.5	1.23	1.2
7.0	2.12	2.12
7.5	2.13	2.05

Relative hazard of mortality by dialysis modality by calcium-phosphate product levels.

Serum calcium-phosphate product level mmol/L	Relative hazard of mortality – HD	Relative hazard of mortality - PD
2.0	1.02	1.07
2.5	1.00	1.03
3.0	1.00	1.00
3.5	1.00	1.00
4.0	1.00	1.00
4.5	1.02	1.05
5.0	1.07	1.09
5.5	1.12	1.17
6.0	1.19	1.29
6.5	1.29	1.46
7.0	1.41	1.76
7.5	1.57	2.26

8.2 Appendix 2: Expert advisory group

Ms. Caroline Ashley, Renal Pharmacist, Royal Free Hospital

Dr. Henry Brown, Consultant Nephrologist, Belfast City Hospital

Prof. Terry Feest, Professor of Nephrology, Richard Bright Renal Unit, University of Bristol

Dr. Jonathan Kwan, Clinical Director of Renal Services, SW Thames Renal & Transplantation Unit, St. Helier Hospital

Prof. Alison MacLeod, Professor of Nephrology, Dept. of Medicine & Therapeutics, University of Aberdeen

Dr. Paul Roderick, Senior Lecturer in Public Health, Cochrane Renal Group, Centre for Kidney Research, University of Sydney

Dr. R.J. Winney, Consultant Nephrologist, (Retired), Royal Infirmary of Edinburgh

8.3 Appendix 3: Protocol.

Technology Assessment Report commissioned by the NHS R&D HTA Programme on behalf of the National Institute for Health and Clinical Excellence

Protocol

August 2005

1. PROJECT TITLE

The Effectiveness and Cost-Effectiveness of Cinacalcet for the Treatment of Hyperparathyroidism Secondary to Impaired Renal Function

2. PROJECT TEAM

Ruth Garside[1]	Research Fellow (Lead)
Dr Martin Pitt[1]	Research Fellow
Stuart Mealing[1]	Research Assistant
Dr Rob Anderson[1]	Senior Lecturer in Health Economics
Karen Welch[2]	Information Officer
Joanne Perry[1]	Programme Administrator
Dr Richard D'Souza[3]	Consultant Nephrologist
Dr Ken Stein[1]	Senior Lecturer in Public Health

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3. Plain English Summary

This project will review the evidence for the use of cinacalcet, a new treatment for hyperparathyroidism, which is a common complication of renal failure. Hyperparathyroidism disrupts the body's biochemical balance and may result in a range of symptoms; fractures sustained without significant trauma; problems with blood vessels and the heart; and increased risk of death. The assessment report will draw together all relevant evidence on cinacalcet in a systematic review. It will also assess whether the introduction of cinacalcet is likely to represent good value for money to the NHS.

4. Decision problem

Purpose

The purpose of the report is to support the NICE Appraisal Committee in the development of Guidance for the NHS in England and Wales on the use of cinacalcet.

Cinacalcet

Cinacalcet (Mimpara®) is indicated for the treatment of secondary hyperparathyroidism in patients with end stage renal disease on maintenance dialysis therapy. It is the first of a new class of calcimimetic drugs, which acts by increasing parathyroid sensitivity to serum calcium to reduce secretion of parathyroid hormone (PTH). This, in turn, reduces serum calcium. Cinacalcet received marketing approval in October 2004.[100]

Cinacalcet is a first-in-class agent and so has no direct comparator. Vitamin D and phosphate binders are used to ameliorate the effects of increased PTH secretion in CKD. In some cases of advanced hyperparathyroidism, where parathyroidectomy may be considered, there is interest in whether cinacalcet may obviate or delay the need for surgery. Cinacalcet is an oral preparation, with dosage titrated according to PTH response up to 180mg per day.

Hyperparathyroidism in Chronic Kidney Disease

Secondary hyperparathyroidism is common in chronic kidney disease (CKD).[1] It may develop early in CKD, at glomerular filtration rates (GFR) of less than 60 mL/min, as a response to reduced serum calcium, and progresses as renal function deteriorates. The pathogenesis of hyperparathyroidism in CKD is complex and incompletely understood. A range of factors have been implicated[101]:

- Reduced serum calcium
- Increase in plasma phosphate levels
- Decreased vitamin D activity through a range of possible effects (e.g. reductions in renal calcitriol synthesis and reserve capacity and reduced parathyroid responsiveness to calcitriol)
- Parathyroid tissue hyperplasia in response to uraemia
- Altered parathyroid sensitivity to plasma calcium

Elevated PTH levels from secondary hyperparathyroidism are seen in around 40% of patients on dialysis.[3] Very high levels of PTH may develop in uncontrolled hyperparathyroidism (>800 pg/mL), with nodular hyperplasia of the parathyroid glands. In such cases, parathyroidectomy may be considered. Around 10% of people on dialysis have such increased levels of PTH.[3]

Parathyroid stimulation in CKD has a range of clinical consequences, mediated by increased PTH synthesis and PTH-secreting cell proliferation.[1] PTH increases osteoclast activity and bone resorption, leading to high turnover bone disease, which may include the typical features of osteitis fibrosa. High turnover bone disease may be present in up to 75% of people on dialysis and results in raised serum calcium, phosphate and calcium-phosphate product (Ca-PP). Fracture risk may be increased[3]. Treatment with vitamin D and phosphate binding agents may result in over-suppression of PTH so that bone turnover is reduced, resulting in adynamic bone disease. This predisposes to hypercalcaemia and may also be associated with pathological fractures.

Secondary hyperparathyroidism may also be complicated by calcification at a range of sites. Of particular interest is cardiovascular calcification, possibly related to elevated calcium-phosphate product. Direct effects on the heart, resulting in left ventricular hypertrophy and

dysfunction may also result from raised PTH levels. These effects account for a proportion of the increased overall and cardiovascular mortality noted in people with CKD.[102]

Symptoms of hyperparathyroidism include tiredness, malaise, muscle weakness, bone and joint pain, abdominal pain, weakness, pruritis.

The Renal Association Register has demonstrated considerable variation in serum phosphate, calcium and PTH control in the UK[12]. In particular, phosphate control is considered to be poor and wide variation in levels of PTH are noted in relation to the Renal Association recommendation that PTH concentration should be three to four times the upper limit of the assay used. The Renal Association Standard does not suggest that there is any clinical risk from over-suppression of PTH.[12]

Current management and place of cinacalcet

Prophylaxis is considered appropriate in asymptomatic patients with hyperparathyroidism as bone changes and parathyroid hyperplasia may be difficult or impossible to reverse.[1;101] National and international guidelines support the attainment of target levels for serum PTH, calcium and phosphate concentrations.[9;103;104] The main approaches to treatment are:

- Reduction in serum phosphate by the use of phosphate binding agents and, to a lesser extent, dietary restriction
- Reduction in PTH by supplementation of vitamin D

The optimum choice of phosphate binding agent is unclear. Aluminium containing agents (e.g. aluminium hydroxide or aluminium carbonate) may contribute to increased aluminium toxicity and are discouraged.[9] Calcium-containing binders (e.g. calcium carbonate or calcium acetate) were the mainstay of treatment until the development of concerns about associated risk of vascular calcification in people on haemodialysis.[1] Sevelamer hydrochloride is a non-calcium containing phosphate binder which also reduces serum lipid levels. It is licensed for use only in people on haemodialysis and is considerably more expensive than other phosphate binders. The Renal Association recommends that the choice of phosphate binding agent should be individualised to each patient.[9]

In cases of uncontrolled secondary hyperparathyroidism, typically with nodular parathyroid hypertrophy and very high levels of PTH, parathyroidectomy may be indicated.

Cinacalcet is an additional therapeutic option in hyperparathyroidism. The extent to which the need for other treatments may be reduced is unclear.

4. Report methods for synthesis of evidence of clinical effectiveness

The assessment report will include a systematic review of the evidence for clinical effectiveness of cinacalcet. The review will be undertaken systematically following the general principles published by the NHS Centre for Reviews and Dissemination.[63] The research protocol will be updated as necessary as the research programme progresses. Any changes to the protocol will be reported to NCCHTA and NICE.

Population

Inclusion criteria:

- People on peritoneal or haemodialysis for end stage renal failure of any underlying cause with hyperparathyroidism.

Exclusion criteria:

- People with CKD not on dialysis.

Interventions

- Cinacalcet HCl in licensed doses

Comparators

- "Standard care", which may include:
    - Phosphate binders
    - Vitamin D
    - Parathyroidectomy

Outcomes

The following outcomes will be included in the systematic review if reported in available primary studies.

- Mortality
- Incidence of cardiovascular events
- Incidence of fractures
- Health related quality of life
- Symptoms related to hyperparathyroidism

- Serum PTH, calcium, phosphate and calcium x phosphate product levels
- Parathyroidectomy
- Hospitalisation

Search Strategy and Inclusion Criteria

The search strategy will comprise the following main elements:

- Searching of electronic databases
- Contact with manufacturers of cinacalcet through the NICE
- Contact with experts in the field
- Scrutiny of bibliographies of retrieved papers

Databases:

Electronic databases: including MEDLINE (Ovid); PubMed (previous 6 months for latest publications); EMBASE (Ovid); The Cochrane Library including the Cochrane Systematic Reviews Database, CENTRAL, DARE, NHS EED and HTA databases; Biosis (EDINA); NRR (National Research Register); Web of Science: Science Citation Index (SCI) & ISI Proceedings; Current Controlled Trials; Clinical Trials.gov; FDA website; EMEA website.

Inclusion:

For the review of clinical effectiveness, only RCTs will be included. This criteria will be relaxed for consideration of adverse events, for which observational studies may be included.

Titles and abstracts will be examined for inclusion by two reviewers independently. Disagreement will be resolved by consensus.

Exclusion

- Non-randomised studies (except for adverse events)
- Animal models
- Preclinical and biological studies
- Narrative reviews, editorials, opinions
- Non-English language papers
- Reports published as meeting abstracts only, where insufficient methodological details are reported to allow critical appraisal of study quality

8.3.1.1

Data extraction strategy

Data will be extracted by one researcher and checked by another.

Quality assessment

Consideration of study quality will include the following factors:

Trial characteristics:

- Timing, duration and location of the study
- Method of randomisation
- Allocation concealment
- Blinding
- Numbers of participants randomized, excluded and lost to follow up.
- Whether intent to treat analysis is performed
- Methods for handling missing data
- Appropriateness of statistical analysis

Study participants:

- Baseline characteristics: age, sex, cause of ESRD, baseline laboratory values, use of phosphate binders and vitamin D
- Inclusion criteria
- Exclusion criteria

Methods of analysis/ synthesis

Data will be tabulated and discussed in a narrative review. Where appropriate, meta-analysis will be employed to estimate a summary measure of effect on relevant outcomes based on intention to treat analyses.

Meta-analysis will be carried out using fixed and random effects models, using STATA software. Heterogeneity will be explored through consideration of the study populations, methods and interventions, by visualisation of results and, in statistical terms, by the χ^2 test for homogeneity and the I^2 statistic.

5. Report methods for synthesising evidence of cost-effectiveness

The sources detailed in section 4 will be used to identify studies of the cost effectiveness of cinacalcet. Stand alone cost analyses based in the UK NHS will also be sought. We consider it very unlikely that cost effectiveness analyses will have been published in the scientific literature at this early point in the diffusion of cinacalcet. Contact with the manufacturers of cinacalcet, and other agencies (e.g. INAHTA) are more likely to identify relevant evaluations.

Available cost effectiveness analyses will be critically appraised using the frameworks established by the Consensus on Health Economic Criteria[105] and the International Society for Pharmacoeconomics and Outcomes Research (ISPOR).[106]

In addition, a new economic evaluation will be carried out from the perspective of the UK NHS using a decision analytic modelling approach. Model structure will be determined in consultation with clinical experts and will include the longer term consequences of hyperparathyroidism (fractures, cardiovascular events and mortality), if appropriate data are available. Further literature searches will be carried out to identify studies which relate serum PTH and biochemistry to these longer term outcomes. As the evidence base for long term use of cinacalcet is extremely limited, a range of assumptions will be made regarding sustained effectiveness. If possible, impact on the need for parathyroidectomy will be included.

Resource use will be specified and valued from the perspective of the NHS in 2004. Cost data will be extracted from published work, NHS reference costs and sponsor submissions to NICE as appropriate. If insufficient data are retrieved from published sources, costs may be derived from individual NHS Trusts or groups of Trusts. Costs will be discounted at 3.5%.

Health related quality of life will be incorporated by the application of preference weights (utility) to disease states. Utility values will be sought using the sources detailed in section 4. Outcomes will be discounted at 3.5%.

The evaluation will be constrained by available evidence. If possible, the incremental cost effectiveness of cinacalcet will be estimated in terms of:

- cost to achieve normalisation of PTH
- cost per event avoided (fracture, cardiovascular event)
- cost per life year gained

- cost per QALY.

Analysis of uncertainty will focus on cost utility, assuming cost per QALY can be estimated. Uncertainty will be explored through one way sensitivity analysis and, if the data and modelling approach permit, probabilistic sensitivity analysis (PSA). The outputs of PSA will be presented using plots on the cost effectiveness plane and cost effectiveness acceptability curves.

6. Handling the company submission(s)

Information provided by sponsors will be included in the report if, in the judgement of the assessment group, it meets relevant inclusion criteria.

A critique of any economic evaluations, including models, submitted by industry will be carried out using the frameworks established by the Consensus on Health Economic Criteria[105] and the International Society for Pharmacoeconomics and Outcomes Research (ISPOR).[106]

Any data designated as “commercial in confidence” or “academic in confidence” in sponsor submissions and incorporated in the assessment report will be highlighted and the source identified.

7. Competing interests of authors

Dr Richard D’Souza received an honorarium from Amgen in 2004 for making a presentation to clinical nephrology staff in Devon on secondary hyperparathyroidism and its management.

8.4 Appendix 4: Search strategy

Clinical searches **Databases and years searched**	**Date searched and search files**
Medline (OVID) 1966-2006	1. cinacalcet.tw. 2. (mimpara or sensipar).tw. 3. (AMG adj "073").mp. 4. calcimimetic$1.tw. 5. 1 or 2 or 3 or 4 6. hyperparathyroidism secondary/ 7. "secondary hyperparathyroidism".tw. 8. kidney failure chronic/ 9. "ESRD".tw. 10. renal dialysis/ 11. hemodialysis/ 12. peritoneal dialysis/ 13. peritoneal dialysis continuous ambulatory/ 14. "CAPD".tw. 15. kidney diseases/ 16. "chronic kidney disease$1".tw. 17. "CKD".tw. 18. renal osteodystrophy/ 19. phosphorus/bl 20. calcium/bl 21. Hypocalcemia/ 22. parathyroid hormone/ 23. "PTH".tw. 24. parathyroid glands/ 25. or/6-24 26. 5 and 25 27. vitamin d/tu, dt 28. lanthanum/ 29. phosphates/ 30. "vitamin D analogue$1".tw. 31. calcitriol.tw. 32. receptors calcitriol/ 33. receptors calcium sensing/ 34. doxercalciferol.tw. 35. paracalcitol.tw. 36. zemplar.tw. 37. alfacalcidol.tw. 38. falecalcitriol.tw. 39. alfacalcidol.tw. 40. hydroxycalciferol$1.tw. 41. ergocalciferols/ 42. (sevelamer or RenaGel).tw. 43. or/27-42

	44. 5 and 43 45. 26 or 44 46. parathyroidectomy/ 47. 5 and 46 48. (surviv$3 or outcome or mortality or morbidity).tw. 49. quality of life/ 50. HRQOL.tw. 51. mortality/ 52. morbidity/ 53. or/48-52 54. 5 and 53 55. 45 or 54 56. limit 55 to humans
Embase (OVID) 1980-2006	1. cinacalcet/ 2. cinacalcet.tw. 3. (mimpara or senispar).tw. 4. (AMG adj1 "073").tw. 5. calcimimetic$1.tw. 6. calcimimetic agent/ 7. or/1-6 8. secondary hyperparathyroidism/ 9. chronic kidney failure/ 10. "ESRD".tw. 11. dialysis/ 12. hemodialysis/ 13. peritoneal dialysis/ 14. continuous ambulatory peritoneal dialysis/ 15. "CAPD".tw. 16. kidney disease/ 17. "chronic kidney disease$1".tw. 18. "chronic renal disease$1".tw. 19. "CKD".tw. 20. renal osteodystrophy/ 21. hypocalcemia/ 22. parathyroid hormone/ 23. "PTH".tw. 24. parathyroid gland/ 25.or/ 8-24 26. 7 and 25 27. vitamin d derivative/ 28. lanthanum carbonate/ 29. phosphate binding agent/ 30. calcitriol/ 31. calcitriol receptor/ 32. calcitriol derivative/ 33. receptors calcitriol/ 34. doxercalciferol/ 35. paricalcitol/ 36. zemplar.tw.

	37. alfacalcidol/ 38. falecalcitriol/ 39. oxacalcitriol/ 40. "25 hydroxycalciferol"/ 41. calcium carbonate/ 42. calcium acetate/ 43. calcium sensing receptor/ 44. sevelamer hydrochloride/ 45. (Sevelemar or RenaGel).tw. 46. or/27-45 47. 7 and 46 48. parathyroidectomy/ 49. 7 and 48 50. (surviv$3 or outcome or mortality or morbidity).tw. 51. quality of life/ 52. HRQOL.tw. 53. HRQOL.ti. 54. wellbeing/ 55. 7 and (50 or 51 or 52 or 53 or 54) 56. 26 or 47 or 49 or 55 57. limit 56 to human 58. from 57 keep 1-233
Quality of Life and Economic searches	
Databases.Yrs searched	**Date searched and search files**
Medline (OVID) **1995-2006**	Utility Values Parathyroidectomy 1995-2006 1 parathyroidectomy/ 2 parathyroidectomy.ti,ab. 3 1 or 2 4 utility value$1.ti,ab. 5 utility analys$.ti,ab. 6 cost utility.ti,ab. 7 (health adj5 utility).ti,ab. 8 utility assessment$.ti,ab. 9 utility difference$.ti,ab. 10 (time trade$ or time tradeoff or timetradeoff).ti,ab. 11 TTO.ti,ab. 12 trade off index score$.ti,ab. 13 standard gamble$.ti,ab. 14 (utility measure or utility scor$).ti,ab. 15 quality weight$.ti,ab. 16 cost of illness/ 17 utility loss.ti,ab. 18 factor analysis statistical/ 19 sickness impact profile/ 20 everett rogers$.ti,ab. 21 DOI.ti,ab. 22 diffusion of innovation$.ti,ab. 23 willingness to pay.ti,ab. 24 *health status/ 13338

	25 (health state adj5 value$).ti,ab. 26 (utility adj5 value$).ti,ab. 27 or/4-26 28 3 and 27
1995-2006	<u>Utility Values MI 1995-2006</u> 1 utility value$1.ti,ab. 2 utility analys$.ti,ab. 3 cost utility.ti,ab. 4 (health adj5 utility).ti,ab. 5 utility assessment$.ti,ab. 6 utility difference$.ti,ab. 7 (time trade$ or time tradeoff or timetradeoff).ti,ab. 8 TTO.ti,ab. 9 trade off index score$.ti,ab. 10 standard gamble$.ti,ab. 11 (utility measure or utility scor$).ti,ab. 12 quality weight$.ti,ab. 13 cost of illness/ 14 utility loss.ti,ab. 15 factor analysis statistical/ 16 sickness impact profile/ 17 everett rogers$.ti,ab. 18 DOI.ti,ab. 19 diffusion of innovation$.ti,ab. 20 willingness to pay.ti,ab. 21 *health status/ 22 (health state adj5 value$).ti,ab. 23 (utility adj5 value$).ti,ab. 24 or/1-23 25 myocardial infarction/ 26 24 and 25 27 *myocardial infarction/ 28 24 and 27
1995-2006	29 limit 28 to (humans and english language) 31 limit 29 to yr="1995 - 2005"
	<u>Fractures Spontaneous Utility Values 1995-2006</u> 1 utility value$1.ti,ab. 2 utility analys$.ti,ab. 3 cost utility.ti,ab. 4 (health adj5 utility).ti,ab. 5 utility assessment$.ti,ab. 6 utility difference$.ti,ab. 7 (time trade$ or time tradeoff or timetradeoff).ti,ab. 8 TTO.ti,ab. 9 trade off index score$.ti,ab. 10 standard gamble$.ti,ab.

1966-2006	11 (utility measure or utility scor$).ti,ab. 12 quality weight$.ti,ab. 13 cost of illness/ 14 utility loss.ti,ab. 15 factor analysis statistical/ 16 sickness impact profile/ 17 everett rogers$.ti,ab. 18 DOI.ti,ab. 19 diffusion of innovation$.ti,ab. 20 willingness to pay.ti,ab. 21 *health status/ 22 (health state adj5 value$).ti,ab. 23 (utility adj5 value$).ti,ab. 24 or/1-23 25 fractures spontaneous/ 26 pathological fracture$.ti,ab. 27 25 or 26 5327 28 24 and 27 10 29 from 28 keep 1-10 30 (osteoporosis adj5 fracture$).ti,ab. 31 24 and 30 40 32 fractures/ 30477 33 dialysis/ 10281 34 hyperparathyroidism secondary/ 35 kidney failure chronic/ 36 ESRD.ti,ab. 37 end stage renal disease.ti,ab. 38 renal osteodystrophy/ 39 renal dialysis/ 40 hemodialysis/ 41 peritoneal dialysis/ 42 or/33-41 43 32 and 42 44 24 and 43 45 29 or 31 46 limit 45 to (humans and english language) 47 limit 46 to yr="1995 - 2005" <u>Cost Effectiveness Medline 1966-2006</u> 1 exp economics/ 2 exp economics hospital/ 3 exp economics pharmaceutical/ 4 exp economics nursing/ 5 exp economics medical/ 6 exp "costs and cost analysis"/ 7 value of life/ 8 exp models economic/ 9 exp fees/ and charges/ 10 exp budgets/

	11 (economic$ or price$ or pricing or pharmacoeconomic$ or pharmaeconomic$).tw. 12 (cost$ or costly or costin$ or costed).tw. 13 (cost$ adj2 (benefit$ or utilit$ or minim$)).tw. 14 (expenditure$ not energy).tw. 15 (value adj2 (money or monetary)).tw. 16 budget$.tw. (9480) 17 (economic adj2 burden).tw. 18 "resource use".ti,ab. 19 or/1-18 20 letter.pt. 21 editorial.pt. 22 comment.pt. 23 or/20-22 24 19 not 23 25 exp hyperparathyroidism/ 26 "secondary hyperparathyroidism".ti,ab. 27 hyperparathyroidism secondary/ 28 or/25-27 29 ESRD.ti,ab. 30 "end stage renal disease$".ti,ab. 31 dialysis/ 32 dialysis.ti,ab. 33 hemodialysis/ 34 peritoneal dialysis/ 35 peritoneal dialysis continuous ambulatory/ 36 CAPD.ti,ab. 37 "chronic kidney disease$".ti,ab. 38 "chronic renal disease$".ti,ab. 39 "chronic kidney failure".ti,ab. 40 "chronic renal failure".ti,ab. 41 or/29-40 42 24 and 28 and 41 43 limit 42 to (humans and english language)
Embase (OVID) **1980-2006**	Utility Values Parathyroidectomy 1980-2006 1 parathyroidectomy/ 2 parathyroidectomy.ti,ab. 3 1 or 2 4 utility value$1.ti,ab. 5 utility analys$.ti,ab. 6 cost utility.ti,ab. 7 (health adj5 utility).ti,ab. 8 utility assessment$.ti,ab. 9 utility difference$.ti,ab. 10 health care utilization/ 11 health state utility values/ 12 (time trade$ or time tradeoff or timetradeoff).ti,ab. 13 TTO.ti,ab. 14 wilcoxon signed ranks test/

	15 trade off index score$.ti,ab. 16 standard gamble$.ti,ab. 17 or/4-16 17493 18 3 and 17 19 linear regression analysis/ 20 3 and 19 21 18 or 20
1980-2006	<u>Utility Values Fracture Spont 1980-2006</u> 1 spontaneous fracture$.ti,ab. 2 pathologic fracture/ 3 pathologic$ fracture.ti,ab. 4 1 or 2 or 3 5 utility value$.ti,ab. 6 utility analys$.ti,ab. 7 cost utility.ti,ab. 8 (health adj5 utility).ti,ab. 9 utility assessment$.ti,ab. 10 utility difference$.ti,ab. 11 (time trade off or timetradeoff or timetrade off).ti,ab. 12 TTO.ti,ab. 13 trade off index scor$.ti,ab. 14 standard gamble$.ti,ab. 15 (utility measure or utility scor$).ti,ab. 16 quality weight$.ti,ab. 17 utility loss.ti,ab. 18 or/5-17
1995-2006	19 4 and 18 <u>Utility Values MI 1995-2006</u> 1 utility value$.ti,ab. 2 utility analys$.ti,ab. 3 cost utility.ti,ab. 4 (health adj5 utility).ti,ab. 5 utility assessment$.ti,ab. 6 utility difference$.ti,ab. 7 (time trade off or timetradeoff or timetrade off).ti,ab. 8 TTO.ti,ab. 9 trade off index scor$.ti,ab. 10 standard gamble$.ti,ab. 11 (utility measure or utility scor$).ti,ab. 12 quality weight$.ti,ab. 13 utility loss.ti,ab. 14 or/1-13 15 myocardial infarction.ti. 16 heart infarction/ 17 acute heart infarction/ 18 myocardial infarction.ti,ab. 19 14 and (15 or 16 or 17 or 18)

1980-2006	20 limit 19 to (human and english language) 21 limit 20 to yr="1995 - 2005" 37 DISPLAY <u>Cost Effectiveness Embase 1980-2006</u> 1 (cost$ adj2 effective$).ti,ab. 2 (cost$ adj2 benefit$).ti,ab. 3 cost effectiveness analysis/ 4 cost benefit analysis/ 5 budget$.ti,ab. 6 cost$.ti. 7 (cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$)).ab. 8 (economic$ or pharmacoeconomic$ or pharmaco economic$).ti. 9 (price$ or pricing$).ti,ab. 10 (financial or finance or finances or financed).ti,ab. 11 (fee or fees).ti,ab. 12 cost/ 13 cost minimization analysis/ 14 cost of illness/ 15 cost utility analysis/ 16 drug cost/ 17 health care cost/ 18 health economics/ 19 economic evaluation/ 20 economics/ 21 pharmacoeconomics/ 22 budget/ 23 "resource use".ti,ab. 24 economic burden.ti,ab. 25 or/1-24 26 (editorial or letter).pt. 27 25 not 26 28 ESRD.ti. 29 "end stage renal failure".ti. 30 dialysis/ 31 dialysis.ti,ab. 32 hemodialysis/ 33 peritoneal dialysis/ 34 exp hyperparathyroidism/ 35 secondary hyperparathyroidism/ 36 continuous ambulatory peritoneal dialysis/ 37 CAPD.ti,ab. 38 chronic kidney failure/ 39 "chronic renal disease$".ti,ab. 40 "chronic kidney disease$".ti,ab. 41 28 or 29 or 30 or 31 or 32 or 33 or 36 or 37 or 38 or 39 or 40 42 34 or 35 43 27 and 41 and 42 44 27 and 41 45 27 and 42

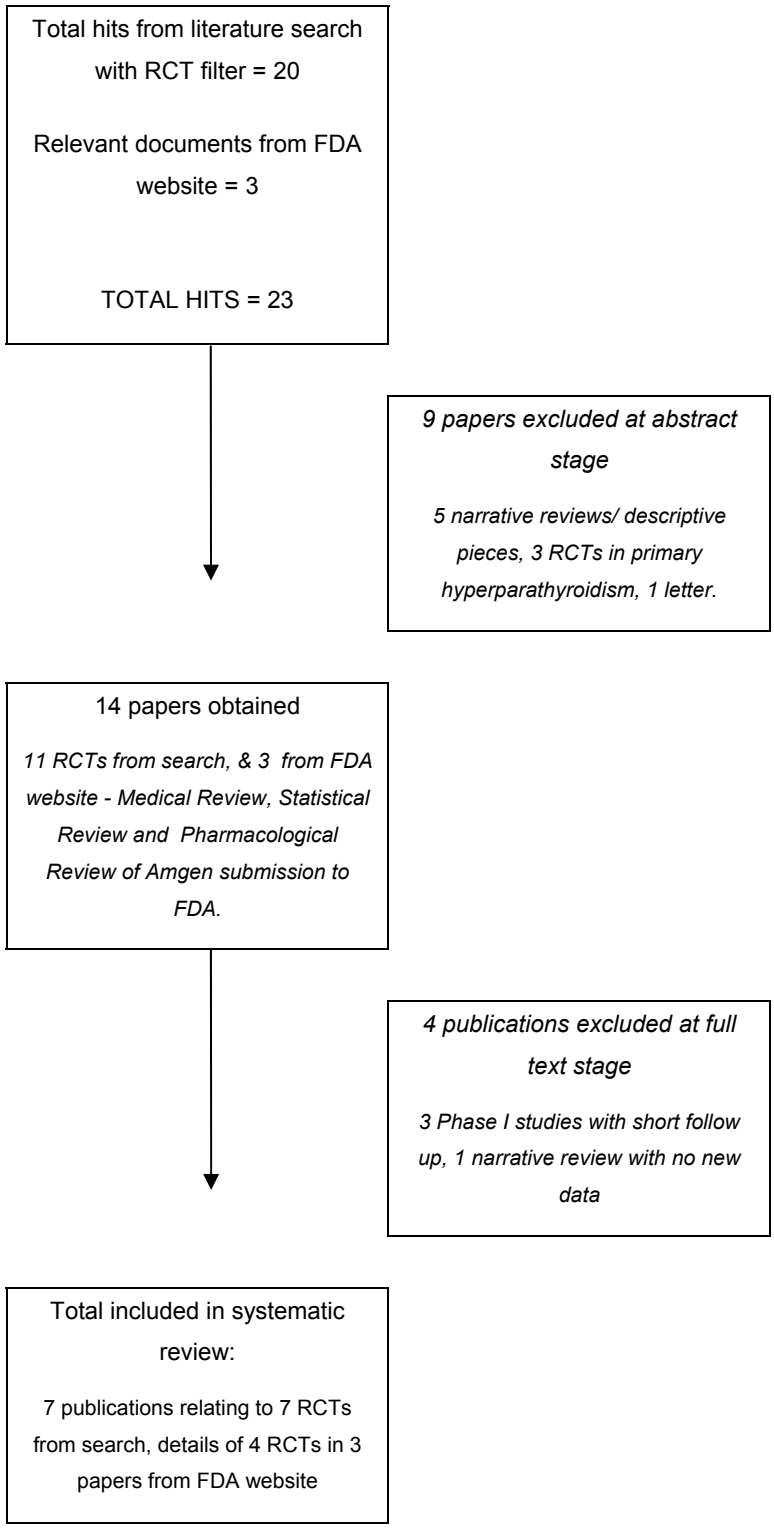
	46 parathyroidectomy/ 47 parathyroidectomy.ti,ab. 48 27 and (46 or 47) 49 limit 43 to (human and english language)
Epidemiology searches **Databases. Yrs searched**	**Date searched and search files**
Medline (OVID) **2000-2006**	1 hyperparathyroidism secondary/ep 2 *hyperparathyroidism secondary/et 3 hyperparathyroidism secondary/ 4 "secondary hyperparathyroidism".tw. 5 exp incidence/ 6 exp prevalence/ 7 (incidence or prevalence).tw. 8 exp risk-factors/ 173611 9 (etiolog$ or epidemiolog$ or aetiolog$).ti,ab. 10 1 or 2 11 or/5-9 12 11 and (3 or 4) 13 10 or 12 14 limit 13 to (humans and english language) 15 limit 14 to yr="2000 - 2005"
Embase (OVID) **2000-2006**	1 secondary hyperparathyroidism/ep 2 *secondary hyperparathyroidism/et 3 secondary hyperparathyroidism/ 4 "secondary hyperparathyroidism".tw. 5 (incidence or prevalence).tw. 6 (etiolog$ or epidemiolog$ or aetiolog$).ti,ab. 7 1 or 2 173 DISPLAY 8 (pathogenesis and hyperparathyroidism and secondary).ti. 9 (develop$ adj1 secondary adj1 hyperparathyroidism).ti. 10 (develop$ adj secondary adj1 hyperparathyroidism).ab. 11 3 and (5 or 6 or 8 or 9 or 10) 12 1 or 2 or 11 13 *secondary hyperparathyroidism/ 14 13 and (5 or 6 or 8 or 9 or 10) 15 1 or 2 or 14 16 limit 15 to (human and english language and yr="2000 - 2005") 17 limit 12 to (human and english language and yr="2000 - 2005") 18 (letter or editorial or comment).pt. 19 17 not 18
Risk Factors Modelling **Embase (Ovid) 1980-2006 and Medline (Ovid) 1966-2006**	**Combined Embase and Medline with deduplicated set** 1 esrd.tw. 2 "end stage renal disease".ti,ab. 3 *kidney failure chronic/ 4 *chronic kidney failure/

	5 or/1-4 6 dialysis/ or hemodialysis/ 7 CAPD.tw. 8 peritoneal dialysis/ or peritoneal dialysis continuous ambulatory/ 9 continuous ambulatory peritoneal dialysis/ 10 or/6-9 11 5 and 10 12 renal osteodystrophy/ 13 *fracture/ 14 *fractures/ 15 fracture.ti. 16 *cardiovascular disease/co, si 17 *cardiovascular diseases/et, me, co 18 (cardiovascular or cardiac or vascular).ti. 19 or/12-18 20 11 and 19 21 phosphate blood level/ 22 calcium blood level/ 23 hypercalcemia/si 24 calcium/ec 25 *mineral metabolism/ 26 phosphate/ec 27 phosphorus/bl 28 calcium/bl 29 or/21-28 30 20 and 29 31 risk.tw. 32 risk factors/ 33 time factors/ 34 risk assessment/ 35 risk factor/ 36 high risk population/ 37 disease severity/ 38 disease association/ 39 mortality/ or morbidity/ 40 "cardiovascular mortality".ti,ab. 41 "cardiovascular risk factor$1".ti,ab. 42 death.ti,ab. 43 or/31-42 44 30 and 43 45 limit 44 to english language 46 limit 45 to humans 47 from 46 keep 1-67 48 remove duplicates from 47 49 from 48 keep 1-66 50 from 48 keep 1-46 51 from 50 keep 1-46 52 from 48 keep 47-66 53 from 52 keep 1-20

	54 parathyroid hormone/ 55 20 and 43 and 54 56 limit 55 to english language 57 limit 56 to humans 58 57 not 48 59 remove duplicates from 58
Quality of Life searches	
Databases. Yrs searched	**Date searched and search files**
Medline (OVID) 1995-2006	Search 1 QOL - ESRD, Dialysis 1995-2006 1 "end stage renal failure".ti,ab 2 quality of life/ 3 (hrqol or qol).ti,ab. 4 quality adjusted life year/ 5 quality adjusted life.ti,ab. 6 (qaly$ or qald$ or qale$ or qtime$).ti,ab. 7 disability adjusted life.ti,ab. 8 daly$.ti,ab. 353 9 (euroqol or euro qol or eq5d).ti,ab. 10 (hql or hqol or h qol or hrqol or hr qol).ti,ab. 11 quality of well being.ti,ab. 12 quality of wellbeing.ti,ab. 13 qwb.ti,ab. 14 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab. 15 or/2-14 54094 16 esrd.ti,ab. 4437 17 dialysis.ti. 20099 18 end stage renal disease.ti,ab. 19 *renal dialysis/ 20 1 or 16 or 17 or 18 or 19 21 15 and 20 1073 DISPLAY 22 limit 21 to (humans and english language) 23 child/ 24 infant/ 25 22 not 23 26 25 not 24 27 (letter or editorial or comment).pt. 28 26 not 27 29 limit 28 to (humans and english language and yr="1995 - 2005") 30 limit 29 to yr="2000 - 2005"
Medline (OVID) 1996-2006	**Search Two on Medline 1966-2005 QOL - Primary or secondary hyperparathyroidism or parathyroidectomy** 1 quality of life/ 2 (hrqol or qol).ti,ab. 3 quality adjusted life year/ 4 quality adjusted life.ti,ab.

	5 (qaly$ or qald$ or qale$ or qtime$).ti,ab. 6 disability adjusted life.ti,ab. 7 daly$.ti,ab. 8 (euroqol or euro qol or eq5d).ti,ab. 9 (hql or hqol or h qol or hrqol or hr qol).ti,ab. 10 quality of well being.ti,ab. 11 quality of wellbeing.ti,ab. 12 qwb.ti,ab. 13 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab. 14 or/1-13 15 child/ 16 infant/ 17 (letter or editorial or comment).pt. 18 hyperparathyroidism secondary/ 19 "secondary hyperparathyroidism".ti,ab. 20 14 and (18 or 19) 21 from 20 keep 1-9 22 hyperparathyroidism/ 23 14 and 22 24 parathyroidectomy/ 25 14 and 24 26 20 or 23 or 25 27 KDQOL.ti,ab. 28 "kidney disease quality of life".ti,ab. 29 18 and (27 or 28) 30 19 and (27 or 28) 31 22 and (27 or 28) 32 24 and (27 or 28) 33 29 or 30 or 32 2 34 26 or 33 29 35 limit 34 to (humans and English language)

8.5 Appendix 5: Flow chart for included trials



8.6 Appendix 6: Excluded studies

Goodman WG, Frazao JM, Goodkin DA, Turner SA, Liu W, Coburn JW. A calcimimetic agent lowers plasma parathyroid hormone levels in patients with secondary hyperparathyroidism. Kidney International 2000; 58(1):436-445. Abstract: Background: The calcimimetic agent R-568 lowers plasma parathyroid hormone (PTH) levels in hemodialysis patients with mild secondary hyperparathyroidism, but its efficacy in those with more severe secondary hyperparathyroidism has not been studied. Methods: Twenty-one patients undergoing hemodialysis three times per week with plasma PTH levels between 300 and 1200 pg/mL were randomly assigned to 15 days of treatment with either 100 mg of R-568 (N = 16) or placebo (N = 5). Plasma PTH and blood ionized calcium levels were measured at intervals of up to 24 hours after oral doses on days 1, 2, 3, 5, 8, 11, 12, and 15. Results: Pretreatment PTH levels were 599 +/- 105 (mean +/- SE) and 600 +/- 90 pg/mL in subjects given R-568 or placebo, respectively, and values on the first day of treatment did not change in those given placebo. In contrast, PTH levels fell by 66 +/- 5%, 78 +/- 3%, and 70 +/- 3% at one, two, and four hours, respectively, after initial doses of R-568, remaining below pretreatment values for 24 hours. Blood ionized calcium levels also decreased after the first dose of R-568 but did not change in patients given placebo. Despite lower ionized calcium concentrations on both the second and third days of treatment, predose PTH levels were 422 +/- 70 and 443 +/- 105 pg/mL, respectively, in patients given R-568, and values fell each day by more than 50% two hours after drug administration. Predose PTH levels declined progressively over the first nine days of treatment with R-568 and remained below pretreatment levels for the duration of study. Serum total and blood ionized calcium concentrations decreased from pretreatment levels in patients given R-568, whereas values were unchanged in those given placebo. Blood ionized calcium levels fell below 1.0 mmol/L in 7 of 16 patients receiving R-568; five patients withdrew from study after developing symptoms of hypocalcemia, whereas three completed treatment after the dose of R-568 was reduced. Conclusions. The calcimimetic R-568 rapidly and markedly lowers plasma PTH levels in patients with secondary hyperparathyroidism caused by end-stage renal disease
Goodman WG, Hladik GA, Turner SA, Blaisdell PW, Goodkin DA, Liu W et al. The calcimimetic agent AMG 073 lowers plasma parathyroid hormone levels in hemodialysis patients with secondary hyperparathyroidism. J Am Soc Nephrol 2002; 13(4):1017-1024. Abstract: Treatment with vitamin D sterols can lower plasma parathyroid hormone (PTH) in many patients with secondary hyperparathyroidism due to end-stage renal disease, but hypercalcemia, hyperphosphatemia, or both often develop during treatment. As such, alternative therapeutic approaches to managing excess PTH secretion are needed. Calcimimetic agents directly inhibit PTH secretion by activating the calcium-sensing receptor in the parathyroid glands, but clinical experience with them is limited. Fifty-two hemodialysis patients with secondary hyperparathyroidism were given single orally administered doses of the calcimimetic agent AMG 073 ranging from 5 to 100 mg, or placebo. Plasma PTH levels decreased 2 h after 25-, 50-, 75-, or 100-mg doses, falling by a maximum of 43 +/- 29%, 40 +/- 36%, 54 +/- 28%, or 55 +/- 39%, respectively. Plasma PTH levels decreased in all patients given doses of >=25 mg but did not change in those who received placebo. In patients treated with daily doses of 25 or 50 mg of AMG 073 for 8 d, plasma PTH levels declined for the first 3 to 4 d and remained below baseline values after 8 d of treatment. Serum calcium concentrations also decreased by 5 to 10% from pretreatment levels in patients given 50 mg of AMG 073 for 8 d, but values were unchanged in those who received lower doses. Serum phosphorus levels and values for the calcium-phosphorus ion product both decreased after treatment with AMG 073. Thus, 8 d of treatment with AMG 073 effectively lowers plasma PTH levels and improves several disturbances in mineral metabolism that have been associated with soft tissue and vascular calcification and with adverse cardiovascular outcomes in patients with end-stage renal disease
Ohashi N, Uematsu T, Nagashima S, Kanamaru M, Togawa A, Hishida A et al. The calcimimetic agent KRN 1493 lowers plasma parathyroid hormone and ionized calcium concentrations in patients with chronic renal failure on haemodialysis both on the day of haemodialysis and on the day without haemodialysis. British Journal of Clinical Pharmacology 2004; 57(6):726-734. Abstract: Aims: Treatment with vitamin D sterols can lower plasma parathyroid hormone (PTH) in patients with secondary hyperparathyroidism; however, hypercalcaemia, hyperphosphataemia, or both, often develop. Calcimimetic agents, employed in alternative therapeutic approaches, directly inhibit PTH secretion by activating the calcium-sensing receptor in the

parathyroid glands. Methods: In this study, patients were given orally 25, 50, and 100 mg doses of the calcimimetic agent KRN 1493 each on two occasions, on the day of haemodialysis and on the day without haemodialysis. Results: In the pharmacokinetic results, because the clearance of KRN 1493 by haemodialysis was much smaller than the systemic clearance, the influence of haemodialysis was not remarkable. In the pharmacodynamic study, on both the days with or without haemodialysis, plasma PTH concentrations decreased in a dose-dependent manner. Serum calcium concentrations decreased in association with the decrease in plasma PTH concentrations. Mild dose-dependent adverse effects (mainly nausea) were seen after the administration of KRN 1493 on both the day of haemodialysis and the day without haemodialysis. Conclusions: We conclude that the pharmacokinetics of KRN 1493 after a single administration were similar on the day of haemodialysis and the day without haemodialysis. KRN 1493 is safe and effective in suppressing PTH secretion and serum calcium concentrations on the day of haemodialysis and on the day without haemodialysis in patients with secondary hyperparathyroidism

Szczech LA. The impact of calcimimetic agents on the use of different classes of phosphate binders: results of recent clinical trials. [Review] [8 refs]. Kidney International - Supplement 2004;(90):S46-S48.

Abstract: Calcimimetic agents bind to and activate the calcium-sensing receptor in the parathyroid glands, lowering the threshold for its activation by extracellular calcium and diminishing parathyroid hormone release from parathyroid cells. In three large randomized, controlled trials, cinacalcet given at doses of 30 to 180 mg orally each day was associated with effective reduction in parathyroid hormone levels over 26 weeks compared with placebo, and was consistently associated with a decrement in serum calcium, phosphorus levels, as well as a decrement in calcium-phosphorus product. In one study, there was a 5% incidence of hypocalcemia (serum calcium levels < 7.5 mg/dL on at least two consecutive measurements) among patients receiving cinacalcet, and less than 1% of patients receiving standard therapy (P < 0.0001). While there were no demonstrated differences between groups with regard to use of phosphate binders and vitamin D sterols in these randomized controlled trials, arguably, the combination of the effects on serum calcium, phosphorus, and calcium-phosphorus product may bring increased focus on the increased mortality risk associated with hypocalcemia.

8.7 Appendix 7: Data extraction tables

STUDY	INTERVENTION
Block *et al*., 2004 ***Country:*** International: North America, Europe and Australia ***Setting:*** Multiple centres (125 sites) ***Recruitment dates:*** December 2001 – January 2003 ***Study design:*** Combined analysis of two identical phase 3 randomised, double-blind, placebo-controlled trials	After screening period, subjects were randomised to cinacalcet or placebo Intervention: Cinacalcet Intervention regimen: 12 week dose titration phase ▪ Subjects initially received 30 mg Cinacalcet (or placebo) orally, once daily. ▪ Doses were increased sequentially every 3 weeks during the dose-titration phase to 60, 90, 120 and 180

SUBJECTS

Total number: 741

Cinacalcet n = 371; Placebo n = 370

Inclusion criteria:

- Mean plasma iPTH level of ≥31.8 pmol/L established by three measurements obtained within a 30-day screening period
- 18 years of age or older and in medically stable condition.
- Treated with haemodialysis 3 times/week for at least 3 months

Exclusion criteria:

- Evidence of cancer, active infection, diseases known to cause hypercalcaemia, or serum Ca^{2+} level ≤2.1 mmol/L, corrected for albumin.
- Subjects receiving drugs such as flecainide, thioridazine, and most tricyclic antidepressants, which have a narrow therapeutic index and are metabolised by P-450 2D6

mg once daily

- o Increases in dose were permitted if:
  - iPTH ≥ 21.2 pmol/L, and
  - serum Ca^{2+} ≥ 1.95 mmol/L.
- o Dose was not increased if:
  - symptoms of hypocalcaemia or
  - serum Ca^{2+} < 1.95 mmol/L or
  - adverse event that precluded an increase in the dose.
- o The dose was reduced if:
  - iPTH < 10.6 pmol/L on three consecutive study visits or
  - adverse event requiring a reduction in the dose.

14 week efficacy-assessment phase

- Dose adjustments were permitted at 4 week intervals as above

Comparator regimen:

Placebo

Concurrent treatment:

- Concurrent phosphate binder permitted without restriction
- Vitamin D sterols permitted
  - o Dose increase permitted if:
    - iPTH increased by >50% from baseline or
    - Serum Ca^{2+} < 2.1 mmol/L or
    - Symptomatic hypocalcaemia
  - o Dose reduction permitted if:
    - Serum Ca^{2+} ≥ 2.75 mmol/L or
    - Serum phosphorus ≥ 2.1 mmol/L or
    - Ca x P ≥ 5.65 $mmol^2/L^2$ or
    - iPTH < 10.6 pmol/L on three consecutive study visits and the subject was on the lowest dose of cinacalcet

Notes:

Proportion of subjects with PTH >84.8 pmol/L was limited to 20% of the total

SUBJECT CHARACTERISTICS

	Placebo	Cinacalcet
N:	370	371
Age:	55 (15)	54 (14)
Sex:		
M	62	61
F	38	39
Race:		
White	61	56
Black	32	35
Other	7	9
Duration of dialysis (months): mean (SD)	72 (68)	72 (63)
Concomitant diabetes (%)	29	30
Use of vitamin D sterols (%)	67	66
Use of phosphate binders (%)	93	92

OUTCOME MEASURES

Primary outcome measure:

- Proportion of subjects achieving mean PTH level of ≤ 26.5pmol/L during efficacy-assessment phase.

Secondary measures:

- Proportion of subjects with reduction from baseline of ≥30% in mean PTH
- Percent change in values for
  - o PTH
  - o Ca^{2+}
  - o phosphorus
  - o Ca x P.

Method of assessing outcomes:

- Plasma PTH levels, serum Ca^{2+} and phosphorus levels were measured at each study visit before haemodialysis.
  - o Plasma PTH levels were measured using Nichols Allegro immunometric assay
  - o Full length PTH was measured using Nichols BioIntact PTH assay
- Serum levels of bone-specific alkaline phosphatase were measured at baseline and 26 weeks
  - o Bone-specific alkaline phosphatase was measured using Tandem-R Ostase two-site immunoradiometric assay
- Biochemical measurements were made at three regional reference laboratories (Europe, North America, Australia)

Length of follow-up:

Study duration 26 weeks

RESULTS

PRIMARY OUTCOMES	Placebo (N = 370)	Cinacalcet (N = 371)	P value
Mean PTH ≤250pg/mL	19 (5%)	160 (43%)	P<0.001

SECONDARY OUTCOMES	Placebo (N= 370)	Cinacalcet (N = 371)	P value
≥30% reduction in PTH level	42 (11%)	239 (64%)	P<0.001

≥30% reduction in PTH level (%) stratified according to baseline PTH level:			
o 300-500 pg/ml	10%	61%	P<0.001
o 501-800pg/ml	15%	69%	P<0.001
o >800 pg/ml	7%	63%	P<0.001

Biochemistry results	Placebo	**from graph		Mean ± SE		Cinacalcet	**from graph		Mean ± SE		
	Baseline	Wk 12	Wk 26	Wk 13-26	% change	Baseline	Wk 12	Wk 26	Wk 13-26	% change	P value
Plasma PTH (pg/mL)	642 ±19	680	660	693 ± 23	9 ± 2	643 ± 18	380	340	374 ± 19	-43 ± 2	<0.001 between groups
Plasma full length PTH (pg/mL) (N. American subjects only n = 410)	337 ±16	375	375	396 ± 18	23 ± 4	326 ± 14	200	200	200 ± 15	-38 ± 3	<0.001 between groups
Serum Ca2+ (mg/dL)	9.9 ±0.0			9.9 ± 0.0	0.4 ±0.3	9.9 ± 0.0			9.2 ± 0.0	- 6.8±0.4	<0.001 between groups
Serum Phosphorus (mg/dL)	6.2 ±0.1			6.0 ± 0.1	0.2 ±1.3	6.2 ± 0.1			5.6 ± 0.1	-8.4 ± 1.3	<0.001 between groups
Calcium - phosphorus product $(mg/dL)^2$	61 ± 0.8	59	60	60 ± 0.8	0.5 ±1.3	62 ± 0.8	48	53	51 ± 0.8	-14.6 ±1.3	<0.001 between groups
Bone specific alkaline phosphate (ng/ml) Median (interquartile range)	24.2 (16.5 – 36.8)		22.6 (14.3-36.4)		– 4 (– 32.1 to 29.6)	23.3 (16.5 – 35.3)		15.6 (9.8-23.6)		– 35.1 (–58.6 to – 1.7)	
PTH level <250pg/ml (% of subjects)		7%	8%				46%	58%			
% change in PTH level (relative to baseline)	0	9%	9%		9 ± 2	0	- 46%	- 48%		-43 ± 2	<0.001 between groups

	Placebo	Cinacalcet	
Adverse Events			
Mortality	2%	2%	
Withdrawal due to adverse events	7%	15%	
Withdrawal due to nausea or vomiting	<1%	<5%	
≥1 adverse event reported	346/369 (94%)	333/365 (91%)	P=0.21
Nausea	19%	32%	P<0.001
Vomiting	16%	30%	P<0.001
URTI	13%	7%	P=0.007
Hypotension	12%	6%	P=0.014
Serum Ca^{2+} <7.5mg/dL on at least 2 consecutive measurements	<1%	5%	P<0.001

METHODOLOGICAL COMMENTS

Selection / randomisation: Randomisation methods not detailed
Stratification according to disease severity and baseline values for Ca x P.
No more than 20% population could have PTH > 84.8 pmol/L

Groups similar at baseline? Yes. No significant differences but 5% more white race in placebo group and 4%more were using calcium containing only phosphate binders

Eligibility criteria stated? Yes

Blinding: Stated as double blind.
Method not detailed

Outcome measures: Objective

ITT: Yes

Protocol violations specified: No

Follow-up / attrition:

All subjects accounted for?

No, 32% cinacalcet subjects did not complete 26 weeks treatment. Reasons for 25% subject's withdrawal provided.

22% placebo subjects did not complete 26 weeks treatment. Reasons for 16% subject's withdrawal provided.

Withdrawal specified?

	Placebo	Cin
Completed titration	325	306
Completed full 26 weeks	78%	68%
Discd due to A/E	7%	15%
Withdrew consent	3%	4%
Kidney transplant	4%	4%
Died	2%	2%

Data analysis:

Statistical tests used:

- Combined analysis of two phase 3 randomised, double-blind controlled trials
- Cochran-Mantel-Haenszel test, stratified according to baseline PTH levels and Ca x P values, was used to examine differences between treatment groups during the efficacy-assessment phase.
- Generalised Cochran-Mantel-Haenszel test was used for continuous variables
- Cochran-Mantel-Haenszel tests were used to estimate relative risk of primary end point in cinacalcet group, as compared with placebo, according to age, sex, race, duration of dialysis, baseline biochemical variable, presence or absence of diabetes, and use of vitamin D sterols.
- Logistic regression was used to identify factors that predicted a reduction in parathyroid hormone value of at least 30%.
- T-tests used to compare efficacy period with baseline for continuous variables

Power calculation at design?

Not stated

Generalisability:

Few exclusion criteria stated in publication.

High proportion of non-Caucasians.

No more than 20% population could have PTH >84.8 pmol/L

Conflict of interest:

Studies supported by Amgen.

Trial and lead authors substantially funded by Amgen and other pharmaceutical companies.

GENERAL COMMENTS

COMBINED ANALYSIS OF 2000172 and 2000183

STUDY	INTERVENTION
Cunningham *et al*., 2005] ***Country:*** ***Pooled analysis of 4 trials*** ***International: Europe, North America and Australia*** ***Study 1 – United States and Europe*** ***Study 2 – North America*** ***Study 3 – Europe and Australia*** ***Study 4 – North America and Australia*** ***Setting:*** Multiple centres (202 sites) ***Recruitment dates:*** Not stated ***Study design:*** Pooled analysis of a 12-month phase 2 trial and three 6-month phase 3 trials All trials were randomised, double-blind and placebo controlled. A 6 month extension trial of participants in 2 of the phase 3 studies was also included	Study 1 (Phase 2 trial) - 24 week titration phase and 28 week assessment phase Study 2 and 3 (phase 3 trials) -12 week dose titration phase followed by 14 week evaluation phase Study 4 (phase 3 study) - 16 week dose titration followed by 10 week evaluation phase ***Intervention:*** Cinacalcet ***Intervention regimen:*** ▪ Subjects initially received 30 mg cinacalcet orally, once daily ▪ Dose increased, at 20mg (study 1) or 30 mg (trials 2,3 and 4) increments from 30mg to 180mg/day at 3 or 4 weekly intervals. ***Comparator regimen:*** Placebo ***Concurrent treatment:*** ▪ Phosphate binders were permitted, with dose changes allowed at the discretion of the investigator

SUBJECTS

Total number: 1184

Cinacalcet n = 697; Placebo n = 487

Inclusion criteria:

- ≥18 years old
- intact PTH level ≥300 pg/ml
- albumin-corrected serum Ca^{2+} ≥8.4 mg/dL
- subjects had received haemodialysis 3 times/week for a minimum of 1 to 3 months or peritoneal dialysis for ≥1 month.

Exclusion criteria:

- Parathyroidectomy or myocardial infarction within 3 to 6 months of the start of treatment.
- Change of vitamin D therapy within 30 days of the start of treatment
- Use of flecainide, lithium, thoridazine, haloperidol, or tricyclic antidepressant (except for amitriptyline) therapy within 21 days of the start of the trial
- Gastrointestinal disturbances that could impair the absorption of the study drug
- The existence of an unstable medical condition
- Pregnancy or nursing

Vitamin D sterols permitted

- o Dose reduction permitted if:
  - Serum Ca^{2+} ≥11 mg/dl or
  - Serum phosphorus ≥6.5 mg/dl or
  - Ca x P ≥70 mg^2/dl^2
- o Dose increase permitted if:
  - Serum Ca^{2+} <8.4 mg/dl

Notes:

Some of the trials limited the proportion of subjects with PTH >800 pg/ml to 20% of the total (trials 2 and 3)

SUBJECT CHARACTERISTICS

	Placebo	Cinacalcet
N:	487	697
Age:		
Age at randomisation, mean ± SD	54.7 ± 14.6	53 ± 14.2
<65 years*	348 (71%)	538 (77%)
≥65 years	139 (29%)	159 (23%)
Sex:		
M	306 (63%)	425 (61%)
F	181 (37%)	272 (39%)
Race:		
White*	270 (55%)	332 (48%)
Black	166 (34%)	265 (38%)
Other	51 (10%)	100 (14%)
Duration of dialysis	70.1 ± 67.1	65.8 ± 59.9
Dialysis modality:		
Haemodialysis*	475 (98%)	663 (95%)
Peritoneal dialysis	12 (2%)	34 (5%)
Concomitant diabetes	154 (32%)	217 (31%)
Use of vitamin D sterols	327 (67%)	453 (65%)
Use of phosphate binders	451 (93%)	648 (93%)
Plasma PTH *pg/ml*, mean (SD)	682 (399)	731 (531)
Serum Ca x P mg^2/dl^2, mean (SD)	61.1 (15.1)	60.9 (16.0)
Serum calcium *mg/dl*, mean (SD)	9.9 (0.8)	9.9 (0.8)
Serum Phosphorus *mg/dl*, mean (SD)	6.2 (1.5)	6.2 (1.7)

* significantly different at baseline

OUTCOME MEASURES

Primary outcome measure:

- Parathyroidectomy
- Fracture
- Cardiovascular hospitalisation
- All-cause and non-cardiovascular hospitalisation
- Health related quality of life (Medical Outcomes Study Short Form-36 SF36) (not study 1)
- Cognitive Functioning scale from the Kidney Disease Quality of Life (KDQOL) instrument (KDQOL-CF) (not study 1).

Method of assessing outcomes:

- Outcomes were identified prospectively based on reasons for discontinuation and adverse-event data collected in all trials.
- Hospitalisations captured from adverse event form with reason for hospitalisation provided for each event.
- Reported events were confirmed using source document verification, and the medical records of all subjects were monitored during the study to facilitate complete event capture.
- Touch screen technology for translated and culturally adapted versions of the subject-reported outcome instruments.

Length of follow-up:

Study 2,3 and 4 (phase 3 trials) 26 week duration
Study 1 (phase 2 trial) 52 week duration

RESULTS

PRIMARY OUTCOMES	Events per 100 subject years		RR for Cinacalcet (95% CI)	P value
	Placebo	Cinacalcet		
Mortality	7.4	5.2	0.81 (0.45-1.45)	0.47
Cardiovascular hospitalisation	19.7	15.9	0.61 (0.43-0.86)	0.005
All-cause hospitalisation	71.0	67.0	1.03 (0.87-1.22)	0.74
Fracture	6.9	3.2	0.46 (0.22-0.95)	0.04
Parathyroidectomy	4.1	0.3	0.07(0.01-0.55)	0.009
Associated statistics	Placebo (n = 487)	Cinacalcet (n = 697)		
CV hospitalisation (N):	77	72		
- Ischaemic heart disease	29	22		
- Heart failure	19	26		
- Arrythmia	18	17		
- Peripheral vascular disease	7	2		
- Stroke	4	5		
Number of fractures of lower extremities	7	11		
Number of other fractures	13	1		
Number of parathyroidectomies	12	1		
Changes in HRQoL scores (baseline to end of study): (+ scores indicate improvement)	Placebo	Cinacalcet	Difference in score change (placebo-cinacalcet)	P value
SF-36 Physical Component Summary Score:	- 0.8	+ 0.5	1.3	0.01
SF-36- Mental component Summary			0.3 (graph)	NS
SF-36 Physical functioning			1.0 (graph)	NS
SF-36 Role limitations, physical			1.2 (graph)	NS
SF-36 Social functioning			0.5 (graph)	NS
SF-36 Vitality			0.5 (graph)	NS
SF-36 Role limitation, emotional			0.5 (graph)	NS
SF-36 Mental Health			0.7 (graph)	NS
Bodily pain scale:	- 1.0	+ 0.6	1.6	0.03
General Health Perception Scale:	- 1.0	+ 0.2	1.2	0.02
Decline in self-reported physical function (Physical Component Summary decrease >5 points): (% subjects)	23%	21%		0.52
Improvement in self-reported physical function (Physical Component Summary increase >5 points): (% subjects)	20%	26%		0.03
Mean change in KDQOL-CF score:	- 0.8	+ 0.2	1.0	0.12

METHODOLOGICAL COMMENTS

Selection / randomisation: All four trials randomised by computer generated system
Stratification in two phase 3 trials (study 2 and 3) according to baseline PTH and Ca x P
Remaining phase 3 study (study 4) randomised 3:1 (cinacalcet: placebo) and stratified according to dialysis modality and baseline pTH
No stratification in phase 2 study (study 1)

Groups similar at baseline? Yes
Characteristics with differences p<0.05 were:

- Age <65 years (Cinacalcet 77% vs control 71%) >65 years (cinacalcet 23% vs control 29%) p = 0.025
- Age at randomisation (cinacalcet 53 ± 14.2 vs control 54.7 ± 14.6) p = 0.037
- Ethnicity p = 0.018
- Dialysis modality p = 0.034

Eligibility criteria stated? Yes

Blinding: Not detailed "blinds were maintained through numbered drug bottles"
Subjects, provider and assessors

Outcome measures: Objective measures for primary outcomes; however, these were obtained from safety data and were not adjudicated
Subjective quality of life (QOL) measures were also assessed

ITT: Yes, but subjective data excluded those with missing baseline (n=22) and efficacy phase data (n=238)

Protocol violations specified: No

Follow-up / attrition: All subjects accounted for? Not detailed
Withdrawal specified? Not detailed
Withdrawal reasons given? Not detailed

Data analysis: Statistical tests used:

- Cox proportional hazards models, stratified by study, used for parathyroidectomy, fracture and death
- Andersen-Gill model for hospitalisations
- Kaplan Meier time to event method for survival
- T-tests using LSM for the SF-36 and KDQOL-CF scores

Power calculation at design? Not stated

Generalisability: Effect of limiting proportion of subjects with PTH >800 pg/ml
High proportion of non-Caucasians

Conflict of interest: Two authors are employees of Amgen. One author is a former employee of Amgen. Two authors served as scientific advisors to Amgen and have received financial support from Amgen.

GENERAL COMMENTS

COMBINED ANALYSIS OF 2000172, 2000183, 2000188 and 2010141

STUDY

Lien et al., 2005

Country:

United States

Setting:

Single centre

Recruitment dates:

Not stated

Study design:

Part of randomised, double-blind, placebo-controlled, multicentre trials to evaluate the safety and efficacy of cinacalcet for treating secondary hyperparathyroidism.

SUBJECTS

Total number: 14

Cincalcet n = 8; Placebo n = 6

(10 receiving haemodialysis and 4 who had stage 4 chronic kidney disease (pre-dialysis subjects)

Inclusion criteria:

- Mean plasma iPTH level of ≥31.8 pmol/L established by three measurements obtained within a 30-day screening period
- 18 years of age or older and in medically stable condition.
- Treated with haemodialysis 3 times/week for at least 3 months

Exclusion criteria:

- Evidence of cancer, active infection, diseases known to cause hypercalcaemia, or serum Ca^{2+} level ≤2.1 mmol/L, corrected for albumin.
- Subjects receiving drugs such as flecainide, thioridazine, and most tricyclic antidepressants, which have a narrow therapeutic index and are metabolised by P-450 2D6

NB. Inclusion/exclusion criteria taken from Block et al., 2004 as referenced in this paper

INTERVENTION

(NB study design section taken from Block et al., 2004 which was referenced in this paper)

Intervention:

Cinacalcet

Intervention regimen:

12 week dose titration phase

- Subjects initially received 30 mg Cinacalcet (or placebo) orally, once daily.
- Doses were increased sequentially every 3 weeks during the dose-titration phase to 60, 90, 120 and 180 mg once daily
  - Increases in dose were permitted if:
    - iPTH ≥ 21.2 pmol/L and
    - serum Ca^{2+} ≥ 1.95 mmol/L.
  - Dose was not increased if:
    - symptoms of hypocalcaemia or
    - serum Ca^{2+} < 1.95 mmol/L or
    - adverse event that precluded an increase in the dose.
  - The dose was reduced if:
    - iPTH < 10.6 pmol/L on three consecutive study visits
    - adverse event requiring a reduction in the dose.

14 week maintenance phase

- Dose adjustments were permitted at 4 week intervals as above

Pre-dialysis subjects

- As above but efficacy assessment phase shortened to 6 weeks

Comparator regimen:

Placebo

Concurrent treatment:

- Concurrent phosphate binder permitted without restriction
- Vitamin D sterols permitted
  - Dose increase permitted if:
    - iPTH increased by >50% from baseline or
    - Serum Ca^{2+} < 2.1 mmol/L or
    - Symptomatic hypocalcaemia
  - Dose reduction permitted if:
    - Serum Ca^{2+} ≥ 2.75 mmol/L or
    - Serum phosphorus ≥ 2.1 mmol/L or
    - Ca x P ≥ 5.65 $mmol^2/L^2$ or
    - iPTH < 10.6 pmol/L on three consecutive study visits and the subject was on the lowest dose of cinacalcet

SUBJECT CHARACTERISTICS

	Placebo	Cinacalcet
N:	6	8
Age (years)(SD)	47 (17)	55 (16)
Sex:		
M	5	4
F	1	4
Race:		
Caucasian	2	4
African American	1	1
Hispanic	3	3
Dialysis status:		
Haemodialysis	4	6
Pre-dialysis	2	2

Notes: Significant difference in sex composition of the groups ($p<0.05$)

Concomitant vitamin D used by all but 1 of the HD subjects (group not stated), not used in any pre-dialysis pts.

OUTCOME MEASURES

Primary outcome measure:

Not stated; however, study rationale was to compare BMD measurements between groups as this centre routinely recorded this as part of routine care.

- Lumbar spine (L2-L4) BMD
- Total proximal femur BMD including femoral neck, greater trochanter and proximal femur shaft

Secondary measures:

Serum levels of iPTH, calcium, phosphorus, alkaline phosphatase

Method of assessing outcomes:

- Lumbar spine (L2-L4) and total proximal femur BMD measured by GE Medical systems Lunar in-office DEXA scanner at baseline and study end.
- Plasma iPTH and serum calcium and phosphorus levels were measured at each study visit before the dose of study medication
- Serum levels of alkaline phosphatase were measured at baseline and at the end of the study.

Length of follow-up:

26 weeks for HD subjects, 18 weeks for pre-dialysis subjects.

RESULTS

PRIMARY OUTCOMES	**Placebo (N=6)**		**Cinacalcet (N=8)**	
	Baseline (mean ± SD)	**End of study (mean ± SD)**	**Baseline (mean ± SD)**	**End of study (mean ± SD)**
Bone Mineral Density and T-scores				
Femur BMD (g/cm^2)	0.921 ± 0.250	0.904 ± 0.244*	0.945 ± 0.169	0.961 ± 0.174*
Femur T-score	-1.03 ± 1.56	-1.30 ± 1.70	-0.76 ± 1.10	-0.65 ± 1.16*
Lumbar spine BMD (g/cm^2)	1.156 ± 0.276	1.149 ± 0.288	1.283 ± 0.219	1.269 ± 0.221
Lumbar Spine T-score	-0.72 ± 2.31	-0.63 ± 2.23	-0.52 ±1.69	-0.39 ± 1.69

Notes:
*p<0.05 vs before treatment

SECONDARY OUTCOMES	**Placebo (N=6)**		**Cinacalcet (N=8)**	
	Baseline (mean ± SD)	**End of study (mean ± SD)**	**Baseline (mean ± SD)**	**End of study (mean ± SD)**
Chronic Haemodialysis:	**N=4**		**N=6**	
iPTH (pg/ml)	1009 ± 584	1295 ± 642	912 ± 296	515 ± 359*
Ca (mg/ml)	10.8 ± 1.0	10.4 ± 1.0	9.7 ±1.0	9.2± 0.9
Phosphorus (mg/dl)	5.9 ± 1.3	6.5 ± 2.6	7.1 ± 2.5	6.4 ± 1.6
Alkaline phosphatase (U/L)	279 ± 371	223 ± 176	152 ± 72	128 ± 48
Pre-dialysis:	**N = 2**		**N=2**	
GFR	21 ± 6	22 ± 2	25 ± 3	27± 11
iPTH (pg/ml)	207 ± 43	179 ± 33	210 ± 46	57 ± 51*
Ca (mg/ml)	9.6 ± 0.2	9.4 ± 0.4	9.3 ± 0.6	8.8 ± 0.7
Phosphorus (mg/dl)	4.0 ± 0.6	3.5 ± 0.3	3.8 ± 0.6	3.9 ± 0.6
Alkaline phosphatase (U/L)	73 ± 6	68 ± 18	90 ± 8	97 ± 37

Notes:
*p<0.05 vs before treatment

METHODOLOGICAL COMMENTS

Selection / randomisation:	Completers at one centre participating in two separate RCTs
Groups similar at baseline?	No, placebo group had more male subjects ($p<0.05$; however, part of larger multicentre trial so not designed to be similar)
Eligibility criteria stated?	No details. Reference Block et al., 2004
Blinding:	Stated as double blind. No details.
Outcome measures:	Objective
ITT:	No
Protocol violations specified:	One haemodialysis subjects admitted non-compliance
Follow-up / attrition:	Analysis was on 'completers' from two other trials
Data analysis:	Statistical tests used: • Statistical comparisons between pre-and post-treatment values were performed by paired, one-tailed Student's t-tests • For comparisons of data between the cinacalcet and placebo groups, non-paired, two-tailed Student's t-tests were used.
Power calculation at design?	No. Part of larger study
Generalisability:	Small sample of subjects at one centre. Groups not well matched for age, race, or dialysis status. Substantial differences in baseline PTH between HD and pre-dialsis subjects High proportion of non-caucasian subjects
Conflict of interest:	Supported by Amgen Inc (study 20000188 and study 20000239)

GENERAL COMMENTS

"Study supported by Amgen Inc (study 2000188 and study 20000239)"; however, dose titration and efficacy assessment phase length do not match up with these trials.

Were all completers at centre included?

Lumbar spine BMD decreased in both groups but T-score improved??

STUDY

Lindberg *et al.*, 2003

Country:

United States and Canada

Setting:

Multiple centres (25)

Recruitment dates:

Not stated

Study design:

Randomised, double-blind, placebo-controlled trial

SUBJECTS

Total number: 78

Cinacalcet n = 39; Placebo n = 39

Inclusion criteria:

- Treated for at least 3 months with haemodialysis
- iPTH levels ≥300 pg/mL despite receiving standard care (phosphate binders and/or vitamin D sterols)
- Age ≥18 years
- Serum Ca^{2+} ≥8.8 mg/dL and <11.0 mg/dL (corrected for serum albumin).
- Serum phosphorus ≥2.5 mg/dL
- Calcium x phosphorus <70 $(mg/dL)^2$

Exclusion criteria:

- Vitamin D sterol dose changes during 21 days before enrolment.
- Dialysis calcium concentration, the dose of any supplements, and the dose of oral phosphate binders changed during the 7 days before enrolment.
- Evidence of active infectious or malignant process or diseases known to cause hypercalcaemia
- Haemoglobin concentration <9 g/dl or a haematocrit <27%
- Liver transaminases and bilirubin concentrations more than twice the upper limit of normal

INTERVENTION

After screening period, subjects randomised 1:1 to receive cinacalcet or placebo

Intervention:

Cinacalcet

Intervention regimen:

12 week dose titration

- Subjects initially received 20 mg cinacalcet orally, once daily.
  - Dose increased, through 30, 40, or 50mg daily every 3 weeks if PTH ≥ 250 pg/ml or had not reduced by ≥ 30% from baseline, unless serum Ca^{2+} < 7.8 mg/dl or symptomatic hypocalcaemia
  - Dose reduced if PTH < 100 pg/ml on two consecutive weekly visits.

6 week maintenance phase

Comparator regimen:

Placebo

Concurrent treatment:

- Concurrent phosphate binders permitted without restriction and
- Vitamin D sterols permitted;
  - Dose increase permitted if:
    - iPTH increased by > 50% from baseline or
    - iPTH was ≥600 pg/mL
  - Dose reduction permitted if:
    - serum Ca^{2+} ≥ 11.0 mg/dl or
    - serum phosphorus ≥ 6.5 mg/dl or
    - Ca x P ≥ 70 mg^2/dl^2 or
    - iPTH was ≤100pg/mL on the lowest dose of cinacalcet

SUBJECT CHARACTERISTICS

	Control	Cinacalcet
N:	39	39
Age: mean (SD)	48.8 (15.6)	52.7 (16.4)
Sex:		
M	22 (56%)	24 (62%)
F	17 (44%)	15 (38%)
Race:		
Black	29 (74%)	26 (67%)
White	6 (15%)	10 (26%)
Asian	2 (5%)	2 (5%)
Hispanic	2 (5%)	1 (3%)
Duration of dialysis (months):		
mean (SD)	69.7 (53.9)	60.3 (58.3)
Use of vitamin D sterols	24 (62%)	26 (67%)
Use of phosphate binders	34 (87%)	34 (87%)

OUTCOME MEASURES

Primary outcome measure:

Proportion of subjects with reduction in iPTH ≥30% between treatment groups during the maintenance phase

Secondary measures:

Mean % change from baseline for iPTH, serum calcium, serum phosphorus and calcium x phosphorus between treatment groups during the maintenance phase.

Safety was assessed by monitoring adverse events, laboratory variables (haematology and biochemistry), and vital signs

Method of assessing outcomes:

- Laboratory assessments were made at weekly visits throughout the study.
- Assessments were made immediately before administering daily oral dose of study medication (24 hours after previous dose)
- All laboratory determinations were determined at a central laboratory. iPTH levels were determined using double-antibody immunoradiometric assay for the intact hormone.

Length of follow-up:

18 weeks

RESULTS

PRIMARY OUTCOMES	**Placebo (n = 39)**	**Cinacalcet (N =38)**
Proportion of subjects achieving mean reduction in PTH≥30% during the maintenance phase	8%	38%

P=0.001

SECONDARY OUTCOMES

Mean % change in PTH from baseline: (From Graphical data)

Week

	Wk 13	**Wk 14**	**Wk 15**	**Wk 16**	**Wk 17**	**Wk 18**
Placebo	17	22	22	27	24	28
Cinacalcet	-22	-29	-20	-29	-33	-26

P<0.001

Mean % change in serum calcium from baseline: (From Graphical data)

Week

	Wk 13	Wk 14	Wk 15	Wk 16	Wk 17	Wk 18
Placebo	-0.3	-0.3	0.3	-0.3	-1.2	1.5
Cinacalcet	-5.6	-6.2	-3.8	-5.3	-4.0	-2.8
p<0.001						

Mean % change in Phosphorus from baseline: (From Graphical data)

Week	**Wk 13**	**Wk 14**	**Wk 15**	**Wk 16**	**Wk 17**	**Wk 18**
Placebo	10.0	12.8	13.9	8.9	9.4	10.0
Cinacalcet	-8.3	-3.3	-2.8	-6.1	-12.8	-14.4
p<0.001						

Mean % change in Ca x P from baseline: (From Graphical data)

Week	**Wk 13**	**Wk 14**	**Wk 15**	**Wk 16**	**Wk 17**	**Wk 18**
Placebo	10.7	14.6	15.3	9.3	9.8	12.0
Cinacalcet	-12.9	-8.7	-8.0	-10.7	-16.0	-16.7
P<0.001						

Adverse Effects	**Placebo**	**Cinacalcet**
Nausea	31%	21%
Dyspnoea	13%	18%
Hypocalcaemia (asymptomatic)	Not stated	8%

BIOCHEMISTRY RESULTS mean (SD)	**Placebo**			**Cinacalcet**			
	Baseline	**Wk 13-18**	**% change**	**Baseline**	**Wk 13-18**	**% change**	**p**
Intact Plasma parathyroid hormone (pg/ml)	637 (456)	701 (70)	22%	632 (280)	460 (47)	-26%	<0.001
Serum Ca^{2+} (mg/dl)	9.7 (0.64)	Not stated	0%	9.7(0.67)	Not stated	-4.7%	<0.001
Serum Phosphorus (mg/dl)	5.6 (1.38)	Not stated	10.9%	6.3 (1.42)	Not stated	-7.5%	=0.003
Calcium-phosphorus product $(mg/dl)^2$	53.8 (13.63)	Not stated	10.9%	60.7 (13.2)	Not stated	-11.9%	<0.001

METHODOLOGICAL COMMENTS

Selection / randomisation: Subjects randomised 1:1 to receive cinacalcet or placebo. Details not specified

Groups similar at baseline? Yes

Eligibility criteria stated? Yes

Blinding: Double-blind – not detailed

Outcome measures: Objective

ITT: Yes

Protocol violations specified: None specified

Follow-up / attrition: All subjects accounted for?

	Placebo	Cinacalcet
randomised	39	39
Withdrew (no reasons stated)	5	7
Number completing 18 weeks	34	32

Data analysis: Statistical tests used:

- Proportion of subjects with reductions in iPTH $\geq$30% between treatment groups was compared using the two-group χ^2 test
- Mean % change from baseline for iPTH, serum Ca^{2+}, phosphorus and calcium x phosphorus between groups was compared using analysis of variance (ANOVA) model
- The effect of the baseline demographic factors, gender, age, race, duration of dialysis, and vitamin D use on iPTH reductions was assessed by stepwise logistic regression analysis.
- Stepwise logistic regression analysis was also used to assess the effect of baseline iPTH, serum calcium, phosphorus and calcium x phosphorus levels on iPTH reductions.

Power calculation at design? Not stated

Generalisability: High proportion of ethnic minorities in study – representative of dialysis population in UK?
Many centres but relatively small numbers of subjects

Conflict of interest: Funding for study provided by Amgen

GENERAL COMMENTS

Maximum titrated dose was smaller than in some other trials; proportion of subjects achieving >30% PTH REDUCTION was correspondingly lower.

STUDY

Lindberg et al., 2005

Country:

United States, Canada and Australia

Setting:

60 centres

Recruitment dates:

May 2002

Study completed March 2003

Study design:

Randomised, double-blind, placebo-controlled, parallel group 26 – week multicentre study of the efficacy and safety of cinacalcet in patients with secondary hyperparathyroidism and those who were on haemodialysis and peritoneal dialysis and receiving traditional therapy.

SUBJECTS

Total number: 395

Cincalcet n = 294; Placebo n = 101

Inclusion criteria:

- ≥18 years of age
- Mean of 2 central laboratory iPTH values ≥300 pg/ml obtained during screening phase
- Mean of 2 central laboratory serum calcium values ≥ 8.4 mg/dL (2.1 mmol/L) obtained during screening phase
- Prescribed haemodialysis or peritoneal dialysis (continuous ambulatory peritoneal dialysis or automated peritoneal dialysis) for ≥ 1 months before day 1

Exclusion criteria:

- Unstable medical condition
- Parathyroidectomy
- Received vitamin D sterol therapy for <30 days before day 1 or required a change in vitamin D sterol brand or dose within 30 days before day 1
- Experienced a myocardial infarction within 3 months before day 1

Sub-groups

Stratification into following 4 groups:

- Haemodialysis, and iPTH ≥300 pg/ml (31.8 pmol/L) to ≤500 pg/ml (53 pmol/L)
- Haemodialysis, and iPTH >500 pg/ml ≤800 pg/ml (84.8 pmol/L)
- Haemodialysis, and iPTH >800 pg/ml
- Peritoneal dialysis, and iPTH ≥300 pg/ml

INTERVENTION

After screening period, subjects were randomised in 3:1 ratio to cinacalcet or placebo

Intervention:

Cinacalcet

Intervention regimen:

16 week dose titration phase

- Subjects initially received 30 mg cinacalcet orally, once daily .
- Doses were increased sequentially every 4 weeks during the dose-titration phase to 60, 90, 120 and 180 mg once daily
  - Increases in dose were permitted if;
    - iPTH was >200 pg/ml and or
    - serum calcium was >7.8 mg/dl and
    - symptoms of hypocalcaemia were not present and
    - the highest study dose had not been reached and
    - an adverse event that precluded and increase in dose had not occurred

10 week efficacy assessment phase

Comparator regimen:

- As above with placebo

Concurrent treatment:

- Concurrent phosphate binder permitted without restriction
- Vitamin D sterols permitted

o Dose increase permitted if:

· Serum Ca^{2+} < 8.4 mg/dl that did not respond to changes in calcium supplements and/or phosphate binders

· Symptomatic hypocalcaemia

o Dose reduction permitted if:

· Serum Ca^{2+} ≥ 11 mg/dl or

· Serum phosphorus ≥ 6.5 mg/dl or

· Ca x P ≥ 70 mg^2/dl^2

SUBJECT CHARACTERISTICS

	Placebo N (%)		Cinacalcet N (%)	
N:	**101**		**294**	
Age (*years*, mean (SD)):	53.5 ± 13.9		51.8 ± 14.0	
Sex:				
M	64	63%	181	62%
F	37	37%	113	38%
Race:				
Caucasian	39	39%	115	39%
Black	35	35%	114	39%
Other	27	27%	65	22%
Duration of dialysis (*mo*; mean (SD))	63.6	(65.0)	56.4	(53.1)
Baseline biochemistry values:				
IPTH (pg/ml; mean (SE))	832.1	(48.4)	847.9	(40.1)
Serum calcium (mg/dl; mean (SE))	10.01	(0.09)	9.79	(0.05)
Serum phosphorus (mg/dl; mean (SE))	6.10	(0.14)	6.10	(0.10)
Ca x P (mg^2/dl^2; mean (SE))	60.9	(1.4)	59.6	(1.0)
Use of vitamin D sterol		69%		65%

OUTCOME MEASURES

Primary outcome measure:

- Proportion of subjects with a mean plasma intact parathyroid hormone (iPTH value) ≤250 pg/ml during efficacy-assessment phase

Secondary measures:

- Proportion of subjects with a reduction from baseline in mean iPTH of ≥30%
- Percentage change from baseline in mean iPTH during efficacy-assessment phase
- Percentage changes from baseline in mean Ca x P, serum calcium, and serum phosphorus during efficacy-assessment phase
- Proportion of patients with a mean iPTH level of ≤300pg/ml or reductions in iPTH of at least 20, 40 or 50% from baseline
- Proportion of patients with Ca x P <55 mg^2/dl^2
- Proportion of patients with a mean reduction in Ca x P of at least 5 or 10 mg^2/dl^2

Method of assessing outcomes:

- Visits occurred biweekly during 16 week titration phase and 10 week efficacy-assessment phase
- Laboratory assessments of plasma iPTH, serum calcium, and serum phosphorus were performed at a central laboratory.
- Plasma iPTH levels were determined using a double-antibody immunoradiometric assay (Nichols)

Length of follow-up:

Study duration 26 weeks

ESULTS

	Placebo (N=101)		Cinacalcet (N=294)		P value
Primary Outcomes					
Mean iPTH ≤250 pg/mL (overall)	7/100	7%	111/288	39%	P<0.001
- haemodialysis subgroup with baseline iPTH ≥300 and ≤500 (n = 74)			54/70	77%	
- haemodialysis subgroup with baseline iPTH >500 and ≤800 (n = 84)			34/83	41%	
- haemodialysis subgroup with baseline iPTH >800 (n = 102)			10/101	10%	
- peritoneal dialysis subgroup with baseline iPTH > 300 (n = 34)			13/34	38%	

Secondary Outcomes	**Placebo (N=101)**		**Cinacalcet (N=294)**		**P value**
	N	Mean (SE)	N1	Mean (SE)	
Percentage change from baseline in mean iPTH (overall)	101	4.1 (3.4)	288	-40.30 (2.1)	P<0.001
- haemodialysis subgroup with baseline iPTH ≥300 and ≤500			70	-46.7 (3.9)	
- haemodialysis subgroup with baseline iPTH >500 and ≤800			83	-44.0 (3.80)	
- haemodialysis subgroup with baseline iPTH >800			101	-33.3 (3.6)	
- peritoneal dialysis subgroup with baseline iPTH > 300			34	-38.8 (5.7)	

	Placebo (N=101)		**Cinacalcet (N=294)**		**P value**
Mean iPTH ≤300 pg/mL (overall)	9/100	9%	132/288	46%	P<0.001
- haemodialysis subgroup with baseline iPTH ≥300 and ≤500 (n = 74)			57/70	81%	
- haemodialysis subgroup with baseline iPTH >500 and ≤800 (n = 84)			41/83	49%	
- haemodialysis subgroup with baseline iPTH >800 (n = 102)			17/101	17%	
- peritoneal dialysis subgroup with baseline iPTH > 300 (n = 34)			17/34	50%	

	Placebo (N=101)		**Cinacalcet (N=294)**		**P value**
Proportion of subjects with reduction from baseline in mean iPTH of ≥30% (overall)	13/100	13%	187/288	65%	P<0.001
- haemodialysis subgroup with baseline iPTH ≥300 and ≤500 (n = 74)			55/70	79%	
- haemodialysis subgroup with baseline iPTH >500 and ≤800 (n = 84)			57/83	69%	
- haemodialysis subgroup with baseline iPTH >800 (n = 102)			53/101	51%	
- peritoneal dialysis subgroup with baseline iPTH > 300 (n = 34)			22/34	65%	

	Placebo (N=101)		**Cinacalcet (N=294)**		**P value**
Proportion of subjects with reduction from baseline in mean iPTH of ≥20% (overall)	21/100	21%	213/288	74%	P<0.001
- haemodialysis subgroup with baseline iPTH ≥300 and ≤500 (n = 74)			58/70	83%	
- haemodialysis subgroup with baseline iPTH >500 and ≤800 (n = 84)			64/83	77%	
- haemodialysis subgroup with baseline iPTH >800 (n = 102)			66/101	65%	
- peritoneal dialysis subgroup with baseline iPTH > 300 (n = 34)			25/34	74%	

	Placebo (N=101)		Cinacalcet (N=294)		P value
Proportion of subjects with reduction from baseline in mean iPTH of ≥40% (overall)	10/100	10%	172/288	60%	P<0.001
- haemodialysis subgroup with baseline iPTH ≥300 and ≤500 (n = 74)			49/70	70%	
- haemodialysis subgroup with baseline iPTH >500 and ≤800 (n = 84)			55/83	66%	
- haemodialysis subgroup with baseline iPTH >800 (n = 102)			48/101	48%	
- peritoneal dialysis subgroup with baseline iPTH > 300 (n = 34)			20/34	59%	

	Placebo (N=101)		Cinacalcet (N=294)		P value
Proportion of subjects with reduction from baseline in mean iPTH of ≥50% (overall)	6/100	6%	139/288	48%	P<0.001
- haemodialysis subgroup with baseline iPTH ≥300 and ≤500 (n = 74)			45/70	64%	
- haemodialysis subgroup with baseline iPTH >500 and ≤800 (n = 84)			42/83	51%	
- haemodialysis subgroup with baseline iPTH >800 (n = 102)			38/101	38%	
- peritoneal dialysis subgroup with baseline iPTH > 300 (n = 34)			14/34	41%	

	Placebo (N=101)		Cinacalcet (N=294)		P value
	N	Mean /SE	N1	Mean/SE	
Serum Ca^{2+} (mg/dl) (overall)	100	10.1 (0.1)	288	9.1 (0.1)	P<0.001
- haemodialysis subgroup with baseline iPTH ≥300 and ≤500			70	9.1 (0.1)	
- haemodialysis subgroup with baseline iPTH >500 and ≤800			83	9.1 (0.1)	
- haemodialysis subgroup with baseline iPTH >800			101	9.1 (0.1)	
- peritoneal dialysis subgroup with baseline iPTH > 300			34	9.4 (0.1)	

	Placebo (N=101)		Cinacalcet (N=294)		P value
	N	Mean /SE	N1	Mean/SE	
Percentage change from baseline in mean Ca^{2+} (overall)	100	0.9 (0.5)	288	-6.5 (0.6)	P<0.001
- haemodialysis subgroup with baseline iPTH ≥300 and ≤500			70	-5.5 (1.0)	
- haemodialysis subgroup with baseline iPTH >500 and ≤800			83	-5.8 (1.1)	
- haemodialysis subgroup with baseline iPTH >800			101	-7.4 (1.0)	
- peritoneal dialysis subgroup with baseline iPTH > 300			34	-7.4 (1.4)	

	Placebo (N=101)		Cinacalcet (N=294)		P value
	N	Mean /SE	N1	Mean/SE	

Serum phosphorus (mg/dl) (overall)	100	5.8 (0.1)	289	5.5 (0.1)	
- haemodialysis subgroup with baseline iPTH ≥300 and ≤500			71	5.1 (0.2)	
- haemodialysis subgroup with baseline iPTH >500 and ≤800			83	5.3 (0.2)	
- haemodialysis subgroup with baseline iPTH >800			101	6.0 (0.2)	
- peritoneal dialysis subgroup with baseline iPTH > 300			34	5.0 (0.2)	

	Placebo (N=101)		**Cinacalcet (N=294)**		**P value**
	N	Mean (SE)	N1	Mean (SE)	
Percentage change from baseline in mean phosphorus (overall)	100	-2.2 (2.5)	289	-7.2 (1.6)	P=0.039
- haemodialysis subgroup with baseline iPTH ≥300 and ≤500			71	-8.6 (2.7)	
- haemodialysis subgroup with baseline iPTH >500 and ≤800			83	-2.9 (3.6)	
- haemodialysis subgroup with baseline iPTH >800			101	-11.7 (2.3)	
- peritoneal dialysis subgroup with baseline iPTH > 300			34	-1.5(4.0)	

	Placebo (N=101)		**Cinacalcet (N=294)**		**P value**
	N	Mean /SE	N1	Mean/SE	
Ca x P (mg/dl)^2	100	58.1 (1.3)	288	50.0 (0.9)	P<0.001
- haemodialysis subgroup with baseline iPTH ≥300 and ≤500			70	46.9 (1.8)	
- haemodialysis subgroup with baseline iPTH >500 and ≤800			83	48.5 (1.7)	
- haemodialysis subgroup with baseline iPTH >800			101	54.1 (1.5)	
- peritoneal dialysis subgroup with baseline iPTH > 300			34	47.4 (2.2)	

	Placebo (N=101)		**Cinacalcet (N=294)**		**P value**
	N	Mean /SE	N1	Mean/SE	
Percentage change from baseline in mean Ca x P	100	-1.4 (2.4)	287	-12.8 (1.7)	P<0.001
- haemodialysis subgroup with baseline iPTH ≥300 and ≤500			69	-12.0 (3.4)	
- haemodialysis subgroup with baseline iPTH >500 and ≤800			83	-9.1 (3.5)	
- haemodialysis subgroup with baseline iPTH >800			101	-18.0 (2.5)	
- peritoneal dialysis subgroup with baseline iPTH > 300			34	-8.5 (4.1)	

	Placebo (N=101)	**Cinacalcet (N=294)**	**P value**

	N	%	N	%	
Number (%) achieving Ca x P target <55mg^2/dl^2	45/100	45%	186/288	65%	P<0.001
- haemodialysis subgroup with baseline iPTH ≥300 and ≤500			51/70	73%	
- haemodialysis subgroup with baseline iPTH >500 and ≤800			58/83	70%	
- haemodialysis subgroup with baseline iPTH >800			51/101	50%	
- peritoneal dialysis subgroup with baseline iPTH > 300			26/34	76%	

	Placebo (N=101)		**Cinacalcet (N=294)**		**P value**
	N	%	N	%	
Number (%) achieving Ca x P target reduction ≤5mg^2/dl^2	39/100	39	175/287	61	P<0.001
- haemodialysis subgroup with baseline iPTH ≥300 and ≤500			41/69	59	
- haemodialysis subgroup with baseline iPTH >500 and ≤800			48/83	58	
- haemodialysis subgroup with baseline iPTH >800			67/101	66	
- peritoneal dialysis subgroup with baseline iPTH > 300			19/34	56	

Safety	**Placebo (N=101)**		**Cinacalcet (N=294)**		**P value**
	N	%	N	%	
Number (%) achieving Ca x P target reduction ≤10mg^2/dl^2	24/100	24	135/287	47	P<0.001
- haemodialysis subgroup with baseline iPTH ≥300 and ≤500			26/69	42	
- haemodialysis subgroup with baseline iPTH >500 and ≤800			32/83	39	
- haemodialysis subgroup with baseline iPTH >800			59/101	58	
- peritoneal dialysis subgroup with baseline iPTH > 300			15/34	44	

	Placebo (N=101)		**Cinacalcet (N=291)**		**P value**
Safety	N	%	N	%	
Deaths on study (total):	2		3		
Serious adverse events (total):		26		27	
Withdrawal due to GI events		3		9	
All AEs (total):		93		91	
Nausea		22		30	
Vomiting		12		23	
Headache		12		17	
Upper respiratory infection		13		18	
Abdominal pain		18		12	
Diarrhoea		19		24	
Asthenia		2		8	

Hypotension	12	7
Hypocalcaemia <7.5 mg/dl	<1%	5

METHODOLOGICAL COMMENTS

Selection / randomisation: Randomised 3:1 ratio to cinacalcet or placebo
Stratification into 4 groups defined by baseline iPTH and dialysis modality
Randomisation and dosing determined by a programmatic algorithm using an interactive voice-response system to maintain the blinded nature of the study design.

Groups similar at baseline? Yes
At baseline, mean iPTH and serum calcium levels were similar between placebo and cinacalcet-treated patients overall but were higher in cinacalcet-treated patients who received peritoneal dialysis than in cinacalcet-treated patients who received haemodialysis.

Eligibility criteria stated? Yes

Blinding: Stated as double blind. Placebo and cinacalcet tablets were identical in appearance at the same dose strength.

Outcome measures: Objective?
Yes

ITT: No. **Some patients are missing/added in to analysis in table 2 when compared with data from 20000188
For patients who withdrew before the efficacy assessment phase, the mean of the last two on-study, post-baseline values was carried forward.
Safety was analysed for all patients who received at least one dose of study medication.

Protocol violations specified: No

Follow-up / attrition: All patients accounted for?
No. A number of patients were removed/added to the analysis relative to the FDA document
Withdrawal specified?
83% of placebo treated and 81% of cinacalcet treated subjects completed 16 week dose-titration phase. 76% of placebo treated and 74% of cinacalcet treated subject completed 26 week study
Withdrawal reason given?
Yes

Reasons for withdrawal		
	Placebo (%)	Cinacalcet (%)
Adverse events	8	13
Withdrawal of consent	1	4
Kidney transplantation	6	3
Parathyroidectomy	2	0
Death	2	1

Data analysis: Statistical tests used:

- Generalised Cochran-Mantel-Haenszel test was used for statistical comparisons

Power calculation at design? Yes
Sample size calculation was based on χ^2 test of equal proportions of subjects with a mean value of iPTH $\leq$250pg/ml during the efficacy-assessment phase, with a

	statistical significance level of 0.05 (2-sided) Placebo response was predicted on the basis of previous cinacalcet phase 2 studies to be ≤13% With a cinacalcet response rate of 30% assumed for the purpose of sample size considerations, a sample size of 380 patients (285 cinacalcet, 95 placebo), yielded 91% power.
Generalisability:	Sub-group analysis allows for individual variation in iPTH and dialysis modality High proportion of non-caucasians Compliance with study medication was 87% in each treatment group
Conflict of interest:	Amgen study

STUDY	INTERVENTION
Moe *et al.*, 2005 ***Country:*** Combined results from 3 trials A. N America – United States and Canada B. Europe and Australia- Australia, Austria, Belgium, Denmark, France, Germany, Ireland, Italy, Netherlands Portugal, Spain, Sweden, United Kingdom C. United States, Canada and Australia ***Setting:*** Multiple centres (182) ***Recruitment dates:*** Study A Dec 2001 – Dec 2002 Study B Feb 2002 – Jan 2003 Study C May 2002 – March 2003 ***Study design:*** Combined analysis of three phase 3 randomised, double-blind, placebo-controlled placebo-controlled trials	<u>Study A and Study B</u> 12 week dose titration followed by 14 week maintenance phase <u>Study C</u> 16 week dose titration followed by 10 week maintenance phase After screening period, subjects were randomised to cinacalcet or placebo ***Intervention:*** ***Cinacalcet*** ***Intervention regimen:*** ▪ Subjects initially received 30 mg cinacalcet orally, once daily. ▪ Dose increased, through 60, 90, 120, 180 mg daily every 3 weeks (trials A & B) or every 4

SUBJECTS

Total number: ***1136***

Study A – Cinacalcet (n = 205), Placebo (n = 205)

Study B – Cinacalcet (n = 165), Placebo (n = 166)

Study C – Cinacalcet (n = 294), Placebo (n = 101)

Inclusion criteria:

- Study A
- iPTH ≥ 31.8 pmol/L;
- serum Ca^{2+} ≥ 2.1 mmol/L;
- haemodialysis duration > 3 months

- Study B
- iPTH ≥ 31.8 pmol/L;
- serum Ca^{2+} ≥ 2.1 mmol/L;
- haemodialysis duration > 3 months

- Study C
- iPTH ≥ 31.8 pmol/L;
- serum Ca^{2+} ≥ 2.1 mmol/L;
- haemodialysis or peritoneal dialysis > 1 month duration

Exclusion criteria:

Study A and study B

- History of an unstable medical condition,
- Change in dose or brand of vitamin D in the preceding 30 days.
- Change in dose or brand of phosphate binder, oral calcium supplement, or dialysate calcium concentration in the preceding 30 days

Study C

- History of an unstable medical condition,
- Change in dose or brand of vitamin D in the preceding 30 days.

Sub-groups

Trials A and B

Stratification by baseline iPTH

- >31.8 pmol/L to 53.0 pmol/L
- >53.0 pmol/L to 84.8 pmol/L
- >84.8 pmol/L

and by baseline Ca x P

- ≤ 5.65 $mmol^2/L^2$
- > 5.65 $mmol^2/L^2$

Study C

Stratification by dialysis modality and baseline iPTH level

weeks (study C), if iPTH ≥21.2 pmol/L and Ca^{2+} ≥1.95mmol/L

- Dose reduced if iPTH < 10.6 pmol/L

Comparator regimen:

Placebo

Concurrent treatment:

- Concurrent phosphate binders permitted without restriction
- Vitamin D sterols permitted;
  - o Dose increases permitted if:
    - iPTH increased by > 50% from baseline or
    - serum Ca^{2+} <2.1mmol/L or
    - symptomatic hypocalcaemia.
  - o Dose reductions permitted if:
    - serum Ca^{2+} ≥2.74mmol/L or
    - serum phosphorus ≥2.1mmol/L or
    - Ca x P ≥ 5.6$mmol^2/L^2$ or
    - iPTH <10.6 pmol/L on three consecutive study visits and the subject was on the lowest dose of cinacalcet

Notes:

Study C included peritoneal dialysis and haemodialysis subjects

This paper presents a secondary analysis of the data from the trials to compare outcomes with target values of the United States National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI)

SUBJECT CHARACTERISTICS

	Placebo		Cinacalcet	
N:	471		665	
Age <65:	335	71%	510	77%
Sex:				
M	295	63%	407	61%
F	176	37%	258	39%
Race				
White	265	56%	324	49%
Black	155	33%	245	37%
Other	51	11%	96	14%
Dialysis Modality				
Haemodialysis	459	97%	631	95%
Peritoneal dialysis	12	3%	34	5%
Use of vitamin D sterols	318	68%	437	66%
Use of phosphate binders	438	93%	617	93%
Baseline values (median (Q1, Q3)				
iPTH *pg/ml*	564	(411,785)	596	(429,863)
Ca^{2+} *mg/dl*	9.8	(9.4,10.5)	9.9	(9.3,10.4)
phosphorus *mg/dl*	6.2	(5.1,7.1)	6.0	(5.1,7.1)
Ca x P mg^2 /dl^2	61.3	(50.7,70.8)	60.2	(49.0,70.5)

OUTCOME MEASURES

Primary outcome measure:

- Proportion of subjects during the maintenance phase achieving target values of the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI):
- For subjects on dialysis
- mean iPTH value < 31.8 pmol/L
- mean serum calcium 2.10 to 2.37 mmol/L
- mean serum phosphorus 1.13 to 1.78 mmol/L
- mean Ca x P < 4.44 $(mmol/L)^2$
- both a mean iPTH value < 31.8 pmol/L and mean Ca x P < 4.44 $mmol^2/L^2$

Secondary measures:

- Frequency, severity and relationship of all reported adverse events
- Changes in laboratory parameters and vital signs compared with placebo

Method of assessing outcomes:

Blood samples for the measurement of iPTH, serum calcium, serum phosphorus, and Ca x P were obtained at least every 2 weeks during the dose-titration and maintenance phases

Biochemical results obtained in the separate trials pooled and compared with the NKF-K/DOQI target values

Length of follow-up:

Study duration 26 weeks

RESULTS

PRIMARY OUTCOMES Number (%)of subjects achieving K/DOQI targets	Placebo (N=409)	Cinacalcet (N=547)
Mean iPTH $\leq$ 31.8 pmol/L		
Baseline	2 (<1%)	2 (<1%)
Maintenance phase	42 (10%)	307 (56%)
P<0.001		
Mean Serum Calcium 2.10-2.37 mmol/L		
Baseline	133 (33%)	176 (32%)

Maintenance phase	100 (24%)	270 (49%)
P<0.001		
Mean Serum Phosphorus 1.13-1.78 mmol/L		
Baseline	126 (31%)	179 (33%)
Maintenance Phase	136 (33%)	250 (46%)
P<0.001		
Mean Ca x P <4.44 $mmol^2/L^2$		
Baseline	139 (34%)	203 (37%)
Maintenance Phase	148 (36%)	357 (65%)
P<0.001		
Mean iPTH ≤ 31.8 pmol/L and mean Ca x P <4.44 $mmol^2/L^2$		
Baseline	0 (0%)	0 (0%)
Maintenance Phase (from graph)	25 (6%)	224 (41%)
Week 14	7.9%	38.6%
Week 16	7.5%	39.9%
Week18	8.8%	40.4%
Week 20	8.8%	41.2%
Week 22	9.7%	43.4%
Week 24	8.8%	41.7%
Week 26	7.9%	43.0%
P<0.001		
P values are for comparison of cinacalcet and placebo during the maintenance phase		

Proportion (%)of subjects achieving K/DOQI targets in individual trials

	Study A		Study B		Study C	
	Placebo	Cinacalcet	Placebo	Cinacalcet	Placebo	Cinacalcet
PTH	10%	60%	11%	60%	10%	51%
Ca x P	34%	63%	35%	67%	43%	66%
Calcium	26%	54%	23%	55%	24%	43%
Phosphorus	32%	40%	30%	48%	42%	48%
PTH and Ca x P	5%	44%	7%	40%	6%	39%

Proportion (%) of subjects achieving K/DOQI targets by baseline PTH stratification

(mild= 31-53, mod = 53.1-84.8, sev = >84.8 pmol/L)

	Placebo (N = 409)					Cinacalcet (N = 547)				
	PTH	Ca x P	Calcium	Phos	PTH and Ca x P	PTH	Ca x P	Calcium	Phos	PTH and Ca x P

Mild	21%	51%	28%	40%	14%	81%	70%	48%	48%	59%
Mod	4%	28%	24%	30%	<1%	60%	68%	54%	47%	42%

Proportion of subjects achieving K/DOQI target levels by baseline Ca x P stratification

	Placebo (N = 409)					Cinacalcet (N=547)				
	PTH	Ca x P	Calcium	Phos	PTH and Ca x P	PTH	Ca x P	Calcium	Phos	PTH and Ca x P
< 5.65 $mmol^2/L^2$	13%	46%	26%	42%	8%	60%	77%	51%	53%	50%
≥ 5.65 $mmol^2/L^2$	4%	10%	19%	10%	<1%	46%	37%	46%	27%	19%
Severe	1%	21%	19%	26%	1%	22%	56%	45%	40%	18%

SECONDARY OUTCOMES	Placebo (n = 470)	Cinacalcet (N = 656)
Adverse Events		
Mortality	3%	2%
Withdrawal due to adverse events	8%	15%
Serious adverse events	31%	29%
Adverse events >5% more frequently in cinacalcet-treated subjects compared with placebo:		
Nausea	19%	31%
Vomiting	15%	27%

METHODOLOGICAL COMMENTS

Selection / randomisation: Randomisation method not detailed

Trials A and B

- Randomised in 1:1 ratio to receive cinacalcet or placebo
- Randomisation stratified by mean baseline iPTH level (31.8 to 53, 53.1 to 84.8, or >84.8 pmol/L)] and by baseline Ca x P level (≤5.65 or >5.65 $mmol^2/L^2$)

Study C

- Randomised in 3:1 ratio to receive cinacalcet or placebo
- Randomisation stratified by dialysis modality, and randomisation of haemodialysis subjects was further stratified by baseline iPTH level.

Groups similar at baseline? Yes. More peritoneal dialysis subjects in the cinacalcet group as the study from which this data was taken had 3:1 randomisation.

Eligibility criteria stated? Yes

Blinding: Double blind – not details provided

Outcome measures: Objective

ITT: No.

- Efficacy analyses included all subjects with at least one value recorded during the maintenance phase: 547/665 (82%) cinacalcet subjects and 409/471 (87%) placebo subjects.
- Safety analysis included all subjects who received at least one dose of study drug: 656/665 (99%) cinacalcet subjects and 470/471 (99%) placebo subjects

Protocol violations specified: None specified

Follow-up / attrition: All subjects accounted for?

No

Withdrawal specified?

Yes

Withdrawal reasons given? Yes, but for adverse events only.

- 15% of cinacalcet-treated subjects withdrew from study because of adverse events
- 8% of placebo-treated subjects withdrew from study because of adverse events
- Withdrawals in the cinacalcet-treated group were primarily due to nausea or vomiting

Data analysis: Statistical tests used

- Logistic regression model was used to examine whether it was appropriate to combine data from the three trials (treatment effect did not differ between trials)
- Cochran-Mantel-Haenszel (CMH) test, stratified by study, was used to examine differences between treatment groups
- Two-tailed P values <0.05 were considered statistically significant

Power calculation at design? Not stated

Generalisability: Nearly all subjects had iPTH values > 31.8 pmol/L at baseline

More than 20% of subjects overall had severe secondary hyperparathyroidism (iPTH >800 pg/mL) at baseline.

Approximately two thirds of subjects had baseline values for serum calcium, phosphorus and Ca x P above the K/DOQI targets.

Most subjects were undergoing haemodialysis (peritoneal dialysis only accounts for 4% of subjects)

Conflict of interest: Study A (20000172), study B (20000183) and study C (20000188) were supported by Amgen.

GENERAL COMMENTS

COMBINED ANALYSIS OF 20000172, 20000183 and 20000188

STUDY	INTERVENTION
Quarles *et al.*, 2003 ***Country:*** United States ***Setting:*** Multiple centres (17) ***Recruitment dates:*** Not stated ***Study design:*** Randomised, double blind, placebo-controlled study	After screening period, subjects were randomised at 1:1 ratio to placebo or cinacalcet. ***Intervention:*** Cinacalcet ***Intervention regimen:*** <u>12 week dose titration phase</u> ▪ Initially cinacalcet 25mg orally once daily

SUBJECTS

Total number: 71

Cinacalcet n = 36; Placebo n = 35

Inclusion criteria:

- Treated for at least 3 months with haemodialysis
- Subjects had uncontrolled secondary hyperparathyroidism (mean PTH ≥ 300pg/ml) despite availability of standard care (phosphate binders and/or vitamin D sterols)
- Age ≥18 yr
- Serum Ca^{2+} ≥8.8 mg/dl and <11.0 mg/dl
- Serum phosphorus ≥2.5 mg/dl
- Calcium x phosphorus <70 mg^2/dl^2

Exclusion criteria:

- Vitamin D sterol dose changes during 21 days before enrolment.
- Dialysis calcium concentration, the dose of any supplements, and the dose of oral phosphate binders changed during the 7 days before enrolment.
- Evidence of active infectious or malignant process or diseases known to cause hypercalcaemia
- Haemoglobin concentration <9 g/dl or a haematocrit <27%
- Liver transaminases and bilirubin concentrations more than twice the upper limit of normal

Sub-groups

Randomisation was not stratified; however, sensitivity analysis was conducted on the following groups:

Group 1 – Increase in vitamin D sterol from enrolment to maintenance phase
Group 2 - Decrease in vitamin D sterol from enrolment to maintenance phase
Group 3 – No change in vitamin D sterol dose from enrolment to maintenance.

- Dose increases through 50, 75 or 100mg were permitted at week 3,6, and 9 of the study, until subjects had achieved both a reduction in iPTH of ≥30% from baseline and an absolute PTH ≤250pg/ml.
  - o Dose increase was permitted provided;
    - serum Ca^{2+} was ≥7.8 mg/dl
    - subject was not receiving the 100mg/day dose
    - subject was not experiencing an adverse event that would preclude a dose increase.
  - o Dose reduction occurred if the mean iPTH was <100pg/ml

6 week maintenance phase

- Subjects remained on dose of cinacalcet reached at end of the titration phase (25mg n = 7, 50mg n = 4, 75mg n = 6, 100 mg n=17)

Comparator regimen:

Placebo

Concurrent treatment:

- Phosphate binders permitted without restrictions, dose changes permitted without restriction.
- Vitamin D sterols permitted.
  - o Increases in dose permitted if;
    - iPTH≥50% baseline and >600pg/ml or
    - serum Ca^{2+} <8.4mg/dl.
  - o Decreases in dose permitted if;
    - Serum Ca^{2+} >11.0mg/dl or
    - Serum phosphorus ≥ 6.5mg/dl or
    - Ca x P ≥70$(mg/dl)^2$ or
    - iPTH<100pg/ml on lowest dose of Cinacalcet.
- Dialysate Ca^{2+} concentration could be changed as needed

SUBJECT CHARACTERISTICS

Mean	Placebo	Cinacalcet
N:	35	36
Age *yrs* (SD)	47.9 (14.2)	49.6 (8.5)
Sex:		
M	17 (49%)	27 (75%)
F	18 (51%)	9 (25%)
Race:		
African American	23 (66%)	27 (75%)
White	11 (31%)	9 (25%)
Hispanic	1 (3%)	0 (0%)
Duration of dialysis *mths* (SD)	71.1 (66.2)	71.3 (54.3)
Use of vitamin D sterols	24 (69%)	22 (61%)
Use of phosphate binders	33 (94%)	36 (100%)

Notes: significant difference between control and cinacalcet in the number of females per group (p=0.022)

OUTCOME MEASURES

Primary outcome measure:

- % subjects achieving mean reduction of ≥ 30% iPTH during maintenance phase

Secondary measures:

- % subjects achieving mean reduction iPTH to ≤250 pg/ml
- Mean % change from baseline in;
  - o PTH
  - o serum Ca^{2+}
  - o serum phosphorus
  - o calcium x phosphorus

Method of assessing outcomes:

- Biochemical measurements were made at weekly visits.
- All chemistries and PTH determination were performed at a central laboratory.
  - o Plasma PTH concentrations were determined using a double-antibody immunoradiometric assay for the intact hormone.
  - o Calcium and phosphorus levels were performed using standard methodology.
- Safety information was collected from physical exams, electrocardiograms, safety chemistry and haematology laboratory assessments, and subject-reported symptoms and hospitalisations.

Length of follow-up:

Study duration 18 weeks

RESULTS

PRIMARY OUTCOMES	Placebo (N= 35)	Cinacalcet (N=36)
% subjects achieving mean PTH reduction ≥30% from baseline during maintenance phase	23%	53% (p=0.009)

SECONDARY OUTCOMES	Placebo (N = 35)	Cinacalcet (N= 36)
% subjects achieving mean reductions in PTH to ≤250 pg/ml during maintenance phase	20%	44% (p=0.029)

Biochemistry measures (mean (SE))	Placebo			Cinacalcet			P (between groups)
	Baseline	Wk 13 -18	% change	Baseline	Wk13 -18	% change	
Plasma parathyroid hormone (pg/ml]	583 (72)	552 (87)	3.0 (8.5)	626 (53)	451 (74)	-32.5 (7.6)	<0.001
Serum Ca^{2+} (mg/dl)	9.7 (0.1)	9.9 (0.1)	2.6 (1.3)	9.6 (0.1)	9.2 (0.1)	-4.6 (1.4)	<0.001
Serum Phosphorus (mg/dl)	5.5 (0.2)	5.7 (0.2)	7.0 (5.5)	6.0 (0.2)	5.8 (0.2)	-2.6 (3.4)	0.217
Calcium-phosphorus product (mg^2/dl^2)	53.4 (2.3)	56.6 (2.3)	11.0 (6.5)	57.6 (1.6)	53.1 (1.8)	-7.9 (2.9)	0.013

From Grapically presented data

Mean % change from baseline in PTH at week:	**13**	**14**	**15**	**16**	**17**	**18**
Placebo	1	6	2	6	6	6
Cinacalcet	-40	-30	-34	-31	-28	-25

- p<0.001

From Grapically presented data

Mean % change from baseline in Ca at week:	**13**	**14**	**15**	**16**	**17**	**18**
Placebo	2.4	3.0	4.1	0.7	1.1	3.9
Cinacalcet	-5.7	-2.7	-2.5	-5.3	-7.2	-5.5

- p<0.001

From Grapically presented data

Mean % change from baseline in serum phosphorus at week:	**13**	**14**	**15**	**16**	**17**	**18**
Placebo	6.8	8.4	1.2	6.2	6.7	10.0

METHODOLOGICAL COMMENTS

Selection / randomisation:	Subjects randomised by interactive voice response system at a 1:1 ratio No stratification factors
Groups similar at baseline?	Yes, with exception of gender: significant difference between no. of females in treatment groups. (51% in placebo group, vs 25% in Cinacalcet group, p=0.022).
Eligibility criteria stated?	Yes
Blinding:	Double-blind- not detailed
Outcome measures:	Objective
ITT:	Yes
Protocol violations specified:	None stated
Follow-up / attrition:	All subjects accounted for? No Withdrawal specified? 2 subjects from cinacalcet group and 4 subjects from the placebo group withdrew during the dose-titration phase. No subjects withdrew during the maintenance phase. Withdrawal reasons given? No
Data analysis:	Statistical tests used: ▪ ANOVA model used to compare mean % change from baseline for iPTH, serum calcium, phosphorus and calcium x phosphorus between groups. ▪ Unclear what tests were used for primary endpoint
Power calculation at design?	Sample size of 71 allowed an 84% power to show a 33% difference between treatment groups in the proportion of subjects who could achieve a mean reduction in iPTH of $\geq$30% during the maintenance phase of the study (primary endpoint) Study not powered for secondary endpoint
Generalisability:	Yes, although proportion of African American subjects fairly high Compliance was 96% Effects were independent of whether or not subjects received vitamin D sterols and whether the dose was changed.
Conflict of interest:	Funding provided by Amgen Inc.

GENERAL COMMENTS

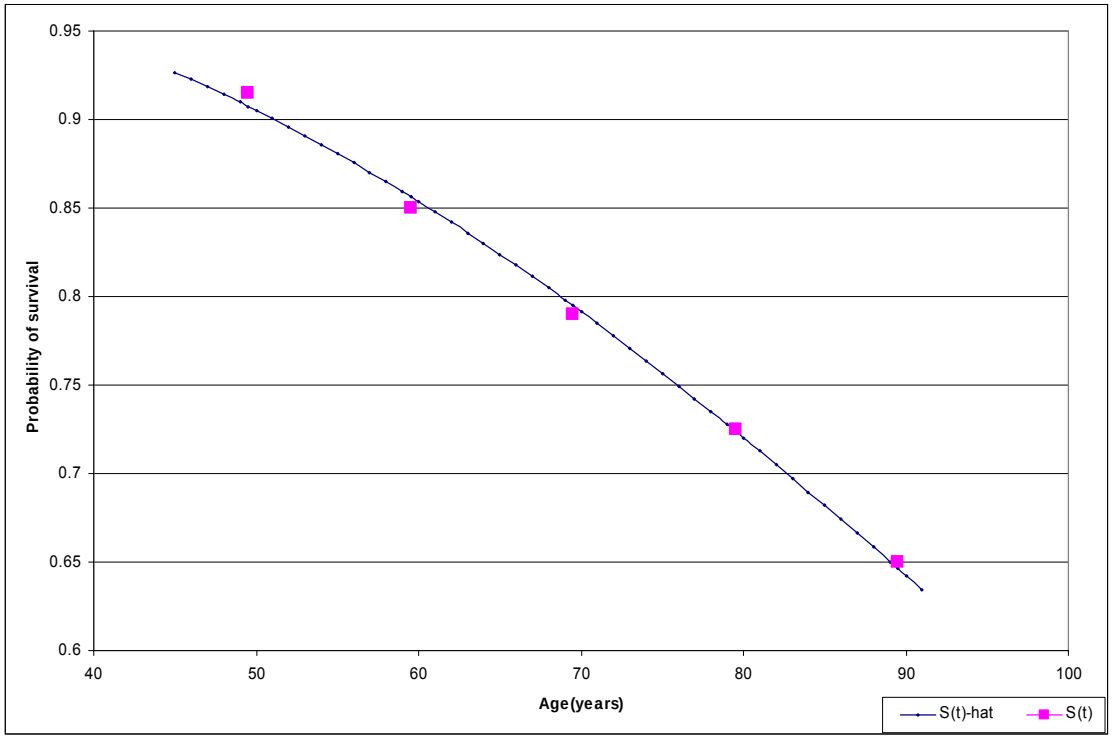
A NUMBER OF THE AUTHORS INVOLVED IN PHASE III TRIALS (2000172, 2000183, 20000188)

8.8 Appendix 8: Estimating the annual death rate from death rate in 10-year age bands

The graph from which mortality rates are derived (Renal Registry Fig 5.18[12]) shows death rates for age groups in 10-year bands. For each of these 10-year categories the probability of death at the start and end are very different. We therefore derived annual probabilities using the following method.

A Weibull curve was fitted to the published data. The lamda and gamma parameters used to describe the curve were derived using the ordinary least squares (OLS) method. The R^2 value derived for the fitted curve was 0.995, suggesting that the Weibull function was an acceptable fit to the data. The figure below shows the curve fitted to the values shown in Table 36 (p.111).

Weibull curve fitted to Renal registry mortality data



The parameter values used in plotting the curve are:

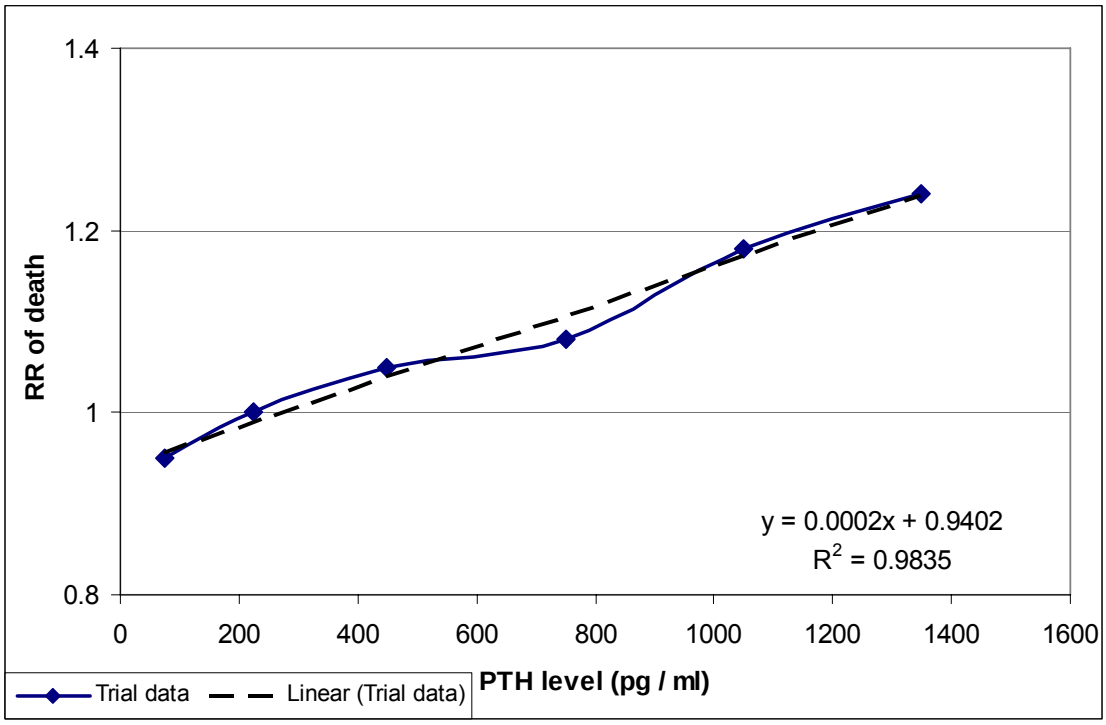
Lamda = $4.85*10^{-6}$

Gamma = 2.538

8.9 Appendix 9: Calculating the relative risk of mortality based on PTH level

A plot of the midpoint of each of the PTH ranges reported by Block and colleagues[18] against the quoted RR is shown in the figure below, with the reference case at 200pg/ml (21.2pmol/L) as the reference population has PTH of 100-300mg/L. The fitted linear trend is shown as a dashed line and is an excellent approximation to the published data. The PenTAG model is based on PTH ranges reported in the RCTs of cinacalcet, these are <32pmol/L, 32–85pmol/L and ≥ 85pmol/L. Relative risk values for mid points in these ranges can be calculated by interpolation.

RR of death by PTH level reported by Block and colleagues (2004)[18]



8.10 Appendix 10: CV death in the economic model

CV Deaths as a proportion of total deaths

To model the probability of CV death from each health state in the model a series of data points and a process of weighting was used. First, the overall probability of death from CV causes was assigned from data provided by the Renal Registry.[12] This shows that for patients who spent 3-5 years on RRT, cardiac disease was responsible for 41.1% of deaths and cerebrovascular disease, which is also likely to be influenced by calcification, was responsible for 7.8%. This gives a total of 48.9% of deaths due to CV causes. This value is similar to figures quoted for the USA.[81] Assuming this reflects the proportion of deaths in patients with SHPT, the proportion of deaths due to other causes will be 51.1%. Since mortality rates increase with age, the value for overall CV death will be a time dependant probability. This value is then modified using the methods described below to derive individual values for this transition probability for each state in the model.

Base level CV death probability (for those with "controlled" levels of PTH) per cycle (55 yr olds) = 0.0312*0.489 = 0.0153
Scale Factors:
Controlled PTH = 1 (ref)
Uncontrolled PTH = 1.06131
Very Unstable PTH = 1.1824
Post surgical (no AE) = 1.0287
Post surgical with AE = 1.0287

Baseline reference State	Index	Wgt Applied	State specific scaling Co-eff.	Resultant Transition Prob. (55 Yr olds) per cycle	Effective yearly rate (%)
	cEVF	1	1 *0.425 (3 d.p)	0.0065	2.6 %
	cCVE	1	13.21*0.425	0.0856	35.8%
cEVF	cFRE	1	1.91*0.425	0.0124	4.98%
(Av. Prob. 0.0153)	cCVH	1	2.9*0.425	0.0188	7.59%
	cFRH	1	1.87*0.425	0.0121	4.88%
	cCFE	1	1.91*0.425	0.0124	4.98%
	cCFH	1	1.91*0.425	0.0124	4.98%
	uEVF	1.06131	1 *0.425 (3 d.p)	0.0069	2.76%
	uCVE	1.06131	13.21*0.425	0.909	38.11%
uEVF	uFRE	1.06131	1.91*0.425	0.0131	5.29%
(Av. Prob. 0.016)	uCVH	1.06131	2.9*0.425	0.0199	8.06%
	uFRH	1.06131	1.87*0.425	0.0129	5.18%
	uCFE	1.06131	1.91*0.425	0.0131	5.29%
	uCFH	1.06131	1.91*0.425	0.0131	5.29%
	vEVF	1.1824	1 *0.425 (3 d.p)	0.0077	3.19%
	vCVE	1.1824	13.21*0.425	0.1013	42.71%
vEVF	vFRE	1.1824	1.91*0.425	0.0146	5.9%
(Av. Prob. 0.0229)	vCVH	1.1824	2.9*0.425	0.0222	9%
	vFRH	1.1824	1.87*0.425	0.0143	5.78%
	vCFE	1.1824	1.91*0.425	0.0146	5.9%
	vCFH	1.1824	1.91*0.425	0.0146	5.9%
	pEVF	1.0287	1 *0.425 (3 d.p)	0.0067	2.67%
	pCVE	1.0287	13.21*0.425	0.0881	36.89%
pEVF	pFRE	1.0287	1.91*0.425	0.0127	5.12%
(Av. Prob. 0.0204)	pCVH	1.0287	2.9*0.425	0.0193	7.81%
	pFRH	1.0287	1.87*0.425	0.0125	5%
	pCFE	1.0287	1.91*0.425	0.0127	5.12%
	pCFH	1.0287	1.91*0.425	0.0127	5.12%
aEVF	aEVF	1.0287	1 *0.425 (3 d.p)	0.0067	2.67%
(Av. Prob. 0.0204)	aCVE	1.0287	13.21*0.425	0.0881	36.89%
	aFRE	1.0287	2.9*0.425	0.0127	5.12%
	aCVH	1.0287	1.22*0.425	0.0193	7.81%
	aFRH	1.0287	1.87*0.425	0.0125	5%
	aCFE	1.0287	1.91*0.425	0.0127	5.12%

	aCFH	1.0287	1.91*0.425	0.0127	5.12%

Calculation of age dependant all cause-mortality probabilities

The general equation for the survival probability S(t) for a variable that follows a Weibull distribution is:

$$S(t) = \exp\{-\lambda * t^{\gamma}\}$$

With the values of Lamda and Gamma being curve specific. Therefore, the probability of death in time period t is 1-S(t). In our model the time period used in these calculations is a year. This death probability is then used to derive the age dependant cycle rate using the formula:

$$Cycle\,rate = [-\ln(1 - yearly\ probability)] / Number\ of\ cycles\ per\ year$$

In the context of our model, these values represent the average rates of death per cycle for all people receiving renal replacement therapy rather than for people with secondary hyperparathyroidism. Finally, the probabilities of death are derived from these rates using the formula

$$Cycle\ probability = 1 - \exp\{-Cycle\,rate\}$$

Age dependant probabilities used in the PenTAG model.

Age	Event probability	Age	Event probability
45	0.01887	73	0.06299
46	0.01994	74	0.06513
47	0.02105	75	0.06731
48	0.02219	76	0.06953
49	0.02337	77	0.07179
50	0.02459	78	0.07409
51	0.02584	79	0.07643
52	0.02713	80	0.07881
53	0.02845	81	0.08123
54	0.02981	82	0.08369
55	0.03121	83	0.08618
56	0.03265	84	0.08872
57	0.03412	85	0.09130
58	0.03564	86	0.09392
59	0.03719	87	0.09658
60	0.03878	88	0.09927
61	0.04040	89	0.10201
62	0.04207	90	0.10479
63	0.04377	91	0.10760
64	0.04552	92	0.11045
65	0.04730	93	0.11335
66	0.04912	94	0.11628
67	0.05099	95	0.11925
68	0.05289	96	0.12225
69	0.05483	97	0.12530
70	0.05681	98	0.12838
71	0.05883	99	0.13150
72	0.06089	100	0.13466

Calculation of Transition Probabilities

For each state within the model the transition probabilities for CV death have been calculated according to the two basic constraints:

1. The total number of CV deaths from each of the strata equals the expected number given the known proportion CV deaths overall, and

2. The relative risk of CV deaths between states at each level of PTH control, as determined by the data sources described above, is maintained. The method for achieving this calculation is described textually and graphically below.

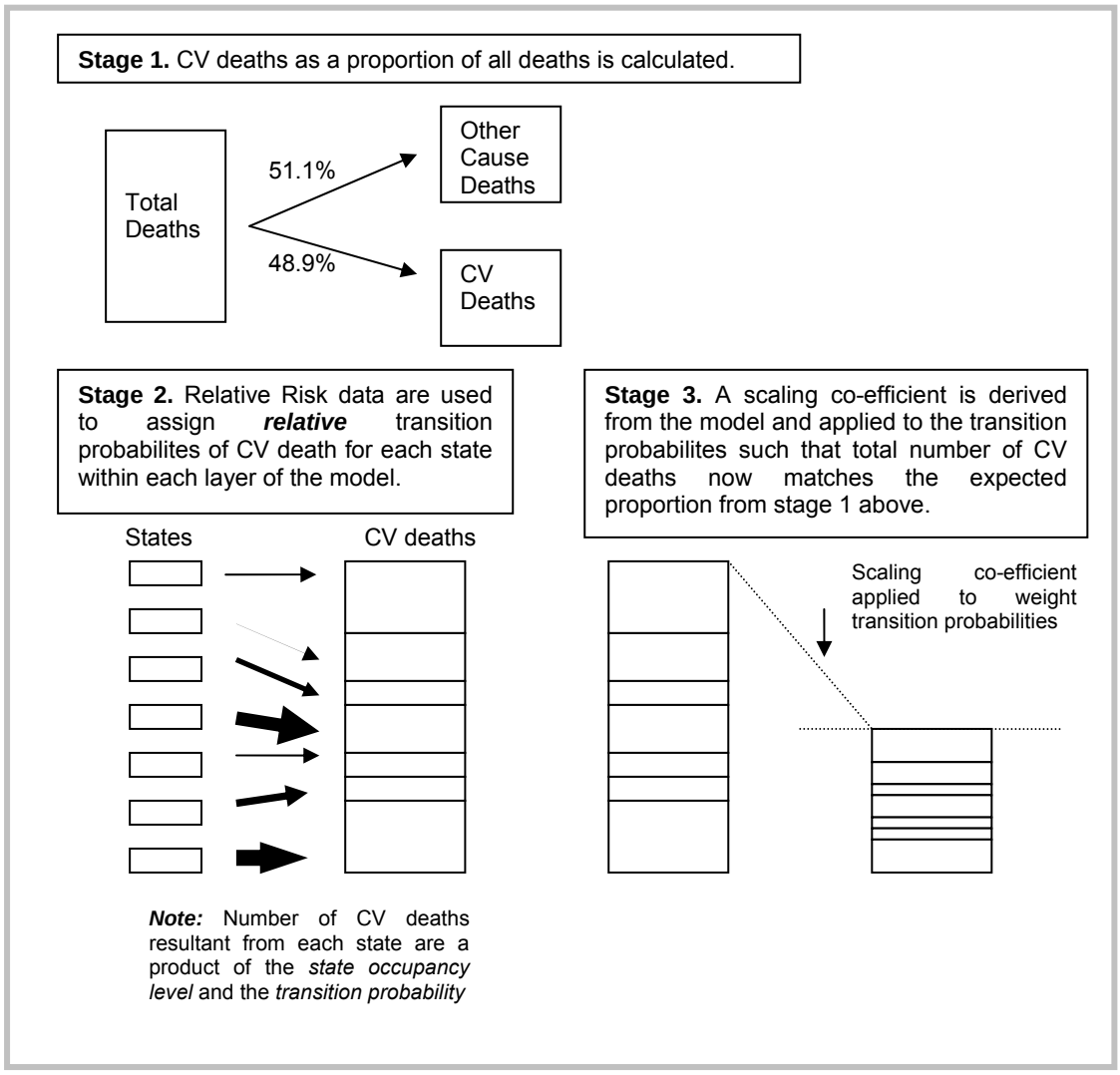
To summarise, the average probability of dying due to CV related causes is scaled in the following ways to compute a transition probability for each specific health state in the model:

1. A scaled weighting factor is used to compute the average probability of CV-related death for each of the model strata.
2. The relative risk of CV-related death from all other health states in the model (EVF, FRE, CVH, FRH, CVE, CFE, CFH) have been assessed from data provided by Table 38. These RR's are used together with the overall state occupancies to derive specific CV death transition probabilities for each health state. This is done by scaling the base level of CV death at each level of PTH control for each health state.
3. The coefficients used for scaling transition probabilities described above are applied uniformly regardless of the degree of control of PTH levels. Microsoft Solver was used to derive the coefficients as a recursive process is involved in this calculation.

The scale factors used in the model and the calculation of the resultant transition probabilities for CV death from each health state are shown above.

The process by which transition probabilities of CV death from each of the individual states within the model is described diagrammatically in Figure 22.

Figure 22 *Illustration of derivation of CV mortality*



8.11 Appendix 11 Calculation of the cost of dialysis

There are few recent or good quality data on the cost of either haemodialysis or peritoneal dialysis in the UK. In a recent *Health Technology Assessment* report, Mowatt and colleagues estimated the cost of haemodialysis at hospital, at satellite renal units and at home.[98] We have used the hospital haemodialysis costs excluding training and access costs, and the cost of interdialytic complications (to avoid possible double-counting of fracture-related and CV-event related hospitalisations). The majority (64%) of haemodialysis patients receive haemodialysis in hospital, with most of the remainder receiving treatment in satellite dialysis units rather than at home.[15] The only available evidence suggests that the cost of receiving haemodialysis in hospital and satellite units is similar.[98]

UK Renal Registry data show that for 55- to 64-year olds the proportion of dialysis patients on haemodialysis and peritoneal dialysis at the end of December 2003 was 71% and 29% respectively.[15] As patients get older, and more unwell, a higher proportion switch from peritoneal dialysis to haemodialysis, so we may have underestimated the proportion of ESRD patients with SHPT who would be on the more expensive mode of dialysis.

The best estimates of the cost of peritoneal dialysis are based on international evidence that suggests it is considerably cheaper than haemodialysis. The only available UK evidence (a 1989 study from Wales, by Smith and colleagues) indicates it was about half the cost of haemodialysis.[107] We have therefore crudely assumed that peritoneal dialysis is half the current cost of haemodialysis, but varied the whole weighted average cost of haemodialysis widely in the sensitivity analysis.

Annual cost of dialysis

	As per Mowatt and colleagues 2003 (£)[a]			*Weighted average (£)*			
	Mean	*Low*	*High*	*%*	*Mean*	*Low*	*High*
Annual cost of haemodialysis	18,296	9,148	27,445	71%[b]	12,990	6,495	19,486
Annual cost of peritoneal dialysis	9,148	4,574	13,722	29%[b]	2,653	1,326	3,979
Weighted average cost of dialysis				100%	15,643	7,822	23,456

a. Source: Table 12, p.60 costs of hospital haemodialysis inflated to 2005 £ values (nb. excluding access costs, training costs and the cost of interdialytic complications)[98]
b. Source: Table 5.10, p.13 of chapter 5, of UK Renal Registry Seventh Annual Report.[15]

8.12 Appendix 12: Reference List

(1) Joint Specialty Committee on Renal Disease. Chronic Kidney Disease in Adults: UK Guidelines for Identification, Management and Referral of Adults. 2005. London, The Renal Association & Royal College of Physicians.

(2) Coladonato JA, Ritz E. Secondary hyperparathyroidism and its therapy as a cardiovascular risk factor among end-stage renal disease patients. Advances in Renal Replacement Therapy 2002; 9(3):193-199.

(3) de Francisco ALM. Secondary hyperparathyroidism: Review of the disease and its treatment. Clinical Therapeutics 2004; 26(12):1976-1993.

(4) DH Renal NSF team. The National Service Framework for Renal Services. Part One: Dialysis and Transplantation. London: Department of Health; 2004.

(5) Renal Association. Chronic Kidney Disease in Adults: UK Guidelines for Identification, Management & Referral. 2005.

(6) Sexton J, Vincent M. Remedying calcium and phosphate problems in chronic kidney disease. Pharmaceutical Journal 2005; 274(7348):561-564.

(7) Drueke TB, Ritz E. Skeletal disorders. In: Davison A, Cameron JS, Grunfeld J-P, Porticelli C, Ritz E, Winearls CG et al., editors. Oxford Textbook of Clinical Nephrology. 3rd ed. Oxford: Oxford University Press; 2005. 1-71.

(8) Drueke TB. The place of calcium and calcimimetics in the treatment of secondary hyperparathyroidism. Nephrol Dial Transplant 2001; 16(SUPPL. 6):15-17.

(9) The Renal Association. Treatment of adults and children with renal failure - Standards and audit measures. 3rd ed. 2002.

(10) Block GA, Hulbert-Shearon TE, Levin NW, Port FK. Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: a national study. Am J Kidney Dis 1998; 31(4):607-617.

(11) Ehrlich JE, Rumberger JA. Detection and Clinical Management of Cardiovascular Calcification in ESRD: A review. Dialysis & Transplantation 2004; 33(6):306-313.

(12) Ansell D, Feest T, Byrne C, Ahmad A, et al. UK Renal Registry - the Sixth Annual Report. Ansell D, Feest D, editors. ISSN 1471-3349, i-414. 2003. The Renal Association.

(13) Cannata Andia JB. Adynamic bone and chronic renal failure: an overview. American Journal of the Medical Sciences 2000; 320(2):81-84.

(14) Khan I, Catto GRD, Edward N, MacLeod AM. Chronic Renal Failure; factors influencing nephrology referral. QJM 1994; 87:559-564.

(15) Ansell D, Feest T, Ahmad A, Rao R. UK Renal Registry 7th Annual Report. 7. 2004. The Renal Association.

(16) Feest TG, Mistry CD, Grimes DS, Mallick NP. Incidence of advanced chronic renal failure and the need for end-stage renal replacement therapy. BMJ 1990; 301:987-990.

(17) DH Renal NSF team. National Service Framework for Renal Services. Part Two: Chronic kidney disease, acute renal failure end of life care. London: Department of Health; 2005.

(18) Block GA, Klassen P, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM. Mineral Metabolism, Mortality, and Morbidity in maintainance Hemodialysis. J Am Soc Nephrol 2004; 15:2208-2218.

(19) Foley RN, Parfrey PS. Cardiovascular disease and mortality in ESRD. Journal of Nephrology 1998; 11(5):239-245.

(20) Chandna SM, Schulz J, Lawrence C, Greenwood RN, Farrington K. Is there a rationale for rationing chronic dialysis? A hospital based cohort study of factors affecting survival and morbidity. BMJ 1999; 318(7178):217-223.

(21) Lowrie EG, Lew NL. Death risk in hemodialysis patients: the predictive value of commonly measured variables and an evaluation of death rate differences between facilities. Am J Kidney Dis 1990; 15(5):458-482.

(22) Goodman WG, Goldin J, Kuizon BD, Yoon C, Gales B, Sider D et al. Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. New England Journal of Medicine 2000; 342(20):1478-1483.

(23) Braun J, Oldendorf M, Moshage W, Heidler R, Zeitler E, Luft F. Electron beam computed tomography in the evaluation of cardiac calcification in chronic dialysis patients. American Journal of Kidney Diseases 1996; 27(3):394-401.

(24) McCullough PA, Soman S. Cardiovascular calcification in patients with chronic renal failure: Are we on target with this risk factor? Kidney International 2004; 66:S18-S24.

(25) Buccianti G, Baragetti I, Bamonti F, Furiani S, Dorighet V, Patrosso C. Plasma homocysteine levels and cardiovascular mortality in patients with end-stage renal disease. Journal of Nephrology 2004; 17(3):405-410.

(26) Ball AM, Gillen DL, Sherrard D, Weiss NS, Emerson SS, Seliger SL et al. Risk of Hip Fracture Among Dialysis and Renal Transplant Recipients. JAMA 2002; 288(23):3014-3018.

(27) Taal MW, Masud T, Green D, Cassidy MJD. Risk factors for reduced bone density in haemodialysis patients. Nephrol Dial Transplant 1999; 14(8):1922-1928.

(28) Jaar BG, Coresh J, Plantinga LC, Fink NE, Klag MJ, Levey AS et al. Comparing the Risk for Death with Peritoneal Dialysis and Hemodialysis in a National Cohort of Patients with Chronic Kidney Disease. Ann Intern Med 2005; 143(3):174-183.

(29) Loghman-Adham M. Medication noncompliance in patients with chronic disease: Issues in dialysis and renal transplantation. American Journal of Managed Care 2003; 9(2):155-171.

(30) Quarles LD. Cinacalcet HCl: A novel treatment for secondary hyperparathyroidism in stage 5 chronic kidney disease. Kidney International 2005; 68:S24-S28.

(31) Oxford Textbook of Medicine. 4th ed. Oxford: Oxford University Press; 2003.

(32) Cozzolino MF, Gallieni MF, Corsi CF, Bastagli AF, Brancaccio D. Management of calcium refilling post-parathyroidectomy in end-stage renal disease. Journal of Nephrology 2004; 17:3-8.

(33) Koonsman M, Hughes K, Dickerman R, Brinker K, Dunn E. Parathyroidectomy in chronic renal failure. The American Journal of Surgery 1994; 168(6):631-635.

(34) Chow KM, Szeto CC, Kum LC, Kwan BC, Fung TM, Wong TY et al. Improved health-related quality of life and left ventricular hypertrophy among dialysis patients treated with parathyroidectomy. Journal of Nephrology 2003; 16(6):878-885.

(35) Chou FF, Chen JB, Lee CH, Chen SH, Sheen-Chen SM. Parathyroidectomy can improve bone mineral density in patients with symptomatic secondary hyperparathyroidism. Arch Surg 2001; 136(9):1064-1068.

(36) Elder G. Parathyroidectomy in the calcimimetic era. Nephrology 2005; 10(5):511-515.

(37) Young EW, Albert JM, Satayathum S, Goodkin DA, Pisoni RL, Akiba T et al. Predictors and consequences of altered mineral metabolism: The Dialysis Outcomes and Practice Patterns Study. Kidney International 2005; 67(3):1179-1187.

(38) Young EW, Akiba T, Albert JM, McCarthy JT, Kerr PG, Mendelssohn DC et al. Magnitude and impact of abnormal mineral metabolism in hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study (DOPPS). American Journal of Kidney Diseases 2004; 44(5):34-38.

(39) Chow FY, Briganti EM, Kerr PG, Chadban SJ, Zimmet PZ, Atkins RC. Health-related quality of life in Australian adults with renal insufficiency: a population-based study. American Journal of Kidney Diseases 2003; 41(3):596-604.

(40) Cagney KA, Wu AW, Fink NE, Jenckes MW, Meyer KB, Bass EB et al. Formal literature review of quality-of-life instruments used in end-stage renal disease. American Journal of Kidney Diseases 2000; 36(2):327-336.

(41) Moreno F, Lopez Gomez JM, Sanz-Guajardo D, Jofre R, Valderrabano F. Quality of life in dialysis patients. A Spanish multicentre study. Nephrol Dial Transplant 1996; 11(SUPPL. 2):125-129.

(42) Rebollo P, Ortega F. New trends on health related quality of life assessment in end-stage renal disease patients. International Urology & Nephrology 2002; 33(1):195-202.

(43) Churchill DN, Morgan J, Torrance GW. Quality of life in end stage renal disease. Peritoneal Dialysis International 1984; 4(1):20-23.

(44) Churchill DN, Torrance GW, Taylor DW, Barnes CC, Ludwin D, Shimizu A et al. Measurement of quality of life in end-stage renal disease: the time trade-off approach. Clin Invest Med 1987; 10(1):14-20.

(45) Churchill DN, Wallace JE, Ludwin D, Beecroft ML, Taylor DW. A comparison of evaluative indices of quality of life and cognitive function in hemodialysis patients. Control Clin Trials 1991; 12(4 Suppl):159S-167S.

(46) de Wit GA, Ramsteijn PG, de Charro FT. Economic evaluation of end stage renal disease treatment. Health Policy 1998; 44(3):215-232.

(47) de Wit GA, Merkus MP, Krediet RT, de Charro FT. Health profiles and health preferences of dialysis patients. Nephrol Dial Transplant 2002; 17(1):86-92.

(48) Hornberger JC, Redelmeier DA, Petersen J. Variability among methods to assess patients' well-being and consequent effect on a cost-effectiveness analysis. J Clin Epidemiol 1992; 45(5):505-512.

(49) Molzahn AE, Northcott HC, Hayduk L. Quality of life of patients with end stage renal disease: a structural equation model. Qual Life Res 1996; 5(4):426-432.

(50) Devine EB, Smith KL, Stehman-Breen C, Patrick DL. Health-related quality of life assessment in chronic kidney disease. Expert Review of Pharmacoeconomics & Outcomes Research 2003; 3(1):89-100.

(51) Knight EL, Ofsthun N, Teng M, Lazarus JM, Curhan GC. The association between mental health, physical function, and hemodialysis mortality. Kidney International 2003; 63(5):1843-1851.

(52) Fukuhara S, Lopes AA, Bragg-Gresham JL, Kurokawa K, Mapes DL, Akizawa T et al. Health-related quality of life among dialysis patients on three continents: the Dialysis Outcomes and Practice Patterns Study. Kidney International 2003; 64(5):1903-1910.

(53) Valderrabano F, Jofre R, Lopez-Gomez JM. Quality of life in end-stage renal disease patients. American Journal of Kidney Diseases 2001; 38(3):443-464.

(54) Davison SN. Quality end-of-life care in dialysis units. Seminars in Dialysis 2002; 15(1):41-44.

(55) Kurella M, Suri RS, Chertow GM. Frequent hemodialysis and psychosocial function. Seminars in Dialysis 2005; 18(2):132-136.

(56) Kutner NG. Quality of life and daily hemodialysis. Seminars in Dialysis 2004; 17(2):92-98.

(57) Heidenheim AP, Kooistra MP, Lindsay RM. Quality of life. Contributions to Nephrology 2004; 145:99-105.

(58) McFarlane PA, Bayoumi AM, Pierratos A, Redelmeier DA. The quality of life and cost utility of home nocturnal and conventional in-center hemodialysis. Kidney International 2003; 64(3):1004-1011.

(59) Mingardi G, Cornalba L, Cortinovis E, Ruggiata R, Mosconi P, Apolone G. Health-related quality of life in dialysis patients. A report from an Italian study using the SF-36 Health Survey. Nephrol Dial Transplant 1999; 14(6):1503-1510.

(60) Lew SQ, Piraino B. Quality of life and psychological issues in peritoneal dialysis patients. [Review] [37 refs]. Seminars in Dialysis 2005; 18(2):119-123.

(61) Stefanovic V, Milojkovic M. Effects of physical exercise in patients with end stage renal failure, on dialysis and renal transplantation: current status and recommendations. International Journal of Artificial Organs 2005; 28(1):8-15.

(62) Byrnes CA, Shepler BM. Cinacalcet: A new treatment for secondary hyperparathyroidism in patients receiving hemodialysis. Pharmacotherapy 2005; 25(5 I):709-716.

(63) NHS Centre for Reviews and Dissemination. Undertaking Systematic Reviews of Research on Effectiveness. 2nd ed. York: NHS Centre for Reviews and Dissemination; 2001.

(64) Lindberg JS, Culleton B, Wong G, Borah MF, Clark RV, Shapiro WB et al. Cinacalcet HCl, an oral calcimimetic agent for the treatment of secondary hyperparathyroidism in hemodialysis and peritoneal dialysis: a randomized, double-blind, multicenter study. J Am Soc Nephrol 2005; 16(3):800-807.

(65) Goodman WG, Frazao JM, Goodkin DA, Turner SA, Liu W, Coburn JW. A calcimimetic agent lowers plasma parathyroid hormone levels in patients with secondary hyperparathyroidism. Kidney International 2000; 58(1):436-445.

(66) Harris RZ, Padhi D, Marbury TC, Noveck RJ, Salfi M, Sullivan JT. Pharmacokinetics, pharmacodynamics, and safety of cinacalcet hydrochloride in hemodialysis patients at doses up to 200 mg once daily. American Journal of Kidney Diseases 2004; 44(6):1070-1076.

(67) Goodman WG, Hladik GA, Turner SA, Blaisdell PW, Goodkin DA, Liu W et al. The calcimimetic agent AMG 073 lowers plasma parathyroid hormone levels in hemodialysis patients with secondary hyperparathyroidism. J Am Soc Nephrol 2002; 13(4):1017-1024.

(68) Block GA, Martin KJ, de Francisco ALM, Turner SA, Avram MM, Suranyi MG et al. Cinacalcet for Secondary Hyperparathyroidism in Patients Receiving Hemodialysis. New England Journal of Medicine 2004; 350(15):1516-1525.

(69) Cunningham J, Danese MD, Olson KA, Klassen P, Chertow GM. Effects of the calcimimetic cinacalcet HCl on cardiovascular disease, fracture, and health related quality of life in secondary hyperparathryoidism. Kidney International 2005; 68:1793-1800.

(70) Lindberg JS, Moe SM, Goodman WG, Coburn JW, Sprague SM, Liu W et al. The calcimimetic AMG 073 reduces parathyroid hormone and calcium x phosphorus in secondary hyperparathyroidism. Kidney International 2003; 63(1):248-254.

(71) Moe SM, Chertow GM, Coburn JW, Quarles LD, Goodman WG, Block GA et al. Achieving NKF-K/DOQI bone metabolism and disease treatment goals with cinacalcet HCl. Kidney International 2005; 67(2):760-771.

(72) Quarles LD, Sherrard DJ, Adler S, Rosansky SJ, McCary LC, Liu W et al. The calcimimetic AMG 073 as a potential treatment for secondary hyperparathyroidism of end-stage renal disease. J Am Soc Nephrol 2003; 14(3):575-583.

(73) Lien YH, Silva AL, Whittman D. Effects of cinacalcet on bone mineral density in patients with secondary hyperparathyroidism. Nephrol Dial Transplant 2005; 20(pp 1232-1237):-1237.

(74) Moe SM, Cunningham J, Bommer J, Adler S, Rosansky SJ, Urena-Torres P et al. Long term treatment of secondary hyperparathyroidism with the calcimimetic cinacalcet HCl. Nephrol Dial Transplant 2005; 20:2186-2193.

(75) Centre for Drug Evaluatiuon and Research FDA. Cinacalcet Medical Review. 2005 Available from: URL:http://www.fda.gov/cder/foi/nda/2004/21-688_Sensipar.htm

(76) Gupta A, Kallenbach LR, Zasuwa G, Divine GW. Race is a major determinant of secondary hyperparathyroidism in uremic patients. J Am Soc Nephrol 2000; 11(2):330-334.

(77) Department of Health. Reference Costs 2004. 2005. London, Department of Health.

(78) Brouwer W, Rutten F, Koopmanschapp M. Costing in economic evaluations. In: Drummond M, McGuire A, editors. Economic evaluation in health care: merging theory with practice. Oxford: Oxford University Press; 2005. 68-93.

(79) Garber AM, Weinstein MC, Torrance GW, Kamlet MS. Theoretical foundations of cost-effectiveness analysis. In: Gold MR, Siegel JE, Russell LB, Weinstein MC, editors. Cost-effectiveness in health and medicine. New York: Oxford University Press; 1996. 25-53.

(80) Stevens LA, Djurdjev O, Cardew S, Cameron EC, Levin A. Calcium, Phosphate, and Parathyroid Hormone Levels in Combination and as a Function of Dialysis Duration Predict Mortality: Evidence for the Complexity of the Association between Mineral Metabolism and Outcomes. J Am Soc Nephrol 2004; 15(3):770-779.

(81) Herzog CA, Ma JZ, Collins AJ. Poor Long-Term Survival after Acute Myocardial Infarction among Patients on Long-Term Dialysis. N Engl J Med 1998; 339(12):799-805.

(82) Mittalhenkle A, Gillen DL, Stehman-Breen CO. Increased risk of mortality associated with hip fracture in the dialysis population. Am J Kidney Dis 2004; 44(4):672-679.

(83) Trespalacios FC, Taylor AJ, Agodoa LY, Bakris GL, Abbott KC. Heart failure as a cause for hospitalization in chronic dialysis patients. American Journal of Kidney Diseases 41[6], 1267-1277. 2003.

(84) van Staa TP, Dennison EM, Leufkens HG, Cooper C. Epidemiology of Fractures in England and Wales. Bone 2001; 29(6):517-522.

(85) Kanis JA, Brazier JE, Stevenson M, Calvert NW, Lloyd Jones M. Treatment of established osteoporosis: a systematic review and cost-utility analysis. Health Technology Assessment 2002; 6(29):i-146.

(86) Association of elevated parathyroid hormone (PTH) and calcium with risk of hip, vertebral or pelvic fracture in hemodialysis patients. 41st European Renal Association-European Translant Association Congress; 2004.

(87) Stevenson M, Lloyd Jones M, De Nigris E, Brewer N, Davis S, Oakley J. A systematic review and economic evaluation of alendronate, etidronate, risedronate, raloxifene and teriparatide for the prevention andf treatment of osteoporosis. Health Technology Assessment 2005; 9(22):i-160.

(88) Jofre R, Lopez-Gomez JM, Menargues J, Polo JR, Guinsburg M, Villaverde T et al. Parathyroidectomy: whom and when? Kidney International - Supplement 2003; 63(85):S97-S100.

(89) Kim HC, Cheigh JS, David DS, Stubenbord W, Sullivan J, Rubin AL et al. Long term results of subtotal parathyroidectomy in patients with end-stage renal disease. Am Surg 1994; 60(9):641-649.

(90) Kestenbaum B, Andress DL, Schwartz SM, Gillen DL, Seliger SL, Jadav PR et al. Survival following parathyroidectomy among United States dialysis patients. Kidney International 2004; 66:2010-2016.

(91) Dolan P. Modeling Valuations for EuroQol Health States. Medical Care 1997; 35(11):1095-1108.

(92) Nease RF, Kneeland T, O'Connor GT, Sumner W, Lump[kins C, Shaw L et al. Variation in patient utilities for outcomes of the management of chronic stable angina. Implications for clinical practice guidelines. Ischemic heart disease team. JAMA 1995; 273(15):1185-1190.

(93) Harvard Centre for Risk Analysis. Preference Weights 1998-2001. The Cost-Effectiveness Analysis Registry. 2006 [cited 6 A.D. Jan. 11]; Available from: URL:http://www.hsph.harvard.edu/cearegistry/data/phaseIIpreferenceweights.pdf

(94) Brazier JE, Green C, Kanis JA, Committee Of Scientific Advisors International Osteoporosis Foundation. A systematic review of health state utility values for osteoporosis-related conditions. Osteoporosis International 2002; 13(10):768-776.

(95) BMA & RPSGB. British National Formulary No. 50 (September 2005) 1644. 2005. Wallingford, Oxfordshire, Pharmaceutical Press.

(96) Singer B, McLaughlin G, Robinson C, Christie J. Epidemiology of fractures in 15,000 adults: the influence of age and gender. Journal of Bone & Joint Surgery 1998; 80B:243-248.

(97) National Institute for Clinical Excellence. Guide to the Methods of Technology Appraisal 17. 2004. London, National Institute for Clinical Excellence.

(98) Mowatt G, Vale L, Perez J, Wyness L, Fraser C, Macleod A et al. Systematic review of the effectiveness and cost-effectiveness, and economic evaluation, of home versus hospital or satellite unit haemodialysis for people with end-stage renal failure. Health Technology Assessment 2003; 7(2):1-174.

(99) Martin AJ, Glasziou PP, Simes RJ. A cardiovascular extension of the Health Measurement Questionnaire. J Epidemiol Community Health 1999; 53(9):548-557.

(100) UK Medicines Information. New Medicines Profile: Cinacalcet. 05/06. 2005. Liverpool, UK Medicines Information Service.

(101) Davison A, Cameron JS, Grunfeld J-P, Ponticelli C, Ritz E, Winearls C et al. The Oxford Textbook of Clinical Nephrology. 3rd ed. Oxford: OUP; 2005.

(102) Foley.RN, Parfrey P. Cardiovascular disease and mortality in ESRD. Journal of Nephrology 1998; 11(5):239-245.

(103) Dotsch J, Plank C, Bosch B, Dorr HG, Rascher W. Endocrine disorders with chronic renal insufficiency. Padiatrische Praxis 2002; 61(3):435-446.

(104) Eknoyan G, Levin A, Levin N. Bone metabolism and disease in chronic kidney disease. Am J Kidney Dis 2003; 42(4 suppl 3):1-201.

(105) Evers S, Goossens M, de Vet H, van Tulder M, Ament A. Criteria list for assessment of methodological quality of economic evaluations: Consensus on Health Economic Criteria. International Journal of Technology Assessment in Health Care 2005; 21(2):240-254.

(106) Weinstein MC, O'Brien B, Hornberger J, Jackson J, Johannesson M, McCabe C et al. Principles of good practice for decision analytic modeling in health-care evaluation: report of the ISPOR Task Force on Good Research Practices--Modeling Studies. Value Health 2003; 6(1):9-17.

(107) MacLeod A, Grant A, Donaldson C, Khan I, Campbell A, Daly C et al. Effectiveness and efficiency of methods of dialysis therapy for end-stage renal disease: systematic reviews. Health Technology Assessment 1998; 2(5).